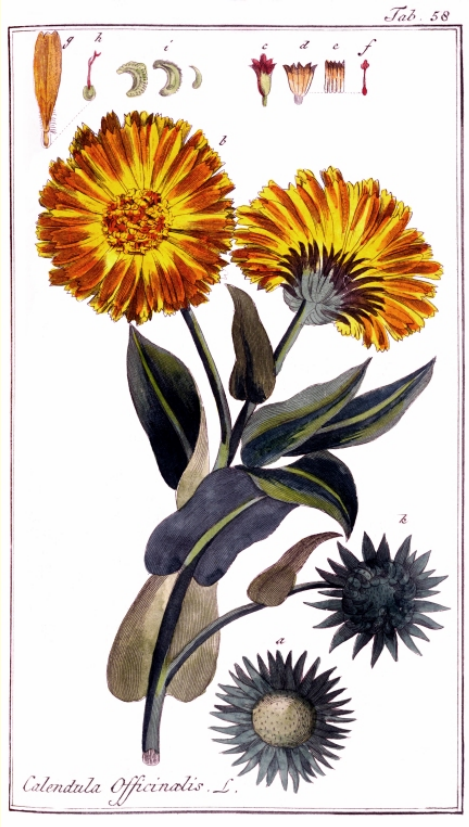


CD to accompany

Herbs & Natural Supplements

An Evidence-based Guide

Second Edition

CD to accompany

Herbs & Natural Supplements

An Evidence-based Guide

Second Edition

Lesley Braun

Pharmacist, Naturopath, Herbalist and
Industry Consultant and Lecturer at RMIT and
Monash Universities

Marc Cohen

Professor and Head of Department of
Complementary Medicine,
RMIT University, Melbourne

Sydney Edinburgh London New York
Philadelphia St Louis Toronto

Disclaimer Complementary medicine and pharmacology are ever-changing fields. Standard safety precautions must be followed but, as new research and clinical experience broaden our knowledge, changes in treatment become necessary or appropriate. The authors and publisher have, in so far as it is possible, taken every care to ensure that the information contained within the text is as accurate and as up-to-date as possible. Readers are, however, advised to always check available product information with the herb, supplement or drug manufacturer to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating person to determine dosages and the best treatment for the patient. Neither the publisher nor the editors assume any responsibility for any injury and/or damage to persons or property.


indicates a herb or supplement action with particular significance for pregnant women


indicates a warning or cautionary note regarding the action of a herb or supplement

ELSEVIER

Churchill Livingstone is an imprint of Elsevier

Elsevier Australia
(a division of Reed International Books Australia Pty Ltd)
30-52 Smidmore Street, Marrickville, NSW 2204
ACN 001 002 357

CONTENTS

Click on the name of the item that you are interested in, or use the PDF bookmarks to navigate through this document.

An index to the herbal medicines, conditions and main actions (clinical uses) discussed in the book is located at the end of the PDF.

Adhatoda

Historical note Used for hundreds of years as an important herb in Ayurvedic medicine, adhatoda is used traditionally for cough, asthma, bronchitis and tuberculosis.

COMMON NAMES
Adhatoda, Malabar nut tree

OTHER NAMES
Adhatoda zeylanica, arusha, bakash justicia adhatoda, vasaka, vasa

BOTANICAL NAME/FAMILY
Adhatoda vasica (family Acanthaceae)

PLANT PARTS USED
Leaves and roots

CHEMICAL COMPONENTS
The leaves contain several different alkaloids, including vasicine, vasicinone, vasicinol, adhatodine, adhatonine, adhavasinone, anisotine, peganine (Claeson et al 2000), betaine, steroids and alkanes. The root also contains alkaloids (vasicinol, vasicinolone, vasicinone, adhatonine), a steroid (daucosterol), carbohydrates and alkanes (Claeson et al 2000).

Clinical note
One of the alkaloids found in the herb (vasicine) has been chemically modified and is referred to as RLX (6,7,8,9,10,12-hexahydro-azepino-[2,1-b]-quinazoline-12-one) in the medical literature (Johri & Zutshi 2000). It has been shown in animal studies

to inhibit antigen-induced mast-cell degranulation and histamine release and exert bronchodilator activity.

MAIN ACTIONS

Adhatoda has not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies and is largely speculative. As with many Ayurvedic herbs, most investigation has been undertaken in India and locating original research from these sources is difficult.

ANTITUSSIVE EFFECTS

Results from animal studies show that *Adhatoda vasica* extract exerts considerable antitussive activity when administered orally and is comparable to codeine when cough is due to irritant stimuli (Dhuley 1999). The antitussive activity may be due to the action of vasicinone and vasicinol, which have activity in the cerebral medulla.

ANTI-INFLAMMATORY

Potent anti-inflammatory activity has also been demonstrated for the alkaloid fraction and shown to be equivalent to that of hydrocortisone in one study (Chakraborty & Brantner 2001).

BRONCHODILATOR AND ANTI-ASTHMATIC ACTIVITY

According to a 2002 review, both vasicine and vasicinone possess in vitro and in vivo bronchodilatory activity and inhibit allergen-induced bronchial obstruction in a manner comparable to that of sodium cromoglycate (Dorsch & Wagner 1991, Jindal et al 2002).

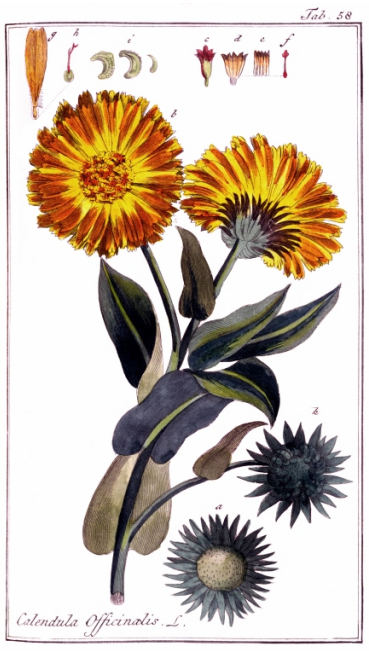
OTHER ACTIONS

HEPATOPROTECTIVE

Adhatoda vasica leaf (50–100 mg/kg) was shown to protect against induced liver damage in rats (Bhattacharyya et al 2005); 100 mg/kg of *Adhatoda vasica* was comparable to the hepatoprotective ability of silymarin at 25 mg/kg. An earlier study showed that *Adhatoda vasica* (100–200 mg/kg) protected against carbon tetrachloride-induced liver damage in rats (Pandit et al 2004). The leaf extract significantly enhanced the protective enzymes superoxide dismutase and catalase in the liver: 200 mg/kg of *Adhatoda vasica* was shown to be comparable to 25 mg/kg of silymarin.

PROTECTS AGAINST RADIATION DAMAGE

Adhatoda vasica (800 mg/kg) protects hematopoietic stem cells against radiation damage by inhibiting glutathione deletion, reducing lipid peroxidation and increas-



ing phosphatase activity in mice (Kumar et al 2005). Animals pretreated with oral doses of adhatoda showed an 81.25% survival rate at 30 days as compared to control animals who could not survive past 25 days.

ENZYME INDUCTION

In vitro tests show that *Adhatoda vasica* acts as bifunctional inducer, since it induces both phase I and phase II enzyme systems (Singh et al 2000).

ABORTIFACIENT

One of the traditional uses of the herb is as an abortifacient; however, inconsistent results from in vivo studies have made it difficult to determine whether adhatoda has significant abortifacient activity. One study investigating oral administration of leaf extracts showed 100% abortive rates at doses equivalent to 175 mg/kg of starting dry material (Nath et al 1992). Another study found that an *Adhatoda vasica* extract had anti-implantation activity in 60–70% of test animals (Prakash et al 1985).

ANTISPASMODIC

The essential oil from the leaves has been shown to exert antispasmodic action on guinea pig tracheal chain (Claeson et al 2000).

ANTIOXIDANT ACTIVITY

In vitro tests also show the extract is effective in inducing glutathione S-transferase and DT-diaphorase in lungs and forestomach, and superoxide dismutase and catalase in kidneys (Singh et al 2000).

CLINICAL USE

Adhatoda has not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies and is largely speculative.

COUGH

The antitussive activity of adhatoda extract has been compared to that of codeine in two different models of coughing and in two different animal species (Dhuley 1999). When administered orally, *Adhatoda vasica* extract produced antitussive effects comparable to those of codeine against coughing induced by peripheral irritant stimuli. When coughing was induced by electrical stimulation of the tracheal mucosa, adhatoda extract was only one-quarter as active as codeine. Intravenous administration was far less effective in both cough models. A double-blind, randomised, controlled trial of *Adhatoda vasica* in combination with *Echinacea purpurea* and *Eleutherococcus senticosus* was compared with an *Echinacea* and *Eleutherococcus* mixture and bromhexine (Narimanian et al 2005). Bromhexine is a semi-synthetic derivative of the alkaloid vasicine found in *Adhatoda vasica* (Grange & Snell 1996)

and is found in some pharmaceutical cough mixtures. The *Adhatoda vasica* combination reduced the severity of cough, increased mucus discharge and reduced nasal congestion compared to the other two formulas. Both the herbal mixtures reduced the frequency of cough compared to bromhexine.

ASTHMA

Although used for asthma in combination with other herbs, clinical evidence is unavailable to determine effectiveness. Evidence of bronchodilator activity from in vitro and animal studies provides a theoretical basis for use in this indication.

OTHER USES

Adhatoda is traditionally used to treat cough, asthma, bronchitis and colds, but has also been used to treat fever, dysentery, diarrhoea, jaundice, to stimulate the birthing process and aid healing afterwards, tuberculosis, headache, and as an antispasmodic (Claeson et al 2000). It has also been used as an abortifacient in some Indian villages.

Topical application of leaves that have been warmed on the fire is used in the treatment of joint pain, lumber pain and sprains.

The powder is reported to be used as a poultice on rheumatic joints, as a counterirritant for inflammatory swelling, on fresh wounds, and in urticaria and neuralgia (Dhuley 1999).

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturer recommendations.

- Liquid extract tincture (1:2): 1–3 mL/day.
- Dried herb: 0.5–1.5 g/day.

ADVERSE REACTIONS

Insufficient reliable information is available.

SIGNIFICANT INTERACTIONS

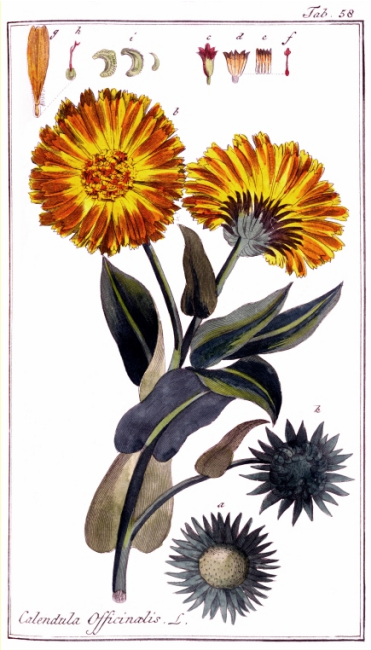
Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

CODEINE AND OTHER ANTITUSSIVE DRUGS

Theoretically, adhatoda may increase antitussive effects of these drugs — beneficial interaction possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.



PREGNANCY USE

Adhatoda is contraindicated in pregnancy, as the herb may have abortifacient activity.

PRACTICE POINTS/PATIENT COUNSELLING

- Adhatoda is an important Ayurvedic medicine used in the treatment of cough, asthma, bronchitis and colds.
- Traditional use further includes fever, dysentery, diarrhoea, jaundice, tuberculosis and headache.
- Preliminary evidence suggests that adhatoda may have bronchodilator activity and inhibit allergen-induced bronchoconstriction; however, clinical studies are unavailable to determine clinical significance.
- Antitussive effects comparable to those of codeine have also been reported in animal studies in which cough has been peripherally induced.
- Adhatoda has been used to stimulate the birthing process and aid healing afterwards and may have abortifacient activity.
- Overall, little clinical evidence is available, so much of the available information is speculative and based on in vitro and animal research and traditional use.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Adhatoda has mainly been investigated in animal and test tube studies so it is uncertain what effects it will have in humans. Based on this preliminary information and historical use, it may suppress cough and have some beneficial effects in asthma.

When will it start to work?

This is uncertain because insufficient research data are available.

Are there any safety issues?

Some research suggests that adhatoda may stimulate uterine contractions, so it is not recommended in pregnancy.

REFERENCES

Bhattacharyya D et al. Hepatoprotective activity of Adhatoda vasica aqueous leaf extract on D-galactosamine-induced liver damage in rats. Fitoterapia 76(2) (2005): 223-5.

Chakraborty A, Brantner AH. Study of alkaloids from Adhatoda vasica Nees on their antiinflammatory activity. Phytother Res 15.6 (2001): 532-4.

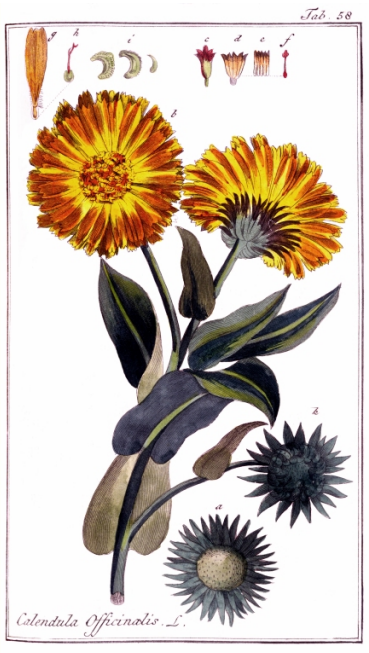
Claeson UP et al. Adhatoda vasica: a critical review of ethnopharmacological and toxicological data. J Ethnopharmacol 72.1-2 (2000): 1-20.

Dhuley JN. Antitussive effect of Adhatoda vasica extract on mechanical or chemical stimulation-induced coughing in animals. J Ethnopharmacol 67.3 (1999): 361-5.

Dorsch W, Wagner H. New antiasthmatic drugs from traditional medicine? Int Arch Allergy Appl Immunol 94.1-4 (1991): 262-5.

Grange JM, Snell NJ. Activity of bromhexine and ambroxol, semi-synthetic derivatives of vasicine from the Indian shrub Adhatoda vasica, against Mycobacterium tuberculosis in vitro. J Ethnopharmacol 50.1 (1996): 49-53.
Jindal DP et al. Synthesis and bronchodilatory activity of some nitrogen bridgehead compounds. Eur J Med Chem 37.5 (2002): 419-25.
Johri RK, Zutshi U. Mechanism of action of 6, 7, 8, 9, 10, 12-hexahydro-azepino-[2, 1-b] quinazolin-12-one (RLX): a novel bronchodilator. Indian J Physiol Pharmacol 44.1 (2000): 75-81.
Kumar A et al. Modulatory influence of Adhatoda vasica Nees leaf extract against gamma irradiation in Swiss albino mice. Phytomedicine 12(4) (2005): 285-93.
Narimanian M et al. Randomized trial of a fixed combination (Kan Jang) of herbal extracts containing Adhatoda vasica, Echinacea purpurea and Eleutherococcus senticosus in patients with upper respiratory tract infections. Phytomedicine 12(8) (2005): 539-47.
Nath D et al. Commonly used Indian abortifacient plants with special reference to their teratologic effects in rats. J Ethnopharmacol 36.2 (1992): 147-54.
Pandit S et al. Prevention of carbon-tetrachloride induced hepatotoxicity in rats by Adhatoda vasica leaves. Indian J Pharmacol 36 (2004): 312-13.
Prakash AO et al. Anti-implantation activity of some indigenous plants in rats. Acta Eur Fertil 16.6 (1985): 441-8.
Singh RP, Padmavathi B, Rao AR. Modulatory influence of Adhatoda vesica (Justicia adhatoda) leaf extract on the enzymes of xenobiotic metabolism, antioxidant status and lipid peroxidation in mice. Mol Cell Biochem 213.1-2 (2000): 99-109.

Albizia



Historical note It is believed that albizia received its name because Filipo del Albizi, an 18th century Florentine nobleman, introduced the species into cultivation (The Plants Database 2004). It has been used in Ayurvedic medicine for many years and is still a popular treatment for asthma, allergy and eczema.

COMMON NAME
Albizia

OTHER NAMES
Pit shirish shirisha

BOTANICAL NAME/FAMILY
Albizia lebbeck (family Fabaceae)

PLANT PARTS USED
Leaves and stem bark

CHEMICAL COMPONENTS
These are poorly understood, but albizia has been reported to contain albiziasaponins A, B and C, epicatechin, procyanidins and stigmastadienone.

MAIN ACTIONS
Albizia has not been significantly investigated in clinical studies; therefore, information is generally derived from in vitro and animal studies and is largely speculative.

STABILISING MAST CELLS
Both in vitro and in vivo tests have reported significant mast-cell-stabilisation effects similar to those of cromoglycate (Johri et al 1985, Tripathi et al 1979). One study found that degranulation was inhibited by 62% (Tripathi et al 1979). The saponin fraction is believed to be the key group responsible for activity.

ALTERING NEUROTRANSMITTER ACTIVITY
Albizia has an influence on GABA, serotonin and dopamine levels, according to in vivo studies (Chintawar et al 2002, Kasture et al 2000). It appears that different fractions within the herb exert slightly different effects on neurotransmitters. In one study, a saponin-containing fraction from the extract of dried leaves of *Albizia* was shown to decrease brain concentrations of GABA and dopamine, whereas serotonin

levels increased. Another study that tested the methanolic fraction of an ethanolic extract of *Albizia* leaves found that it raised brain levels of GABA and serotonin (Kasture et al 2000). Additionally, anticonvulsant activity has been demonstrated in vivo for this fraction.

MEMORY ENHANCEMENT

Saponins isolated from *Albizia* have been shown to significantly improve the memory retention ability of normal and amnesic mice, compared with their respective controls (Une et al 2001).

REDUCES MALE FERTILITY

Two studies using animal models have demonstrated that *Albizia* significantly reduces fertility in males (Gupta et al 2004, 2005).

Albizia saponins A, B and C (50 mg/kg) isolated from the stem bark have been shown to significantly reduce the weight of the testis, epididymides, seminal vesicle and ventral prostate of male rats (Gupta et al 2005). A significant reduction in sperm concentration was also noted and *Albizia* reduced fertility by 100% after 60 days. The methanolic extract of *Albizia* pods (50, 100 and 200 mg/kg) was also shown to significantly decrease fertility and arrest spermatogenesis in rats after 60 days (Gupta et al 2004).

OTHER ACTIONS

Other actions seen in vitro and in vivo include antifungal and antibacterial action, antispasmodic effect on smooth muscle, positive inotropy and an immunostimulant effect (Barua 2000, Bone 2001, Kasture et al 2000). Cholesterol-lowering activity has been demonstrated in vivo (Tripathi et al 1979).

CLINICAL USE

Albizia has not been significantly investigated under clinical trial conditions, so evidence is derived from tradition, in vitro and animal studies.

ALLERGY AND ASTHMA

Albizia is mainly used to treat allergic rhinitis, urticaria and asthma in clinical practice. In vitro and in vivo evidence of mast-cell stabilisation provide a theoretical basis for its use in allergic conditions; however, the clinical significance is unknown.

OTHER USES

Traditionally, a juice made from the leaves has been used internally to treat night blindness. The bark and seeds have been used to relieve diarrhoea, dysentery and treat haemorrhoids, most likely because of their astringent activity. The flowers have

been used as an emollient to soothe eruptions, swellings, boils and carbuncles. In Ayurvedic medicine, it is used to treat bronchitis, asthma, allergy and inflammation.

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturer recommendations.

- Liquid extract (1:2): 3.5–8.5 mL/day or 25–60 mL/week.
- Dried herb: 3–6 g/day.

TOXICITY

This is unknown; however, research with the methanolic fraction of *Albizia* extract has identified a median lethal dose of 150 mg/kg (Kasture et al 2000).

ADVERSE REACTIONS

Insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

BARBITURATES

Additive effects are theoretically possible, as potentiation of pentobarbitone-induced sleep has been observed in vivo — use with caution.

ANTIHISTAMINES AND MAST-CELL-STABILISING DRUGS

Additive effects are theoretically possible because both in vitro and in vivo tests have identified significant mast-cell-stabilisation activity similar to that of cromoglycate — potentially beneficial interaction.

TRICYCLIC AND SELECTIVE SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANT DRUGS

Increased risk of serotonin syndrome is theoretically possible, as *Albizia* increases serotonin levels, according to in vivo studies — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS

Significant reductions in male fertility have been reported in tests using animal models; however, it is not known whether the effects also occur in humans. Until further research is conducted, caution is advised.

PREGNANCY USE

Insufficient reliable information available.

PRACTICE POINTS/PATIENT COUNSELLING

- *Albizia* is a traditional Ayurvedic herb used to treat allergies, asthma, eczema and inflammation.
- Preliminary research has shown that it has significant mast-cell-stabilisation activity comparable to cromoglycate, and has also identified memory enhancement activity and possible anticonvulsant effects.
- Overall, little clinical evidence is available; therefore, much information is speculative and based on in vitro and animal research.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Albizia is a traditional Ayurvedic medicine used to reduce allergic conditions, such as allergic rhinitis and urticaria. It is also used for atopic conditions, such as eczema and asthma, when indicated. Controlled trials have not been conducted, so it is uncertain whether it is effective.

When will it start to work?

This is uncertain because insufficient research data are available.

Are there any safety issues?

This is uncertain because insufficient research data are available. It is advised that people with asthma be monitored by a healthcare professional.

REFERENCES

Barua CC et al. Immunomodulatory effects of Albizia lebbeck. Pharmaceut Biol 38.3 (2000): 161-6.

Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 2001.

Chintawar SD et al. Nootropic activity of Albizia lebbeck in mice. J Ethnopharmacol 81.3 (2002): 299-305.

Gupta RS, Kachhawa JB, Chaudhary R. Antifertility effects of methanolic pod extract of Albizia lebbeck (L.) Benth in male rats. Asian J Androl 6.2 (2004): 155-9.

Gupta RS et al. Effect of saponins of Albizia lebbeck (L.) Benth bark on the reproductive system of male albino rats. J Ethnopharmacol 96.1-2 (2005): 31-6.

Johri RK et al. Effect of quercetin and Albizia saponins on rat mast cell. Indian J Physiol Pharmacol 29.1 (1985): 43-6.

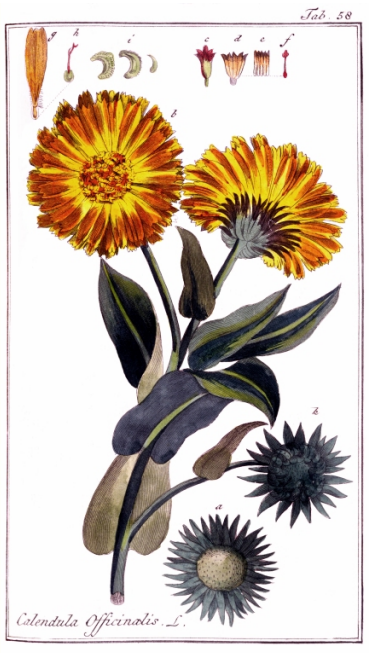
Kasture VS, Chopde CT, Deshmukh VK. Anticonvulsive activity of Albizia lebbeck, Hibiscus rosa sinesis and Butea monosperma in experimental animals. J Ethnopharmacol 71.1-2 (2000): 65-75.

The Plants Database. www.plantsdatabase.com (accessed March 2004).

Tripathi RM, Sen PC, Das PK. Studies on the mechanism of action of Albizia lebbeck, an Indian indigenous drug used in the treatment of atopic allergy. J Ethnopharmacol 1.4 (1979): 385-96.

Une HD et al. Nootropic and anxiolytic activity of saponins of Albizia lebbeck leaves. Pharmacol Biochem Behav 69.3-4 (2001): 439-44.

Aloe vera



Historical note *Aloe vera* has been used since ancient times as a medicinal plant. In fact, evidence of use has been found on a Mesopotamian clay tablet dating back to 2100 BC (Atherton 1998). It has been used as a topical treatment for wounds, burns and other skin conditions and internally as a general tonic, anti-inflammatory agent, carminative, laxative, aphrodisiac and anthelmintic by the ancient Romans, Greeks, Arabs, Indians and Spaniards. According to legend, Alexander the Great captured an island in the Indian Ocean in order to gain the *Aloe vera* for his wounded army. Today aloe is used to soothe skin complaints and heal burns, and is one of the most common ingredients in many cosmetic products.

OTHER NAMES
Aloes, Barbados aloe, Curacao aloe

BOTANICAL NAME/FAMILY
Aloe vera (L.)/*Aloe barbadensis* (Mill.) (family Aloeaceae)

PLANT PARTS USED
The leaf, from which several different products are made; namely the exudate, gel, extract and juice. The exudate ('aloes' in older pharmacy texts) is a thick residue, yellow in colour and bitter in taste, that comes from the latex that oozes out when the leaf is cut. The 'gel' refers to the clear gel or mucilage produced by the inner parenchymal cells in the central part of the leaf. Diluted aloe gel is commonly known as 'aloe vera extract' or 'aloe juice'.

CHEMICAL COMPONENTS
Aloe vera extract, or diluted aloe gel, is made of mostly water (99%) and mono- and polysaccharides, most important of which is the monosaccharide mannose-6-phosphate and the polysaccharide gluco-mannans, which are long-chain sugars containing glucose and mannose. Gluco-mannan has been named acemannan and is marketed as Carrisyn. A glycoprotein with anti-allergic properties has also been isolated, and has been named alprogen. Recently, C-glucosyl chromone, an anti-inflammatory compound, has also been identified.

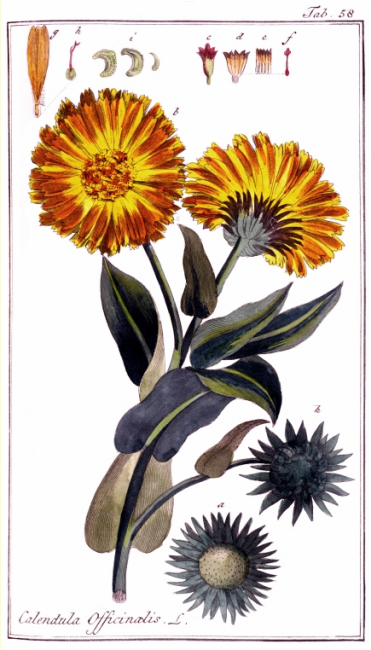
Aloe gel also contains lignans, saponins, salicylic acid, sterols and triterpenoids, vitamins A, C, E, B12, thiamine, niacin and folic acid, and the minerals sodium,

calcium, potassium, manganese, magnesium, copper, chromium, zinc and iron (Shelton 1991, Yamaguchi et al 1993).

The fresh gel contains glutathione peroxidase, isozymes of superoxide dismutase, and the proteolytic enzyme carboxypeptidase (Klein & Penneys 1988, Sabeh et al 1993).

Ultimately, the types and levels of components present in aloe gel vary according to geographic origin, variety and processing method.

The exudate contains the pharmacologically active anthraquinone glycosides: aloin, aloe-emodin, barbaloin and emodin (Choi & Chung 2003).



MAIN ACTIONS

The active ingredients, whether acting alone or in concert, include glycoproteins, anthraquinones, polysaccharides, and low-molecular-weight species such as beta-sitosterol (Choi & Chung 2003).

ASSISTS IN WOUND HEALING

Wound healing is associated with various mechanisms and constituents. Thromboxane inhibits wound healing and aloe has been shown to inhibit thromboxane in vitro (Zachary et al 1987). Enzymes in aloe have also been shown to break down damaged tissue, which can then be removed by phagocytosis (Bunyapraphatsara et al 1996). A glycoprotein fraction was found to increase proliferation of human keratinocytes and increase the expression of receptors for epidermal growth factor and fibronectin in vitro (Choi et al 2001). The same research team then demonstrated that this glycoprotein enhanced wound healing by increasing cell proliferation in vivo. Beta-sitosterol appears to improve wound healing by stimulating angiogenesis and neovascularisation in vivo (Moon et al 1999). Aloe polysaccharides have been shown to ameliorate UV-induced immunosuppression (Strickland et al 1994).

Tests in animal models Several animal studies support the application of aloe gel to skin damaged by frostbite as a means to maintain circulation and reduce the vasoconstrictive effects of thromboxane in the affected dermis (Heggers et al 1987, Klein & Penneys 1988, McCauley et al 1990, Miller & Koltai 1995). In combination with pentoxifylline, it will act synergistically to further increase tissue survival (Miller & Koltai 1995).

A study to test the effectiveness of topical application versus oral administration in rats with full-thickness wounds showed topical use of aloe gel to be slightly more effective than internal use. The collagen content in granulation tissue was measured to be 89% in the topical group compared with 83% in the oral group (Chithra et al

1998). Other studies have found that aloe gel not only increases collagen content, but also changes collagen composition, in addition to increasing collagen cross-linking, which in turn increases the breaking strength of scar tissue, making the seal stronger (Chithra et al 1998, Heggers et al 1996).

Full thickness hot-plate burns (3% total surface area) to test animals healed more quickly with the application of aloe gel compared to silver sulfadiazine (SSD) or salicylic acid cream (aspirin) (Rodriguez-Bigas et al 1988). Guinea pigs treated with aloe recovered in 30 days as compared to 50 days for control animals (dressing only) and wound bacterial counts were effectively decreased. *Aloe vera* was also found to promote healing and decrease inflammation in second-degree burns in vivo (Somboonwong et al 2000). A significant reduction in vasodilation and post-capillary venular permeability was recorded on day 7 in the aloe group. At day 14 arteriolar diameter had returned to normal and the size of the wound was greatly reduced as compared to controls.

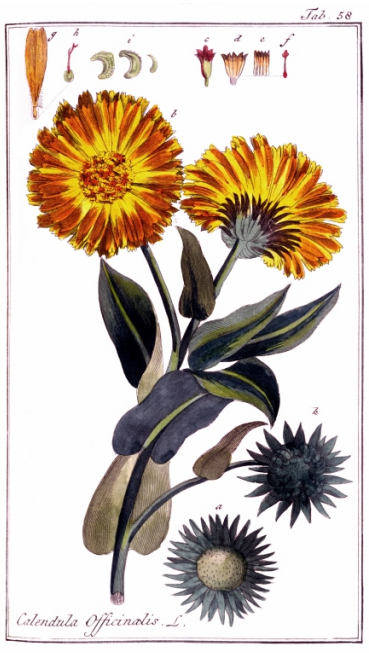
Aloe gel prevented delayed hypersensitivity of UV-irritated skin as well as contact hypersensitivity in animal models with allergic reactions (Strickland et al 1994). Acemannan gel (beta-(1,4)-acetylated mannan) has demonstrably improved radiation burns in mice. Best results were obtained when the gel was applied during the first week after injury (Roberts & Travis 1995).

Use with pharmaceutical agents Several topical pharmaceutical antimicrobial agents, such as SSD, inhibit wound contraction, thereby slowing the rate of wound healing. An experimental model was used to investigate whether co-administration of aloe could reverse this effect and improve wound healing rate (Muller et al 2003). Full-thickness excised wounds were treated with placebo (aqueous cream or saline), SSD cream 0.5%, 1% or 1% with *A. vera* three times daily for 14 days, then observed until healed. *Aloe vera* was found to reverse the delayed wound healing produced by SSD, resulting in the shortest wound half-life and healing time.

Aloe vera (100 and 300 mg/kg daily for 4 days) blocked the ability of hydrocortisone acetate to suppress wound healing by up to 100% (Davis et al 1994a). Growth factors in *A. vera* were thought to mask sterols and certain amino acids that prevent wound healing. An earlier study identified the sugar mannose-6-phosphate to be one of the chief constituents responsible for wound healing (Davis et al 1994b).

Clinical note — Wound healing models
Acute wound healing occurs in four stages that tend to overlap: haemostasis, inflammation, proliferation and remodelling. Underlying metabolic disturbances and/or disease may disrupt the regenerative process, causing delayed healing. Much

investigation is conducted with in vitro assays based on cell culture models of the various phases of healing, which provides information about possible mechanisms of action. Experimental models using animals are undertaken to determine the reduction of wound size (usually in terms of area) and hence the rate of healing. Histological examination of granulation and epidermal tissues provides a concurrent analysis at the molecular level. Human models of wound healing provide an opportunity to observe a variety of healing disorders that are less predictable than their cell or animal-based counterparts. *Aloe vera* is the only traditional wound healing herbal medicine that has been subjected to a variety of cell culture-based, animal and human-based studies (Krishnan 2006).



ANTIOXIDANT

Studies have found that several compounds present in aloe gel protect tissues against oxidative damage caused by free radicals ('t Hart et al 1990, Singh et al 2000, Wu et al 2006, Yagi et al 2002, Zhang et al 2006). This is achieved by direct antioxidant activity and indirect activity through stimulation of endogenous antioxidant systems.

Treatment with aloe gel extract decreased lipid peroxidation and hydroperoxides in diabetic rats to near normal levels (Rajasekaran et al 2005). The extract also significantly increased superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidney. In another study, data obtained 3, 7 and 10 days after exposure to radiation showed that aloe gel significantly reduced oxidative damage in the liver, lungs, and kidney tissues of irradiated rats (Saada et al 2003).

Three-year-old aloe plants appear to have the highest amounts of flavonoids and polysaccharides and hence the best free radical scavenging capacity, as compared to 2- and 4-year-old plants (Hu et al 2003). Interestingly, the 3-year-old plant demonstrated antioxidant activity of 72.19%, compared to alpha-tocopherol at 65.20%.

IMMUNOSTIMULANT

It has been suggested that aloe may have immune-stimulating capabilities. Much of the available research has been performed on mice or in vitro and aloe shows antiviral, antitumour and non-specific immunostimulant activity. An experiment in 1980 demonstrated that mice given aloe extract 2 days before exposure to pathogens were protected against a variety of fungi and bacteria (Brossat et al 1981). Later, the isolated compound acemannan (beta-(1,4)-acetylated mannan) was shown to increase the response of lymphocytes to antigens in vitro (Womble & Helderman 1988). In mice, acemannan stimulated cytokines, bringing about an immune attack

on implanted sarcoma cells, leading to necrosis and regression of cancer cells (Peng et al 1991). A later trial investigated the effects of acemannan on mouse macrophages (Zhang & Tizard 1996). Acemannan stimulated macrophage cytokine production (IL-6 and TNF-alpha), NO release, surface molecule expression, and cellular morphologic changes. Similarly, a polysaccharide fraction isolated from *Aloe vera* promoted human keratinocytes to secrete TGF-alpha, TGF-beta-1, IL-1-beta, IL-6, IL-8 and TNF, and inhibited the release of NO as compared to control (Chen et al 2005). The immune enhancing effects of acemannan may be due in part to the compound's ability to promote differentiation of immature dendritic cells (Lee et al 2001). These cells are crucial for the initiation of primary immune responses.

Three purified polysaccharide fractions (PAC-I, PAC-II, and PAC-III) from *A. vera* stimulated peritoneal macrophages, splenic T and B cells, and increased the ability of these cells to secrete TNF-alpha, IL-1-beta, IFN-gamma, IL-2, and IL-6 (Leung et al 2004). The compound with the highest mannose content, and therefore the highest molecular weight (PAC-I), demonstrated the most potential. A 99% pure carbohydrate compound (purified acemannan) isolated from aloe demonstrated potent haematopoietic and haematologic activity in myelosuppressed mice (Talmadge et al 2004).

Specific manufacturing methods can be applied to enhance the extracts. For example, 1 g of extract obtained from leaves subjected to cold and dark treatment contained 400 mg of neutral polysaccharide compared with 30 mg in leaves not specially treated (Shida et al 1985).

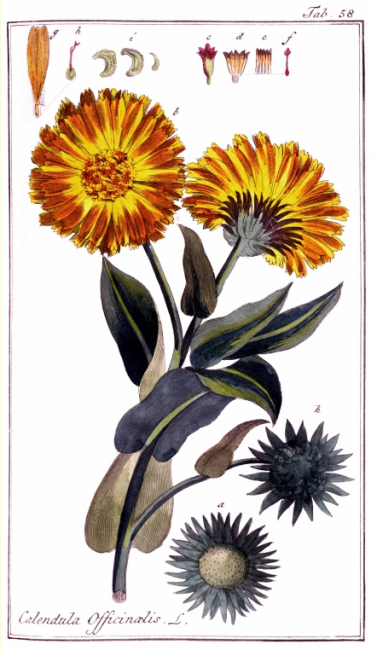
ANTI-INFLAMMATORY

A number of in vitro and in vivo studies confirm the anti-inflammatory activity of *Aloe vera*.

The gel reduces oxidation of arachidonic acid, thereby reducing PG synthesis and inflammation (Davis et al 1987). It inhibits the production of PGE_2 by 30% and IL-8 by 20%, but has no effect on thromboxane B2 production in vitro (Langmead et al 2004). Following burn injury in vivo, *A. vera* was also found to inhibit inflammation by reducing leukocyte adhesion and decreasing the pro-inflammatory cytokines TNF-alpha and IL-6 (Duansak et al 2003).

One study conducted on rats with croton oil-induced oedema reported a 47% reduction in swelling after the application of topical aloe gel (Davis et al 1989). Another study found aloe gel to reduce vascularity and swelling by 50% in the inflamed synovial pouch in rats, along with a 48% reduction in the number of mast cells in the synovial fluid within the pouch. When aloe gel was applied topically there was also an increase in fibroblast cell numbers (Davis et al 1992). C-glucosyl

chromone, isolated from aloe gel extracts, is chiefly responsible for the anti-inflammatory effect, with activity comparable to hydrocortisone in experimental models (Hutter et al 1996). A study of streptozotocin-induced diabetic mice further confirmed the anti-inflammatory activity of *A. vera* and identified the isolated constituent gibberellin as also effective (Davis and Maro 1989). Both compounds inhibited inflammation in a dose dependant manner.



LAXATIVE

The aloe latex contains anthraquinones, which have a stimulant laxative activity. Studies in rats have shown that aloe latex increases intestinal water content, stimulates mucus secretion, and induces intestinal peristalsis (Ishii et al 1994). However, aloe as a laxative is more irritating than other herbs (Reynolds & Dweck 1999) and long-term use can cause an electrolyte imbalance through depletion of potassium salts. Alternatives are recommended if long-term treatment is required.

ANTI-ULCER

The anti-ulcer activity of *Aloe vera* has been proposed to be due to anti-inflammatory, cytoprotective, healing and mucus stimulatory effects. According to an in vivo study, *A. vera* promotes gastric ulcer healing (Eamlamnam et al 2006). In contrast to these results, a stabilised fresh aloe gel preparation prolonged the effect of histamine-stimulated acid secretion but inhibited pepsin in another study (Suvitayavat et al 2004).

HYPOGLYCAEMIC

Glucomannan slows carbohydrate absorption and slows the postprandial insulin response by up to 50% (McCarty 2002).

Aloe vera leaf gel has been investigated as a possible hepatoprotective and kidney protective agent in diabetes type 2 using animal models. In one study, the leaf gel and glibenclamide both decreased degenerative kidney changes, serum urea levels and creatinine levels, but only aloe further reduced kidney lipid peroxidation (Bolkent et al 2004). Can et al (2004) tested aloe pulp, aloe gel extract and glibenclamide, finding that all treatments decreased liver tissue damage as compared to control animals. Aloe gel extract also increased glutathione levels and decreased non-enzymatic glycosylation, lipid peroxidation, serum alkaline phosphatase and alanine transaminase.

ANTIBACTERIAL

Aloe vera is active against a wide variety of bacteria in vitro, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Escherichia coli* (Heck et al 1981, Shelton 1991).

ANTIVIRAL

In vitro studies suggest that *Aloe vera* has antiviral activity due to its interference with DNA synthesis (Saoo et al 1996). The polysaccharide fractions of aloe gel inhibit the binding of benzopyrene to primary rat hepatocytes and thus prevent the formation of potentially cancer-initiating benzopyrene-DNA adducts in vitro. This was later confirmed by in vivo studies (Kim & Lee 1997). Moreover, in vitro experiments have shown the anthraquinones in aloe to be virucidal against HSV 1 and 2, vaccinia virus, parainfluenza virus and vesicular stomatitis virus (Anderson 2003).

Investigation with the acemannan component has identified antiviral activity, particularly against feline AIDS, HIV type 1, influenza virus, measles virus and herpes simplex (Kahlon et al 1991a,b, Sydiskis et al 1991).

CLINICAL USE

Although *Aloe vera* products are used for many indications, the chief use is treating skin conditions.

SKIN CONDITIONS

Aloe is used in the treatment of wounds, burns, radiation burns, ulcers, frostbite, psoriasis and genital herpes. The healing properties may be attributed to antimicrobial, immune-stimulating, anti-inflammatory and antithromboxane activities. Allantoin has also been shown to stimulate epithelialisation, and acemannan has been shown to stimulate macrophage production of IL-1 and TNF, which are associated with wound healing (Liptak 1997).

Most human studies have found that topical application of aloe vera gel increases wound healing rate and effectively reduces microbial counts; however, there are some negative studies, most likely related to the fact that the composition of aloe vera gel varies, even within the same species. Chemical composition depends on source, climate, region, and the processing method used (Choi & Chung 2003).

Dry-coated aloe vera gloves were tested by 30 women suffering from dry, cracked hands, with or without contact dermatitis due to occupational exposure, in an open contralateral comparison study (West & Zhu 2003). Women wore a glove on one hand for 8 hours daily for 30 days followed by a rest period for 30 days and then 10 more days of treatment. Results indicated that the aloe vera glove significantly reduced dry skin, irritation, wrinkling, dermatitis, redness and improved skin integrity.

It would be interesting to see this study repeated using a standard non-aloe fortified glove on the opposing hand.

The effects of aloe gel applied to skin following dermabrasion in humans are more controversial, with some patients responding well (Fulton 1990), while others have had severe adverse reactions, including burning sensations and dermatitis (Hunter & Frumkin 1991). A standard polyethylene oxide gel dressing saturated with stabilised aloe vera gel was compared to the standard oxide dressing alone in the study by Fulton. The addition of *Aloe vera* produced a significant vasoconstriction and anti-inflammatory effect 24 and 48 hours after application. By the 4th day it produced less crusting and exudate and by the 5th and 6th day re-epithelialisation was almost complete (90% for aloe compared with 50% for the standard treatment). Overall, wound healing was quicker with *A. vera* and completed by an average of 72 hours before the oxide gel-treatment.

In contrast, one study found that topical aloe vera gel actually slowed healing after caesarean delivery (Schmidt & Greenspoon 1991).

Burns One study involving 27 patients with a partial-thickness burn injury found that topical aloe gel significantly increased the healing rate compared with controls who used a vaseline gauze. The mean healing time for the aloe gel group was 11.89 days compared with the control group, which was 18.18 days. Additionally, the aloe treatment brought about full epithelialisation after 14 days (Visuthikosol et al 1995).

Another study involving 18 outpatients with moderate to deep second-degree burns ranging from 2% to 12% of total body surface area showed that a commercial aloe vera ointment was as effective as SSD in regard to protection against bacterial colonisation and healing time. More specifically, the mean healing time with aloe vera treatment was 13 days compared with 16.15 days for SSD (Heck et al 1981).

Results are less encouraging for sunburn protection and healing. A randomised double-blind trial in 20 healthy volunteers evaluated the effect of aloe vera cream for both prevention and treatment of sunburn (Puvabanditsin & Vongtongsri 2005). The cream (70% aloe) was applied 30 minutes before, immediately after, or both before and after UV irradiation. The cream was then continually applied daily for 3 weeks. The results showed that the aloe vera cream did not protect against sunburn and was not an effective treatment.

Frostbite In combination with other treatments, topical *Aloe vera* significantly enhances healing and has a beneficial effect in frostbite. One clinical study compared the effects of topical aloe vera cream in combination with standard treatment, such as rapidly rewarming the affected areas, analgesics, antibiotics and debridement

($n = 56$) with another group of 98 patients who did not receive aloe vera treatment. Of those receiving aloe vera in addition to usual treatment, 67% healed without tissue loss compared with 32.7% in the control group. Additionally, 7.1% of the total group of 56 required amputation compared with 32.7% in the control group. Although encouraging, this study is difficult to interpret because the groups were not well matched and combination therapies differed (Heggers et al 1987).

Radiation-induced dermatitis A recent review concluded that aloe gel was as effective as mild steroid creams, such as 1% hydrocortisone, to reduce the severity of radiation burn, without the side-effects associated with steroid creams (Maddocks-Jennings et al 2005). In contrast, another review concluded that aloe was ineffective for the prevention or reduction of side-effects to radiation therapy in cancer patients (Richardson et al 2005). That review analysed 1 past review, 5 published RCTs and 2 unpublished RCTs. It is important to note that various preparations such as creams, juices, gels and fresh aloe had been tested, which makes it difficult to assess the evidence.

Ulcers A number of case reports tell of a positive effect on leg ulcers with topical use of aloe gel, including cases that did not respond to standard medical interventions (Zawahry et al 1973). Application of water-based aloe-gel saline soaks, broad-spectrum antibiotics and antifungals allowed a wound, caused by necrotising fasciitis, to heal in 45 days in a 72-year-old woman. Aloe gel and saline-soaked sponges were also used to treat two large seroma cavities caused by deep vein thrombosis in a 48-year-old man (Ardire 1997).

Although aloe gel is commonly used as a topical agent for wound healing it is also used internally. A small study of six patients with chronic leg ulcers found that ingesting 60 mL aloe juice daily and applying aloe gel directly to the ulcer and surrounding area resulted in less exudate, odour and seepage through the bandaging (Atherton 1998).

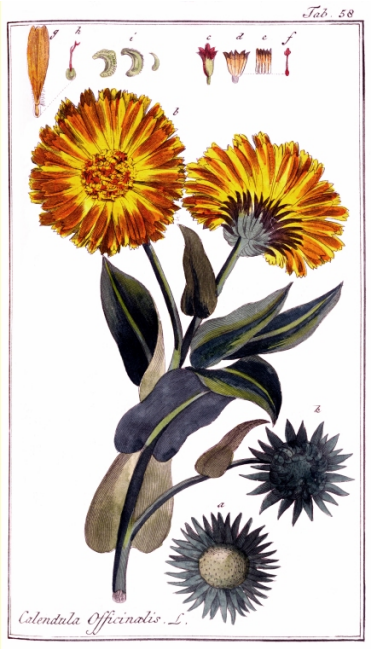
Psoriasis A double-blind placebo-controlled study found topical aloe vera extract 0.5% in a hydrophilic cream to be beneficial in the treatment of psoriasis. Sixty patients aged 18–50 years with slight to moderate chronic psoriasis and PASI (psoriasis area and severity index) scores between 4.8 and 16.7 (mean 9.3) participated in the study, which was scheduled for 16 weeks with 12 months of follow-up. Patients were examined on a weekly basis and those showing a progressive reduction of lesions, desquamation followed by decreased erythema, infiltration and lowered PASI score were considered healed. By the end of the study, the aloe vera extract cream had cured 83.3% of patients compared with the placebo cure rate of 6.6% ($P < 0.001$). Psoriatic plaques decreased in 82.8% of patients versus only 7.7%

in the placebo group ($P < 0.001$). PASI scores decreased to a mean of 2.2 (Syed et al 1996a). In contrast, a randomised, double-blind, placebo-controlled trial found no significant benefits with a commercial aloe vera gel in 41 patients with stable plaque psoriasis (Paulsen et al 2005). Following a 2-week washout period patients applied either the aloe gel or placebo twice daily for 1 month. Redness and desquamation decreased by 72.5% in the active treatment group as compared to 82.5% in the placebo group. It should be pointed out that 82.5% is an extremely high placebo responder rate. Fifty-five per cent of patients reported local side-effects, mainly drying of the skin on test areas.

Genital herpes Two clinical studies have investigated the effects of *Aloe vera* 0.5% topical preparations in genital herpes, producing good results.

A double-blind, placebo-controlled study has demonstrated that aloe vera extract (0.5%) in a hydrophilic cream is more efficacious than placebo in the treatment of initial episodes of genital herpes in men ($n = 60$, aged 18–40 years). Each patient was provided with a 40 g tube, containing placebo or active preparation with instructions on self-application of the trial medication to their lesions three times daily for 5 consecutive days (maximum 15 topical applications per week). The treatment was well tolerated by all patients (Syed et al 1997).

The other study involving 120 subjects used a preparation containing 0.5% of whole aloe leaf extract in hydrophilic castor and mineral oil cream base, which was applied three times daily for 5 days per week for 2 weeks. Treatment resulted in a shorter mean duration of healing compared with placebo. Aloe cream also increased the overall percentage of healed patients and there were no significant adverse reactions reported (Syed et al 1996b).



HIV

The acemannan component of *Aloe vera* has been used as adjunctive therapy to antiretroviral therapy in HIV infection. A preliminary clinical trial found that acemannan may enhance the activity of the anti-HIV drug AZT. A dose of 800 mg acemannan daily significantly increased circulating monocytes (macrophages) in 14 HIV patients. Aloe increased the number and activity of the monocytes (McDaniel et al 1990). Subsequently, a randomised, double-blind placebo-controlled study of 63 male subjects with advanced HIV, taking zidovudine and didanosine, investigated the effects of 400 mg of acemannan taken four times daily for 48 weeks. Results showed a decrease in CD4 cell numbers in the acemannan group compared with placebo (Montaner et al 1996).

GASTROINTESTINAL CONDITIONS

Oral *Aloe vera* is a popular treatment for a variety of gastrointestinal disorders. It has been shown to improve different parameters of gastrointestinal function in normal subjects, such as colonic bacterial activity, gastrointestinal pH, stool specific gravity and gastrointestinal motility (Bland 1986). Due to its anthraquinone content, it is used as a stimulant laxative.

Besides this indication, there is still a need for scientific validation to establish which gastrointestinal conditions are most receptive to treatment with aloe.

IRRITABLE BOWEL SYNDROME

Aloe vera may be effective for patients with diarrhoea-predominant IBS, according to a recent randomised, placebo-controlled study ($n = 58$) (Davis et al 2006). Both treatments were administered for 1 month with a follow-up period of 3 months. Within the first month, 35% of the patients receiving *A. vera* responded compared to 22% with placebo. Overall, diarrhoea-predominant IBS patients had a more statistically significant responder rate than placebo (43% vs 22%).

ULCERATIVE COLITIS

A double-blind, randomised, placebo-controlled trial evaluated the efficacy and safety of *Aloe vera* gel (100 mL twice daily for 4 weeks) in ulcerative colitis (Davis et al 2006). Aloe induced clinical remission in 30% of subjects compared to 7% for placebo and symptom improvement in 37% compared to 7% for placebo. The Simple Clinical Colitis Activity Index and histological scores also decreased significantly for patients on the aloe treatment, but not for those receiving placebo.

OTHER USES

ASTHMA

According to a small open study ($n = 33$), long-term oral administration of aloe may have benefits for some people with chronic asthma, as one-third of subjects reported improvement (Afzal et al 1991, Shida et al 1985).

DIABETES

Three systemic reviews of herbal medicines for glycaemic control in diabetes found that *Aloe vera* can lower blood glucose levels in diabetic patients (Grover et al 2002, Vogler & Ernst 1999, Yeh et al 2003). In one trial aloe juice consisting of 80% gel or placebo was given in a trial of 40 patients who were recently diagnosed with type 1 diabetes at the dose of 1 tablespoon twice daily. From day 14 the blood sugar levels in the aloe group began to fall significantly compared with the control group and continued to steadily drop during the period of study ($P < 0.01$). Blood triglyceride

levels were also substantially reduced but cholesterol levels remained the same (Yongchaiyudha et al 1996). A single blind, placebo-controlled trial found that oral aloe gel was more effective in reducing blood sugar levels when combined with glibenclamide than glibenclamide alone in 72 patients with type 2 diabetes. Patients took 5 mg of glibenclamide twice daily and 1 tablespoon aloe gel. Fasting blood glucose levels dropped appreciably after just 2 weeks' treatment, and were still falling after 42 days (Bunyapraphatsara et al 1996).

CANCER

There are some epidemiological studies suggesting that aloe may reduce the risk of certain cancers; however, further research is required to clarify its place in practice (Sakai et al 1989, Siegers et al 1993).

DOSAGE RANGE

- Aloe vera gel: fresh from a living plant or as stabilised juice 25 mL (4.5:1) up to four times daily.
- Extracts standardised to acemannan: preparation containing up to 800 mg/day.
- Topical application: gel, cream or ointment as needed.
- 1.5–4.5 mL daily of 1:10 tincture of resin (latex).

ADVERSE REACTIONS

Although adverse reactions are rare, hypersensitivities and contact dermatitis to aloe have been reported (Morrow et al 1980, Nakamura & Kotajima 1984). Hypersensitivity manifested by generalised nummular eczematous and papular dermatitis, and presumably by contact urticaria, developed in a 47-year-old man after 4 years of using oral and topical aloe. Patch tests for aloe were positive in this patient (Morrow et al 1980).

SIGNIFICANT INTERACTIONS

HYPOGLYCAEMIC AGENTS

Oral *Aloe vera* may have hypoglycaemic activity, therefore additive effects are theoretically possible — observe patients taking this combination.

LAXATIVES

Additive effects are theoretically possible with oral aloe latex inducing griping pains — use with caution.

TOPICAL CORTISONE PREPARATIONS

In addition to its own anti-inflammatory effects, animal studies have shown that *Aloe vera* increases the absorption of hydrocortisone by hydrating the stratum corneum,

inhibits hydrocortisone's suppressive effects on wound healing and increases wound tensile strength — possible beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Strong laxatives such as aloe latex are contraindicated in children. Avoid in patients with known hypersensitivity to aloe or with nausea, vomiting or signs and symptoms of gastrointestinal obstruction. Avoid excessive use and long-term use (more than 2 weeks), as potassium losses may occur, which may alter cardiac electrophysiology.

Use with caution in people with thyrotoxicosis.

A case study of depression of thyroid hormones in a woman taking *Aloe vera* juice has been reported (Pigatto & Guzzi 2005). The patient consumed 10 mL daily for 11 months and laboratory testing showed reduced levels of thyroxine and triiodothyonine. Levels returned to normal progressively after discontinuing the aloe juice and the patient achieved full clinical remission after 16 months. Reduced serum levels of the thyroid hormones T_3 and T_4 have been reported for *Aloe vera* in vivo (Kar et al 2002).

PREGNANCY USE

Strong laxatives such as aloe latex are contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Different parts of the *Aloe vera* plant are used therapeutically. The gel is used topically and the latex is used internally.
- The gel may be beneficial in the treatment of skin conditions (wounds, burns, radiation burns, ulcers, frostbite, psoriasis and genital herpes). There is good scientific evidence for these indications.
- Traditionally, aloe latex is also used internally for gastrointestinal ulcers, dyspepsia and what is known today as IBS. Aloe is also used in conditions such as food allergies and disturbed bowel flora.
- Aloe may be a useful adjunct in the treatment of chronic poor immunity, HIV, cancer and chronic fatigue. There is preliminary scientific support for these indications.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Aloe gel is traditionally used for burns, wounds and inflammatory skin disorders. There is good scientific evidence that aloe may be of benefit in these conditions; however, the chemical composition of *Aloe vera* products will vary depending on geographical and processing factors. Traditionally, aloe is also used internally for dyspepsia, gastrointestinal ulcers and IBS.

When will it start to work?

Aloe has an immediate effect on burns and inflammatory skin diseases. Improvement occurs within several weeks with the condition continuing to improve with use. Chronic conditions may require long-term use. Internal use of *Aloe vera* as a laxative can produce results within 12–24 hours.

Are there any safety issues?

Aloe gel is safe and non-toxic. Avoid chronic use of laxative preparations that contain highly irritant compounds, known as anthraquinone glycosides, in the latex.

REFERENCES

Afzal M et al. Identification of some prostanoids in Aloe vera extracts. Planta Med 57 (1991): 38-40.

Anderson D. Wound dressings unravelled. In Practice 25.2 (2003): 70-83.

Ardire L. Necrotizing fasciitis: case study of a nursing dilemma. Ostomy Wound Manage 43.5 (1997): 30-40.

Atherton P. Aloe vera: magic or medicine? Nurs Stand 12.41 (1998): 49-52, 54.

Bland J. Aloe vera juice: an important role in gastrointestinal disorders? Altern Med 1 (1986): 280.

Bolkent S et al. Effect of Aloe vera (L.) Burm. fil. leaf gel and pulp extracts on kidney in type-II diabetic rat models. Indian J Exp Biol 42.1 (2004): 48-52.

Brossat JY et al. Immunostimulating properties of an extract isolated from Aloe vahombe. 2. Protection in mice by fraction F1 against infections by Listeria monocytogenes, Yersinia pestis, Candida albicans and Plasmodium berghei. Arch Inst Pasteur Madagascar 48.1 (1981): 11-34.

Bunyapraphatsara N et al. Antidiabetic activity of Aloe vera juice, II: clinical trial in diabetes mellitus patients in combination with glibenclamide. Phytomedicine 3 (1996): 245-8.

Can A et al. Effect of Aloe vera leaf gel and pulp extracts on the liver in type-II diabetic rat models. Biol Pharm Bull 27.5 (2004): 694-8.

Chen XD et al. [Effect of aloe vera polysaccharide on the release of cytokines and nitric oxide in cultured human keratinocytes]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 17.5 (2005): 296-8.

Chithra P, Sajithlal GB, Chandrakasan G. Influence of Aloe vera on collagen characteristics in healing dermal wounds in rats. Mol Cell Biochem 181.1-2 (1998): 71-6.

Choi S, Chung MH. A review on the relationship between aloe vera components and their biologic effects. Semin Integr Med 1.1 (2003): 53-62.

Choi SW et al. The wound-healing effect of a glycoprotein fraction isolated from aloe vera. Br J Dermatol 145.4 (2001): 535-45.

Davis RH, Maro NP. Aloe vera and gibberellin: Anti-inflammatory activity in diabetes. J Am Podiatr Med Assoc 79.1 (1989): 24-6.

Davis K et al. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract. 2006 [Epub ahead of print].

Davis RH et al. Biological activity of Aloe vera. Med Sci Res 15.5 (1987): 235.

Davis RH et al. Processed Aloe vera administered topically inhibits inflammation. J Am Podiatr Med Assoc 79.8 (1989): 395-7.

Davis RH et al. Aloe vera and the inflamed synovial pouch model. J Am Podiatr Med Assoc 82.3 (1992): 140-8.

Davis RH et al. Aloe vera, hydrocortisone, and sterol influence on wound tensile strength and anti-inflammation. J Am Podiatr Med Assoc 84.12 (1994a): 614-21.

Davis RH et al. Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. J Am Podiatr Med Assoc 84.2 (1994b): 77-81.

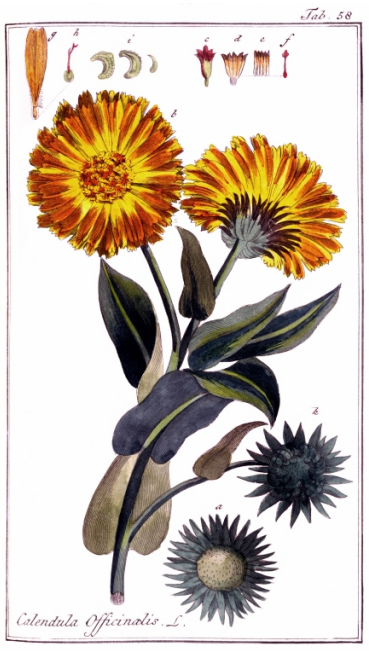
Duansak D, Somboonwong J, Patumraj S. Effects of Aloe vera on leukocyte adhesion and TNF-alpha and IL-6 levels in burn wounded rats. Clin Hemorheol Microcirc 29.3-4 (2003): 239-46.

Eamlamnam K et al. Effects of Aloe vera and sucralfate on gastric microcirculatory changes, cytokine levels and gastric ulcer healing in rats. World J Gastroenterol 12.13 (2006): 2034-9.
Fulton JE Jr. The stimulation of postdermabrasion wound healing with stabilized aloe vera gel-polyethylene oxide dressing. J Dermatol Surg Oncol 16.5 (1990): 460-7.
Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol 81.1 (2002): 81-100.
Heck E, Head M, Nowak D. Aloe vera (gel) cream as a topical treatment for outpatient burns. Burns 7.4 (1981): 291-4.
Heggers JP et al. Beneficial effect of Aloe on wound healing in an excisional wound model. J Altern Complement Med 2.2 (1996): 271-7.
Heggers JP et al. Experimental and clinical observations on frostbite. Ann Emerg Med 16.9 (1987): 1056-62.
Hu Y, Xu J, Hu Q. Evaluation of antioxidant potential of aloe vera (Aloe barbadensis miller extracts). J Agric Food Chem 51.26 (2003): 7788-91.
Hunter D, Frumkin A. Adverse reactions to vitamin E and aloe vera preparations after dermabrasion and chemical peel. Cutis 47.3 (1991): 193-6.
Hutter JA et al. Antiinflammatory C-glucosyl chromone from Aloe barbadensis. J Nat Prod 59.5 (1996): 541-3.
Ishii Y, Tanizawa H, Takino Y. Studies of aloe. V: Mechanism of cathartic effect. (4). Biol Pharm Bull 17.5 (1994): 651-3.
Kahlon JB et al. Inhibition of AIDS virus replication by acemannan in vitro. Mol Biother 3.3 (1991a): 127-35.
Kahlon JB et al. In vitro evaluation of the synergistic antiviral effects of acemannan in combination with azidothymidine and acyclovir. Mol Biother 3.4 (1991b): 214-23.
Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol 81.2 (2002): 281-5.
Kim HS, Lee BM. Inhibition of benzo[a]pyrene-DNA adduct formation by Aloe barbadensis Miller. Carcinogenesis 18.4 (1997): 771-6.
Klein AD, Penneys NS. Aloe vera. J Am Acad Dermatol 18(4 Pt 1) (1988): 714-20.
Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther 19.5 (2004): 521-7.
Lee JK et al. Acemannan purified from Aloe vera induces phenotypic and functional maturation of immature dendritic cells. Int Immunopharmacol 1.7 (2001): 1275-84.
Leung MY et al. Chemical and biological characterization of a polysaccharide biological response modifier from Aloe vera L. var. chinensis (Haw. Berg). Glycobiology 14.6 (2004): 501-10.
Liptak JM. An overview of the topical management of wounds. Aust Vet J 75.6 (1997): 408-13.
Maddocks-Jennings W, Wilkinson JM, Shillington D. Novel approaches to radiotherapy-induced skin reactions: a literature review. Complement Ther Clin Pract 11.4 (2005): 224-31.
McCarty MF. Glucomannan minimizes the postprandial insulin surge: a potential adjuvant for hepatothermic therapy. Med Hypotheses 58.6 (2002): 487-90.
McCauley RL, Heggers JP, Robson MC. Frostbite: Methods to minimize tissue loss. Postgrad Med 88.8 (1990): 67.
McDaniel HR et al. Extended survival and prognostic criteria for acemannan (ACE-M) treated HIV-1 patients. Antiviral Res Suppl 1 (1990): 117.
Miller MB, Koltai PJ. Treatment of experimental frostbite with pentoxifylline and aloe vera cream. Arch Otolaryngol Head Neck Surg 121.6 (1995): 678-80.
Montaner JS et al. Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease. J Acquir Immune Defic Syndr Hum Retrovirol 12.2 (1996): 153-7.
Moon EJ et al. A novel angiogenic factor derived from Aloe vera gel: beta-sitosterol, a plant sterol. Angiogenesis 3.2 (1999): 117-23.
Morrow DM, Rapaport MJ, Strick RA. Hypersensitivity to aloe. Arch Dermatol 116.9 (1980): 1064-5.
Muller MJ et al. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. Burns 29.8 (2003): 834-6.

Nakamura T, Kotajima S. Contact dermatitis from aloe arborescens. Contact Dermatitis 11.1 (1984): 51.
Olsen DL et al. The effect of aloe vera gel/mild soap versus mild soap alone in preventing skin reactions in patients undergoing radiation therapy. Oncol Nurs Forum 28.3 (2001): 543-7.
Paulsen E, Korsholm L, Brandrup F. A double-blind, placebo-controlled study of a commercial Aloe vera gel in the treatment of slight to moderate psoriasis vulgaris. J Eur Acad Dermatol Venereol 19.3 (2005): 326-31.
Peng SY et al. Decreased mortality of Norman murine sarcoma in mice treated with the immunomodulator, Acemannan. Mol Biother 3.2 (1991): 79-87.
Pigatto PD, Guzzi G. Aloe linked to thyroid dysfunction. Arch Med Res 36.5 (2005): 608.
Puvabanditsin P, Vongtongsri R. Efficacy of aloe vera cream in prevention and treatment of sunburn and suntan. J Med Assoc Thai 88 (Suppl 4) (2005): S173-6.
Rajasekaran S, Sivagnanam K, Subramanian S. Antioxidant effect of Aloe vera gel extract in streptozotocin-induced diabetes in rats. Pharmacol Rep 57.1 (2005): 90-6.
Reynolds T, Dweck AC. Aloe vera leaf gel: A review update. J Ethnopharmacol 68.1-3 (1999): 3-37.
Richardson J et al. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. Clin Oncol (R Coll Radiol) 17.6 (2005): 478-84.
Roberts DB, Travis EL. Acemannan-containing wound dressing gel reduces radiation-induced skin reactions in C3H mice. Int J Radiat Oncol Biol Phys 32.4 (1995): 1047-52.
Rodriguez-Bigas M, Cruz NI, Suarez A. Comparative evaluation of aloe vera in the management of burn wounds in guinea pigs. Plast Reconstr Surg 81.3 (1988): 386-9.
Saada HN, Ussama ZS, Mahdy AM. Effectiveness of Aloe vera on the antioxidant status of different tissues in irradiated rats. Pharmazie 58.12 (2003): 929-31.
Sabeh F, Wright T, Norton SJ. Purification and characterization of a glutathione peroxidase from the Aloe vera plant. Enzyme Protein 47.2 (1993): 92-8.
Sakai K et al. Effect of water extracts of aloe and some herbs in decreasing blood ethanol concentration in rats. II. Chem Pharm Bull (Tokyo) 37.1 (1989): 155-9.
Saoo K et al. Antiviral activity of aloe extracts against cytomegalovirus. Phytother Res 10.4 (1996): 348-50.
Schmidt JM, Greenspoon JS. Aloe vera dermal wound gel is associated with a delay in wound healing. Obstet Gynecol 78.1 (1991): 115-17.
Shelton RM. Aloe vera. Its chemical and therapeutic properties. Int J Dermatol 30.10 (1991): 679-83.
Shida T et al. Effect of Aloe extract on peripheral phagocytosis in adult bronchial asthma. Planta Med 3 (1985): 273-5.
Siegers CP, Siemers J, Baretton G. Sennosides and aloin do not promote dimethylhydrazine-induced colorectal tumors in mice. Pharmacology 47 Suppl 1 (1993): 205-8.
Singh RP, Dhanalakshmi S, Rao AR. Chemomodulatory action of Aloe vera on the profiles of enzymes associated with carcinogen metabolism and antioxidant status regulation in mice. Phytomedicine 7.3 (2000): 209-19.
Somboonwong J et al. Therapeutic effects of Aloe vera on cutaneous microcirculation and wound healing in second degree burn model in rats. J Med Assoc Thai 83.4 (2000): 417-25.
Strickland FM, Pelley RP, Kripke ML. Prevention of ultraviolet radiation-induced suppression of contact and delayed hypersensitivity by Aloe barbadensis gel extract. J Invest Dermatol 102.2 (1994): 197-204.
Suvitayavat W et al. Effects of Aloe preparation on the histamine-induced gastric secretion in rats. J Ethnopharmacol 90.2-3 (2004): 239-47.
Sydiskis RJ et al. Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob Agents Chemother 35.12 (1991): 2463-6.
Syed TA et al. Management of psoriasis with Aloe vera extract in a hydrophilic cream: A placebo-controlled, double-blind study. Trop Med Int Health 1.4 (1996a): 505-9.
Syed TA et al. Aloe vera extract 0.5% in hydrophilic cream versus Aloe vera gel for the management of genital herpes in males: A placebo-controlled, double-blind, comparative study [3]. J Eur Acad Dermatol Venereol 7.3 (1996b): 294-5.

Syed TA et al. Management of genital herpes in men with 0.5% Aloe vera extract in a hydrophilic cream: A placebo-controlled double-blind study. J Dermatol Treat 8.2 (1997): 99-102.
Talmadge J et al. Fractionation of Aloe vera L. inner gel, purification and molecular profiling of activity. Int Immunopharmacol 4.14 (2004): 1757-73.
't Hart LA et al. Effects of low molecular constituents from Aloe vera gel on oxidative metabolism and cytotoxic and bactericidal activities of human neutrophils. Int J Immunopharmacol 12.4 (1990): 427-34.
Visuthikosol V et al. Effect of aloe vera gel to healing of burn wounds: a clinical and histologic study. J Med Assoc Thai 78.8 (1995): 403-9.
Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. Br J Gen Pract 49.447 (1999): 823-8.
West DP, Zhu YF. Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. Am J Infect Control 31.1 (2003): 40-2.
Williams MS et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. Int J Radiat Oncol Biol Phys 36.2 (1996): 345-9.
Womble D, Helderman JH. Enhancement of allo-responsiveness of human lymphocytes by acemannan (Carrisyn(TM)). Int J Immunopharmacol 10.8 (1988): 967-74.
Wu JH et al. Antioxidant properties and PC12 cell protective effects of APS-1, a polysaccharide from Aloe vera var. chinensis. Life Sci 78.6 (2006): 622-30.
Yagi A et al. Antioxidant, free radical scavenging and anti-inflammatory effects of aloesin derivatives in Aloe vera. Planta Med 68.11 (2002): 957-60.
Yamaguchi I, Mega N, Sanada H. Components of the gel of Aloe vera (L.) burm. f. Biosci Biotechnol Biochem 57.8 (1993): 1350-2.
Yeh GY et al. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 26.4 (2003): 1277-94.
Yongchaiyudha S et al. Antidiabetic activity of Aloe vera L. juice: clinical trial in new cases of diabetes mellitis. Phytomedicine 3.3 (1996): 241-3.
Zachary LS, Smith DJ Jr, Heggers JP. The role of thromboxane in experimental inadvertent intra-arterial drug injections. J Hand Surg 12.2 (1987): 240-5.
Zawahry ME, Hegazy MR, Helal M. Use of aloe in treating leg ulcers and dermatoses. Int J Dermatol 12.1 (1973): 68-73.
Zhang L, Tizard IR. Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from Aloe vera gel. Immunopharmacology 35.2 (1996): 119-28.
Zhang XF et al. Isolation, structure elucidation, antioxidative and immunomodulatory properties of two novel dihydrocoumarins from Aloe vera. Bioorg Med Chem Lett 16.4 (2006): 949-53.

Andrographis



Historical note Andrographis has long been used in traditional medicine systems in numerous countries. It has been included in the pharmacopoeias of India, Korea and China, possibly because it grows abundantly in India, Pakistan and various parts of South-East Asia. In TCM, andrographis is considered a 'cold' herb and is used to rid the body of heat, as in fevers and acute infections, and to dispel toxins from the body. In Ayurvedic medicine it is used as a bitter tonic, to stimulate digestion and as a treatment for a wide range of conditions such as diabetes and hepatitis. It is still a common household remedy and found in over half the combination tonics used to treat liver conditions in India. Also used to treat the common cold, it is sometimes called Indian echinacea.

COMMON NAMES

Andrographis, chirayata, chiretta, green chiretta, Indian echinacea kalmegh, king of bitters.

Andrographis paniculata is often studied as the herbal combination known as Kan Jang.

BOTANICAL NAME/FAMILY

Andrographis paniculata (family Acanthaceae)

PLANT PARTS USED

Leaves, aerial parts

CHEMICAL COMPONENTS

The main active constituent group is considered to be the bitter diterpenoid lactones known as andrographolides. Other constituents include diterpenoid glucosides, diterpene dimers, flavonoids (Koteswara et al 2004, Rao et al 2003) and xanthones (Dua et al 2004).

Clinical studies show that andrographis is well absorbed, with peak plasma concentrations reached after 1.5–2 hours and a half-life of 6.6 hours (Panossian et al 2000).

MAIN ACTIONS

The mechanism of action of andrographis has not been significantly investigated in clinical studies, so results from in vitro and animal tests provide most of the evidence for this herbal medicine.

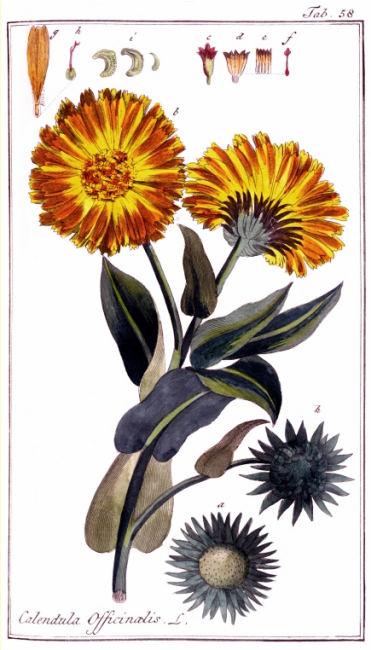
IMMUNOSTIMULANT

According to in vivo research, andrographis stimulates both antigen-specific and non-specific immune responses (Puri et al 1993). One of the main constituents responsible for the immunostimulant activity is andrographolide, which has an effect on the stimulation and proliferation of immunocompetent cells and the production of key cytokines and immune markers in vitro (Panossian et al 2002). Although important, other pharmacologically active constituents are also present as demonstrated by a study that found the immunostimulant activity of the whole extract is greater than that of the isolated andrographolide constituent alone. Investigation with a combination of the whole extract and *Eleutherococcus senticosus* in the formula Kan Jang demonstrated a more profound effect.

ANTICANCER

Twenty patients with various end-stage cancers were given 500 mg twice daily for 6 months. After 6 months 16 patients were still alive with a statistically significant increase in both NK function and TNF-alpha levels. Haemoglobin, haematocrit and glutathione levels were all greatly increased (See et al 2002). Although these results are interesting it is difficult to examine the direct effect of *Andrographis paniculata* as many other nutritional supplements were given concurrently.

In vitro experiments have demonstrated the possible benefits of andrographolide on various cancer cells. The compound has been shown to increase apoptosis of prostate cancer cells (Kim et al 2005), inhibit proliferation of human cancer cells and increase IL-2 induction in human peripheral blood lymphocytes in vitro (Kumar et al 2004, Rajagopal et al 2003). However, contradictory results have been described from a murine model. Andrographolide was found to decrease IFN-gamma and IL-2 production and therefore shown to have an immunosuppressive effect. Burgos et al (2005) concluded that andrographis may be useful for autoimmune disease, especially where high levels of IFN-gamma are present, for example, in multiple sclerosis and RA. In vitro and in vivo data has recently shown that andrographolide has the ability to interfere with T-cell proliferation, cytokine release and maturation of dendritic cells, as well as drastically decreasing the antibody response in delayed-type hypersensitivity (Iruretagoyena et al 2005). Additionally, andrographolide demonstrated a capacity to inhibit T-cell and antibody responses in experimental autoimmune encephalomyelitis in mice and protect against myelin sheath damage.



ANTIMICROBIAL

Aqueous extract of *Andrographis paniculata* has demonstrated significant antibacterial and antifungal activity in vitro when compared with standard antibiotics (Singha et al 2003).

HYPOTENSIVE

In vivo experiments suggest a mechanism of action involving adrenoceptors, autonomic ganglia receptors and a reduction in circulating ACE (Zhang et al 1998). The constituents responsible appear to be other than andrographolide.

HYPOGLYCAEMIC

Observed in animal tests, this activity does not appear to involve the stimulation of insulin release from the pancreas. The results from one animal test suggest that andrographis alters glucose absorption from the gut (Borhanuddin et al 1994). In vitro data suggests that andrographolide may also lower plasma glucose by increasing glucose uptake in cultured myoblast cells via the phospholipase C/protein kinase C pathway (Hsu et al 2004).

HEPATOPROTECTIVE

The hepatoprotective activity of andrographis has been investigated using several different experimental rat models: galactosamine, paracetamol and carbon tetrachloride (Handa & Sharma 1990a, b, Rana & Avadhoot 1991). In all models, treatment led to complete normalisation of toxin-induced increases in the levels of key biochemical parameters, and significantly reduced toxin-induced histopathological changes to the liver. Andrographolide is one of the key active constituents responsible for this activity (Handa & Sharma 1990b, Rana & Avadhoot 1991). Results from animal studies suggest that the hepatoprotective effect of andrographolide is more potent than that of silymarin, from the herb St Mary's thistle (Rana & Avadhoot 1991, Visen et al 1993).

Analogous to silymarin, the activity is a result of several similar mechanisms working together. Andrographis increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver (Trivedi & Rawal 2001). A hepatocyte cell-membrane-stabilising activity has also been observed (Puri et al 1993, Upadhyay et al 2001).

DIGESTIVE STIMULANT/CHOLERETIC

Andrographolide produces a significant dose-dependent increase in bile flow and bile salt and acid production (Shukla et al 1992).

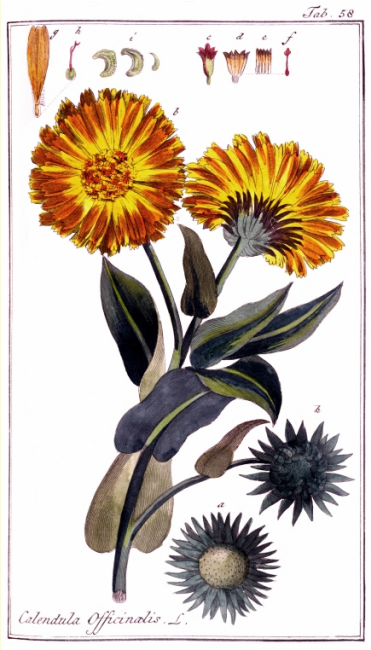
ANTIPYRETIC AND ANTI-INFLAMMATORY

Testing in different animal models has identified antipyretic activity (Mandal et al 2001). Clinical testing in randomised double-blind trials involving volunteers with the common cold suggests that this activity is clinically relevant. The mechanism of action is unlike that of NSAIDs, as andrographis does not influence the biosynthesis of any lipoxygenase pathways, but may involve promoting ACTH production and enhancing adrenocortical function (Amroyan et al 1999).

Interestingly, a combination of andrographolide and *Eleutherococcus senticosus, Schisandra chinensis* and *Glycyrriza glabra* inhibited neutrophil adhesion and transmigration (Shen et al 2002) and stabilised NO and IL-6 in functional Mediterranean fever, according to a randomised, double-blind trial (Panossian et al 2003). The study involved 14 people (age 3–15 years) with the fever and it was found that the herbal combination significantly reduced the frequency, severity and duration of attacks (Amaryan et al 2003). The daily dose of andrographolide was 48 mg, divided into three doses for 1 month.

ANTIPLATELET AND ANTITHROMBOTIC ACTIVITY

Andrographolide inhibits platelet-activating-factor-induced human blood platelet aggregation in a dose-dependent manner (Amroyan et al 1999). Results from in vivo studies suggest that andrographis prevents the formation of thrombi and reduces the size of myocardial ischaemia by promoting synthesis of prostaglandin I_2, inhibiting production of thromboxane A2, stimulating synthesis of cyclic AMP in platelets, and inhibiting platelet aggregation (Zhao & Fang 1990, 1991). Clinical research in humans has confirmed the observed antiplatelet effect (Zhang et al 1994).



CLINICAL USE

UPPER RESPIRATORY TRACT INFECTIONS AND THE COMMON COLD

Although sometimes investigated as a sole treatment, andrographis is also tested as part of a herbal combination known as Kan Jang. This is a standardised formula of *Andrographis paniculata* extract 85 mg, containing 5.25 mg andrographolide and deoxyandrographolide per tablet, and *Eleutherococcus senticosus* extract 9.7 mg, containing total eleutheroside B and eleutheroside E 2% (Melchior et al 2000). Although more representative of real-life practice, results obtained with Kan Jang make it difficult to assess the individual role of andrographis.

COMMON COLD — SYMPTOM RELIEF AND REDUCED INCIDENCE

In 2004, two different systematic reviews that investigated whether andrographis is a suitable treatment in acute respiratory infections were published (Coon & Ernst 2004, Poolsup et al 2004). The one conducted by Coon and Ernst from the Peninsula

Medical School, Universities of Exeter and Plymouth, Exeter, UK was a review of seven double-blind, controlled trials ($n = 896$), from which the authors concluded that *A. paniculata* is more effective than placebo in treating uncomplicated URTI and is associated with relatively few adverse events. They also concluded that preliminary data suggested a protective effect. In five of the seven trials, the daily dose was equivalent to 60 mg of andrographolide, which was administered for 3–8 days.

The second systematic review conducted by Poolsup et al from the Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon-Pathom, Thailand, was a review of four randomised controlled trials ($n = 433$) and they came to a similar conclusion, finding that *Andrographis paniculata* either by itself or in combination with *Eleutherococcus senticosus* (Kan Jang) is effective for uncomplicated acute URTI.

Symptoms responding According to double-blind studies, numerous symptoms respond to treatment with andrographis. According to two trials that used a dose of 340 mg andrographis taken three times daily, total symptom scores improved, with throat signs and symptoms responding most strongly (Melchior et al 2000). A third study observed a decrease in rhinitis, sinus pain and headache compared with placebo (Hancke et al 1995). A fourth study using a treatment dose of 1200 mg andrographis daily found a significant reduction in tiredness and sleepiness, as well as in sore throat and nasal secretions, by day 4 (Caceres et al 1999).

A double-blind placebo-controlled study ($n = 185$) that tested Kan Jang in the treatment of acute URTI and sinusitis showed it effectively reduced headache, nasal and throat symptoms and general malaise, but had no significant effects on cough and ocular symptoms. Additionally, fever was moderately reduced with active treatment (Gabrielian et al 2002).

Comparisons with *Echinacea* Although no direct head-to-head study could be located, one study was found that compared the effects of Kan Jang to a product known as Immunal (containing *Echinacea purpurea* (L.) extract) when both were used as adjuncts to standard treatment in children with the common cold. One hundred and thirty children were divided into three groups and received either of the combination treatments or solely standard treatment over a 10-day period (Spasov et al 2004). The addition of Kan Jang was shown to be significantly more effective than Immunal when started at an early stage and produced better symptomatic relief. The amounts of nasal secretion and congestion were particularly improved. In regards to altering recovery time, Kan Jang was also superior to Immunal and children required less standard medication than in the other two groups. Additionally, Kan Jang treatment was well tolerated and no side-effects or adverse reactions were reported.

PHARYNGOTONSILLITIS

One randomised double-blind study involving 152 volunteers compared the effects of paracetamol with two different doses of andrographis (3 g and 6 g) taken daily for 7 days (Thamlikitkul et al 1991). By day 3 the symptom-relieving effects of both paracetamol treatment and high-dose *A. paniculata* were significant and by day 7 andrographis was as effective as paracetamol.

HEPATOTOXICITY PROTECTION

No clinical studies are available; however, several in vivo studies confirm hepatoprotective effects against such hepatotoxins as paracetamol.

OTHER USES

TRADITIONAL USES

The herb is traditionally given as a restorative and tonic in convalescence and used as a choleretic to stimulate bile production and flow, which improves appetite and digestion. It is often used in combination with aromatic herbs, such as peppermint, for stronger digestive effects and to prevent gastrointestinal discomfort at higher doses.

DIABETES

Although no clinical studies are available, three in vivo studies suggest that andrographis exerts significant dose-dependent hypoglycaemic activity comparable to that of metformin (Borhanuddin et al 1994, Zhang & Tan 2000a, b). A 49.8% reduction in fasting serum triglyceride levels was also achieved with andrographis treatment compared with 27.7% with metformin; however, neither treatment affected cholesterol levels. A more recent animal trial also concluded that andrographolide (1.5 mg/kg) lowers plasma glucose by enhancing glucose utilisation in diabetic rats (Yu et al 2003).

CARDIOVASCULAR DISEASE

Although clinical trials are not available, the results from several in vivo studies have suggested a potential role for andrographis in cardiovascular disease.

Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty According to two animal studies, andrographis significantly improved atherosclerotic iliac artery stenosis induced by both de-endothelialisation and a high-cholesterol diet, and reduced the restenosis rate after experimental angioplasty (Wang & Zhao 1993, 1994).

Prevention of myocardial reperfusion injury and malignant arrhythmias postoperatively Using an animal model, pretreatment with intravenous

andrographis significantly protected the myocardium from ischaemic reperfusion injury and eliminated malignant arrhythmia development after reperfusion, compared with controls (Guo et al 1996). As a result of treatment, infarct size was also smaller and myocardial damage lessened.

Hypertension Andrographis produced significant dose-dependent falls in mean arterial blood pressure and heart rate when administered as an intraperitoneal infusion in one animal study (Zhang et al 1998).

MALARIA

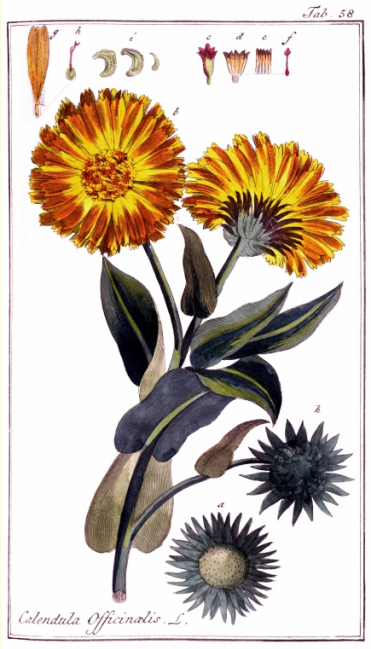
In vitro and in vivo studies have identified considerable antimalarial effects (Najib et al 1999, Siti Najila et al 2002). Administration of andrographis immediately after infection and for an additional 4 days extended the life span of mice infected with *Plasmodium berghei* strain ANKA (Rahman et al 1999). Four xanthones recently isolated from *A. paniculata* have demonstrated antimalarial activity against *Plasmodium berghei* in vivo (Dua et al 2004). Treatment with 30 mg/kg for 4 days produced a 62% decrease in parasites in infected mice.

SNAKE BITE

Prolonged survival has been reported with intraperitoneal administration of andrographis before administration of cobra venom (Martz 1992).

HIV INFECTION

A phase 1 clinical trial involving non-medicated HIV-positive patients and healthy controls found that oral andrographolides taken for 6 weeks at increasing doses produced no significant benefits and a high incidence of adverse effects, causing the trial to be stopped prematurely (Calabrese et al 2000).



DOSAGE RANGE

URTI

Prevention dose

- 1200–3000 mg andrographis (standardised to contain no less than 11.2 mg andrographolides) or 4–6 mL of 1:2 liquid extract, daily in divided doses, taken for at least 3 months for preventive effects to become established.

Treatment dose for infection

- 1200–6000 mg/day or fluid extract (1:2): up to 12 mL/day or equivalent in solid dose form.

DYSPEPSIA

- Andrographis can be taken as a tea before meals: 5 g of herb in 1 cup of hot water, which should be allowed to stand for 10 minutes before drinking.

TOXICITY
Animal tests suggest low toxicity (Mills & Bone 2000).

ADVERSE REACTIONS
Generally well tolerated, but high doses may cause vomiting, anorexia and gastrointestinal discomfort. One source states that urticaria is also possible (Ernst 2001).

SIGNIFICANT INTERACTIONS
Controlled studies are not available; therefore, interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

ANTICOAGULANTS
Increased risk of bruising and bleeding is theoretically possible, because andrographolide inhibits platelet aggregation factor-induced platelet aggregation — use with caution.

ANTIPLATELET DRUGS
Additive effects are possible, because the herb exhibits antiplatelet activity — observe patient.

BARBITURATES
Additive effects are possible, according to an animal study (Mandal et al 2001) — observe patient. Beneficial interaction is theoretically possible under professional supervision.

HEPATOTOXIC DRUGS (E.G. PARACETAMOL, TRICYCLIC ANTIDEPRESSANTS)
Hepatoprotection is possible, according to studies in various experimental models — beneficial interaction.

HYPOGLYCAEMIC AGENTS
Additive effects are theoretically possible — andrographis has hypoglycaemic activity comparable to that of metformin in vivo. Use together with caution; however, interaction may be beneficial.

DRUGS METABOLISED CHIEFLY VIA THE CYTOCHROME P450 SYSTEM
It is currently unclear whether there is a significant interaction between andrographis and these medications, as in vivo evidence is suggestive of enzyme induction, but this observation has not yet been investigated in clinical studies (Singh et al 2001). It is recommended that patients be observed to ensure that drug effectiveness is not compromised.

IMMUNOSUPPRESSANTS

Reduced drug activity is theoretically possible, as immunostimulant activity has been demonstrated in vivo (Puri et al 1993) — use caution in the immunosuppressed.

CONTRAINDICATIONS AND PRECAUTIONS

Suspend use of concentrated extracts 1 week before major surgery.

PREGNANCY USE

Not recommended for use in pregnancy. There is conflicting evidence about the safety of andrographis in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Several clinical studies suggest that andrographis, both as a stand-alone treatment and in combination with Siberian ginseng, is a useful treatment in cases of common cold, pharyngotonsillitis and uncomplicated URTIs, with significant symptom relief experienced after 3 days' use.
- Clinical studies are lacking, but animal experiments suggest that andrographis may be useful in cases of hepatotoxicity (paracetamol), to reduce myocardial reperfusion injury, improve blood glucose management in diabetes, and in hypertension.
- Traditionally, the herb is used to increase bile production and relieve symptoms of dyspepsia and flatulence, loss of appetite and general debility.
- Due to the extreme bitterness of the herb, solid-dose forms may be better tolerated than liquid preparations.
- Andrographis is not recommended in pregnancy.
- There are several theoretical drug interactions with this herb — check interaction data for more details.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Andrographis has been traditionally used to improve digestion, as a liver tonic and to fight off infection. Clinical studies confirm that it is an effective symptom-reliever for the common cold, uncomplicated URTIs and pharyngotonsillitis. It has also been used to reduce the risk of developing the common cold in winter.

When will it start to work?

During an acute infection, effects may be seen within 3–4 days of starting the correct dose. Used in lower doses for prevention, effects are seen after 3 months' continual use.

Are there any safety issues?

Andrographis is not recommended in pregnancy and may interact with a range of pharmaceutical drugs, so advice from a health professional is required.

REFERENCES

Amaryan G et al. Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard: a standardized fixed combination of Andrographis paniculata Nees, with Eleutherococcus senticosus Maxim, Schizandra chinensis Bail. and Glycyrrhiza glabra L. extracts in patients with familial Mediterranean fever. Phytomedicine 10.4 (2003): 271-85.

Amroyan E et al. Inhibitory effect of andrographolide from Andrographis paniculata on PAF-induced platelet aggregation. Phytomedicine 6.1 (1999): 27-31.

Borhanuddin M, Shamsuzzoha M, Hussain AH. Hypoglycaemic effects of Andrographis paniculata Nees on non-diabetic rabbits. Bangladesh Med Res Council Bull 20.1 (1994): 24-6.

Burgos RA et al. Andrographolide inhibits IFN-gamma and IL-2 cytokine production and protects against cell apoptosis. Planta Med 71.5 (2005): 429-34.

Caceres DD et al. Use of visual analogue scale measurements (VAS) to asses the effectiveness of standardized Andrographis paniculata extract SHA-10 in reducing the symptoms of common cold: A randomized double blind-placebo study. Phytomedicine 6.4 (1999): 2172-3, 101-4.

Calabrese C et al. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res 14.5 (2000): 333-8.

Coon JT, Ernst E. Andrographis paniculata in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy. Planta Med 70.4 (2004): 293-8.

Dua VK et al. Anti-malarial activity of some xanthones isolated from the roots of Andrographis paniculata. J Ethnopharmacol 95.23 (2004): 247-51.

Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.

Gabrielian ES et al. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine 9.7 (2002): 589-97.

Guo Z, Zhao H, Fu L. Protective effects of API0134 on myocardial ischemia and reperfusion injury. J Tongji Med Univ 16.4 (1996): 193-7.

Hancke J et al. A double-blind study with a new monodrug Kan Jang: decrease of symptoms and improvement in the recovery from common colds. Phytother Res 9(8) (1995): 559-62.

Handa SS, Sharma A. Hepatoprotective activity of andrographolide against galactosamine and paracetamol intoxication in rats. Indian J Med Res 92 (1990a): 284-92.

Handa SS, Sharma A. Hepatoprotective activity of andrographolide from Andrographis paniculata against carbon tetrachloride. Indian J Med Res 92 (1990b): 276-83.

Hsu JH et al. Activation of alpha1A-adrenoceptor by andrographolide to increase glucose uptake in cultured myoblast C2C12 cells. Planta Med 70.12 (2004): 1230-3.

Iruretagoyena MI et al. Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse. J Pharmacol Exp Ther 312.1 (2005): 366-72.

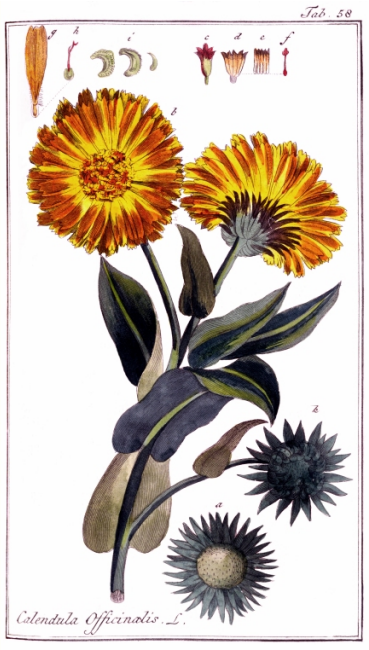
Kim TG, Hwi KK, Hung CS. Morphological and biochemical changes of andrographolide-induced cell death in human prostatic adenocarcinoma PC-3 cells. In Vivo 19.3 (2005): 551-7.

Koteswara Rao Y et al. Flavonoids and andrographolides from Andrographis paniculata. Phytochemistry 65.16 (2004): 2317-21.

Kumar RA et al. Anticancer and immunostimulatory compounds from Andrographis paniculata. J Ethnopharmacol 92.23 (2004): 291-5.

Mandal SC, Dhara AK, Maiti BC. Studies on psychopharmacological activity of Andrographis paniculata extract. Phytother Res 15.3 (2001): 253-6.

Martz W. Plants with a reputation against snakebite. Toxicon 30.10 (1992): 1131-42.
Melchior J et al. Double-blind, placebo-controlled pilot and phase III study of activity of standardized Andrographis paniculata Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection. Phytomedicine 7.5 (2000): 341-50.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Najib N et al. Antimalarial activity of extracts of Malaysian medicinal plants. J Ethnopharmacol 64.3 (1999): 249-54.
Panossian A et al. Effect of andrographolide and Kan Jang (fixed combination of extract SHA-10 and extract SHE-3) on proliferation of human lymphocytes, production of cytokines and immune activation markers in the whole blood cells culture. Phytomedicine 9.7 (2002): 598-605.
Panossian A et al. Pharmacokinetic and oral bioavailability of andrographolide from Andrographis paniculata fixed combination Kan Jang in rats and human. Phytomedicine 7.5 (2000): 351-64.
Panossian A et al. Plasma nitric oxide level in functional Mediterranean fever and its modulations by ImmunoGuard. Nitric Oxide 9 (2003): 103-10.
Poolsup N et al. Andrographis paniculata in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials. J Clin Pharm Ther 29.1 (2004): 37-45.
Puri A et al. Immunostimulant agents from Andrographis paniculata. J Nat Prod 56.7 (1993): 995-9.
Rahman N et al. Antimalarial activity of extracts of Malaysian medicinal plants. J Ethnopharmacol 64.3 (1999): 249-54.
Rajagopal S et al. Andrographolide, a potential cancer therapeutic agent isolated from Andrographis paniculata. J Exp Ther Oncol 3.3 (2003): 147-58.
Rana AC, Avadhoot Y. Hepatoprotective effects of Andrographis paniculata against carbon tetrachloride-induced liver damage. Arch Pharm Res 14.1 (1991): 93-5.
Rao YK et al. Flavonoids from Andrographis viscosula. Chem Pharm Bull (Tokyo) 51.12 (2003): 1374-6.
See D, Mason S, Roshan R. Increased tumor necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers. Immunol Invest 31.2 (2002): 137-53.
Shen YC, Chen CF, Chiou WF. Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol 135.2 (2002): 399-406.
Shukla B et al. Choleretic effect of andrographolide in rats and guinea pigs. Planta Med 58.2 (1992): 146-9.
Singh RP, Banerjee S, Rao AR. Modulatory influence of Andrographis paniculata on mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status. Phytother Res 15.5 (2001): 382-90.
Singha PK, Roy S, Dey S. Antimicrobial activity of Andrographis paniculata. Fitoterapia 74.78 (2003): 692-4.
Siti Najila MJ et al. The screening of extracts from Goniothalamus scortechinii, Aralidium pinnatifidum and Andrographis paniculata for anti-malarial activity using the lactate dehydrogenase assay. J Ethnopharmacol 82.23 (2002): 239-42.
Spasov AA et al. Comparative controlled study of Andrographis paniculata fixed combination, Kan Jang and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children. Phytother Res 18.1 (2004): 47-53.
Thamlikitkul V et al. Efficacy of Andrographis paniculata nees for pharyngotonsillitis in adults. J Med Assoc Thai 74.10 (1991): 437-42.
Trivedi NP, Rawal UM. Hepatoprotective and antioxidant property of Andrographis paniculata (Nees) in BHC induced liver damage in mice. Indian J Exp Biol 39.1 (2001): 41-6.
Upadhyay L et al. An experimental study of some indigenous drugs with special reference to hydraulic permeability. Indian J Exp Biol 39.12 (2001): 1308-10.
Visen PK et al. Andrographolide protects rat hepatocytes against paracetamol-induced damage. J Ethnopharmacol 40.2 (1993): 131-6.
Wang DW, Zhao HY. Experimental studies on prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with Andrographis paniculata nees and fish oil. J Tongji Med Univ 13.4 (1993): 193-8.



Wang DW, Zhao HY. Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with Andrographis paniculata nees and fish oil. Experimental studies of effects and mechanisms. Chin Med J (Engl) 107.6 (1994): 464-70.
Yu BC et al. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med 69.12 (2003): 1075-9.
Zhang XF, Tan BK. Anti-diabetic property of ethanolic extract of Andrographis paniculata in streptozotocin-diabetic rats. Acta Pharmacol Sin 21.12 (2000a): 1157-64.
Zhang XF, Tan BK. Antihyperglycaemic and anti-oxidant properties of Andrographis paniculata in normal and diabetic rats. Clin Exp Pharmacol Physiol 27.56 (2000b): 358-63.
Zhang YZ, Tang JZ, Zhang YJ. Study of Andrographis paniculata extracts on antiplatelet aggregation and release reaction and its mechanism. Zhongguo Zhong Xi Yi Jie He Za Zhi 14.1 (1994): 5, 28-30, 34.
Zhang C, Kuroyangi M, Tan BK. Cardiovascular activity of 14-deoxy-11,12-didehydroandrographolide in the anaesthetised rat and isolated right atria. Pharmacol Res 38.6 (1998): 413-17.
Zhao HY, Fang WY. Protective effects of Andrographis paniculata nees on post-infarction myocardium in experimental dogs. J Tongji Med Univ 10.4 (1990): 212-17.
Zhao HY, Fang WY. Antithrombotic effects of Andrographis paniculata nees in preventing myocardial infarction. Chin Med J (Engl) 104.9 (1991): 770-5.

Astragalus

Historical note The roots of astragalus have been used for more than two thousand years by the Chinese and are considered among the most important and popular herbs for invigorating vital energy, health promotion and strengthening Qi. Western herbalists began using astragalus in the 1800s in various tonics and the gummy sap (tragacanth) is still used as an emulsifier, food thickener and antidiarrhoeal agent.

COMMON NAME
Astragalus

OTHER NAMES
Astragali, beg kei, bei qi, hwanggi, huang-qi, milk vetch, goat's horn, green dragon, Mongolian milk, ogi, Syrian tragacanth

BOTANICAL NAME/FAMILY
Astragalus membranaceus (family Fabaceae)

PLANT PART USED
Root

CHEMICAL COMPONENTS
Saponins such as cycloastragenol, astragalosides, and cyclocanthoside are present and suspected to be the main active group; flavonoids, polysaccharides, phytosterols (including beta-sitosterol), essential oil, amino acids (including gamma-aminobutyric acid) (Duke 2003, Mills and Bone 2000).

MAIN ACTIONS
Astragalus has not been significantly investigated in clinical studies, so in vitro and animal tests provide the evidence for its pharmacological activities.

IMMUNE ENHANCING
Several in vitro and in vivo studies confirm immune-enhancing activity. Astragalus stimulates macrophage activity and enhances antibody responses (Chu et al 1998, Jin et al 1994, Sugiura et al 1993). Astragalus enhances lymphocyte blastogenesis in vitro (Sun et al 1983). Immunostimulant effects have also been observed in the presence of immunosuppressive therapy in vivo (Jin et al 1999).

Although usually administered in the oral form, research has also been undertaken with injectable forms. A study conducted with both normal and immunosuppressed mice found that astragalus administration increased antibody responses and T helper cell activity (Zhao et al 1990). A flavonoid identified in the stem and leaves of astragalus is believed to be one of the main constituents responsible for immune modulation (Jiao et al 1999) and more recently, several studies have identified that astragalus polysaccharide (APS) also exerts significant biological effects.

One study investigating the effects of APS identified that it stimulates mouse B cells and macrophage activity, but not T cells (Shao et al 2004). It has been demonstrated that APS stimulates macrophages to produce nitric oxide (NO) through induction of NO synthase transcription (Lee & Jeon 2005) leading to increased cytolytic function of macrophages.

Guo et al found that the polysaccharide increases cellular and humoral immune responses in *Eimeria tenella*-infected chickens when administered as 1 g in every kg of food. When given for 1 week, it increased systemic antibodies, intestinal antibodies, antigen-specific splenocytes and erythrocyte-antibody-complement cells as compared with controls (Guo et al 2004a). The same research team used both in vitro and animal models to further investigate the effects of APS and found increased beneficial gut flora and decreased harmful gut bacteria (Guo et al 2003, 2004b).

Clinical note – Polysaccharides and immunity

One of the most promising recent alternatives to antibiotic treatment is the use of immunomodulators for enhancing host defence responses. Several types of immunomodulators have been identified, most recently botanically sourced polysaccharides isolated from mushrooms, algae, lichens and higher plants. These polysaccharides tend to have a broad spectrum of therapeutic properties and relatively low toxicity. One of the primary mechanisms responsible for immunomodulation involves non-specific induction of the immune system, which is thought to occur via macrophage stimulation and modulation of the complement system. According to one report, polysaccharides isolated from 35 plant species among 20 different families have been shown to increase macrophage cytotoxic activity against tumour cells and microorganisms, activate phagocytic activity, increase reactive oxygen species (ROS) and nitric oxide (NO) production, and enhance secretion of cytokines and chemokines, such as TNF-alpha, IL-1beta, IL-6, IL-8, IL-12, IFN-gamma and IFN-beta2 (Schepetkin & Quinn 2005). These effects have a major influence on the body's ability to respond rapidly and potently to a diverse array of pathogens, giving the polysaccharides wide clinical application.

CARDIOVASCULAR EFFECTS — POSITIVE INOTROPIC AND HYPOTENSIVE ACTIVITY

The effect of astragalus on heart function has been the subject of several investigations and, most recently, a Cochrane systematic review, which analysed studies of Chinese herbs used in viral myocarditis and concluded that astragalus significantly improves cardiac function, arrhythmia and creatinine kinase levels (Liu et al 2004a). The review assessed data from 10 randomised clinical trials that used a single preparation of astragalus and one that used a combination containing mainly astragalus; however, the authors stated that the trials had poor quality in terms of design, reporting and methodology.

Several constituents from *Astragalus* spp. have demonstrated effects on heart contractility, heart rate and blood pressure. In particular, 3-nitropropionic acid (NPA) has been shown to decrease blood pressure and induce bradycardia when administered as an IV preparation in normotensive rats or renal hypertensive dogs (Castillo et al 1993). Another compound, astragaloside IV, demonstrated positive inotropic activity in patients with congestive heart failure (Luo et al 1995).

ANTIOXIDANT

In vivo studies have found that astragalus raises superoxide dismutase activity in the brain and liver, thus demonstrating an indirect antioxidant activity (Jin et al 1999). The constituent, astragaloside IV (20 and 40 mg/kg), prevented the formation of cerebral infarction after induced focal ischaemia in an animal model, most likely due to its antioxidant and anti-inflammatory actions (Luo et al 2004)

ANTICARCINOGENIC EFFECTS

Both in vitro and animal studies indicate that astragalus may have a role as adjunctive therapy in the treatment of some cancers. In vivo studies have shown that astragalus extract exerts anticarcinogenic effects in carcinogen-treated mice, mediated through activation of cytotoxic activity and the production of cytokines (Kurashige et al 1999). An extract of the root (90 and 180 mg/kg) prevented the development of preneoplastic lesions and delayed hepatic cancer in chemically-induced hepatocarcinogenesis in a rat model (Cui et al 2003). The saponin, astragaloside IV, can increase the fibrinolytic potential of cultured human umbilical vein endothelial cells by downregulating the expression of plasminogen activator inhibitor type 1 (Zhang et al 1997). Another constituent (astragalan) increased the secretion of TNF-alpha and TNF-beta (Zhao and Kong 1993).

An animal study using a combination of *Astragalus membranaceus* and *Ligustrum lucidumastragalus* demonstrated anti-tumour effects by augmenting phagocyte and lymphokine-activated killer cell activities (Lau et al 1994).

DIGESTIVE EFFECTS

Astragalus strengthens the movement and muscle tone of the small intestine (especially the jejunum) in animal tests, which may account for its clinical application in a variety of common digestive symptoms (Yang 1993).

IMPROVED SPERM MOTILITY

An aqueous extract of *Astragalus membranaceus* was tested in vitro and found to have a significant stimulatory effect on sperm motility (Hong et al 1992). Astragalus has shown a significant effect on human sperm motility in vitro when compared with controls (Liu et al 2004)

HEPATOPROTECTIVE ACTIONS

Astragalus has hepatoprotective qualities against paracetamol, carbon tetrachloride and D-galactosamine poisoning (Zhang et al 1990). Increases in liver glutathione levels observed as a result of the herbal treatment may be partly responsible. Studies have identified the constituent betaine as an important contributor to this activity.

OTHER ACTIONS

Astragalus is also thought to have adaptogenic activity. It also has shown weak oestrogenic activity in vitro when compared with other Chinese herbs and controls (17-beta-estradiol) (Zhang et al 2005). This could partially explain its traditional use in menopause.

CLINICAL USE

As a reflection of clinical practice, astragalus is often tested in combination with other herbal medicines. As such, it is difficult from these trials to determine the role of astragalus as a stand-alone treatment.

VIRAL INFECTION

Owing to its immunomodulatary actions, astragalus is widely used for preventing and treating various viral infections. A popular use is as a preventive treatment against common colds and influenza. To date, scientific evidence is scant to confirm effectiveness, although one review stated that astragalus has been tested in clinical trials in China, reducing the incidence and shortening the duration of the common cold (Murray 1995).

VIRAL MYOCARDITIS

Findings from a recent Cochrane systematic review of Chinese herbs used in viral myocarditis provide limited supportive evidence for its use; however, further research is required before a definitive conclusion can be made (Liu JP et al 2004). Several in vivo and in vitro studies have found some antagonistic effects on the enterovirus coxsackie B and a reduction in myocardial injury (Lu et al 1999, Peng et al 1995, Rui et al 1993, Yang et al 1990) thought to be due to the astragalosides in the herb (Lu et al 1999).

CARDIOVASCULAR DISEASE, INCLUDING ISCHAEMIC HEART DISEASE, CONGESTIVE HEART FAILURE, ANGINA PECTORIS

Congestive heart failure Some of the clinical signs and symptoms recognised as indicators for this medicine by TCM practitioners suggest that the herb may be useful for congestive heart failure. Recent positive results obtained in clinical studies have reinforced this possibility.

The two clinical trials have investigated continuous intravenous administration of astragalus. One study involving 19 patients found that after 2 weeks' continuous administration of astragaloside IV, major symptoms were alleviated in 15 patients. Treatment produced a positive inotropic effect, improved left ventricular modelling and ejection function (Luo et al 1995).

The second study, involving 38 patients with congestive heart failure who were administered astragalus 24 g intravenously for 2 weeks, found that 13.6% had significantly shortened ventricular late potentials (Shi et al 1991).

Angina pectoris Two clinical studies have suggested that astragalus may be an effective treatment for angina pectoris. One study used Doppler echocardiography to study the action of astragalus on left ventricular function in 20 patients with angina pectoris. Treatment resulted in increased cardiac output after 2 weeks, but no improvement in left ventricular diastolic function (Lei et al 1994). One Chinese study reported 92 patients with ischaemic heart disease who were successfully treated with astragalus as measured by electrocardiogram readings. Results obtained with the herb were considered superior to those obtained with nifedipine (Li et al 1995).

CANCER

Astragalus is used in cancer patients to enhance the effectiveness of chemotherapy and reduce associated side-effects. It is additionally used to enhance immune function.

A Cochrane systematic review of Chinese herbs for chemotherapy side-effects in colorectal cancer patients analysed the results of four trials that used a decoction

containing astragalus (huang-qi) as the intervention with chemotherapy (Taixiang et al 2005). Adjunctive treatment with astragalus was compared with chemotherapy alone in three trials and two other Chinese herbal treatments in the fourth trial. When astragalus was used, there was a significant reduction in nausea and vomiting and a decrease in the rate of leucopenia (WBC $<3 \times 10^9$/L). Increases in the proportions of T-lymphocyte subsets (CD3, CD4 and CD8) were also reported, with no significant effects on immunoglobulins G, A or M. Taixiang et al concluded that despite the low quality of the trials, decoctions of astragalus may stimulate immunocompetent cells and decrease side-effects in patients treated with chemotherapy. Additionally, no evidence of harm was identified with use.

In a recent placebo-controlled, randomised clinical trial in 60 patients receiving chemotherapy for non-small cell lung cancer, astragalus was shown to significantly increase quality of life (Zou & Liu 2003). The treatment group ($n = 30$) received 60 mL of astragalus per day intravenously and improved survival rates and quality of life scores were observed.

Reducing adverse effects of treatment (in combination) Zee-Cheng screened and evaluated 116 Kampo formulas and identified 15 that potentiated therapeutic effects, reduced adverse toxicity of various anticancer drugs, and exhibited immune-modulating effects in cancer patients. Among these, shi-quan-da-bu-tang (SQT) was selected as the most effective and studied further. SQT is a popular TCM herbal combination consisting of 10 medicinal herbs, including *Astragalus membranaceus*. Using both animal models and clinical studies, the herbal combination produced several promising results (Zee-Cheng 1992).

Prostate cancer (in combination) Although no human studies could be located, encouraging results were obtained from an in vitro study investigating the effects of a proprietary product known as Equiguard™ on prostate cancer cells. It is prepared according to TCM principles and contains standardised extracts of nine herbs: herba epimedium brevicornum maxim (stem and leaves), radix morindae officinalis (root), fructus rosae laevigatae michx (fruit), rubus chingii hu (fruit), *Schisandra chinensis* (Turz.) Baill (fruit), *Ligustrum lucidum* Ait (fruit), *Cuscuta chinensis* Lam (seed), *Psoralea corylifolia* L. (fruit), and *Astragalus membranaceus* (root). It is used in TCM to restore Qi in the urogenital region. The product was shown to significantly reduce cancer cell growth, induce apoptosis, suppress expression of the androgen receptor and lower intracellular and secreted prostate-specific antigen (Hsieh et al 2002).

OTHER USES

TRADITIONAL USES

Used within the traditional Chinese herbal medicine system, astragalus is used to invigorate and tonify Qi and the blood, as an adaptogen, for severe blood loss, fatigue, anorexia, organ prolapse, chronic diarrhoea, shortness of breath, sweating and to enhance recuperation (Mills and Bone 2000).

Clinical note — The concept of an adaptogen is foreign to Western medicine but often used in Chinese medicine

Adaptogens are considered natural bioregulators that increase the ability of the organism to adapt to environmental factors and to avoid damage from such factors. Herbal medicines with adaptogenic activity are used when extremes of physical or emotional activity are present, environmental influences are severe, or allostatic load has developed over time. The aim of treatment is to improve the patient's endurance and ability to deal with these changes in a healthy way, and for abnormal parameters to shift towards normal (see also Siberian ginseng and Glossary).

CHOLESTEROL REDUCTION (IN COMBINATION WITH OTHER HERBS)

A randomised, double-blind clinical trial compared the effects of a traditional Chinese herbal medicine combination known as jian yan ling (which includes astragalus as a main ingredient) to placebo in 128 hyperlipidaemic patients. After 3 months' treatment it was found that total cholesterol, triglyceride, apoproteins and lipoprotein-a levels were significantly reduced in the treatment group, compared with placebo (Lu et al 1994).

ASTHMA (IN COMBINATION WITH OTHER HERBS)

A herbal combination consisting of *Astragalus membranaceus, Codonopsis pilulosa* and *Glycyrrhiza uralensis* was investigated in an open study for effects on airway responsiveness. Twenty-eight patients with asthma were treated with the herbal combination for 6 weeks, after which values for FVC, FEV1 and PEF were all higher than at baseline (Wang et al 1998).

MEMORY DEFICITS (IN COMBINATION WITH OTHER HERBS)

In TCM, invigorating Qi and warming Yang are believed to have a beneficial therapeutic effect on some brain diseases, such as senile dementia. Some studies have been conducted to determine the outcome of following this ancient principle.

A decoction of astragalus produced neuroprotective effects in rats with experimentally induced cerebral ischaemia (Quan and Du 1998), and memory enhancement has been observed in vivo (Jin et al 1999).

One article reports on 100 cases of children with minimal brain dysfunction and compared the effects of a TCM combination (*Bupleurum chinense, Scutellaria baicalensis, Astragalus membranaceus, Codonopsis pilulosa, Ligustrum lucidum, Lophatherum gracile* and thread of ivory) to the Western medical approach (methylphenidate (Ritalin™) 5–15 mg/day). A collation of results found that the herbal treatment produced a clinically effective rate of 87.5% compared with 90% in the Ritalin group, with the herbal treatment group reporting fewer side-effects (Zhang and Huang 1990).

DOSAGE RANGE

- Dried root: 2–30 g/day.
- Liquid extract (1:2) or solid dose equivalent: 4.5–8.5 mL/day.
- Decoction: 8–12 g divided into two doses daily on an empty stomach.

TOXICITY

Animal studies have shown that the herb has a wide safety margin.

ADVERSE REACTIONS

None known.

SIGNIFICANT INTERACTIONS

Interactions are theoretical and based on in vitro and in vivo data; therefore, clinical significance is unclear and remains to be confirmed.

IMMUNOSUPPRESSANT MEDICATION

Reduced drug activity is theoretically possible, as immunostimulant activity has been demonstrated — use caution in the immunosuppressed.

POSITIVE INOTROPIC DRUGS

Additive effects are theoretically possible with intravenous administration of astragalus, based on positive inotropic activity identified in clinical studies. The clinical significance of these findings for oral dose forms is unknown — observe patients using high-dose astragalus preparations.

CHEMOTHERAPY

Adjunctive treatment with astragalus may have beneficial effects in regards to improving patient wellbeing and reducing adverse effects associated with treatment such as nausea and vomiting — only use combination under professional supervision

CONTRAINDICATIONS AND PRECAUTIONS

According to the principles of TCM, astragalus should not be used during the acute stages of an infection.

PREGNANCY USE

Safety is unknown although no evidence of fetal damage has been reported in animal studies (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Astragalus is widely used as an immunostimulant medicine to reduce the incidence of the common cold and influenza.
- It is also used to enhance recuperation and reduce fatigue.
- According to TCM practice it is widely used to invigorate and tonify Qi and the blood, and as an important adaptogen.
- Under the TCM system of use, astragalus is not used during periods of acute infection.
- In clinical practice it is often used in combination with other herbs such as *Bupleurum chinense, Scutellaria baicalensis* and *Codonopsis pilulosa*. As such, most clinical trials have tested combination formulas.
- It appears to be well tolerated; however, several theoretical interactions exist.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Astragalus appears to have numerous biological effects, such as digestive and immune system stimulation and heart muscle stimulation. Early research suggests that it may have a role in the treatment of asthma, memory deficits, elevated cholesterol levels and as an adjunct to chemotherapy treatment for cancer.

When will it start working?

This will depend on the indication and dose; some studies have shown that effects can begin within 2 weeks.

Are there any safety issues?

Overall the herb appears to be safe, although it has the potential to interact with some medicines.

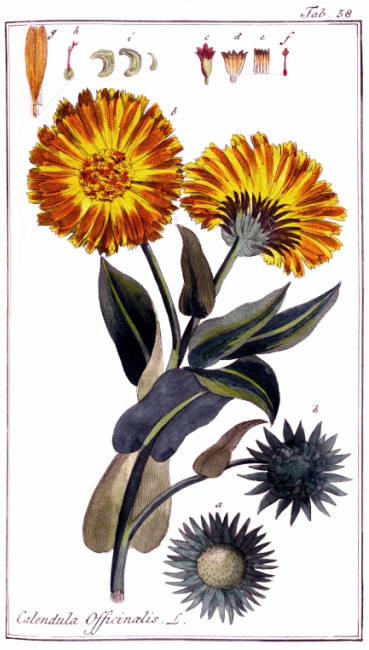
REFERENCES

Castillo C et al. An analysis of the antihypertensive properties of 3-nitropropionic acid, a compound from plants in the genus Astragalus. Arch Inst Cardiol Mex 63.1 (1993): 11-16.

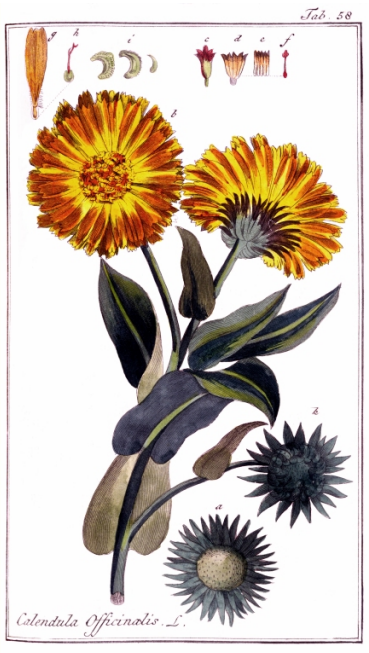
Chu DT, Wong WL, Mavligit GM. Immunotherapy with Chinese medicinal herbs. I. Immune restoration of local xenogeneic graft-versus-host reaction in cancer patients by fractionated Astragalus membranaceus in vitro. J Clin Lab Immunol 25.3 (1988): 119-23.

Cui R et al. Suppressive effect of Astragalus membranaceus Bunge on chemical hepatocarcinogenesis in rats. Cancer Chemother. Pharmacol 51.1 (2003): 75-80.
Duke JA. Dr Duke's phytochemical and ethnobotanical databases. US Department of Agriculture, Agricultural Research Service, National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, March 2003. www.ars-grin.gov/duke.
Guo FC et al. In vitro fermentation characteristics of two mushroom species, an herb, and their polysaccharide fractions, using chicken cecal contents as inoculum. Poult Sci 82.10 (2003): 1608-15.
Guo FC et al. Effects of mushroom and herb polysaccharides on cellular and humoral immune responses of Eimeria tenella-infected chickens. Poult Sci 83.7 (2004a): 1124-32.
Guo FC et al. Effects of mushroom and herb polysaccharides, as alternatives for an antibiotic, on the cecal microbial ecosystem in broiler chickens. Poult Sci 83.2 (2004b): 175-82.
Hong CY, Ku J, Wu P. Astragalus membranaceus stimulates human sperm motility in vitro. Am J Chin Med 20.3-4 (1992): 289-94.
Hsieh TC et al. Effects of herbal preparation Equiguard™ on hormone-responsive and hormone-refractory prostate carcinoma cells: mechanistic studies. Int J Oncol 20.4 (2002): 681-9.
Jiao Y, Wen J, Yu X. Influence of flavonoid of Astragalus membranaceus's stem and leaves on the function of cell mediated immunity in mice. Zhongguo Zhong Xi Yi Jie He Za Zhi 19.6 (1999): 356-8.
Jin R et al. Effect of shi-ka-ron and Chinese herbs on cytokine production of macrophage in immunocompromised mice. Am J Chin Med 22.3-4 (1994): 255-66.
Jin R et al. Studies on pharmacological junctions of hairy root of Astragalus membranaceus. Zhongguo Zhong Yao Za Zhi 24.10 (1999): 619-21, 639.
Kurashige S, Akuzawa Y, Endo F. Effects of astragali radix extract on carcinogenesis, cytokine production, and cytotoxicity in mice treated with a carcinogen, N-butyl-N-butanolnitrosoamine. Cancer Invest 17.1 (1999): 30-5.
Lau BH et al. Chinese medicinal herbs inhibit growth of murine renal cell carcinoma. Cancer Biother 9.2 (1994): 153-61.
Lee KY, Jeon YJ. Macrophage activation by polysaccharide isolated from Astragalus membranaceus. Int Immunopharmacol 5.7-8 (2005): 1225-33.
Lei ZY, Qin H, Liao JZ. Action of Astragalus membranaceus on left ventricular function of angina pectoris. Zhongguo Zhong Xi Yi Jie He Za Zhi 14.4 (1994): 195, 199-202.
Li SQ, Yuan RX, Gao H. Clinical observation on the treatment of ischemic heart disease with Astragalus membranaceus. Zhongguo Zhong Xi Yi Jie He Za Zhi 15.2 (1995): 77-80.
Liu JP, Yang M, Du XM. Herbal medicines for viral myocarditis. Cochrane Database Syst Rev 3 (2004): CD003711.
Liu J et al. Effects of several Chinese herbal aqueous extracts on human sperm motility in vitro. Andrologia 36.2 (2004): 78-83.
Lu DC, Su ZJ, Rui T. Effect of jian yan ling on serum lipids, apoprotein and lipoprotein-a. Zhongguo Zhong Xi Yi Jie He Za Zhi 14.3 (1994): 142.
Lu S, Zhang J, Yang D. Effects of Astragaloside in treating myocardial injury and myocardial sarco/endoplasmic $Ca^{(2+)}$-ATPase of viral myocarditis mice. Zhongguo Zhong Xi Yi Jie He Za Zhi 19.11 (1999): 672-4.
Luo HM, Dai RH, Li Y. Nuclear cardiology study on effective ingredients of Astragalus membranaceus in treating heart failure. Zhongguo Zhong Xi Yi Jie He Za Zhi 15.12 (1995): 707-9.
Luo Y et al. Astragaloside IV protects against ischemic brain injury in a murine model of transient focal ischemia. Neurosci Lett 363.3 (2004): 218-23.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Mills S, Bone K. The Essential Guide to Herbal Safety. Edinburgh: Churchill Livingstone, 2005.
Murray M. The Healing Power of Herbs. Prima Health, USA 1995.
Peng T et al. The inhibitory effect of Astragalus membranaceus on coxsackie B-3 virus RNA replication. Chin Med Sci J 10.3 (1995): 146-50.

Quan J, Du G. Protective effect of Astragalus membranaceus (Fisch.) Bge and Hedysarum polybotrys Hand.-Mazz. on experimental model of cerebral ischemia in rats. Zhongguo Zhong Yao Za Zhi 23.6 (1998): 371-3.
Rui T et al. Effect of Astragalus membranaceus on electrophysiological activities of acute experimental coxsackie B-3 viral myocarditis in mice. Chin Med Sci J 8.4 (1993): 203-6.
Schepetkin IA, Quinn MT. Botanical polysaccharides: Macrophage immunomodulation and therapeutic potential. Int Immunopharmacol 6 (2006): 317-33.
Shao BM et al. A study on the immune receptors for polysaccharides from the roots of Astragalus membranaceus, a Chinese medicinal herb. Biochem Biophys Res Commun 320.4 (2004): 1103-11.
Shi HM, Dai RH, Wang SY. Primary research on the clinical significance of ventricular late potentials (VLPs), and the impact of mexiletine, lidocaine and Astragalus membranaceus on VLPs. Zhong Xi Yi Jie He Za Zhi 11.5 (1991): 259, 265-7.
Sugiura H et al. Effects of exercise in the growing stage in mice and of Astragalus membranaceus on immune functions. Nippon Eiseigaku Zasshi 47.6 (1993): 1021-31.
Sun Y et al. Preliminary observations on the effects of the Chinese medicinal herbs Astragalus membranaceus and Ligustrum lucidum on lymphocyte blastogenic responses. J Biol Response Mod 2.3 (1983): 227-37.
Taixiang W, Munro AJ, Guanjian L. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. Cochrane Database Syst Rev 1 (2005): CD004540.
Wang H, Chang B, Wang B. The effect of herbal medicine including Astragalus membranaceus (fisch) bge, Codonopsis pilulosa and Glycyrrhiza uralensis fisch on airway responsiveness. Zhonghua Jie He He Hu Xi Za Zhi 21.5 (1998): 287-8.
Yang DZ. Effect of Astragalus membranaceus on myoelectric activity of small intestine. Zhongguo Zhong Xi Yi Jie He Za Zhi 13.10 (1993): 582, 616-17.
Yang YZ et al. Treatment of experimental coxsackie B-3 viral myocarditis with Astragalus membranaceus in mice. Chin Med J (Engl) 103.1 (1990): 14-18.
Zee-Cheng RK. Shi-quan-da-bu-tang (ten significant tonic decoction), SQT: A potent Chinese biological response modifier in cancer immunotherapy, potentiation and detoxification of anticancer drugs. Methods Find Exp Clin Pharmacol 14.9 (1992): 725-36.
Zhang H, Huang J. Preliminary study of traditional Chinese medicine treatment of minimal brain dysfunction: analysis of 100 cases. Zhong Xi Yi Jie He Za Zhi 10.5 (1990): 260, 278-9.
Zhang ZL, Wen QZ, Liu CX. Hepatoprotective effects of astraglus root. J Ethnopharmacol 30.2 (1990): 145-9.
Zhang WJ, Wojta J, Binder BR. Regulation of the fibrinolytic potential of cultured human umbilical vein endothelial cells: astragaloside IV downregulates plasminogen activator inhibitor-1 and upregulates tissue-type plasminogen activator expression. J Vasc Res 34.4 (1997): 273-80.
Zhang CZ et al. In vitro estrogenic activities of Chinese medicinal plants traditionally used for the management of menopausal symptoms. J Ethnopharmacol 98.3 (2005): 295-300.
Zhao KW, Kong HY. Effect of Astragalan on secretion of tumor necrosis factors in human peripheral blood mononuclear cells. Zhongguo Zhong Xi Yi Jie He Za Zhi 13.5 (1993): 259, 263-5.
Zhao KS, Mancini C, Doria G. Enhancement of the immune response in mice by Astragalus membranaceus extracts. Immunopharmacology 20.3 (1990): 225-33.
Zou YH, Liu XM. Effect of astragalus injection combined with chemotherapy on quality of life in patients with advanced non-small cell lung cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 23.10 (2003): 733-5.



Baical skullcap



Historical note Baical skullcap is a TCM herb used to clear 'heat and dry dampness'. Diseases with heat are associated with symptoms such as fever, irritability, thirst, cough and expectoration of thick, yellow sputum. Damp diseases may be associated with diarrhoea, a feeling of heaviness of the chest and painful urination (Bensky & Gamble 1986). From a modern perspective this suggests that baical may be useful for infection and inflammation of the respiratory, digestive and urinary systems. Scientific investigations have indeed shown that baical skullcap and its constituents have antibacterial, antiviral, anti-inflammatory, hepatoprotective and diuretic actions (Zhang et al 2001).

OTHER NAMES

Baical skullcap, Chinese skullcap, Huang qin (Mandarin), ogon (Japanese), scute

BOTANICAL NAME/FAMILY

Scutellaria baicalensis Georgi (family Lamiaceae)

PLANT PART USED

Root

CHEMICAL COMPONENTS

Baical skullcap contains numerous flavonoids and their glycosides. The main flavonoids are baicalin and its aglycone, baicalein and wogonin. Resin and tannins are also present.

Baical also contains melatonin. It has been shown that dietary melatonin directly contributes to the circulating level of the hormone. The clinical effects of plant-derived melatonin remains to be investigated (Hardeland & Poeggeler 2003). Baicalin itself is poorly absorbed from the gut, but is hydrolysed to its aglycone, baicalein, by intestinal bacteria and then restored to its original form from the absorbed baicalein in the body (Akao et al 2000).

MAIN ACTIONS

The actions of baical skullcap, some of its individual constituents, and combination formulations have been studied in various models.

ANTI-INFLAMMATORY

The anti-inflammatory activity of baical skullcap has been well documented by in vitro and in vivo studies. The main constituents responsible are baicalein and wogonin (Chang et al 2001, Chi et al 2001, Chung et al 1995, Krakauer et al 2001, Li et al 2000, Park et al 2001, Wakabayashi 1999).

In a study using mice, baicalein 50 mg/kg has been shown to ameliorate the inflammatory symptoms of induced colitis, including body weight loss, blood haemoglobin content, rectal bleeding and other histological and biochemical parameters (Hong et al 2002). Pretreatment with wogonin also significantly reduced ethanol-induced gastric damage in vivo (Park et al 2004) and reduced immunoglobulin E, IL-4, IL-5 and IL-10 secretion in a colitis-induced mouse model (Lim 2004). The methanolic extract of the baical skullcap root and its flavonoids wogonin, baicalein and baicalin have been shown to inhibit lipopolysaccharide-induced inflammation of the gingivae (gums) in vivo. The three flavonoids exerted an anti-inflammatory effect similar to prednisolone. In addition, the flavonoids exerted a moderate inhibition (33–36%) of collagenolytic activity, comparable to the 40% inhibition by tetracycline. Meanwhile, the cellular activity of fibroblasts was augmented remarkably (40%) by baicalein and slightly by baicalin and wogonin. Consistent with the cellular activation, the flavonoids enhanced the synthesis of both collagen and total protein in fibroblasts in vitro (Chung et al 1995).

The anti-inflammatory mechanisms are varied and summarised below.

Chemokine binding It has been proposed that the anti-inflammatory activity is partly caused by limiting the biological function of chemokines.

Excessive release of pro-inflammatory cytokines mediates the toxic effect of superantigenic staphylococcal exotoxins. In vitro data suggest that baicalin may be therapeutically useful for mitigating the pathogenic effects of staphylococcal exotoxins by inhibiting the signalling pathways activated by superantigens (Krakauer et al 2001).

Baicalin inhibited the binding of a number of chemokines to human leukocytes or cells expressing specific chemokine receptors, with an associated reduced capacity of the chemokines to induce cell migration. Based on these results, it is possible that the anti-inflammatory mechanism of baicalin is to bind a variety of chemokines and limit their biological function (Bao et al 2000, Li et al 2000).

Four major flavonoids from baical have been shown in vitro to suppress eotaxin. Eotaxin is an eosinophil-specific chemokine associated with the recruitment of eosinophils to sites of allergic inflammation. Eotaxin is produced by IL-4 plus TNF-alpha-stimulated human fibroblasts. This may explain why it has been used

traditionally in the treatment of bronchial asthma (Nakajima et al 2001). Various flavonoids, including wogonin and baicalein, have been shown to inhibit chemically induced histamine release from rat mast cells in vitro (Kubo et al 1984).

COX-2 inhibition Wogonin is a direct COX-2 inhibitor. Wogonin inhibits both inducible nitric oxide synthase and cyclo-oxygenase 2 induction (Chen et al 2001, Chi et al 2001, Wakabayashi & Yasui 2000). Wogonin has been shown to inhibit inducible PGE_2 production in macrophages by inhibiting COX-2 (Wakabayashi & Yasui 2000).

Wogonin may be beneficial for COX-2-related skin disorders. When applied topically to the dorsal skin of mice, it inhibited COX-2 expression and PGE_2 production (Byoung et al 2001, Chi et al 2003, Park et al 2001).

Lipoxygenase inhibition The inhibition of the 5-lipoxygenase pathway of arachidonic acid metabolism may be one of the mechanisms of baicalein's anti-inflammatory activity according to an in vivo study (Butenko et al 1993).

Nitric oxide synthase inhibition Baicalein and wogonin attenuate lipopolysaccharide-stimulated nitric oxide synthase induction in macrophages, which helps to explain the anti-inflammatory action of these flavonoid compounds (Wakabayashi 1999).

Antioxidant activity The anti-inflammatory activity of baicalein may be associated with inhibition of leukocyte adhesion by the scavenging of reactive oxygen intermediates (Shen et al 2003).

ANTIFIBROTIC

A methanolic extract of baical skullcap has been shown to inhibit fibrosis and lipid peroxidation induced by bile duct ligation or carbon tetrachloride in rat liver. Bile duct ligation in rodents is an experimental model for extrahepatic cholestasis caused by, for example, cholelithiasis (gall stones). Liver fibrosis was assessed by histological observation and by measuring levels of liver hydroxyproline, lipid peroxidation based on malondialdehyde production, and serum enzyme activities. Treatment with baical skullcap significantly reduced the levels of liver hydroxyproline and malondialdehyde, with improved histological findings (Nan 2002).

HEPATOPROTECTIVE

Baicalein, baicalin and wogonin have been shown to have hepatoprotective effects in vivo. The flavonoids decrease the toxicity produced by a variety of chemicals. Significant protective effects were seen by comparing the serum levels of AST and ALT and histopathologic examination (Lin & Shieh 1996).

The combination Sho-saiko-to has been shown to inhibit chemical hepatocarcinogenesis in animals, act as a biological response modifier and suppress the proliferation of hepatoma cells by inducing apoptosis and arresting the cell cycle. These effects may be due to baicalin, baicalein and saikosaponins (from *Bupleurum falcatum*), which have the ability to inhibit cell proliferation (Shimizu 2000).

Baical flavonoids inhibit hepatic CYP1A2, suggesting that baical extract may be hepatoprotective via prevention of CYP1A2-induced metabolic activation of toxins (Kim et al 2002).

ANTIOXIDANT

Several studies have shown baical skullcap constituents to be antioxidant in vitro and in vivo. Flavones produced a concentration-dependent protection of liposome membrane against UV-induced oxidation. The ability to scavenge free radicals and protect against the effects of lipid peroxidation (in this case caused by sunlight irradiation) may in part account for the herb's underlying mechanism of action (Gabrielska et al 1997).

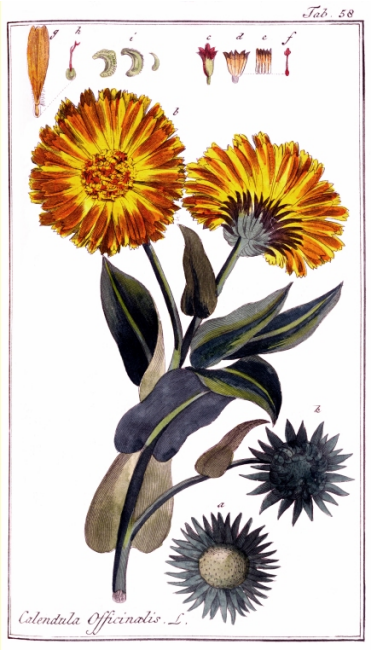
Fourteen flavonoids and flavone glycosides have been demonstrated to possess good free radical scavenging properties in vitro (Gao et al 1999, Lin & Shieh 1996). Baicalin has been found to have the most potent antioxidant effect (Bochorakova et al 2003).

Baicalin's antioxidant effect is based on scavenging superoxide radicals, whereas baicalein is a good xanthine oxidase inhibitor. Xanthine oxidase inhibitors are known to be therapeutically useful for the treatment of hepatitis and brain tumours (Gao et al 2001).

Oxidative stress plays an important role in the pathological process of neurodegenerative diseases including Alzheimer's disease. The protective effects of baical flavonoids on the oxidative injury of neuronal cells have been demonstrated in vitro (Choi et al 2002, Gao et al 2001).

ANTI-ALLERGIC

Flavonoids have anti-allergic activities and are known to inhibit histamine release from basophils and mast cells. Luteolin and baicalein have been shown to inhibit IgE antibody-mediated immediate and late phase allergic reactions in mice. In an in-vitro study, luteolin and baicalein inhibited IgE-mediated histamine release from mast cells. The compounds also inhibited IgE-mediated TNF-alpha and IL-6 production from mast cells. However, the compounds did not affect the histamine, serotonin or platelet-activating factor-induced cutaneous reactions in rats (Kimata et al 2000).



Wogonin, wogonoside and 3,5,7,2',6'-pentahydroxyl flavanone isolated from baical skullcap decrease histamine, leukotriene B4 and IgE in vitro (Lim 2004).

Baicalein is 5–10-fold more potent than the anti-allergic drug, azelastine. Baicalein significantly suppressed leukotriene C4 release by polymorphonuclear leukocytes obtained from asthmatic patients compared with healthy subjects (Niitsuma et al 2001).

NEUROPROTECTIVE

Many in vitro and in vivo trials have demonstrated the neuroprotective effects of flavonoids derived from baical skullcap (Cho & Lee 2004, Heo et al 2004, Piao et al 2004, Shang et al 2006, Son et al 2004).

Cerebral ischaemia can cause a significant elevation in the concentrations of amino acid neurotransmitters in the cerebral cortex. Baicalin administration can attenuate the elevations of glutamic acid and aspartic acid induced by cerebral ischaemia. This research demonstrates that baicalin may act as a neuroprotectant during cerebral ischaemia. Wogonin has been shown to exert a neuroprotective effect by inhibiting microglial activation, which is a critical component of pathogenic inflammatory responses in neurodegenerative diseases. Wogonin inhibited inflammatory activation of cultured brain microglia by diminishing lipopolysaccharide-induced TNF-alpha, IL-1-beta and NO production. Wogonin inhibited NO production by suppressing iNOS induction and NF-kappa-B activation in microglia. The neuroprotective effect of wogonin has also been shown in vivo using two experimental brain injury models (Lee et al 2003).

A recent in vivo study in rats induced with permanent global ischaemia demonstrated that daily oral doses of baical skullcap flavonoids (35 mg/kg) for 19–20 days statistically increased learning and memory ability and attenuated neural injury (Shang et al 2005).

Baical skullcap is used in TCM for the treatment of stroke. Methanol extracts from the dried roots (0.1–10 mg/kg IP) significantly protected neurons against 10 min transient forebrain ischaemia. The extract inhibited microglial TNF-alpha and NO production, and protected cells from hydrogen peroxide-induced toxicity in vitro (Kim et al 2001).

HYPOTENSIVE

Treatment with baicalein lowered blood pressure in hypertensive but not in normotensive rats according to one study (Takizawa et al 1998). Baical extract and baicalein have also been shown to lower blood pressure in rats and cats (Kaye et al 1997, Takizawa et al 1998). The exact mechanisms underlying the hypotensive action

are unclear. One in vivo study has shown that *Scutellaria baicalensis* extract produces peripheral vasodilatation (Lin et al 1980). A recent review concluded that baical skullcap is effective for renin-dependent hypertension and that in vivo effects may be due to the inhibition of lipoxygenase, reducing the production and release of arachidonic-acid derived vasoconstrictor substances (Huang et al 2005).

VASCULAR ACTIVITY

Monocyte chemotactic protein-1 (MCP-1), a potent chemoattractant for monocytes, plays a crucial role in cases of early inflammatory responses, including atherosclerosis. Wogonin has been shown to inhibit MCP-1 induction by endothelial cells in a dose-dependent manner. Wogonin and baical skullcap may be potentially beneficial in inflammatory and vascular disorders (Chang et al 2001).

ANTIPLATELET

Baical flavonoids have been shown to inhibit platelet aggregation in vitro (Kubo et al 1985). Baicalein inhibited the elevation of calcium induced by thrombin and thrombin receptor agonist peptide. These findings suggest a potential benefit of baicalein in the treatment of arteriosclerosis and thrombosis (Kimura et al 1997).

CHOLESTEROL REDUCTION

Flavonoids are known to reduce cholesterol. A 30-day study of induced hyperlipidaemia in rats found that baicalein, quercetin, rutin and naringin reduced cholesterol, with baicalein being the most potent. Baicalein was also the most effective flavonoid in reducing triglyceride levels (De Oliveira et al 2002). In another in vivo study, rats were fed a cholesterol-laden diet and half were also given *S. baicalensis* radix extract (Regulska-Ilow et al 2004). The treatment rats displayed a significant reduction in plasma triglycerides and total cholesterol as compared with control animals.

ANXIOLYTIC

Wogonin, baicalein, scutellarein and baicalin (in reducing order of potency), which all contain a certain flavonoid phenylbenzopyrone nucleus, have been shown in vitro to bind with the benzodiazepine site of the GABA-A receptor (Hui et al 2000).

Oral administration of wogonin (7.5–30 mg/kg) has been shown to interact with GABA-A receptors and produce an anxiolytic response that was similar to diazepam in the elevated plus-maze. Unlike benzodiazepines, wogonin was able to reduce anxiety without causing sedation or myorelaxation (Hui et al 2002, Kwok et al 2002).

Baicalin (10 mg/kg IP) and baicalin (20 mg/kg IP) have also been shown in vivo to produce an anxiolytic effect, mediated through activation of the benzodiazepine binding sites of GABA-A receptors (Liao et al 2003).

Two other flavones, 5,7-dihydroxy-6-methoxyflavone (oroxylin A) and 5,7,2'-trihydroxy-6,8-dimethoxyflavone (K36), also act as antagonist at the GABA-A recognition site and have demonstrated anxiolytic activity in vivo (Huen et al 2003a, b).

A water-extract of baical skullcap demonstrated anticonvulsant activity against electroshock-induced tonic seizures in vivo. Interestingly, the authors suggest that the effect might not be via the activation of the benzodiazepine binding site of GABA-A receptors, but probably via the prevention of seizure spread (Liao et al 2003, Wang et al 2000).

ANTIMICROBIAL

Numerous studies have found that baical extract and flavonoids exert antibacterial, antiviral and antifungal actions. The antimicrobial effect of baical extract is mild and the clinical efficacy of baical in infectious diseases may be more associated with its anti-inflammatory rather than its antimicrobial activities.

Antibacterial Baical skullcap decoction was investigated for bacteriostatic and bactericidal activity against a selection of oral bacteria, including suspected periodontopathogens. At a concentration of 2%, the decoction was bacteriostatic for 8 of 11 bacteria tested, but a concentration of 3.13% or greater was required for bactericidal effect (Tsao et al 1982).

Baical aqueous-extract, but not its flavonoids, baicalin and baicalein, demonstrated antibacterial effects against the enteric pathogen *Salmonella typhimurium*. The effect was compatible with commercial antibiotics including ampicillin, chloramphenicol, and streptomycin. In contrast, the growth of a non-pathogenic *Escherichia coli* strain was unaffected by baical (Hahm et al 2001). One study demonstrated that the addition of baical skullcap in vitro improved the responsiveness of antibiotics for the treatment of MRSA (Yang et al 2005).

Antiviral Antiviral effects have been demonstrated for baical in numerous in vitro and in vivo tests. Baical extract significantly inhibit hepatitis C RNA replication in vivo (Tang et al 2003) and in vitro studies have found that:

- Intraperitoneal and intranasal administration of baical flavonoids significantly inhibits influenza virus in vivo and in vitro (Nagai et al 1989, 1992a, b, 1995a, b).
- Baical extract was bactericidal in vitro against periodontal pathogens isolated from patients with periodontal disease (Tsao et al 1982).

- Baicalein inhibits HIV-1 infection at the level of viral entry (a process known to involve interaction between HIV-1 envelope proteins and the cellular CD4 and chemokine receptors) (Li et al 2000b).
- Bacalin inhibits human T-cell leukaemia virus type I (HTLV-I) (Baylor et al 1992).
- Aqueous extract inhibits HIV type-1 protease (Lam et al 2000).
- Baicalin inhibits HIV-1 infection and replication (Li et al 1993).
- Baical flavonoids inhibit Epstein-Barr virus early antigen activation (Konoshima et al 1992).
- Wogonin suppresses hepatitis B virus surface antigen production without evidence of cytotoxicity (Huang et al 2000).
- 5,7,4'-trihydroxy-8-methoxyflavone inhibits the fusion of influenza virus with endosome/lysosome membrane (Nagai et al 1995a).
- Virus replication is suppressed, partly by inhibiting the fusion of viral envelopes with the endosome/lysosome membrane which occurs at the early stage of the virus infection cycle (Nagai et al 1995b).
- The flavones in baical have potent influenza virus sialidase inhibitory activity and anti-influenza virus activity in vivo (Nagai et al 1992b).
- Baicalin reduces the pathogenic effects of superantigenic staphylococcal exotoxins by inhibiting the signalling pathways activated by superantigens (Krakauer et al 2001).
- Baicalin may selectively induce apoptosis of HIV-infected human T-leukaemia (CEM-HIV) cells, which have a high virus-releasing capacity, and stimulate proliferation of CEM-HIV, which have a relatively lower capacity of HIV-production (Wu et al 1995).

Antifungal Antifungal activity has been demonstrated by several studies (Blaszczyk et al 2000, Yang et al 1995). Baical extract showed clear fungistatic activities in vitro against some cutaneous and unusual pathogenic fungi, and particularly upon strains of *Candida albicans*, *Cryptococcus neoformans* and *Pityrosporum ovale*. The antifungal substance was isolated and found to be baicalein (Yang et al 1995). Of 56 Chinese antimicrobial plants, baical root extract had the highest activity against *C. albicans* (Blaszczyk et al 2000).

ANTI-ULCEROGENIC

Extracts prepared from grass and roots of *S. baicalensis* showed high antiulcerogenic activity in vivo (Amosova et al 1998).

ANTIDIABETIC

5-alpha-aldose inhibition Diabetic patients may accumulate intracellular quantities of the sugars sorbitol and dulcitol, because of an increase in the polyol pathway involving the enzyme 5-alpha-aldose. Oral baicalin and liquid extract of licorice (also rich in flavonoids) reduced the sorbitol levels in the red blood cells of diabetic rats (Lin et al 1980, Zhou & Zhang 1989).

Alpha-glucosidase inhibition Alpha-glucosidase inhibitors (e.g. acarbose) are a class of oral medicine for type 2 diabetes, which blocks the enzymes that digest starches in food. The result is a slower and lower rise in blood glucose throughout the day, especially immediately after meals. Methanol extracts of *Scutellaria baicalensis, Rheum officinale* and *Paeonia suffruticosa* showed potent inhibitory activity against rat intestinal sucrase. The active principles were identified as baicalein and methyl gallate (from the latter two plants). In addition to its activity against the rat enzyme, baicalein also inhibited human intestinal sucrase in vitro (Nishioka et al 1998).

ANTI-EMETIC

Pretreatment with baical root extract has been shown to decrease cisplatin-induced pica in rats (animal models use the level of kaolin [a type of clay] intake as a measure of the intensity of nausea). This suggests that baical may help to reduce cisplatin-induced nausea and emesis during cancer therapy (Aung et al 2003, Mehendale et al 2004, Wu et al 1995), although clinical testing is required to confirm significance.

In a recent in vivo trial, *S. baicalensis* was found to significantly attenuate ritonavir-induced pica, and demonstrate possible efficacy for the management of ritonavir-induced nausea in HIV treatment (Aung et al 2005).

RENAL–URINARY ACTIVITY

Baicalein inhibited angiotensin II-induced increases in the cellular protein content of aortic smooth muscle cells in vitro (Natarajan et al 1994). In another in vitro study, baicalein prevented the angiotensin II-induced increase in renal vascular resistance by 50% and promoted glomerular filtration rate (Bell-Quilley et al 1993). Pretreatment with baicalein significantly inhibited a decrease in nephrotoxin-induced glomerular filtration rate and renal blood flow in vivo (Wu et al 1993). Oral intake of baical flavonoids and extract has been shown to produce a diuretic effect.

ANTICANCER

Immunostimulation Sho-saiko-to has been shown to stimulate granulocyte colony-stimulating factor (G-CSF), which may explain its use in infectious diseases and cancer (Yamashiki et al 1992). Like growth hormone, IL-2 and -4 and interferon, G-CSF is a signalling ligand that stimulates immune function. G--CSF, a glycoprotein

produced mainly by macrophages, induces proliferation of neutrophil colonies and differentiation of precursor cells to neutrophils. It also stimulates the activity of mature neutrophils (Hill et al 1993).

Sho-saiko-to is known to significantly suppress cancer development in the liver. Moderate regulation of the cytokine production system in patients with hepatitis C by using Sho-saiko-to may be useful in the prevention of disease progression (Yamashiki et al 1997). One possible mechanism for the beneficial effects of this formula in patients with liver cirrhosis may be the improvement in production of IL-12, which is an important cytokine for maintenance of normal systemic defence and bioregulation. This effect of Sho-saiko-to is attributed to two of its seven herb components, baical and licorice root (Yamashiki et al 1999).

Patients who were given baical skullcap showed a tendency towards an increase in the relative number of T-lymphocytes and their theophylline-resistant population during antitumour chemotherapy. The immunoregulation index in this case was approximately twice the background value during the whole period of investigation. The inclusion of baical skullcap in the therapeutic complex promoted an increase in the number of immunoglobulins A at a stable level of IgG (Smolianinov et al 1997).

Apoptosis induction Baicalein, baicalin and wogonin have been shown to induce apoptosis, disrupt the mitochondria and inhibit proliferation in various human hepatoma cell lines (Chang et al 2002, Chen et al 2000). The platelet-type 12-lipoxygenase (12-LOX) pathway is a critical regulator of prostate cancer progression and apoptosis by affecting various proteins regulating these processes. Baicalein inhibits 12-LOX and may be a potential therapeutic agent in the treatment of prostate cancer (Pidgeon et al 2002) as well as breast cancer (Tong et al 2002).

Antiproliferative Baicalein, baicalin and wogonin have been shown to induce apoptosis and inhibit proliferation in various human hepatoma cell lines (Chang et al 2002).

Baicalin has been shown to inhibit the proliferation of prostate cancer cells in vitro. However, the response to baicalin differed among different cell lines (Chan et al 2000).

COX-2, which converts arachidonic acid to PGE_2, is highly expressed in head and neck squamous cell carcinoma (HNSCC). *Scutellaria baicalensis*, but not baicalein, suppressed proliferation cell nuclear antigen expression and PGE_2 synthesis. A 66% reduction in tumour mass was observed in the mice with HNSCC. Baical selectively and effectively inhibits cancer cell growth in vitro and in vivo and can be an effective chemotherapeutic agent for HNSCC (Zhang et al 2003).

In a recent study designed to determine the ability of baical skullcap to inhibit various human cancer cells in vitro, *S. baicalensis* demonstrated a significant dose-dependent, growth inhibition on squamous cell carcinoma, breast cancer, hepatocellular carcinoma, prostate carcinoma and colon cancer cell lines (Ye et al 2002). Prostate and breast cancer cells were particularly sensitive. Baical skullcap has also been shown to arrest mouse leukaemia cell proliferation in vivo (Ciesielska et al 2002, 2004). Inhibition of PGE_2 synthesis via suppression of COX-2 expression may be responsible for its anticancer activity (Ye et al 2002). Differences in the biological effects of baical compared with baicalein suggest the synergistic effects among components in baical (Zhang et al 2003).

Baicalein, baicalin and wogonin have been shown to reduce proliferation of human bladder cancer cell lines in a dose-dependent manner, but baicalin exhibited the greatest antiproliferative activity. In an in vivo study baical skullcap extract had a significant inhibition of tumour growth ($P < 0.05$) (Ikemoto et al 2000).

Adjunct to chemotherapy In experiments with murine and rat transplantable tumours, baical skullcap extract treatment improved cyclophosphamide and 5-fluorouracil-induced myelotoxicity and to decrease tumour cell viability (Razina et al 1987).

Prevention of metastases The advancement of Pliss' lymphosarcoma in rats is associated with disorders of platelet-mediated haemostasis, presenting with either lowered or increased aggregation activity of platelets. Extract of baical was shown to produce a normalising effect on platelet-mediated haemostasis whatever the pattern of alteration. This activity is thought to be important for antitumour and, particularly, metastasis-preventing effects (Razina et al 1989).

Experiments in mice inoculated with metastasing Lewis lung carcinoma showed that the antitumour and antimetastatic effects of cyclophosphamide are potentiated by baical, rose root (*Rhodiola rosea*), licorice (*Glycyrrhiza glabra*), and their principal acting components, baicalin, paratyrosol and glycyrrhizin (Razina et al 2000).

Chemoprevention Baicalein prevents chemically-induced DNA damage in a cell culture model (Chan et al 2002).

Anti-angiogenesis Baicalein and baicalin have demonstrated anticancer activity against several cancers in vitro. The flavonoids have also been shown to be potent inhibitors of angiogenesis in vitro and in vivo. Baicalein was found to be more potent than baicalin (Liu et al 2003).

CLINICAL USE

Baical skullcap is an ingredient in the very popular traditional Chinese/Japanese formulation, Minor Bupleurum Combination, known as Xiao Chai Hu Tang (Chinese)

and Sho-saiko-to (Japanese). Minor Bupleurum Combination has been used in China for about 3000 years for the treatment of pyretic diseases.

Minor Bupleurum Combination (Sho-saiko-to) is now a prescription drug approved by the Ministry of Health and Welfare of Japan and widely used in the treatment of chronic viral liver diseases. Since 1999, Sho-saiko-to has been administered to 1.5 million patients with chronic liver diseases, because it can significantly suppress cancer development in the liver (Yamashiki et al 1999). Sho-saiko-to is also used for the treatment of bronchial asthma in Japan (Nakajima et al 2001).

Minor Bupleurum Combination (Sho-saiko-to, Xiao Chai Hu Tang)

- *Bupleurum falcatum* (bupleurum)
- *Scutellaria baicalensis* (baical skullcap)
- *Pinellia ternate* (pinellia)
- *Panax ginseng* (Korean ginseng)
- *Zizyphus jujube* (zizyphus)
- *Glycyrrhiza uralensis* (Chinese licorice)
- *Zingiber officinale* (ginger)

RESPIRATORY INFECTION

Sixty patients with respiratory infection (mainly nosocomial pneumonia) were treated either by injection of baical compound or piperacillin sodium (IV). The total efficacy was evaluated after treatment for 1 week.

- Total effective treatment rates were 73.3% for baical compared with 76.7% in the antibiotic treatment group.
- Body temperature was decreased similarly and symptoms disappeared or were relieved in 11.67 ± 6.75 days with the herb and 11.53 ± 7.30 days with the antibiotic.
- In the piperacillin sodium group, fungal infections occurred in 4 of 30 patients, but there were none in the baical treatment group (Lu 1990).

BONE MARROW STIMULATION DURING CHEMOTHERAPY

Haemopoiesis was studied in 88 patients with lung cancer during combination treatment with chemotherapy and a *S. baicalensis* extract. Administration of the plant preparation was associated with haemopoiesis stimulation, intensification of bone marrow erythrocytopoiesis and granulocytopoiesis, and increased numbers of circulating precursors of erythroid and granulomonocytic colony-forming units (Goldberg et al 1997).

EPILEPSY (IN COMBINATION WITH OTHER HERBS)

Saiko-keishi-to, a spray-dried decoction of Bupleurum, (cinnamon, peony, ginger, licorice, ginseng, pinellia, zizyphus and baical) was administered to 24 people with epilepsy, who had frequent uncontrollable seizures (3–5 seizures per day in the most severe case and 5 seizures per month in the mildest case) of various types, despite treatment with pharmaceutical anticonvulsants. Of them, 6 were well controlled with Saiko-keishi-to whereas 13 experienced improvement and 3 showed no effect. No patients experienced worsening of their condition. Two patients dropped out during treatment (Narita et al 1982).

CHRONIC ACTIVE HEPATITIS (IN COMBINATION WITH OTHER HERBS)

In a double-blind, multicentre clinical study of 222 patients with chronic active hepatitis, Sho-saiko-to was found to significantly decrease AST and ALT values compared with placebo. The difference between the treatment and placebo groups in the mean value was significant after 12 weeks. In patients with chronic active type B hepatitis, a tendency towards a decrease of HBeAg and an increase of anti-HBe antibodies was also observed. No remarkable side effects were noticed (Hirayama et al 1989).

LIVER FIBROSIS (IN COMBINATION WITH OTHER HERBS)

Minor Bupleurum Combination (Sho-saiko-to) has been shown to play a chemopreventive role in the development of hepatocellular carcinoma in cirrhotic patients in a prospective study and several studies have demonstrated the preventive and therapeutic effects of Sho-saiko-to on experimental hepatic fibrosis (Shimizu 2000). Sho-saiko-to has been shown to inhibit the activation of hepatic stellate cells, the major collagen-producing cells. Sho-saiko-to has a potent antifibrotic effect by inhibiting oxidative stress in hepatocytes and hepatic stellate cells. It is proposed that the active components are baicalin and baicalein, because they both have chemical structures very similar to silybinin, the active compound in *Silybum marianum* (St Mary's thistle), which exhibits antifibrotic activities.

OTHER USES

Because of its wide range of pharmacological effects, baical skullcap is used for many different indications. Although controlled trials are not yet available to determine its effectiveness, evidence from in vitro and animal studies provides a theoretical basis for the following uses:

- Chronic inflammatory conditions such as asthma, arthritis and allergies (anti-allergic and anti-inflammatory effects).
- Hepatitis (as a hepatoprotective agent).

- Common infections such as the common cold (antimicrobial and immunostimulant effects).
- Nausea and vomiting (anti-emetic effect).
- Mild hypertension (hypotensive activity demonstrated in several animal models).

In practice, baical skullcap is used in combination with other herbs for these conditions.

DOSAGE RANGE

- Dried herb: 6–15 g/day (Bensky & Gamble 1986).
- Liquid extract (1:2): 30–60 mL/week or 4.5–8.5 mL/day in divided doses.

ADVERSE REACTIONS

There have been several case reports of Sho-saiko-to-induced interstitial pneumonia (Liu et al 2002). One case of Sho-saiko-to-induced pneumonia in a patient with autoimmune hepatitis was reported (Katou et al 1999); however, direct toxicity is very low.

Toxicity studies of three different traditional Chinese/Japanese formulations containing baical suggests a very low acute or subchronic toxicity for the herbs in them. The studies found no herb-related abnormalities such as changes in body weight or food consumption, abnormalities on ophthalmological and haematological examination, urinalysis and gross pathological examination, changes in organ weights or optical microscopic examination (Iijima et al 1995, Kanitani et al 1995, Kobayashi et al 1995, Minematsu et al 1992, 1995). The acute lethal activity of wogonin is low, with an LD_{50} of 3.9 g/kg (Kwok et al 2002).

SIGNIFICANT INTERACTIONS

There are reports of baical flavonoids interacting with P450 enzymes. Baical flavonoids inhibit hepatic CYP1A2 (Kim et al 2002) and CYP2E1 expression (Jang et al 2003). Theoretically, inhibition of CYP1A2 and CYP2E1 may affect certain medical drugs metabolised by these P450 enzymes. There are, however, no clinical reports of such herb–drug interactions.

Sho-saiko-to during interferon therapy Sho-saiko-to, as well as interferon, is used for the treatment of chronic hepatitis. There have been reports of acute pneumonitis due to a possible interferon–herb interaction. Pneumonitis, also called extrinsic allergic alveolitis, is a complex syndrome caused by sensitisation to an allergen. The mechanism of the Sho-saiko-to–interferon interaction seems to be due to an allergic–immunological mechanism rather than direct toxicity (Ishizaki et al 1996) — contraindicated.

Cyclosporine A decoction of *S. baicalensis* has been reported to significantly decrease plasma levels of cyclosporine in rats. The co-administration of these two substances should be avoided until further research is available (Lai et al 2004).

Warfarin/anticoagulants Increased risk of bleeding is theoretically possible — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS

Baical skullcap and the formulation Sho-saiko-to (Minor Bupleurum Combination, Xiao Chai Hu Tang) are contraindicated during interferon therapy. Baical is contraindicated in cold conditions in TCM.

PREGNANCY USE

Baical is used in TCM for restless fetus (threatened abortion) and toxaemia of pregnancy. A recent animal study found that baical skullcap combined with *Atractylodes macrocephala* had an anti-abortive effect through inhibition of maternal–fetal interface immunity. The herbs prevented lipopolysaccharide-induced abortion by reducing natural killer cells and interleukin 2 activity (Zhong et al 2002). Although this is encouraging, safety in pregnancy is still unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- Baical skullcap is a traditional Chinese herb used to treat fever, cough with thick yellow sputum, thirst and irritability, nausea, jaundice and diarrhoea.
- Baical skullcap extract, many of its constituents, and as part of herbal combination treatments, has been studied in many different experimental models. However, few clinical trials have been conducted using baical as a stand-alone treatment.
- It is used to treat chronic inflammatory conditions such as asthma, arthritis and allergy, because of its anti-inflammatory and anti-allergic effects.
- It is used as a hepatoprotective agent in the treatment of hepatitis.
- Because of its antimicrobial and immunostimulant effects, baical is used to treat infections such as the common cold and bronchitis.
- Anti-emetic effects suggest a role in nausea and vomiting.
- Hypotensive activity demonstrated in various animal models provides a basis for its use in hypertension.
- In practice, it is combined with other herbal medicines for a more targeted approach.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What can this herb do for me?

Baical skullcap may be useful as an adjunctive therapy during cancer treatment to reduce nausea and immune suppression. Baical skullcap may also be beneficial in the

treatment of vascular disorders, allergies, liver disease and infections, hypertension and arthritis; however, effectiveness is largely unknown.

When will it start to work?

For acute allergic and infectious conditions, the beneficial effects of baical skullcap should be noticeable within a few days. For chronic diseases, long-term use is recommended.

Are there any safety issues?

Baical skullcap is a safe and non-toxic herb, which is used in both acute and chronic conditions. It should only be used during pregnancy on the recommendation of a healthcare practitioner. Baical and the formulation Sho-saiko-to (Minor Bupleurum Combination known as Xiao Chai Hu Tang in Mandarin) are contraindicated during interferon therapy.

REFERENCES

Akao T et al. Baicalin, the predominant flavone glucuronide of Scutellariae radix, is absorbed from the rat gastrointestinal tract as the aglycone and restored to its original form. J Pharm Pharmacol 52(12) (2000): 1563-8.

Amosova EN et al. The search for new anti-ulcer agents from plants in Siberia and the Far East. Eksp Klin Farmakol 61(6) (1998): 31-5.

Aung HH et al. Scutellaria baicalensis extract decreases cisplatin-induced pica in rats. Cancer Chemother Pharmacol 52(6) (2003): 453-8.

Aung HH et al. Scutellaria baicalensis decreases ritonavir-induced nausea. AIDS Res Ther 2(1) (2005): 12.

Bao QL et al. The flavonoid baicalin exhibits anti-inflammatory activity by binding to chemokines. Immunopharmacology 49(3) (2000): 295-306.

Baylor NW et al. Inhibition of human T cell leukemia virus by the plant flavonoid baicalin (7-glucuronic acid, 5,6-dihydroxyflavone). J Infect Dis 165(3) (1992): 433-7.

Bell-Quilley CP et al. Renovascular actions of angiotensin II in the isolated kidney of the rat: Relationship to lipoxygenases. J Pharmacol Exper Ther 267(2) (1993): 676-82.

Bensky D, Gamble A. Chinese Herbal Medicine: Materia Medica. Seattle, WA: Eastland Press, 1986.

Blaszczyk T, Krzyzanowska J, Lamer-Zarawska E. Screening for antimycotic properties of 56 traditional Chinese drugs. Phytother Res 14(3) (2000): 210-12.

Bochorakova H et al. Main flavonoids in the root of Scutellaria baicalensis cultivated in Europe and their comparative antiradical properties. Phytother Res 17(6) (2003): 640-4.

Butenko IG, Gladtchenko SV, Galushko SV. Anti-inflammatory properties and inhibition of leukotriene C4 biosynthesis in vitro by flavonoid baicalein from Scutellaria baicalensis georgi roots. Agents Actions 39(Spec. No.) (1993): C49-51.

Byoung KP et al. Inhibition of TPA-induced cyclooxygenase-2 expression and skin inflammation in mice by wogonin, a plant flavone from Scutellaria radix. Eur J Pharmacol 425(2) (2001): 153-7.

Chan FL et al. Induction of apoptosis in prostate cancer cell lines by a flavonoid, baicalin. Cancer Lett 160(2) (2000): 219-28.

Chan HY et al. Baicalein inhibits DMBA-DNA adduct formation by modulating CYP1A1 and CYP1B1 activities. Biomed Pharmacother 56(6) (2002): 269-75.

Chang YL et al. Chinese herbal remedy wogonin inhibits monocyte chemotactic protein-1 gene expression in human endothelial cells. Mol Pharmacol 60(3) (2001): 507-13.

Chang W-H, Chen C-H, Lu F-J. Different effects of baicalein, baicalin and wogonin on mitochondrial function, glutathione content and cell cycle progression in human hepatoma cell lines. Planta Med 68(2) (2002): 128-32.
Chen C-H et al. Baicalein, a novel apoptotic agent for hepatoma cell lines: A potential medicine for hepatoma. Nutr Cancer 38(2) (2000): 287-95.
Chen YC et al. Wogonin, baicalin, and baicalein inhibition of inducible nitric oxide synthase and cyclooxygenase-2 gene expressions induced by nitric oxide synthase inhibitors and lipopolysaccharide. Biochem Pharmacol 61(11) (2001): 1417-27.
Chi YS, Cheon BS, Kim HP. Effect of wogonin, a plant flavone from Scutellaria radix, on the suppression of cyclooxygenase-2 and the induction of inducible nitric oxide synthase in lipopolysaccharide-treated RAW 264.7 cells. Biochem Pharmacol 61(10) (2001): 1195-203.
Chi YS et al. Effects of wogonin, a plant flavone from Scutellaria radix, on skin inflammation: in vivo regulation of inflammation-associated gene expression. Biochem Pharmacol 66(7) (2003): 1271-8.
Cho J, Lee HK. Wogonin inhibits ischemic brain injury in a rat model of permanent middle cerebral artery occlusion. Biol Pharm Bull 27(10) (2004): 1561-4.
Choi J et al. Flavones from Scutellaria baicalensis Georgi attenuate apoptosis and protein oxidation in neuronal cell lines. Biochim Biophys Acta Gen Subj 1571(3) (2002): 201-10.
Chung CP, Park JB, Bae KH. Pharmacological effects of methanolic extract from the root of Scutellaria baicalensis and its flavonoids on human gingival fibroblast. Planta Med (1995) 61(2): 150-3.
Ciesielska E, Gwardys A, Metodiewa D. Anticancer, antiradical and antioxidative actions of novel Antoksyd S and its major components, baicalin and baicalein. Anticancer Res 22(5) (2002): 2885-91.
Ciesielska E et al. In vitro antileukemic, antioxidant and prooxidant activities of Antoksyd S (C/E/XXI): a comparison with baicalin and baicalein. In Vivo 18(4) (2004): 497-503.
De Oliveira TT et al. Effect of different doses of flavonoids on hyperlipidemic rats. Rev Nutr 15(1) (2002): 45-51 [in Portuguese].
Gabrielska J et al. Antioxidant activity of flavones from Scutellaria baicalensis in lecithin liposomes. Z Naturforsch [C] 52(11-12) (1997): 817-23.
Gao Z et al. Free radical scavenging and antioxidant activities of flavonoids extracted from the radix of Scutellaria baicalensis Georgi. Biochim Biophys Acta 1472(3) (1999): 643-50.
Gao Z, Huang K, Xu H. Protective effects of flavonoids in the roots of Scutellaria baicalensis Georgi against hydrogen peroxide-induced oxidative stress in HS-SY5Y cells. Pharmacol Res 43(2) (2001): 173-8.
Goldberg VE et al. Dry extract of Scutellaria baicalensis as a hemostimulant in antineoplastic chemotherapy in patients with lung cancer. Eksp Klin Farmakol 60(6) (1997): 28-30.
Hahm D-H et al. Effect of Scutellariae radix as a novel antibacterial herb on the ppk (polyphosphate kinase) mutant of Salmonella typhimurium. J Microbiol Biotechnol 11(6) (2001): 1061-5.
Hardeland R, Poeggeler B. Non-vertebrate melatonin. J Pineal Res 34(4) (2003): 233-41.
Heo HJ et al. Potent inhibitory effect of flavonoids in Scutellaria baicalensis on amyloid beta protein-induced neurotoxicity. J Agric Food Chem 52(13) (2004): 4128-32.
Hill CP, Osslund TD, Eisenberg D. The structure of granulocyte-colony-stimulating factor and its relationship to other growth factors. Proc Natl Acad Sci USA 90(11) (1993): 5167-71.
Hirayama C et al. A multicenter randomized controlled clinical trial of Sho-saiko-to in chronic active hepatitis. Gastroenterol Jpn 24(6) (1989): 715-19.
Hong T et al. Evaluation of the anti-inflammatory effect of baicalein on dextran sulfate sodium-induced colitis in mice. Planta Med 68(3) (2002): 268-71.
Huang RL et al. Anti-hepatitis B virus effects of wogonin isolated from Scutellaria baicalensis. Planta Med 66(8) (2000): 694-8.
Huang Y et al. Biological properties of baicalein in cardiovascular system. Curr Drug Targets Cardiovasc Haematol Disord 5(2) (2005): 177-84.
Huen MS et al. Naturally occurring 2'-hydroxyl-substituted flavonoids as high-affinity benzodiazepine site ligands. Biochem Pharmacol 66(12) (2003a): 2397-407.

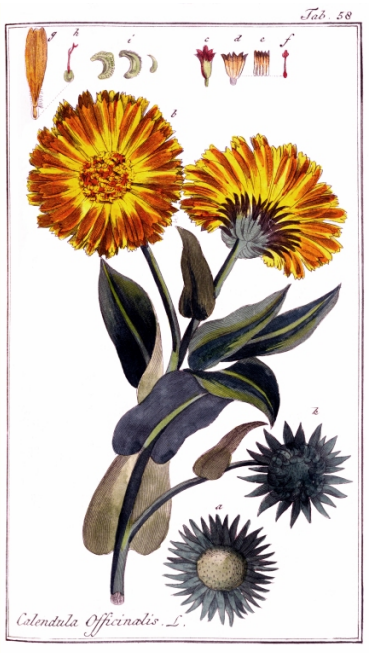
Huen MS et al. 5,7-Dihydroxy-6-methoxyflavone, a benzodiazepine site ligand isolated from Scutellaria baicalensis Georgi, with selective antagonistic properties. Biochem Pharmacol 66(1) (2003b): 125-32.
Hui KM, Wang XH, Xue H. Interaction of flavones from the roots of Scutellaria baicalensis with the benzodiazepine site. Planta Med 66(1) (2000): 91-3.
Hui KM et al. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi. Biochem Pharmacol 64(9) (2002): 1415-24.
Iijima OT et al. A single oral dose toxicity study and a 13-week repeated dose study with a 4-week recovery period of TSUMURA Saiko-ka-ryukotsu-borei to (TJ-12) in rats. Jpn Pharmacol Ther 23(Suppl. 7) (1995): 53-67 [in Japanese].
Ikemoto S et al. Antitumor effects of Scutellariae radix and its components baicalein, baicalin, and wogonin on bladder cancer cell lines. Urology 55(6) (2000): 951-5.
Ishizaki T et al. Pneumonitis during interferon and/or herbal drug therapy in patients with chronic active hepatitis. Eur Respir J 9(12) (1996): 2691-6.
Jang SI et al. Hepatoprotective effect of baicalin, a major flavone from Scutellaria radix, on acetaminophen-induced liver injury in mice. Immunopharmacol Immunotoxicol 25(4) (2003): 585-94.
Kanitani M et al. A single oral dose toxicity study and a 13-week repeated dose study with a 4-week recovery period of TSUMURA Sairei-to (TJ-114) in rats. Jpn Pharmacol Ther 23(Suppl. 7) (1995): 371-87 [in Japanese].
Katou K, Mori K. Autoimmune hepatitis with drug-induced pneumonia due to Sho-saiko-to. Nippon Kokyuki Gakkai Zasshi 37(8) (1999): 641-6.
Kaye AD et al. Effects of phospholipase A2, 12-lipoxygenase, and cyclooxygenase inhibitors in the feline pulmonary bed. Am J Physiol 272(4) (1997): L573-9.
Kim YO et al. Cytoprotective effect of Scutellaria baicalensis in CA1 hippocampal neurons of rats after global cerebral ischemia. J Ethnopharmacol 77(2-3) (2001): 183-8.
Kim J-Y et al. Effects of flavonoids isolated from Scutellariae radix on cytochrome P-450 activities in human liver microsomes. J Toxicol Environ Health 65(5-6) (2002): 373-81.
Kimata M, Inagaki N, Nagai H. Effects of luteolin and other flavonoids on IgE-mediated allergic reactions. Planta Med 66(1) (2000): 2529.
Kimura Y et al. Effects of flavonoids isolated from Scutellariae radix on the production of tissue-type plasminogen activator and plasminogen activator inhibitor-1 induced by thrombin and thrombin receptor agonist peptide in cultured human umbilical vein endothelial cells. J Pharm Pharmacol 49(8) (1997): 816-22.
Kobayashi Y et al. A single oral dose toxicity study and a 13-week repeated dose study with a 4-week recovery period of TSUMURA Oren-gedoku-to (TJ-15) in rats. Jpn Pharmacol Ther 23 (Suppl. 7) (1995): 69-89 [in Japanese].
Konoshima T et al. Studies on inhibitors of skin tumor promotion. XI. Inhibitory effects of flavonoids from Scutellaria baicalensis on Epstein-Barr virus activation and their anti-tumor-promoting activities. Chem Pharm Bull (Tokyo) 40(2) (1992): 531-3.
Krakauer T, Li BQ, Young HA. The flavonoid baicalin inhibits superantigen-induced inflammatory cytokines and chemokines. FEBS Lett 500(1-2) (2001): 52-5.
Kubo M, Matsuda H, Kimura Y. Scutellariae radix. X: Inhibitory effects of various flavonoids on histamine release from rat peritoneal mast cells in vitro. Chem Pharm Bull 32(12) (1984): 5051-4.
Kubo M, Matsuda H, Tani T. Studies on Scutellariae radix. XII: Anti-thrombic actions of various flavonoids from Scutellariae radix. Chem Pharm Bull 33(6) (1985): 2411-15.
Kwok MH et al. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi. Biochem Pharmacol 64(9) (2002): 1415-24.
Lai MY et al. Significant decrease of cyclosporine bioavailability in rats caused by a decoction of the roots of Scutellaria baicalensis. Planta Med 70(2) (2004): 132-7.
Lam TL et al. A comparison of human immunodeficiency virus type-1 protease inhibition activities by the aqueous and methanol extracts of Chinese medicinal herbs. Life Sci 67(23) (2000): 2889-96.

Lee H et al. Flavonoid wogonin from medicinal herb is neuroprotective by inhibiting inflammatory activation of microglia. FASEB J 17(13) (2003): 1943-4.
Li BQ et al. Inhibition of HIV infection by baicalin: a flavonoid compound purified from Chinese herbal medicine. Cell Mol Biol Res 39(2) (1993): 119-24.
Li BQ et al. The flavonoid baicalin exhibits anti-inflammatory activity by binding to chemokines. Immunopharmacology 49(3) (2000a): 295-306.
Li BQ et al. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun 276(2) (2000b): 534-8.
Li H et al. Determination of amino acid neurotransmitters in cerebral cortex of rats administered with baicalin prior to cerebral ischemia by capillary electrophoresis-laser-induced fluorescence detection. J Chromatogr B: Anal Technol Biomed Life Sci 788(1) (2003): 93-101.
Liao J-F, Hung W-Y, Chen C-F. Anxiolytic-like effects of baicalein and baicalin in the Vogel conflict test in mice. Eur J Pharmacol 464(2-3) (2003): 141-6.
Lim BO. Efficacy of wogonin in the production of immunoglobulins and cytokines by mesenteric lymph node lymphocytes in mouse colitis induced with dextran sulfate sodium. Biosci Biotechnol Biochem 68(12) (2004): 2505-11.
Lin C-C, Shieh D-E. In vivo hepatoprotective effect of baicalein, baicalin and wogonin from Scutellaria rivularis. Phytother Res 10(8) (1996): 651-64.
Lin MT et al. Effects of Chinese herb, Huang Chin (Scutellaria baicalensis Georgi) on thermoregulation in rats. Jpn J Pharmacol 30(1) (1980): 59-64.
Liu ZL, Tanaka S, Horigome H, Hirano T, Oka K. Induction of apoptosis in human lung fibroblasts and peripheral lymphocytes in vitro by Sho-saiko-to derived phenolic metabolites. Biol Pharm Bull 25(1) (2002): 37-41.
Liu JJ et al. Baicalein and baicalin are potent inhibitors of angiogenesis: inhibition of endothelial cell proliferation, migration and differentiation. Int J Cancer 106(4) (2003): 559-65.
Lu Z. Clinical comparative study of intravenous piperacillin sodium or injection of scutellaria compound in patients with pulmonary infection. Zhong Xi Yi Jie He Za Zhi 10(7) (1990): 389, 413-15.
Mehendale SR et al. Effects of antioxidant herbs on chemotherapy-induced nausea and vomiting in a rat-pica model. Am J Chin Med 32(6) (2004): 897-905.
Minematsu S et al. A subchronic (3-month) oral toxicity study of Tsumura Sho-saiko-to (TJ-9) in the rat via oral gavage administration with a 4-week recovery period. Pharmacometrics 43(1) (1992): 19-42 [in Japanese].
Minematsu S et al. A single oral dose toxicity study of TSUMURA Sho-saiko-to (TJ-9) in rats. Jpn Pharmacol Ther 23(Suppl. 7) (1995): 29-32 [in Japanese].
Nagai T, Yamada H, Otsuka Y. Inhibition of mouse liver sialidase by the root of Scutellaria baicalensis. Planta Med 55(1) (1989): 27-9.
Nagai T et al. In vivo anti-influenza virus activity of plant flavonoids possessing inhibitory activity for influenza virus sialidase. Antiviral Res 19(3) (1992a): 207-17.
Nagai T et al. Anti-influenza virus activity of plant flavonoids having inhibitory activity against influenza virus sialidase. J Pharmacobio-Dynamics 15(1) (1992b): S-1.
Nagai T et al. Mode of action of the anti-influenza virus activity of plant flavonoid, 5,7,4'-trihydroxy-8-methoxyflavone, from the roots of Scutellaria baicalensis. Antiviral Res 26(1) (1995a): 11-25.
Nagai T et al. Antiviral activity of plant flavonoid, 5,7,4'-trihydroxy-8-methoxyflavone, from the roots of Scutellaria baicalensis against influenza A (H3N2) and B viruses. Biol Pharm Bull 18(2) (1995b): 295-99.
Nakajima T et al. Inhibitory effect of baicalein, a flavonoid in scutellaria root, on eotaxin production by human dermal fibroblasts. Planta Med 67(2) (2001): 132-5.
Nan J-X et al. Scutellaria baicalensis inhibits liver fibrosis induced by bile duct ligation or carbon tetrachloride in rats. J Pharm Pharmacol 54(4) (2002): 555-63.
Narita Y et al. Treatment of epileptic patients with the Chinese herbal medicine 'Saiko-Keishi-To' (SK). IRCS Med Sci 10(2) (1982): 88-9.

Natarajan R et al. Role of the lipoxygenase pathway in angiotensin II-induced vascular smooth muscle cell hypertrophy. Hypertension 23(1 Suppl.) (1994): I142-7.
Niitsuma T et al. Effects of absorbed components of Saiboku-to on the release of leukotrienes from polymorphonuclear leukocytes of patients with bronchial asthma. Methods Find Exp Clin Pharmacol 23(2) (2001): 99-104.
Nishioka T, Kawabata J, Aoyama Y. Baicalein, an alpha-glucosidase inhibitor from Scutellaria baicalensis. J Natural Products 61(11) (1998): 1413-15.
Park BK et al. Inhibition of TPA-induced cyclooxygenase-2 expression and skin inflammation in mice by wogonin, a plant flavone from Scutellaria radix. Eur J Pharmacol 425(2) (2001): 153-7.
Park S et al. Preventive effect of the flavonoid, wogonin, against ethanol-induced gastric mucosal damage in rats. Dig Dis Sci 49(3) (2004): 384-94.
Piao HZ et al. Neuroprotective effect of wogonin: potential roles of inflammatory cytokines. Arch Pharm Res 27(9) (2004): 930-6.
Pidgeon GP et al. Mechanisms controlling cell cycle arrest and induction of apoptosis after 12-lipoxygenase inhibition in prostate cancer cells. Cancer Res 62(9) (2002): 2721-7.
Razina TG et al. Enhancement of the selectivity of the action of the cytostatics cyclophosphane and 5-fluorouracil by using an extract of the Baikal skullcap in an experiment. Vopr Onkol 33(2) (1987): 80-4.
Razina TG et al. The role of thrombocyte aggregation function in the mechanism of the antimetastatic action of an extract of Baikal skullcap. Vopr Onkol 35(3) (1989): 331-5.
Razina TG et al. Medicinal plant preparations used as adjuvant therapeutics in experimental oncology. Eksp Klin Farmakol 63(5) (2000): 59-61.
Regulska-Ilow B et al. Influence of bioflavonoids from the radix extract of Scutellaria baicalensis on the level of serum lipids, and the development of laboratory rats fed with fresh and oxidized fats. Nahrung 48(2) (2004): 123-8.
Shang Y et al. Scutellaria flavonoid reduced memory dysfunction and neuronal injury caused by permanent global ischemia in rats. Pharmacol Biochem.Behav 82(1) (2005): 67-73.
Shang YZ et al. Prevention of oxidative injury by flavonoids from stems and leaves of Scutellaria Baicalensis georgi in PC12 cells. Phytother Res 20(1) (2006): 53-7.
Shen Y-C et al. Mechanisms in mediating the anti-inflammatory effects of baicalin and baicalein in human leukocytes. Eur J Pharmacol 465(1-2) (2003): 171-81.
Shimizu I. Sho-saiko-to: Japanese herbal medicine for protection against hepatic fibrosis and carcinoma. J Gastroenterol Hepatol 15(Suppl.) (2000): D84-90.
Smolianinov ES et al. Effect of Scutellaria baicalensis extract on the immunologic status of patients with lung cancer receiving antineoplastic chemotherapy. Eksp Klin Farmakol 60(6) (1997): 49-51.
Son D et al. Neuroprotective effect of wogonin in hippocampal slice culture exposed to oxygen and glucose deprivation. Eur J Pharmacol 493(1-3) (2004): 99-102.
Takizawa H, DelliPizzi A, Nasjletti A. Prostaglandin I2 contributes to the vasodepressor effect of baicalein in hypertensive rats. Hypertension 31(3) (1998): 866-71.
Tang ZM, Peng M, Zhan CJ. Screening 20 Chinese herbs often used for clearing heat and dissipating toxin with nude mice model of hepatitis C viral infection. Zhongguo Zhong Xi Yi Jie He Za Zhi 23(6) (2003): 447-8.
Tong WG, Ding XZ, Adrian TE. The mechanisms of lipoxygenase inhibitor-induced apoptosis in human breast cancer cells. Biochem Biophys Res Commun 296(4) (2002): 942-8.
Tsao TF et al. Effect of Chinese and western antimicrobial agents on selected oral bacteria. J Dent Res 61(9) (1982): 1103-6.
Wakabayashi I. Inhibitory effects of baicalein and wogonin on lipopolysaccharide-induced nitric oxide production in macrophages. Pharmacol Toxicol 84(6) (1999): 288-91.
Wakabayashi I, Yasui K. Wogonin inhibits inducible prostaglandin E2 production in macrophages. Eur J Pharmacol 406(3) (2000): 477-81.
Wang H-H, Liao J-F, Chen C-F. Anticonvulsant effect of water extract of Scutellariae radix in mice. J Ethnopharmacol 73(1-2) (2000): 185-90.

Wu S-H, Bresnahan BA, Lianos EA. Hemodynamic role of arachidonate 12- and 5-lipoxygenases in nephrotoxic serum nephritis. Kidney Int 43(6) (1993): 1280-5.
Wu X, Akatsu H, Okada H. Apoptosis of HIV-infected cells following treatment with Sho-saiko-to and its components. Jpn J Med Sci Biol 48(2) (1995): 79-87.
Yamashiki M et al. Herbal medicine sho-saiko-to induces in vitro granulocyte colony-stimulating factor production on peripheral blood mononuclear cells. J Clin Lab Immunol 37(2) (1992): 83-90.
Yamashiki M et al. Effects of the Japanese herbal medicine 'Sho-saiko-to' (TJ-9) on in vitro interleukin-10 production by peripheral blood mononuclear cells of patients with chronic hepatitis C. Hepatology 25(6) (1997): 1390-7.
Yamashiki M et al. Effects of the Japanese herbal medicine Sho-saiko-to (TJ-9) on interleukin-12 production in patients with HCV-positive liver cirrhosis. Dev Immunol 7(1) (1999): 17-22.
Yang D et al. Antifungal activity in vitro of Scutellaria baicalensis Georgi upon cutaneous and ungual pathogenic fungi. Ann Pharm Fr 53(3) (1995): 138-41.
Yang ZC et al. The synergistic activity of antibiotics combined with eight traditional Chinese medicines against two different strains of Staphylococcus aureus. Colloids Surf B Biointerfaces 41(2-3) (2005): 79-81.
Ye F et al. Anticancer activity of Scutellaria baicalensis and its potential mechanism. J Altern Complement Med 8(5) (2002): 567-72.
Zhang X-P, Li Z-F, Liu X-G. Review in pharmacological study of Baicalein. Chin Pharmacol Bull 17(6) (2001): 711-13 [in Chinese].
Zhang DY et al. Inhibition of cancer cell proliferation and prostaglandin E2 synthesis by Scutellaria baicalensis. Cancer Res 63(14) (2003): 4037-43.
Zhong XH et al. Anti-abortive effect of Radix scutellariae and Rhizoma atractylodis in mice. Am J Chin Med 30(1) (2002): 109-17.
Zhou Y, Zhang J. Oral baicalin and liquid extract of licorice reduce sorbitol levels in red blood cell of diabetic rats. Chin Med J 102(3) (1989): 203-6.

Beta-carotene



BACKGROUND AND RELEVANT PHARMACOKINETICS

CAROTENOIDS

The carotenoids are a family of bright yellow-, orange- and red-coloured compounds found in fruit, vegetables and some animal products such as salmon, lobster and egg yolk. Carotenoids can be divided into the provitamin A group, such as beta-carotene, and xanthophylls such as lutein, zeaxanthin and lycopene, which are important fat-soluble antioxidants. Of the 600 or so carotenoids known to exist in nature, approximately 20 are found in humans. In plants, carotenoids play a vital role in photosynthesis and participate in the energy-transfer process, as well as protecting plants from oxidative damage. The red, orange and yellow colour of these compounds is because they preferentially absorb blue light, which is the most energetic and hence the most biologically damaging part of the visible spectrum.

In animals, carotenoids have many functions. In addition to providing direct photoprotection via absorption of blue light, carotenoids act as powerful fat-soluble antioxidants linked to oxidation prevention, as well as playing a role in cellular communication, including stimulation of gap-junction communication, which is important for cancer prevention by regulating cell growth, differentiation, apoptosis and angiogenesis. Carotenoids may also be involved in detoxification of carcinogens, DNA repair and immunosurveillance. These properties are believed to contribute to their antioxidant, immune-enhancing, anticarcinogenic and photoprotective activity.

Beta-carotene was the first of the carotenoids to be discovered, being initially isolated from carrots. The bioavailability of beta-carotene is dependent on its source, with the amount being absorbed from raw foods such as carrots, where it forms part of a protein-polysaccharide matrix, being only about 20% of that absorbed from supplemental forms. Although beta-carotene is lipid soluble its absorption requires only a limited amount of fat (Roodenburg et al 2000); however, there is a wide individual variation in serum response to beta-carotene administration (Bowen et al 1993, Pryor et al 2000).

Although it has been suggested that different carotenoids compete for absorption, this was not confirmed by a postprandial study (Tyssandier et al 2002). Beta-carotene is absorbed in the intestine and released into the lymphatic circulation within chylomicrons. It is then taken up by hepatocytes and released into the blood and transported predominantly within LDLs. It is distributed to adipose tissue and the

skin and excreted in the faeces (Micromedex 2003). The time to reach peak concentration is up to 4–6 weeks with oral dosing (Mathews-Roth 1990a).

Animal feeding studies suggest that a natural algae-derived beta-carotene isomer mixture is more readily absorbed than synthetic all-*trans* beta-carotene and that this higher bioavailability can be enhanced by increasing dietary lipid levels (Mokady & Ben-Amotz 1991). Natural algal beta-carotene has also been shown to have higher accumulation in rat liver than synthetic all-*trans* beta-carotene (Ben-Amotz et al 1989, Takenaka et al 1993) with at least a 10-fold higher accumulation having been observed in chick and rat liver (Ben-Amotz et al 1989).

Animal studies suggest that there is some bioconversion within the body between different stereoisomers of beta-carotene (Ben-Amotz et al 2005) and further studies in humans suggest that, regardless of the isomer mix, there is preferential absorption or transport of the all-*trans* isomer in comparison with the 9-*cis* isomer, with plasma levels of the all-*trans* isomer being around 10-fold that of the 9-*cis* form (Gaziano et al 1995a, Jensen 1987, Morinobu et al 1994, Stahl & Sies 1993, Tamai et al 1993).

It is suggested that *Helicobacter pylori* infection may impair the protective role of alpha-tocopherol and beta-carotene in the stomach, because infected people have been found to have reduced beta-carotene concentrations in gastric juice and the presence of gastric atrophy and intestinal metaplasia is associated with reduced mucosal alpha-tocopherol and beta-carotene concentrations (Zhang et al 2000).

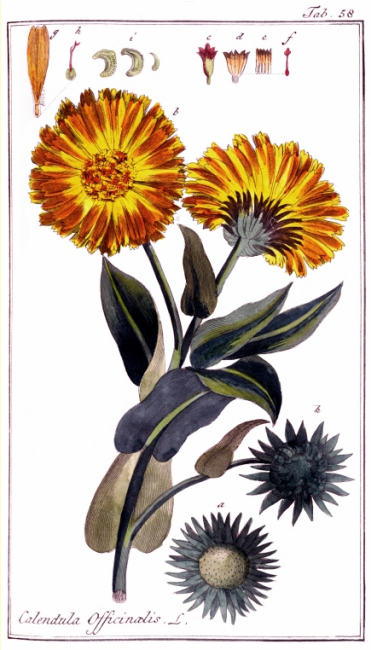
CHEMICAL COMPONENTS

Beta-carotene comes in natural and synthetic forms, with the natural form being derived mainly from algal sources and consisting of roughly equal amount of 9-*cis* and all-*trans* isomers, with small amounts of the 13-*cis* isomer. Synthetic beta-carotene is primarily composed of the all-*trans* isomer with small residues of the 13-*cis* isomer (PDRHealth 2005). Although all-*trans* beta-carotene is converted into vitamin A, which plays an essential role in vision, growth, reproduction, immune function and maintenance of the skin and mucous membranes (see Vitamin A monograph), the 9-*cis* isomer is not converted into vitamin A but does act as an antioxidant (Ben-Amotz & Levy 1996).

FOOD SOURCES

Carrots are the major contributors of beta-carotene in the diet, but it is also found in cantaloupe, broccoli and spinach. Carotenoids have emerged as the best single tissue marker for a diet rich in fruits and vegetables, and measurements of plasma and tissue carotenoids have an important role in defining the optimal diets for humans (Handelman 2001).

Natural beta-carotene for use in supplements is generally obtained from palm oil or the micromarine algae (phytoplankton) *Dunaliella salina* (also known as *D. bardawil*), which is the richest natural source of beta-carotene. Whole dried *D. salina* is also available in a supplemental form that contains between 1% and 2% beta-carotene. The typical western diet is estimated to provide approximately 2–4 mg/day of beta-carotene (Pryor et al 2000).



DEFICIENCY SIGNS AND SYMPTOMS

Beta-carotene is considered a conditionally essential nutrient and becomes an essential nutrient when the dietary intake of retinol (vitamin A) is inadequate.

Low serum beta-carotene levels have been associated with male gender, younger age, lower non-HDL-cholesterol, greater ethanol consumption and higher BMI (Brady et al 1996), increased lipoprotein density and the presence of inflammation (Kritchevsky 1999), high C-reactive protein (Erlinger et al 2001), high blood glucose (Abahusain et al 1999), hypertension (Coudray et al 1997), exposure to environmental tobacco smoke (Farchi et al 2001), as well as all measures of obesity (Wallstrom et al 2001), including obesity in children (Strauss 1999).

Low serum beta-carotene and/or low beta-carotene intake has also been associated with a number of clinical conditions, such as type 2 diabetes and poor glycaemic control (Abahusain et al 1999, Coudray et al 1997), non-melanoma and melanoma skin cancer (Gollnick & Siebenwirth 2002), breast cancer (Hacisevki et al 2003), rheumatoid arthritis (Kacsur et al 2002), Alzheimers dementia (Jimenez-Jimenez et al 1999) and age-related macular degeneration (Cooper et al 1999a).

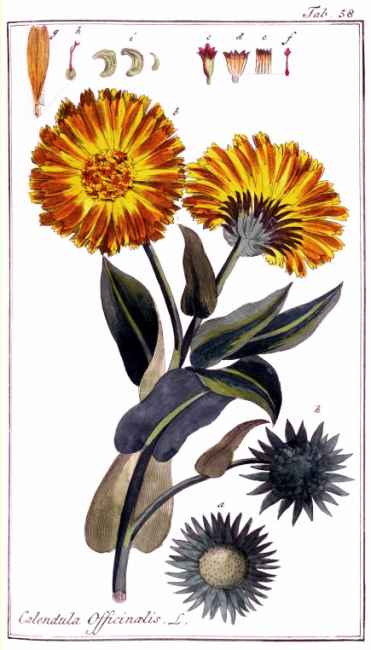
Low serum beta-carotene has been independently associated with an increased all-cause mortality risk in older men. Apparently, a synergistic effect occurs between low beta-carotene and high inflammation burden in predicting higher mortality rates (Hu et al 2004). In another study of 668 hospitalised patients aged 70 years or more and 104 healthy controls, the diseased elderly people had reduced plasma levels of retinol, beta-carotene, and alpha-tocopherol (Tebi et al 2000). It is unclear whether these observed low levels of beta-carotene seen in disease states are a cause or result of disease processes.

MAIN ACTIONS

PRO-VITAMIN A

Beta-carotene is converted to retinoic acid (vitamin A: see Vitamin A monograph) by an enzyme found in the intestinal mucosa and liver, with 2 μg of all-*trans* carotene being equal to 1 μg of all-*trans* retinol (vitamin A) or 3.33 IU (PDRHealth 2005). This conversion is regulated by vitamin A status and may be enhanced by alpha-

tocopherol (Wang & Krinsky 1998). Zinc may also be important for bioconversion, as indicated by a double-blind, placebo-controlled trial of 170 pregnant women that found that supplementation zinc improved the postpartum vitamin A status of both mothers and infants (Dijkhuizen et al 2004).



IMMUNOMODULATION

The mechanisms by which beta-carotene influences immune function are not well understood and both direct and indirect effects on immune function, via its pro-vitamin A activity, have been demonstrated (Watson et al 1991). Beta-carotene directly influences immune function by reducing oxidative damage to cell membranes and their receptors, by influencing the activity of redox-sensitive transcription factors and the production of cytokines and prostaglandins and enhancing cell-to-cell communication (Hughes 2001).

These actions are influenced by several factors, such as dose and timing of supplementation, age and health status of the individual. A double-blind, placebo-controlled, randomised crossover study in 25 healthy, adult male non-smokers found that 15 mg/day of beta-carotene enhanced cell-mediated immune responses, with significant increases in the percentages of monocytes expressing the major histocompatibility complex class II molecule HLA-DR and adhesion molecules, as well as increased ex vivo TNF-alpha secretion by blood monocytes (Hughes et al 1997). Beta-carotene has also been shown to increase plasma levels of TNF-alpha in patients given 30 mg/day for the treatment of oral leukoplakia (Prabhala et al 1993).

In controlled trials, supplementation with 30 mg beta-carotene was shown to protect against UV-induced photosuppression of immune function in young men (Fuller et al 1992), as well as in older men, with serum beta-carotene levels being significantly associated with maintenance of the delayed-type hypersensitivity response (Herraiz et al 1998). Another controlled trial found that 60 mg/day beta-carotene for 44 weeks increased the CD4-CD8 ratio after 9 months without affecting NK cells, virgin T cells, memory T cells or cytotoxic T cells in healthy male non-smokers, and supplementation with 60 mg/day beta-carotene for 4 weeks was shown to significantly increase lymphocyte counts and $CD4^+$ in a pilot study of seven patients with AIDS (Murata et al 1994).

Natural killer cell activity was also found to increase in older adults in a dose-finding study in which 30 mg/day beta-carotene for 2 months significantly increased in a dose-dependent manner the percentage of lymphoid cells with surface markers for T-helper and NK cells, and cells with IL-2 and transferrin receptors (Watson et al 1991). In a further study of 59 men participating in the Physicians Health Study, 10–12 years of supplementation with 50 mg beta-carotene on alternate days was

found to increase NK cell activity without increasing the percentage of NK cells, IL-2 production or receptor expression in elderly but not middle-aged men (Santos et al 1996).

Although beta-carotene supplementation has been shown to enhance NK cell responses, there are a number of RCTs that suggest that it does not influence other aspects of immune activity in healthy individuals. In separate RCTs, supplementation with 90 mg beta-carotene for 3 weeks or 50 mg on alternate days for more than 10 years was not found to influence T-cell-mediated immunity of healthy elderly people (Santos et al 1997) and supplementation with 30 mg beta-carotene was not found to affect the T-lymphocyte proliferative response to phytohaemagglutinin in healthy lactating and non-lactating women (Gossage et al 2000). A further study found that supplementation with 8.2 mg/day of beta-carotene for 12 weeks did not influence several markers of T-cell-mediated immunity in well-nourished, healthy elderly individuals (Corridan et al 2001).

ANTIOXIDANT

Beta-carotene has consistently demonstrated antioxidant activity in vitro, although the mechanism of action is poorly understood. At low partial pressures of oxygen, such as those found in most tissues under physiological conditions, it exhibits good radical-trapping antioxidant behaviour, whereas this capacity is lost at high oxygen pressures in vitro with autocatalytic, pro-oxidant effects observed (Burton & Ingold 1984).

Beta-carotene has been shown to quench singlet oxygen, scavenge peroxyl radicals and inhibit lipid peroxidation in vitro; however, there is ongoing debate as to beta-carotene's ability to act as an antioxidant in vivo, with some evidence suggesting this varies from system to system for reasons that are poorly understood (Pryor et al 2000).

Beta-carotene acts synergistically with other antioxidants, such as vitamins E and C, or other dietary components as part of the antioxidant network (see Vitamin E monograph). A combination of beta-carotene and alpha-tocopherol has been shown to inhibit lipid peroxidation significantly more than the sum of the individual inhibitions in a membrane model (Palozza & Krinsky 1992) and a synergistic effect has also been demonstrated in vitro and in vivo with vitamins E and C (Bohm et al 1997, 1998).

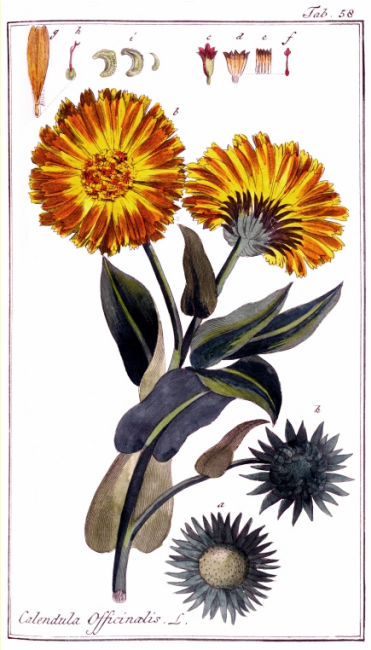
In vivo studies A number of studies have demonstrated that beta-carotene has antioxidant activity in vivo. Supplementation with 180 mg of beta-carotene for 2 weeks was found to increase the beta-carotene content of LDL and significantly reduce plasma lipid peroxidation and LDL susceptibility to oxidation, as analysed by

malondialdehyde generation (Levy et al 1996). Similarly, lipid peroxidation as measured by breath pentane output was found to be significantly reduced in healthy subjects by 4 weeks of daily supplementation with 120 mg of beta-carotene (Gottlieb et al 1993). In a case-controlled trial involving 20 patients with long-standing type 1 diabetes mellitus, as well as age- and sex-matched controls, supplementation with 60 mg/day of natural algae-derived beta-carotene for 3 weeks was found to significantly reduce malondialdehyde and lipid peroxide production and the increased susceptibility towards LDL oxidation seen in the diabetic subjects (Levy et al 2000). Beta-carotene supplementation was also found to significantly reduce serum lipid peroxidation in a dose-dependent manner in a number of double-blind, placebo-controlled trials (Greul et al 2002, Lee et al 2000).

These results contrast with those from a number of studies that failed to demonstrate any in vivo antioxidant activity. A study of 79 healthy volunteers found that normal concentrations of carotenoids in plasma and tissues did not correlate with total antioxidant capacity of the plasma or breath pentane measurements (Borel et al 1998). In other studies supplementation was seen to increase LDL beta-carotene without changing LDL susceptibility to oxidation (Princen et al 1992, Reaven et al 1993).

It is possible that beta-carotene is more likely to demonstrate antioxidant activity in conditions of increased oxidative stress. This is suggested by the results of a randomised, double-blind controlled trial involving 42 non-smokers and 28 smokers who received either 20 mg of beta-carotene or placebo and showed that beta-carotene reduced lipid peroxidation as indicated by breath pentane output in smokers but not in non-smokers (Allard et al 1994). It is further supported by a study of whole-body irradiation in rats that found that supplementation with natural algae-derived beta-carotene protected against the reduction in growth rate and the selective decline in 9-*cis* beta-carotene and retinol seen in irradiated animals, as well as partially reversing the effect of irradiation when given after the irradiation (Ben-Amotz et al 1996). Algae-derived beta-carotene was also found to protect against CNS oxygen toxicity in rats, as indicated by a significant increase in the latent period preceding oxygen seizures in supplemented animals (Bitterman et al 1994).

Isomer differences Individual isomers and isomer mixtures demonstrate different antioxidant properties in vivo. The 9-*cis* isomer, which is present in greater amounts in natural beta-carotene, exhibits higher antioxidant potency than the all-*trans* isomer in vitro (Levin & Mokady 1994). Natural beta-carotene, such as that obtained from algal sources, also exhibits greater antioxidant activity than synthetic beta-carotene in vivo (Takenaka et al 1993).



In humans, supplementation with natural algal beta-carotene containing a 50:50 mix of all-*trans* and 9-*cis* isomers has been shown to be a more effective lipophilic antioxidant than all-*trans* beta-carotene (Ben-Amotz & Levy 1996). Human supplementation with natural algal and synthetic beta-carotene has also been shown to produce similar reductions in LDL oxidation, despite the synthetic beta-carotene producing double the rise in LDL beta-carotene content (Levy et al 1995).

These studies are contrasted by in vitro studies that suggest that 9-*cis* beta-carotene and all-*trans* beta-carotene have equal antioxidant activities (Liu et al 2000) and that synthetic beta-carotene is twice as effective as algal beta-carotene in inhibiting LDL lipid peroxidation following LDL incubation with copper ions (Lavy et al 1993).

PHOTOPROTECTION

Beta-carotene, together with other carotenoids, is present in all photosynthetic organisms where it serves an important photoprotective role either by dissipating excess excitation energy as heat or by scavenging reactive oxygen species and suppressing lipid peroxidation (Penuelas & Munne-Bosch 2005). Studies in bacteria, animals and humans have demonstrated that carotenoids can prevent or lessen photosensitivity by endogenous and exogenous photosensitisers (Mathews-Roth 1993) and high doses of beta-carotene (180 mg/day, up to 300 mg/day) have been used to treat the photosensitivity associated with erythropoietic protoporphyria (Mathews-Roth 1987). There is also consistent evidence from animal and human studies that beta-carotene has photoprotective effects.

Beta-carotene is present at the target sites of light-induced damage, being present in the dermis, epidermis and stratum corneum with levels varying between skin areas with higher concentration in the forehead and palms (Alaluf et al 2002). Skin levels are related to the levels found in the plasma (Sies & Stahl 2004) and beta-carotene and other endogenous antioxidants are reduced in both skin and blood by UV exposure (Gollnick et al 1996).

Although it is presumed that beta-carotene exerts a light-protective function by quenching excited species such as singlet oxygen and free radicals (Mathews-Roth 1987), there are a number of other ways that beta-carotene may contribute to photoprotection (i.e. absorption of UV light). These include the protection of target molecules through its antioxidant activity, enhancement of the repair of UV damage, modulation of enzyme activity and gene expression, enhancement of cell-to-cell communication and suppression of cellular responses and inflammation (Sies & Stahl 2004). It is also suggested that the effect of UVA protection provided by beta-

carotene is due to the siting of beta-carotene deep inside membranes in proximity to the UVA chromophores that initiate the cell damage (Bohm et al 1998b).

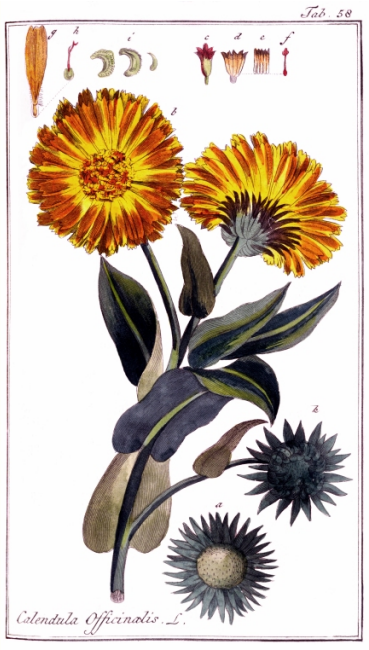
As a strong natural pigment, beta-carotene produces a yellow-orange colouration in the skin that adds to the red colouration from haemoglobin and the brown colouration from melanin to create the normal human skin colour (Alaluf et al 2002). Beta-carotene acts as a blue light filter by absorbing light in the range of 360–550 nanometers (Pathak 1982) with the *cis* isomers having been found to exhibit an additional absorption maximum in the UV range (Sies & Stahl 2004), thus suggesting a possible advantage for natural beta-carotene over synthetic all-*trans* beta-carotene in providing photoprotection.

As with titanium dioxide, the beta-carotene in the skin takes the form of finely dispersed particles that can increase the natural pigment action. This was observed in a human trial involving 20 subjects that found that supplementation with 50 mg of natural algal beta-carotene for 6 weeks increased the reflection capacity of the skin 2.3-fold, irrespective of the wavelength (Heinrich et al 1998). A study on whole albino hairless mouse skin and epidermis, however, suggests that although beta-carotene did impart a visible change in skin colour its absorbance was insufficient to impart significant photoprotection, which indicates that its photoprotective action is mediated through processes other than blue light absorption (Sayre & Black 1992).

In a controlled study injection of phytoene, the colourless triene precursor of beta-carotene was found to significantly reduce radiation-induced erythema in guinea pigs (Mathews-Roth & Pathak 1975); however, a further study on albino hairless mice found that 10 g/kg feed of beta-carotene and 200 mg/kg feed of 13-*cis* retinoic acid for 12 weeks did not prevent UVB-induced dermal damage (Kligman & Mathews-Roth 1990).

An in vitro study on human keratinocytes suggests that beta-carotene dose-dependently suppressed UVA-induction of matrix metalloproteases through quenching of singlet oxygen and that this action was not enhanced by vitamin E (Wertz et al 2004). Further studies suggest that beta-carotene also interferes with UVA-induced gene expression by multiple pathways, including inhibition of UVA-induced extracellular matrix degradation, enhanced UVA induction of tanning-associated protease-activated receptor-2, promotion of keratinocyte differentiation and synergistic induction of cell cycle arrest and apoptosis (Wertz et al 2005).

Beta-carotene has also been observed to have synergistic effects with other antioxidants in protecting cultured human fibroblasts from UVA, although only additive effects were observed for UVB (Bohm et al 1998b). The interaction between different antioxidants and/or other as yet unidentified phytochemicals has been used



to explain the finding that UV carcinogenesis was enhanced with a beta-carotene-supplemented semi-defined diet in mice (Black 2004, Black & Gerguis 2003, Black et al 2000).

ENHANCE INTERCELLULAR COMMUNICATION

In addition to its antioxidant activity, beta-carotene enhances gap junction intercellular communication by upregulation of the gap junction protein connexin 43. This action may be important in its control of tumour growth (Yeh & Hu 2003) and is likely to be independent of its ability to quench singlet molecular oxygen (Stahl et al 1997).

Animal studies have indicated that a beta-carotene dose of 50 mg/kg/day for 5 days inhibits, whereas a lower dose (5 mg/kg/day) increases, gap junction intercellular communication in rat liver. Further in vitro studies suggest that the observed inhibition is due, at least in part, to oxidised beta-carotene (Yeh & Hu 2003).

ANTICARCINOGENIC ACTIVITY

Observational epidemiological studies have consistently shown a relationship between dietary beta-carotene intake and low risk of various cancers (Cooper et al 1999b, Pryor et al 2000). In animal studies beta-carotene has been found to be chemoprotective, with inhibition of spontaneous mammary tumours (Fujii et al 1993, Nagasawa et al 1991), as well as prevention of skin carcinoma formation (Ponnamperuma et al 2000), UV-induced carcinogenesis in mice (Epstein 1977, Mathews-Roth 1982) and oral cancer in laboratory and animal models (Garewal 1995). Studies in ferrets suggest that the beta-carotene molecule becomes unstable in smoke-exposed lungs and that when given with alpha-tocopherol and ascorbic acid to stabilise the beta-carotene molecule, there is a protective effect against smoke-induced lung squamous metaplasia (Russell 2002).

A review of carotenoid research by the International Agency for Research on Cancer suggests there is sufficient evidence that beta-carotene has cancer-preventive activity in experimental animals, based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters (Vainio & Rautalahti 1998), despite a review suggesting that beta-carotene does not protect against lung cancer in animals (De Luca & Ross 1996).

Whether beta-carotene has anticancer properties in humans is unclear. It has been suggested any such effects could be mediated through multiple mechanisms that may include antioxidant activity preventing oxidative damage to DNA and inhibition of lipid peroxidation, stimulation of gap junction communication, effects on cell transformation and differentiation, inhibition of cell proliferation and oncogene expression, effects on immune function and inhibition of endogenous formation of

carcinogens (Cooper et al 1999). Additional mechanisms may include the metabolic conversion of beta-carotene to retinoids, which may in turn modulate the gene expression of factors linked to differentiation and cell proliferation. The modulation of enzymes that metabolise xenobiotics and inhibition of endogenous cholesterol synthesis by modulation of HMG-CoA reductase expression may also lead to a possible inhibition of cell proliferation and malignant transformation (PDRHealth 2005).

None of these mechanisms has been conclusively found to contribute to preventing cancer in vivo and there is ongoing debate as to the role of beta-carotene in cancer prevention (Cooper et al 1999, Patrick 2000). This debate has been further fuelled by the findings of two large intervention studies, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (the 'Finnish study'; Heinonen et al 1994) and the Carotene and Retinol Efficacy Trial (CARET; Omenn et al 1996a), which found a significantly increased risk of lung cancer in high-risk individuals supplemented with synthetic beta-carotene (see Clinical Use for more details).

The mixed findings from beta-carotene intervention trials has produced much controversy in the scientific literature and although it has been suggested that there is no known biologically plausible explanation for the finding, a number of hypotheses have been put forward (Bendich 2004).

It has been suggested that the dose, duration of study and/or choice of synthetic all-*trans*- beta-carotene may have been inappropriate to use in the intervention trials (Cooper et al 1999) and that supplementation with monotherapy using synthetic beta-carotene may have inhibited the absorption of other carotenoids (Woodall et al 1996). It is also suggested that, although beta-carotene may be effective in the prevention of lung cancer before or during the phases of initiation and early promotion of cancer, the intervention studies that involved heavy smokers and asbestos workers probably included individuals in whom these processes were already initiated (Bendich 2004).

Additional possible explanations for the observed increase in lung cancer risk with beta-carotene supplementation include possible pro-oxidant activity of beta-carotene or its oxidative metabolites in the high oxygen environment of smokers' lungs, with oxidised beta-carotene metabolites inducing carcinogen-bioactivating enzymes, facilitating the binding of metabolites to DNA, enhancing retinoic acid metabolism by P450 enzyme induction and acting as pro-oxidants, causing damage to DNA (Russell 2002), as well as inhibition of retinoid signalling (Wang et al 1999). It is further suggested that the beta-carotene molecule may become unstable due to a low level of antioxidants, such as ascorbic acid, being present in smokers compared with non-

smokers (Bohm et al 1997), together with significant oxidative stress also being in present in smokers who consume high amounts of alcohol (PDRHealth 2005).

It has further been suggested that beta-carotene may increase lung cancer risk in smokers because of its ability to improve lung function. Thus smokers supplemented with beta-carotene may have increased lung capacity, resulting in deeper breathing of carcinogens and other oxidants. It is also suggested that beta-carotene may improve smokers' immune responses and thus reduce the number of days they suffered from upper respiratory tract infections and enabling them to smoke more (Bendich 2004).

The suggestion that beta-carotene may have pro-oxidant effects is supported by an in vitro study showing that although cell viability and DNA integrity was not affected by beta-carotene, it was significantly and dose-dependently decreased by oxidised beta-carotene (Yeh & Hu 2001). There was a dose-dependent increase of beta-carotene cleavage products, together with increasing genotoxicity in vitro when beta-carotene was supplemented during oxidative stress induced by hypoxia/reoxygenation (Alija et al 2004, 2005). Carotenoid cleavage products have also been found to impair mitochondrial function and increase oxidative stress in vitro (Siems et al 2002, 2005), as well as produce a booster effect on phase I carcinogen-bioactivating enzymes in the rat lung (Paolini et al 1999). Beta-carotene has also been shown to be degraded by stimulated polymorphonuclear leukocytes in vitro, producing highly reactive and potentially toxic cleavage products (Sommerburg et al 2003). These pro-oxidant effects have not been conclusively demonstrated in vivo and beta-carotene at a dose of 50 mg/day for several years was not found to have pro-oxidant effects in either smokers or non-smokers, as measured by urinary excretion of F2-isoprostanes (Mayne et al 2004).

CARDIOVASCULAR PROTECTION

There are a number of ways in which beta-carotene may act to protect against cardiovascular disease. Free radical scavenging may prevent cellular transformations leading to atherosclerosis and protection of LDL oxidation may further act to protect against atheroma formation (Halliwell 1993). Other mechanisms proposed for the possible favourable effect of antioxidants include an increase of HDL cholesterol and the preservation of endothelial functions (Tavani & La Vecchia 1999). Patients with acute myocardial infarction (AMI) have also been shown to have reduced plasma antioxidant vitamins and enhanced lipid peroxidation upon thrombolysis, suggesting that antioxidants may reduce free radical generation processes in reperfusion injury in AMI (Levy et al 1998).

In an animal study, atherosclerosis was inhibited in rabbits fed a high-cholesterol diet supplemented with all-*trans* beta-carotene. In that study all-*trans* beta-carotene

was undetectable in LDL, although tissue levels of retinyl palmitate were increased, suggesting that any anti-atherogenic effect is separate from the resistance of LDL to oxidation and that metabolites of beta-carotene may inhibit atherosclerosis in hypercholesterolaemic rabbits, possibly via stereospecific interactions with retinoic acid receptors in the artery wall (Shaish et al 1995). A randomised, placebo-controlled trial in 149 male smokers taking 20 mg/day of beta-carotene for 14 weeks, however, found no influence on haemostatic measures, suggesting that it is unlikely that cardiovascular protection from beta-carotene is via an effect on haemostasis (Van Poppel et al 1995).

OTHER ACTIONS

An animal study found that rats supplemented with beta-carotene-rich algae had improved reproduction and body growth with a markedly lower still-birth rate, a higher litter size or rearing rate, and enhanced body growth in male offspring (Nagasawa et al 1989).

CLINICAL USE

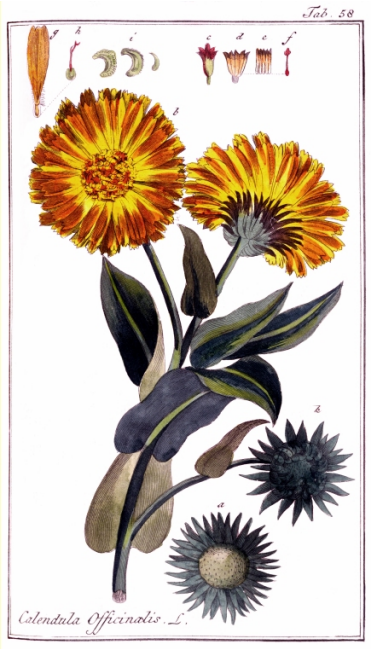
VITAMIN A DEFICIENCY

In a series of large, double-blind, cluster randomised, placebo-controlled field trials involving as many as 44,000 Nepalese women, weekly supplementation with 42 mg of *trans*-beta-carotene was found to reduce the prevalence of selected illness symptoms such as loose stools, night blindness and symptoms of high fever during late pregnancy, at the time of birth and during 6 months postpartum (Christian et al 2000a). Beta-carotene was further found to reduce maternal, but not infant, mortality among smokers and non-smokers by approximately 50%, with a protective effect becoming evident after 18 months of supplementation (Christian et al 2004, West et al 1999). Beta-carotene supplementation has also been found to reduce the 5-fold increased risk of infection-related mortality in women who were night-blind because of vitamin A deficiency (Christian et al 2000b).

These studies are contrasted by one that found an association between self-reports of poor night vision and beta-carotene consumption in women involved in the Blue Mountain Eye Study in which the authors concluded that perceived poor night vision caused an increase in carrot consumption in women (Smith et al 1999).

CANCER PREVENTION

There are at least 35 observational epidemiological studies, including prospective cohort and case-controlled studies, involving smoking and non-smoking men and women from diverse regions of the world, which have consistently found a positive association between dietary or serum beta-carotene levels and reduced risk of cancer

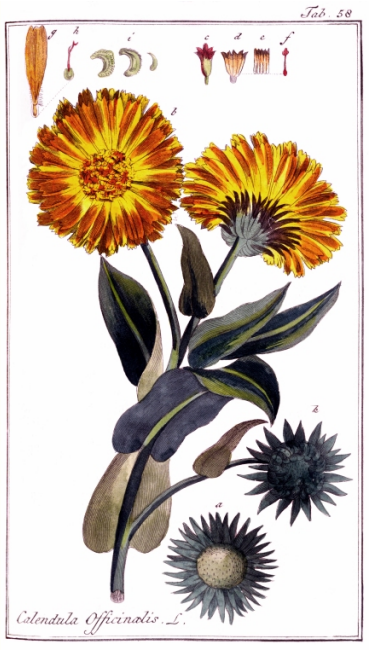


(Cooper et al 1999). This association, however, does not necessarily imply a causal link, because it may be an association between beta-carotene ingestion and other dietary or lifestyle factors (Peto et al 1981). Beta-carotene intake is linked to a variety of healthy dietary and lifestyle factors, as well as being highly correlated with the intake of many other protective dietary phytochemicals and nutrients (Cooper et al 1999).

The link between beta-carotene levels and cancer prevention in epidemiological studies is contrasted with the findings of two large intervention trials that reported increased lung cancer risk with synthetic beta-carotene supplementation (Heinonen et al 1994, Omenn et al 1996b).

The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, also known as the 'Finnish study', was the first large intervention trial to test the hypothesis that beta-carotene reduces the risk of lung cancer. This double-blind, placebo-controlled primary-prevention trial involved 29,133 male smokers, 50–69 years of age, who were randomised to receive daily supplementation with alpha-tocopherol (50 mg/day) alone, synthetic (all-*trans*) beta-carotene (20 mg/day) alone, or both. After a follow-up period of 5–8 years the results suggested that there was an unexpected 18% increase in the incidence of lung cancer with an associated 8% higher mortality among those who received beta-carotene (Heinonen et al 1994). Subgroup analysis revealed that the increased risk with beta-carotene supplementation was only greater for those who smoked at least 20 cigarettes per day, with the risk of those who smoked 5–19 cigarettes/day being no greater than the placebo group. An increased risk was also observed for those who consumed more than 11 g/day alcohol compared with those with a lower intake (Albanes et al 1996). Further analysis found no effect of beta-carotene supplementation on the risk of pancreatic cancer (Rautalahti et al 1999), colorectal cancer (Albanes et al 2000), urothelial or renal cell cancer (Virtamo et al 2000), or gastric cancer (Malila et al 2002).

The Carotene and Retinol Efficacy Trial (CARET) tested the effect of synthetic, all-*trans* beta-carotene (30 mg) and retinyl palmitate (25,000 IU) on the incidence of lung cancer, other cancers, and death in 18,314 participants who were at high risk for lung cancer because of a history of heavy smoking or asbestos exposure. CARET was stopped ahead of schedule in January 1996 because participants who were randomly assigned to receive the active intervention were unexpectedly found to have a 28% increase in incidence of lung cancer, a 17% increase in incidence of death and a higher rate of cardiovascular disease mortality compared with participants in the placebo group (Omenn et al 1996a). Further analysis revealed results similar to the



ATBC study, with the increased risk of lung cancer being greatest for heavy smokers and those with the highest alcohol intake, while former smokers were found to have a similar risk to those taking placebo (Omenn et al 1996a).

The finding of an increased risk of lung cancer in smokers taking beta-carotene in the ATBC and CARET studies is consistent with a number of other studies. A prospective cohort study of 59,910 French women found that self-reported supplemental use of beta-carotene was directly associated with double the risk of cancers among smokers, yet dietary beta-carotene intake was associated with less than half the risk of tobacco-related cancers among non-smokers in a statistically significant dose-dependent relationship (Touvier et al 2005). Similarly, the results of a case-control study of 362 adenoma cases and 427 polyp-free controls suggest a protective effect for colon cancer with beta-carotene in non-smokers and an adverse effect in smokers (Senesse et al 2005). Alcohol intake and cigarette smoking were also observed to modify the effect of beta-carotene supplementation on the risk of colorectal adenoma recurrence in another double-blind, placebo-controlled clinical trial involving 864 patients randomised to receive either beta-carotene (25 mg), vitamin C (1000 mg) or vitamin E (400 mg), beta-carotene with vitamins C and E, or placebo, which after 4 years found no evidence that supplementation reduced the incidence of adenomas (Greenberg et al 1994). Subgroup analysis from this study, however, found that beta-carotene supplementation was associated with a marked decrease in the risk of one or more recurrent adenomas among subjects who neither smoked cigarettes nor drank alcohol, but conferred a modest increase in the risk of recurrence among those who either smoked or drank alcohol and double the risk for those who both smoked and drank (Baron et al 2003).

The results of these studies are contrasted with those from the Physicians' Health Study, which found no effect of beta-carotene supplementation on cancer risk in smokers or non-smokers. This RCT of 50 mg of synthetic beta-carotene given on alternate days involved 22,071 US male physicians, 11% of whom were smokers. After more than 12 years of follow-up, no overall effect on cancer incidence was evident with beta-carotene supplementation (Hennekens et al 1996) and no benefit or harm was observed for lung, prostate or colon cancer (Cook et al 2000) or for squamous cell carcinoma (Frieling et al 2000). Subgroup analysis of this study population revealed that total cancer was modestly reduced with supplementation among those aged more than 70 years, and total cancers and colon cancer was reduced in those who drank alcohol daily (Cook et al 2000). Total cancers and prostate cancer were also reduced in those in the highest BMI quartile (Cook et al 2000) and those with low baseline beta-carotene levels (Cook et al 1999), while those

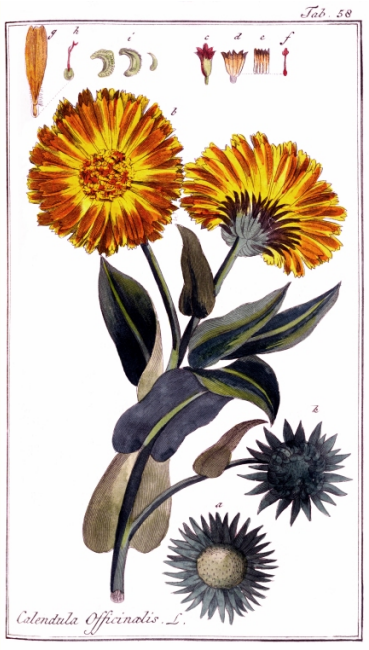
with high baseline levels had a non-significant increased risk of prostate cancer with beta-carotene supplementation (Cook et al 1999).

Similar to the results of the Physicians' Health Study the results of the Women's Health Study, which involved 39,876 women supplemented with 50 mg of beta-carotene on alternate days for 2 years, found no benefit or harm from beta-carotene supplementation on the incidence of cancer or cardiovascular disease in apparently healthy women, with no benefit or harm also being observed for the 13% of women who were smokers at baseline (Lee et al 1999).

In contrast to these results, a RCT performed on a poorly nourished population found a lower cancer incidence with beta-carotene supplementation. This study involved 29,584 adults aged between 40 and 69 years from Linxian County, China, which has one of the world's highest rates of oesophageal/gastric cardia cancer and a persistently low intake of several micronutrients. In this study people were randomised to receive retinol and zinc, riboflavin and niacin, vitamin C and molybdenum, or beta-carotene, vitamin E, and selenium at doses that ranged from 1- to 2-fold the US RDI for a period of 6 years. Results revealed a significantly lower total mortality among those receiving supplementation with beta-carotene, vitamin E, and selenium, mainly attributable to lower cancer rates, especially stomach cancer (Blot et al 1993).

Possible reasons for the mixed results The mixed results from the beta-carotene intervention studies have created significant debate. The results of a review of carotenoid research by the International Agency for Research on Cancer suggest there is a lack of cancer-preventive activity for beta-carotene when it is used as a supplement at high doses (Vainio & Rautalahti 1998). This is supported by a more recent study that examined the relationship between dietary beta-carotene and lung cancer using pooled data from seven cohort studies that involved 399,765 participants and 3155 lung cancer cases. This study found that dietary beta-carotene intake was not associated with increased or decreased lung cancer risk in never, past, or current smokers (Mannisto et al 2004).

The mixed results from beta-carotene intervention studies may also be a reflection of a difference between natural and synthetic beta-carotene, as the negative intervention studies have all used synthetic rather than natural beta-carotene. These studies, however, do provide consistent evidence for a link between dietary and serum beta-carotene levels and reduced cancer risk. Even in the studies that found an adverse effect of beta-carotene supplementation, study participants with the highest intake and serum concentrations of beta-carotene at baseline developed fewer subsequent lung cancers, regardless of their intervention assignment (Albanes 1999, Holick et al 2002). therefore, although monotherapy with synthetic beta-carotene is



no longer generally recommended, there continues to be a consistent call for an increased consumption of beta-carotene-containing foods to assist in prevention of cancer (Mayne 1996, Pryor et al 2000).

Oral leucoplakia Beta-carotene consumption has been found to be inversely associated with precancerous lesions of the oral cavity in tobacco users (Gupta et al 1999) and it is suggested that there is a significant role for antioxidant nutrients in preventing oral cancer (Garewal & Schantz 1995). This is supported by the findings of multiple clinical trials in which beta-carotene and vitamin E have been shown to produce regression of oral leucoplakia, a premalignant lesion for oral cancer (Garewal 1994).

In a more recent, double-blind, randomised controlled trial involving 160 people, 360 mg/week of beta-carotene for 12 months was found to induce regression in oral precancerous lesions with half of the responders relapsing after ceasing supplementation. Similarly, another multicentre, double-blind, placebo-controlled trial found improvement in dysplasia with 60 mg/day of beta-carotene for 6 months (Garewal et al 1999).

These studies are contrasted with a subgroup analysis involving 409 white male cigarette smokers from the ATBC Study that suggested that beta-carotene supplementation does not play an essential role in preventing oral mucosal changes in smokers (Liede et al 1998).

CARDIOVASCULAR DISEASE

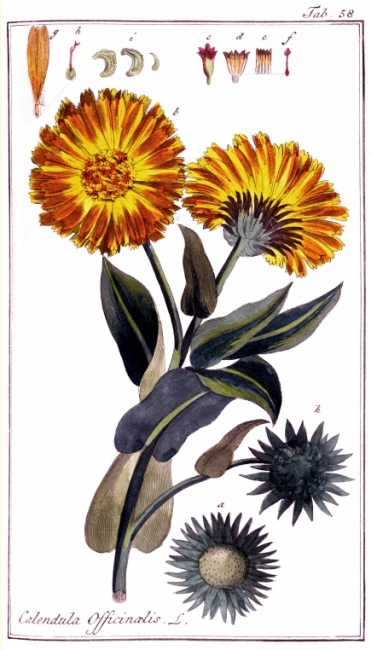
Epidemiological studies support the idea that a diet rich in high carotenoid containing foods is associated with a reduced risk of heart disease (Kritchevsky 1999). A review of observational and intervention studies on beta-carotene and the risk of coronary heart disease found that seven cohort studies (Gaziano et al 1995b, Gey et al 1993, Knekt et al 1994, Manson et al 1991, Morris et al 1994, Rimm et al 1993, Street et al 1994) reported relative risks between 0.27 and 0.78 for high serum beta-carotene levels or high dietary intake and that this was supported by case-control studies (Bobak et al 1998, Bolton-Smith et al 1992, Kardinaal et al 1993, Torun et al 1994, Tavani et al 1997) that reported odds ratios between 0.37 and 0.71, with a possible stronger protection for current smokers (Tavani & La Vecchia 1999). These results contrast with those of four more recent cohort studies (Knekt et al 1994, Kushi et al 1996, Pandey et al 1995, Todd et al 1995) and five large RCTs (Buring et al 1996, Hennekens et al 1996a, Lee et al 1999, Redlich et al 1999, Vlot et al 1995) that have not reported any significant prevention of cardiovascular disease with beta-carotene supplementation.

The final results of the Physicians' Health Study (see Cancer Prevention above) indicated that beta-carotene supplementation had no significant benefit or harm on cancer or cardiovascular disease during more than 12 years of treatment (Hennekens et al 1996). Similarly, the results of the Women's Health Study, which involved 39,876 women aged 45 years or older, found that beta-carotene supplementation of 50 mg on alternate days did not influence cardiovascular disease after 2 years of supplementation and 2 years of further follow-up. Subgroup analysis revealed an apparent benefit of beta-carotene supplementation on subsequent vascular events among 333 men with prior angina or revascularisation (Christen et al 2000).

In contrast, analysis of the data from the ATBC cancer prevention study, which involved 23,144 male smokers, found that beta-carotene supplementation slightly increased the risk of angina (Rapola et al 1996) and intracerebral haemorrhage while having no overall effect on the risk of stroke (Leppala et al 2000a,b), abdominal aortic aneurysm (Tornwall et al 2001), or symptoms and progression of intermittent claudication (Tornwall et al 1999). Beta-carotene, however, was found to decrease the risk of cerebral infarction modestly among a subgroup with greater alcohol consumption (Leppala et al 2000a,b). In a 6-year post-intervention follow-up study, beta-carotene was found to increase the risk of first-ever myocardial infarction while continuing to have no overall effect on the incidence of stroke (Tornwall et al 2004). An analysis of 52 men from the CARET Study concluded that there was no significant effect on total, HDL- or LDL-cholesterol levels that could account for the observed increase risk of cardiovascular disease observed in this study (Redlich et al 1999).

A pooled analysis of four randomised trials of beta-carotene therapy ranging from 20 mg to 50 mg involving 90,054 patients found beta-carotene supplementation to be associated with a significant increase in all-cause mortality and cardiovascular death in patients at risk for coronary disease, with the increased risk being strongest in smokers. A further meta-analysis of eight randomised trials involving 138,113 patients found that supplementation with 15–50 mg of beta-carotene was associated with a small but significant increase in all-cause mortality and a slight increase in cardiovascular death (Vivekananthan et al 2003).

The apparent discrepancy between the findings of observational and intervention studies may be due to several factors, including the length and nature of the intervention (Tavani & La Vecchia 1999). For example the intervention trials involved supplementation with synthetic beta-carotene in isolation or with other single nutrients, whereas the observational studies involved the consumption of beta-carotene-rich foods containing a range of additional antioxidant vitamins, phytonutrients and micronutrients.



PHOTOPROTECTION

Excessive exposure to solar radiation, especially UVA (320–400 nm) and UVB (290–320 nm), may induce UV-carcinogenesis and erythema in the skin (Lee et al 2000). There have been a number of controlled clinical trials that have demonstrated that supplementation with beta-carotene alone, or in combination with other antioxidants, can reduce UV-induced erythema (Gollnick et al 1996, Heinrich et al 1998, 2003, Lee et al 2000, Mathews-Roth et al 1972, Sies & Stahl 2004, Stahl et al 2000). These studies suggest that at least 8–10 weeks of supplementation are required before protection against erythema becomes evident and that doses of at least 24 mg/day of beta-carotene are required (Sies & Stahl 2004).

In uncontrolled studies, a protective effect against UV-induced erythema was observed after supplementation with 180 mg of beta-carotene for 10 weeks (Mathews-Roth et al 1972) and 50 mg for 6 weeks (Heinrich et al 1998). These results are supported by more rigorous studies that have shown photoprotective activity with smaller doses of beta-carotene. A RCT involving supplementation with 30 mg of natural beta-carotene for 8 weeks, with the dose increasing to 60 mg for a further 8 weeks and then to 90 mg for another 8 weeks, found a dose-dependent reduction in UVA- and UVB-induced erythema (Lee et al 2000). In another RCT, supplementation for 12 weeks with 24 mg/day of natural beta-carotene or a natural carotenoid mix supplying similar amounts of beta-carotene, lutein and lycopene also significantly reduced UV-induced erythema (Heinrich et al 2003). Similarly, a randomised trial found that supplementation with 25 mg of natural algal beta-carotene for 12 weeks significantly reduced UV-induced erythema, with the effect enhanced by the addition of alpha-tocopherol (Stahl et al 2000). Yet another trial suggests that the photoprotective action of beta-carotene enhances the action of topical sunscreens. In this randomised, placebo-controlled, double-blind study of 20 healthy young females, 30 mg/day beta-carotene for 10 weeks reduced UV induced erythema and protected against UV-induced drop in serum beta-carotene levels and UV-induced reduction in Langerhans cells, with beta-carotene combined with topical sunscreens being more effective than sunscreen cream alone (Gollnick et al 1996). Another controlled study found a protective effect against photo-immunosuppression, with 30 mg/day of beta-carotene for 4 weeks protecting against UV-induced suppression of delayed-type hypersensitivity in young men (Fuller et al 1992).

It has been suggested that the duration of supplementation may be more important than the dose, as the studies that have not demonstrated significant reduction in UV-induced erythema have all involved supplementation of relatively short duration (Lee et al 2000). No photoprotective effects of beta-carotene were

observed with supplementation with 90 mg for 3 weeks (Garmyn et al 1995), 150 mg/day for 4 weeks (Wolf et al 1988) or 15 mg/day for 8 weeks (McArdle et al 2004).

It has also been suggested that a combination of antioxidants may be more effective than the sum of the separate components because the skin's antioxidant defence system appears to involve an intricate connection between individual antioxidants (Steenvoorden & Beijersbergen van Henegouwen 1997). This is supported by a randomised, double-blind, placebo-controlled study that found that short-term (2-week) supplementation with an anti-oxidative combination containing beta-carotene and lycopene, as well as vitamins C and E, selenium and proanthocyanidins, significantly decreases the UV-induced expression of matrix metallo-proteinases, with a non-statistically significant trend towards reduced minimal erythema dose (Greul et al 2002).

Although beta-carotene supplementation may provide some degree of protection against sunburn, the effect is modest and there is still some debate about its use for routine photoprotection (Biesalski & Obermueller-Jevic 2001, Fuchs 1998). However, beta-carotene is likely to be clinically useful in providing photoprotection for people with specific photosensitivity. High doses (180 mg/day, up to 300 mg/day) have been shown to reduce photosensitivity in people with the genetic condition 'erythropoietic protoporphyria' in a number of case series (Mathews-Roth et al 1970, 1974, Thomsen et al 1979), and the results of a double-blind RCT suggest that beta-carotene may be useful in conjunction with canthaxanthin in preventing polymorphous light eruptions (Suhonen & Plosila 1981).

The ability of beta-carotene to protect against UV-induced erythema and photosensitivity does not appear to extend to protecting against non-melanotic skin cancer. In a randomised placebo-controlled trial involving 1805 subjects with recent non-melanotic skin cancer, daily supplementation with 50 mg beta-carotene for 5 years had no effect on the incidence of new or recurring non-melanotic skin cancers, with similar results for those with low baseline beta-carotene levels and smokers (Greenberg et al 1990). Similarly, in another randomised, placebo-controlled trial of 1621 adults aged 25–74 years daily supplementation with 30 mg beta-carotene did not reduce the development of solar keratoses over the 3-year study period (Darlington et al 2003, Green et al 1999). These results are supported by an analysis of data from the Physicians' Health Study that found no effect of 12 years of beta-carotene supplementation on the incidence of non-melanotic skin cancer (Frieling et al 2000), as well as a subgroup analysis from this study that found no effect on non-melanotic skin cancer in men with low baseline plasma beta-carotene

levels (Schaumberg et al 2004). In a further randomised, placebo-controlled study of 62 patients with numerous atypical naevi, 25 mg of beta-carotene given twice daily for 36 months resulted in a non-significant reduction in newly developed naevi, with a significant reduction observed for the lower arm and feet but not for 10 other body sites (Bayerl et al 2003).

OXIDATIVE STRESS

There are a number of human studies that suggest that supplementation with beta-carotene can reduce the oxidative stress associated with different pathological conditions or stressors such as intense exercise or radiation. Supplementation with beta-carotene (30 mg/day) and vitamin E (500 mg/day) for 90 days has been found to enhance the antioxidant enzyme activity of superoxide dismutase and catalase in the neutrophils of sportsmen (Tauler et al 2002). Similarly, in a study of 13 professional basketball players, 35 days of antioxidant supplementation with 600 mg alpha-tocopherol, 1000 mg ascorbic acid and 32 mg beta-carotene led to a significant decrease in plasma lipid peroxides, with a significant decrease of lactate dehydrogenase serum activity and a non-significant increase in the anabolic/catabolic balance being observed during a 24-hour recuperation time after exercise (Schroder et al 2001).

The results of an Israeli study of 709 children exposed to radiation from the Chernobyl accident suggest that natural algae-derived beta-carotene may act as an in vivo lipophilic antioxidant or radioprotector. This study found that exposed children had increased susceptibility to lipid oxidation and that supplementation with 40 mg of natural 9-*cis* and all-*trans* equal isomer mixture beta-carotene twice daily for a period of 3 months reduced plasma markers of lipid oxidation (Ben-Amotz et al 1998).

A double-blind study has also found that beta-carotene supplementation reduced the severity, but not the incidence, of post-endoscopy pancreatitis which is thought to be mediated by oxidative stress (Lavy et al 2004). A further small, controlled trial involving 15 patients with RA found that 3 weeks of supplementation with natural beta-carotene resulted in a significant increase in plasma antioxidants, but did not change indicators of disease (Kacsur et al 2002).

Further evidence for beta-carotene's ability to reduce oxidative stress comes from a study of conditioning therapy preceding bone marrow transplantation. This therapy consists of high-dose chemotherapy and total body irradiation and has acute and delayed toxic effects that are considered to be due to peroxidation processes and exhaustion of antioxidants. Supplementation with 45 mg beta-carotene, 825 mg alpha-tocopherol and 450 mg ascorbic acid daily for 3 weeks, however, was found to

increase serum antioxidant levels and reduce the post-conditioning rise in plasma lipid hydroperoxides in patients receiving the conditioning therapy prior to transplantation (Clemens et al 1997). Similarly, a combined antioxidant supplement increased plasma antioxidant levels and antioxidative enzyme activities, and lowered LDL lipid peroxides in male hyperlipidaemic smokers, although higher doses of the supplement did not have an additive effect (Chao et al 2002).

These studies are contrasted by two small studies that showed no change in oxidative stress in healthy subjects after beta-carotene supplementation. Normal concentrations of carotenoids in plasma and tissues were not correlated with clinical markers of antioxidant and oxidative stress in a study of 79 healthy volunteers (Borel et al 1998), and a placebo-controlled, single-blind study found that daily supplementation with 15 mg of beta-carotene for 3 months did not significantly improve biomarkers of oxidative stress in healthy males (Hininger et al 2001).

IMMUNE FUNCTION

In a study of 652 non-institutionalised elderly people, the incidence of acute respiratory infections was reduced for those with the highest plasma levels, suggesting that beta-carotene may improve the immune response and result in decreased risk of infectious diseases (van der Horst-Graat et al 2004).

These findings are contrasted by analyses of male smokers who participated in the ATBC study, which found that supplementation with synthetic beta-carotene had no overall effect on the risk of hospital-treated pneumonia or the incidence of the common cold (Hemila et al 2002, 2004), but instead increased the risk of colds in subjects carrying out heavy exercise at leisure but not at work (Hemila et al 2003).

ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Studies have shown increased oxidative stress in patients with chronic airflow limitation (Ochs-Balcom et al 2005) and accumulating evidence suggests that dietary antioxidant vitamins are positively associated with lung function (Schunemann et al 2001), with serum beta-carotene levels being associated with improved FEV_1 (Grievink et al 2000). Thus it has been suggested that antioxidant protection is important for protecting the lungs against high oxygen levels and that oxidative stress may contribute to respiratory pathology such as asthma (Rahman et al 2006, Wood et al 2003).

This is supported by the finding of a significant association between serum vitamin C, vitamin E, beta-cryptoxanthin, lutein/zeaxanthin, beta-carotene, and retinol with FEV_1 (Schunemann et al 2001), together with a study involving a subset from the CARET study of 816 asbestos-exposed men with a high rate of current and former

cigarette smoking, which found that serum beta-carotene was associated with a significant improvement in FEV_1 and FVC (Chuwers et al 1997).

Studies on the correlation between serum beta-carotene levels and asthma, however, have produced mixed results. One small study of 15 asthmatic subjects and 16 healthy controls found that despite similar dietary intake, whole blood levels of total carotenoids, including beta-carotene, lycopene, lutein, beta-cryptoxanthin and alpha-carotene, were significantly lower in the asthmatics with no differences in plasma or sputum carotenoid levels (Wood et al 2005). Another small study found that beta-carotene, alpha-tocopherol and ascorbic acid were significantly lower in asthmatics at remission compared to controls and that beta-carotene was significantly lower and lipid peroxidation products significantly higher during attacks than periods of remission (Kalayci et al 2000). A further small study found that increased dietary consumption of beta-carotene was associated with better QOL (Moreira et al 2004).

These results are supported by an analysis of 7505 youths (4–16 years) from the Third National Health and Nutrition Examination Survey, which found that increased serum beta-carotene was associated with reduced asthma prevalence (Rubin et al 2004). Another analysis involving 4093 children from the same study, 9.7% of whom reported a diagnosis of asthma, found that asthma diagnosis was associated with lower levels of serum beta-carotene, vitamin C, alpha-carotene and beta-cryptoxanthin (Harik-Khan et al 2004).

In contrast to these findings, a much larger study involving 771 persons with self-reported asthma, 352 persons with former asthma and 15,418 persons without asthma, asthma status was not significantly associated with serum antioxidant concentrations (Ford et al 2004). Similarly, in a study of 15 mild asthmatics and 15 age-and sex-matched controls, oxidative stress was found to be increased in the asthmatics, with no difference in plasma dietary antioxidant vitamins (Wood et al 2000).

Although the role of antioxidant vitamins in prevention and/or treatment of asthma remains to be determined (Kalayci et al 2000), the results of one intervention study suggest that there may be a role for beta-carotene in exercise-induced asthma. This randomised, double-blind, placebo-controlled trial, involving 38 subjects with proven exercise-induced asthma, found that supplementation with 64 mg/day of natural algal beta-carotene for 1 week protected against post-exercise reduction in FEV_1 (Neuman et al 1999).

CYSTIC FIBROSIS

Cystic fibrosis (CF) is characterised by exocrine pancreatic insufficiency and reduced absorption of fat-soluble vitamins, as well as chronic lung inflammation and an associated increased oxygen free radical generation. Patients with CF have been found to have lower levels of beta-carotene and it has been suggested that they would benefit from beta-carotene supplementation (Cobanoglu et al 2002, Walkowiak et al 2004). This suggestion is supported by a study of 52 patients with CF that found a statistically significant correlation between serum beta-carotene and the clinical course of the disease as indicated by faecal elastase-1 and FEV_1 (Walkowiak et al 2004), together with a study showing that the plasma levels of beta-carotene and vitamin E increased and the plasma levels of TNF-alpha and malondialdehyde decreased after 6 months of beta-carotene supplementation (Cobanoglu et al 2002). This is further supported by a RCT of 24 CF patients supplemented with up to 50 mg/day beta-carotene for 12 weeks and 10 mg/day beta-carotene for a further 12 weeks, which found a significant decrease in oxidative stress, correction of total antioxidative capacity and improved pulmonary response to treatment in the supplemented group (Rust et al 2000).

CATARACTS

Although a high intake of beta-carotene containing foods has been associated with the prevention of cataracts, the role of supplementation is uncertain. An assessment of dietary beta-carotene intake in a subgroup of 472 non-diabetic women, aged 53–73 years, who participated in the Nurses' Health Study found that the odds of posterior subcapsular cataracts was 72% lower in those with the highest intakes of beta-carotene who had never smoked, whereas beta-carotene intake and cataract risk were not associated in current or past smokers (Taylor et al 2002). This finding is contrasted with findings from intervention studies that have found that beta-carotene may help prevent cataracts in smokers (Christen et al 2003, 2004). Two years of beta-carotene treatment was found to have no large beneficial or harmful effect on the development of cataract in a randomised, double-masked, placebo-controlled trial of 39,876 female health professionals aged 45 years or older who participated in the Women's Health Study, although a subgroup analysis suggests a possible beneficial effect in smokers (Christen et al 2004). Similarly, a randomised, double-masked, placebo-controlled trial of 22,071 male physicians aged 40–84 years found that supplementation with 50 mg of beta-carotene on alternate days for 12 years did not reduce the overall incidence of cataracts or cataract extraction; however, in a subgroup of smokers the risk of cataract was reduced by approximately 25% (Christen et al 2003).

In two randomised, double-masked trials involving 5390 nutritionally deprived subjects in Linxian, China, supplementation with selenium, alpha-tocopherol and beta-carotene for 5–6 years was found to significantly reduce the prevalence of nuclear but not cortical cataracts in older subjects (Sperduto et al 1993). This is contrasted with the finding that 500 mg of vitamin C, 400 IU of vitamin E and 15 mg of beta-carotene had no apparent effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss in a relatively well-nourished older adult cohort of 4629 people aged from 55 to 80 years who participated in the Age-Related Eye Disease Study (AREDS) (Kassoff et al 2001).

AGE-RELATED MACULA DEGENERATION

A high intake of beta-carotene-containing foods has been associated with the prevention of ARMD and observational and experimental data suggest that carotenoid supplements may delay progression of both ARMD and vision loss. This is supported by the findings from the ARED Study, an 11-centre, double-masked clinical trial involving 3640 participants with ARMD that found supplementation with vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg and zinc 80 mg for 6 years significantly reduced the development of advanced ARMD and moderate visual acuity loss (Kassoff et al 2001). Although beta-carotene and other nutrients may have been found to be beneficial for preventing ARMD, the carotenoids lutein and zeaxanthin appear to provide the most protection (see Lutein/zeaxanthin monograph).

ERYTHROPOIETIC PROTOPORPHYRIA AND PHOTOSENSITIVITY

Studies in bacteria, animals and humans have demonstrated that carotenoid pigments can prevent or lessen photosensitivity by endogenous photosensitisers, such as chlorophyll or porphyrins, as well as by exogenous photosensitisers (Mathews-Roth 1993) and high doses of beta-carotene (between 180 and 300 mg/day) have been used to effectively prevent or lessen photosensitivity in most patients with erythropoietic protoporphyria and in some patients with other photosensitivity diseases such as solar urticaria, hydroa aestivale, porphyria cutanea tarda, actinic reticuloid (Mathews-Roth 1986, 1987, 1990, Mathews-Roth et al 1977).

DOSAGE RANGE

Consumption of the recommended five or more servings of fruits and vegetables per day provides between 3 and 6 mg of beta-carotene. Supplemental intake of beta-carotene ranges from 3 to 30 mg/day, although medicinal doses to treat erythropoietic protoporphyria or prevent a reaction to sun in patients with polymorphous light eruption range from 30 to 300 mg/day (PDRHealth 2005). The dose

required to provide photoprotection is greater than 24 mg/day for more than 2 months (Sies & Stahl 2004).

To enhance absorption, supplementation should be taken with meals.

TOXICITY

Beta-carotene is readily converted into vitamin A when required by the body and is considered to be non-toxic, even when given in doses as high as 300 mg/day (Mathews-Roth 1990a, 1993).

A review of the literature on adverse effects of carotenoids on human and animal development suggests that beta-carotene does not have any genotoxic affects (Mathews-Roth 1988) and a toxicity study performed on rats suggests a no-observed-adverse-effect-level (NOAEL) is at a dietary level of at least 5.0% or more than 3000 mg/kg/day (Nabae et al 2005). Beta-carotene overdose is not reported in the literature.

ADVERSE REACTIONS

At doses greater than 30 mg/day beta-carotene may cause an orange-yellow colouration of the skin (carotenodermia), which is usually seen first as yellowness of the palms and soles. This condition is harmless and reversible when intake ceases (Micozzi et al 1988). Carotenodermia is distinguished from jaundice by the absence of yellowed ocular sclerae. [For some people, this skin colouration is actually considered desirable (Mathews-Roth 1990b) and is utilised in tanning tablets to produce a natural-looking skin tan (DerMarderosian & Beutler 2002).]

At present it is unclear if there is a true link between increased lung cancer risk and long-term beta-carotene supplementation in smokers, because supplementation studies with synthetic beta-carotene have produced mixed results, with two studies finding an increased lung cancer risk with heavy smokers or those with high asbestos exposure (Group 1994, Heinonen et al 1994, Omenn et al 1996b) and other studies finding either no effect (Hennekens et al 1996, Lee et al 1999) or a protective effect (Blot et al 1993).

The association between increased lung cancer risk and beta-carotene has not been found with natural beta-carotene and there is no suggestion that heavy smokers should reduce their intake of beta-carotene rich foods. A review suggests that there is no evidence at present that consuming small amounts of supplemental beta-carotene in a multivitamin tablet at amounts that exist in foods (<6 mg) is unwise for any population (Pryor et al 2000).

SIGNIFICANT INTERACTIONS

DRUGS REDUCING FAT ABSORPTION (E.G. CHOLESTYRAMINE, ORLISTAT)

Drugs that reduce fat absorption, such as cholestyramine, colestipol and orlistat, may also reduce absorption of beta-carotene (PDRHealth 2005). This can be avoided by spacing the administration of these substances by at least 2 hours. Plant sterols have been found to reduce beta-carotene bioavailability by approximately 50% in normocholesterolaemic men (Richelle et al 2004).

FIBRATES

There may be a positive interaction between fibrate and natural beta-carotene, which has been found to significantly increase HDL-cholesterol levels in fibrate-treated mice and humans (Shaish et al 2006).

VALPROATE

Epileptic patients who gain weight with valproate therapy have been found to have reduced plasma concentrations of beta-carotene and other fat soluble antioxidant vitamins, which is reversible after valproate withdrawal (Verrotti et al 2004).

CONTRAINDICATIONS AND PRECAUTIONS

Heavy smokers should be advised not to take synthetic beta-carotene supplements for long periods of time.

PREGNANCY USE

Beta-carotene crosses the placenta. Adequate and well-controlled studies in humans have not been documented. No problems with pregnancy have been documented in women taking up to 30 milligrams of beta-carotene daily (Micromedex 2003).

PRACTICE POINTS/PATIENT COUNSELLING

- Beta-carotene is an antioxidant found in carrots and other fruit and vegetables, as well as in seaweed and algae. Together with other carotenoids, it is an effective marker for a diet rich in fruits and vegetables.
- Beta-carotene is fat soluble and should be consumed with meals.
- Although beta-carotene is converted into vitamin A in the body, unlike vitamin A it is considered non-toxic even in large doses.
- When supplementing with beta-carotene it is preferable to use supplements containing natural beta-carotene from the algae *Dunaliella salina* or palm oil rather than synthetic beta-carotene.
- Beta-carotene is a powerful pigment that contributes to the normal yellow component of skin and increased beta-carotene intake may protect from the effects of excessive exposure to sunlight and the symptoms of sunburn.

- Consumption of beta-carotene-rich food is associated with reduced risk of cancers, heart disease and eye disease; however, these benefits have not been found in large studies that have used synthetic beta-carotene with two studies finding an increase in lung cancer in heavy smokers and asbestos workers taking large doses of synthetic beta-carotene.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Beta-carotene supplementation will ensure you maintain adequate vitamin A levels, as well as possibly assist in preventing cancer and cardiovascular disease, help maintain a healthy immune system, prevent sunburn and photoageing of the skin, assist with asthma, and deal with oxidative stress.

When will it start to work?

It may take up to 2–3 months to see a benefit with UV protection, whereas other benefits may be observable over many years.

Are there any safety issues?

Beta-carotene is considered non-toxic. Large doses may cause a yellowing of the skin, but this is harmless and reversible.

REFERENCES

Abahusain MA et al. Retinol, A-tocopherol and carotenoids in diabetes. Eur J Clin Nutr 53(8) (1999): 630-5.

Alaluf S et al. Dietary carotenoids contribute to normal human skin color and UV photosensitivity. J Nutr 132(3) (2002): 399-403.

Albanes D. Beta-carotene and lung cancer: a case study. Am J Clin Nutr 69(6) (1999): 1345-50S.

Albanes D et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 88(21) (1996): 1560-70.

Albanes D et al. Effects of supplemental alpha-tocopherol and beta-carotene on colorectal cancer: results from a controlled trial (Finland). Cancer Causes Control 11(3) (2000): 197-205.

Alija AJ et al. Cytotoxic and genotoxic effects of beta-carotene breakdown products on primary rat hepatocytes. Carcinogenesis 25(5) (2004): 827-31.

Alija AJ et al.Cyto- and genotoxic potential of beta-carotene and cleavage products under oxidative stress. BioFactors 24(1-4) (2005): 159-63.

Allard JP et al. Effects of beta-carotene supplementation on lipid peroxidation in humans. Am J Clin Nutr 59(4) (1994): 884-90.

Baron JA et al. Neoplastic and antineoplastic effects of beta-carotene on colorectal adenoma recurrence: Results of a randomized trial. J Natl Cancer Inst 95(10) (2003): 717-22.

Bayerl C et al. A three-year randomized trial in patients with dysplastic naevi treated with oral beta-carotene. Acta Dermato-Venereol 83(4) (2003): 277-81.

Ben-Amotz A, Levy Y. Bioavailability of a natural isomer mixture compared with synthetic all-trans beta-carotene in human serum. Am J Clin Nutr 63(5) (1996): 729-34.

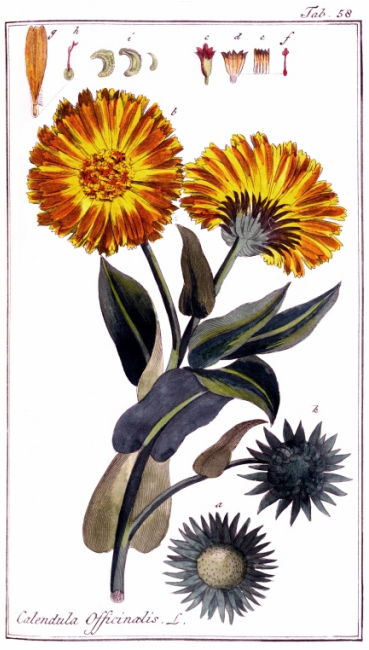
Ben-Amotz A et al. Bioavailability of a natural isomer mixture as compared with synthetic all-trans-[beta]-carotene in rats and chicks. J Nutr 119(7) (1989): 1013-19.

Ben-Amotz A et al. Natural beta-carotene and whole body irradiation in rats. Radiat Environ Biophys 35(4) (1996): 285-8.

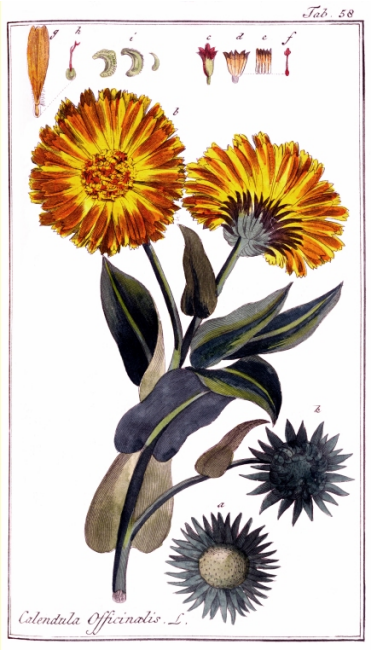
Ben-Amotz A et al. Effect of natural beta-carotene supplementation in children exposed to radiation from the Chernobyl accident. Radiat Environ Biophys 37(3) (1998): 187-93.
Ben-Amotz A et al. Selective distribution of beta-carotene stereoisomers in rat tissues. Nutr Res 25(11) (2005): 1005-12.
Bendich A. From 1989 to 2001: What have we learned about the biological actions of beta-carotene? J Nutr 134(1) (2004): 225-30S.
Biesalski HK, Obermueller-Jevic UC. UV light, beta-carotene and human skin: beneficial and potentially harmful effects. Arch Biochem Biophys 389(1) (2001): 1-6.
Bitterman N et al. Beta-carotene and CNS oxygen toxicity in rats. J Appl Physiol 76(3) (1994): 1073-6.
Black HS. Pro-carcinogenic activity of beta-carotene, a putative systemic photoprotectant. Photochem Photobiol Sci 3(8) (2004): 753-8.
Black HS, Gerguis J. Modulation of dietary vitamins E and C fails to ameliorate beta-carotene exacerbation of UV carcinogenesis in mice. Nutr Cancer 45(1) (2003): 36-45.
Black HS et al. Diet potentiates the UV-carcinogenic response to beta-carotene. Nutr Cancer 37(2) (2000): 173-8.
Blot WJ et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85(18) (1993): 1483-92.
Bobak M et al. Could antioxidants play a role in high rates of coronary heart disease in the Czech Republic? Eur J Clin Nutr 52 (1998): 632.
Bohm F et al. Carotenoids enhance vitamin E antioxidant efficiency. J Am Chem Soc 119(3) (1997): 621-2.
Bohm F et al. [beta]-Carotene with vitamins E and C offers synergistic cell protection against NOx. FEBS Lett 436(3) (1998a): 387-9.
Bohm F et al. Enhanced protection of human cells against ultraviolet light by antioxidant combinations involving dietary carotenoids. J Photochem Photobiol B Biol 44(3) (1998b): 211-15.
Bolton-Smith C et al. Dietary intake by food frequency questionnaire and odds ratios of coronary heart disease risk. II: The antioxidants vitamins and fibre. Eur J Clin Nutr 46 (1992): 85.
Borel P et al. Oxidative stress status and antioxidant status are apparently not related to carotenoid status in healthy subjects. J Lab Clin Med 132(1) (1998): 61-6.
Bowen PE et al. Carotenoid absorption in humans. Methods Enzymol 214 (1993): 3-17.
Brady WE et al. Human serum carotenoid concentrations are related to physiologic and lifestyle factors. J Nutr 126(1) (1996): 129-37.
Burton GW, Ingold KU. Beta-Carotene: an unusual type of lipid antioxidant. Science 224(4649) (1984): 569-73.
Chao JCJ et al. Effects of beta-carotene, vitamin C and E on antioxidant status in hyperlipidemic smokers. J Nutr Biochem 13(7) (2002): 427-34.
Christen WG et al. Design of Physicians' Health Study II: a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol 10(2) (2000): 125-34.
Christen WG et al. A randomized trial of beta carotene and age-related cataract in US physicians. Arch Ophthalmol 121(3) (2003): 372-8.
Christen WG et al. Age-related cataract in a randomized trial of beta-carotene in women. Ophthalmic Epidemiology 11(5) (2004): 401-412.
Christian P et al. Vitamin A or beta-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. J Nutr 130(11) (2000a): 2675-82.
Christian P et al. Night blindness during pregnancy and subsequent mortality among women in Nepal: effects of vitamin A and beta-carotene supplementation. Am J Epidemiol 152(6) (2000b): 542-7.
Christian P et al. Cigarette smoking during pregnancy in rural Nepal: Risk factors and effects of beta-carotene and vitamin A supplementation. Eur J Clin Nutr 58(2) (2004): 204-11.

Chuwers P et al. The protective effect of [beta]-carotene and retinol on ventilatory function in an asbestos-exposed cohort. Am J Resp Crit Care Med 155(3) (1997): 1066-71.
Clemens MR et al. Supplementation with antioxidants prior to bone marrow transplantation. Wiener Klin Wochensch 109(19) (1997): 771-6.
Cobanoglu N et al. Antioxidant effect of beta-carotene in cystic fibrosis and bronchiectasis: Clinical and laboratory parameters of a pilot study. Int J Paediatr 91(7) (2002): 793-8.
Cook NR et al. Beta-carotene supplementation for patients with low baseline levels and decreased risks of total and prostate carcinoma. Cancer 86(9) (1999): 1783-92.
Cook NR et al. Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). Cancer Causes Control 11(7) (2000): 617-26.
Cooper DA et al. Dietary carotenoids and certain cancers, heart disease, and age-related macular degeneration: a review of recent research. Nutr Rev 57(7) (1999a): 201-14.
Cooper DA et al. Dietary carotenoids and lung cancer: a review of recent research. Nutr Rev 57(5) (1999b): 133-45.
Corridan BM et al. Low-dose supplementation with lycopene or beta-carotene does not enhance cell-mediated immunity in healthy free-living elderly humans. Eur J Clin Nutr 55(8) (2001): 627-35.
Coudray C et al. Lipid peroxidation level and antioxidant micronutrient status in a pre-aging population; correlation with chronic disease prevalence in a French epidemiological study (Nantes, France). J Am Coll Nutr 16(6) (1997): 584-91.
Darlington S et al. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Arch Dermatol 139(4) (2003): 451-5.
De Luca LM, Ross SA. Beta-carotene increases lung cancer incidence in cigarette smokers. Nutr Rev 54(6) (1996): 178-80.
DerMarderosian A, Beutler JA (eds). The Review of Natural Products. St Louis: Facts and Comparisons (2002).
Dijkhuizen MA et al. Zinc plus beta-carotene supplementation of pregnant women is superior to beta-carotene supplementation alone in improving vitamin A status in both mothers and infants. Am J Clin Nutr 80(5) (2004): 1299-307.
Epstein JH. Effects of beta-carotene on ultraviolet induced cancer formation in the hairless mouse skin. Photochem Photobiol 25(2) (1977): 211-13.
Erlinger TP et al. Relationship between systemic markers of inflammation and serum [beta]-carotene levels. Arch Intern Med 161(15) (2001): 1903-8.
Farchi S et al. Exposure to environmental tobacco smoke is associated with lower plasma [beta]-carotene levels among nonsmoking women married to a smoker. Cancer Epidemiol Biomarkers Prev 10(8) (2001): 907-9.
Ford ES et al. Serum antioxidant concentrations among U.S. adults with self-reported asthma. J Asthma 41(2) (2004): 179-87.
Frieling UM et al. A randomized, 12-year primary-prevention trial of beta carotene supplementation for nonmelanoma skin cancer in the Physician's Health Study. Arch Dermatol 136(2) (2000): 179-84.
Fuchs J. Potentials and limitations of the natural antioxidants RRR-alpha-tocopherol, L-ascorbic acid and beta-carotene in cutaneous photoprotection. Free Radic Biol Med 25(7) (1998): 848-73.
Fujii Y et al. Effects of beta-carotene-rich algae Dunaliella bardawil on the dynamic changes of normal and neoplastic mammary cells and general metabolism in mice. Anticancer Res 13(2) (1993): 389-93.
Fuller CJ et al. Effect of beta-carotene supplementation on photosuppression of delayed-type hypersensitivity in normal young men. Am J Clin Nutr 56(4) (1992) 684-90.
Garewal H. Chemoprevention of oral cancer: Beta-carotene and vitamin E in leukoplakia. Eur J Cancer Prev 3(2) (1994): 101-7.
Garewal HS. Antioxidants in oral cancer prevention. Am J Clin Nutr 62(6 Suppl.) (1995): 1410-16S.
Garewal HS, Schantz S. Emerging role of beta-carotene and antioxidant nutrients in prevention of oral cancer. Arch Otolaryngol Head Neck Surg 121(2) (1995): 141-4.
Garewal HS et al. Beta-carotene produces sustained remissions in patients with oral leukoplakia: results of a multicenter prospective trial. Arch Otolaryngol Head Neck Surg 125(12) (1999): 1305-10.

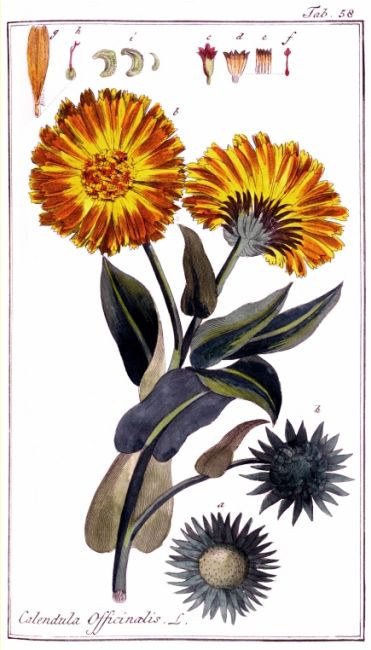
Garmyn M et al. Effect of beta-carotene supplementation on the human sunburn reaction. Exp Dermatol 4(2) (1995): 104-11.
Gaziano JM et al. Discrimination in absorption or transport of beta-carotene isomers after oral supplementation with either all-trans- or 9-cis-beta-carotene. Am J Clin Nutr 61(6) (1995a): 1248-52.
Gaziano JM et al. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. Ann Epidemiol 5 (1995b): 255.
Gey KF et al. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischaemic heart diease and stroke: Basel Prospective Study. Clin Invest 71 (1993): 3.
Gollnick HP, Siebenwirth C. Beta-carotene plasma levels and content in oral mucosal epithelium is skin type associated. Skin Pharmacol Appl Skin Physiol 15(5) (2002): 360-6.
Gollnick HPM et al. Systemic beta carotene plus topical UV-sunscreen are an optimal protection against harmful effects of natural UV-sunlight: Results of the Berlin-Eilath study. Eur J Dermatol 6(3) (1996): 200-5.
Gossage C et al. Effect of [beta]-carotene supplementation and lactation on carotenoid metabolism and mitogenic T lymphocyte proliferation. Am J Clin Nutr 71(4) (2000): 950-5.
Gottlieb K et al. Beta-carotene decreases markers of lipid peroxidation in healthy volunteers. Nutr Cancer 19(2) (1993): 207-12.
Green A et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 354(9180) (1999): 723-9.
Greenberg ER et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. N Engl J Med 323(12) (1990): 789-95.
Greenberg ER et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. New England J Med 331(3) (1994): 141-7.
Greul AK et al. Photoprotection of UV-irradiated human skin: an antioxidative combination of vitamins E and C, carotenoids, selenium and proanthocyanidins. Skin Pharmacol Appl Skin Physiol 15(5) (2002): 307-15.
Grievink L et al. Serum carotenoids, alpha-tocopherol, and lung function among Dutch elderly. Am J Resp Crit Care Med 161(3) (2000): 790-5.
Group AT. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330 (1994): 1029-35.
Gupta PC et al. Influence of dietary factors on oral precancerous lesions in a population-based case-control study in Kerala, India. Cancer 85(9) (1999): 1885-93.
Hacisevki AY et al. An evaluation of serum retinol and beta-carotene levels and the risk of breast cancer. Gazi Univ Eczacilik Fakult Dergisi 20(2) (2003): 87-94.
Halliwell B. Free radicals and vascular disease: how much do we know? BMJ 1093(307) (1993): 885.
Handelman GJ. The evolving role of carotenoids in human biochemistry. Nutrition 17(10) (2001): 818-22.
Harik-Khan RI et al. Serum vitamin levels and the risk of asthma in children. Am J Epidemiol 159(4) (2004): 351-7.
Heinonen OP et al. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330(15) (1994): 1029-35.
Heinrich U et al. Photoprotection for ingested carotenoids. Cosmetics Toiletries 113 (1998): 61.
Heinrich U et al. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. J Nutr 133(1) (2003): 98-101.
Hemila H et al. Vitamin C, vitamin E, and beta-carotene in relation to common cold incidence in male smokers. Epidemiology 13(1) (2002): 32-7.
Hemila H et al. Physical activity and the common cold in men administered vitamin E and beta-carotene. Med Sci Sports Exercise 35(11) (2003): 1815-20.
Hemila H et al. Vitamin E and beta-carotene supplementation and hospital-treated pneumonia incidence in male smokers. Chest 125(2) (2004): 557-65.
Hennekens CH et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 334(18) (1996): 1145-9.



Herraiz LA et al. Effect of UV exposure and [beta]-carotene supplementation on delayed-type hypersensitivity response in healthy older men. J Am Coll Nutr 17(6) (1998): 617-24.
Hininger IA et al. No significant effects of lutein, lycopene or beta-carotene supplementation on biological markers of oxidative stress and LDL oxidizability in healthy adult subjects. J Am Coll Nutr 20(3) (2001): 232-8.
Holick CN et al. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol: beta-carotene cohort study. Am J Epidemiol 156(6) (2002): 536-47.
Hu P et al. The effects of serum beta-carotene concentration and burden of inflammation on all-cause mortality risk in high-functioning older persons: MacArthur studies of successful aging. J Gerontol Series A Biol Sci Med Sci 59(8) (2004): 849-54.
Hughes DA et al. The effect of [beta]-carotene supplementation on the immune function of blood monocytes from healthy male nonsmokers. J Lab Clin Med 129(3) (1997): 309-17.
Hughes DA. Dietary carotenoids and human immune function. Nutrition 17(10) (2001): 823-7.
Jensen CD et al. Observations on the effects of ingesting cis-and trans-beta-carotene isomers on human serum concentrations. Nutr Rep Int 35 (1987): 413-22.
Jimenez-Jimenez FJ et al. Serum levels of beta-carotene, alpha-carotene and vitamin A in patients with Alzheimer's disease. Eur J Neurol: 6(4) (1999): 495-7.
Kacsur C et al. Plasma antioxidants and rheumatoid arthritis. Harefuah 141(2) (2002): 148-50.
Kalayci O et al. Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma. Turk J Pediatr 42(1) (2000): 17-21.
Kardinaal AFM et al. Antioxidants in adipose tissue and risk of myocardial infarction: the EURAMIC study. Lancet 342 (1993): 1379.
Kassoff A et al. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 119(10) (2001): 1417-36.
Kligman LH, Mathews-Roth MM. Dietary beta-carotene and 13-cis-retinoic acid are not effective in preventing some features of UVB-induced dermal damage in hairless mice. Photochem Photobiol 51(6) (1990): 733-5.
Knekt P et al. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 139 (1994): 1180.
Kritchevsky SB. BETA-carotene, carotenoids and the prevention of coronary heart disease. J Nutr 129(1) (1999): 5-8.
Kushi LH et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 334 (1996): 1156.
Lavy A et al. Preferential inhibition of LDL oxidation by the all-trans isomer of beta-carotene in comparison with 9-cis beta-carotene. Eur J Clin Chem Clin Biochem 31(2) (1993): 83-90.
Lavy A et al. Natural beta-carotene for the prevention of post-ERCP pancreatitis. Pancreas 29(2) (2004): e45-50.
Lee IM et al. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. J Natl Cancer Inst 91(24) (1999): 2102-6.
Lee J et al. Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. Proc Soc Exp Biol Med 223(2) (2000): 170-4.
Leppala JM et al. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. Arterioscler Thromb Vasc Biol 20(1) (2000a): 230-5.
Leppala JM et al. Vitamin E and beta carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Arch Neurol 57(10) (2000b): 1503-9.
Levin G, Mokady S. Antioxidant activity of 9-cis compared to all-trans [beta]-carotene in vitro. Free Radic Biol Med 17(1) (1994): 77-82.
Levy Y et al. Effect of dietary supplementation of different [beta]-carotene isomers on lipoprotein oxidative modification. J Nutr Environ Med 5(1) (1995): 13-22.



Levy Y et al. Effect of dietary supplementation of beta-carotene on human monocyte-macrophage-mediated oxidation of low density lipoprotein. Israel J Med Sci 32(6) (1996): 473-8.
Levy Y et al. Plasma antioxidants and lipid peroxidation in acute myocardial infarction and thrombolysis. J Am Coll Nutr 17(4) (1998): 337-41.
Levy Y et al. Dietary supplementation of a natural isomer mixture of beta-carotene inhibits oxidation of LDL derived from patients with diabetes mellitus. Ann Nutr Metab 44(2) (2000): 54-60.
Liede K et al. Long-term supplementation with alpha-tocopherol and beta-carotene and prevalence of oral mucosal lesions in smokers. Oral Dis 4(2) (1998): 78-83.
Liu Q et al. Antioxidant activities of natural 9-cis and synthetic all-trans [beta]-carotene assessed by human neutrophil chemiluminescence. Nutr Res 20(1) (2000): 5-14.
Malila N et al. Effects of alpha-tocopherol and beta-carotene supplementation on gastric cancer incidence in male smokers (ATBC Study Finland). Cancer Causes Control 13(7) (2002): 617-23.
Mannisto S et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. Cancer Epidemiol Biomarkers Prev 13(1) (2004): 40-8.
Manson JE et al. A prospective study of antioxidant vitamins and incidence of coronary heart disease in women. Circulation 84 (1991): 546.
Mathews-Roth MM. Antitumor activity of beta-carotene, canthaxanthin and phytoene. Oncology 39(1) (1982): 33-7.
Mathews-Roth MM. Systemic photoprotection. Dermatol Clin 4(2) (1986): 335-9.
Mathews-Roth MM. Photoprotection by carotenoids. Fed Proc 46(5) (1987): 1890-3.
Mathews-Roth MM. Lack of genotoxicity with beta-carotene. Toxicol Lett 41(3) (1988): 185-91.
Mathews-Roth MM. Plasma concentrations of carotenoids after large doses of [beta]-carotene. Am J Clin Nutr 52(3) (1990a): 500-1.
Mathews-Roth MM. Carotenoid functions in photoprotection and cancer prevention. J Environ Pathol Toxicol Oncol 10(4-5) (1990b): 181-92.
Mathews-Roth MM. Carotenoids in erythropoietic protoporphyria and other photosensitivity diseases. Ann NY Acad Sci 691 (1993): 127-38.
Mathews-Roth MM, Pathak MA. Phytoene as a protective agent against sunburn (>280 nm) radiation in guinea pigs. Photochem Photobiol. 21(4) (1975): 261-3.
Mathews-Roth MM et al. Beta-carotene as a photoprotective agent in erythropoietic protoporphyria. N Engl J Med 282(22) (1970): 1231-4.
Mathews-Roth MM et al. A clinical trial of the effects of oral beta-carotene on the responses of human skin to solar radiation. J Invest Dermatol 59(4) (1972): 349-53.
Mathews-Roth MM et al. Beta-carotene as an oral photoprotective agent in erythropoietic protoporphyria. JAMA 228(8) (1974): 1004-8.
Mathews-Roth MM et al. Beta carotene therapy for erythropoietic protoporphyria and other photosensitivity diseases. Arch Dermatol 113(9): 1229-32.
Mayne ST. Beta-carotene, carotenoids, and disease prevention in humans. FASEB J 10(7) (1996): 690-701.
Mayne ST et al. Supplemental beta-carotene, smoking, and urinary F2- isoprostane excretion in patients with prior early stage head and neck cancer. Nutr Cancer 49(1) (2004): 1-6.
McArdle F et al. Effects of oral vitamin E and beta-carotene supplementation on ultraviolet radiation-induced oxidative stress in human skin. Am J Clin Nutr 80(5) (2004): 1270-5.
Micozzi MS et al. Carotenodermia in men with elevated carotenoid intake from foods and beta-carotene. Am J Clin Nutr 48 (1988): 1061-4.
Micromedex. Beta-carotene. Thomson, 2003. Available at: www.micromedex.com (accessed 06-06).
Mokady S, Ben-Amotz A. Dietary lipid level and the availability of beta-carotene of Dunaliella-bardawil in rats. Nutr Cancer 15(1) (1991): 47-52.
Moreira A et al. Increased dietary beta-carotene intake associated with better asthma quality of life. Alergol Inmunol Clin 19(3) (2004): 110-12.



Morinobu T et al. Changes in beta-carotene levels by long-term administration of natural beta-carotene derived from Dunaliella bardawil in humans. J Nutr Sci Vitaminol 40(5) (1994): 421-30.
Morris DL, Kritchevsky SB, Davis CE. Serum carotenoids and coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study. JAMA 272 (1994): 1439.
Murata T et al. Effect of long-term administration of beta-carotene on lymphocyte subsets in humans. Am J Clin Nutr 60(4) (1994): 597-602.
Nabae K et al. A 90-day oral toxicity study of beta-carotene derived from Blakeslea trispora, a natural food colorant, in F344 rats. Food Chem Toxicol 43(7) (2005): 1127-33.
Nagasawa H et al. Effects of beta-carotene-rich algae Dunaliella on reproduction and body growth in mice. In Vivo 3(2) (1989): 79-81.
Nagasawa H et al. Suppression by beta-carotene-rich algae Dunaliella bardawil of the progression, but not the development, of spontaneous mammary tumours in SHN virgin mice. Anticancer Res 11(2) (1991): 713-17.
Neuman I et al. Prev of exercise-induced asthma by a natural isomer mixture of beta-carotene. Ann Allergy Asthma Immunol 82(6) (1999): 549-53.
Ochs-Balcom HM et al. Oxidative stress and pulmonary function in the general population. Am J Epidemiol 162(12) (2005): 1137-45.
Omenn GS et al. Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. J Natl Cancer Inst 88(21) (1996a): 1550-9.
Omenn GS et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334(18) (1996b): 1150-5.
Palozza PN, Krinsky I. [beta]-Carotene and [alpha]-tocopherol are synergistic antioxidants. Arch Biochem Biophys 297(1) (1992): 184-7.
Pandey DK et al. Dietary vitamin C and beta carotene and risk of death in middle aged men: The Western Electric Study. Am J Epidemiol 142 (1995): 1269.
Paolini M et al. Co-carcinogenic effect of beta-carotene. Nature 398(6730) (1999): 760-1.
Pathak MA. Sunscreens: topical and systemic approaches for protection of human skin against harmful effects of solar radiation. J Am Acad Dermatol 7(3) (1982): 285-312.
Patrick L. Beta carotene: The controversy continues. Altern Med Rev 5(6) (2000): 530-45.
PDRHealth [online] (2005). Beta carotene. Thomson Healthcare. Available at: http://www.pdrhealth.
Penuelas J, Munne-Bosch S. Isoprenoids: an evolutionary pool for photoprotection. Trends Plant Sci 10(4): 166-9.
Peto R et al. Can dietary betacarotene materially reduce human cancer rates? Nature 290 (1981): 201-8.
Ponnamperuma RM et al. [beta]-Carotene fails to act as a tumor promoter, induces RAR expression, and prevents carcinoma formation in a two-stage model of skin carcinogenesis in male sencar mice. Nutr Cancer 37(1) (2000): 82-8.
Prabhala RH et al. Influence of beta-carotene on immune functions. Ann NY Acad Sci 691 (1993): 262-3.
Princen HM et al. Supplementation with vitamin E but not beta-carotene in vivo protects low density lipoprotein from lipid peroxidation in vitro: Effect of cigarette smoking. Arterioscler Thromb 12(5) (1992): 554-62.
Pryor WA et al. Beta carotene: From biochemistry to clinical trials. Nutr Rev 58 (2000): 39-53.
Rahman I et al. Oxidant and antioxidant balance in the airways and airway diseases. Eur J Pharmacol 533(1-3) (2006): 222-9.
Rapola JM et al. Effect of vitamin E and beta carotene on the incidence of angina pectoris: A randomized, double-blind, controlled trial. JAMA 275(9) (1996): 693-8.
Rautalahti MT et al. The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer 86(1) (1999): 37-42.
Reaven PD et al. Effect of dietary antioxidant combinations in humans: Protection of LDL by vitamin E but not by [beta]-carotene. Arterioscler Thromb 13(4) (1993): 590-600.

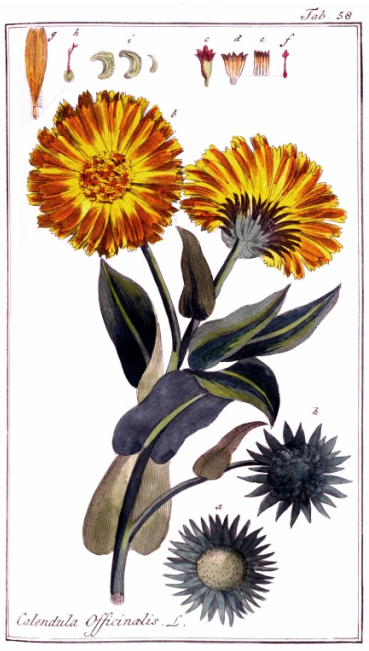
Redlich C et al. Effect of long-term beta-carotene and vitamin A on serum cholesterol and triglyceride levels among participants in the Carotene and Retinol Efficacy Trial (CARET). Atherosclerosis 145(2) (1999): 425-32.
Richelle M et al. Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. Am J Clin Nutr 80(1) (2004): 171-7.
Rimm TV et al. Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 328 (1993): 1450.
Roodenburg AJ et al. Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. Am J Clin Nutr 71(5) (2000): 1187-93.
Rubin RN et al. Relationship of serum antioxidants to asthma prevalence in youth. Am J Resp Crit Care Med 169(3) (2004): 393-8.
Russell RM. Beta-carotene and lung cancer. Pure Appl Chem 74(8) (2002): 1461-7.
Rust P et al. Long-term oral beta-carotene supplementation in patients with cystic fibrosis: effects on antioxidative status and pulmonary function. Ann Nutr Metab 44(1) (2000): 30-7.
Santos MS et al. Natural killer cell activity in elderly men is enhanced by [beta]-carotene supplementation. Am J Clin Nutr 64(5) (1996): 772-7.
Santos MS et al. Short- and long-term beta-carotene supplementation do not influence T cell-mediated immunity in healthy elderly persons. Am J Clin Nutr 66(4) (1997): 917-24.
Sayre RM, Black HS. Beta-carotene does not act as an optical filter in skin. J Photochem Photobiol B Biol 12(1) (1992): 83-90.
Schaumberg DA et al. No effect of beta-carotene supplementation on risk of nonmelanoma skin cancer among men with low baseline plasma beta-carotene. Cancer Epidemiol Biomarkers Prev 13(6) (2004): 1079-80.
Schroder H et al. Effects of alpha-tocopherol, beta-carotene and ascorbic acid on oxidative, hormonal and enzymatic exercise stress markers in habitual training activity of professional basketball players. Eur J Nutr 40(4) (2001): 178-84.
Schunemann HJ et al. The relation of serum levels of antioxidant vitamins C and E, retinol and carotenoids with pulmonary function in the general population. Am J Resp Crit Care Med 163(5) (2001): 1246-55.
Senesse P et al. Tobacco use and associations of beta-carotene and vitamin intakes with colorectal adenoma risk. J Nutr 135(10) (2005): 2468-72.
Shaish A et al. Beta-carotene inhibits atherosclerosis in hypercholesterolemic rabbits. J Clin Invest 96(4) (1995): 2075-82.
Shaish A et al. 9-cis [beta]-carotene-rich powder of the alga Dunaliella bardawil increases plasma HDL-cholesterol in fibrate-treated patients. Atherosclerosis (in press) (2006).
Siems W et al. Beta-carotene cleavage products induce oxidative stress in vitro by impairing mitochondrial respiration. FASEB J 16(10) (2002): 1289-91.
Siems W et al. [beta]-Carotene breakdown products may impair mitochondrial functions – potential side effects of high-dose [beta]-carotene supplementation. J Nutr Biochem 16(7) (2005): 385-97.
Sies H, Stahl W. Nutritional protection against skin damage from sunlight. Annu Rev Nutr 24 (2004): 173-200.
Smith W et al. Carrots, carotene and seeing in the dark. Aust NZ J Ophthalmol 27(3-4) (1999): 200-3.
Sommerburg O et al. beta-carotene cleavage products after oxidation mediated by hypochlorous acid: A model for neutrophil-derived degradation. Free Radic Biol Med 35(11) (2003): 1480-90.
Sperduto RD et al. The Linxian cataract studies: Two nutrition intervention trials. Arch Ophthalmol 111(9) (1993): 1246-53.
Stahl WS, Sies H. Human serum concentrations of all-trans beta- and alpha-carotene but not 9-cis beta-carotene increase upon ingestion of a natural isomer mixture obtained from Dunaliella salina (Betatene). J Nutr 123 (1993): 847-51.
Stahl W et al. Biological activities of natural and synthetic carotenoids: induction of gap junctional communication and singlet oxygen quenching. Carcinogenesis 18(1) (1997): 89-92.
Stahl W et al. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. Am J Clin Nutr 71(3) (2000): 795-8.

Steenvoorden DPT, Beijersbergen van Henegouwen GMJ. The use of endogenous antioxidants to improve photoprotection. J Photochem Photobiol B Biol 41(1-2) (1997): 1-10.
Strauss RS. Comparison of serum concentrations of alpha-tocopherol and beta-carotene in a cross-sectional sample of obese and nonobese children (NHANES III): National Health and Nutrition Examination Survey. J Pediatr 134(2) (1999): 160-5.
Street DA et al. Are low levels of carotenoids and alpha tocopherol risk factors for myocardial infarction? Circulation 90 (1994): 1154.
Suhonen R, Plosila M. The effect of beta-carotene in combination with canthaxanthin, Ro 8-8427 (Phenoro), in treatment of polymorphous light eruptions. Dermatologica 163(2) (1981): 172-6.
Takenaka H et al. Protective effect of Dunaliella bardawil on water-immersion-induced stress in rats. Planta Med 59(5) (1993): 421-4.
Tamai H et al. Bioavailability of beta-carotene in a carotenoid preparation derived from Dunaliella bardawil in human male adults. Ann NY Acad Sci 691 (1993): 238-40.
Tauler P et al. Diet supplementation with vitamin E, vitamin C and beta-carotene cocktail enhances basal neutrophil antioxidant enzymes in athletes. Pflugers Archiv Eur J Physiol 443(5-6) (2002): 791-7.
Tavani A, La Vecchia C. [beta]-Carotene and risk of coronary heart disease: A review of observational and intervention studies. Biomed Pharmacother 53(9) (1999): 409-16.
Tavani A et al. Beta Carotene intake and risk of nonfatal acute myocardial infarction in women. Eur J Epidemiol 13 (1997): 631.
Taylor A et al. Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. Am J Clin Nutr 75(3) (2002): 540-9.
Tebi A et al. Plasma vitamin, [beta]-carotene, and [alpha]-tocopherol status according to age and disease in hospitalized elderly. Nutr Res 20(10) (2000): 1395-408.
Thomsen K et al. Beta-carotene in erythropoietic protoporphyria: 5 years' experience. Dermatologica 159(1) (1979): 82-6.
Todd S et al. An investigation of the relationship between antioxidant vitamin intake and coronary heart disease in men and women using logistic regression analysis. J Clin Epidemiol 48 (1995): 307.
Tornwall ME et al. The effect of alpha-tocopherol and beta-carotene supplementation on symptoms and progression of intermittent claudication in a controlled trial. Atherosclerosis 147(1) (1999): 193-7.
Tornwall ME et al. Alpha-tocopherol (vitamin E) and beta-carotene supplementation does not affect the risk for large abdominal aortic aneurysm in a controlled trial. Atherosclerosis 157(1) (2001): 167-73.
Tornwall ME et al. Postintervention effect of alpha tocopherol and beta carotene on different strokes: A 6-year follow-up of the alpha tocopherol, beta carotene cancer prevention study. Stroke 35(8) (2004): 1908-13.
Torun M et al. Evaluation of serum beta carotene levels in patients with cardiovascular diseases. J Clin Pharm Ther 19 (1994): 61.
Touvier M et al. Dual association of beta-carotene with risk of tobacco-related cancers in a cohort of French women. J Natl Cancer Inst 97(18) (2005): 1338-44.
Tyssandier V et al. Vegetable-borne lutein, lycopene, and beta-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. Am J Clin Nutr 75(3) (2002): 526-34.
Vainio H, Rautalahti M. An international evaluation of the cancer preventive potential of carotenoids. Cancer Epidemiol Biomarkers Prev 7(8) (1998): 725-8.
van der Horst-Graat JM et al. Plasma carotenoid concentrations in relations to acute respiratory infections in elderly people. Br J Nutr 92(1) (2004): 113-18.
Van Poppel G et al. No influence of beta-carotene on haemostatic balance in healthy male smokers. Blood Coagul Fibrinolysis 6(1) (1995): 55-9.
Verrotti A et al. Obesity and plasma concentrations of alpha-tocopherol and beta-carotene in epileptic girls treated with valproate. Neuroendocrinology 79(3) (2004): 157-62.
Virtamo J et al. Effects of supplemental alpha-tocopherol and beta-carotene on urinary tract cancer: incidence and mortality in a controlled trial (Finland). Cancer Causes Control 11(10) (2000): 933-9.

Vivekananthan DP et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet 361(9374) (2003): 2017-23.
Vlot WJ et al. The Lixian trials: mortality rates by vitamin-mineral intervention group. Am J Clin Nutr 62 (Suppl) (1995): 1424.
Walkowiak J et al. The deficiency of beta-carotene in cystic fibrosis patients is related to the clinical course of the disease. Pediatr Polska 79(7) (2004): 534-7.
Wallstrom P et al. Serum concentrations of beta-carotene and alpha-tocopherol are associated with diet, smoking, and general and central adiposity. Am J Clin Nutr 73(4) (2001): 777-85.
Wang XD, Krinsky NI. The bioconversion of beta-carotene into retinoids. SubCell Biochem 30 (1998): 159-80.
Wang XD et al. Retinoid signaling and activator protein-1 expression in ferrets given [beta]-carotene supplements and exposed to tobacco smoke. J Natl Cancer Inst 91(1) (1999): 60-6.
Watson RR et al. Effect of beta-carotene on lymphocyte subpopulations in elderly humans: evidence for a dose-response relationship. Am J Clin Nutr 53(1) (1991): 90-4.
Wertz K et al. Beta-carotene inhibits UVA-induced matrix metalloprotease 1 and 10 expression in keratinocytes by a singlet oxygen-dependent mechanism. Free Radic Biol Med 37(5) (2004): 654-70.
Wertz K et al. Beta-carotene interferes with ultraviolet light A-induced gene expression by multiple pathways. J Invest Dermatol 124(2) (2005): 428-34.
West KP Jr et al. Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal: The NNIPS-2 Study Group. BMJ (Clin Res Ed) 318(7183) (1999): 570-5.
Wolf C et al. Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage? J Invest Dermatol 90(1) (1988): 55-7.
Wood LG et al. Lipid peroxidation as determined by plasma isoprostanes is related to disease severity in mild asthma. Lipids 35(9) (2000): 967-74.
Wood LG et al. Biomarkers of lipid peroxidation, airway inflammation and asthma. Eur Resp J 21(1) (2003): 177-86.
Wood LG et al. Airway and circulating levels of carotenoids in asthma and healthy controls. J Am Coll Nutr 24(6) (2005): 448-55.
Woodall A et al. Caution with beta-carotene supplements. Lancet 347(9006) (1996): 967-8.
Yeh SL, Hu ML. Induction of oxidative DNA damage in human foreskin fibroblast Hs68 cells by oxidized beta-carotene and lycopene. Free Radic Res 35(2) (2001): 203-13.
Yeh SL, Hu ML. Oxidized [beta]-carotene inhibits gap junction intercellular communication in the human lung adenocarcinoma cell line A549. Food Chem Toxicol 41(12) (2003): 1677-84.
Zhang ZW et al. Gastric [alpha]-tocopherol and [beta]-carotene concentrations in association with Helicobacter pylori infection. Eur J Gastroenterol Hepatology 12(5) (2000): 497-503.

Bilberry

Historical note Bilberries have been used as a food for many centuries and are valued for their taste and high nutritional content. They are still commonly used to make jams, pies, syrups and beverages. Medicinally, the berries have been used internally to treat diarrhoea and haemorrhoids and externally for inflammation of the mouth and mucous membranes as they have significant astringent activity. According to folklore, World War II British Royal Air Force pilots noticed that their night vision seemed to improve after consuming bilberries or bilberry preserves, sparking a renewed interest in the medicinal properties of the fruits.



COMMON NAME
Bilberry

OTHER NAMES
Baies de myrtille, blaubeeren, dwarf bilberry, European bilberry, European blueberries, huckleberry, hurtleberry, heidelbeeren, petit myrte, whortleberry, wine berry

BOTANICAL NAME/FAMILY
Vaccinium myrtillus (family Ericaceae)

PLANT PARTS USED
Dried ripe fruit or fresh fruit

CHEMICAL COMPONENTS
The fruit contains catechin tannins (up to 10%), invert sugar, fruit acids, flavonol glycosides including astragalin, hyperoside, isoquercitrin and quercitrin, phenolic acids, pectins, triterpenes, and polyphenols such as anthocyanosides. The volatile oil includes methyl salicylate, farnesol, vanillin, myristicin and citronellol. Bilberry also contains vitamin C and chromium, which are suspected of playing a role in its pharmacological activities.

Some of the anthocyanosides are responsible for the deep blue pigment of the fruit (Kahkonen et al 2001). As the fruit ripens, the anthocyanoside content increases. Some commercially available extracts are standardised to anthocyanoside content.

Clinical note — Tannins
Tannins are polyphenolic compounds that have an affinity for proteins. They also complex with alkaloids and therefore should not be mixed with alkaloid-containing herbs.

Anthocyanosides are condensed tannins. When they come into contact with mucous membranes they have an astringent action, making the mucosa less permeable. This activity has been used therapeutically in a variety of ways.

Taken internally, herbs with a high tannin content such as bilberry have been used to treat diarrhoea; applied externally, a styptic action occurs that reduces blood loss.

MAIN ACTIONS

The pharmacological actions of bilberry have not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies or based on known information about key constituents found within the herb. Most of the research undertaken to understand the pharmacology of the herb has focused on the polyphenol content.

ANTIOXIDANT

Anthocyanosides are the main phenolic constituents in bilberry and have well established antioxidant activity (Kahkonen et al 2001, Roy et al 2002).

Reduces ischaemic reperfusion injury Bilberry anthocyanosides have been shown to improve ischaemia damage, preserve capillary perfusion, inhibit increased permeability of reperfusion and save arteriolar tone in an animal model of ischaemic reperfusion injury (Bertuglia et al 1995).

Ophthalmic conditions Bilberry's significant antioxidant activity is believed to be responsible for much of its activity in the eye, in particular, prevention of cataract.

Clinical note — Cataract
Growing evidence suggests that senile cataract development may in part be linked to the endogenous generation of free radical molecules, such as superoxide derived from oxygen and light in the aqueous humour and lens (Varma & Richards 1988, Varma et al 1982, 1994). As such, substances with significant antioxidant activity such as anthocyanins, vitamin C and vitamin E have been investigated as potential prophylactic treatments.

ANTI-INFLAMMATORY AND ANTI-OEDEMA ACTIVITY

Biochemical and histochemical data show that the anthocyanins decrease vascular permeability and alter capillary wall dynamics by increasing the endothelium barrier

effect by stabilising membrane phospholipids, and by increasing synthesis of mucopolysaccharides of the connective ground substance and thus restoring the altered pericapillary sheath (Mian et al 1977).

These effects have been demonstrated in animal models for both oral administration and topical application of bilberry anthocyanins (1% alcoholic solution) and seen to be stronger and longer lasting than those of rutin (Lietti et al 1976).

ASTRINGENT

The astringent properties of bilberry are well established and attributed to its significant tannin content.

IMPROVES VISUAL FUNCTION

Epidemiological investigations have indicated that moderate consumption of anthocyanin-containing herbs such as bilberry extract is associated with an improvement of visual function (Hou 2003). Several animal studies suggest a positive effect on dark adaptation (Canter & Ernst 2004). More specifically, bilberry enhances regeneration of rhodopsin in the retina, which is essential for optimal functioning of the rods and therefore light adaptation and night vision (Blumenthal et al 2000). Other possible mechanisms of action in the eye include accelerated modulation of retinal enzyme activity and improved microcirculation (Canter & Ernst 2004).

GASTROPROTECTIVE ACTIVITY

In vitro results have found that a specific anthocyanin found in bilberry causes an increase in the efficiency of the gastric mucosal barrier (Cristoni et al 1989). When administered orally in an animal model it was shown to retard the development of gastric ulcers induced by stress, NSAIDs, ethanol, reserpine and histamine (Magistretti et al 1988).

HYPOGLYCAEMIC ACTIVITY

A dried hydroalcoholic extract of bilberry leaf administered orally to streptozotocin-diabetic rats for 4 days decreased plasma glucose levels by 26% (Cignarella et al 1996).

REDUCES TRIGLYCERIDE LEVELS

A dried hydro-alcoholic extract of bilberry leaf administered orally to streptozotocin-diabetic rats for 4 days decreased plasma triglyceride levels by 39% (Cignarelli et al 1996).

OTHER ACTIONS

Preliminary research has found that components of the hexane/chloroform fraction of bilberry exhibits anticarcinogenic activity (Bomser et al 1996). More recently,

antiangiogenic activity has also been identified (Roy et al 2002). Bilberry extract inhibits platelet aggregation according to ex vivo tests (Pulliero et al 1989).

CLINICAL USE

Bilberry extracts are popular in Europe and have been investigated in numerous clinical trials, primarily in non-English speaking European countries. As a result, many research papers have been published in other languages. To provide a more complete description of the evidence available, secondary sources have been used when necessary.

NON-SPECIFIC ACUTE DIARRHOEA

The considerable astringent activity of bilberry provides a theoretical basis for its use in non-specific acute diarrhoea. Commission E approved crude fruit preparations for this indication (Blumenthal et al 2000).

MILD INFLAMMATION OF THE MOUTH AND THROAT

The considerable astringent, anti-inflammatory and anti-oedema activity of bilberry provides a theoretical basis for its use as a topical application in these indications. Commission E approved for this indication (Blumenthal et al 2000).

HAEMORRHOIDS, VARICOSE VEINS, VENOUS INSUFFICIENCY

The considerable astringent, anti-inflammatory and anti-oedema activity of bilberry provides a theoretical basis for its use in these conditions. Several human case series and a single-blind trial report significant improvements in lower extremity discomfort and oedema related to chronic venous insufficiency; however, further research is required to confirm these findings (Ulbricht & Basch 2005).

PREGNANCY

A bilberry product (Myrtocyan®) was taken at a dose of 320 mg daily in the last trimester by women aged 24–37 years with pregnancy-induced lower extremity oedema and found to significantly improve symptoms of burning and itching, heaviness, pain, diurnal and nocturnal leg cramps, oedema and capillary fragility (Ghiringhelli et al 1978 and reported in Blumenthal 2003).

OPHTHALMIC CONDITIONS

Bilberry preparations have been used to improve poor night vision, light adaptation and photophobia, myopia and to prevent or retard diabetic retinopathy, macular degeneration and cataracts. Primarily the collagen-enhancing and antioxidant activities of bilberry provide a theoretical basis for these indications.

Visual acuity and light adaptation A systemic review of 12 placebo-controlled trials (5 RCTs and 7 placebo-controlled non-randomised trials) concluded that the

anthocyanosides from *Vaccinium myrtillus* were not effective for improving night vision; however, the authors point out that the potential therapeutic role of these constituents should not yet be dismissed because confounding factors and supportive auxiliary evidence exists (Canter & Ernst 2004). Four of the RCTs showed no positive effects for *V. myrtillus* anthocyanosides on outcome measures relevant to vision in reduced light whereas the fifth RCT and all seven non-randomised trials reported positive effects on outcome measures relevant to night vision. Seventeen other studies were located by Canter and Ernst but not included in the analysis because they did not contain a placebo group. Sixteen of those studies produced positive results on measures relevant to night vision in either healthy subjects or patients with a range of visual disorders and only one was negative.

The authors point out several confounding factors, in particular the wide range of doses, possible geographical variations in extract composition, choice of subject (generally healthy) and methods used to obtain and interpret electroretinograms, which varied between older and newer studies. For example, two of the negative RCTs tested the lowest dose levels of any of the trials: 36 mg daily for acute treatment and ≤48 mg for short-term treatment.

A significant improvement in visual performance has been demonstrated for bilberry extract in people with retinitis pigmentosa and hemeralopia (inability to see distinctly in bright light), suggesting that effects may be more pronounced in cases of impaired visual acuity (Gloria & Peria 1966, Junemann 1967).

Glaucoma In one small study of eight patients, a single oral dose of 200 mg bilberry anthocyanosides was shown to improve glaucoma, as assessed by electroretinography (Caselli 1985).

Retinopathy In Europe, bilberry anthocyanoside extracts are recognised as highly effective in preventing or treating diabetic retinopathy, with clinical research supporting its use (Lietti et al 1976, Orsucci et al 1983, Perossini 1987, Scharrer & Ober 1981).

One double-blind study involving 40 patients with diabetic and/or hypertensive retinopathy showed that a dose of bilberry extract (Tegens™) equivalent to 160 mg anthocyanosides taken twice daily for 1 month significantly improved ophthalmoscopic parameters and angiographic parameters (Perossini 1987). Another study of 31 subjects with different forms of retinopathy (diabetic retinopathy, retinitis pigmentosa, macular degeneration or haemorrhage due to anticoagulant use) found that treatment with bilberry extract (Difrarel 100™) reduced vascular permeability and the tendency to haemorrhage in all patients (Scharrer & Ober 1981). A small open study by Orsucci et al of 10 subjects with diabetic retinopathy found that 6 months of

treatment with bilberry extract (Tegens™) equivalent to 240 mg anthocyanosides daily resulted in reduction or disappearance of haemorrhages and improvement in the retinal picture (Orsucci et al 1983 and reported in Blumenthal 2003).

Myopia Uncontrolled trials report a beneficial effect of the extract on patients with myopia (Canter & Ernst 2004).

Cataract In practice, bilberry has been recommended to delay cataract progression. A case series of 50 elderly subjects with early-stage cataract found that a combination of anthocyanosides extracted from bilberry and vitamin E slowed progression of lens opacities by 97% (Ulbricht & Basch 2005). Placebo-controlled trials are now required to confirm these results.

OTHER USES

Traditionally, bilberry has been used to treat dysentery, diabetes, gastrointestinal inflammatory conditions, vaginal discharges, haemorrhoids, and to stop lactation. Externally, bilberry preparations have been used to treat wounds, ulcers and skin infections. More recently, other uses include treatment for bleeding gums, nose bleeds, spider veins, capillary fragility, peptic ulcers, Raynaud's syndrome and venous insufficiency (such as claudication).

Additionally, a double-blind placebo-controlled study confirmed that bilberry improves peripheral vascular disorders by improving subjective symptoms after 30 days' treatment (Mills & Bone 2000).

DOSAGE RANGE

INTERNAL

- Fluid extract (1:1) standardised to provide 50–120 mg daily of anthocyanins: 6–12 mL/day taken in three divided doses.
- Oral dose forms: bilberry extracts providing 50–288 mg of anthocyanins daily.
- Decoction of dried herb: 5–10 gm of crushed, dried fruit in 150 mL of cold water, which is then boiled for up to 10 minutes and strained while hot. For symptomatic treatment of diarrhoea, drink the cold decoction several times daily.
- Gargle: Make a 10% decoction using the above preparation.
- Fresh fruit : 20–50 g daily.

EXTERNAL

- 5–10 g crushed dried fruit in 150 mL of cold water, brought to the boil for 10 minutes then strained while hot to make a decoction for local application.

TOXICITY

Rats administered high doses of up to 400 mg/kg showed no adverse effects (Murray 1995).

ADVERSE REACTIONS

No adverse effects were reported in a systematic review of 12 placebo-controlled trials of *V. myrtillus* anthocyanosides (Canter & Ernst 2004). According to the same authors, a post-marketing surveillance study of 2295 people identified that 4% experienced side-effects related to the skin, nervous system or gastrointestinal tract.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

ANTICOAGULANT AND ANTIPLATELET DRUGS

A theoretical risk exists that high doses (>170 mg anthocyanidins) may increase bleeding risk.

IRON

Reduced absorption is theoretically possible if taken at the same time because of the tannin content of the herb — separate doses by 2 hours.

HYPOGLYCAEMIC AGENTS

Additive effects theoretically possible with leaf preparations — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS

High doses (>170 mg anthocyanidins) should be use with caution by people with haemorrhagic disorders.

PREGNANCY USE

A study investigating bilberry extract for pregnancy-induced lower extremity oedema reported no adverse effects (Ulbricht & Basch 2005) — likely to be safe when berry is consumed in dietary amounts.

PRACTICE POINTS/PATIENT COUNSELLING

- Bilberry has antioxidant, anti-inflammatory and astringent actions and has considerable polyphenol content.
- Bilberry extract is a popular treatment in Europe for preventing and treating retinopathy. It is also used to treat several other ophthalmic conditions such as poor night vision, poor light adaptation, and sensitivity to glare, photophobia, glaucoma, myopia and cataract.

- Some research also suggests that it is useful in venous insufficiency, peripheral vascular disorders (such as Raynaud's syndrome) and capillary fragility.
- Approved by Commission E for the treatment of non-specific, acute diarrhoea and mild inflammatory conditions of the mouth and throat.
- Preliminary evidence suggests it may reduce serum glucose levels and triglycerides in diabetes and prevent peptic ulcer formation due to NSAIDs or stress; however, clinical research is still required to confirm these effects.
- In vitro investigation has identified anticarcinogenic activity.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Bilberry is used to relieve the symptoms of mild diarrhoea and improve poor night vision, sensitivity to glare, photophobia, peptic ulcers, varicose veins, venous insufficiency and haemorrhoids when taken internally. It is also used as a mouthwash, gargle or paint for mild inflammation of the mouth or throat, such as gingivitis or pharyngitis.

When will it start to work?

This depends on the indication. Improvements in night vision, photophobia and glare sensitivity have been reported within 2–4 weeks of use in some people whereas preventive effects are likely to require long-term use. In peripheral vascular diseases, 30 days' treatment may be required before effects are noticed.

Are there any safety issues?

Considered a safe herb overall, bilberry can theoretically reduce blood glucose levels in people with diabetes and so should be used carefully in these patients. At very high doses it may interact with warfarin and antiplatelet drugs.

REFERENCES

Anon. Vaccinium myrtillus (bilberry) [Monograph]. Altern Med Rev 6.5 (2001): 500-4.

Bertuglia S, Malandrino S, Colantuoni A. Effect of Vaccinium myrtillus anthocyanosides on ischaemia reperfusion injury in hamster cheek pouch microcirculation. Pharmacol Res 31.3-4 (1995): 183-7.

Blumenthal M. The ABC Clinical Guide to Herbs. American Botanical Council and Thieme, 2003.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bomser J et al. In vitro anticancer activity of fruit extracts from Vaccinium species. Planta Med 62.3 (1996): 212-16.

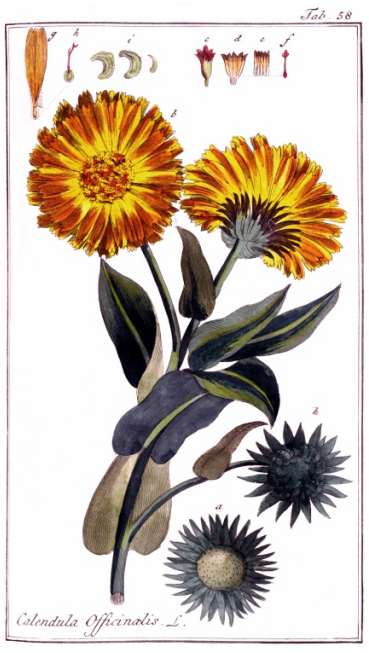
Canter PH, Ernst E. Anthocyanosides of Vaccinium myrtillus (bilberry) for night vision: a systematic review of placebo-controlled trials. Surv Opthalmol 49.1 (2004): 38-50.

Caselli L. Clinical and electroretinographic study on activity of anthocyanosides. Arch Med Int 37 (1985): 29-35.

Cignarella A et al. Novel lipid-lowering properties of Vaccinium myrtillus L. leaves, a traditional antidiabetic treatment, in several models of rat dyslipidaemia: a comparison with ciprofibrate. Thromb Res 84.5 (1996): 311-22.

Cristoni A, S Malandrino, Magistretti MJ. Effect of a natural flavonoid on gastric mucosal barrier. Arzneimittelforschung 39.5 (1989): 590-2.
Ghiringhelli C, Gregoratti L, Marastoni F. Capillarotropic action of anthocyanosides in high dosage in phlebopathic stasis. Minerva Cardioangiol 24.4 (1978); 255-76.
Gloria E, Peria A. Effect of anthocyanosides on the absolute visual threshold. Ann Ottalmol Clin Ocul 92 (1966): 595-607 [in Italian].
Hou DX. Potential mechanisms of cancer chemoprevention by anthocyanins. Curr Mol Med 3.2 (2003): 149-59.
Junemann G. On the effect of anthocyanosides on hemeralopia following quinine poisoning. Klin Monatsbl Augenheilkd 151 (1967): 891-6 [in German].
Kahkonen MP, Hopia AI, Heinonen M. Berry phenolics and their antioxidant activity. J Agric Food Chem 49.8 (2001): 4076-82.
Lietti A, Cristoni A, Picci M. Studies on Vaccinium myrtillus anthocyanosides. I. Vasoprotective and antiinflammatory activity. Arzneimittelforschung 26.5 (1976): 829-32.
Magistretti MJ, Conti M, Cristoni A. Antiulcer activity of an anthocyanidin from Vaccinium myrtillus. Arzneimittelforschung 38.5 (1988): 686-90.
Mian E et al. Anthocyanosides and the walls of the microvessels: further aspects of the mechanism of action of their protective effect in syndromes due to abnormal capillary fragility. Minerva Med 68.52 (1977): 3565-81.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Murray M. The Healing Power of Herbs. Rocklin, CA: Prima Health, 1995.
Muth ER, Laurent JM, Jasper P. The effect of bilberry nutritional supplementation on night visual acuity and contrast sensitivity. Altern Med Rev 5.2 (2000): 164-73.
Orsucci P et al. Treatment of diabetic retinopathy with anthocyanosides: a preliminary report. Clin Ocul 4 (1983): 377.
Perossini M et al. Diabetic and hypertensive retinopathy therapy with Vaccinium myrtillus anthocyanosides (Tegens™): Double-blind placebo controlled clinical trial. Ann Ottalmol Clin Ocul 113 (1987): 1173 [in Italian].
Pulliero G et al. Ex vivo study of the inhibitory effects of Vaccinium myrtillus anthocyanosides on human platelet aggregation. Fitoterapia LX.I (1989): 69-75.
Rhee DJ et al. Complementary and alternative medicine for glaucoma. Surv Ophthalmol 46.1 (2001): 43-55.
Roy S et al. Anti-angiogenic property of edible berries. Free Radic Res 36.9 (2002): 1023-31.
Scharrer A, Ober M. Anthocyanosides in the treatment of retinopathies (author's transl). Klin Monatsbl Augenheilkd 178.5 (1981): 386-9.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby Inc., 2005.
Varma SD, Richards RD. Ascorbic acid and the eye lens. Ophthalmic Res 20.3 (1988): 164-73.
Varma SD, Srivastava VK, Richards RD. Photoperoxidation in lens and cataract formation: preventive role of superoxide dismutase, catalase and vitamin C. Ophthalmic Res 14.3 (1982): 167-75.
Varma SD et al. Studies on Emory mouse cataracts: oxidative factors. Ophthalmic Res 26.3 (1994): 141-8.

Bitter melon



Historical note Bitter melon is used as a traditional medicine wherever it is found. It has a long history of use in Asia, Africa and Latin America and has been widely acclaimed as an important remedy for diabetes mellitus since ancient times. The term *momordica* means 'to bite' and refers to the jagged edges of the leaf, which appear as if bitten. Bitter melon has been used to treat fevers, viral infections and as an emmenagogue in reproductive health. It has also been used as a treatment for gastrointestinal complaints, worms, constipation, headaches, skin conditions and diabetes. The fruit is used topically for wound healing. The plant has also been used in traditional ceremonies and considered a powerful charm which is worn as a necklace, wrist or ankle bracelet or crown (Beloin et al 2005). The ritual ceremonial importance of the plant is accompanied by its considerable reputation as a medicinal plant for the treatment of disease.

OTHER NAMES
African cucumber, balsam pear, bitter gourd, kakara, karela, ku gua, sushavi, wild cucumber

BOTANICAL NAME/FAMILY
Momordica charantia (family Curcubitaceae)

PLANT PARTS USED
Fruit, leaves

CHEMICAL COMPONENTS
It contains several biologically active constituents that include glycosides (e.g. momordicins I and II), steroidal saponins (e.g. charantins), alkaloids, fixed oils and proteins (e.g. MAP30: *Momordica* anti-HIV protein; molecular weight, 30 kD). The immature fruits are a good source of vitamin C and also provide vitamin A, phosphorus, and iron (Grover & Yadav 2004).

MAIN ACTIONS
Bitter melon has been the subject of countless studies and has demonstrated significant pharmacological activity in a variety of experimental models.

ANTIDIABETIC

The antidiabetic potential of bitter melon is well established in normal, streptozocin- or alloxan-induced diabetic animals and in genetic models of diabetes (Ahmed et al 2004, Bailey et al 1985, Day et al 1990, Jayasooriya et al 2000, Kar et al 2003, Miura et al 2001, 2004, Reyes et al 2005, Sarkar et al 1996, Shibb et al 1993). All parts of the plant (fruit pulp, seeds, leaves and whole plant) have shown activity.

A systematic study comparing the hypoglycaemic activity of three extracts in vivo found that the methanolic extract of dried whole fruits and seeds reduced blood glucose by 49% at the end of the first week, which became 39% by week 5; the aqueous extract of fresh, unripe, whole fruits reduced fasting blood glucose by 50%, which was consistent until the study ended, and the chloroform extract of dried whole fruits and seeds showed almost no hypoglycaemic activity (Virdi et al 2003).

These observations have special significance when one considers that the whole bitter gourd is cooked in water and consumed in many cultures, particularly in India.

The hypoglycaemic activity is attributed to a mixture of steroidal saponins known as charantins, insulin-like peptides and alkaloids that are concentrated in the fruit (Grover & Yadav 2004).

Based on studies with animal models, it appears that *Momordica charantia* increases the renewal of beta-cells in the pancreas, or may permit the recovery of partially destroyed beta-cells (Ahmed et al 1998), and stimulates pancreatic insulin secretion (Welihinda et al 1982). It also improves peripheral glucose uptake (Welihinda & Karunanayake 1986). A study with streptozocin-induced diabetic animals found that bitter melon juice normalises the structural abnormalities of peripheral nerves, regulates glucose uptake into the jejunum membrane brush border vesicles and stimulates glucose uptake into skeletal muscle cells (Ahmed et al 2004).

LIPID-LOWERING

Lipid-lowering activity has been reported in studies of normal and diabetic animals for the fruit extract, flavonoids extracted from bitter melon or a methanolic fraction of the plant (Ahmed et al 2001, Anila & Vijayalakshmi 2000, Chaturvedi 2005, Chaturvedi et al 2004, Senanayake et al 2004, Singh et al 1989). Typically, decreases in triglyceride and LDL levels and increases in HDL levels are seen.

In contrast, karela oil increased total lipid levels and phospholipid concentrations in heart and brain as compared with linseed, according to an in vivo study (Dhar & Bhattacharyya 1998).

ANTIVIRAL

Several constituents found in bitter melon (e.g. alpha- and beta-momorcharin, lectin and MAP 30) have demonstrated in vitro antiviral activity against Epstein-Barr, HSV-1, HIV, coxsackievirus B3 and polio viruses (Beloin et al 2005, Bourinbaiar & Lee-Huang 1998, Foa-Tomasi et al 1982, Grover & Yadav 2004, Sun et al 2001).

A study using a lyophilised extract of *Momordica charantia* against HSV-1 suggests that the presence of light may be important for antiviral activity (Beloin et al 2005). The active antiviral constituents are not the main bitter principles momordicins I and II, as these have not shown activity against HSV-1 (Beloin et al 2005). One constituent referred to as MAP30 has received special attention as it exhibits potent inhibition of HIV-1 and HSV (Schreiber et al 1999).

ANTIBACTERIAL

Broad-spectrum antibacterial activity has been demonstrated for the leaf extracts (aqueous, ethanol, and methanol) (Grover & Yadav 2004). In vitro antimicrobial activity occurred against *Escherichia coli*, *Salmonella paratyphi*, *Shigella dysenterae* and against *Streptomyces griseus* (Grover & Yadav 2004, Ogata et al 1991, Omoregbe et al 1996). In a phase II study, the leaf extracts inhibited the growth of *Mycobacterium tuberculosis* in vitro, using the BACTEC 460 susceptibility test method (Frame et al 1998).

Tests with an extract of the entire plant demonstrated antiprotozoal activity against *Entamoeba histolytica* (Grover & Yadav 2004) and a fruit extract exhibited activity against *Helicobacter pylori* (Yesilada et al 1999).

ANTHELMINTIC

The anthelmintic activity of the leaves of *Momordica charantia* against *Caenorhabditis elegans* was identified and described as high in one study (Beloin et al 2005). Triterpene glycosides of bitter melon (momordicins I and II) were found to be very active nematicides. A preparation of *M. charantia* exhibited stronger anthelmintic activity in vitro than piperazine hexahydrate against *Ascaridia galli* (Lal et al 1976).

ABORTIFACIENT

Experimental studies with mice have demonstrated that bitter melon can induce abortions (Chan et al 1984, 1985, Tam et al 1984). According to an in vivo study, the glycoproteins alpha- and beta-momorcharin isolated from the seeds are effective in inducing early and midterm abortions (Chan et al 1986) and the momorcharins were teratogenic in cultured mouse embryos (Chan et al 1986).

OTHER ACTIONS

ANTICANCER

Various preliminary studies (in vitro and in vivo) with crude bitter melon extract and its various constituents (e.g. MAP 30, momordin I, alpha-momorcharin) have shown anticancer activity (Basch et al 2003).

ANALGESIC

An in vivo study identified a dose-dependent analgesic effect for a methanolic extract of bitter melon seeds (Biswas et al 1991). The dose that produced a 50% response was 5 mg/kg SC. Analgesic activity was rapid and short lived. The opiate pathway was not involved, as naloxone pretreatment did not modify the analgesic response.

CLINICAL USE

Although bitter melon and several of its constituents have been investigated in many experimental studies, few clinical studies have been conducted.

DIABETES

Various bitter melon preparations have demonstrated hypoglycaemic activity in experimental models, but double-blind controlled studies are not available to determine its clinical effects.

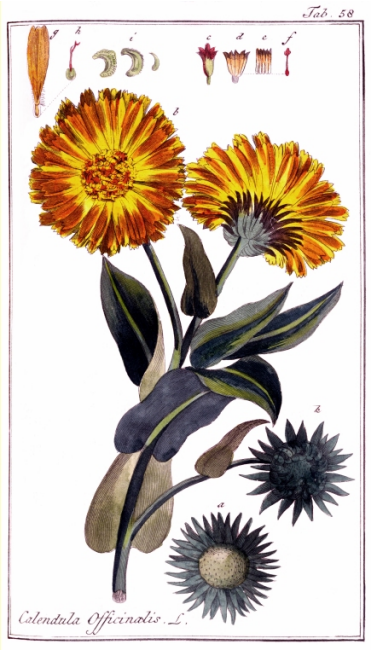
Current evidence of efficacy in diabetes comes from case series and an open study that have shown that bitter melon juice, fruit, and dried powder exerts a moderate hypoglycaemic effect (Basch et al 2003, Ahmad et al 1999). The largest study involved 100 people with type 2 diabetes and found that drinking a homogenised suspension of the vegetable pulp of *M. charantia* caused a significant reduction ($P < 0.001$) of postprandial serum glucose in 86% cases and fasting glucose in 5% cases (Ahmad et al 1999).

Bitter melon has shown promising effects in prevention as well as delay in progression of diabetic complications (e.g. nephropathy, neuropathy, cataract and insulin resistance) in experimental animals (Grover & Yadav 2004).

CANCER

Controlled studies are not available to determine the clinical significance of the encouraging experimental findings.

According to an intriguing case report from the 1970s, a patient with gall-bladder carcinoma who was given an estimated survival of 2 years after surgery survived a further 10 years, possibly because of drinking bitter melon tea daily. The signs and symptoms of disease reappeared after consumption of the tea ceased for 4 months because of lack of availability and the patient subsequently died (West et al 1971).



HIV

Nine case reports of people with HIV taking bitter melon, sometimes in combination with other herbal medicines, suggest it may normalise the CD4/CD8 ratio; however, further investigation is required (Zhang & Khanyile 1992).

OTHER USES

Traditionally, bitter melon has been used as a treatment for a variety of conditions such as diabetes, gastrointestinal complaints, worms, constipation, headaches, skin conditions, viral infections and as an emmenagogue in reproductive health. Experimental studies support its use in some of these indications; however, controlled studies are still required to determine its role in practice.

DOSAGE RANGE

GENERAL GUIDE

- Juice: 50–100 mL/day

ACCORDING TO CLINICAL STUDIES

- Diabetes: aqueous extract of bitter melon fruit juice containing 100 g of fruit in 100 mL of extract taken daily

ADVERSE REACTIONS

There are two case reports of bitter melon tea inducing hypoglycaemic coma and convulsions in children (Basch et al 2003). Headaches have been reported with ingestion of the seeds (Ulbricht & Basch 2005).

SIGNIFICANT INTERACTIONS

Controlled studies are not available therefore interactions are based on evidence of activity and are largely theoretical and speculative.

HYPOGLYCAEMIC AGENTS

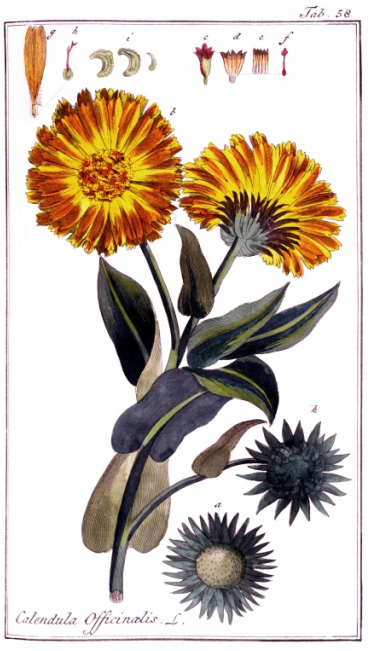
Theoretically an additive effect is possible, resulting in increased hypoglycaemic effects — caution. Possible beneficial interaction when used under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Avoid bitter melon seed or the outer rind due to the presence of toxic lectins and avoid use of bitter melon in people with glucose-6-phosphate dehydrogenase deficiency (Ulbricht & Basch 2005).

When low doses of bitter melon extract were ingested for up to 2 months in experimental models, no signs of nephrotoxicity, hepatotoxicity or adverse effects on food intake, growth organ weights and haematological parameters were observed.

However, toxicity and even death in laboratory animals have been reported when extracts in high doses were administered intravenously or intraperitoneally (Kusamran et al 1998).



PREGNANCY USE

Based on experimental studies in animal models and traditional use, bitter melon is contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Bitter melon is used as a traditional remedy for diabetes mellitus. Evidence from experimental studies and case reports support moderate hypoglycaemic activity; however, controlled studies have not yet been conducted.
- Traditionally, bitter melon has also been used as a treatment for gastrointestinal complaints, worms, constipation, headaches, skin conditions, viral infections and as an emmenagogue.
- According to experimental studies, bitter melon and/or its various constituents exert lipid-lowering, antibacterial, anthelmintic, abortifacient, antineoplastic and analgesic activities.
- Bitter melon is contraindicated in pregnancy and people with glucose-6-phosphate dehydrogenase deficiency.
- Avoid bitter melon seed or the outer rind, which have toxic lectins.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

According to preliminary research, bitter melon may lower blood glucose levels and aid in the management of diabetes.

When will it start to work?

This is difficult to predict. Diabetics should monitor their blood glucose readings when taking bitter melon.

Are there any safety issues?

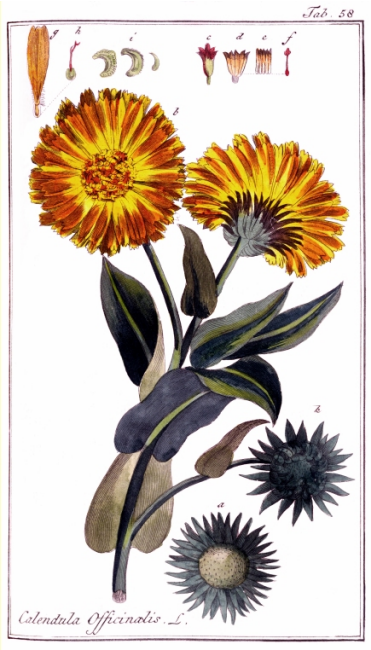
Bitter melon is contraindicated in pregnancy and people with glucose-6-phosphate dehydrogenase deficiency. The seeds and outer rind should be avoided because they contain toxic lectins. Diabetic patients should monitor their blood glucose when taking bitter melon to prevent hypoglycaemia.

REFERENCES

Ahmad N et al. Effect of Momordica charantia (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients. Bangladesh Med Res Council Bull 25 (1999): 11-13.

Ahmed I et al. Effects of Momordica charantia fruit juice on islet morphology in the pancreas of the streptozotocin-diabetic rat. Diabetes Res Clin Pract 40 (1998): 145-51.

Ahmed I et al. Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic Momordica charantia (karela) fruit extract in streptozotocin-induced diabetic rats. Diabetes Res Clin Pract 51 (2001): 155-61.
Ahmed I et al. Beneficial effects and mechanism of action of Momordica charantia juice in the treatment of streptozotocin-induced diabetes mellitus in rat. Mol Cell Biochem 261 (2004): 63-70.
Anila L, Vijayalakshmi NR. Beneficial effects of flavonoids from Sesamum indicum, Emblica officinalis and Momordica charantia. Phytother Res 14 (2000): 592-5.
Bailey CJ et al. Cerasee, a traditional treatment for diabetes: Studies in normal and streptozotocin diabetic mice. Diabetes Res 2 (1985): 81-4.
Basch E, Gabardi S, Ulbricht C. Bitter melon (Momordica charantia): a review of efficacy and safety. Am J Health Syst Pharm 60 (2003): 356-9.
Beloin N et al. Ethnomedicinal uses of Momordica charantia (Cucurbitaceae) in Togo and relation to its phytochemistry and biological activity. J Ethnopharmacol 96 (2005): 49-55.
Biswas AR, Ramaswamy S, Bapna JS. Analgesic effect of Momordica charantia seed extract in mice and rats. J Ethnopharmacol 31 (1991): 115-18.
Bourinbaiar AS, Lee-Huang S. The activity of plant-derived antiretroviral proteins MAP30 and GAP31 against herpes simplex virus in vitro. Biochem Biophys Res Commun 219 (1996): 923-9.
Chan WY et al. The termination of early pregnancy in the mouse by beta-momorcharin. Contraception 29 (1984): 91-100.
Chan WY et al. The inhibitory effects of beta-momorcharin on endometrial cells in the mouse. Contraception 31 (1985): 83-90.
Chan WY et al. Effects of momorcharins on the mouse embryo at the early organogenesis stage. Contraception 34 (1986): 537-44.
Chaturvedi P. Role of Momordica charantia in maintaining the normal levels of lipids and glucose in diabetic rats fed a high-fat and low-carbohydrate diet. Br J Biomed Sci 62 (2005): 124-6.
Chaturvedi P et al. Effect of Momordica charantia on lipid profile and oral glucose tolerance in diabetic rats. Phytother Res 18 (2004): 954-6.
Day C et al. Hypoglycaemic effect of Momordica charantia extracts. Planta Med 56 (1990): 426-9.
Dhar P, Bhattacharyya DK. Nutritional characteristics of oil containing conjugated octadecatrienoic fatty acid. Ann Nutr Metab 42 (1998): 290-6.
Foa-Tomasi L et al. Effect of ribosome-inactivating proteins on virus-infected cells. Inhibition of virus multiplication and of protein synthesis. Arch Virol 71 (1982): 323-32.
Frame AD et al. Plants from Puerto Rico with anti-Mycobacterium tuberculosis properties. Puerto Rico Health Sci J 17 (1998): 243-52.
Grover JK, Yadav SP. Pharmacological actions and potential uses of Momordica charantia: a review. J Ethnopharmacol 93 (2004): 123-32.
Jayasooriya AP et al. Effects of Momordica charantia powder on serum glucose levels and various lipid parameters in rats fed with cholesterol-free and cholesterol-enriched diets. J Ethnopharmacol 72 (2000): 331-6.
Kar A et al. Comparative evaluation of hypoglycaemic activity of some Indian medicinal plants in alloxan diabetic rats. J Ethnopharmacol 84 (2003): 105-8.
Kusamran WR et al. Effects of neem flowers, Thai and Chinese bitter gourd fruits and sweet basil leaves on hepatic monooxygenases and glutathione S-transferase activities, and in vitro metabolic activation of chemical carcinogens in rats. Food Chem Toxicol 36 (1998): 475-84.
Lal J et al. In vitro anthelmintic action of some indigenous medicinal plants on Ascardia galli worms. Indian J Physiol Pharmacol 20 (1976): 64-8.
Miura T et al. Hypoglycemic activity of the fruit of the Momordica charantia in type 2 diabetic mice. J Nutr Sci Vitaminol (Tokyo) 47 (2001): 340-4.
Miura T et al. Suppressive activity of the fruit of Momordica charantia with exercise on blood glucose in type 2 diabetic mice. Biol Pharm Bull 27 (2004): 248-50.



Ogata F et al. Purification and amino acid sequence of a bitter gourd inhibitor against an acidic amino acid-specific endopeptidase of Streptomyces griseus. J Biol Chem 266 (1991): 16715-21.
Omoregbe RE, Ikuebe OM, Ihimire IG. Antimicrobial activity of some medicinal plants extracts on Escherichia coli, Salmonella paratyphi and Shigella dysenteriae. Afr J Med Med Sci 25 (1996): 373-5.
Reyes BA et al. Anti-diabetic potentials of Momordica charantia and Andrographis paniculata and their effects on estrous cyclicity of alloxan-induced diabetic rats. J Ethnopharmacol 105 (2006): 196-200.
Sarkar S, Pranava M, Marita R. Demonstration of the hypoglycemic action of Momordica charantia in a validated animal model of diabetes. Pharmacol Res 33 (1996): 1-4.
Schreiber CA et al. The antiviral agents, MAP30 and GAP31, are not toxic to human spermatozoa and may be useful in preventing the sexual transmission of human immunodeficiency virus type 1. Fertil Steril 72 (1999): 686-90.
Senanayake GV et al. The effects of bitter melon (Momordica charantia) extracts on serum and liver lipid parameters in hamsters fed cholesterol-free and cholesterol-enriched diets. J Nutr Sci Vitaminol (Tokyo) 50 (2004): 253-7.
Shibib BA et al. Hypoglycaemic activity of Coccinia indica and Momordica charantia in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. Biochem J 292 (1993): 267-70.
Singh N et al. Effects of long term feeding of acetone extract of Momordica charantia (whole fruit powder) on alloxan diabetic albino rats. Indian J Physiol Pharmacol 33 (1989): 97-100.
Sun Y et al. Anti-HIV agent MAP30 modulates the expression profile of viral and cellular genes for proliferation and apoptosis in AIDS-related lymphoma cells infected with Kaposi's sarcoma-associated virus. Biochem Biophys Res Commun 287 (2001): 983-94.
Tam PP et al. Effects of alpha-momorcharin on preimplantation development in the mouse. J Reprod Fertil 71 (1984): 33-8.
Ulbricht C, Basch E. Bitter melon. In: Natural Standard Herb and Supplement Reference. St Louis: Mosby (2005): 76-80.
Virdi J et al. Antihyperglycemic effects of three extracts from Momordica charantia. J Ethnopharmacol 88 (2003): 107-11.
Welihinda J, Karunanayake EH. Extra-pancreatic effects of Momordica charantia in rats. J Ethnopharmacol 17 (1986): 247-55.
Welihinda J et al. The insulin-releasing activity of the tropical plant Momordica charantia. Acta Biol Med Ger 41 (1982): 1229-40.
West ME et al. The anti-growth properties of extracts from Momordica charantia L. West Indian Med J 20 (1971): 25-34.
Yesilada E et al. Screening of Turkish anti-ulcerogenic folk remedies for anti-Helicobacter pylori activity. J Ethnopharmacol 66 (1999): 289-93.
Zhang QC, Khanyile C. Primary report on the use of Chinese herbal extract of Momordica charantia (bitter melon) in HIV infected patients (Abstract). In: Proceedings of the VIII International Conference on AIDS/III STD World Congress, Vol. 3. Amsterdam, The Netherlands, July 19-24, 1992; as cited in Micromedex. Thomson 2003. Available at: www.micromedex.com (accessed 17-03-06).

Black cohosh

Historical note Native Americans first used black cohosh many centuries ago, mainly as a treatment for female reproductive problems but also for fatigue, snakebite and arthritis. It was widely adopted by European settlers, eventually becoming a very popular treatment in Europe for gynaecological conditions.

COMMON NAME
Black cohosh

OTHER NAMES
Baneberry, black snakeroot, bugbane, rattle-root, rattle-top, rattleweed, squawroot, traubensilberkerze, wanzenkraut

BOTANICAL NAME/FAMILY
Cimicifuga racemosa now known as *Actaea racemosa* Linnaeus (family Ranunculaceae)

PLANT PARTS USED
Rhizome and root

CHEMICAL COMPONENTS
Black cohosh contains various triterpene glycosides, including cimicifugoside and actein, 27-deoxyactein, N-methylcytisine and other quinolizidine alkaloids, phenolic acids, isoferulic and salicylic acids, resins, fatty acids and tannins.

Until recently, the isoflavone, formononetin, was believed to be a pharmacologically important constituent of the herb; however, recent testing of numerous samples has failed to detect it in any sample, including the commercial products Remifemin (Schaper & Brummer GmbH & Co. KG, Salzgitter, Germany) and CimiPure (Kennelly et al 2002).

MAIN ACTIONS

HORMONE MODULATION

It appears unlikely that black cohosh exerts oestrogenic activity. Although oestrogenic activity has been detected in some tests (Duker et al 1991, Kruse et al 1999, Liu et al 2001) it has not been observed in others (Beck et al 2003, Einer-Jensen et al 1996, Zierau et al 2002). Additionally, the herb has demonstrated anti-oestrogenic activity in one test (Zierau et al 2002) and in 2003, black cohosh was investigated in a variety

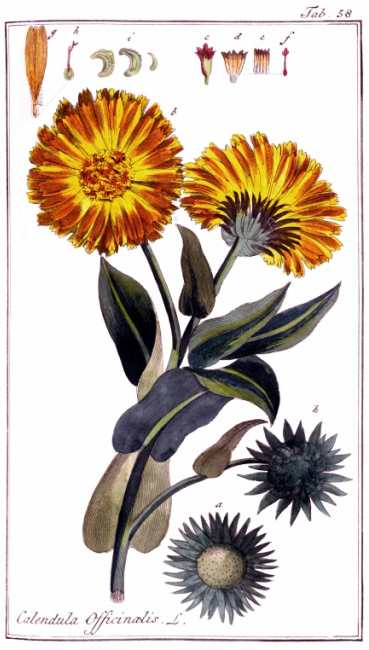
of different assays and did not demonstrate oestrogenic activity in any assay system (Lupu et al 2003).

More recently, results from a study using black cohosh extract BNO 1055 in ovariectomised rats found it has selective oestrogen receptor modulator activity with no action in the uterus, but beneficial effects in the hypothalamopituitary unit and in the bone (Seidlova et al 2003). This has been confirmed in a double-blind, randomised, multicentre study using the same black cohosh extract (Wuttke et al 2003). In that study, the herbal extract was equipotent with conjugated oestrogens in reducing menopausal symptoms, had beneficial effects on bone metabolism and significantly increased vaginal superficial cells; however, it did not exert uterotrophic activity.

Overall it is generally agreed that black cohosh reduces LH secretion. This has been confirmed in a human study and is believed to be the result of at least three different active constituents acting synergistically (Duker et al 1991).

Clinical note – Selective oestrogen receptor modulators

These are compounds that, in contrast to pure oestrogen agonists or antagonists, have a mixed and selective pattern of oestrogen agonist–antagonist activity, which largely depends on the tissue targeted. The therapeutic aim of using these substances is to produce oestrogenic actions in those tissues in which it would be beneficial (e.g. bone, brain, liver) and have either no activity or antagonistic activity in tissues, such as breast and endometrium, where oestrogenic actions (cellular proliferation) might be deleterious. They are a relatively new class of pharmacologically active agents and are being used by women who cannot tolerate pharmaceutical HRT or are unwilling to use it. The most actively studied are tamoxifen and raloxifen (Hernandez & Pluchino 2003).



ANTI-INFLAMMATORY

Animal studies have identified some anti-inflammatory activity (Hirabayashi et al 1995).

SEROTONERGIC

In vitro tests identified compounds in a black cohosh methanol extract that were capable of strong binding to the 5-HT(1A), 5-HT(1D), and 5-HT(7) receptor subtypes (Burdette et al 2003). Further investigation by these authors found that the components functioned as a partial agonist of the 5-HT(7) receptor.

DOPAMINERGIC

It is suggested that the effects of *A. racemosa* may be due to dopaminergic activity, because black cohosh extract BNO 1055 displayed dopaminergic activity with a D(2)-receptor assay (Jarry et al 2003). Considering that dopaminergic drugs reduce some symptoms (e.g. hot flushes) associated with menopause, this theory is feasible; however, further studies are required to explain why black cohosh is devoid of the typical side-effects associated with dopaminergic drugs (Borelli & Ernst 2002).

OTHER ACTIONS

A dose-dependent antihypertensive effect was identified for a triterpene found in black cohosh (actein) in animals tests. The clinical significance of this finding for humans using black cohosh root is unknown (Genazzani & Sorrentino 1962). Black cohosh is traditionally thought to act as a tonic and nervous system restorative medicine and exert antispasmodic and anti-inflammatory activity.

No effect on CYP3A was detected in a recent human study (Gurley et al 2006).

CLINICAL USE

MENOPAUSAL SYMPTOMS

Most clinical research has tested the commercial preparation of black cohosh known as Remifemin, which is standardised to contain triterpene glycosides (0.8–1.2 mg/tablet), but recently there has been some investigation of BNO 1055, an aqueous ethanolic extract (58% vol/vol), sold as Klimadynon and Menofem (Bionorica AG, Neumarkt, Germany).

A review of eight clinical trials published in 1998 found that black cohosh (Remifemin) is a safe and effective alternative to HRT for menopausal patients in whom HRT is contraindicated (Lieberman 1998). Symptoms responding to treatment with black cohosh include hot flushes, vaginal thinning and drying, night sweats, sleep disturbances, anxiety and depression.

Two clinical studies have been conducted in recent years with the BNO 1055 black cohosh extract. A double-blind, randomised, multicentre study compared the effects of BNO 1055 (40 mg/day) to conjugated oestrogens (0.6 mg/day) and placebo on climacteric complaints, bone metabolism and endometrium (Wuttke et al 2003). The study involved 62 postmenopausal women who took their allocated treatment for 3 months. BNO 1055 proved to be equipotent to conjugated oestrogens and superior to placebo in reducing climacteric symptoms and both active treatments produced beneficial effects on bone metabolism. Vaginal superficial cells increased with both active treatments; however, BNO 1055 had no effect on endometrial thickness, which was significantly increased by conjugated oestrogens.

A randomised study (Hernandez & Pluchino 2003) was also performed with 136 young premenopausal breast cancer survivors experiencing hot flushes as a result of tamoxifen therapy. When BNO 1055 (Menofem/Klimadynon, corresponding to 20 mg of herbal drug) was used together with tamoxifen for 12 months, the number and severity of hot flushes were reduced, with almost 50% of subjects becoming free of hot flushes, and severe hot flushes were reported by only 24% compared with 74% for those using tamoxifen alone.

In contrast, a previous double-blind, placebo controlled study ($n = 85$) failed to detect significant improvements with black cohosh for hot flush frequency or severity when used by patients with breast cancer for 2 months and who were also taking tamoxifen (Jacobson et al 2001). Unfortunately, the authors of that study did not specify which black cohosh product was being used or the dosage, making a comparison with the previous study difficult.

Recently, a Swiss multicentre, randomised, placebo-controlled, double-blind study (Frei-Kleiner et al 2005) was conducted with 122 menopausal women and found that daily black cohosh root extract Cr 99 (6.5 mg dried rhizome extract, drug/extract ratio 4.5–8.5:1 corresponding to 29–55 mg with an average of 42 mg crude drug, extraction solvent 60% ethanol v/v) had a significant effect in women with menopausal disorders of moderate intensity according to a Kupperman Index ≥20. Concerning the Menopause Rating Scale, active treatment decreased score values by 48% in the *A. racemosa* group compared with 14% for placebo.

Herbal combination studies One study has investigated the effects of a fixed combination of isopropanolic black cohosh (Remifemin; standardised to 1 mg triterpene glycosides) and ethanolic St John's wort (standardised to 0.25 mg total hypericine) in women with menopausal symptoms with pronounced psychological symptoms (Uebelhack et al 2006). The double-blind, randomised study of 301 women found that 16 weeks of herbal treatment produced a significant 50% reduction in the Menopause Rating Scale score compared with 20% with placebo and a significant 42% reduction in the Hamilton Depression Rating Scale compared with only 13% in the placebo group. Each treatment tablet contained black cohosh extract (corresponding on average to 3.75 mg native extract and 22.5–41.25 mg rootstock) and St John's wort extract (corresponding to 70 mg native extract and 245–350 mg herb). Patients took two tablets twice daily for 8 weeks then reduced to one tablet twice daily for the remainder of the study. There were no relevant group differences regarding adverse events, laboratory values, or tolerability.

A combination of soy isoflavones, black cohosh and nutritional supplements failed to have a significant effect on menopausal symptoms in a 12-week randomised,

placebo-controlled, double-blind study of 124 women (Verhoeven et al 2005). Women in the supplement group received 125 mg soy extract daily (providing 50 mg isoflavones including 24 mg genistein and 21.5 mg daidzein), 1,500 mg evening primrose oil extract (providing 150 mg gamma linoleic acid), 100 mg *Actaea racemosa* L. extract (providing 8 mg deoxyacetein), 200 mg calcium, 1.25 μg vitamin D, and 10 IU vitamin E, whereas the women in the placebo group received 2000 mg olive oil daily.

Commission E has approved the use of this herb as a treatment for menopausal symptoms (Blumenthal et al 2000). Similarly, the World Health Organization (WHO) recognises its use for the 'treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability'. The North American Menopause Society recommends black cohosh, in conjunction with lifestyle approaches, as a treatment option for women with mild menopause-related symptoms (2004).

PREMENSTRUAL SYNDROME AND DYSMENORRHOEA

Although no clinical studies are available, the pharmacological activity of the herb suggests that it may be useful. Commission E has approved the use of black cohosh as a treatment in these conditions (Blumenthal et al 2000).

OTHER USES

Black cohosh has been used traditionally to treat a variety of female reproductive disorders, inflammation, diarrhoea and rheumatism. It has also been used to promote menstruation. The British Herbal Pharmacopoeia states it is indicated in ovarian dysfunction and ovarian insufficiency.

MENSTRUAL MIGRAINE

A RCT of 49 women with menstrual migraines tested placebo against a herbal combination consisting of 60 mg soy isoflavones, 100 mg dong quai, and 50 mg black cohosh, with each component standardised to its primary alkaloid (Burke et al 2002). Over the course of the study, the average frequency of menstrually associated migraine episodes was significantly reduced in the active treatment group.

DOSAGE RANGE

- Decoction or powdered root: 0.3–2 g three times daily.
- Tincture (1:10): 2–4 mL three times daily.
- Fluid extract (1:1) (g/mL): 0.3–2 mL three times daily.

Many practitioners have used black cohosh long term without safety concerns; however, Commission E does not recommend more than 6 months' continuous use.

TOXICITY

Overdose has produced nausea and vomiting, vertigo and visual disturbances.

IDIOSYNCRATIC HEPATIC REACTIONS

In February 2006 the TGA announced that based on the appraisal of case reports, a causal association between black cohosh and serious hepatitis exists; however, the incidence is very low considering its widespread use. As a result, products available in Australia containing black cohosh will have to carry label warnings informing consumers of the risk by 2007.

The conclusion made by the TGA is considered controversial by some experts because numerous confounding factors were present in many of the case reports, such as the use of multiple ingredient preparations, concurrent use of at least one pharmaceutical medicine and the presence of other medical conditions.

ADVERSE REACTIONS

Although large doses are reported to produce dizziness, headache, tremors or giddiness in some people, gastrointestinal disturbances and rashes are the most common adverse effects, according to data from clinical studies and spontaneous reporting programs (Huntley & Ernst 2003). The adverse effects tend to be rare, mild and reversible.

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Results from a 2002 study testing the safety of black cohosh in an in vitro model for oestrogen-dependent breast tumours found that the herbal extract significantly inhibited tumour cell proliferation, oestrogen-induced proliferation and enhanced the antiproliferative effects of tamoxifen (Bodinet & Freudenstein 2002). It is suggested that black cohosh only be used under professional supervision for treatment of oestrogen-dependent tumours or during pregnancy.

PREGNANCY USE

Although it has been used to assist in childbirth, black cohosh is not recommended in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Several clinical trials have tested black cohosh in menopause and generally found it to be an effective symptom reliever.
- It appears that 4–12 weeks' continuous treatment are required for adequate menopausal symptom relief.

- Black cohosh is also used in the treatment of premenstrual syndrome and dysmenorrhea and is Commission E-approved for these uses; however, controlled studies are not available to confirm efficacy.
- There is some evidence suggesting black cohosh exerts selective oestrogen receptor modulator activity, serotonergic activity and possibly dopaminergic activity.
- Black cohosh should be only used under professional supervision for treatment of oestrogen-dependent tumours or during pregnancy.
- Black cohosh is well tolerated; however, rare case reports of idiosyncratic hepatic reactions have been described.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Black cohosh has been well tested and shown to be an effective treatment for menopausal symptoms in most women, especially those with mild to moderate symptoms. It may also be useful in the treatment of premenstrual syndrome and prevention of period cramping.

When will it start to work?

Studies suggest that benefits are seen within 4–12 weeks' for the treatment of menopausal symptoms.

Are there any safety issues?

Black cohosh should only be used under professional supervision for treatment of oestrogen-dependent tumours or during pregnancy.

REFERENCES

Beck V et al. Comparison of hormonal activity (estrogen, androgen and progestin) of standardized plant extracts for large scale use in hormone replacement therapy. J Steroid Biochem Mol Biol 84.2-3 (2003): 259-68.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bodinet C, Freudenstein J. Influence of Cimicifuga racemosa on the proliferation of estrogen receptor-positive human breast cancer cells. Breast Cancer Res Treat 76.1 (2002): 1-10.

Borrelli F, Ernst E. Cimicifuga racemosa: a systematic review of its clinical efficacy. Eur J Clin Pharmacol. 58 (2002): 235-41.

Burdette JE et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. J Agric Food Chem 51.19 (2003): 5661-70.

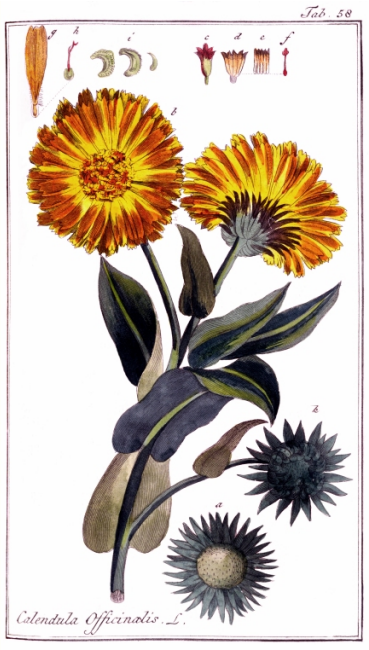
Burke BE, Olson RD, Cusack BJ. Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. Biomed Pharmacother 56.6 (2002): 283-8.

Duker EM et al. Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats. Planta Med 57.5 (1991): 420-4.

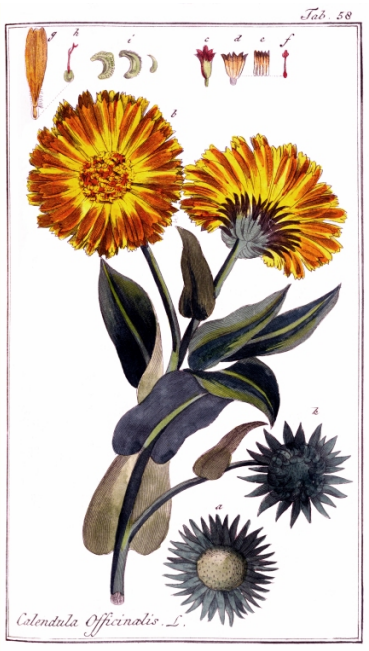
Einer-Jensen N et al. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. Maturitas 25.2 (1996): 149-53.

Frei-Kleiner S et al. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 51 (2005): 397-404.

Genazzani E, Sorrentino L. Vascular action of actein: active constituent of Actaea racemosa L. Nature 194.4828 (1962): 544-5 (as cited in Micromedex Thomsen 2003. www.micromedex.com)
Gurley B et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. J Clin Pharmacol 46 (2006): 201-13.
Hernandez MG, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. Maturitas 44 Suppl 1 (2003): S59-65
Hirabayashi T et al. Inhibitory effect of ferulic acid and isoferulic acid on murine interleukin-8 production in response to influenza virus infections in vitro and in vivo. Planta Med 61.3 (1995): 221-6 (as cited in Micromedex Thomsen 2003. www.micromedex.com)
Huntley A, Ernst E. A systematic review of the safety of black cohosh. Menopause 10.1 (2003): 58-64.
Jacobson JS et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 19.10 (2001): 2739-45.
Jarry H et al. In vitro effects of the Cimicifuga racemosa extract BNO 1055. Maturitas 44 Suppl 1 (2003): S31-8.
Kennelly EJ et al. Analysis of thirteen populations of black cohosh for formononetin. Phytomedicine 9.5 (2002): 461-7.
Kruse SO et al. Fukiic and piscidic acid esters from the rhizome of Cimicifuga racemosa and the in vitro estrogenic activity of fukinolic acid. Planta Med 65.8 (1999): 763-4.
Lieberman S. A review of the effectiveness of Cimicifuga racemosa (black cohosh) for the symptoms of menopause. J Womens Health 7.5 (1998): 525-9.
Liu Z et al. Estrogenicity of black cohosh (Cimicifuga racemosa) and its effect on estrogen receptor level in human breast cancer MCF-7 cells. Wei Sheng Yan Jiu 30.2 (2001): 77-80.
Lupu R et al. Black cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. Int J Oncol 23(5); 1407-12.
North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 11 (2004): 11-33.
Seidlova-Wuttke D et al. Evidence for selective estrogen receptor modulator activity in a black cohosh (Cimicifuga racemosa) extract: comparison with estradiol-17beta. Eur J Endocrinol 149 (2003): 351-62.
Uebelhack R et al. Black cohosh and St John's wort for climacteric complaints: A randomized trial. Obstet Gynecol 107 (2006): 247-55.
Verhoeven MO et al. Effect of a combination of isoflavones and Actaea racemosa Linnaeus on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study. Menopause 12 (2005): 412-20.
Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas 44 Suppl 1 (2003): S67-77.
Zierau O et al. Antiestrogenic activities of Cimicifuga racemosa extracts. J Steroid Biochem Mol Biol 80.1 (2002): 125-30.



Brahmi



Historical note Brahmi is the Sanskrit name for the herb *Bacopa monniera* and has been used in Ayurvedic medicine as a nerve tonic since time immemorial. Under this system, *B. monniera* is classified under 'Medhya rasayana', that is, medicinal plants rejuvenating intellect and memory. The ancient classical Ayurvedic treatises recommend it for the promotion of memory, intelligence and general performance. Over time it has earned a reputation as an important brain tonic (Williamson 2002).

COMMON NAME
Brahmi

OTHER NAMES
Bacopa, jalanimba, jalnaveri, sambrani chettu, thyme-leave gratiola

Centella asiatica (gotu kola) and *Merremia gangetica* have also been referred to by the name brahmi but most authorities associate brahmi with *Bacopa monniera*

BOTANICAL NAME/FAMILY
Bacopa monniera (family Scrophulariaceae)

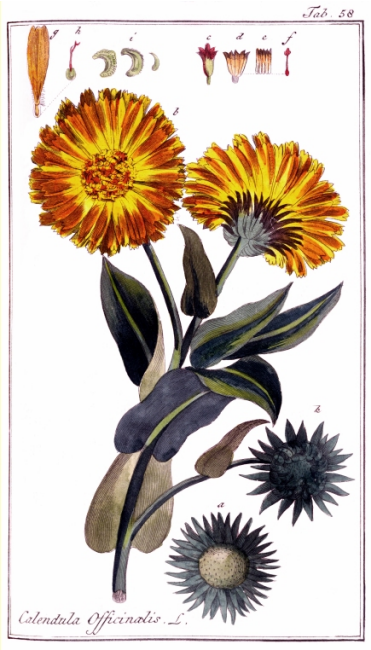
PLANT PARTS USED
Dried whole plant or herb, mainly leaves and stems (aerial parts)

CHEMICAL COMPONENTS
Dammarene-type saponins (bacosides and bacosaponins, based on the bacogenins A1–A5, are considered the most important) and alkaloids (brahmine, herpestine and flavonoids).

MAIN ACTIONS
The mechanism of action of brahmi has not been significantly investigated in clinical studies, so results from in vitro and animal tests provide most of the evidence. Some studies have investigated the effects of an Ayurvedic herbal combination known as brahmi rasayan, which consists of 10 parts bacopa, 2 parts cloves, 1 part cardamom, 1 part *Piper longum* and 40 parts sucrose.

ANTIOXIDANT
Brahmi has potent antioxidant activity, which appears to be a result of both direct free-radical scavenging activity and increasing the activity of endogenous antioxidant

systems (Bhattacharya et al 2000, Tripathi et al 1996). Administration of bacoside A reduced the effects of cigarette smoke in an animal model by increasing lactate dehydrogenase and its isoenzymes (Anbarasi et al 2005). Bacoside A has also been shown to reduce creatine kinase in brain and cardiac tissue, thus preventing smoking induced damage (Anbarasi et al 2005). An extract of brahmi provided protection against DNA damage in both animal cells (Russo et al 2003a) and human cells (Russo et al 2003b) in vitro. Dose-related increases in superoxide dismutase, catalase and glutathione peroxidase activities in several important regions of the brain has been demonstrated in animal models (Bhattacharya et al 2000). Additionally, brahmi induces increased activity of superoxide dismutase and catalase in the liver (Kar et al 2002).



COGNITIVE ACTIVATOR

Both antioxidant and anticholinesterase activity have been demonstrated in vivo and suggested as the mechanisms responsible for cognitive activation (Das et al 2002). Results from a double-blind placebo-controlled trial using brahmi (300 mg/day) support this view, as one of the major effects seen was on speed of early information processing, a function predominantly modulated by the cholinergic system (Stough et al 2001).

REDUCTION IN BETA-AMYLOID LEVELS

Bacopa extract significantly reduced beta-amyloid levels when administered prior to beta-amyloid deposition in a study using an Alzheimer's dementia animal model (Dhanasekaran et al 2004).

ANTIDEPRESSANT ACTIVITY

A rodent model of depression found that an extract of brahmi produced significant antidepressant activity comparable to that of imipramine after 5 days of oral administration (Sairam et al 2002).

ANTIULCER EFFECTS

Although no clinical studies are available, one study using an animal model of aspirin-induced gastric ulceration has identified significant antiulcer activity for the fresh juice from the whole plant of *Bacopa monniera* (Rao et al 2000). The study found that brahmi had a beneficial influence on the natural mucosal defensive factors, such as enhanced mucin secretion, mucosal glycoprotein production and decreased cell shedding, thereby reducing ulceration (Rao et al 2000). A follow-up in vivo study in various gastric ulcer models further confirmed brahmi's ability to increase the body's natural defence factors and showed that *B. monniera* is effective for both the

prophylaxis and treatment of gastric ulcers (Sairam et al 2001). In addition, brahmi was shown to reduce lipid peroxidation. An in vitro study demonstrated that *B. monniera* significantly inhibited *Helicobacter pylori* and the effect was comparable to that of bismuth subcitrate, a known *H. pylori* growth inhibitor (Goel et al 2003).

ANTI-INFLAMMATORY EFFECTS

An ethanolic extract of *B. monniera* exhibited marked anti-inflammatory activity against carrageenan-induced paw oedema in mice and rats (Channa et al 2005). The effect was mediated via PGE_2 inhibition and found to be comparable to aspirin. Bacopa has also exhibited anti-inflammatory activity comparable to indomethacin without causing an associated gastric irritation (Jain et al 1994). Several constituents are thought to be responsible for the anti-inflammatory action, chiefly the triterpene, betulinic acid but also saponins and flavonoids.

OTHER ACTIONS

ADAPTOGEN

A standardised extract of *B. monniera* possesses adaptogenic effects in an animal model, which were found to be comparable to *Panax quinquefolium* (Rai et al 2003).

ANTINOCICEPTIVE ACTIVITY

Brahmi rasayan (see under MAIN ACTIONS) has demonstrated antinociceptive activity in animal experiments (Shukia et al 1987). An interaction with the GABA-ergic system is believed to be involved. Although encouraging, it is not certain to what extent brahmi was responsible for these results.

MAST-CELL STABILISATION

The methanolic fraction of brahmi exhibits potent mast-cell-stabilising activity in vitro, which was found to be comparable to that of disodium cromoglycate (Samiulla et al 2001).

INCREASED THYROID HORMONE LEVELS

Results from animal experiments have found that brahmi increases T_4 concentrations by 41% without enhancing hepatic lipid peroxidation (Kar et al 2002).

ANTISPASMODIC EFFECT ON SMOOTH MUSCLE

A spasmolytic effect on smooth muscle has been demonstrated in vivo, and is predominantly due to inhibition of calcium influx into the cell (Dar & Channa 1999). More recent studies have also shown bronchodilatory effects, most likely due to the same mechanism (Channa et al 2003).

CLINICAL USE

Brahmi has not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies and traditional evidence, and is still largely speculative.

Clinical note — Scientific investigation of Ayurvedic medicines in India

Modern-day interest in many Ayurvedic herbs, such as brahmi, really started in 1951 when the then Prime Minister of India set up the Central Drug Research centre in Lucknow. The goal of this initiative was to encourage scientists to investigate many of the traditional Ayurvedic herbs in a scientific way, and to determine their potential as contemporary drugs or as potential sources for newer drugs.

IMPROVING COGNITIVE FUNCTION — LEARNING, MEMORY, INTELLIGENCE

In Ayurvedic medicine, bacopa is used to improve cognitive function and increase intelligence. Over time it has developed an excellent reputation, prompting scientific researchers to investigate the activity of bacopa more closely.

To date, results from animal studies are encouraging. Oral administration of brahmi extract (40 mg/kg) for at least 3 days produced positive effects on learning skills, memory and reaction times compared with controls in one learning model (Singh & Dhawan 1982). Another study found that bacopa extract significantly reversed the cognitive impairment induced by the antiepileptic drug phenytoin, without affecting its anticonvulsant activity (Vohora et al 2000). More recent animal studies have shown that bacopa attenuates scopolamine-induced dementia and significantly inhibits acetylcholinesterase activity in vitro (Das et al 2002). Studies indicate that bacosides A and B present in the ethanolic extract are responsible for the cognition facilitating effects (Russo 2005).

Clinical studies have generally produced encouraging results. A double-blind placebo-controlled trial using a dose of 300 mg bacopa over 12 weeks in 46 healthy volunteers found that it significantly improved the speed of visual information processing, learning rate and memory consolidation and that it has a significant anxiolytic effect (Stough et al 2001). Another study of the same design tested brahmi in 76 adults over 3 months (Roodenrys et al 2002); significant improvements in a test for new information retention was observed, but there were no changes in the rate of learning. Results from a double-blind placebo-controlled trial involving 38 healthy subjects suggest that cognitive activator effects may require long-term use and are not evident after single-dose administration (Nathan et al 2001). However, results from a double-blind, placebo-controlled study using a product (Blackmore's Ginkgo Brahmi) containing both *Bacopa monniera* (300 mg) and *Ginkgo biloba* (120 mg) in

healthy subjects failed to show any significant differences in memory, attention, comprehension, learning or motor responsiveness after 4 weeks (Nathan et al 2004).

ANXIETY

A placebo-controlled randomised study of healthy subjects found that 300 mg of brahmi daily reduced anxiety compared with placebo, an effect most pronounced after 12 weeks of treatment (Stough et al 2001).

OTHER USES

TRADITIONAL USES

Bacopa has been traditionally used as a brain tonic and is commonly recommended to improve memory and heighten learning capacity. It is also used as a nerve tonic to treat anxiety, nervous exhaustion or debility and is prescribed to enhance rehabilitation after any injury causing nervous deficit, such as stroke. Other traditional uses include promoting longevity, and treating diarrhoea and asthma. It is used as an anti-inflammatory, analgesic, anxiolytic and antiepileptic agent with some support for these uses provided by in vitro and in vivo studies.

IRRITABLE BOWEL SYNDROME

An Ayurvedic herbal combination consisting of *Aegle marmelos correa* and *Bacopa monniera* successfully treated 65% of patients with irritable bowel syndrome (IBS) under double-blind randomised conditions (Yadav et al 1989). Herbal treatment was particularly useful in the diarrhoea-predominant form of IBS, compared with the placebo. Follow-up reviews 6 months after the trial found that relapse rates were the same among all test subjects. Although encouraging, it is not certain to what extent brahmi was responsible for these results.

DOSAGE RANGE

- Dried aerial parts of herb: 5–10 g/day.
- Fluid extract (1:2) or equivalent oral dose form: 5–13 mL/day in divided doses.

ACCORDING TO CLINICAL STUDIES

- Cognitive activator effects: 300 mg/day.

Positive results obtained in one controlled study have found 3 months' use is required before clinical effects are observed (Stough et al 2001).

TOXICITY

The LD_{50} data for an ethanolic extract of bacopa is 17 g/kg (oral) (Mills & Bone 2005).

ADVERSE REACTIONS

Insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

CHOLINERGIC DRUGS

Cholinergic activity has been identified for brahmi, therefore increased drug activity is theoretically possible — observe patient, although a beneficial interaction is possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Caution is advised in hyperthyroidism — bacopa has been shown to significantly elevate T_4 levels in vivo.

PREGNANCY USE

Insufficient reliable information available.

PRACTICE POINTS/PATIENT COUNSELLING

- Brahmi is an Ayurvedic herb that has been used for several thousand years as a brain tonic, to enhance intellect, treat psychiatric illness, epilepsy, insomnia and as a mild sedative.
- Evidence of cognitive activator activity from animal models of learning is positive and clinical studies have produced generally encouraging results.
- Brahmi has potent antioxidant activity, which appears to be a result of both direct free-radical scavenging activity and increasing endogenous antioxidant systems in the brain and liver.
- Anticholinesterase, antidepressant, antiulcer, antispasmodic, anti-inflammatory and antinociceptive activity has been demonstrated in animal studies. Elevated T_4 levels have also been observed.
- Overall, large controlled studies are not available to determine the clinical significance of these effects.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

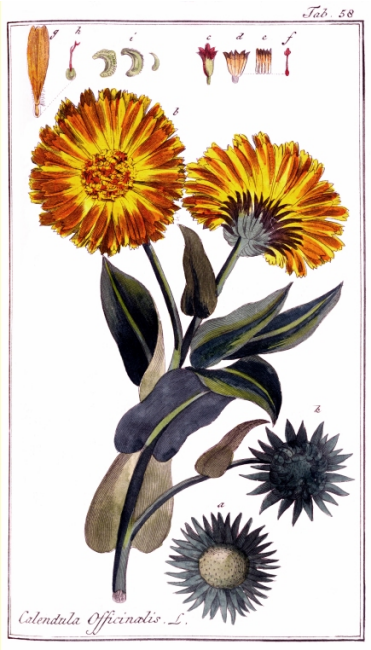
Brahmi has a long history of use as a brain tonic. Results from scientific studies suggest that it may enhance memory and cognitive function and reduce anxiety with long-term use.

When will it start to work?

Studies suggest that 12 weeks' continual use is required for benefits on cognitive function to become apparent.

Are there any safety issues?

Information from traditional sources suggests that brahmi is well tolerated at the usual therapeutic doses, but scientific investigation has yet to establish safety and whether drug interactions exist.



REFERENCES

Anbarasi K et al. Creatine kinase isoenzyme patterns upon chronic exposure to cigarette smoke: protective effect of Bacoside A. Vascul Pharmacol 42.2 (2005): 57-61.

Anbarasi K, Sabitha KE, Devi CS. Lactate dehydrogenase isoenzyme patterns upon chronic exposure to cigarette smoke: Protective effects of bacoside A. Envir Tox Pharm (2005): 20, 345-350.

Bhattacharya SK et al. Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum and hippocampus. Phytother Res 14.3 (2000): 174-9.

Channa S et al. Broncho-vasodilatory activity of fractions and pure constituents isolated from Bacopa monniera. J Ethnopharmacol 86.1 (2003): 27-35.

Channa S et al: Anti-inflammatory activity of Bacopa monniera in rodents. J Ethnopharmacol (2005) (in Press).

Dar A, Channa S. Calcium antagonistic activity of Bacopa monniera on vascular and intestinal smooth muscles of rabbit and guinea-pig. J Ethnopharmacol 66.2 (1999): 167-74.

Das A et al. A comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba. Anticholinesterase and cognitive enhancing activities. Pharmacol Biochem Behav 73.4 (2002): 893-900.

Dhanasekaran M et al. Bacopa monniera extract reduces beta-amyloid deposition in doubly transgenic PSAPP Alzheimer's disease mouse model. Neurology 63.8 (2004): 1548.

Goel RK et al. In vitro evaluation of Bacopa monniera on anti-Helicobacter pylori activity and accumulation of prostaglandins. Phytomedicine 10.6-7 (2003): 523-7.

Jain P et al. Anti-inflammatory effects of an Ayurvedic preparation, Brahmi Rasayan, in rodents. Indian J Exp Biol 32 (1994): 633-6.

Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol 81.2 (2002): 281-5.

Mills S, Bone K. The Essential Guide to Herbal Safety. Edinburgh: Churchill Livingstone, 2005.

Nathan PJ et al. Effects of a combined extract of Ginkgo biloba and Bacopa monniera on cognitive function in healthy humans. Hum Psychopharmacol 19.2 (2004): 91-6.

Nathan PJ et al. The acute effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy normal subjects. Hum Psychopharmacol 16.4 (2001): 345-51.

Rai D et al. Adaptogenic effect of Bacopa monniera (Brahmi). Pharmacol Biochem Behav 75.4 (2003): 823-30.

Rao CV, Sairam K, Goel RK. Experimental evaluation of Bocopa monnieri on rat gastric ulceration and secretion. Indian J Physiol Pharmacol 44.4 (2000): 435-41.

Roodenrys S et al. Chronic effects of Brahmi (Bacopa monnieri) on human memory. Neuropsychopharmacology 27.2 (2002): 279-81.

Russo A et al. Free radical scavenging capacity and protective effect of Bacopa monniera L. on DNA damage. Phytother Res 17.8 (2003b) 870-5.

Russo A et al. Nitric oxide-related toxicity in cultured astrocytes: effect of Bacopa monniera. Life Sci 73.12 (2003a): 1517-26.

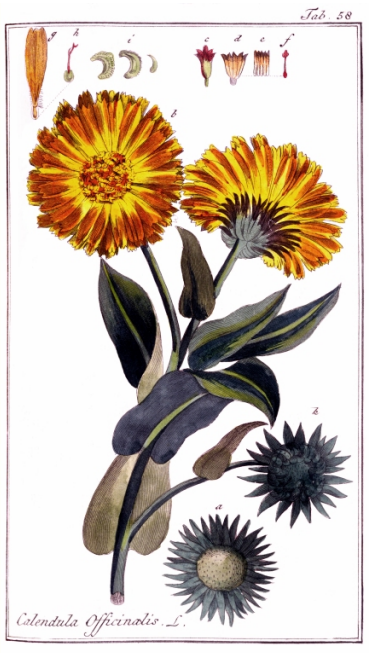
Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: an overview. Phytomedicine 12 (2005): 305-17.

Sairam K et al. Antidepressant activity of standardized extract of Bacopa monniera in experimental models of depression in rats. Phytomedicine 9.3 (2002): 207-11.

Sairam K et al. Prophylactic and curative effects of Bacopa monniera in gastric ulcer models. Phytomedicine 8.6 (2001): 423-30.

Samiulla DS, Prashanth D, Amit A. Mast cell stabilising activity of Bacopa monnieri. Fitoterapia 72.3 (2001): 284-5.
Shukia B, Khanna NK, Godhwani JL. Effect of Brahmi Rasayan on the central nervous system. J Ethnopharmacol 21.1 (1987): 65-74.
Singh HK, Dhawan BN. Effect of Bacopa monniera Linn. (brahmi) extract on avoidance responses in rat. J Ethnopharmacol 5.2 (1982): 205-14.
Stough C et al. The chronic effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy human subjects. Psychopharmacology (Berl) 156.4 (2001): 481-4.
Tripathi YB et al. Bacopa monniera Linn. as an antioxidant: mechanism of action. Indian J Exp Biol 34.6 (1996): 523-6.
Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by Bacopa monniera, a reputed Indian nootropic plant. J Ethnopharmacol 71.3 (2000): 383-90.
Williamson EM, Dabur Research Foundation and Dabur Ayurvet Ltd. Churchill Livingstone, 2002.
Yadav SK et al. Irritable bowel syndrome: therapeutic evaluation of indigenous drugs. Indian J Med Res 90 (1989): 496-503.

Calcium



BACKGROUND AND RELEVANT PHARMACOKINETICS

Calcium found in the diet or in commercially made supplements exists as a salt form, from which calcium must be released for absorption to occur. Adequate hydrochloric acid levels are required to make soluble the majority of these calcium ions, whereas any unabsorbed calcium entering the higher pH environment of the small intestine is more likely to be precipitated and rendered insoluble (Wahlqvist et al 2002). Low or moderate calcium intakes are absorbed via active transport mechanisms that are influenced by vitamin D. When intake is high, active transport mechanisms become saturated, leading to greater passive absorption. Although most absorption occurs in the small intestine, the large intestine may also be responsible for up to 4% of absorption and provides compensatory mechanisms for those individuals with compromised small intestine absorption (Groff & Groper 2000).

Calcium's bioavailability from both food and supplements shows enormous variation, from 4 to 45% (Recker 1985) and is dramatically influenced by other foods present in the gastrointestinal tract. Phytates, oxalates, all types of fibres, unabsorbed dietary fatty acids and other divalent minerals all potentially compromise its absorption, while lactose (especially in children) and other sugars, as well as protein and the presence of vitamin D all enhance uptake (Groff & Groper 2000).

Distribution results in 99% of absorbed calcium being deposited in bones. The remainder of the absorbed calcium is present in teeth and the intracellular or extracellular fluids. Calcium is excreted in faeces, sweat and urine. Calcium homeostasis is tightly regulated by the actions of parathyroid hormone (PTH), calcitonin and vitamin D. Together these hormones determine the level of absorption, excretion or retention by the kidneys, and sequestering or mobilisation of stores through bone mineralisation and resorption.

FOOD SOURCES

Good dietary sources of calcium include dairy products, fish with bones, especially salmon and sardines, tofu, broccoli, collard greens, mustard greens, bok choy, clams and black strap molasses.

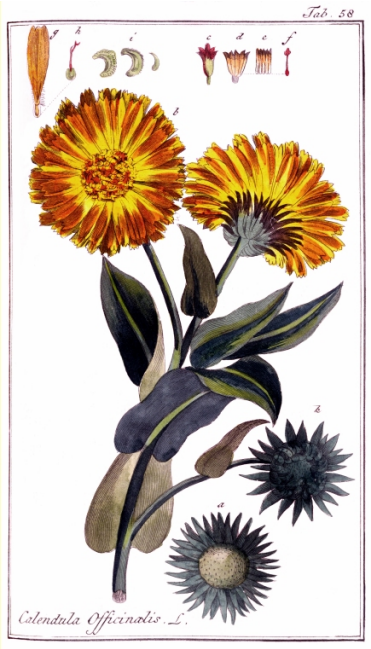
DEFICIENCY SIGNS AND SYMPTOMS

While there is little information available about the prevalence of deficiency across the general Australian population, a Melbourne study of 1045 women aged 20–92 years in 2000 revealed that approximately 76% of women consumed calcium at levels less

than the RDI and an additional 14% demonstrated a grossly inadequate intake of <300 mg/day (Pasco et al 2000). These figures are similar to those obtained by larger studies in the United States (Groff & Groper 2000).

- Tetany: muscle pain, spasms and paraesthesias.
- Rickets.
- Osteomalacia.
- Increased neuromuscular irritability.
- Altered heart rate.
- Ambulatory developmental delays in children.
- Osteoporosis and increased risk of fractures.
- Bone pain and deformity.
- Tooth discolouration and increased decay.
- Hypertension.
- Increased risk of pre-eclampsia.
- Increased risk of colon cancer (controversial).

There are many situations and conditions in which the risk of hypocalcaemia may be increased.



PRIMARY DEFICIENCY

Primary deficiency occurs as a result of inadequate dietary intake. Populations with increased calcium requirements are at greater risk of deficiency when intakes are not modified to meet their increased needs; these include children, adolescents, pregnant and lactating women, postmenopausal women, particularly those taking HRT (Wahlqvist et al 2002), people experiencing rapid weight loss or patients receiving TPN.

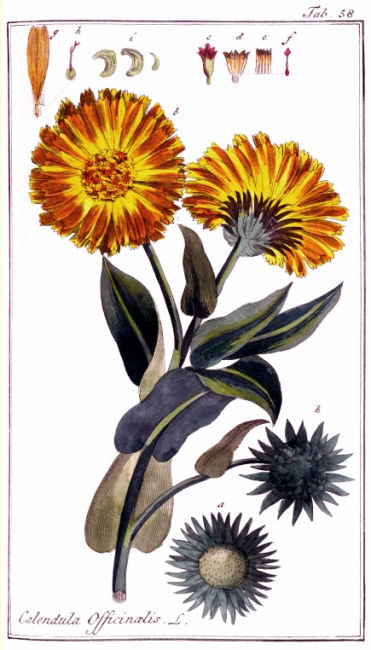
SECONDARY DEFICIENCY

Calcium absorption is impaired in achlorhydria, intestinal inflammation and any malabsorptive disorder accompanied by steatorrhoea (Wilson et al 1991). Increased faecal loss of calcium occurs with higher intakes of fibre and in fat malabsorption, while renal excretion has been shown in some studies to be increased in those patients ingesting a high protein diet (Kerstetter et al 1998).

Factors that compromise vitamin D status or activity will also affect calcium status (Pattanaungkul et al 2000, Prince et al 1997).

Other conditions that can predispose to hypocalcaemia include hypoparathyroidism (a deficiency in or absence of PTH), idiopathic hypoparathyroidism (an uncommon condition in which the parathyroid glands are absent or atrophied), pseudohypoparathyroidism (characterised not by deficiency of

PTH, but by target organ resistance to its action), renal tubular disease, renal failure, magnesium depletion, acute pancreatitis, hypoproteinaemia, septic shock or the use of certain medicines such as anticonvulsants (phenytoin, phenobarbital) and rifampin, and both oral and inhaled corticosteroids, which alter vitamin D metabolism (Beers et al 2003, Rossi et al 2005).



MAIN ACTIONS

Calcium is an essential mineral required for the proper functioning of numerous intracellular and extracellular processes, including muscle contraction, nerve conduction, beating of the heart, hormone release, blood coagulation, energy production and maintenance of immune function. It also plays a role in intracellular signalling and is involved in the regulation of many enzymes.

BONE AND TEETH MINERALISATION

Calcium is found in bone where it is mainly complexed with other ions in the form of hydroxyapatite crystals. Approximately 1% of calcium in bone can be freely exchanged into the extracellular fluid in order to buffer changes in calcium balance.

MUSCLE CONTRACTION

Ionised serum calcium helps to initiate both smooth and skeletal muscle contraction and in particular, the regulation of rhythmic contraction of the heart muscle in combination with sodium and potassium.

BLOOD CLOTTING

Calcium is involved in several steps of the blood clotting cascade.

ALTERED MEMBRANE FUNCTIONS

Calcium fluxes across membranes, both within the cell and across the plasma membrane, and acts as a vehicle for the signal transduction necessary for neurotransmitter and hormone function. It also selectively alters cell wall permeability to regulate passage of fluids in and out of cells.

OTHER ACTIONS

Regulates various enzyme systems responsible for muscle contraction, fat digestion and protein metabolism.

CLINICAL USE

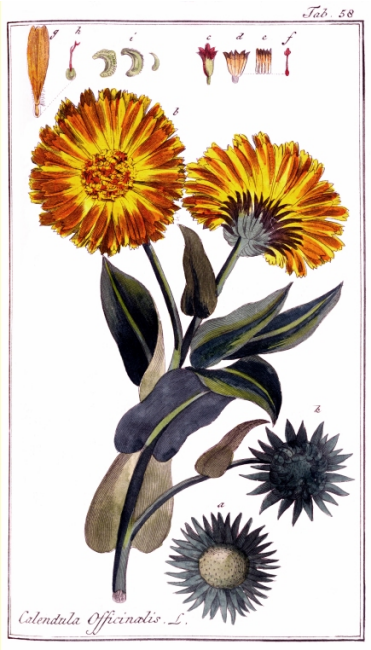
Many of the clinical uses of calcium supplements are conditions thought to arise from a gross or marginal deficiency, but some indications are based on the concept of high-dose calcium supplements as a therapeutic agent.

CALCIUM DEFICIENCY

Traditionally, calcium supplementation has been used to treat deficiency or prevent deficiency in high-risk conditions or people with increased calcium requirements such as pregnant women. Acute severe hypocalcaemic states are treated initially with IV infusion of calcium salts. In chronic cases, oral calcium supplements and occasionally vitamin D supplements are used.

Rickets and osteomalacia A deficiency of either calcium or vitamin D can produce these bone disorders. (See Vitamin D monograph for further information.)

Infants The percentage and type of fats within an infant formula and their ability to bind calcium salts and increase excretion has been shown to influence the bone mineral content (BMC) of infants. One hundred 8-week-old infants given formulas considered to be more similar to breastmilk and less likely to form calcium soaps in the gut showed increased BMC after only 1 month's treatment compared with those infants on standard formula (Kennedy et al 1999).



BONE MINERAL DENSITY (BMD) AND OSTEOPOROSIS PROPHYLAXIS

Children A 2006 Cochrane review of 19 trials including 2859 participants found there was no effect of calcium supplementation on femoral neck or lumbar spine BMD (Winzenberg et al 2006). There was a small effect on total body BMC and upper limb BMD; however, only the effect in the upper limb persisted after supplementation ceased. The effect is approximately equivalent to a 1.7% greater increase in supplemented groups, which at best would reduce absolute fracture risk in children by 0.1–0.2% annually. Additionally, there was no evidence of effect modification by baseline calcium intake, sex, ethnicity, physical activity or pubertal stage.

Adolescents Peak bone mass is one of the main determinants of osteoporotic fracture in humans and therefore there is significant research dedicated to determining the influence of calcium status on the 40–50% peak bone mass accretion that occurs during adolescence. Overall, studies in adolescent girls have shown that calcium supplementation significantly improves bone mineral status. Numerous studies, including one by Stear in 2003 of 144 pubertal girls, have confirmed a synergistic relationship between mechanical load, through physical activity, calcium status and bone calcium accumulation; however, it is important to note that physical activity has a positive effect on BMD only at high calcium intakes, with no effect at calcium intakes <1000 mg/day (Harkness & Bonny 2005).

Until recently, all clinical trials with calcium supplements in children and adolescents, demonstrating a positive effect on bone mass, were conducted over durations of 1–3 years. As such, it is uncertain whether supplementation and resultant increases in bone mass had a beneficial effect in the long-term. A 2005

placebo-controlled study addressed this issue by using calcium supplements (670 mg/day) over a 7-year period. The study of 354 pubertal girls reported significant increases in BMD during growth spurts in the supplemented group; however, these gains did not uniformly persist into late adolescence and only girls of tall stature received long-lasting benefits. Interestingly, the placebo group exhibited a 'catch-up' in bone mineral accretion subsequent to the pubertal growth spurt (Matkovic et al 2005). These results introduce two novel concepts: the first being that dietary calcium requirement for skeletal development may be size dependent and secondly the possibility that a calcium mineral deficit may be a transient feature of the pubertal growth spurt, with a 'catch-up' possible during bone consolidation. In spite of these findings, the temporary gains in BMD may be important in the prevention of fractures during adolescence (Matkovic et al 2005).

A second study introduces other issues regarding the impact of variable calcium status in adolescents. The randomised, double-blind, placebo controlled study of 144 prepubertal girls used 850 mg/day of calcium over 1 year. After follow-up some 7 years later, in addition to positive effects on BMD outcomes, an inverse relationship became apparent between calcium supplementation and the age of menarche. The authors consequently speculate that higher calcium intake prior to menarche may favourably impact on long-term BMD through this dual mechanism (Chevalley et al 2005).

Postmenopausal women Numerous studies have confirmed an important role for calcium in the prevention of osteoporosis in postmenopausal women. Clinical studies have assessed its efficacy as a sole agent against placebo, in comparison with steroid hormones, antiresorptive drugs and as part of combination therapy.

Long-term calcium supplementation protects against bone loss according to a 2-year study involving 60 postmenopausal, non-osteoporotic women. The trial showed that in comparison with the 3% BMD loss evident in the placebo group, those consuming 1633 mg/day on average of supplemental calcium suffered no bone loss, as measured at the greater trochanter, and in fact their BMD improved at other sites tested (Storm et al 1998). A similar trend was demonstrated by Daniele et al (2004) in their study of 120 women, given only 500 mg of calcium and 200 IU of vitamin D per day over 30 months. In general though, the efficacy of calcium supplements in postmenopausal women appears to be largely dependent upon the baseline calcium intake. Those with an initial poor intake tend to achieve significant improvements over placebo, with more modest or no effect evident in groups with higher intakes at baseline (Daniele et al 2004, Fardellone et al 1998).

Whether calcium supplements are sufficient as a stand-alone preventative measure against osteoporosis is still being investigated. The results of one study suggest that the effects of calcium on BMD may require additional supplementation with the trace minerals zinc, manganese and copper (Strause et al 1994). However, the most impressive results obtained to date are for the combination of high-dose calcium with antiresorptive drugs such as oestrogen or calcitonin. A review of these studies highlights the gain in bone mass that resulted from the addition of calcium in contrast to the halt in BMD depletion commonly observed with use of calcitonin alone (Nieves et al 1998).

Other studies of both male ($n = 50$) and female ($n = 200$) populations using a combination of fluoride, as monofluorophosphate, and calcium over a 3–4-year period, found this combination to be superior to calcium alone in the prevention of BMD loss. Increased lumbar spine BMD and reduced risk of fractures was evident in both trials using the two minerals (Ringe et al 1998, Reginster et al 1998).

The elderly A number of large studies investigating the preventative effect of calcium alone or in combination with vitamin D have produced mixed results in the elderly. Earlier studies by Chapuy et al (1992, 1994, 2002) and Dawson Hughes et al (1997) demonstrated a significant reduction in risk of fracture in the elderly, and Larsen et al in 2004 demonstrated up to 16% reduction in an open-label, 3-year intervention in 9605 community dwelling elderly people. However, the RECORD Trial in 2005 failed to yield positive results. It was a randomised, placebo-controlled trial of 5292 people aged 70 years or older who received either 1000 mg of calcium or 800 IU of vitamin D/day, alone or together, for 24–62 months (The RECORD Trial group 2005). The authors postulate that improved results in previous studies may be due to the increased age (>80 years) of study volunteers and poorer vitamin D status at baseline.

Glucocorticoid-induced osteoporosis Approximately one in six people with asthma receiving inhaled and/or systemic glucocorticoids developed fractures over 5 years. The interaction with calcium plays a small role in this process, with glucocorticoids directly inhibiting vitamin D mediated intestinal absorption of calcium. High vitamin D doses (50,000 IU twice weekly) in combination with 1.5 g calcium daily can overcome this interference (Wilson et al 1991), whereas a randomised study found that treatment with calcium alone or in combination with etidronate may not be effective. That study of 352 volunteers found that treatment for 5 years did not significantly reduce fracture rate (Campbell et al 2004).

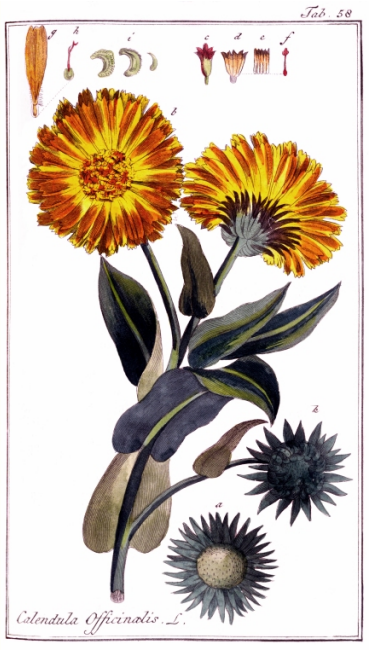
SUPPLEMENTATION DURING PREGNANCY AND LACTATION

Calcium is considered a critical nutrient during pregnancy with at least a twofold increase in requirements observed. Its metabolism during gestation significantly changes from as early as 12 weeks, with doubling of both absorption and excretion, followed by additional losses through lactation, which can account for reductions in maternal bone mineral content of 3–10% (Prentice 2003). While it is clear that general supplementation would be necessary in those women with poor preconception calcium levels, it is suggested that for healthy women the metabolic compensation evident in pregnancy should be sufficient to guarantee adequate fetal levels.

Prevention of pre-eclampsia Epidemiological evidence illustrates an inverse relationship between calcium status and the prevalence of pre-eclampsia (Frederick et al 2005, Lopez-Jaramillo et al 2001) and recent studies confirm abnormalities in markers of calcium metabolism and status in a pre-eclamptic population compared to controls, including low urinary and serum calcium levels (Ingec et al 2006, Sukonpan & Phupong 2005). Trials that included a 1996 meta-analysis of studies involving calcium and hypertension in pregnancy have shown a substantial mean reduction in both SBP and DBP, which was also confirmed by more recent reviews (Atallah et al 2002, Bucher et al 1996).

Positive correlations demonstrated in original smaller trials between calcium supplementation and reduced prevalence of pre-eclampsia, involving over 400 women, were put into question when the Calcium for Prevention of Pre-eclampsia study (CPEP), the largest trial to date, found no effect on the incidence or severity of the condition (Levine et al 1997). However, the CPEP study, involving over 4000 healthy nulliparous women, is not a replication of the existing trials. While the original studies used populations with a low calcium intake to ascertain the connection between correction of this deficiency and prevalence of pre-eclampsia, this more recent trial represented a 'pharmacological intervention in women with a normal calcium intake' (Lopez-Jaramillo et al 2001). Further reviews of all the evidence have supported calcium's preventative role and researchers have concluded that calcium supplementation should be recommended for those women with a low calcium intake who are at risk of developing gestational hypertension (Crowther et al 1999, Hofmeyr et al 2003).

A 2003 review of calcium and the prevention of pre-eclampsia concluded that while considerable evidence from observational and experimental studies links calcium intake and hypertension during pregnancy, there is currently no satisfactory



explanation of the mechanisms (Villar et al 2003). One possible explanation may be the antagonistic relationship between calcium and lead (Sowers et al 2002).

A small number of studies have investigated the effects of calcium in combination with other nutrients, including antioxidant and omega-3 oils in this population. One randomised, placebo-controlled, double-blind study involving a sample of 48 primigravidas, using a combination of 600 mg/day calcium and 450 mg/day of conjugated linoleic acid (CLA) from weeks 18–22 until delivery, resulted in a significantly reduced incidence of pregnancy-induced hypertension (8% vs 42% of the control group) (Herrera et al 2005). Further studies are warranted to elicit the individual impact of both nutrients and to determine the superiority of sole or combination treatment.

Leg cramps Calcium supplements are commonly prescribed in pregnancy when leg cramps are a problem. A Cochrane review of five trials involving 352 women taking various supplements for the treatment of leg cramps in pregnancy included only one placebo-controlled trial of calcium. From this, researchers concluded that any improvement in cramps in those groups treated solely with calcium was likely due to a placebo effect, with significant findings limited to the groups taking other nutrients (Young & Jewell 2002).

Fetal growth The greatest period of fetal mineral accretion has been identified as the gestational period of 20–33 weeks, with daily needs escalating from 50 mg/day to 330 mg/day at its peak. The average newborn contains about 20–30 g calcium, and one study of 256 women in their second trimester showed that supplementation in women with poor calcium status significantly increased neonatal bone mineral content, as determined by X-ray absorptiometry measurements at 1 week postpartum (Koo et al 1999). However, the full relationship between maternal calcium intake and fetal growth, particularly in non-deficient women, has yet to be elucidated (Prentice 2003). One suggested effect of gestational mineral intake has been the determination of calcium concentration in the mother's breastmilk, while it has been established that this concentration is not the result of calcium intake postpartum (Prentice et al 1999).

Lead toxicity Increased blood lead levels are commonly a result of bone resorption during pregnancy and are considered a potential risk to fetal and infant health. Lead can be transferred to the fetus and infant via cord blood and breastmilk. Several studies suggest a low placental barrier to lead, with 79% of the mobilised lead from maternal bone passed to the infant (Dorea & Donangelo 2005). While a number of studies have indicated lead levels in the breastmilk of Australian women appear to be well within a safe range, recent data from a study conducted by Ettinger et al

revealed that even low lead content in human milk appears to be highly influential on the lead levels of infants in their first month of life (2004). A separate review published in 2005 discussed additional related trends such as increased lead concentrations in cord blood during winter months, because of lower vitamin D status (Dorea 2004).

A RCT of 617 lactating women supplemented with high-dose calcium carbonate found that the women in the calcium group showed significant reductions in blood lead levels. Those subjects who showed improved compliance and also had baseline higher bone lead content produced an overall reduction of 16.4% (Hernandez-Avila et al 2003). Similar positive findings came from a study in Mexico of 367 lactating women; however, the maximal reduction in lead concentrations reached only 10% (Ettinger et al 2006). Nevertheless, when considered together these results suggest that calcium supplementation may represent an important interventional strategy, albeit with a modest effect, for reducing infant lead exposure.

Neonatal benefits Calcium supplementation during pregnancy has been postulated to have prolonged benefits in the offspring, as indicated in a study of nearly 600 children aged 5–9 years whose mothers had previously participated in a calcium trial during their pregnancy. The children demonstrated reduced SBP, compared with the children whose mothers had taken placebo, with significance reached particularly for those in the upper BMI bracket (Belizan et al 1997).

DYSPEPSIA

A first-line OTC treatment for heartburn, indigestion and dyspepsia has often been an antacid based on calcium carbonate in combination with magnesium and aluminum salts. Calcium in combination with the other ingredients reduces stomach acid and increases the rate of gastric emptying (Vatier et al 1996). In trials comparing H_2 blockers with calcium carbonate tablets, calcium was found to be equipotent, yet delivered a more rapid response and shorter duration of action (Feldman 1996). There have been many papers highlighting the dangers of prolonged use of these traditional antacids; however, pure calcium carbonate formulas attract the least concern, with the incidence of 'milk alkali syndrome' resulting from their over use reported to be rare (Ching & Lam 1994, Herzog & Holtermuller 1982).

PREVENTION OF COLORECTAL CANCER

High dietary intake of calcium has demonstrated a reasonably consistent risk reduction of between 15% and 40% for colorectal cancer. Clear parameters for dosing are not yet available, with some studies showing no further benefit above

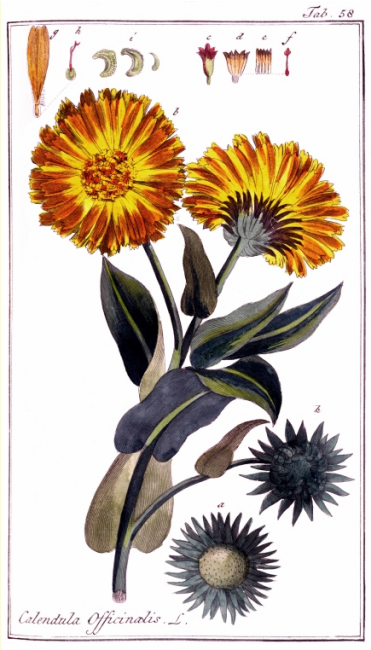
700–800 mg/day of total calcium, while other studies suggest an ongoing inverse dose-dependent relationship without cut-off (Schatzkin & Peters 2004).

A 2005 Cochrane review examining the effect of supplementary calcium on the incidence of colorectal cancer and the incidence or recurrence of adenomatous polyps included two double-blind, placebo-controlled trials with a pooled population of 1346 subjects. The doses of supplementary elemental calcium used were 1200–2000 mg/day for 3–4 years. The reviewers concluded that while the evidence to date appears promising and suggests a moderate degree of prevention against colorectal adenomatous polyps, more research with similar findings is required before this can be translated into any preventative protocol (Weingarten et al 2005).

Not included in the Cochrane review was a multicentre, placebo-controlled randomised study assessing the independent and joint effects of calcium supplementation and vitamin D status on adenoma recurrence in 803 subjects. Interestingly only those subjects with baseline vitamin D levels above the median (29.1 mg/mL) experienced a risk reduction with calcium supplementation (RR 0.71). Similarly, high vitamin D status was not independently associated with risk reduction, but was protective in combination with calcium supplementation (Grau et al 2003). These findings are suggestive of a synergistic action between the nutrients. Earlier hypotheses regarding the action of calcium in this role focused on calcium's ability to bind bowel-irritating substances secreted into bile. This notion is further supported by a number of studies demonstrating enhanced chemoprotection when high doses of calcium have been combined with dietary factors such as reduced fat and increased carbohydrate, fibre and fluid intakes (Hyman et al 1998, Rozen et al 2001, Schatzkin & Peters 2004).

One significant development in our understanding has been the discovery of human parathyroid calcium-sensing receptors in the human colon epithelium, which function to regulate epithelial proliferation and differentiation. New in vitro studies suggest that expression of these receptors may be induced by the presence of extracelullar calcium and vitamin D, therefore promoting greater differentiation of the epithelial cells (Chakrabarty et al 2005) and inducing apoptosis (Miller et al 2005).

The emerging evidence to date for a combined role of calcium, either dietary or supplemental, and vitamin D is strong and further elucidation of the independent and combined effects of these nutrients will assist in the development of preventative protocols.



HYPERTENSION

A 2006 Cochrane review of 13 RCTs involving 485 volunteers found that when the results of all trials were combined, calcium supplementation produced a statistically

significant reduction in SBP (mean difference: –2.5 mmHg), but not DBP (mean difference: –0.8 mmHg) compared with controls (Dickinson et al 2006). The authors temper their conclusion by stating that the quality of included trials was poor and the heterogeneity between trials means there is a tendency to overestimate the effects of treatment. Earlier, an extensive systematic review, updated in 1999 to include 42 randomised comparative trials, shows modest reductions in both SBP and DBP (–2 mmHg and –1 mmHg respectively) with 1–2 g/day calcium over a 4–14-week intervention (Griffith et al 1999). Although dietary calcium appeared to have a larger effect than supplementation, the difference was not statistically significant. The clinical significance of these small effects has been questioned and the recommendation of calcium as a therapy for all types of hypertension appears premature (Kawano et al 1998). Some studies have proposed that it is only a particular subset of hypertension that demonstrates the greatest improvement with calcium. A number of researchers, for example, have hypothesised a physiological correlation between 'salt sensitive' hypertension and responsiveness to calcium treatment (Coruzzi & Mossini 1997, Resnick 1999).

In recent years, ongoing international epidemiological data have continued to link low dietary calcium intake with a slightly increased risk of hypertension, such as the study by Geleijnse et al published in 2005. A recent prospective cohort study of 5880 Spanish adults free from hypertension and CVD at baseline found that with a 27-month follow-up period, low-fat, but not full-fat, dairy products could be found to be protective (Alonso et al 2005).

Additional findings that are attracting attention include epidemiologic links between markers of low calcium status or calcium metabolism abnormalities, hypertension and insulin resistance. In support of the possible link between these phenomena are the results of a Japanese study of 34 non-diabetic hypertensive and 34 non-diabetic normotensive women. Multiple assessments of the group revealed statistically significant increased urinary calcium, lower BMD, depressed serum calcium and elevated circulating PTH in the hypertensive sample (Gotoh et al 2005).

With another study implicating high serum calcium as an independent indicator of both increased coronary heart disease risk and its severity (Rasouli & Mohseni Kiasari 2006), it is clear that whatever calcium's relationship to cardiovascular disease, it is a complex one and more research with consistent findings is required before any conclusions can be drawn.

PREMENSTRUAL SYNDROME

Of all the vitamins and minerals used in the treatment of PMS, calcium supplements show overwhelmingly positive results.

One of the earliest trials to show that calcium supplementation can alleviate symptoms in PMS was conducted in 1989 (Thys-Jacobs et al 1989). A randomised, double-blind crossover trial involving 33 women with confirmed PMS compared the effects of daily 1000 mg calcium carbonate with placebo over 6 months. Results showed that 73% of women reported improved symptoms while taking calcium supplementation whereas 15% preferred placebo. The premenstrual symptoms responding significantly to calcium supplementation were mood changes, water retention and premenstrual pain. Menstrual pain was also significantly alleviated.

In 1993, the *American Journal of Obstetrics and Gynecology* published a study that compared the effects of calcium (587 mg or 1336 mg) and manganese (1.0 mg or 5.6 mg) on menstrual symptoms. Ten women with normal menstrual cycles were observed over four 39-day periods during the trial (Penland & Johnson 1993). The researchers found that increasing calcium intake reduced mood, concentration and behavioural symptoms generally and reduced water retention during the premenstrual phase. Additionally, menstrual pain was reduced.

A more recent large, double-blind, placebo-controlled, randomised parallel-group study was conducted in the United States and supports the previous findings (Thys-Jacobs et al 1998). Four hundred and sixty-six premenopausal women with confirmed moderate to severe PMS were randomly assigned to receive either 1200 mg elemental calcium (from calcium carbonate) or placebo for three menstrual cycles. Symptoms were documented daily by the subjects based on 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings and pain). Additionally, adverse effects and compliance were monitored daily. During the luteal phases of both the second and third treatment cycles, a significantly lower mean symptom score was observed in the calcium group. By the third treatment cycle, calcium treatment resulted in a 48% reduction in total symptom score compared with baseline, whereas placebo achieved a 30% reduction. Furthermore, all four symptom factors responded in the calcium treated group.

A 1999 review of multiple trials investigating calcium supplementation as an effective therapy for PMS has found overwhelming positive results (Ward & Holiman 1999).

Some researchers in this area have hypothesised that part of the PMS aetiology lies in calcium dysregulation in the luteal phase and have highlighted the dramatic similarities between symptoms of PMS and hypocalcaemia (Thys-Jacobs 2000). Recent data from the Nurses Health Study II support this theory, with evidence of low calcium and vitamin D levels in PMS populations when compared to controls (Bertone-Johnson et al 2005).

WEIGHT LOSS

A review by Teegarden (2003) was one of the most substantial early contributions to the hypothesis regarding calcium's role in accelerating weight loss. The review brought together a broad range of trials dating back 10 years to the original findings demonstrated on hypertensive rats. In an updated review published in 2005, while acknowledging the promising data that has emerged over the intervening 2 years, Teegarden notes that the current body of evidence has a number of limitations and flaws that need to be addressed before the full extent of calcium's effect on weight loss can be determined.

Although the underlying mechanism of action remains unclear, there is general acceptance that high calcium intake depresses PTH levels and $1,25(OH)_2D$, which in turn decreases intracellular calcium, thereby potentially inhibiting lipogenesis and stimulating lipolysis within the cells (McCarty & Thomas 2003, Schrager 2005, Zemel et al 2004). Additional proposed actions include increased rates of faecal fat and energy excretion (14.2 g/day vs 5.9 g/day and 1045 kJ/day vs 684 kJ/day), as observed in a preliminary study of 10 subjects, during a 1-week high-calcium and normal protein diet (1800 mg/day and 15% of total energy intake, respectively) (Jacobsen et al 2005). Interestingly, these increased losses were not evident when high calcium and protein intake was combined (23%).

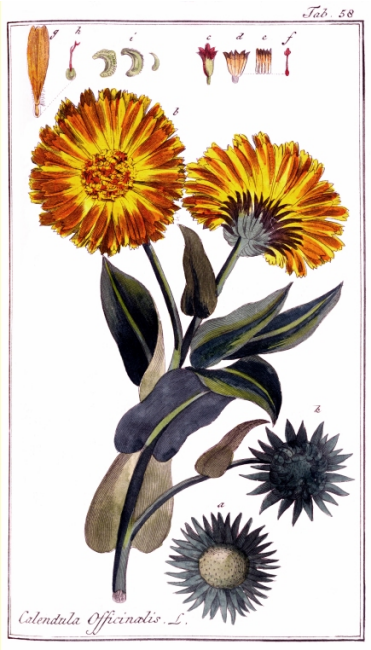
One prolific researcher in this area is Zemel (2004, Zemel et al 2004, 2005a, b), who has published three small trials investigating the effects of dietary and supplemental calcium in patients for weight maintenance or weight loss. These trials have consistently yielded positive results, demonstrating that in addition to enhanced weight loss on isocaloric and identical macronutrient profiles, with or without energy restriction, a diet providing high calcium levels of 1100–1200 mg/day results in central fat loss and corresponding improvements in blood pressure, insulin sensitivity and retention of lenan tissue. Australian researchers Bowen et al have also demonstrated similar results (2004).

Zemel et al conclude that dietary calcium and, in particular, dairy based foods are the most effective form of calcium for weight loss and that results are significant within 12 weeks.

In stark contrast to this, there have been a number of studies reporting negative results. A trial of isocaloric energy restricted diets in 54 overweight subjects with either low or high calcium intake from dairy products found that over 12 months there was no significant difference in weight loss between the two groups (Harvey-Berino et al 2005). Other studies incorporating calcium supplements of 1000 mg/day yielded negative results over 3 25-week periods in pre- and postmenopausal women

(Shapses et al 2004), as did a longitudinal study of dietary habits in adolescents (Berkey et al 2005).

Finally caution is being encouraged by many authorities who are keen to remind researchers that epidemiological data have positively linked high dairy diets with a range of other conditions, most notably prostate cancer (Lanou 2005).



NEPHROLITHIASIS

In spite of previous concerns regarding a causal relationship between dietary or supplemental calcium intake and the recurrence of oxalate stones, recent studies demonstrate that this fear is unfounded. A study comprised 120 men who experienced recurrent calcium oxalate stones as a sequel to idiopathic hypercalcuria and who were randomly assigned to either a low-calcium diet or low-animal-protein, low-salt normal-calcium diet and assessed for changes in frequency of stone formation. Results clearly showed reduced oxalate excretion in those on a normal calcium intake, as well as a greater decrease in calcium oxalate saturation (Borghi et al 2002).

In another study of 14 healthy men, assessment of the influence of dietary calcium on the given amount of oxalate demonstrated that with the inclusion of additional calcium (1121 mg) urinary oxalate levels did not increase, while they did in the control group (Hess et al 1998). The view is that, rather than being a contributing factor for oxalate stones, dietary calcium, through its binding of oxalate in the gut, can minimise recurrence, and this is substantiated by other studies (Curhan et al 1997, Liebman & Chai 1997). A preventative role for supplemental calcium remains less clear.

OTHER USES

HYPERLIPIDAEMIA

In a randomised, placebo-controlled crossover trial of 56 patients with mild–moderate hypercholesterolaemia on a controlled low cholesterol diet, calcium carbonate supplementation was shown to significantly reduce LDL levels by 4.4%, with additional 4.1% increases in HDL levels. No other effects on other blood lipids or blood pressure were observed (Bell et al 1992).

DRY EYE

A controlled double-masked study of petrolatum ointment containing 10% w/w calcium carbonate applied on the lower lid twice daily for 3 months resulted in significant improvements in all criteria assessed. However, significance over placebo was only found in ocular surface staining, therefore determination of the action of

petrolatum needs to be established and controlled for in future studies to identify the therapeutic value of calcium (Tsubota et al 1999).

FLUOROSIS

Calcium has been shown to reduce the clinical manifestations of fluorosis in children exposed to contaminated water (Gupta et al 1996).

DOSAGE RANGE

AUSTRALIAN RDIS

- Infants
  - 1–3 years: 500 mg/day.
  - 4–8 years: 700 mg/day.
- Children
  - 9–11 years: 1000 mg/day.
  - 12–18 years: 1300 mg/day.
- Adults
  - <70 years: 1000 mg/day.
  - >70 years: 1300 mg/day.
- Pregnancy: 1000–1300 mg/day.
- Lactation: 1000–1300 mg/day.

ACCORDING TO CLINICAL STUDIES

- Osteoporosis prophylaxis: 1500 mg/day in combination with accessory nutrients (e.g. zinc, manganese, copper and fluoride, HRT or antiresorptive drugs).
- Premenstrual syndrome: 1200–1600 mg/day.
- Prevention of pre-eclampsia: 2000 mg/day.
- Increased BMD in children with low intake: 100 mg/day.
- Supplementation during pregnancy to increase mineral accretion in fetus: 2000 mg/day for last trimester.
- Allergic rhinitis: 100 mg/day.
- Hyperacidity: 500–1500 mg/day as required.
- Hyperlipidaemia: 400 mg three times daily.
- Hypertension: 1000–2000 mg/day.
- Dry eye: 10% w/w calcium carbonate in petrolatum base applied twice daily.
- Fluorosis in children: 250 mg/day.
- Prevention of colorectal cancer: 1200 mg/day.
- Weight loss: 1000 mg/day.

ADVERSE REACTIONS

Oral administration of calcium supplements may cause gastrointestinal irritation, constipation and flatulence.

Hypercalcaemia Increased serum calcium may be associated with anorexia, nausea and vomiting, constipation, hypotonia, depression and occasionally lethargy and coma. Prolonged hypercalcaemic states, especially if associated with normal or elevated serum phosphate, can precipitate ectopic calcification of blood vessels, connective tissues around joints, gastric mucosa, cornea and renal tissue (Wilson et al 1991).

SIGNIFICANT INTERACTIONS

Calcium carbonate when taken as an antacid alters the absorption and excretion of a wide range of drugs. Please refer to a drug interaction guide for specific concerns. Only those interactions encountered with oral administration of calcium supplements will be included in this section.

ZINC

Calcium supplementation has been shown in some studies to increase faecal losses of zinc (McKenna et al 1997) — ensure adequate zinc intake and monitor for signs and symptoms of deficiency.

MAGNESIUM

Magnesium decreases calcium absorption as they compete for the same absorption pathway — separate doses by at least 2 hours.

PHOSPHORUS

Excess intake (soft drinks, meat consumption) can increase urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

CAFFEINE

Caffeine increases urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

EXCESS DIETARY FAT

This increases urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

EXCESS FIBRE, INCLUDING GUAR GUM

May simply delay or decrease absorption of calcium — separate doses by at least 2 hours.

CARDIAC GLYCOSIDES
Administered concurrently, high-dose calcium supplements can act synergistically with these drugs, which may induce arrythmias and potentiate their toxicity — use this combination with caution.

CALCIUM-CHANNEL BLOCKERS
Calcium supplements can have an antagonistic effect on the desired action of calcium channel blockers that could precipitate the re-emergence of arrythmias — avoid high-dose supplements unless under professional supervision.

TETRACYCLINES
Calcium supplements form complexes with these antibiotics and render 50% or more insoluble, therefore reducing the efficacy of the drug and absorption of calcium — separate doses by at least 2 hours.

THIAZIDE DIURETICS
These diuretics decrease urinary excretion of calcium. Monitor serum calcium and look for signs of hypercalcaemia, such as anorexia, polydipsia, polyuria, constipation and muscle hypertonia when using high-dose calcium supplements. Contributing risk factors are the presence of hyperparathyroidism or concurrent use of vitamin D.

CORTICOSTEROIDS
Both oral and long-term inhaled corticosteroids inhibit vitamin-D-mediated calcium absorption: overall levels of calcium may be decreased — ensure adequate calcium intake and monitor for signs and symptoms of deficiency. Consider supplementation with long-term drug therapy.

OESTROGEN AND PROGESTERONE
Calcium supplementation in combination with these hormones will have an additive effect on minimising bone resorption in postmenopausal women — potential beneficial interaction, so consider increasing intake.

ALENDRONATE
Calcium causes decreased absorption of this drug. However, as calcium supplementation is a fundamental adjuvant to the prevention of BMD loss, supplementation should still be encouraged — separate doses by at least 2 hours.

ETIDRONATE
Calcium may reduce drug absorption; however, adequate calcium is required for optimal drug effects — separate doses by at least 2 hours.

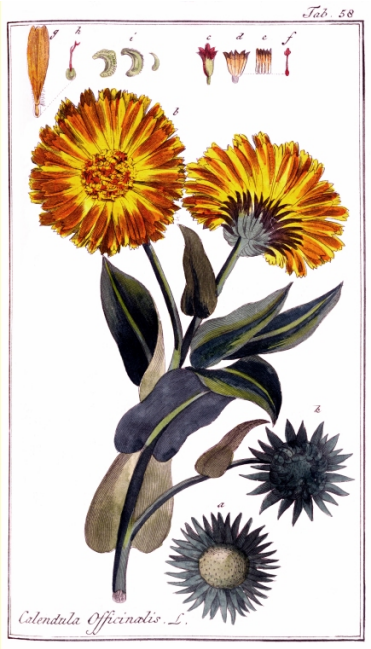
LEVOTHYROXINE
Calcium administered concurrently may reduce drug absorption — separate doses by at least 4 hours.

LYSINE
Additive effects may occur as lysine enhances intestinal absorption and reduces renal excretion of calcium — potentially beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS
People with hyperparathyroidism or chronic kidney disease should only take calcium supplements under medical supervision. Calcium supplementation is contraindicated in hypercalcaemia.

PREGNANCY USE
Many trials have established the safety of calcium supplementation during pregnancy in doses up to 2000 mg elemental calcium per day.

PRACTICE POINTS/PATIENT COUNSELLING
- Calcium is an essential mineral required for the proper functioning of numerous intracellular and extracellular processes, including muscle contraction, nerve conduction, beating of the heart, hormone release, blood coagulation, energy production and maintenance of immune function.
- Low calcium states are associated with several serious diseases such as colorectal cancer, osteoporosis types I and II, hypertension, pre-eclampsia and eclampsia.
- Although supplementation is traditionally used to correct or avoid deficiency states, research has also shown a role in the prevention of osteoporosis, pre-eclampsia and management of numerous disease states (e.g. PMS).
- Calcium can interact with numerous drugs and should be used with caution by people with renal disease or hyperparathyroid conditions.



ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this supplement do for me?
Calcium is essential for health and wellbeing. Although used to prevent or treat deficiency states, and primarily associated with BMD, it is also beneficial in a wide range of conditions such as prevention of pre-eclampsia, some forms of hypertension, maintenance of fetal growth, treatment of lead toxicity and PMS. It is considered to be a critical nutrient in pregnancy.
When will it start to work?
This will depend on the indication it is being used to treat; however, in most instances long-term administration is required (i.e. months to years).

Are there any safety issues?

In very high doses, calcium supplements can cause some side-effects, including constipation, but generally calcium is considered very safe and has a wide therapeutic range. High-dose supplements should not be used by people taking some medications. (See SIGNIFICANT INTERACTIONS above for specific information.)

REFERENCES

Alonso A, Beunza JJ, Delgado-Rodriguez M, Martinez JA, Martinez-Gonzalez MA. Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. Am J Clin Nutr 82(5) (2005): 972-9.

Atallah AN, Hofmeyr GJ, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 1 (2002): CD001059.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Rahway, NJ: Merck & Co. Inc., 2003.

Belizan JM et al. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial. BMJ 315(7103) (1997): 281-5.

Bell L, Halstenson CE, Halstenson CJ, Macres M, Keane WF. Cholesterol-lowering effects of calcium carbonate in patients with mild to moderate hypercholesterolemia. Arch Intern Med 152.12 (1992): 2441-4.

Berkey CS, Rockett HR, Willett WC, Colditz GA. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents. Arch Pediatr Adolesc Med 159(6) (2005): 543-50.

Bertone-Johnson ER, Hankinson SE, Bendich A, Johnson SR, Willett WC, Manson JE. Calcium and vitamin D intake and risk of incident premenstrual syndrome. Arch Intern Med 165(11) (2005): 1246-52.

Borghi L et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 346(2) (2002): 77-84.

Bowen J, Noakes M, Clifton P. A high dairy protein, high-calcium diet minimizes bone turnover in overweight adults during weight loss. J Nutr 2004; 134: 568-73.

Bucher HC et al. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia. JAMA 275 (1996): 1113-17.

Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid D M. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax 59 (2004): 761-8.

Chakrabarty S, Wang H, Canaff L, Hendy GN, Appelman H, Varani J. Calcium sensing receptor in human colon carcinoma: interaction with Ca(2+) and 1,25-dihydroxyvitamin D(3). Cancer Res 65(2) (2005): 493-8.

Chapuy MC et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 327 (1992): 1637-42.

Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for 3 years on hip fractures in elderly women. BMJ 308 (1994): 1081-2.

Chapuy MC et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporosis Int 13 (2002): 257-64.

Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour J-P. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab 90.1 (2005): 44-51.

Ching CK, Lam SK. Antacids: indications and limitations. Drugs 47.2 (1994): 305-17.

Coruzzi P, Mossini G. Central hypervolemia does not invariably modulate calcium excretion in essential hypertension. Nephron 75 (1997): 368-9.

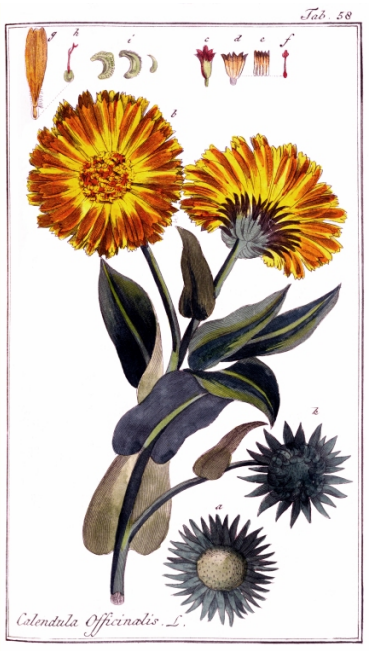
Crowther CA et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial: FRACOG and the ACT Study Group. Aust NZ J Obstet Gynaecol 39.1 (1999): 12-18.
Curhan GC et al. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 126 (1997): 497-504.
Daniele ND, Carbonelli MG, Candeloro N, Iacopino L, De Lorenzo A, Andreoli A. Effect of supplementation of calcium and Vitamin D on bone mineral density and bone mineral content in peri- and post-menopause women A double-blind, randomized, controlled trial. Pharmacol Res 50.6 (2004): 637-41.
Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 337 (1997): 670-6.
Dickinson HO et al. Calcium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev 2 (2006): CD004639.
Dorea JG. Mercury and lead during breast-feeding. Br J Nutr 92 (2004): 21-40.
Dorea JG, Donangelo C M. Early (in uterus and infant) exposure to mercury and lead. Clin Nutr 2005 [Epub ahead of print].
Ettinger AS et al. Effect of breast milk lead on infant blood lead levels at 1 month of age. Environ Health Perspect 112(14) (2004): 1381-5.
Ettinger AS et al. Influence of maternal bone lead burden and calcium intake on levels of lead in breast milk over the course of lactation. Am J Epidemiol 163(1) (2006): 48-56.
Fardellone P et al. Biochemical effects of calcium supplementation in postmenopausal women: influence of dietary calcium intake. Am J Clin Nutr 67 (1998): 1273-8.
Feldman M. Comparison of the effects of over-the-counter famotidine and calcium carbonate antacid on postprandial gastric acid: A randomized controlled trial. JAMA 275.18 (1996): 1428-31.
Frederick IO, Williams MA, Dashow E, Kestin M, Zhang C, Leisenring WM. Dietary fiber, potassium, magnesium and calcium in relation to the risk of preeclampsia. J Reprod Med 50(5) (2005): 332-44.
Geleijnse JM, Grobbee DE, Kok FJ. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. J Hum Hypertens 19 [Suppl 3] (2005): S1-4.
Gotoh M, Mizuno K, Ono Y, Takahashi M. High blood pressure, bone-mineral loss and insulin resistance in women. Hypertens Res 28(7) (2005): 565-70.
Grau MV et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J Natl Cancer Inst 95.23 (2003): 1765-71.
Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomised controlled trials. Am J Hypertens 1291 (1999): 84-92.
Groff JL, Groper SS. Advanced Nutrition and Human Metabolism. Wadsworth, 2000.
Gupta SK, Gupta RC, Seth AK, Gupta A. Reversal of fluorosis in children. Acta Paediatri Jpn 38.5 (1996): 513-19.
Harkness LS, Bonny AE. Calcium and vitamin D status in the adolescent: key roles for bone, body weight, glucose tolerance, and estrogen biosynthesis. J Pediatr Adolesc Gynecol 18.5 (2005): 305-11.
Harvey-Berino J, Gold BC, Lauber R, Starinski A. The impact of calcium and dairy product consumption on weight loss. Obes Res 13(10) (2005): 1720-6.
Hernandez-Avila M et al. Dietary calcium supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. Epidemiology 14.2 (2003): 206-12.
Herrera JA, Shahabuddin AKM, Ersheng G, Wei Y, Garcia RG, López-Jaramillo P. Calcium plus linoleic acid therapy for pregnancy-induced hypertension. Int J Gynecol Obstet 91.3 (2005): 221-7.
Herzog P, Holtermuller KH. Effect of antacids on mineral metabolism in persons with healthy kidneys: Double-blind study using an antacid containing magnesium aluminum silicate hydrate. MMW Munch Med Wochenschr 124(42) (1982): 921-3.
Hess B et al. High-calcium intake abolishes hyperoxaluria and reduces urinary crystallization during a 20-fold normal oxalate load in humans. Nephrol Dial Transplant 13 (1998): 2241-7.

Hofmeyr GJ, Roodt A, Atallah AN, Duley L. Calcium supplementation to prevent pre-eclampsia: a systematic review. S Afr Med J 93.3 (2003): 224-8.
Hyman J et al. Dietary and supplemental calcium and the recurrence of colorectal adenomas. Cancer Epidemiol Biomarkers 7.4 (1998): 291-5.
Ingec M, Nazik H, Kadanali S. Urinary calcium excretion in severe preeclampsia and eclampsia. Clin Chem Lab Med 44(1) (2006): 51-3.
Jacobsen R, Lorenzen JK, Toubro S, Krog-Mikkelsen I, Astrup A. Effect of short-term high dietary calcium intake on 24-h energy expenditure, fat oxidation, and fecal fat excretion. Int J Obes (Lond) 29(3) (2005): 292-301.
Kawano Y, Yoshimi H, Matsuoka H, Takishita S, Omae T. Calcium supplementation in patients with essential hypertension assessment by office, home and ambulatory blood pressure. J Hypertens 16(11) (1998): 1693-9.
Kennedy K et al. Double-blind, randomized trial of a synthetic triacylglycerol in formula-fed term infants: effects on stool biochemistry, stool characteristics, and bone mineralization. Am J Clin Nutr 70.5 (1999): 920-7.
Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein affects intestinal calcium absorption. Am J Clin Nutr 68 (1998): 859-65.
Koo WW et al. Maternal calcium supplementation and fetal bone mineralization. Obstet Gynecol 94.4 (1999): 577-82.
Lanou AJ. Data do not support recommending dairy products for weight loss [Letter to the Editor]. Obes Res 13 (2005): 191.
Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res 19 (2004): 370-8.
Levine RJ et al. Trial of calcium to prevent preeclampisa. N Engl J Med 337 (1997): 60-77.
Liebman M, Chai W. Effect of dietary calcium on urinary oxalate excretion after oxalate loads. Am J Clin Nutr 65 (1997): 1453-9.
Lopez-Jaramillo P, Casas JP, Serrano N. Preeclampsia: from epidemiological observations to molecular mechanisms. Braz J Med Biol Res 349 (10) (2001): 1227-35.
Matkovic V et al. Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomized controlled trial. Am J Clin Nutr 81.1 (2005): 175-88.
McCarty MF, Thomas CA. PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. Med Hypotheses 61(5-6) (2003): 535-42.
McKenna AA et al. Zinc balance in adolescent females consuming a low- or high-calcium diet. Am J Clin Nutr 65 (1997): 1460-4.
Miller EA, Keku TO, Satia JA, Martin CF, Galanko JA, Sandler RS. Calcium, vitamin D, and apoptosis in the rectal epithelium. Cancer Epidemiol Biomarkers Prev 14(2) (2005): 525-8.
Nieves JW et al. Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. Am J Clin Nutr 67 (1998): 18-24.
Pasco JA et al. Calcium intakes among Australian women: Geelong Osteoporosis Study. Aust NZ J Med 30.1 (2000): 21-7.
Pattanaungkul S et al. Relationship of intestinal calcium absorption to 1,25-dihydroxyvitamin D [1,25(OH)2D] levels in young versus elderly women: evidence for age-related intestinal resistance to 1,25(OH)2D action. J Clin Endocrinol Metab 85.11 (2000): 4023-7.
Penland JG, Johnson PE. Dietary calcium and manganese effects on menstrual cycle symptoms. Am J Obstet Gynecol 168 (1993): 1417-23.
Prentice A, Laskey MA, Jarjou LM. Lactation and bone development implications for the calcium requirements of infants and lactating mothers. Nutr Bone Dev 1999; 127-45.

Prentice A. Micronutrients and the bone mineral content of the mother, fetus and newborn. J Nutr 133 (2003): 1693-9S.
Prince RL, Dick IM, Lemmon J, Randell D. The pathogenesis of age-related osteoporotic fracture: effects of dietary calcium deprivation. J Clin Endocrinol Metab 82.1 (1997): 260-4.
Rasouli M, Mohseni Kiasari A. Serum calcium and phosphorus associate with the occurrence and severity of angiographically documented coronary heart disease, possibly through correlation with atherogenic (apo)lipoproteins. Clin Chem Lab Med 44(1) (2006): 43-50.
Recker RR. Calcium absorption and achlorhydria. N Engl J Med 1985; 313: 70-3.
Reginster JY et al. The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis: a randomized, controlled trial. Ann Intern Med 129(1) (1998): 1-8.
Resnick LM. The role of dietary calcium in hypertension: a hierarchal overview [Review]. Am J Hypertens 12 (1999): 99-112.
Ringe JD et al. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. Osteoporos Int 8 (1998): 47-52.
Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulm Pharmacol Ther 2005 [Epub ahead of print] .
Rozen P et al. Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. Cancer 91.4 (2001): 833-40.
Schatzkin A, Peters U. Advancing the calcium–colorectal cancer hypothesis [Editorial]. J Natl Cancer Inst 96.12 (2004): 893-4.
Schrager S. Dietary calcium intake and obesity evidence-based clinical practice. J Am Board Fam Pract 18 (2005): 205-10.
Shapses SA, Heshka S, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. J Clin Endocrinol Metab 89.2 (2004): 632-7.
Sowers M, Jannausch M, Scholl T, Li W, Kemp FW, Bogden JD. Blood lead concentrations and pregnancy outcomes. Arch Environ Health 57(5) (2002): 489-95.
Stear SJ, Prentice A, Jones SC, Cole TJ. Effect of a calcium and exercise intervention on the bone mineral status of 16-18-year-old adolescent girls. Am J Clin Nutr 77.4 (2003): 985-92.
Storm D et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo controlled trial. J Clin Endocrinol Metab 83.11 (1998): 3817-25.
Strause L et al. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. J Nutr 124 (1994): 1060-4.
Sukonpan K, Phupong V. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. Arch Gynecol Obstet 273(1) (2005): 12-16.
Teegarden D. Calcium intake and reduction in weight or fat mass. J Nutr 133 (2003): 249-51S.
Teegarden D. The influence of dairy product consumption on body composition. J Nutr 135(12) (2005): 2749-52.
The RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 365.9471 (2005): 1621-8.
Thys-Jacobs S. Micronutrients and the premenstrual syndrome: the case for calcium. J Am Coll Nutr 19.2 (2000): 220-7.
Thys-Jacobs S et al. Calcium supplementation in premenstrual syndrome: a randomized crossover trial. J Gen Intern Med 4 (1989): 183-9.
Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. Am J Obstet Gynecol 179.2 (1998): 444-52.

Tsubota K, Monden Y, Yagi Y, Goto E, Shimmura S. New treatment of dry eye: the effect of calcium ointment through eyelid skin delivery. Br J Ophthalmol 83.7 (1999): 767-70.
Vatier J, Cai S, Celice-Pingaud C, Castela-Papin N, Mignon M, Farinotti R. In vitro assessment of antacid efficacy using a computer-controlled artificial stomach-duodenum model reproducing gastroduodenal flux regulation. Therapie 51.2 (1996): 147-54.
Villar J et al. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. J Nutr 133[Suppl] (2003): 1606-25S.
Wahlqvist ML (ed.) Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Ward MW, Holimon TD. Calcium treatment for premenstrual syndrome. Ann Pharmacother 33.12 (1999): 1356-8.
Weingarten M A, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev 4 (2005): CD003548
Wilson JD et al. Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991.
Winzenberg TM, Shaw K, Fryer J, Jones G. Calcium supplementation for improving bone mineral density in children. Cochrane Database Syst Rev 2 (2006): CD005119.
Young GL, Jewell D. Interventions for leg cramps in pregnancy. Cochrane Database Syst Rev 1 (2002): CD000121.
Zemel MB. Role of calcium and dairy products in energy partitioning and weight management. Am J Clin Nutr (2004) 79.5 907-12S.
Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. Obes Res 12 (2004): 582-90.
Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond) 29(4) (2005a): 391-7.
Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res 13(7) (2005b): 218-25.

Calendula



Historical note Calendula is indigenous to Eastern Europe and the Mediterranean where its medicinal value has been respected since ancient times. Calendula was popular in Ancient Greece and in earlier Indian and Arabic cultures. It has been a common garden plant since the 12th century and it is mentioned in several older herbals. The name calendula comes from the Latin *calends*, meaning the first day of the month, referring to the plant's near continual flowering habit.

COMMON NAME
Marigold

OTHER NAMES
Pot or garden marigold, gold-bloom, holligold.

Field marigold (*Calendula arvensis*) is also used medicinally for the same indications because it has similar constituents.

BOTANICAL NAME/FAMILY
Calendula officinalis (family Asteraceae [Compositae or Daisy])

PLANT PARTS USED
The flowers are primarily used, but the stems, younger leaves, seeds and roots all have medicinal properties.

CHEMICAL COMPONENTS
The major constituents are triterpene saponins (2–10%) based on oleanolic acid and flavonols (3-o-glycosides of isorhamnetin and quercetin), including astraglin, hyperoside, isoqueritrin and rutin, as well as the carotenoids flavoxanthin and auroxanthin (Bako et al 2002). The triterpendiol esters faradiol laurate, faradiol myristate and faradiol palmitate have been identified as the major active compounds, which are also used as marker compounds for standardisation of calendula extracts (Hamburger et al 2003, Zitterl-Eglseer et al 2001). The terpenoids faradiol, amidiol and calenduladiol have been shown to have anti-inflammatory activity (Neukirch et al 2005).

Other constituents include essential oil, sesquiterpenes, including caryophyllene, and triterpenes, including amyrins, lupeol and lupenone. Calendula also contains

polysaccharides (WHO 2003), as well as minerals such as calcium, sodium, potassium, magnesium, iron, copper and manganese (Ahmed et al 2003).

MAIN ACTIONS

ANTIMICROBIAL

Hydro-alcoholic extracts have been shown to have antibacterial, antiviral and antifungal activities. The in vitro antifungal activity of calendula flower extracts has been investigated against *Aspergillus niger*, *Rhizopus japonicum*, *Candida albicans*, *C. tropicalis* and *Rhodotorula glutinis*. Calendula extract showed a high degree of activity against all fungi and the inhibitory effect was comparable to that of standard antifungals (Kasiram et al 2000). A flower extract has been shown to inhibit trichomonas. The oxygenated terpenes are thought to be the main active compounds (Gracza & Szasz 1968, Samochowiec et al 1979). A 70% hydro-alcoholic extract demonstrated virucidal activity against influenza virus and suppressed the growth of HSV (Bogdanova et al 1970). Calendula flower extract has also been shown to possess anti-HIV activity in vitro (Kalvatchev et al 1997).

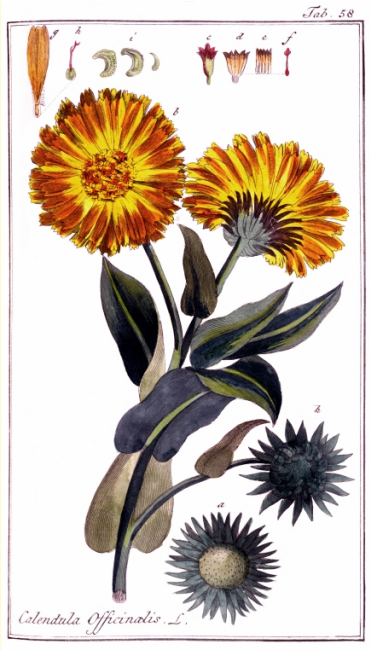
PROMOTES WOUND HEALING

An ointment containing 5% calendula flower extract, as well as an ointment containing two different fractions of calendula extract combined with allantoin, has been shown to stimulate physiological regeneration and epithelisation in experimentally induced surgical wounds. The effect is thought to be due to more intensive metabolism of glycoproteins, nucleoproteins and collagen proteins during regeneration of the tissues (Klouchek-Popova et al 1982). A combination of calendula, *Actium lappa* and *Geranium robertianum* has been shown to improve healing of ulceration in 52 patients suffering herpetic keratitis compared with treatment with acyclovir alone (Corina et al 1999).

ANTI-INFLAMMATORY

Anti-inflammatory activity has been demonstrated in several animal models. Pretreatment with an 80% hydro-alcoholic extract reduced carrageenan-induced rat paw oedema at a dose of 100 mg extract/kg. Endomethacin 5 mg/kg was shown to be 4-fold more potent in the same experiment (Mascolo et al 1987). Both a 70% hydro-alcoholic extract and a CO_2-extract have been shown to inhibit experimentally induced inflammation and oedema. The triterpenoids were shown to be the main active anti-inflammatory compounds, with the faradiol monoester appearing to be the most relevant compound due to its quantitative prevalence (Della et al 1994). A freeze-dried extract of calendula was found to suppress both the inflammatory effect

and leukocyte infiltration in an inflammatory model induced by the simultaneous injection of carrageenan and PGE_1 (Shipochliev et al 1981).



OTHER ACTIONS

REDUCES OEDEMA

Oral administration of a triterpene-containing fraction prevented the development of ascites and increased survival time compared with controls in mice inoculated with a carcinoma (Boucaud-Maitre et al 1988). The main triterpendiol esters of calendula, the faradiol esters, have been shown to possess anti-oedema activity by inhibiting croton oil-induced oedema of the mouse ear (Zitterl-Eglseer et al 1997).

IMMUNOMODULATION

Isolated polysaccharides have been shown to stimulate phagocytosis of human granulocytes (Varljen et al 1989, Wagner et al 1985). A 70% ethanol extract of calendula was shown to completely inhibit the proliferation of lymphocytes in the presence of phytohaemagglutinin in vitro (Amirghofran et al 2000).

ANTIOXIDANT

Calendula has free radical scavenging and antioxidant activity, with aqueous extracts having greater activity than methanolic extracts and antioxidant activity being related to the total phenolic content and flavonoid content (Cetkovic et al 2004).

The butanolic fraction of a calendula extract has been shown to reduce superoxide and hydroxyl radicals, suggesting a free radical scavenging effect. Lipid peroxidation in liver microsomes is also reduced (Cordova et al 2002). Isorhamnetin glycosides isolated from calendula have been shown to inhibit the activity of lipo-oxygenase (Bezakova et al 1996).

HYPOGLYCAEMIC ACTIVITY

A methanolic extract and its butanol-soluble fraction have been found to have hypoglycaemic and gastroprotective effects and to slow gastric emptying. From the butanol-soluble fraction, four new triterpene oligoglycosides, calendasaponins A, B, C and D, were isolated, together with eight known saponins, seven known flavonol glycosides, and a known sesquiterpene glucoside. Their structures were elucidated on the basis of chemical and physicochemical evidence. The principal saponin constituents, glycosides A, B, C, D and F, exhibited potent inhibitory effects on an increase in serum glucose levels in glucose-loaded rats, gastric emptying in mice, and ethanol and indomethacin-induced gastric lesions in rats (Yoshikawa et al 2001).

HYPOLIPIDAEMIC ACTIVITY

Oral administration of an isolated saponin fraction has been shown to reduce serum lipid levels in hyperlipidaemic rats (ESCOP 1996).

HEPATOPROTECTIVE

Calendula extracts have been shown to have hepatoprotective effects on rat hepatocytes both in vitro and in vivo (Barajas-Farias et al 2006, Rusu et al 2005), with cytotoxic and genotoxic effects being evident at very high doses (Barajas-Farias et al 2006, Perez-Carreon et al 2002).

CLINICAL USE

Calendula is generally used in the treatment of inflammatory skin disorders or inflammation of the mucosa and as an aid to wound healing (Blumenthal et al 2000, ESCOP 1996). It is used both internally and topically for a variety of indications.

WOUNDS AND BURNS

Historically, calendula flower preparations have been used to accelerate the healing of wounds, burns, bruises, grazes and minor skin infections. In recent times, it has been investigated for its effects on wound healing in a variety of experimental models and clinical studies as either a stand-alone topical treatment or in combination with other ingredients.

In a RCT involving 254 patients treated with adjuvant radiotherapy for breast cancer, topical treatment with calendula to the irradiated skin was found to be significantly more effective than trolamine in reducing acute dermatitis, with patients receiving calendula having less frequent interruption of radiotherapy and significantly reduced radiation-induced pain (Pommier et al 2004). In another controlled trial involving 34 patients with venous leg ulcers, a calendula extract applied twice daily for 3 weeks was found to produce a statistically significant acceleration in healing compared to a saline solution (Duran et al 2005).

Calendula ointment (8%, 1:10 tincture in 70% alcohol) is a useful adjuvant treatment during cosmetic surgery, according to a study of 19 cleft lip patients with discoloured scar tissue. Pretreatment with the calendula ointment under a gauze dressing every evening for 1 month improved the results of dermatography, a refined tattooing technique used to improve the appearance of scars (Van der Velden & Van der Dussen 1995). Another clinical study used a mixture of chlorhexidine acetate and a 2% calendula extract as a haemostatic aerosol, producing good results (Garg & Sharma 1992).

A larger, open, randomised parallel study of 156 patients in four burn centres in France compared the effects of three different topical ointments (calendula, a

proteolytic ointment and vaseline) on the management of second and third degree burns. A thick layer of the test ointment was applied daily under a closed dressing until grafting or spontaneous healing occurred and effectiveness was evaluated between the 8th and 12th day of treatment. Failure was defined as the presence of an eschar, local infection, premature treatment discontinuation or failure to complete the study. A marginally significant difference in favour of calendula over vaseline was observed and calendula was significantly better tolerated than the other treatments (Lievre et al 1992).

Prophylactic treatment with calendula ointment has also been used successfully to reduce the incidence and severity of bedsores in an open multicentre study. In other studies, positive results have been demonstrated in the treatment of poor venous return associated with ulcers, thrombophlebitis and other cutaneous changes such as inflammation, cracks and eczema (Issac 1992).

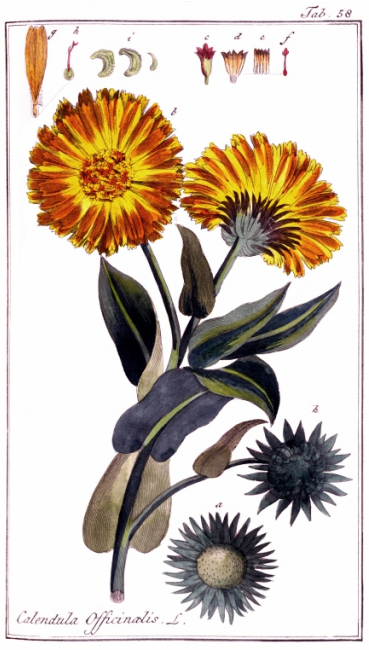
In practice, calendula is sometimes used together with St John's wort for stronger effects. The combination of *Calendula arvensis* (field marigold) and *Hypericum perforatum* oils has been shown to improve the epithelial reconstruction of surgical wounds in childbirth with caesarean section (Lavagna et al 2001).

Commission E approves the external use of calendula for poorly healing wounds and leg ulcers (Blumenthal et al 2000).

GASTROINTESTINAL INFLAMMATORY DISORDERS

An oral mixture of *Symphytum officinalis* (comfrey) and calendula was beneficial in the treatment of duodenal ulcers and gastroduodenitis according to a study involving 170 patients. Of these, 137 were treated with the herbal combination and 33 also received an antacid. A dramatic 90% of treated patients became pain free and 85% had a reduction in dyspeptic complaints. Gastric acidity showed a statistically insignificant tendency to decrease in both groups. Gastroscopy later revealed that the ulcers had healed in 90% of patients (Chakurski et al 1981). Interestingly, a smaller study conducted by the same researchers involving only 32 patients with the same condition failed to detect a beneficial effect (Matev et al 1981).

A further study by the same authors found another mixture containing calendula to be beneficial in the treatment of chronic colitis. A combination of *Taraxacum officinale*, *Hypericum perforatum*, *Melissa officinalis*, *Calendula officinalis* and *Foeniculum vulgare* was shown to relieve the spontaneous and palpable pains along the large intestine in over 95% of the patients ($n = 24$) by day 15 of treatment. Defecation was normalised in patients with diarrhoea and constipated patients were successfully treated with the addition of *Rhamus frangula*, *Citrus aurantium* and



Carum carvi. The pathological admixtures in faeces disappeared (Chakurski et al 1981).

Although encouraging, the role of calendula as a stand-alone treatment is difficult to determine from these studies.

GINGIVITIS

Calendula has been shown in an open, clinical study to be beneficial in the treatment of chronic catarrhal gingivitis (Krazhan & Garazha 2001). Interestingly, calendula extract failed to show any significant activity against common oral microorganisms in a second study that tested it against the saliva and dental plaque from 20 infants in vitro (Modesto et al 2000); however, a homeopathic preparation of calendula has been found to inhibit *Streptococcus mutans* (Giorgi et al 2004).

Commission E approves the internal and topical use of calendula flowers for inflammation of the oral and pharyngeal mucosa (Blumenthal et al 2000).

OTHER USES

The British Herbal Pharmacopoeia recommends calendula for gastric and duodenal ulcers, amenorrhoea, dysmenorrhoea and epistaxis (BHMA 1983). Topically it is recommended for leg ulcers, varicose veins, haemorrhoids, eczema and proctitis. The specific indications are for enlarged or inflamed lymphatic nodes, sebaceous cysts, duodenal ulcers, and acute and chronic inflammatory skin conditions. Its styptic activity makes it a popular topical treatment for bleeding.

DOSAGE RANGE

- Dried herb: 1–2 g as an infusion daily in divided doses.
- Liquid extract (1:2): 15–30 mL/week for internal use or 1.5–4.5 mL/day in divided doses. Dilute 1:3 for external application.
- Tincture (1:5): 0.3–1.2 mL three times daily.
- Calendula oil can be produced by steeping fresh flowers in vegetable oil for 1 week. Strain before use.

TOXICITY

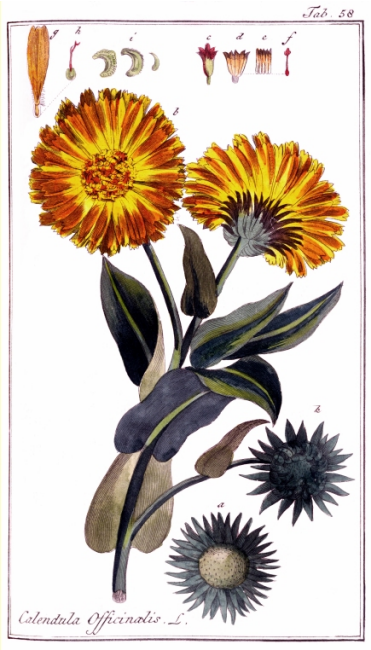
Calendula has low toxicity. No symptoms of toxicity were found after long-term administration of a calendula extract in animal studies (Elias et al 1990, ESCOP 1996). Calendula has also been found to be neither mutagenic nor carcinogenic (Elias et al 1990).

ADVERSE REACTIONS

Irritant dermatitis from calendula has been reported (Paulsen 2002, Reider et al 2001) but is rare. Sesquiterpene lactones are the most important allergens present in

Compositae species, but there are a few cases of sensitisation from a coumarin, a sesquiterpene alcohol and a thiophene (Paulsen 2002).

A study of over 1000 patients randomly chosen from several different patch test clinics identified only one who reacted to calendula (Bruynzeel et al 1992). Patch test results need to be carefully interpreted because false positives can occur, as the following case shows. A 35-year-old woman with recalcitrant atopic dermatitis, with a positive patch-test reaction to Compositae mix, was told she was allergic to calendula. However, it turned out that she followed a self-devised diet consisting largely of food products of the Compositae family (which includes lettuces and artichoke). On excluding these foods her skin condition improved quickly. This case report underscores the difficulty in determining the relevance of positive patch tests, and shows that thorough analysis of positive patch tests, by both patient and physician, may reveal unexpected or less common sources of contact allergens (Wintzen et al 2003).



SIGNIFICANT INTERACTIONS

Controlled studies are not available to assess the interaction potential of calendula.

CONTRAINDICATIONS AND PRECAUTIONS

Use with caution in patients with confirmed allergy to herbs or foods from the Compositae family.

PREGNANCY USE

Insufficient reliable information available to assess safety.

PRACTICE POINTS/PATIENT COUNSELLING

- Calendula has antimicrobial and anti-inflammatory activity and promotes wound healing.
- European text books recommend calendula for inflammation of the skin, poorly healing wounds, bruises, boils, rashes, bed sores, dermatitis resulting from chilblains, wound healing after amputations, cracked nipples during pregnancy and lactation, acne, sunburns, burns and nappy rashes. Calendula is also indicated for pharyngitis and tonsillitis (Bisset 1994, Bruneton 1999, Evans 2002, Issac 1992).
- There is some evidence from clinical trials that calendula may be beneficial in the treatment of burns, wounds and gastrointestinal inflammation and ulceration.
- People who are sensitive or allergic to foods or plants from the Compositae family should use calendula with caution.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Calendula is used for inflammatory skin conditions, including poor wound healing, burns and ulcers, due to its non-irritant, antiseptic and healing properties. Internally it is used for inflammation and ulceration of the digestive tract.

When will it start to work?

Topical effects are quickly established and should improve with continuous use. Internal use may take longer.

Are there any safety issues?

Although there have been some reports of allergic reactions to calendula, these are very rare. Calendula is generally well tolerated by children and adults.

REFERENCES

Ahmed S et al. Elemental analysis of Calendula officinalis plant and its probable therapeutic role in health. Pakistan J Sci Ind Res 46.4 (2003): 283-7.

Amirghofran Z, Azadbakht M, Karimi MH. Evaluation of the immunomodulatory effects of five herbal plants. J Ethnopharmacol 72.1-2 (2000): 167-72.

Bako E, Deli J, Toth G. HPLC study on the carotenoid composition of Calendula products. J Biochem Biophys Meth 53.1-3 (2002): 241-50.

Barajas-Farias LM et al. A dual and opposite effect of Calendula officinalis flower extract: Chemoprotector and promoter in a rat hepatocarcinogenesis model. Planta Med 72.3 (2006): 217-21.

Bezakova L et al. Inhibitory activity of isorhamnetin glycosides from Calendula officinalis L. on the activity of lipoxygenase. Pharmazie 51.2 (1996): 126-7.

Bisset NG. Herbal Drugs and Phytopharmaceuticals. Boca Raton (1994): CRC Press.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bogdanova NS et al. Study of antiviral properties of Calendula officinalis. Farmakol Toksikol 33.3 (1970): 349-55.

Boucaud-Maitre Y, Algernon O, Raynaud J. Cytotoxic and antitumoral activity of Calendula officinalis extracts. Pharmazie 43.3 (1988): 220-1.

British Herbal Medicine Association Scientific Committee. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA, 1983.

Bruneton J. Pharmcognosy, Phytochemistry, Medicinal Plants. Paris (1999): Lavoisier.

Bruynzeel DP et al. Contact sensitization by alternative topical medicaments containing plant extracts. Contact Dermatitis 27.4 (1992): 278-9.

Cetkovic GS et al. Antioxidant properties of marigold extracts. Food Res Int 37.7 (2004): 643-50.

Chakurski I et al. Treatment of chronic colitis with an herbal combination of Taraxacum officinale, Hipericum perforatum, Melissa officinalis, Calendula officinalis and Foeniculum vulgare. Vutr Boles 20.6 (1981): 51-4.

Cordova CA et al. Protective properties of butanolic extract of the Calendula officinalis L. (marigold) against lipid peroxidation of rat liver microsomes and action as free radical scavenger. Redox Rep 7.2 (2002): 95-102.

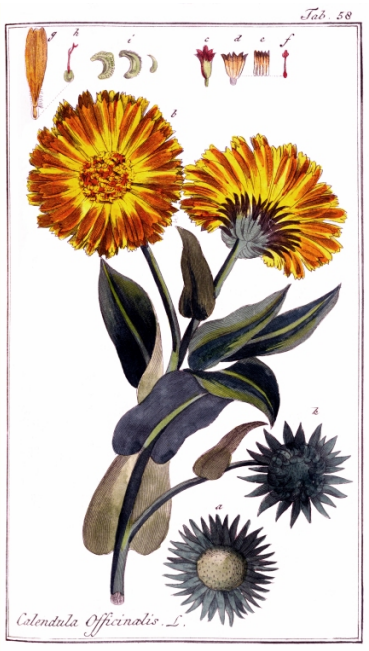
Corina P et al. Treatment with acyclovir combined with a new Romanian product from plants. Oftalmologia 46.1 (1999): 55-7.

Della LR et al. The role of triterpenoids in the topical anti-inflammatory activity of Calendula officinalis flowers. Planta Med 60.6 (1994): 516-20.

Duran V et al. Results of the clinical examination of an ointment with marigold (Calendula officinalis) extract in the treatment of venous leg ulcers. Int J Tissue React 27.3 (2005): 101-6.
Elias R et al. Antimutagenic activity of some saponins isolated from Calendula officinalis L., C. arvensis L. and Hedera helix L. Mutagenesis 5.4 (1990): 327-31.
European Scientific Co-operative On Phytomedicine (ESCOP) 1996, Calendulae Flos – Calendula flower monograph. Stuttgart: Thieme,.
Evans W. 2002, Trease and Evans: Pharmacognosy, 15th edn, Edinburgh: WS Saunders.
Garg S, Sharma SN. Development of medicated aerosol dressings of chlorhexidine acetate with hemostatics. Pharmazie 47.12 (1992): 924-6.
Giorgi JSJ et al. In vitro study of Calendula officinalis, Echinacea angustifolia and Streptococcus mutans. Arztezeitschr Naturheilverfahr 45.4 (2004): 205-13.
Gracza L, Szasz K. Examination of active agents of petals of marigold (Calendula officinalis L). Acta Pharm Hung 38.2 (1968): 118-25.
Hamburger M et al. Preparative purification of the major anti-inflammatory triterpenoid esters from Marigold (Calendula officinalis). Fitoterapia 74.4 (2003): 328-38.
Issac O. 1992, Die Ringelblume: Botanik, Chemie, Pharmakologie, Toxikologie, Pharmazie und therapeutische Verwendung Wiss. Stuttgart: Verl. Ges.
Kalvatchev Z, Walder R, Garzaro D. Anti-HIV activity of extracts from Calendula officinalis flowers. Biomed Pharmacother 51.4 (1997): 176-80.
Kasiram K, Sakharkar PR, Patil AT. Antifungal activity of Calendula officinalis. Indian J Pharm Sci 62.6 (2000): 464-6.
Klouchek-Popova E et al. Influence of the physiological regeneration and epithelialization using fractions isolated from Calendula officinalis. Acta Physiol Pharmacol Bulg 8.4 (1982): 63-7.
Krazhan IA, Garazha NN. Treatment of chronic catarrhal gingivitis with polysorb-immobilized calendula. Stomatologiia (Mosk) 80.5 (2001): 11-13.
Lavagna SM et al. Efficacy of Hypericum and Calendula oils in the epithelial reconstruction of surgical wounds in childbirth with caesarean section. Farmaco 56.5-7 (2001): 451-3.
Lievre M et al. Controlled study of three ointments for the local management of 2nd and 3rd degree burns. Clin Trials Meta-Analysis 28.1 (1992): 9-12.
Mascolo N, Autore G, Capasso G. Biological screening of Italian medicinal plants for anti-inflammatory activity. Phytother Res 1.1 (1987): 28-31.
Matev M et al. Use of an herbal combination with laxative action on duodenal peptic ulcer and gastroduodenitis patients with a concomitant obstipation syndrome. Vutr Boles 20.6 (1981): 48-51.
Modesto A, Lima KC, de Uzeda M. Effects of three different infant dentifrices on biofilms and oral microorganisms. J Clin Pediatr Dent 24.3 (2000): 237-43.
Neukirch H et al. Improved anti-inflammatory activity of three new terpenoids derived, by systematic chemical modifications, from the abundant triterpenes of the flowery plant Calendula officinalis. Chem Biodiversity 2.5 (2005): 657-71.
Paulsen E. Contact sensitization from Compositae-containing herbal remedies and cosmetics. Contact Dermatitis 47.4 (2002): 189-98.
Perez-Carreon JI et al. Genotoxic and anti-genotoxic properties of Calendula officinalis extracts in rat liver cell cultures treated with diethylnitrosamine. Toxicol in Vitro 16.3 (2002): 253-8.
Pommier P et al. Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. J Clin Oncol 22.8 (2004): 1447-53.
Reider N et al. The seamy side of natural medicines: Contact sensitization to arnica (Arnica montana L.) and marigold (Calendula officinalis L.). Contact Dermatitis 45.5 (2001): 269-72.
Rusu MA et al. The hepatoprotective action of ten herbal extracts in CCl4 intoxicated liver. Phytother Res 19.9 (2005): 744-9.
Samochowiec E et al. Evaluation of the effect of Calendula officinalis and Echinacea angustifolia extracts of Trichomonas vaginalis in vitro. Wiad Parazytol 25.1 (1979): 77-81.

Shipochliev T, Dimitrov A, Aleksandrova E. Anti-inflammatory action of a group of plant extracts. Vet Med Nauki 18.6 (1981): 87-94.
Van der Velden EM, Van der Dussen MFN. Dermatography as an adjunctive treatment for cleft lip and palate patients. J Oral Maxillofac Surg 53.1 (1995): 9-12.
Varljen J, Liptak A, Wagner H. Structural analysis of a rhamnoarabinogalactan and arabinogalactans with immuno-stimulating activity from Calendula officinalis. Phytochemistry 28 (1989): 2379-83.
Wagner H et al. Immunostimulating action of polysaccharides (heteroglycans) from higher plants. Arzneimittelforschung 35.7 (1985): 1069-75.
Wintzen M, Donker AS, Van Zuuren EJ. Recalcitrant atopic dermatitis due to allergy to Compositae. Contact Dermatitis 48.2 (2003): 87-8.
World Health Organization (WHO). 2003, Flos Calendulae. Available: http://www.who.int/medicines/library/trm/medicinalplants/vol2/035to044.pdf.
Yoshikawa M et al. Medicinal flowers. III. Marigold. (1): Hypoglycemic, gastric emptying inhibitory, and gastroprotective principles and new oleanane-type triterpene oligoglycosides, calendasaponins A, B, C, and D, from egyptian Calendula officinalis. Chem Pharm Bull 49.7 (2001): 863-70.
Zitterl-Eglseer K et al. Anti-oedematous activities of the main triterpendiol esters of marigold (Calendula officinalis L.). J Ethnopharmacol 57.2 (1997): 139-44.
Zitterl-Eglseer K et al. Morphogenetic variability of faradiol monoesters in marigold Calendula officinalis L. Phytochem Anal 12.3 (2001): 199-201.

Carnitine



BACKGROUND AND RELEVANT PHARMACOKINETICS

Carnitine was discovered in 1905, although its role in metabolism was only described in the mid 1950s and deficiency symptoms outlined in 1972. It is a trimethylated amino acid, roughly similar in structure to choline, that is ingested through the diet and also synthesised from lysine and methionine in the body. To do this, a large number of cofactors are required, such as *S*-adenosyl methionine (SAMe), methionine, magnesium, vitamins C, B6, B2, B3, iron, alpha-ketoglutarate and oxygen (Kelly 1998).

Dietary carnitine is absorbed in the intestine via a combination of active transport and passive diffusion (Li et al 1992). Mucosal absorption is saturated at around 2 g carnitine (Harper et al 1988). The bioavailability of carnitine is difficult to establish as reports vary widely from 16–87% (Harper et al 1988, Rebouche & Chenard 1991). Peak blood levels occur 3.5 hours after digestion and excretion is primarily via the kidneys (Bach et al 1983).

CHEMICAL COMPONENTS

L-Carnitine is the form most commonly used. As the D form is not biologically active, there is concern that it might interfere with the use of the L isomer by competitive inhibition and thus cause L-carnitine deficiency (Tsoko et al 1995).

Clinical note — Acetyl-L-carnitine shows promise as a strong therapeutic agent

Acetyl-L-carnitine, an ester form of L-carnitine, has also been researched for its use in the treatment of Alzheimer's disease (Brooks et al 1998, Pettegrew et al 1995, Sano et al 1992, Thal et al 1996), depression in the elderly (Garzya 1990), diabetic neuropathy (De Grandis & Minardi 2002), peripheral neuropathy (Onofrj et al 1995), prevention of neuropathy in chemotherapy (Bianchi et al 2005; Maestri et al 2005), fatigue in multiple sclerosis (Tomassini et al 2004), Peyronie's disease (Biagiotti & Cavallini 2001), degenerative cerebellar ataxia (Sorbi et al 2000) and cognitive disturbances in chronic alcoholics (Tempesta et al 1990).

FOOD SOURCES

Red meat is the richest dietary source. Vegetarian sources include avocado and tempeh (Hendler & Rorvik 2001). Human colostrum also contains carnitine (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

L-Carnitine deficiency leads to an accumulation of free fatty acids in the cell cytoplasm and of acyl-coenzyme A (CoA) in the mitochondria. This produces a toxic effect and disturbs fatty acid use for energy production (Kletzmayr et al 1999).

Deficiency symptoms (Kelly 1998) include the following:

- hypoglycaemia
- progressive myasthenia
- hypotonia
- fatigue
- cardiomyopathy
- congestive heart failure
- encephalopathy
- hepatomegaly
- neuromuscular disorders
- failure to thrive in infants
- muscle fatigue and cramps
- myoglobinaemia following exercise.

Elevation of triglycerides may also occur due to the role of carnitine in fatty acid metabolism.

PRIMARY DEFICIENCY

People at risk of primary deficiency are vegetarians, preterm infants and infants receiving a carnitine-free formula, and those with an inherited functional defect.

Clinical note — Primary carnitine deficiency: an uncommon inherited disorder

Primary carnitine deficiency is an uncommon inherited disorder, related to a functional defect in plasma membrane carnitine transport in muscle and the kidneys. These conditions have been classified as either systemic or myopathic (Evangeliou & Vlassopoulos 2003, Matera et al 2003). Systemic carnitine deficiency is reflected by low levels of carnitine in plasma and muscle and may result in cardiomyopathy, skeletal myopathy, hypoglycaemia and hyperammonaemia (Hendler & Rorvik 2001). Myopathic deficiency presents with normal plasma but low muscle carnitine levels and is a defect of carnitine transport across the muscle cell membrane (Winter et al 1987).

SECONDARY DEFICIENCY

Secondary carnitine deficiency is associated with several inborn errors of metabolism and acquired medical or iatrogenic conditions, such as the following (Evangeliou & Vlassopoulos 2003):

- genetic defects of metabolism, including methylmalonic aciduria, cytochrome C oxidase deficiency, fatty acyl-CoA dehydrogenase deficiency
- medications — patients taking valproate and the anti-HIV drug azidothymidine are at risk
- dialysis — carnitine depletion in haemodialysis patients is caused by insufficient carnitine synthesis and particularly by loss through the dialytic membranes. Many studies have shown that L-carnitine supplementation leads to improvements in several complications seen in uraemic patients, including cardiac complications, impaired exercise and functional capacities, muscle symptoms, increased symptomatic intradialytic hypotension, and erythropoietin-resistant anaemia, normalising the reduced carnitine palmitoyl transferase activity in red cells (Matera et al 2003)
- liver disease, which impairs the last stage of carnitine synthesis, resulting in deficiencies in cardiac and skeletal muscle
- chronic renal failure and renal tubular disorders, in which excretion of carnitine may be excessive
- intestinal resection
- coeliac disease — a case report exists of a 48-year-old man developing encephalopathy due to carnitine deficiency as a result of coeliac disease (Karakoc et al 2005). In patients with idiopathic dilated cardiomyopathy associated with coeliac disease a gluten-free diet has been shown to increase serum carnitine levels (Curione et al 2005)
- preterm neonates develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis
- hypopituitarism (Martindale 1999)
- adrenal insufficiency (Hendler & Rorvik 2001)
- advanced AIDS (Hendler & Rorvik 2001)
- vitamin C deficiency (Hendler & Rorvik 2001)
- other chronic conditions — diabetes mellitus, heart failure, Alzheimer's disease.

MAIN ACTIONS

Carnitine is involved in a myriad of biochemical processes important for health and wellbeing.

CELLULAR ENERGY PRODUCTION

Carnitine assists the transport of fat across cell membranes in muscle tissue for use as an energy source (Wahlqvist 2002). It is essential for mitochondrial fatty acid oxidation, which is the primary fuel source for the heart and skeletal muscles and therefore required for proper functioning (Evangeliou & Vlassopoulos 2003, Kelly 1998). This process is also required in order to maintain CoA levels.

IMPROVES BLOOD SUGAR CONTROL (IMPROVES INSULIN SENSITIVITY)

Administration of L-carnitine reduces insulin secretion and improves peripheral glucose use (Grandi et al 1997) and tissue insulin sensitivity (Negro et al 1994).

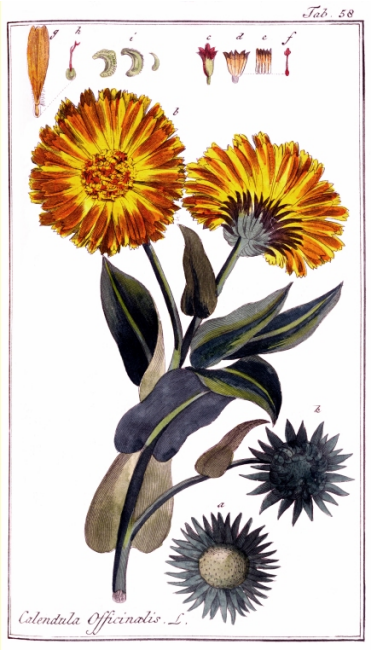
CELLULAR FUNCTION AND INTEGRITY

Carnitine is involved in the protection of membrane structures, stabilising a physiological CoA-sulfate hydrate/acetyl-CoA ratio, and reduction of lactate production (Matera et al 2003).

OTHER ACTIONS

INCREASES MALE FERTILITY

Based on the high concentrations of L-carnitine in the epididymis, it has been proposed that spermatozoa, which require beta oxidation for energy, may require L-carnitine for proper maturation (Lenzi et al 1992). Human trials have found carnitine therapy (2–3 g/day) to be effective in increasing semen quality, sperm concentration and total and forward sperm motility, especially in groups with lower baseline levels (Lenzi et al 2003). One trial also reported that improvements in sperm motility were only observed in the presence of normal mitochondrial function, determined by phospholipid hydroperoxide glutathione peroxidase levels (Garolla et al 2005).



ANTIOXIDANT

Carnitine acts as an antioxidant in the cell membrane, preventing protein oxidation and pyruvate and lactate oxidative damage (Peluso et al 2000). In vitro studies suggest a dose-dependent inhibition of lipid peroxidation of linoleic acid emulsion superior to (alpha)-tocopherol. In addition, L-carnitine may have an effect on superoxide anion radical scavenging, hydrogen peroxide scavenging, total reducing power and metal chelating on ferrous ions activities (Gulcin 2005).

PREVENTS APOPTOSIS

In vitro and animal studies show that L-carnitine can prevent apoptosis of skeletal muscle cells (Vescovo et al 2002). In patients with HIV it decreases numbers of $CD4^+$ and $CD8^+$ cells undergoing apoptosis, and significantly increases $CD4^+$ counts (Moretti et al 2002).

NEUROPROTECTIVE

Animal studies have demonstrated a reduction in mortality and neuronal degeneration in experimentally induced neurotoxicity (Binienda et al 2004) and a reduction in hypoglycaemia-induced neuronal damage (Hino et al 2005) in rats that were pretreated with carnitine. In vitro studies suggest that the anti-apoptotic and antioxidant actions of L-carnitine contribute to the neuroprotective effect (Ishii et al 2000, Tastekin et al 2005).

LIPID-LOWERING

The role of carnitine in fatty acid metabolism suggests a potential role in hyperlipidaemia. Several studies have indicated that oral L-carnitine significantly reduces lipoprotein-a levels; however, effects on other lipids are inconsistent. L-Carnitine (2 g/day) significantly reduced serum lipoprotein-a levels in 77.8% of subjects receiving active treatment after 12 weeks, according to one placebo-controlled, double-blind randomised study. No significant change was observed in other lipid parameters (Sirtori et al 2000). L-Carnitine (2 g/day) was also shown to significantly lower lipoprotein-a levels at 3 and 6 months in a double-blind placebo-controlled trial of 94 hypercholesterolemic patients with newly diagnosed type 2 diabetes (Derosa et al 2003). In a trial of children with hyperlipidaemia, lipoprotein-a levels were only reduced in those with type II homozygotes and other lipid parameters worsened (Gunes et al 2005). L-Carnitine has also been shown to decrease apolipoprotein B levels in paediatric peritoneal dialysis patients (Kosan et al 2003). A study of elderly people taking L-carnitine (2 g twice daily) demonstrated improvements in total serum cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoproteins A1 and B at 30 days (Pistone et al 2003). Animal studies have also suggested the potential for carnitine to lower triglyceride levels (Eskandari et al 2004); however, clinical trials using oral doses in type 2 diabetes have indicated an increase in triglycerides (Rahbar et al 2005). Further human trials are required to confirm which population groups may benefit from carnitine supplementation.

CLINICAL USE

Carnitine supplementation may be administered as intravenous or oral doses. This review will only focus on oral supplementation as this is the form generally used by the public and available over the counter.

TREATMENT OF DEFICIENCY

L-Carnitine supplementation is traditionally used to treat or prevent deficiency. It is indicated in primary L-carnitine deficiency and secondary deficiency due to inborn

errors of metabolism or haemodyalisis. L-Carnitine 50–200 mg/kg/day has been shown to normalise plasma carnitine levels within 10 days (Campos et al 1993).

Apnoea of prematurity Preterm neonates develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis (Evangeliou & Vlassopoulos 2003) and are at risk of developing apnoea of prematurity. Despite a promising preliminary study, a blinded, randomised, placebo-controlled study found that infants who received supplemental carnitine did not demonstrate any reduction in apnoea of prematurity, days requiring ventilator or nasal continuous positive airway pressure, or the need for supplemental oxygen therapy (O'Donnell et al 2002). A recent Cochrane review was unable to locate studies of significant quality to confirm any effects (Kumar et al 2004a). Further studies are needed to determine the role of this treatment in clinical practice as present evidence does not support its use (Kumar et al 2004b).

CARDIOVASCULAR DISEASE

L-Carnitine supplementation in doses ranging from 2 g to 4 g/day has been investigated in a number of controlled studies involving subjects with angina, heart failure, cardiogenic shock, cardiomyopathy and post myocardial infarction. Overall, positive results have been obtained and reduced mortality reported for some populations.

Chronic stable angina Controlled studies indicate that L-carnitine supplements increase exercise tolerance and reduce frequency of angina attacks, enabling some patients to reduce nitrate requirements.

One RCT of 47 patients with chronic stable angina found that 2 g L-carnitine taken daily for 3 months moderately improved the duration of exercise and the time taken for ST changes to recover to baseline (Iyer et al 2000). This study confirmed the results of an earlier multicentre, double-blind, randomised, placebo-controlled crossover trial that examined the effects of L-carnitine 1 g twice daily for 4 weeks in 44 men with stable chronic angina (Cherchi et al 1985). This study showed that active treatment resulted in increased exercise tolerance and reduced ECG indices of ischaemia in stable effort-induced angina. A meta-analysis also highlighted a significant reduction in the number of angina attacks and nitrate requirements with doses of 2 g/day (Fernandez & Proto 1992).

Post myocardial infarction A dose of 4 g/day L-carnitine over 12 months improved quality of life and increased life expectancy in patients who had suffered a MI, according to a controlled study (Davini et al 1992). This included an improvement in heart rate, systolic arterial pressure, a decrease in anginal attacks, and improve-

ment in the lipid profile. Changes were also accompanied by lower mortality in the treated group (1.2% vs 12.5% in the control group).

In a randomised, double-blind placebo-controlled trial, the effects of oral L-carnitine (2 g/day) for 28 days were assessed in patients with suspected acute MI. Total cardiac events, including cardiac deaths and non-fatal infarction, were 15.6% in the carnitine group and 26.0% in the placebo group. Angina pectoris (17.6 vs 36.0%), New York Heart Association class III or IV heart failure plus left ventricular enlargement (23.4 vs 36.0%) and total arrhythmias (13.7% vs 28.0%) were significantly less in the carnitine group compared with placebo (Singh et al 1996).

Cardiomyopathy Cardiomyopathy appears to cause leakage of carnitine from heart stores, which may make cardiac tissue vulnerable to damage; however, it is unclear whether carnitine leakage is a cause or effect of cardiomyopathy (Baker et al 2005). Long-term placebo-controlled studies (10–54 months) using an oral dose of 2 g/day L-carnitine for treatment of heart failure caused by cardiomyopathy found a statistically significant advantage in survival rates with carnitine treatment (Rizos 2000). In patients with idiopathic dilated cardiomyopathy associated with coeliac disease, a gluten-free diet has been shown to increase serum carnitine levels (Curione et al 2005).

Cardiogenic shock Several studies confirm the role of L-carnitine in the reversible phase of cardiogenic shock in terms of enzymic protection in the course of cellular oxidative damage. This has been reflected in improved survival rates (Corbucci & Lettieri 1991, Corbucci & Loche 1993).

Congestive heart failure In congestive heart failure a specific myopathy secondary to myocyte apoptosis triggered by high levels of circulating TNF-alpha has been described. The role of carnitine in preventing apoptosis in skeletal muscle and reducing TNF-alpha provides a theoretical basis for its use in the treatment of myopathy associated with congestive heart failure (Vescovo et al 2002).

Myocarditis resulting from diphtheria Two studies using D,L-carnitine (100 mg/kg/day in two divided doses orally for 4 days) found a reduction in the incidence of, and mortality from, myocarditis in diphtheria (Ramos et al 1984, 1992).

HYPERTHYROIDISM

Considering that this condition is associated with reduced body stores of carnitine and that L-carnitine is a peripheral antagonist of thyroid hormone action in some tissues according to in vivo studies, carnitine treatment has been investigated in hyperthyroidism.

One 6-month, randomised, double-blind placebo-controlled trial involving 50 women with induced suppression of thyroid-stimulating hormone showed that doses

of 2 g or 4 g/day oral L-carnitine both reversed and prevented symptoms of the disease and had a beneficial effect on bone mineralisation (Benvenega et al 2001).

MALE FERTILITY

A placebo-controlled, double-blind crossover trial of 100 infertile males (aged 20–40 years) found that L-carnitine therapy (2 g/day) was effective in increasing semen quality, sperm concentration and total and forward sperm motility, especially in groups with lower baseline levels (Lenzi et al 2003). The positive effects on sperm motility have also been shown in previous trials using L-carnitine 3 g/day (Costa et al 1994, Vitali et al 1995). In a later trial, improvements in sperm motility were only observed in the presence of normal mitochondrial function, determined by phospholipid hydroperoxide glutathione peroxidase levels (Garolla et al 2005).

PERIPHERAL VASCULAR DISEASE

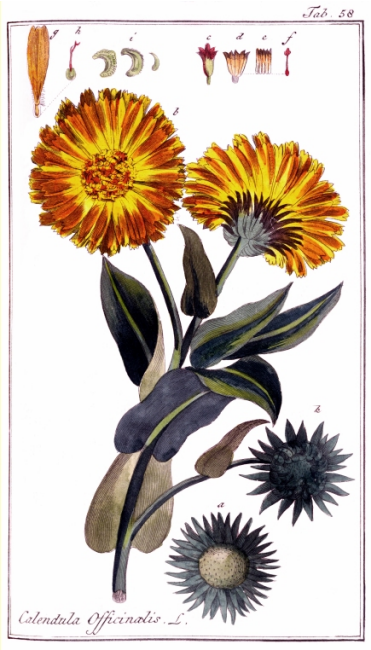
Due to its anti-ischaemic activity, L-carnitine supplements have also been used in peripheral vascular disease. A double-blind crossover study supports this use, finding L-carnitine supplements (2 g/day) taken for 3 weeks increased walking time in people with peripheral vascular disease (Brevetti et al 1988). A derivative of L-carnitine, known as propionyl-L-carnitine, taken for 6 months (2 g/day orally) has also demonstrated significant improvements in walking distance and speed in patients with claudication (Hiatt et al 2001).

ERGOGENIC AID

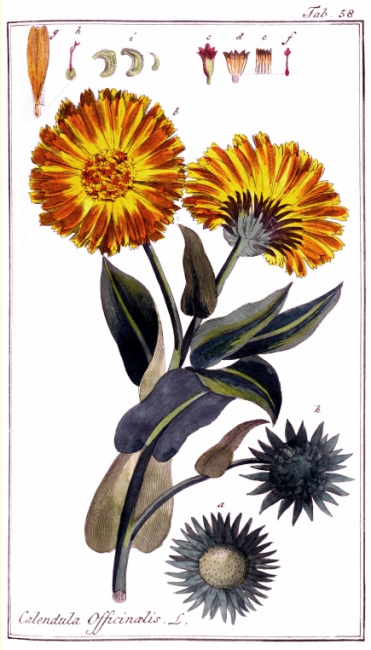
L-Carnitine is a popular supplement amongst athletes in the belief that it will increase performance and recovery. This concept is largely based on the fact that carnitine assists in the transport of fat across cell membranes in muscle tissue and is involved in cellular energy production. Additionally, carnitine reduces insulin secretion and significantly improves peripheral glucose use, when administered with glucose, according to human research (Grandi et al 1997). There is evidence that L-carnitine supplementation may increase maximal oxygen consumption, stimulate lipid metabolism and reduce post-exercise plasma lactate (Karlic & Lohninger 2004).

In a placebo-controlled crossover trial using an L-carnitine–L-tartrate (LCLT) supplement (2 g L-carnitine/day) for 3 weeks, researchers suggested that LCLT supplementation was effective in assisting recovery from high-repetition squat exercise (Volek et al 2002). However, other clinical trials using 2 g L-carnitine twice daily for 3 months found no significant increase in muscle carnitine content, mitochondrial proliferation, or physical performance (Wachter et al 2002).

Trials in subjects with cardiovascular disorders have been more promising. This is supported by the clinical trial discussed earlier involving patients with chronic stable



angina (Iyer 2000). In addition, a clinical trial using 1 g L-carnitine or placebo three times daily for 120 days has indicated a potential for improved performance and effort tolerance in patients with cardiac insufficiency (Loster et al 1999).



OTHER USES

CHRONIC FATIGUE SYNDROME

Studies investigating whether people with CFS have lower levels of free L-carnitine have shown contradictory results (Jones et al 2005), and trials using L-carnitine supplementation in CFS have generally produced mixed results (Plioplys & Plioplys 1995, 1997, Soetekouw et al 2000). One randomised controlled trial did find that 1 g L-carnitine (three times daily) produced a significant clinical improvement, especially between the fourth and eighth week of treatment (Plioplys & Plioplys 1997).

ATTENTION DEFICIT HYPERACTIVITY DISORDER

In a randomised, double-blind, placebo-controlled double-crossover trial, treatment with L-carnitine (100 mg/kg twice daily, maximum 4 g/day) over 24 weeks significantly decreased the attention problems, delinquency and aggressive behaviour in boys with ADHD (Van-Oudheusden & Scholte 2002). At 6 month follow-up 19 of 24 boys had responded to treatment as judged by parents and teachers.

DIABETES

Carnitine is essential for lipid and carbohydrate metabolism, and correct metabolic control. It has been suggested that some people with diabetes may have reduced levels of total and free carnitine (Mamoulakis et al 2004). Administration of L-carnitine reduces insulin secretion and improves peripheral glucose use (Grandi et al 1997) and tissue insulin sensitivity (Negro et al 1994). Additionally in type 2 diabetes, L-carnitine (1 g 3 times daily) significantly lowers fasting plasma glucose, but may increase fasting triglycerides (Rahbar et al 2005). Although promising, further research is required to elucidate the possible benefits and safety of carnitine supplementation in this population.

HAEMODIALYSIS

Carnitine depletion in haemodialysis patients is caused by insufficient carnitine synthesis and excessive loss through the dialytic membranes (Matera et al 2003). Carnitine supplementation has been approved by the US FDA for the treatment and prevention of carnitine depletion in dialysis patients. Supplementation in such patients is said to improve lipid metabolism, protein nutrition, antioxidant status, and anaemia and may reduce the incidence of intradialytic muscle cramps, hypotension, asthenia, muscle weakness, and cardiomyopathy (Bellinghieri et al 2003). However,

the routine use of L-carnitine in dialysis patients to manage anaemia and refractory dialysis-associated hypotension is contentious and some authors believe that there is insufficient evidence to support this indication (Steinman et al 2003).

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a major complication of cirrhosis. Human trials have demonstrated a protective effect of L-carnitine (2 g twice daily) in ammonia-precipitated hepatic encephalopathy in cirrhotic patients at 30 days and more significantly at 60 days (Malaguarnera et al 2003).

RETT SYNDROME

A case is reported of a 17-year-old girl with Rett syndrome whose condition improved while using L-carnitine (50 mg/kg/day). Upon cessation, she relapsed whereas re-establishing the treatment saw improvements after 1 week. More specifically, alertness increased, she started reaching for objects with both hands, and answered simple questions with one or two words. Interestingly, serum carnitine levels (free and total) were within normal limits before and after L-carnitine treatment (Plioplys & Kasnicka 1993). An 8-week randomised, placebo-controlled, double-blind crossover trial of L-carnitine has since been completed detecting improvements on the Hand Apraxia Scale and in the subjects' general wellbeing (Ellaway et al 1999).

BETA THALASSAEMIA MAJOR

L-Carnitine treatment 100 mg/kg/day for 3 months improved transfusion time in patients with thalassaemia (Yesilipek et al 1998).

AGEING

In a randomised, double-blind, placebo-controlled trial of 84 elderly subjects (aged 70–92 years) who experienced onset of fatigue after slight physical activity, L-carnitine (2 g twice daily) for 30 days resulted in significant improvements in total fat mass, total muscle mass, lipid profiles, as well as overall improvements in physical and mental fatigue (Pistone et al 2003). Animal studies have demonstrated that supplementation of carnitine (300 mg/kg/day) and lipoic acid (100 mg/kg/day) for 30 days protects mitochondria from ageing by raising mitochondrial energy production and reversing the age-associated decline in mitochondrial enzyme activity (Savitha et al 2005). Studies using standard oral doses of L-carnitine in humans are required to confirm these effects.

WEIGHT LOSS

Carnitine is a popular supplement for weight loss when combined with an exercise program. This is based on its biochemical role in the production of energy from fatty

acids. Currently, one clinical trial that has investigated carnitine supplementation together with an aerobic training program failed to detect a significant effect on weight loss (Villani et al 2000).

DOSAGE RANGE

- Deficiency: L-carnitine 50–200 mg/kg/day.
- Most conditions: 2–4 g/day L-carnitine or in divided dose (maximum single dose 2 g).

ACCORDING TO CLINICAL STUDIES

- Cardiovascular disorders: 2 g/day for at least 3 months may improve exercise tolerance and recovery in people with conditions such as chronic stable angina and cardiac insufficiency, and may also reduce lipoprotein-a levels and improve peripheral vascular disease.
- Hyperthyroidism: 2–4 g/day in divided doses.
- Chronic fatigue syndrome: 1 g three times daily.
- Ergogenic aid: 2 g/day.
- Fertility: 2–3 g/day may be useful to increase sperm motility and concentration.

ADVERSE REACTIONS

Carnitine is well tolerated at recommended doses. Mild gastrointestinal symptoms including abdominal cramps, diarrhoea, nausea and vomiting, heartburn or gastritis may occur. Mild myasthenia has been reported in uraemic patients using the D,L form (Hendler & Rorvik 2001). Changes in body odour have also been noted (Sigma-Tau Pharmaceuticals 1999, Van-Oudheusden & Scholte 2002).

SIGNIFICANT INTERACTIONS

ANTICOAGULANTS

According to one case report, L-carnitine 1 g/day may potentiate the anticoagulant effects of acenocoumarol (also known as nicoumalone or acenocumarin) (Martinez et al 1993). Use this combination with caution. Monitor bleeding time and signs and symptoms of excessive bleeding.

ANTICONVULSANTS (INCLUDING VALPROATE, PHENOBARBITAL, PHENYTOIN, CARBAMAZEPINE)

Trials with children and adults have shown a reduction in carnitine levels during anticonvulsant therapy (Hug et al 1991, Rodriguez-Segade et al 1989). L-Carnitine deficiency may cause or potentiate valproate toxicity and supplementation is known to reduce the toxicity of valproate, as well as symptoms of fatigue. In a trial using L-carnitine for acute valproate poisoning no adverse events were noted (LoVecchio et

al 2005). Increased carnitine intake may be required with long-term therapy — potentially beneficial interaction under professional supervision.

INTERFERON-ALPHA

Clinical trials with patients being treated with IFN-alpha for hepatitis C observed reduced fatigue when carnitine 2 g/day was co-administered (Neri et al 2003). Increased carnitine intake may be required with long-term therapy — potentially beneficial interaction under professional supervision.

ADRIAMYCIN (DOXORUBICIN)

Animal studies suggest long-term carnitine administration may reduce the cardiotoxic side effects of adriamycin (Kawasaki et al 1996). Increased carnitine intake may be required with long term therapy — potentially beneficial interaction.

INTERLEUKIN-2 IMMUNOTHERAPY

Clinical trials using L-carnitine (1 g/day orally) found that it may be used successfully to prevent cardiac complications during IL-2 immunotherapy in cancer patients with clinically relevant cardiac disorders (Lissoni et al 1993). Thus a beneficial interaction is possible under professional supervision.

CHEMOTHERAPY (CISPLATIN)

Research into the use of L-carnitine 4 g/day for 7 days showed a reduction in fatigue resulting from treatment with cisplatin (Graziano et al 2002) — beneficial interaction is possible under professional supervision.

HIV DRUGS (ZIDOVUDINE)

In vitro studies indicate prevention of muscle damage due to carnitine depletion (Dalakas et al 1994, Moretti et al 2002, Semino-Mora et al 1994). Patients with HIV infection undergoing highly active antiretroviral therapy can be carnitine deficient and supplementation of L-carnitine has been proposed to 'increase the number of CD4 cells and reduce lymphocyte apoptosis; improve symptoms of polyneuropathy; prevent cardiovascular damage from wasting and diarrhoea syndromes; decrease serum levels of triglycerides and TNF(alpha)' (Ilias et al 2004). Beneficial interaction is possible. Increased carnitine intake may be required with long-term therapy.

BETAMETHASONE

A RCT has shown that a combination of low-dose betamethasone (2 mg/day) and L-carnitine (4 g/5 days) was more effective in the prevention of respiratory distress syndrome (7.3% vs 14.5%) and death (1.8% vs 7.3%) in preterm infants than high-dose betamethasone given alone (8 mg/2 days) (Kurz et al 1993) — beneficial interaction possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

- Chronic liver disease — may impair metabolism or increase biosynthesis of L-carnitine (Krahenbuhl 1996).
- Seizures — may increase incidence of seizures in those with a pre-existing condition (Sigma-Tau Pharmaceuticals 1999).

PREGNANCY USE

Insufficient reliable information is available. However, animal studies have revealed no evidence of decreased fertility or harm to the fetus (Hendler & Rorvik 2001). In fact, some research suggests a role for carnitine.

Requirements for carnitine may increase during pregnancy and a small trial found a positive effect in women diagnosed with placental insufficiency taking 1 g L-carnitine twice daily (Genger et al 1988). Due to the role of L-carnitine in the synthesis of surfactant, trials have also been conducted using L-carnitine in combination with low-dose betamethasone in women with imminent premature delivery, with an improvement in respiratory distress syndrome and mortality rates (Kurz et al 1993).

PRACTICE POINTS/PATIENT COUNSELLING

- Carnitine is an amino acid that is ingested through the diet and also synthesised from lysine and methionine in the body.
- It is involved in numerous biochemical processes and is essential for energy production in the mitochondria of every cell.
- Vegetarians, and preterm infants or those on a carnitine-free formula, are at risk of deficiency. Secondary risk factors include genetic defects of metabolism, liver and renal disease, dialysis, certain medicines and hypopituitarism.
- L-Carnitine 2 g/day for 3 months has been shown to improve exercise tolerance and recovery, especially in people with cardiovascular disorders such as chronic stable angina and cardiac insufficiency. Preliminary evidence also suggests a possible role in hyperthyroidism, male infertility and peripheral vascular diseases such as intermittent claudication.
- Carnitine supplements are also used to promote weight loss and as an ergogenic aid, although large controlled studies are unavailable to assess effectiveness.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

L-Carnitine supplements improve clinical outcomes in people with cardiovascular disorders by reducing the frequency of angina attacks, and improving outcomes after heart attack, cardiogenic shock and in cardiomyopathy. It may also reduce

symptoms in hyperthyroidism, increase male fertility, increase walking distance in people with peripheral vascular disease and reduce the side-effects of some medicines.

When will it start to work?

People with cardiovascular disorders such as chronic stable angina and cardiac insufficiency should experience benefits within 1–3 months.

Are there any safety issues?

Carnitine is well tolerated, but people with chronic liver disease or epilepsy should use it with caution.

REFERENCES

Anon. Carnitine may boost T cell counts. Treatment Update 10(5) (1998): 4-6.

Bach AC et al. Free and total carnitine in human serum after oral ingestion of L-carnitine. Diabet Metab 9 (1983): 121-4.

Baker H, DeAngelis B, Orlando J, Correia J. Cardiac carnitine leakage is promoted by cardiomyopathy. Nutrition 21(3) (2005): 348-50.

Bellinghieri G, Santoro D, Calvani M, Mallamace A, Savica V. Carnitine and hemodialysis. Am J Kidney Dis 41(3 Suppl 1) (2003): S116-22.

Benvenga S et al. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 86(8) (2001): 3579-94.

Biagiotti G, Cavallini G. Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. BJU Int 88(1) (2001): 63-7.

Bianchi G et al. Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine. Eur J Cancer 41(12) (2005):1746-50.

Binienda Z, Virmani A, Przybyla-Zawislak B, Schmued L. Neuroprotective effect of carnitine in the 3-nitropropionic acid (3-NPA)-evoked neurotoxicity in rats. Neurosci Lett 367(2) (2004): 264-7.

Brevetti G et al. Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, crossover study. Circulation 77 (4) (1988): 767-73.

Brooks JO et al. Acetyl L-carnitine slows decline in younger patients with Alzheimer's disease: a reanalysis of a double-blind, placebo-controlled study using the trilinear approach. Int Psychogeriatr 10(2) (1998): 193-203.

Campos Y et al. Plasma carnitine insufficiency and effectiveness of L-carnitine therapy in patients with mitochondrial myopathy. Muscle Nerve 16(2) (1993): 150-3.

Cherchi A et al. Effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized, placebo controlled crossover study. Int J Clin Pharmacol Ther Toxicol 23(10) (1985): 569-72.

Corbucci GG, Lettieri B. Cardiogenic shock and L-carnitine: clinical data and therapeutic perspectives. Int J Clin Pharmacol Res 11(6) (1991): 283-93.

Corbucci GG, Loche F. L-carnitine in cardiogenic shock therapy: pharmacodynamic aspects and clinical data. Int J Clin Pharmacol Res 13(2) (1993): 87-91.

Costa M et al. L-carnitine in idiopathic asthenozoospermia: a multicentre study. Andrologia 26 (1994): 155-9.

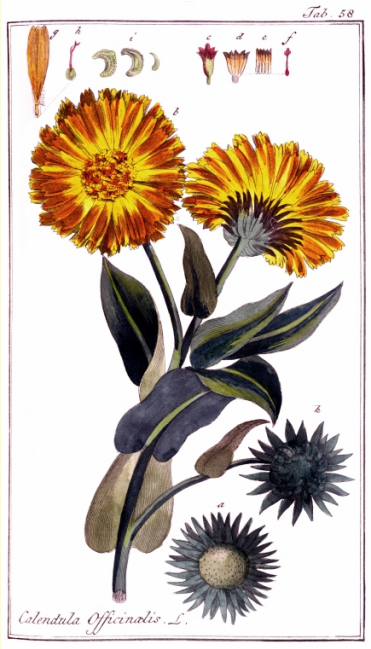
Curione M et al. Carnitine deficiency in patients with coeliac disease and idiopathic dilated cardiomyopathy. Nutr Metab Cardiovasc Dis 15(4) (2005): 279-83.

Dalakas MC et al. Zidovudine-induced mitochondrial myopathy is associated with muscle carnitine deficiency and lipid storage. Ann Neurol 35 (1994): 482-7.

Davini P, Bigalli A, Lamanna F, Boem A. Controlled study on L-carnitine therapeutic efficacy in post-infarction. Drugs Exp Clin Res 18(8) (1992): 355-65.
De Grandis D, Minardi C. Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo-controlled study. Drugs R D 3(4) (2002): 223-31.
Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. Clin Ther 25(5) (2003): 1429-39.
Ellaway C et al. Rett syndrome: randomized controlled trial of L-carnitine. J Child Neurol 14(3) (1999): 162-7.
Eskandari HG, Cimen MYB, Tamer L, Kanik A, Atik U. Short term effects of L-carnitine on serum lipids in STZ-induced diabetic rats. Diabetes Res Clin Pract 66(2) (2004):129-32.
Evangeliou A, Vlassopoulos D. Carnitine metabolism and deficit: When is supplementation necessary? Curr Pharm Biotechnol 4(3) (2003): 211-19.
Fernandez C, Proto C. L-carnitine in the treatment of chronic myocardial ischemia: An analysis of 3 multicenter studies and a bibliographic review. Clin Ther 140(4) (1992): 353-77 [in Italian].
Garolla A, Maiorino M, Roverato A, Roveri A, Ursini F, Foresta C. Oral carnitine supplementation increases sperm motility in asthenozoospermic men with normal sperm phospholipid hydroperoxide glutathione peroxidase levels. Fertil Steril 83(2) (2005): 355-61.
Garzya G. Evaluation of the effects of L-acetylcarnitine on senile patients suffering from depression. Drugs Exp Clin Res 16(2) (1990): 101-6.
Genger H, Enzelsberger H, Salzer H. Carnitine in therapy of placental insufficiency: initial experiences. Z Geburtshilfe Perinatol 192 (1988): 155-7.
Grandi M, Pederzoli A, Sacchetti C. Effect of acute carnitine administration on glucose insulin metabolism in healthy subjects. Int J Clin Pharm Res 17(4) (1997): 143-7.
Graziano F et al. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. Br J Cancer 86(12) (2002): 1854-7.
Gulcin I. Antioxidant and antiradical activities of L-carnitine. Life Sci 78(8) (2006): 803-11.
Gunes B, Yalcin SS, Kalkanoglu HS, Onol S, Dursun A, Coskun T. The effect of oral L-carnitine supplementation on the lipid profiles of hyperlipidaemic children. Acta Paediatr 94(6) (2005): 711-16.
Harper P, Elwin CE, Cederblad G. Pharmacokinetics of intravenous and oral bolus doses of L-carnitine in healthy subjects. Eur J Clin Pharmacol 35 (1988): 555-62.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Hiatt WR et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. Am J Med 110(8) (2001): 616-22.
Hino K, Nishikawa M, Sato E, Inoue M. l-Carnitine inhibits hypoglycemia-induced brain damage in the rat. Brain Res 1053(1-2) (2005): 77-87.
Hug G et al. Reduction of serum carnitine concentrations during anticonvulsant therapy with phenobarbital, valproic acid, phenytoin and carmazepine in children. J Pediatr 119 (1991): 799-802.
Ilias I, Manoli I, Blackman MR, Gold PW, Alesci S. L-Carnitine and acetyl-L-carnitine in the treatment of complications associated with HIV infection and antiretroviral therapy. Mitochondrion 4(2-3) (2004): 163-8.
Ishii T, Shimpo Y, Matsuoka Y, Kinoshita K. Anti-apoptotic effect of acetyl-L-carnitine and L-carnitine in primary cultured neurons. Jpn J Pharmacol 83(2) (2000): 119-24.
Iyer RN, Khan AA, Gupta A, Vajifdar BU, Lokhandwala YY. L-carnitine moderately improves the exercise tolerance in chronic stable angina. J Assoc Physicians India 48(11) (2000): 1050-2.
Jones MG, Goodwin CS, Amjad S, Chalmers RA. Plasma and urinary carnitine and acylcarnitines in chronic fatigue syndrome. Clin Chim Acta 360(1-2) (2005): 173-7.
Karakoc E, Erdem S, Sokmensuer C, Kansu T. Encephalopathy due to carnitine deficiency in an adult patient with gluten enteropathy. Clin Neurol Neurosurg 2005 [Epub ahead of print].
Karlic H, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? Nutrition 20(7-8) (2004): 709-15.

Kawasaki N et al. Long-term L-carnitine treatment prolongs the survival in rats with andiamycin induced heart failure. J Card Fail 2 (1996): 293-9.
Kelly GS. L-Carnitine: Therapeutic applications of a conditionally-essential amino acid. Altern Med Rev 3(5) (1998): 345-60.
Kletzmayr J et al. Anemia and carnitine supplementation in hemodialyzed patients. Kidney Int 55(69) (1999): S93-106.
Kosan C, Sever L, Arisoy N, Caliskan S, Kasapcopur O. Carnitine supplementation improves apolipoprotein B levels in pediatric peritoneal dialysis patients. Pediatr Nephrol 18(11) (2003): 1184-8.
Krahenbuhl S. Carnitine metabolism in chronic liver disease. Life Sci 59(19) (1996): 1579-99.
Kumar M, Kabra NS, Paes B. Carnitine supplementation for preterm infants with recurrent apnea. Cochrane Database Syst Rev (4) (2004a): CD004497.
Kumar M, Kabra NS, Paes B. Role of carnitine supplementation in apnea of prematurity: a systematic review. J Perinatol 24(3) (2004b): 158-63.
Kurz C et al. L-carnitine-betamethasone combination therapy versus betamethasone therapy alone in prevention of respiratory distress syndrome. Z Geburtshilfe Perinatol 197(5) (1993): 215-19 [in German].
Lenzi A et al. Metabolism and action of L-carnitine: its possible role in sperm tail function. Arch Ital Urol Nephrol Androl 64 (1992): 187-96.
Lenzi A et al. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. Fertil Steril 79(2) (2003): 292-300.
Li B et al. The effect of enteral carnitiine administration in humans. Am J Clin Nutr 55 (1992): 838-45.
Lissoni P et al. Prevention by L-carnitine of interleukin-2 related cardiac toxicity during cancer immunotherapy. Tumori 79 (1993): 202-4.
Loster H et al. Prolonged oral L-carnitine substitution increases bicycle ergometer performance in patients with severe, ischemically induced cardiac insufficiency. Cardiovasc Drugs Ther 13(6) (1999): 537-46.
LoVecchio F, Shriki J, Samaddar R. l-carnitine was safely administered in the setting of valproate toxicity. Am J Emerg Med 23(3) (2005): 321-2.
Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crino L. A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy. Tumori 91(2) (2005): 135-8.
Malaguarnera M et al. L-Carnitine in the treatment of mild or moderate hepatic encephalopathy. Dig Dis 21(3) (2003): 271-5.
Mamoulakis D, Galanakis E, Dionyssopoulou E, Evangeliou A, Sbyrakis S. Carnitine deficiency in children and adolescents with type 1 diabetes. J Diabetes Complic 18(5) (2004): 271-4.
Martindale W. Martindale, Extra Pharmacopoeia. London: Pharmaceutical Press, 1999.
Martinez E, Domingo P, Roca-Cusachs A. Potentiation of acenocoumarol action by L-carnitine (Letter). J Intern Med 233 (1993): 94.
Matera M et al. History of L-carnitine: implications for renal disease. J Renal Nutr 13(1) (2003): 2-14.
Matera M, Bellinghieri G, Costantino G, Santoro D, Calvani M, Savica V. History of L-carnitine: implications for renal disease. J Renal Nutr 13(1) (2003): 2-14.
Moretti S et al. L-carnitine reduces lymphocyte apoptosis and oxidant stress in HIV-1-infected subjects treated with zidovudine and didanosine. Antioxid Redox Signal 4(3) (2002): 391-403.
Negro P et al. The effect of L-carnitine, administered through intravenous infusion of glucose, on both glucose and insulin levels in health subjects. Drugs Exp Clin Res 20(6) (1994): 257-62.
Neri S et al. L-carnitine decreases severity and type of fatigue induced by interferon-alpha in the treatment of patients with hepatitis C. Neuropsychobiology 47(2) (2003): 94-7.
O'Donnell J, Finer NN, Rich W, Barshop BA, Barrington KJ. Role of L-carnitine in apnea of prematurity: a randomized, controlled trial. Pediatrics 109(4) (2002): 622-6.
Onofrj M et al. L-acetylcarnitine as a new therapeutic approach for peripheral neuropathies with pain. Int J Clin Pharmacol Res 15(1) (1995): 9-15.
Peluso G et al. Cancer and anticancer therapy-induced modifications on metabolism mediated by carnitine system. J Cell Physiol 182 (2000): 339–50.

Pettegrew JW et al. Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease. Neurobiol Aging 16(1) (1995): 1-4.
Pistone G et al. Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. Drugs Aging 20(10) (2003): 761-7.
Plioplys AV, Kasnicka I. L-carnitine as a treatment for Rett syndrome. South Med J 86(12) (1993): 1411-12.
Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. Neuropsychobiology 35(1) (1997): 16-23.
Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology 32(3) (1995): 132-8.
Rahbar AR, Shakerhosseini R, Saadat N, Taleban F, Pordal A, Gollestan B. Effect of L-carnitine on plasma glycemic and lipidemic profile in patients with type II diabetes mellitus. Eur J Clin Nutr 59(4) (2005): 592-6.
Ramos AC, Barrucand L, Elias PR, Pimentel AM, Pires VR. Carnitine supplementation in diphtheria. Indian Pediatr 29(12) (1992): 1501-5.
Ramos AC, Elias PR, Barrucand L, Da Silva JA. The protective effect of carnitine in human diphtheric myocarditis. Pediatr Res 18(9) (1984): 815-19.
Rebouche CJ, Chenard CA. Metabolic fate of dietary carnitine in human adults: identification and quantification of urinary and fecal metabolites. J Nutr 121 (1991): 539-45.
Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 139(2) (2000): S120-3.
Rodriguez-Segade S et al. Carnitine deficiency associated with anticonvulsant therapy. Clin Chim Acta 181(2) (1989):175-81.
Sano M et al. Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. Arch Neurol 49(11) (1992): 1137-41.
Savitha S, Sivarajan K, Haripriya D, Kokilavani V, Panneerselvam C. Efficacy of levo carnitine and alpha lipoic acid in ameliorating the decline in mitochondrial enzymes during aging. Clin Nutr 24(5) (2005): 794-800.
Semino-Mora MC et al. Effect of L-carnitine on the zidovudine-induced destruction of human myotubes: Part 1: L-carnitine prevents the myotoxicity of AZT in vitro. Lab Invest 71 (1994): 102-12.
Sigma-Tau Pharmaceuticals. Carnitor [levocarnitine] package insert. Gaithersberg, MD: Sigma-Tau Pharmaceuticals Inc., Dec. 1999.
Singh RB et al. A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction. Postgrad Med J 72(843) (1996): 45-50.
Sirtori CR et al. L-carnitine reduces plasma lipoprotein(a) levels in patients with hyperLp(a). Nutr Metab Cardiovasc Dis 10(5) (2000): 247-51.
Soetekouw PM et al. Normal carnitine levels in patients with chronic fatigue syndrome. Neth J Med 57(1) (2000): 20-4.
Sorbi S, Forleo P, Fani C, Piacentini S. Double-blind, crossover, placebo-controlled clinical trial with L-acetylcarnitine in patients with degenerative cerebellar ataxia. Clin Neuropharmacol 23(2) (2000): 114-18.
Steinman TI et al. L-carnitine use in dialysis patients: is national coverage for supplementation justified? What were CMS regulators thinking: or were they? Nephrol News Issues 17(5) (2003): 28-30, 32-4, 36 passim.
Tastekin A, Gepdiremen A, Ors R, Emin Buyukokuroglu M, Halici Z. l-carnitine protects against glutamate- and kainic acid-induced neurotoxicity in cerebellar granular cell culture of rats. Brain Dev 27(8) (2005): 570-3.
Tempesta E et al. Role of acetyl-L-carnitine in the treatment of cognitive deficit in chronic alcoholism. Int J Clin Pharmacol Res 10(1-2) (1990): 101-7.
Thal LJ et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 47(3) (1996): 705-11.
Tomassini V et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci 218(1-2) (2004): 103-8.



Tsoko M et al. Enhancement of activities relative to fatty acid oxidation in the liver of rats depleted of L-carnitine by D-carnitine and gammabutyrobetaine hydroxylase inhibitor. Biochem Pharmacol 49(10) (1995): 1403-10.
Van-Oudheusden LJ, Scholte HR. Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder. Prostaglandins Leukot Essent Fatty Acids 67(1) (2002): 33-8.
Vescovo G et al. L-Carnitine: a potential treatment for blocking apoptosis and preventing skeletal muscle myopathy in heart failure. Am J Physiol Cell Physiol 283(3) (2002): C802-10.
Villani RG, Gannon J, Self M, Rich PA. L-Carnitine supplementation combined with aerobic training does not promote weight loss in moderately obese women. Int J Sport Nutr Exerc Metab 10(2) (2000): 199-207.
Vitali G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. Drugs Exp Clin Res 21 (1995): 157-9.
Volek JS et al. L-Carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. Am J Physiol Endocrinol Metab 282(2) (2002): E474-82.
Wachter S et al. Long-term administration of L-carnitine to humans: effect on skeletal muscle carnitine content and physical performance. Clin Chim Acta 318(1-2) (2002): 51-61.
Wahlqvist ML (ed.) Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Winter S et al. Plasma carnitine deficiency. Am J Dis Child 141(6) (1987): 660-5.
Yesilipek MA, Hazar V, Yegin O. L-carnitine treatment in beta thalassemia major. Acta Haematol 100(3) (1998): 162-3.

Celery

Historical note Celery is widely used as a food. The ancient Greeks used celery to make a wine called selinites, which was served as an award at athletic games. Dioscorides described celery as an effective remedy for 'heated stomach' and breast lumps and used it as a diuretic for urinary retention and dropsy.

OTHER NAMES
Smallage, marsh parsley, wild celery

BOTANICAL NAME/FAMILY
Apium graveolens (family Umbelliferae [Apiaceae])

PLANT PART USED
Fruit (seed)

CHEMICAL COMPONENTS
Celery is high in minerals, including sodium (Murphy et al 1978), and contains furocoumarins such as psoralen and bergapten (Beier et al 1983). The major constituents of celery seed oil include pinene and D-limonene (Saleh et al 1985). Celery also contains flavonoids, such as apigenin, luteolin and isoquercitrin, and phenolic acids and alkaloids (Fisher & Painter 1996).

MAIN ACTIONS

ANTI-INFLAMMATORY ACTIVITY
Celery has been found to have anti-inflammatory activity, with suppression of carrageenan-induced paw oedema observed in rats (Al-Hindawi et al 1989). Several constituents show anti-inflammatory activity, such as apigenin, eugenol, ferulic acid, luteolin and bergapton (Duke 2003). Studies in rats suggest that some celery seed extracts are highly effective in suppressing experimental arthritis without exhibiting any gastrotoxicity (Whitehouse et al 1999). Further in vivo studies suggest that celery seed extracts were gastroprotective for NSAID gastropathy and that this effect is mediated through non-prostaglandin mechanisms (Whitehouse et al 2001).

CHOLAGOGUE
Aqueous celery extract has also been found to increase bile acid excretion and lower total serum cholesterol levels in genetically hypercholesterolaemic rats (Tsi & Tan 2000).

CHEMOPROTECTIVE

Based on in vivo studies in mice, it has been suggested that the phthalide components of celery may be effective chemoprotective agents (Zheng et al 1993). Celery consumption has been linked to a reduced risk of developing colon cancer (Slattery et al 2000) and stomach cancer (Haenszel et al 1976).

OTHER ACTIONS

Celery is said to have antirheumatic, carminative, antispasmodic, diuretic, antihypertensive and urinary antiseptic activity. Celery extracts have also been found to have significant activity as a mosquito repellent (Tuetun et al 2004, 2005).

CLINICAL USE

Celery has not been significantly investigated under clinical trial conditions, so evidence is derived from in vitro and animal studies and is largely speculative.

OSTEOARTHRITIS

Evidence of anti-inflammatory activity in experimental models provides a theoretical basis for its use; however, controlled trials are not available to determine effectiveness.

A small uncontrolled trial of 15 patients with chronic arthritis found that treatment with celery seed extract significantly reduced pain symptoms after 3 weeks (Bone 2003).

URINARY TRACT INFECTION

Celery is used in combination with other herbal medicines for the treatment of this condition. Although it is not certain that the herb has antibacterial activity against microorganisms implicated in urinary tract infection, it is used for its diuretic effect.

OTHER USES

Celery has been traditionally used as a diuretic, to improve appetite and digestion, and as a treatment for nervousness and hysteria. The British Herbal Pharmacopoeia gives the specific indication of celery for rheumatoid arthritis and depression (Fisher & Painter 1996).

Oriental medicine uses the seeds to treat headaches and as a digestive aid and emmenagogue.

DOSAGE RANGE

- Fluid extract (1:2): 4.5–8.5 mL/day in divided doses.
- Decoction of dried fruit: 0.5–2 g three times daily.

TOXICITY/ADVERSE REACTIONS

Celery can cause food allergy (Luttkopf et al 2000), with cross-reactivity to a number of other foods (Moneret-Vautrin et al 2002, Vieths et al 2002). Topical exposure to celery may cause contact dermatitis angiooedema and urticaria (Kauppinen et al 1980). Photodermatitis has been recorded with occupational exposure (Seligman et al 1987) and celery has been suggested to cause ocular phototoxicity (Fraunfelder 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

NSAIDS

Celery seed extract may reduce gastrointestinal symptoms associated with NSAIDs — beneficial interaction possible.

PENTOBARBITAL

Celery juice has been found to prolong the action of pentobarbital in rats (Jakovljevic et al 2002) — use with caution.

WARFARIN

Celery contains naturally occurring coumarins, which may theoretically exert anticoagulant effects; however, interaction is unlikely (Heck et al 2000, Myers 2002) — observe with high-dose extracts.

THYROXINE

May decrease drug effects (according to one case report) — observe patient.

PSORALEN–UV A (PUVA) THERAPY

Although celery has been found to contain psoralens, celery extract does not seem to be photosensitising, even after ingestion of large amounts; however, it may increase the risk of phototoxicity with concurrent PUVA therapy (Gral et al 1993) — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS

Usual dietary intakes are likely to be safe.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities. Avoid high-dose preparations.

PRACTICE POINTS/PATIENT COUNSELLING

- Celery has been traditionally used as a diuretic. It is used to treat osteoarthritis and demonstrates anti-inflammatory activity in experimental models. Celery is likely to be safe when used in quantities commonly used in foods; however, there is the possibility for allergy and contact sensitivity.
- It is prudent to avoid using celery seed essential oil in amounts greater than those ingested when used as a food.

REFERENCES

Al-Hindawi MK et al. Anti-inflammatory activity of some Iraqi plants using intact rats. J Ethnopharmacol 26.2 (1989): 163-8.

Beier RC et al. HPLC analysis of linear furocoumarins (psoralens) in healthy celery (Apium graveolens). Food Chem Toxicol 21.2 (1983): 163-5.

Bone K. A Clinical Guide to Blending Liquid Herbs. Edinburgh: Churchill Livingstone, 2003.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, March 2003. www.ars-grin.gov/duke.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Fraunfelder F. Ocular side effects from herbal medicines and nutritional supplements. Am J Opthalmol 138.4 (2004): 639-48.

Gral N et al. Plasma levels of psoralens after celery ingestion. Ann Dermatol Venereol 120.9 (1993): 599-603.

Haenszel W et al. Stomach cancer in Japan. J Ntl Cancer Inst 56.2 (1976): 265-74.

Heck AM et al. Potential interactions between alternative therapies and warfarin. Am J Health-System Pharm 57.13 (2000): 1221-7; quiz 1228-30.

Jakovljevic V et al. The effect of celery and parsley juices on pharmacodynamic activity of drugs involving cytochrome P450 in their metabolism. Eur J Drug Metab Pharmacokinet 27.3 (2002): 153-6.

Kauppinen K et al. Aromatic plants: a cause of severe attacks of angio-edema and urticaria. Contact Dermatitis 6.4 (1980): 251-4.

Luttkopf D et al. Celery allergens in patients with positive double-blind placebo-controlled food challenge. J Allergy Clin Immunol 106.2 (2000): 390-9.

Moneret-Vautrin DA et al. Food allergy and IgE sensitization caused by spices: CICBAA data (based on 589 cases of food allergy). Allerg Immunol 34.4 (2002): 135-40.

Murphy EW et al. Nutrient content of spices and herbs. J Am Diet Assoc 72.2 (1978): 174-6.

Myers SP. Interactions between complementary medicines and warfarin. Aust Prescrib 25.3 (2002): 54-6.

Saleh MM et al. The essential oil of Apium graveolens var. secalinum and its cercaricidal activity. Pharmaceut Weekblad (Scientific Edn) 7.6 (1985): 277-9.

Seligman PJ et al. Phytophotodermatitis from celery among grocery store workers. Arch Dermatol 123.11 (1987): 1478-82.

Slattery ML et al. Carotenoids and colon cancer. Am J Clin Nutr 71.2 (2000): 575-82.

Tsi D, Tan BK. The mechanism underlying the hypocholesterolaemic activity of aqueous celery extract, its butanol and aqueous fractions in genetically hypercholesterolaemic RICO rats. Life Sci 66.8 (2000): 755-67.

Tuetun B et al. Mosquito repellency of the seeds of celery (Apium graveolens L.). Ann Trop Med Parasitol 98.4 (2004): 407-17.

Tuetun B et al. Repellent properties of celery, Apium graveolens L., compared with commercial repellents, against mosquitoes under laboratory and field conditions. Trop Med Intern Health 10.11 (2005): 1190-8.

Vieths S et al. Current understanding of cross-reactivity of food allergens and pollen. Ann NY Acad Sci 964 (2002): 47-68.

Whitehouse MW et al. NSAID gastropathy: Prevention by celery seed extracts in disease-stressed rats. Inflammopharmacology 9.1-2 (2001): 201-9.
Whitehouse MW et al. Over the counter (OTC) oral remedies for arthritis and rheumatism: How effective are they? Inflammopharmacology 7.2 (1999): 89-105.
Zheng GQ et al. Chemoprevention of benzo[a]pyrene-induced forestomach cancer in mice by natural phthalides from celery seed oil. Nutr Cancer 19.1 (1993): 77-86.

Chamomile

Historical note Chamomiles have been used as medicines since antiquity and traditionally grouped in botanical texts under the same general heading. They were probably used interchangeably. Roman chamomile was reportedly used to embalm the Egyptian Pharaoh, Ramses II, and is thought to have been introduced into Britain by the Romans during their conquests. The Anglo-Saxons used chamomile, presumably the Roman chamomile, as one of their nine sacred herbs. Culpeper lists numerous ailments for which chamomile was used, such as jaundice, fevers, kidney stones, colic, retention of urine and inflammation of the bowel (Culpeper 1995). It was also widely used to treat common conditions in children including colic in infants, teething pains and fever (Grieve 1976). It is used in the treatment of gout and to reduce the severity of sciatic pain, either taken internally or applied as a poultice externally (Culpeper 1995). Today, chamomile tea is one of the most popular herbal teas in Australia and New Zealand, and extracts are also used in cosmetics, as bath preparations, in hair dye for blonde hair, shampoos, mouthwashes and preparations to prevent sunburn (Foster & Leung 1996).

COMMON NAME
German chamomile

OTHER NAMES
Wild chamomile, single chamomile, Hungarian chamomile, pin heads matricaria, blue chamomile, Flos chamomillae vulgaris (Lat)

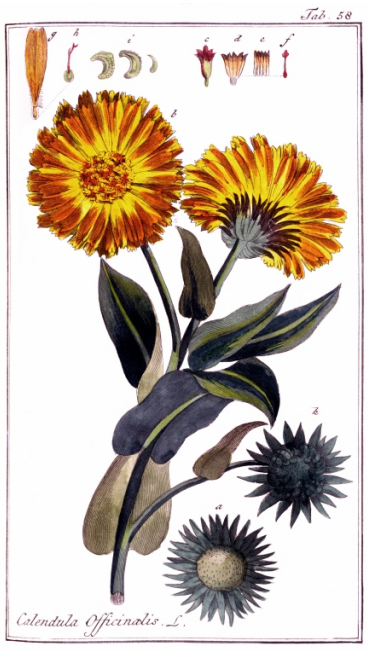
BOTANICAL NAME/FAMILY
Chamomilla recutita (L.) (family Asteraceae [Compositae])

There has been considerable confusion over botanical classification since the plant formerly known as *Matricaria recutita* L. was added to the genus *Chamomilla* in 1974. *Matricaria chamomilla* L. is also used.

PLANT PARTS USED
Flower heads, gathered in summer when they are dry, and carefully dried at low temperatures. Essential oil extracted by steam distillation of the flower heads.

Clinical note — The difference between German and Roman chamomile. *Chamomilla recutita* is widely distributed in waste lands and in the neglected fields of Europe, particularly in Croatia and Hungary. Selected varieties are cultivated (Bruneton 1995). Many plants are referred to as chamomile or have the word 'chamomile' as part of their common name. Of the large number of species of chamomile growing in Europe, North Africa and the temperate region of Asia, five grow wild in the United Kingdom and Europe. Wild varieties are German chamomile (*C. recutita*), Roman chamomile (*C. nobile* (L.)), foetid or stinking mayweed (*Anthemis cotula*), corn chamomile (*Anthemis arvensis*), and yellow chamomile (Grieve 1976).

Roman chamomile, or *Chamaemelum nobile* (L.) (*Anthemis nobile* L.) is the 'chamomile' often referred to in English herbals. It has similar uses to the German chamomile, such as an aromatic bitter for digestive conditions, antispasmodic agent, mild sedative, and topically for its anti-inflammatory and mild analgesic properties.



CHEMICAL COMPONENTS

- Essential oil (see below) 0.24–1.9%.
- Flavonoids (including flavonols and methoxylated flavones), apigenin (other flavonols are partially hydrolysed to apigenin leading to concentrations of up to 8%), apigetrin (apigenin-7-D-glucoside), apigenin-7-acetylglucoside, apiin (apigenin-7-apiosylglucoside), rutin (quercetin-3-rutinoside), luteolin, quercimeritrin (quercetin-7-D-glucoside), quercetin and isorhamnetin.
- Coumarins — umbelliferone (7-hydroxycoumarin) and herniarin (methyl ether of umbelliferone).
- Proazulenes (sesquiterpene lactones) including matricin, matricarin and desacetylmatricarin.
- Plant acids (acidic mucilage), fatty acids, polysaccharide, choline, amino acids.

ESSENTIAL OIL

Chamomile extract produced by a cold extraction process is yellow; steam distillation produces the blue essential oil. This is derived from matricin, also known as proazulene or prochamazulene, a precursor of chamazulene.

Chamazulene (1–15%), farnesene, alpha-bisabolol and bisabolol oxides A and B (up to 50% of the essential oil; proportions vary depending on the chemotype), bisabolone oxide, chamazulene (from matricin on distillation), matricin, chamaviolin, spathulenol and *cis*- and *trans*-enyne dicyclo ethers (spiroether, polyacetylenes).

German chamomile has four chemotypes (variations of the plant product according to chemical composition). These relate to slight variations in the bisabolol oxide content of the essential oil (Gasic et al 1986). Chemotypes, which contain highest levels of alpha-bisabolol (known as C and D chemotypes), should be sourced when an essential oil is required for antiphlogistic or spasmolytic properties.

MAIN ACTIONS

ANTI-INFLAMMATORY

Chamomile extract and various isolated constituents within chamomile have demonstrated anti-inflammatory activity in a variety of tests.

Chamomile extract showed anti-inflammatory effects when applied topically in animal models of inflammation (Al-Hindawi et al 1989, Plevova 1999, Shipochliev et al 1981). In a comparative trial, hydro-alcoholic extracts of chamomile produced anti-inflammatory actions when applied topically in the croton ear test in the mouse. The hydro-alcoholic extract reduced oedema in a dose-dependent manner and was equivalent in effectiveness to benzydamine at twice the usual clinical dose, but hydrocortisone was found to be the most effective treatment (Tubaro et al 1984).

Another comparative study investigated the anti-inflammatory effects of an extract prepared from dried flowers, an extract based on fresh flowers, and the volatile oil, in croton oil-induced dermatitis of mouse ear. The activity of fresh chamomile equalled the activity of the reference drug (benzydamine).

The anti-inflammatory activity of the herb appears to be due to several different constituents, chiefly apigenin, matricin, chamazulene and alpha-bisabolol, although others may also exist.

The previous study determined that apigenin exerts the strongest anti-inflammatory action, which is ten times greater than matricin, which is ten times greater than chamazulene (Della Loggia et al 1990). Another study evaluated the effects of apigenin on the lipopolysaccharide-induced pro-inflammatory cytokines IL6 and TNF-alpha in vitro and in vivo (Smolinski & Pestka 2003). Apigenin reduced IL6, but not TNF-alpha in vitro. Pretreatment with the flavone (50 mg/kg) reduced IL6 by 35% and TNF-alpha by 33% in vivo as compared with control animals. Alpha-bisabolol has demonstrated anti-inflammatory and analgesic effects in a number of experimental inflammatory models: rat paw oedema, adjuvant arthritis of the rat, ultraviolet erythema of the guinea pig, and yeast fever of the rat (Jakovlev et al 1979).

Most studies have investigated the effects of topically applied chamomile or isolated constituents; however, one study using the carrageenan inflammation test on rat paws showed that orally administered matricin produces anti-inflammatory

activity that was greater than chamazulene and almost as effective as (-)-alpha-bisabolol (Jakovlev et al 1979, Shipochliev 1981a).

Chamazulene has been found to inhibit leukotriene B4 formation and blocks chemical peroxidation of arachidonic acid (Safayhi et al 1994).

ANTIPURITIC

An ethyl acetate extract and essential oil of chamomile have both shown anti-puritic activity after a single dose in vivo (Kobayashiet al 2005). Additionally, the antipuritic effects of the antihistamine H1 antagonists, oxatomide and fexofenadine, were significantly increased by the ethyl acetate extract.

ANTISPASMODIC

Chamomile extract and several constituents demonstrate a dose-dependent antispasmodic effect in vitro. The major activity is related to bisabolol, spiroethers, and apigenin. (-)-alpha-bisabolol has an effect equal to papaverine; apigenin was the most potent flavonoid, being significantly more potent than papaverine. The extract of chamomile also has a good spasmolytic activity (Achterrath-Tuckermann et al 1980).

SEDATIVE

Shinomiya et al found that 300 mg/kg of chamomile extract significantly decreased sleep latency in a sleep-disturbed rat model (2005). Extracts of chamomile showed sedative activity on the mouse CNS (Della Loggia et al 1981), and extracts of chamomile, as well as isolated apigenin, have been shown to bind to benzodiazepine receptors in vitro. Apigenin showed antianxiety and sedative activity with intraperitoneal injection in mice (Viola et al 1995).

Ovariectomised rats given inhalations of chamomile oil showed decreased levels of stress-induced ACTH levels compared with controls; the experiment suggested an activity similar to benzodiazepine agonists (Yamada et al 1996).

ANTIMICROBIAL

According to in vitro studies the essential oil has bactericidal and fungicidal activities against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and *Candida albicans* in concentrations above 0.05% v/v, but has no effect against the Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* (Aggag & Yousef 1972) and *Salmonella typhimurium* (Gomes-Carneiro et al 2005). In contrast, extracts of chamomile have demonstrated antimicrobial activity against *E. coli* (Ceska et al 1992). The growth of *S. aureus*, *Streptococcus mutans* and group B streptococcus was inhibited by chamomile extract at concentrations of 10 mg/mL (Cinco et al 1983). In

vitro tests using apigenin have identified inhibitory activity against HIV activation, possibly by affecting viral transcription (Critchfield et al 1997, Trovato et al 2000). Additionally, a semi-purified extract of chamomile has been found to inhibit HSV in vitro (Suganda et al 1983).

ANTI-ULCER

Chamomile extract protected rats from developing experimentally induced ulcers. Bisabolol (and extracts of chamomile) prevented the formation of ulcers in experimental animals exposed to indomethacin (NSAID) stress, and alcohol; and reduced the healing time of ulcers induced by chemical stress (acetic acid) or by heat coagulation. Alpha-bisabolol promotes granulation and tissue regeneration in burns and ulcers, and protects against their formation (Szelenyi et al 1979).

OTHER ACTIONS

IMMUNE ENHANCEMENT

Chamomile extract increased T-lymphocyte rosette formation in vitro in blood samples taken from ear, nose and throat patients with immunodeficiency (Kliachko et al 1994). The polysaccharides (heteroglycans) showed significant immunostimulating activities according to the granulocytes and carbon clearance tests (Wagner et al 1985).

ANTIOXIDANT

Chamazulene is a potent antioxidant. It inhibits lipid peroxidation in vitro (Goeters et al 2001) in a dose-concentration- and time-dependent manner (Rekka et al 1996).

CHOLERETIC

Chamomile increases the production of bile by the liver (Pasechnik 1966).

DRUG DEPENDENCE

Chamomile extract was shown to inhibit the development of morphine dependence and expression of abstinence syndrome in rats. Chamomile reduced frequencies of behaviours associated with withdrawal (paw tremor, rearing, teeth chattering, body shakes, ptosis, diarrhoea and urination) and weight loss (Gomaa et al 2003).

ANTICARCINOGENIC

Apigenin inhibits carcinogenesis in a number of in vitro and animal studies (Aguilera et al 2000, Ali-Shtayeh et al 2000, Birt et al 1986, 1997, Lepley & Pelling 1997, Lepley et al 1996, Panes et al 1996, Umezu 1999, Wei et al 1990).

UTERINE EFFECTS

Water extracts of chamomile increased uterine tonus in isolated rabbit and guinea pig uterine horn (Shipochliev 1981b).

PIGMENTATION

Chamomile extract has been found to decrease UV-induced pigmentation as well as the hyperpigmentation found in lentigo senilis (aged or liver spots). Endothelin-1 is a cytokine responsible for stimulating melanocyte function leading to hyperpigmentation. Chamomile has been shown to interrupt the endothelin-1 induced signalling, thereby reducing the ability of melanocytes to proliferate and to synthesise melanin (Ichihashi et al 1999).

CLINICAL USE

Chamomile is most widely taken as a tea, often after meals or as an alternative to caffeine-containing beverages. In clinical practice, the oral dose form most often used is a concentrated extract, in order to produce stronger therapeutic effects. It is also used as a topical treatment in some indications.

SKIN CONDITIONS

Chamomile is used topically for a variety of dermatological conditions. The most tested topical product is known commercially as Kamillosan.

Wound healing According to a double-blind trial, external application of a chamomile extract improves wound healing. In the study, chamomile extract significantly decreased weeping and improved wound healing after dermabrasion of tattoos (Glowania et al 1987).

Eczema In one comparative study, 161 patients with eczema on the arms and lower legs were treated with 0.25% hydrocortisone, 5% bufexamac (NSAID), 0.75% fluocortin (glucocorticoid) or a chamomile cream known commercially as Kamillosan. The chamomile cream was as effective as hydrocortisone and was superior to the other two treatments (Aertgeerts et al 1985). (Kamillosan is reportedly made from a high bisabolol-containing chemotype of chamomile.)

Dermatitis A study involving experimentally-induced toxic dermatitis found that chamomile ointment (Kamillosan) produced a more soothing effect on human skin than a chamomile ointment base or hydrocortisone ointment 0.1% (Nissen et al 1988). (Note: the hydrocortisone cream used in this study was quite weak compared with the usual strength of 0.5–2.5%.)

Chamomile cream helped protect against skin radiation damage in breast cancer patients receiving radiation (Maiche et al 1991). Chamomile cream (Kamillosan) has been shown to be slightly less effective than 0.25% hydrocortisone, but superior to

fluocortin butyl ester and 5% bufexamac in relieving inflammation associated with dermatoses (Aertgeerts 1984, Aertgeerts et al 1985).

Commission E approves the external use of chamomile for inflammation of the skin and mucous membranes, as well as for bacterial skin diseases, including those of the oral cavity and gums (Blumenthal et al 2000).

SEDATION

Both oral dose forms and the essential oil of chamomile are used for this indication.

A placebo-controlled study involving 22 volunteers found that inhalation of chamomile oil produced sedative effects and improved mood (Roberts & Williams 1992). Chamomile tea (two teabags in 175 mL of hot water) given to 12 patients during cardiac catheterisation induced a deep sleep in 10 patients, even though the procedure usually causes pain and anxiety (Gould et al 1973).

GASTROINTESTINAL CONDITIONS

Chamomile is widely used to relieve stomach cramping, dyspepsia and flatulence. The herb's antispasmodic and relaxant effects provide a theoretical basis for its use in these conditions.

In an open, multicentre study, 104 patients with gastrointestinal complaints, including gastritis, flatulence and minor spasms of the intestines, were treated for 6 weeks with 5 mL/day of an oral chamomile preparation (standardised to contain 50 mg alpha-bisabolol and 150–300 mg apigenin-7-glucoside per 100 g). By self-evaluation, all patients improved with 44.2% becoming symptom free (Stiegelmeyer 1978).

Diarrhoea in children In Europe, chamomile is widely used to treat a variety of paediatric complaints.

A prospective, double-blind, randomised trial was used to document the efficacy of a preparation containing chamomile extract and pectin in children aged 6 months to 5.5 years with uncomplicated diarrhoea. The chamomile preparation reduced the duration and severity significantly faster than placebo (de la Motte et al 1997).

Commission E approves chamomile for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract.

ANTIBACTERIAL PREPARATIONS

A phase III, double-blind, placebo-controlled clinical trial of 164 patients assessed the efficacy of chamomile mouthwash in preventing 5-fluorouracil induced stomatitis and found no difference between chamomile and placebo (Fidler et al 1996).

OTHER USES

The British Herbal Pharmacopoeia (1983) recommends chamomile for flatulent nervous dyspepsia, travel sickness, nasal catarrh, nervous diarrhoea and restlessness. Externally, chamomile is recommended for haemorrhoids, mastitis and leg ulcers. The specific indication is for gastrointestinal disturbance with nervous irritability in children and for teething and colic in infants.

Commission E approves the use of inhalations for inflammation and irritation of the respiratory tract and baths and irrigations for anogenital inflammation (Blumenthal et al 2000).

ORAL MUCOSITIS

Methotrexate-induced oral mucositis in a 76-year-old woman was successfully treated by chamomile mouthwash in a recently reported case study (Mazokopakis et al 2005).

The mouthwash consisted of 8 g of flower heads steeped in 1000 mL of boiling water for 15 minutes and then used as a gargle four times daily.

PREVENTING POSTOPERATIVE SORE THROAT

Chamomile extract spray administered before intubation was not able to prevent postoperative sore throat and hoarseness compared with saline spray in a randomised double-blind study (Chan et al 2003).

HAEMORRHAGIC CYSTITIS

Chamomile extract decreased the symptoms of haemorrhagic cystitis. Thirty-two patients were randomly assigned to receive either the antibiotic cotrimoxazole (trimethoprim/sulfamethoxazole) alone or with a chamomile extract administered on day one as a bladder instillation, followed by daily hipbath use. Symptoms were evaluated after 10 days and indicated that the chamomile group experienced more rapid alleviation of symptoms than the group treated with only cotrimoxazole. The product used was *Kamillenextrakt*, an ethanolic extract of chamomile flowers (Barsom et al 1993).

DOSAGE RANGE

INTERNAL USE

- German chamomile is used either as a tea made from the dried flower heads, or as an extract.
- Dried flower heads: 2–8 g three times daily by infusion.
- Fluid extract (1:2): 3–6 mL/day.
- Tincture (1:5): 3–10 mL three times daily.

- The quality of chamomile varies greatly. For maximum efficacy, use high-grade chamomile (high in alpha-bisabolol). Standardised extracts are usually standardised to either bisabolol or apigenin.

EXTERNAL USE

- The dried flowers can also be made into a poultice with the addition of hot water and applied directly to the skin, or the tea can be used to bathe inflamed skin and eyes.
- Essential oil (external use): 5 drops per 100 mL of oil, or per 100 g of cream or ointment.
- In baths and water for compresses, the dose should not exceed 10 drops.
- Inhalation: 5 drops of essential oil in 1 L hot water.

ADVERSE REACTIONS

ALLERGIC REACTIONS

Occasional rare cases of allergic skin reactions have been reported. However, a bibliographic review of 50 reports of 'chamomile' sensitivity revealed that in only five papers was the botanical identification of the plant material correlated with *Chamomilla recutita*. In the majority of other instances, the effects were caused by species of the genus *Anthemis*, frequently also called chamomile. Experimental studies on pigs using a rigorous testing technique proved that *C. recutita* possesses low sensitising capacity. The suspected allergen is the sesquiterpene lactone, anthecotulide, found in *Anthemis cotula* L. (stinking mayweed), which only occurs in trace amounts in the bisabolol oxide B-chemotype of genuine chamomile (Hausen et al 1984). Allergic conjunctivitis has been reported with the use of chamomile tea eyewashes, and the pollens contained in the teas have been identified as the allergens responsible. The reaction occurred after first exposure and was thought to be due to cross-reactivity to *Artemesia* pollen (Subiza et al 1989). Pollens are not likely to be present or active in aqueous alcohol extracts of chamomile.

German chamomile is thought to be less allergenic than Roman chamomile, but any variety of chamomile can potentially cause allergic reactions. An enema made from German chamomile (Kamillosan) given during labour to a 35-year-old woman with no history of atopy resulted in life-threatening anaphylaxis and fatal asphyxia of the newborn (Jensen-Jarolim et al 1998). Chamomile enemas are not a usual form of administration.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

BENZODIAZEPINES

Theoretically, an additive CNS depressant and antispasmodic effect can occur with concurrent use — observe patients taking this combination, although the combination may be clinically useful when used under supervision.

DRUGS METABOLISED BY CYP3A4

Chamomile has been shown to inhibit cytochrome 3A4 enzymes in vitro (Budzinski et al 2000, Ganzera et al 2006, Gomes-Carneiro et al 2005). The clinical significance of this is unknown; however, drugs that are metabolised by these enzymes could theoretically be affected.

NSAIDS

Chamomile extract protected test animals from experimentally-induced ulcers — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Chamomile is contraindicated in hypersensitivity or known allergy to chamomile or other members of the Asteraceae family (e.g. yarrow, tansy, feverfew, daisy, ragweed).

PREGNANCY USE

Safety has not been established scientifically; however, no teratogenic effects have been observed in vivo.

PRACTICE POINTS/PATIENT COUNSELLING

- German chamomile has demonstrated anti-inflammatory, antispasmodic, sedative and antimicrobial activity.
- It is taken orally either as a tea or tincture, used externally as a poultice, cream or ointment or inhaled as an essential oil.
- Internally, it is used to relieve flatulence, gastrointestinal spasm, dyspepsia and induce a sense of relaxation. It is also used for infants with teething pain and colic.
- Externally, chamomile preparations are used to treat dermatitis, enhance wound healing, nappy rash and soothe irritated skin. Comparative studies show it has an anti-inflammatory effect equivalent to low-dose hydrocortisone preparations.
- There is some evidence from clinical trials to support the use of chamomile in the treatment of wounds, eczema, dermatitis, nervousness and tension, diarrhoea in children and for the symptoms of haemorrhagic cystitis (in association with antibiotic therapy).

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Chamomile is taken to relieve stomach spasms and flatulence, to induce relaxation and promote sleep. It is also popular for children with teething pain and digestive complaints such as colic or diarrhoea. Applied externally as a cream, ointment or poultice, it is used to reduce skin irritation and inflammation.

When will it start to work?

Chamomile relieves gastrointestinal symptoms quickly, within several minutes. For more chronic problems, it may need to be used long term.

Are there any safety issues?

Chamomile is considered a very safe herb. While there have been reports of allergic reactions, the majority have been due to adulteration with other herbs. Chamomile tea is more likely to cause allergic reactions than either extracts or essential oil. Chamomile should not be used by persons with hypersensitivity or known allergy to chamomile or other members of Asteraceae family (e.g. yarrow, tansy, feverfew, wormwood).

REFERENCES

Achterrath-Tuckermann U, Kunde R, Flaskamp E, Isaac O, Thiemer K. Pharmacological investigations with compounds of chamomile. V: Investigations on the spasmolytic effect of compounds of chamomile and Kamillosan on the isolated guinea pig ileum. Plant Med 39.1 (1980): 38-50.

Aertgeerts J. Experiences with Kamillosan(TM). A standardised camomille extract in dermatological practice. Ars Medici Rev Int Therapie Pratique 39.5 (1984): 65-8 [in Dutch].

Aertgeerts P, Albring M, Klaschka F et al. Comparative testing of Kamillosan cream and steroidal (0.25% hydrocortisone, 0.75% fluocortin butyl ester) and non-steroidal (5% bufexamac) dermatologic agents in maintenance therapy of eczematous diseases. Z Hautkr 60.3 (1985): 270-7.

Aggag ME, Yousef RT. Study of antimicrobial activity of chamomile oil. Plant Med 22.2 (1972): 140-4.

Aguilera DB, Souza, Miglioranza E. The effect of controlled release fertilizer and earthworm compost on Chamomile (Matricaria chamomilla L.) yield. Rev Brasil Plant Med 3.1 (2000): 61-5 [in Portuguese].

Al-Hindawi MK, Al-Deen IH, Nabi MH, Ismail MA. Anti-inflammatory activity of some Iraqi plants using intact rats. J Ethnopharmacol 26.2 (1989): 163-8.

Ali-Shtayeh MS, Yaniv Z, Mahajna J. Ethnobotanical survey in the Palestinian area: A classification of the healing potential of medicinal plants. J Ethnopharmacol 73.1-2 (2000): 221-32.

Barsom VS, Mossmayr A, Sakka M. Behandlung der Hamorrhagischen Cystitis (harnblasenschleimhautblutungen) mit Kamillenextrakt. Erfahrungsheilkunde no. 3 (1993): 138-9.

Birt DF, Walker B, Tibbels MG, Bresnick E. Anti-mutagenesis and anti-promotion by apigenin, robinetin and indole-3-carbinol. Carcinogenesis 7.6 (1986): 959-63.

Birt DF, Mitchell D, Gold B, Pour P, Pinch HC. Inhibition of ultraviolet light induced skin carcinogenesis in SKH-1 mice by apigenin, a plant flavonoid. Anticancer Res 17.1A (1997): 85-91.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

British Herbal Medicine Association Scientific Committee. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA, 1983.

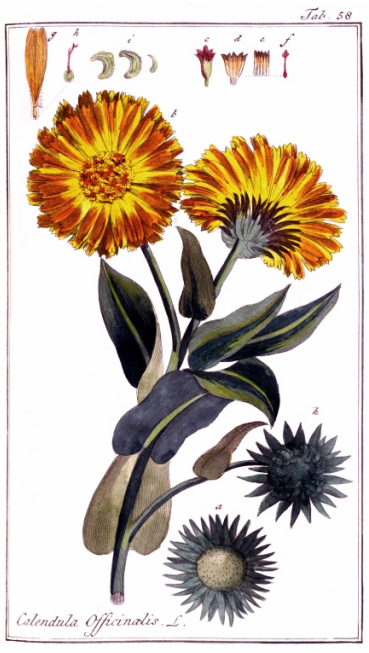
Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants. Paris: Lavosir (1995): 455-7.

Budzinski JW, Foster BC, Vandenhoek S, Arnason JT. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7.4 (2000): 273-82.
Ceska O, Chaudhary SK, Warrington PJ, Ashwood-Smith MJ. Coumarins of chamomile, Chamomilla recutita. Fitoterapia, 63.5 (1992): 387-94.
Chan E, Rappaport LA, Kemper KJ. Complementary and alternative therapies in childhood attention and hyperactivity problems. J Dev Behav Pediatr 24.1 (2003): 4-8.
Cinco M, Banfi E, Tubaro A, Dellaloggia R. A microbiological survey on the activity of a hydroalcoholic extract of camomile. Int J Crude Drug Res 21.4 (1983): 145-51.
Critchfield JW, Coligan JE, Folks TM, Butera ST. Casein kinase II is a selective target of HIV-1 transcriptional inhibitors. Proc Natl Acad Sci USA 94.12 (1997): 6110-15.
Culpeper N. Culpeper's Complete Herbal. Hertfordshire, UK: Wordsworth Reference 1995, 54-5.
de la Motte S, Bose-O'Reilly S, Heinisch M, Harrison F. Double-blind comparison of an apple pectin-chamomile extract preparation with placebo in children with diarrhea. Arzneimittelforschung 47.11 (1997): 1247-9.
Della Loggia R, Tubaro A, Redaelli C. Evaluation of the activity on the mouse CNS of several plant extracts and a combination of them. Riv Neurol 51.5 (1981): 297-310.
Della Loggia R, Carle R, Sosa S, Tubaro A. Evaluation of the anti-inflammatory activity of Chamomile preparations. Plant Med 56.6 (1990): 657-8.
Fidler P, Loprinzi CL, O'Fallon JR et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. Cancer 77.3 (1996): 522-5.
Foster S, Leung A. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics. New York: John Wiley and Sons Inc. 1996, 146-7.
Ganzera M, Schneider P, Stuppner H. Inhibitory effects of the essential oil of chamomile (Matricaria recutita L.) and its major constituents on human cytochrome P450 enzymes. Life Sci 78.8 (2006): 856-61.
Gasic O, Lukic V, Adamovic D, Canak N. Variation in the content and the composition of the essential oils in flower heads of Matricaria chamomilla L. during its ontogenetical development. Acta Pharm Hung 56.6 (1986): 283-8.
Glowania HJ, Raulin C, Swoboda M. Effect of chamomile on wound healing: a clinical double-blind study. Z Hautkr 62.17 (1987): 1262, 1267-71.
Goeters S, Imming P, Pawlitzki G, Hempel B. On the absolute configuration of matricin. Plant Med 67.3 (2001): 292-4.
Gomaa A, Hashem T, Mohamed M, Ashry E. Matricaria chamomilla extract inhibits both development of morphine dependence and expression of abstinence syndrome in rats. J Pharmacol Sci 92.1 (2003): 50-5.
Gomes-Carneiro MR, Dias DM, De-Oliveira AC, Paumgartten FJ. Evaluation of mutagenic and antimutagenic activities of alpha-bisabolol in the Salmonella/microsome assay. Mutat Res 585.1-2 (2005): 105-12.
Gould L, Reddy CV, Gomprecht RF. Cardiac effects of chamomile tea. J Clin Pharmacol 13.11 (1973): 475-9.
Grieve M. A Modern Herbal. Middlesex, UK: Penguin, 1976, 185.
Hausen BM, Busker E, Carle R. The sensitizing capacity of composite plants. VII. Experimental studies with extracts and compounds of Chamomilla recutita (L.) Rauschert and Anthemis cotula L. Plant Med 50.3 (1984): 229-34.
Ichihashi M, Kobayashi A, Okuda M, Imokawa G. Effect of Chamomilla extracts application on UV-induced pigmentation. Skin Res 41.4 (1999): 475-80 [in Japanese].
Jakovlev V, Isaac O, Thiemer K, Kunde R. Pharmacological investigations with compounds of chamomile. II. New investigations on the antiphlogistic effects of (–)-alpha-bisabolol and bisabolol oxides (author's transl). Plant Med 35.2 (1979): 125-40.
Jensen-Jarolim E, Reider N, Fritsch R, Breiteneder H. Fatal outcome of anaphylaxis to camomile-containing enema during labor: A case study. J Allergy Clin Immunol 102.6 I (1998): 1041-2.
Kliachko LL, Ankhimova ES, Svitina NN, Iaremenko KV. The effect of medicinal herbs on lymphocyte rosette-forming function. Vestn Otorinolaringol no. 2 (1994): 31-3.

Kobayashi Y, Takahashi R, Ogino F. Antipruritic effect of the single oral administration of German chamomile flower extract and its combined effect with antiallergic agents in ddY mice. J Ethnopharmacol 101.1-3 (2005): 308-12.
Lepley DM, Li B, Birt DF, Pelling JC. The chemopreventive flavonoid apigenin induces G2/M arrest in keratinocytes. Carcinogenesis 17.11 (1996): 2367-75.
Lepley DM, Pelling JC. Induction of p21/WAF1 and G1 cell-cycle arrest by the chemopreventive agent apigenin. Mol Carcinog 19.2 (1997): 74-82.
Maiche AG, Grohn P, Maki-Hokkonen H. Effect of chamomile cream and almond ointment on acute radiation skin reaction. Acta Oncol 30.3 (1991): 395-6.
Mazokopakis EE, Vrentzos GE, Papadakis JA, Babalis DE, Ganotakis ES. Wild chamomile (Matricaria recutita L.) mouthwashes in methotrexate-induced oral mucositis, Phytomedicine 12.1-2 (2005): 25-7.
Nissen HP, Biltz H, Kreysel HW. Profilometry, a method for the assessment of the therapeutic effectiveness of Kamillosan ointment. Z Hautkr 63.3 (1988): 184-90.
Panes J, Gerritsen ME, Anderson DC, Miyasaka M, Granger DN. Apigenin inhibits tumor necrosis factor-induced intercellular adhesion molecule-1 upregulation in vivo. Microcirculation 3.3 (1996): 279-86.
Pasechnik IK. Choleretic action of Matricaria officinalis. Farmakol Toksikol 29.4 (1966): 468-9.
Plevova P. Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: A review. Oral Oncology 35.5 (1999): 453-70.
Rekka EA, Kourounakis AP, Kourounakis PN. Investigation of the effect of chamazulene on lipid peroxidation and free radical processes. Res Commun Mol Pathol Pharmacol 92.3 (1996): 361-4.
Roberts A, Williams JM. The effect of olfactory stimulation on fluency, vividness of imagery and associated mood: a preliminary study. Br J Med Psychol 65.2 (1992): 197-9.
Safayhi H, Sabieraj J, Sailer ER, Ammon HP. Chamazulene: an antioxidant-type inhibitor of leukotriene B4 formation. Plant Med 60.5 (1994): 410-13.
Shinomiya K, Inoue T, Utsu Y et al. Hypnotic activities of chamomile and passiflora extracts in sleep-disturbed rats. Biol Pharm Bull 28.5 (2005): 808-10.
Shipochliev T, Dimitrov A, Aleksandrova E. Anti-inflammatory action of a group of plant extracts. Vet Med Nauki 18.6 (1981): 87-94.
Shipochliev T. Antiinflammatory activity of aqueous and liofilized plant extracts at carrageenin induced inflammation. Farmatsija 31.2 (1981a): 47-53 [in Bulgarian].
Shipochliev T. Uterotonic action of extracts from a group of medicinal plants. Vet Med Nauki 18.4 (1981b): 94-8.
Smolinski AT, Pestka JJ. Modulation of lipopolysaccharide-induced proinflammatory cytokine production in vitro and in vivo by the herbal constituents apigenin (chamomile), ginsenoside Rb(1) (ginseng) and parthenolide (feverfew). Food Chem Toxicol 41.10 (2003): 1381-90.
Stiegelmeyer H. Therapie unspezifischer Magenbeschwerden mit Kamillosan. Kassenarzt no. 18 (1978): 3605-6.
Subiza J, Subiza JL, Hinojosa M, Garcia R, Jerez M, Valdivieso R, Subiza E. Anaphylactic reaction after the ingestion of chamomile tea: a study of cross-reactivity with other composite pollens. J Allergy Clin Immunol 84.3 (1989): 353-8.
Suganda AG, Amoros M, Girre L, Fauconnier B. Inhibitory effects of some crude and semi-purified extracts of indigenous French plants on the multiplication of human herpesvirus 1 and poliovirus 2 in cell culture. J Nat Prod 46.5 (1983): 626-32.
Szelenyi I, Isaac O, Thiemer K. Pharmacological experiments with compounds of chamomile. III: Experimental studies on the ulcerprotective effect of chamomile. Plant Med 35.3 (1979): 218-27 [author's transl].
Trovato A, Monforte MT, Forestieri AM, Pizzimenti F. In vitro anti-mycotic activity of some medicinal plants containing flavonoids. Bollettino Chimico Farmaceutico 139.5 (2000): 225-7.
Tubaro A, Zilli C, Redaelli C, Della Loggia R. Evaluation of antiinflammatory activity of a chamomile extract topical application. Plant Med 50.4 (1984): 359.
Umezu T. Anticonflict effects of plant-derived essential oils. Pharmacol Biochem Behav 64.1 (1999): 35-40.

Viola H, Wasowski C, Levi de Stein M et al. Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. Plant Med, 61.3 (1995): 213-16.
Wagner H, Proksch A, Riess-Maurer I. Immunostimulating action of polysaccharides (heteroglycans) from higher plants. Arzneimittelforschung, 35.7 (1985): 1069-75.
Wei H, Tye L, Bresnick E, Birt DF. Inhibitory effect of apigenin, a plant flavonoid, on epidermal ornithine decarboxylase and skin tumor promotion in mice. Cancer Res 50.3 (1990): 499-502.
Yamada K, Miura T, Mimaki Y, Sashida Y. Effect of inhalation of chamomile oil vapour on plasma ACTH level in ovariectomized-rat under restriction stress. Biol Pharm Bull 19.9 (1996): 1244-6.

Chaste tree



Historical note Chaste tree has been used since ancient times for a variety of gynaecological conditions, such as aiding expulsion of the placenta after birth and promoting menstruation. Leaves of the chaste tree were worn by vestal virgins in ancient Rome as a symbol of chastity and it was used during that time to promote celibacy. The berries have been used to reduce fever and headaches, stimulate perspiration and to 'check violent sexual desires' in monasteries. A commercially preparation of chaste tree has been available in Germany for over 50 years and it is still commonly used for menstrual irregularities.

OTHER NAMES

Agnus castus, chasteberry, gattilier, hemp tree, keuschlammfruchte, monk's pepper, wild pepper, vitex

BOTANICAL NAME/FAMILY

Vitex agnus-castus (family Labiatae)

PLANT PART USED

Dried ripened or fresh ripe fruits

CHEMICAL COMPONENTS

Vitex agnus-castus contains many different chemical constituents, including luteolin-like flavonoids (casticin, orientin, isovitexin), iridoid glycosides, aucubin, eurostoside, agnuside, essential fatty acids and the essential oils cineole, limonene and sabinene.

MAIN ACTIONS

A mechanism of action has not been conclusively identified, but it is thought to act on the pituitary–hypothalamic axis.

DECREASES PROLACTIN RELEASE

The most thoroughly studied mechanism for vitex is its interaction with dopamine receptors in the anterior pituitary. Several studies have indicated that vitex acts on dopamine D_2 receptors and decreases prolactin levels (Berger et al 2000, Halaska et al 1998, Jarry et al 1994, Meier & Hoberg 1999, Meier et al 2000, Milewicz et al 1993, Sliutz et al 1993, Wuttke et al 2003). It is likely that this mechanism is responsible for the symptom-relieving effects seen with vitex in mastodynia and hyperprolactinaemia (Meier & Hoberg 1999, Milewicz et al 1993, Splitt et al 1997).

Results from one study involving healthy males propose that this effect is dose-dependent, as lower doses (120 mg) were found to increase secretion and higher doses (204–480 mg) were found to decrease secretion (Merz et al 1996).

A study using the vitex extract BNO 1095 (70% ethanol, 30% H_2O extract, Bionorica, Neumarkt, Germany) identified that the major dopaminergic compounds are the clerodadienols, which act as potent inhibitors of prolactin release; however, other active compounds of lesser activity were also identified (Wuttke et al 2003).

OESTROGEN-RECEPTOR BINDING

Chasteberry extract showed significant competitive binding to oestrogen-receptors alpha and beta in vitro (Liu et al 2001).

INCREASES PROGESTERONE LEVELS

A randomised controlled trial of women with hyperprolactinaemia showed that vitex extract (20 mg daily) normalises progesterone levels after 3 months' treatment (Milewicz et al 1993). In vitro research has found that vitex stimulates progesterone receptor expression (Liu et al 2001).

OPIOID RECEPTORS

A recently published study reported that a methanol extract of vitex had affinity to the μ-opiate receptor (Webster et al 2006). Of note, this receptor is the primary action site for beta-endorphin in vivo, a peptide which assists in regulating the menstrual cycle through inhibition of the hypothalamus–pituitary– adrenal axis.

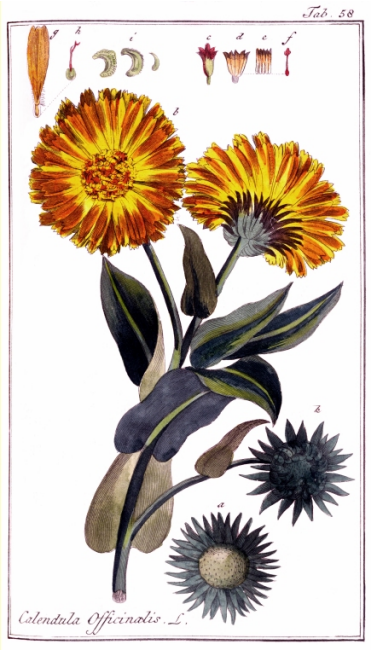
Clinical note — The opiate system and PMS

The opiate system consists of mu, delta and kappa opiate receptors and endogenous opiate peptides such as beta-endorphin (Webster et al 2006). The opiate system plays an essential role in regulating tonic pain perception, mood, appetite, and other functions. PMS is characterised by a reduction of opiate activity and the severity of symptoms such as anxiety, food cravings, and physical discomfort is inversely proportional to the amount of decline in beta-endorphin levels in the luteal phase. Based on recent research, the symptom-relieving effects of vitex in PMS may be due to direct activation of analgesic and mood regulatory pathways via opiate receptor activation and/or reversal of the loss of opiate inhibition in the luteal phase.

CYTOTOXIC ACTIVITY

Cytotoxic activity has been reported for an ethanolic extract of the dried ripe fruit of vitex against various human cancer cell lines (Ohyama et al 2003, 2005, Weisskopf et

al 2005). The extract increased intracellular oxidative stress and mitochondrial damage leading to apoptosis.



OTHER ACTIONS

Conflicting results have been obtained in studies with regard to the effect on FSH and LH levels. One clinical study found that vitex extract did not alter them, whereas another showed that it increased LH release (Lauritzen et al 1997, Milewicz et al 1993).

CLINICAL USE

Although double-blind studies have recently been conducted with chasteberry, uncontrolled trials go back to the 1940s when a product known as Agnolyt was tested. The product was developed and patented by Dr Gerhard Madaus in Germany and contained *Vitex agnus-castus*. Several different vitex products have been investigated to date including: Agnolyt (standardised to 3.5–4.2 mg of dried chasteberry extract), *Vitex agnus-castus* L. extract Ze 440 (each 20 mg tablet standardised for casticin and agnuside), Femicur (contans 1.6–3.0 mg of dried extract per capsule) and Mastodynon (53% v/v ethanol) a homeopathic preparation.

Owing to difficulty in locating the German studies, secondary information sources have sometimes been used to provide a more comprehensive review.

PREMENSTRUAL SYNDROME

Chasteberry relieves some common symptoms associated with PMS, according to several clinical trials (Atmaca et al 2003, Berger et al 2000, Dittmar 1992, Lauritzen 1997, Loch et al 2000, Schellenberg 2001). According to these clinical trials, the PMS symptoms that respond best to treatment are breast tenderness, irritability, depressed mood, anger, mood changes, headache and constipation. The most studied extract investigated in PMS is Ze440 (see Clinical note below).

A multicentre, randomised, controlled, double-blind study investigating the effects of Vitex (Ze 440) for PMS involved 170 women and was published in the British Medical Journal (Schellenberg 2001). Of the group, 13% were also taking OCP. Treatment with a 20 mg tablet of dry extract of chasteberry taken daily resulted in a significant improvement of PMS symptoms, particularly headache, breast fullness, irritability, anger and mood changes. Over 50% of women in the active treatment group achieved at least a 50% reduction in symptoms.

Previously, a number of open studies had generally produced positive results for vitex as a symptomatic treatment in PMS. One multicentre open-label study showed that daily treatment with a 20 mg tablet of Vitex (Ze 440) over three menstrual cycles significantly reduced the Moor menstrual distress self-assessment questionnaire

(MMDQ) with 46% of women experiencing a 50% reduction in the MMDQ. Treatment also reduced the duration of PMS symptoms from 7.5 days to 6 days and was as effective for women taking OCP as for those who were not (Berger et al 2000). Once treatment was stopped, PMS symptoms gradually returned to baseline within three further cycles. The largest multicentre trial was an open study of 1634 women with PMS, which found that treatment with vitex (Femicur) for three menstrual cycles decreased the number of PMS symptoms in 93% of subjects (Loch et al 2000). Symptoms completely resolved in 40% of subjects and 94% overall rated vitex treatment as well tolerated. An early study using vitex (Agnolyt) in 1542 women with PMS reported an improvement in symptoms with an average dose of 42 drops daily taken for an average of 25 days (Dittmar 1992 as reported in Ulbricht & Basch 2005). According to Ulbricht and Basch (2005), three earlier uncontrolled studies produced inconclusive results.

Although vitamin B6 is a popular treatment for PMS symptoms, the results from a double-blind comparative study have found that vitex (Agnolyt) is as effective and possibly more so (Lauritzen et al 1997). The randomised, double-blind study of 175 women compared vitex, pyridoxine and placebo. In the study, 77% of women receiving vitex reported symptom alleviation compared with 61% with pyridoxine (200 mg/day), which was considered a small but significant difference. Additionally, physician assessments were more likely to rate treatment with vitex as 'excellent' compared with pyridoxine.

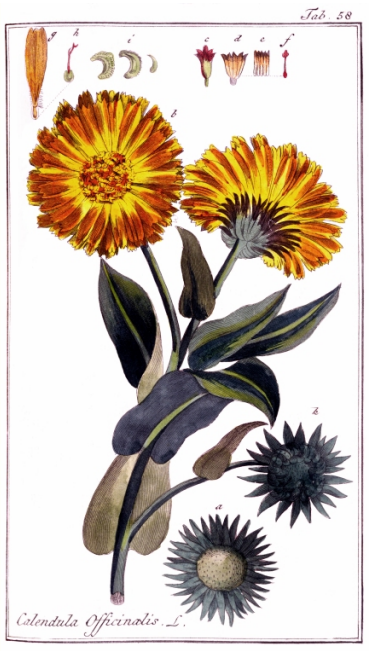
In 2003, a randomised 8 week study involving 42 women compared the effects of 20–40 mg daily of fluoxetine, a SSRI, and 20–40 mg of vitex extract and found no statistically significant difference between the groups with respect to the rate of responders (Atmaca et al 2003). More specifically, patients with premenstrual dysphoric disorder responded well to both treatments; however, fluoxetine was more effective for psychological symptoms such as depression and irritability whereas the herbal extract was more effective for diminishing physical symptoms such as breast tenderness, cramps, food cravings and swelling. Unfortunately, the authors did not report the type of vitex extract used in the study.

Commission E approves the use of chasteberry for this indication.

Clinical note — Ze440 extract

The naming of the Ze440 extract (Premular in Australia) is derived from the name Zeller, the 135-year-old Swiss company manufacturing it, combined with a unique number ascribed during the initial studies. In order to ensure that products deliver consistent results, Ze440 is measured by both composition and consistency from batch to batch. To promote product uniformity, every batch is grown, harvested

and manufactured into tablets under controlled conditions and is extracted in a standardised method that ensures consistent and high levels of the important lipophilic compound casticin and an established marker compound, the iridoid glycoside named agnuside.



MASTALGIA

Mastalgia is considered to relate to latent and increased basal prolactin levels; therefore, agents that reduce prolactin levels are anticipated to reduce symptoms. For this reason, vitex is a popular treatment for mastalgia.

In two randomised, double-blind studies, vitex (Mastodynon) effectively reduced premenstrual mastalgia (Halaska et al 1998, Splitt et al 1997, Wuttke et al 2003). Subjects completed a visual analogue scale (VAS) and rated their breast pain from 0 (lowest breast pain) to 10 (extremely strong breast pain). Active treatment reduced the mastalgia score by 35–40%, an effect significantly stronger than that of placebo (25%). One of these studies also demonstrated that treatment with vitex reduced serum prolactin levels (Splitt et al 1997, as reported in Wuttke et al 2003). According to Halaska et al (1998), symptom relief was experienced after the first month of treatment with continued improvements experienced after the second and third months.

Commission E approves the use of chasteberry for this indication.

IRREGULARITIES OF THE MENSTRUAL CYCLE

Chasteberry is used to normalise menstruation in women with shortened, lengthened or infrequent menstruation, particularly when low progesterone and luteal phase defects are suspected. A randomised controlled trial of women with luteal phase defect due to latent hyperprolactinaemia demonstrated that vitex extract (20 mg daily) effectively reduced prolactin levels and normalised luteal phase length and progesterone levels after 3 months' treatment (Milewicz et al 1993).

Commission E approves the use of chasteberry for this indication.

POOR LACTATION

Vitex has been used since ancient times as a galactagogue to promote milk production. Currently there are no double-blind studies to confirm its efficacy; however, an early uncontrolled study supports the use of vitex in lactation, finding a favourable effect on milk production in 80% of women (Noack et al 1943). Results from a small study of males suggest that increases in prolactin may be possible with low dose vitex (120 mg daily) whereas higher doses (480 mg daily) result in decreased levels (Merz et al 1996).

FERTILITY DISORDERS

Vitex is used in practice with other herbal medicines to enhance fertility in women with progesterone deficiency or luteal phase defects. Currently no large studies have been published to evaluate the effectiveness of this approach; however, a double-blind, randomised, placebo-controlled study of 96 women with fertility disorders (38 with secondary amenorrhea, 31 with luteal insufficiency and 27 with idiopathic infertility) used the vitex product Mastodynon with encouraging results (Gerhard et al 1988). Treatment of 30 drops was administered twice daily for 3 months and resulted in women with amenorrhea or luteal insufficiency achieving pregnancy more than twice as often as the placebo group, with 15 women conceiving during the study period ($n = 7$ with amenorrhoea, $n = 4$ with idiopathic infertility, $n = 4$ with luteal insufficiency). Although promising, this study has been criticised for pooling of diverse conditions, unclear reporting of results and variable significance (Ulbricht & Basch 2005).

ACNE VULGARIS

An open study of 117 subjects with different forms of acne found that after 6 weeks' treatment with a 0.2% dried extract of *Vitex agnus-castus* and a topical disinfectant, 70% of cases experienced total resolution with the highest success rates reported for acne vulgaris, follicularis and excoriated acne (Amann 1975). A group that was not treated with the herb took 30–50% longer to achieve similar results. Although encouraging, it is difficult to determine the contribution of vitex treatment to these results. Until controlled studies using vitex as a stand-alone treatment are conducted, the herb's role in this condition is still uncertain.

OTHER USES

Vitex is used to relieve menopausal symptoms, and aid the expulsion of the placenta after birth. It is also used to treat fibroids, normalise hormones following the use of OCP, and in cases of premature ovarian failure.

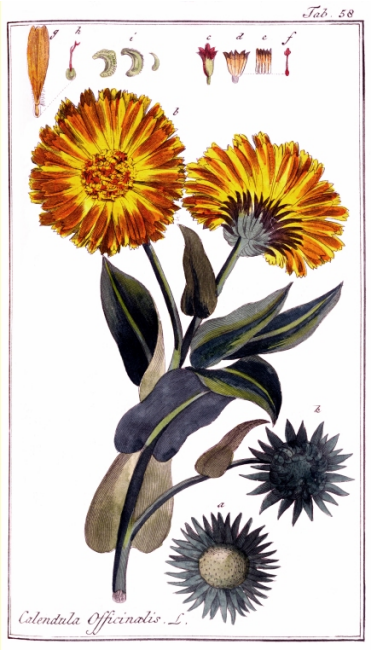
DOSAGE RANGE

GENERAL GUIDE

- Liquid extract (1:2): 1–2.5 mL in the morning.
- Dried fruit: 1.5–3 g in the morning.
- Dry fruit flesh (solid-dose form): 1000–1800 mg/day.
- Manufacturers have recommended vitex preparations be taken daily as a single dose upon rising, before breakfast, throughout the menstrual cycle.

ACCORDING TO CLINICAL STUDIES

- PMS
  Ze440 extract (Premular) 20 mg daily
  Femicur 40 mg daily
- Cyclic mastalgia
  Mastodynon 60 drops daily or 1 tablet daily
- Menstrual irregularities
  20 mg daily (extract unknown)
- Infertility
  Mastodynon 30 drops twice daily



ADVERSE REACTIONS

A systematic review of the herb's safety, published in 2005, analysed data from six electronic databases, postmarketing surveillance studies, spontaneous reporting schemes (including WHO), herbalist organisations and manufacturers (Daniele et al 2005). The review concluded that vitex is a safe herbal medicine and any adverse effects associated with its use tend to be mild and reversible. The most common adverse effects are: nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritis and erythematous rash. Additionally, no drug interactions have been reported.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

DOPAMINE ANTAGONISTS

An antagonistic interaction is theoretically possible — observe patients.

ORAL CONTRACEPTIVES

There has been speculation about the effectiveness of vitex when OCP are being taken. Several clinical studies involving women taking oral contraceptives have confirmed the herb still reduces PMS symptoms and does not affect OCP.

CONTRAINDICATIONS AND PRECAUTIONS

People with tumours sensitive to oestrogen or progesterone should avoid using this herb until safety can be established.

PREGNANCY USE

Vitex is not traditionally recommended in pregnancy. In practice, some herbalists use it during the first 8 weeks of pregnancy in cases of difficult conception.

PRACTICE POINTS/PATIENT COUNSELLING

- Several clinical trials have shown that vitex is an effective treatment for common PMS symptoms, such as mood changes and irritability, breast tenderness, headaches and constipation. According to one study, it is more effective than pyridoxine treatment and has a similar response rate to fluoxetine.
- Clinical research has also shown it to be effective in menstrual irregularities and mastalgia.
- Vitex is also used to relieve menopausal symptoms, enhance fertility in women with progesterone deficiency or luteal phase defects, and aid the expulsion of the placenta after birth, reduce fibroids and normalise hormones following the use of oral contraceptives.
- Traditionally, it is described as a galactagogue (i.e. a medicine able to increase milk production in lactation) and is used in low doses for this indication.
- A mechanism of action has not been conclusively identified, but it appears to inhibit prolactin release by selective stimulation of pituitary dopamine D_2 receptors, increase progesterone levels and works via the opiate system.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Chasteberry is used to relieve common symptoms of PMS, such as irritability, mood swings, breast tenderness, headache and constipation. It is also used in combination with other herbal medicines to enhance fertility, relieve menopausal symptoms, regulate irregular menstruation, improve acne and promote milk production in new mothers.

When does it start to work?

Most trials show that treatment for at least three menstrual cycles may be required before symptom relief is experienced in PMS.

Are there any safety issues?

In cases of irregular menstruation, investigation for serious pathology should be undertaken before use of this herb.

REFERENCES

Amann W. Acne vulgaris and Agnus castus (Agnolyt). Z Allgemeinmed 51.35 (1975): 1645-8.

Atmaca M, Kumru S, Tezcan E. Fluoxetine versus Vitex agnus castus extract in the treatment of premenstrual dysphoric disorder. Hum Psychopharmacol 18(3) (2003): 191-5.

Berger D et al. Efficacy of Vitex agnus castus L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). Arch Gynecol Obstet 264.3 (2000): 150-3.

Cahill DJ et al. Multiple follicular development associated with herbal medicine. Hum.Reprod 9.8 (1994): 1469-70.

Daniele C et al. Vitex agnus castus: a systematic review of adverse events. Drug Saf 28.4 (2005): 319-32.

Dittmar FW. Premenstrual syndrome: treatment with a phytopharmaceutical. TW Gynakologie 5.1 (1992): 60-8.
Gerhard II et al. Mastodynon(R) bei weiblicher Sterilitat. Forsch Komplementarmed 5.6 (1998): 272-8.
Halaska M et al. [Treatment of cyclical mastodynia using an extract of Vitex agnus castus: results of a double-blind comparison with a placebo]. Ceska Gynekol 63.5 (1998): 388-92.
Jarry H et al. In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of Agnus castus: Direct evidence for a dopaminergic principle by the dopamine receptor assay. Exp Clin Endocrinol 102.6 (1994): 448-54.
Lauritzen C, Reuter HD, Repges R, Bohnert K-J, Schmidt U. Treatment of premenstrual tension syndrome with Vitex agnus castus: Controlled, double-blind study versus pyridoxin. Phytomedicine 4 (1997): 183-9.
Liu J et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 49.5 (2001): 2472-9.
Loch EG, Selle H, Boblitz N. Treatment of premenstrual syndrome with a phytopharmaceutical formulation containing Vitex agnus castus. J Womens Health Gend Based Med 9.3 (2000): 315-20.
Meier B, Hoberg E. Agni-casti fructus: An overview of new findings in phytochemistry, pharmacology and biological activity. Zeitschr Phytother 20.3 (1999): 140-58.
Meier B et al. Pharmacological activities of Vitex agnus-castus extracts in vitro. Phytomedicine 7.5 (2000): 373-81.
Merz PG et al. The effects of a special Agnus castus extract (BP1095E1) on prolactin secretion in healthy male subjects. Exp Clin Endocrinol Diabetes 104.6 (1996): 447-53.
Milewicz A et al. Vitex agnus castus extract in the treatment of luteal phase defects due to latent hyperprolactinemia: Results of a randomized placebo-controlled double-blind study. Arzneimittelforschung 43.7 (1993): 752-6.
Noack M. Dtsch Med Wschr, p. 204, 1943 from www.phytotherapies.org
Ohyama K et al. Cytotoxicity and apoptotic inducibility of Vitex agnus-castus fruit extract in cultured human normal and cancer cells and effect on growth. Biol Pharm Bull 26.1 (2003): 10-18.
Ohyama K et al. Human gastric signet ring carcinoma (KATO-III) cell apoptosis induced by Vitex agnus-castus fruit extract through intracellular oxidative stress. Int J Biochem Cell Biol 37.7 (2005): 1496-510.
Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ 322.7279 (2001): 134-7.
Sliutz G et al. Agnus castus extracts inhibit prolactin secretion of rat pituitary cells. Horm Metab Res 25.5 (1993): 253-5.
Splitt G, Sieder, C, Gorkow C, Wuttke W. Behandlung zyklusabhangiger Brustschmerzen mit einem Agnus castus-haltigen Arzneimittel: Ergebnisse einer randomisierten, plazebokontrollierten Doppelblindstudie. Geburtsh u Frauenheilk 57 (1997): 569-74.
Ulbricht C, Basch E. Chasteberry. Missouri: Mosby, 2005; 136-43.
Webster DE et al. Activation of the mu-opiate receptor by Vitex agnus-castus methanol extracts: Implication for its use in PMS. J Ethnopharmacol (2006) [Epub ahead of print].
Weisskopf M et al. A Vitex agnus-castus extract inhibits cell growth and induces apoptosis in prostate epithelial cell lines. Planta Med 71.10 (2005): 910-16.
Wuttke W et al. Chaste tree (Vitex agnus-castus): pharmacology and clinical indications. Phytomedicine 10.4 (2003): 348-57.

Chickweed

Historical note Chickweed is one of the most common weeds worldwide. It has been used since ancient times to treat external inflammatory conditions and is also used as a tasty and nutritious vegetable, as well as poultry fodder to improve egg production.

COMMON NAME
Chickweed

OTHER NAMES
Mouse-ear, star chickweed, starweed, satinflower, starwort, stellaria, winterweed

BOTANICAL NAME/FAMILY
Stellaria media (family Caryophyllaceae)

PLANT PARTS USED
Aerial parts — leaves, stems and flowers

CHEMICAL COMPONENTS
Saponins, coumarins, flavonoids, carotenoids, carboxylic acids, as well as nitrate salts, vitamin C, calcium, iron, vitamins A and C and B complex vitamins (Fisher & Painter 1996). Chickweed essential oil has been found to contain several well-known contact allergens borneol, menthol, linalool, 1,8-cineole, and other terpenes such as epoxy-dehydro-caryophyllene, monoterpene alcohol-ester and caryophyllene (Jovanovic et al 2003).

MAIN ACTIONS
The pharmacological actions of chickweed have not been significantly investigated, so traditional use and an understanding of the actions of individual constituents is used.

INTERNAL USE — ANTITUSSIVE, EXPECTORANT AND DEMULCENT EFFECTS
Herbal saponins are well known to irritate mucous membranes and are successfully used as expectorants (e.g. senega). Herbs, such as chickweed, that contain saponins are also suspected to have a degree of expectorant activity when used internally; however, this has not been investigated in controlled studies.

EXTERNAL USE — SOOTHING IRRITATED SKIN AND ENHANCING WOUND HEALING

Chickweed is traditionally thought to have soothing properties when applied to the skin in an appropriate vehicle, although controlled studies are not available to confirm these effects. The saponin content may account for the herb's ability to help reduce itchiness.

OTHER ACTIONS

An in vitro study identified that a chickweed decoction had activity against human hepatoma cell lines (Lin et al 2002). An ethanolic extract of chickweed has been found to strongly inhibit xanthine oxidase in vitro, suggesting that it may have a use against hyperuricaemia and gout (Pieroni et al 2002).

CLINICAL USE

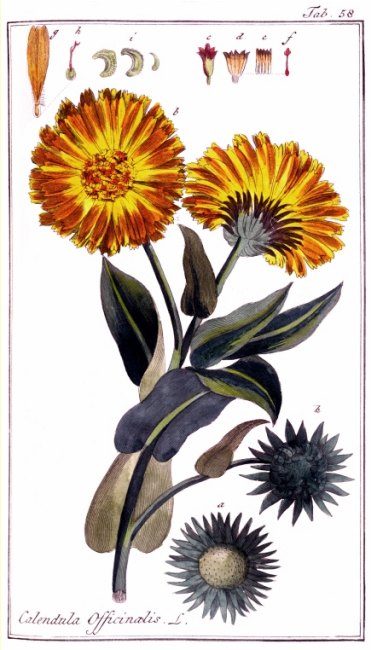
Chickweed has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

URTICARIA, ECZEMA, RASHES, BURNS

Chickweed is most commonly used in external preparations for inflamed and itchy skin conditions such as urticaria, eczema, insect bites and stings, as well as minor wounds and cuts. Anecdotal evidence suggests that it may have some effects; however, controlled studies are not available to confirm effectiveness.

BRONCHIAL PHLEGM AND BRONCHITIS

Taken orally, chickweed is often combined with other herbs for treating conditions characterised by fever and bronchial phlegm; however, controlled studies are not available to confirm effectiveness.



OTHER USES

Chickweed can be eaten raw in salads, served as cooked greens, juiced or infused as a tea. It has also been used as a mild laxative and diuretic substance.

DOSAGE RANGE

- Tincture (1:5): 2–10 mL three times daily.
- Infusion of dried herb: 1–5 g three times daily.
- Chickweed is commonly incorporated into a topical ointment or cream base for external use (1 part chickweed to 5 parts base) and applied as required.

TOXICITY

Allergic skin reactions can occur with topical use.

ADVERSE REACTIONS
There is insufficient reliable information available about the safety of chickweed when used internally or externally. Allergy to chickweed causing contact erythema multiforme has been reported (Jovanovic et al 2003) and it is advised to apply a test patch to a small area before applying more widely.

SIGNIFICANT INTERACTIONS
Not known.

CONTRAINDICATIONS AND PRECAUTIONS
Allergic skin reactions can occur with topical use.

PREGNANCY USE
Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING
- Chickweed has been traditionally used as an ingredient in herbal creams and ointments to soothe inflamed itchy skin and promote wound healing. Although controlled studies are unavailable, the pharmacological actions of several constituents within the herb suggest that it may be useful.
- Although it is likely to be safe, it is prudent in pregnancy to avoid using chickweed in amounts greater than those ingested when used as a food.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
When chickweed is applied topically it may soothe inflamed and itchy skin. It is taken orally as a cough suppressant and expectorant.
How quickly will it work?
In practice, topical preparations are reported to produce symptom relief within 30 minutes; however, there are no controlled trials to confirm this.
Are there any safety issues?
Chickweed can be consumed as a food in salads, cooked as greens or prepared as a juice; however, the safety of larger intakes is unknown. Used as part of a herbal cream it is likely to be safe, although it would be wise to do a test patch in a small area before applying to large areas. The safety of large doses in pregnancy is unknown.

REFERENCES
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. New Zealand: Fisher-Painter Publishers, 1996.
Jovanovic M et al. Erythema multiforme due to contact with weeds: a recurrence after patch testing. Contact Dermatitis 48.1 (2003): 17-25.

Lin L-T et al. In vitro anti-hepatoma activity of fifteen natural medicines from Canada. Phytother Res 16.5 (2002): 440-4.
Pieroni A et al. In vitro antioxidant activity of non-cultivated vegetables of ethnic Albanians in southern Italy. Phytother Res 16.5 (2002): 467-73.

Chitosan

Historical note With the exception of cellulose, chitin is the most abundant natural polysaccharide on Earth. It is produced by different crustaceans, molluscs, insects, algae, fungi and yeasts. Recently, the commercial value of chitin has increased because of the beneficial properties of its soluble derivatives, which are used in chemistry, biotechnology, agriculture, food processing, cosmetics, veterinary science, medicine, dentistry, environmental protection, and paper or textile production. The most useful chitin derivative is chitosan.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Chitosan is a form of poorly soluble fibre, chemically derived from chitin, which is extracted from the exoskeletons of crustaceans or squid. It is a cationic polysaccharide and is in itself a major source of the nutritional supplement glucosamine. Similar to other forms of fibre, such as oatbran, chitosan is thought to bind bile acids and dietary lipids. The solubility, biocompatibility and immunological activity and physicochemical properties of chitosan are altered by its molecular weight and degree of N-acetylation. The most biologically effective products contain a chitosan fraction with a low molecular weight, about 8 kD (Synowiecki et al 2003).

The solubility of chitosan increases in the acidic environment of the stomach, but at a pH above 6.3 (e.g. in the intestines) the amino groups of chitosan and fatty acids, bile acids, cholesterol and lipids form a complex (Ylitalo et al 2002), and the resultant decreased availability of bile acids limits intestinal emulsification and the absorption of lipids, which are then excreted in the faeces.

CHEMICAL COMPONENTS

Chitosan is a cationic polysaccharide prepared by N-deacetylation of chitin.

DEFICIENCY SIGNS AND SYMPTOMS

Chitosan is not an essential nutrient, so deficiencies do not occur.

MAIN ACTIONS

BINDS TO FAT

As it passes through the digestive tract, chitosan binds to ingested fat, bile acids, cholesterol and other lipids, preventing their absorption. The complexes that form between chitosan and various fats are then excreted in the faeces. A human study investigating whether the effect is clinically significant found that a dose of 4.5 g/day,

taken in divided doses 30 minutes before meals, trapped only negligible amounts of fat as measured by fat excretion in stools (Gades & Stern 2003).

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

Animal studies have identified antibacterial activity against *Bifidobacterium* and *Lactobacillus*, which are part of the normal flora of the intestinal tract (Tanaka et al 1997). Clinical trials with a chitosan mouthwash have shown antibacterial activity against *Streptococcus mutans* (Sano et al 2003). Chitosan also inhibits the adhesion of *Candida albicans* to human buccal cells and has antifungal activity (Senel et al 2000).

OTHER ACTIONS

Chitosan can also absorb urea and ammonia and generally displays similar actions to other dietary fibres (Hendler et al 2001).

CLINICAL USE

The most biologically effective products contain a chitosan fraction having a low molecular weight. Unfortunately, not every clinical study indicates whether low molecular weight chitosan has been used. Therefore, aside from the usual variables, discrepant results may be due to differences in the type of chitosan used.

WEIGHT LOSS

Chitosan is widely marketed as a weight-loss aid, primarily due to its ability to bind to fats and reduce their absorption in the digestive tract.

A Cochrane systematic review published in 2005 analysed the results of 14 randomised studies involving 1131 subjects and concluded that use of chitosan resulted in a significantly greater weight loss, decrease in total cholesterol and decrease in systolic and diastolic blood pressure than placebo (Ni et al 2005). The studies had a minimum duration of 4 weeks and were conducted with overweight or obese subjects. In regards to the frequency of adverse events or faecal fat excretion, no clear differences were observed between the placebo and chitosan groups. Although encouraging, the authors noted that the quality of the studies was suboptimal and overall results were variable. A look at the studies of highest quality suggests that the effects are minimal. The mean trial duration was 8.3 weeks (range 4–24 weeks) and 8 of the 14 studies combined the use of chitosan or placebo with a low-calorie or weight-reducing diet. Interpretation of the data is not straightforward because the dose of chitosan used in studies varied considerably, from 0.24 g/day to 15 g/day (mean 3.7 g/day) and six of the studies used treatment preparations that contained other active ingredients in addition to chitosan. Additionally, the review excluded some potentially important trials because they did not meet criteria for

inclusion (e.g. subjects were not enrolled for being overweight but selected for other reasons).

Previously, a 1998 meta-analysis identified five studies evaluating the effectiveness of chitosan for the treatment of obesity (Ernst & Pittler 1998). All studies included were conducted in Italy and published in a single Italian journal over a 2-year period. They concluded that the mean difference in terms of weight reduction between chitosan and placebo was approximately 3.3 kg. It is worth noting that these five studies consistently demonstrated the greatest effects in the 2005 Cochrane systematic review discussed above, were all of short duration, and four of them also included other agents in the chitosan preparations.

A later systematic review conducted by Ernst and Pittler, which included five additional studies, concluded that when these new results were combined with the previous five from the 1998 meta-analysis, the evidence becomes less compelling and raised doubts about the effectiveness of chitosan in weight loss (Pittler & Ernst 2004).

Clearly, further well-reported research is required, using longer time frames and clearly stating the composition of the chitosan preparations.

HYPERLIPIDAEMIA

The ability of chitosan to form complexes with various fats, including cholesterol, provides a theoretical basis for its use in hyperlipidaemia. Dietary chitosan has been tested and found to be effective in reducing serum cholesterol levels and atherosclerosis in normal and diabetic mice, and therefore has been investigated in the treatment of hypercholesterolaemia in humans (Muzzarelli 1999).

A 2002 review states that in humans, dietary chitosan reduces serum total cholesterol levels by 5.8–42.6% and LDL levels by 15.1–35.1% (Ylitalo et al 2002). Based on these figures, the effects of chitosan range from mild to moderate and appear to be inconsistent for total cholesterol. More specifically, lowering of LDL-cholesterol is more consistent, whereas little effect is seen on plasma triglyceride concentration, according to several different experimental and human studies involving obese or diabetic subjects or people with mild to moderate hypercholesterolaemia (Bokura & Kobayashi 2003, Tai et al 2000, Wuolijoki et al 1999, Yihua & Binglin 1997).

Reduction in LDL-cholesterol was evident after 4 weeks' treatment with a microcrystalline chitosan (1.2 g twice daily) according to one double-blind study (Wuolijoki et al 1999) and after 8 weeks' treatment using a low dose of 1.2 g/day of chitosan in another double-blind study (Bokura & Kobayashi 2003). However, not all studies have produced positive results. One double-blind study found no effect with 1.5 g chitosan tablets taken three times daily (Zahorska-Markiewicz et al 2002).

The electrically neutral nature of triglycerides may mean that chitosan is unable to form complexes with it, and therefore is unable to influence its absorption.

DENTAL PLAQUE PREVENTION

Considering that chitosan has antibacterial activity against *Streptococcus mutans* and antifungal action against *Candida albicans*, it has been added to mouthwashes and gels for dental use. One randomised, crossover clinical trial involving 24 volunteers found that rinsing with a mouthwash containing 0.5% chitosan for 14 days was significantly more effective in reducing plaque formation than placebo (Sano et al 2003).

KIDNEY FAILURE

One open study of 80 patients with renal failure undergoing haemodialysis found that 1350 mg of chitosan taken three times daily effectively reduced total serum cholesterol levels (from 10.14 ± 4.40 mmol/L to 5.82 ± 2.19 mmol/L) and increased serum haemoglobin levels (from 58.2 ± 12.1 g/L to 68 ± 9.0 g/L) (Jing et al 1997). After 4 weeks, significant reductions in serum urea and creatinine levels were observed. After 12 weeks, patients reported subjective improvements, such as feeling physically stronger, increased appetite and improved sleep, which were also significantly greater than the placebo group. Importantly, during the treatment period, no clinically problematic symptoms were observed.

WOUND HEALING — TOPICAL USE

Chitosan is applied to burns and wound dressings in the form of films, bandages, cotton-like materials, and non-woven napkins. These dressings have good hydroscopicity, show high bacteriostatic effect, and are completely biodegradable in the human body. Another significant advantage is that repeated dressings are usually not needed (Synowiecki et al 2003). Topical application of chitosan enhances wound healing and has been used to promote donor-site tissue regeneration in plastic surgery. Its use is supported by findings that indicate chitosan accelerates the reformation of connective tissue (Ueno et al 2001).

OTHER USES

DRUG DELIVERY SYSTEMS

Chitosan is considered a good carrier for the controlled release of drugs over an extended period of time. (Synowiecki et al 2003). Additionally, it has been shown to excel in transcellular transport.

Chitosan is also used as a component of different cosmetics, toothpaste, hand and body creams, and hair-care products (Synowiecki et al 2003).

DOSAGE RANGE

- The standard dose of chitosan is 3–6 g/day, taken with food.

ACCORDING TO CLINICAL STUDIES

- Weight loss: 3.0–4.5 g taken daily in divided doses, 30 minutes before meals.
- Hyperlipidaemia: 1.2–4.5 g/day in divided doses.
- Dental plaque prevention: rinse daily with mouthwash containing 0.5%.
- Renal failure: 1.35 g taken three times daily.

ADVERSE REACTIONS

A systematic review of 14 randomised studies found that the most common side-effects reported were constipation, nausea, bloating, indigestion and abdominal pain (Ni et al 2005). Increased water consumption may reduce some of these side-effects.

Overall, chitosan is considered very safe and well tolerated according to safety studies in experimental models (Kim et al 2001).

SIGNIFICANT INTERACTIONS

FAT SOLUBLE NUTRIENTS

Considering chitosan binds to dietary fats and reduces their absorption, chitosan can also affect the absorption of fat-soluble vitamins. However, the effect is dose-dependent as one study using a dose of 2 g/day found no changes to the levels of vitamins A, D, E and beta-carotene after 4 weeks' use (Pittler et al 1999). As a precautionary measure, a multivitamin supplement should be considered for all individuals taking long-term chitosan.

LIPOPHILIC DRUGS

Considering chitosan binds to dietary fats and reduces their absorption, chitosan can also affect the absorption of lipophilic drugs. Separate doses by at least 2 hours.

VITAMIN C

According to a preliminary study in rats, taking vitamin C together with chitosan might provide additional benefit in lowering cholesterol.

CONTRAINDICATIONS AND PRECAUTIONS

Chitosan is contraindicated in people with allergies to shellfish.

PREGNANCY USE

Pregnant women should avoid chitosan as it may reduce absorption of essential dietary nutrients.

PRACTICE POINTS/PATIENT COUNSELLING

- Chitosan is a form of poorly soluble fibre, chemically derived from chitin, which is extracted from the exoskeletons of crustaceans or squid. The most biologically active forms have a low molecular weight.
- It forms insoluble complexes with dietary fats, fatty acids, bile acids, cholesterol and other lipids in the digestive tract and has antibacterial and antifungal activity that is useful in dental hygiene.
- Chitosan is a popular weight-loss supplement. Clinical studies have produced mixed results; however, best effects occur when chitosan is used over several months and combined with dietary and lifestyle modifications.
- Overall, evidence generally supports its use in hyperlipidaemia as it reduces serum levels of total cholesterol and LDL levels, but it has little effect on triglyceride levels.
- Chitosan is contraindicated in people with allergies to shellfish and should be recommended together with a multivitamin supplement with long-term use.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Taken orally, chitosan may aid in weight loss when combined with dietary and lifestyle modifications and reduce cholesterol levels.

When will it start to work?

Effects in weight loss require at least 8 weeks' continual use before effects are seen, according to research, whereas cholesterol lowering requires 4–8 weeks.

Are there any safety issues?

Chitosan is contraindicated in people with allergies to shellfish.

REFERENCES

Bokura H, Kobayashi S. Chitosan decreases total cholesterol in women: a randomized, double-blind, placebo-controlled trial. Eur J Clin Nutr 57.5 (2003): 721-5.

Ernst E, Pittler MH. Chitosan as a treatment for body weight reduction? A meta-analysis. Perfusion 11 (1998): 461-4.

Gades MD, Stern JS. Chitosan supplementation and fecal fat excretion in men. Obes Res 11.5 (2003): 683-8.

Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.

Jing SB et al. Effect of chitosan on renal function in patients with chronic renal failure. J Pharm Pharmacol 49.7 (1997): 721-3.

Kim SK et al. Subacute toxicity of chitosan oligosaccharide in Sprague-Dawley rats. Arzneimittelforschung 51.9 (2001): 769-74.

Muzzarelli RA. Clinical and biochemical evaluation of chitosan for hypercholesterolemia and overweight control. EXS 87 (1999): 293-304.

Ni MC et al. Chitosan for overweight or obesity. Cochrane Database Syst Rev 3 (2005): CD003892.

Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. Am J Clin Nutr 79.4 (2004): 529-36.

Pittler MH et al. Randomized, double-blind trial of chitosan for body weight reduction. Eur J Clin Nutr 53.5 (1999): 379-81.

Sano H et al. Effect of chitosan rinsing on reduction of dental plaque formation. Bull Tokyo Dent Coll 44.1 (2003): 9-16.
Schiller RN, Barrager E, Schauss AG et al. A randomized, double-blind, placebo-controlled study examining the effects of a rapidly soluble chitosan dietary supplement on weight loss and body composition in overweight and mildly obese individuals. J Am Nutraceutical Assoc 4 (2001): 42-9 (as cited in Mosby's Drug Consult 2003).
Senel S et al. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int J Pharm 193.2 (2000): 197-203.
Synowiecki J, Al-Khateeb NA. Production and properties and some new applications of chitin and its derivatives. Crit Rev Food Sci Nutr 43.2 (2003): 145.
Tai TS et al. Effect of chitosan on plasma lipoprotein concentrations in type 2 diabetic subjects with hypercholesterolemia. Diabetes Care 23.11 (2000): 1703-4.
Tanaka Y et al. Effects of chitin and chitosan particles on BALB/c mice by oral and parenteral administration. Biomaterials 18.8 (1997): 591-5.
Ueno H et al. Evaluation effects of chitosan for the extracellular matrix production by fibroblasts and the growth factors production by macrophages. Biomaterials 22.15 (2001): 2125-30.
Wuolijoki E, Hirvela T, Ylitalo P. Decrease in serum LDL cholesterol with microcrystalline chitosan. Methods Find Exp Clin Pharmacol 21.5 (1999): 357-61.
Yihua YU, Binglin HE. A new low density lipoprotein (LDL) adsorbent. Artif Cells Blood Substit Immobil Biotechnol 25.5 (1997): 445-50.
Ylitalo R et al. Cholesterol-lowering properties and safety of chitosan. Arzneimittelforschung 52.1 (2002): 1-7.
Zahorska-Markiewicz B et al. Effect of chitosan in complex management of obesity. Pol Merkuriusz Lek 13.74 (2002): 129-32.

Chondroitin

OTHER NAMES

Chondroitin sulfate, chondroitin sulfuric acid, chondroitin 4-sulfate, chondroitin 4- and 6-sulfate

BACKGROUND AND RELEVANT PHARMACOKINETICS

Chondroitin sulfate is an amino sugar polymer, made up of glucuronic acid and galactosamine, that is in the class of large polymers known as glucosaminoglycans or mucopolysaccharides. These compounds act as the flexible connecting matrix between the protein filaments in cartilage and connective tissue (Liesegang 1990). Chondroitin is manufactured from natural sources, such as shark and bovine (usually tracheal) cartilage and may have a molecular weight that varies from 10 to 50 kD, depending on the product's source or preparation (Ross 2000).

There are differences in the absorption and bioavailability of chondroitin formulations due to differences in molecular mass, charge density, and cluster of disulfated disaccharides of the parental molecules (Volpi 2003). Low-molecular-weight chondroitin appears to be absorbed orally in both animals and humans (Adebowale et al 2002, Du et al 2004) and displays accumulation after multiple dosing (Adebowale et al 2002).

Chondroitin is concentrated in the intestine, liver, kidneys, synovial fluid and cartilage (Conte et al 1995) and the elimination half-life is about 5–6 hours, with 40–50% being excreted in the urine (Conte et al 1991, Ronca & Conte 1993). Oral chondroitin is absorbed as several metabolites, and as the active moiety has not yet been identified it is difficult to establish bioequivalence between different products (Volpi 2003).

CHEMICAL COMPONENTS

Chondroitin sulfate is a linear polymer of two alternating sugars, alpha-D-N-acetylglactosamine and beta-D-glucuronic acid, with the sulfate moiety being a covalent part of the molecule and not a counter ion as is the case with glucosamine sulfate (Ross 2000).

FOOD SOURCES

Chondroitin is naturally present in the gristle in meat. As a supplement it is generally produced from natural sources, such as shark or bovine (usually tracheal) cartilage or can be manufactured in the laboratory using various methods. The purity and content

of products has been questioned in the USA, where it is regarded as a nutritional supplement and its quality is unregulated (Consumer-labs 2).

MAIN ACTIONS

CHONDROPROTECTIVE EFFECT

Chondroitin appears to protect cartilage by providing it with the raw material required for repair, as well as inhibiting the enzymes in synovial fluid, such as elastase and hyaluronidase, that damage joint cartilage. It improves chondrocyte nutrition by increasing hyaluronic acid production in articular cells (Raoudi et al 2005) and hence the fluid content of the extracellular matrix (Sasada et al 2005), which not only acts as a shock absorber but also brings nutrients into the cartilage (Krane & Goldring 1990).

The overall chondroprotective effect of chondroitin has been demonstrated in animal models, whereby oral or intramuscular chondroitin sulfate has been shown to protect rabbit articular cartilage from experimental chymopapain injury (Uebelhart et al 1998a) and inhibit the destruction of the cartilage extracelluar matrix (Sumino et al 2005). The chondroprotective action of chondroitin has been found to be potentiated by high sulfur mineral water in an animal model of osteoarthritis (Caraglia et al 2005).

ANTI-INFLAMMATORY

Chondroitin exerts an anti-inflammatory action with an inhibitory effect over complement (Pipitone 1991). In an in vitro study of bovine cartilage, chondroitin alone and in combination with glucosamine was found to regulate gene expression and synthesis of NO and PGE_2, suggesting a basis for its anti-inflammatory properties (Chan et al 2005). Chondroitin sulfate has been found to increase the levels of antioxidant enzymes and reduce inflammation and cirrhosis of liver tissue in an ovariectomised rat model, suggesting that it enhances antioxidant activity (Ha 2004).

VISCOELASTIC AGENT

Chondroitin sulfate is a viscoelastic agent and together with similar substances such as sodium hyaluronate and hydroxypropylmethylcellulose, it is used in ophthalmic surgery to protect and lubricate cells and tissues (Larson et al 1989, Liesegang 1990).

OTHER ACTIONS

There are suggestions from laboratory studies and uncontrolled human trials that chondroitin may have potential anti-atherogenic properties (Morrison 1969, 1971, Morrison & Enrick 1973).

It has been found that serum levels of chondroitin sulfate are increased in patients with RA or OA and this may provide the basis for systemic detection of OA (Pothacharoen et al 2006).

CLINICAL USE

OSTEOARTHRITIS: SYMPTOM CONTROL AND RETARDING DISEASE PROGRESSION

Chondroitin sulfate appears to produce a slow but gradual reduction of the clinical symptoms of OA. Multiple human clinical trials lasting from a few weeks to 3 years have shown that chondroitin sulfate can significantly alleviate symptoms of pain and improve function in patients with OA of the knee (Bourgeois et al 1998, Bucsi & Poor 1998, Fioravanti et al 1991, Lazebnik 2005, Mazieres et al 2001, Morreale et al 1996, Oliviero et al 1991, Rovetta 1991) and that these effects last months after the cessation of treatment (Mazieres et al 2005), as well as being evident with intermittent treatment (Uebelhart et al 2004).

A meta-analysis of 7 trials of 372 patients taking chondroitin sulfate found at least 50% improvement in pain and function in the chondroitin sulfate group compared with placebo (Leeb et al 2000). A meta-analysis of 15 trials of the use of glucosamine and/or chondroitin raised quality issues about many studies, but found moderate to large clinical effects from these agents, suggesting that they do have efficacy in treating OA (McAlindon et al 2000).

There is also evidence from double-blind clinical trials that chondroitin can reverse, retard or stabilise the pathology of OA (Volpi 2005), as evidenced by stabilisation of the joint space (Uebelhart et al 1998b), less progression of erosions (Rovetta et al 2002, Verbruggen et al 1998) and improved articular cartilage thickness (Pipitone et al 1992) and interarticular space, as observed by X-rays (Conrozier 1998, Michel et al 2005, Uebelhart et al 2004). A subanalysis of patients involved in the GAIT study (see below and Glucosamine monograph) further suggests that chondroitin sulfate may have differential effects on OA symptoms depending on the degree of radiographic involvement, and that chondroitin may provide improvements in knee pain in patients with relatively early radiographic disease (Clegg et al 2005).

Comparisons with NSAIDs Although chondroitin appears to be at least as effective as NSAIDs in treating the symptoms of OA (Fioravanti et al 1991, Morreale et al 1996), it has a slower onset of action, taking 2–4 months to establish an effect (Leeb et al 2000, Morreale et al 1996). Chondroitin may, however, provide benefits that persist after treatment is stopped (Mazieres et al 2001, Morreale et al 1996).

Combined use of chondroitin sulfate and glucosamine sulfate Chondroitin and glucosamine are frequently marketed together in combination products and some studies suggest that this combination is effective in treating symptoms (Das & Hammad 2000, Leffler et al 1999, McAlindon et al 2000, Nguyen et al 2001) and reducing joint space narrowing (Rai et al 2004). These findings are supported by an in

vitro study on horse cartilage that found that a combination of glucosamine and chondroitin was more effective than either product alone in preventing articular cartilage glycosaminoglycan degradation (Dechant et al 2005), as well as an in vivo study on rats that found that the combined treatment prevented the development of cartilage damage and was associated with a reduction in IL-1-beta and matrix metalloprotease-9 synthesis (Chou et al 2005). The recent GAIT trial (see Glucosamine monograph) provides further evidence that glucosamine and chondroitin are more effective when given in combination than when either substance is given alone, with the combined treatment being more effective than the COX-2 inhibitor celecoxib for treating moderate to severe arthritis compared with chondroitin alone (Clegg et al 2006).

A small RCT has suggested that the addition of high-molecular-weight hyaluronate to glucosamine and chondroitin may provide additional benefits to the use of glucosamine and chondroitin alone (Bucci et al 2005).

Topical preparations A topical preparation containing chondroitin with glucosamine and camphor has been shown to reduce pain from OA of the knee in one RCT (Cohen et al 2003).

OTHER USES

HEART DISEASE

There are suggestions that chondroitin in doses of up to 10 g/day may have anti-atherogenic actions, beneficial effects on serum lipid levels and may be useful for reducing the risk of myocardial infarction (Morrison 1969, 1971, Morrison & Enrick 1973, Morrison et al 1969).

SNORING

The results of a pilot crossover study of seven subjects suggest that chondroitin sulfate instilled into the nostril at bedtime may reduce snoring (Lenclud et al 1998).

OPHTHALMIC SURGERY AND DRY EYES

Chondroitin sulfate is used as a viscoelastic substance to protect and lubricate cells and tissues during ophthalmic surgery, as well as to preserve corneas before transplantation (Larson et al 1989, Liesegang 1990). In a double-blind crossover study of 20 subjects, 1% chondroitin sulfate was found to be equally as effective as polyvinyl alcohol artificial tear formulation and 0.1% hyaluronic acid in reducing itching, burning and foreign body sensation in people with keratoconjunctivitis sicca (Limberg et al 1987).

PSORIASIS

It has been found that some patients with psoriasis experience a significant clinical and histological improvement in their psoriatic lesions after taking chondroitin to treat their OA (Verges 2005, Verges et al 2004).

DOSAGE RANGE

- Oral doses of chondroitin range from 800–1200 mg/day in either single or divided doses. Intramuscular, intravenous and topical forms are also available.
- A 4–5-month trial is generally used in order to determine whether it is effective for an individual patient.

ADVERSE REACTIONS

Chondroitin is generally deemed to be extremely safe, with the incidence of adverse reactions being comparable to placebo in studies lasting from 2 months to 6 years (Bourgeois et al 1998, Bucsi & Poor 1998, Leeb et al 2000, McAlindon et al 2000, Uebelhart et al 1998b).

Oral chondroitin may cause mild gastrointestinal disturbance.

While there is a theoretical risk of anticoagulant activity, this has not been demonstrated in clinical trials (Chavez 1997).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

ANTICOAGULANTS

Additive effect theoretically possible — observe patient.

NSAIDS

Chondroitin may enhance drug effectiveness, suggesting a beneficial interaction is possible — drug dosage may require modification.

CONTRAINDICATIONS AND PRECAUTIONS

Due to theoretical anticoagulant activity, chondroitin should be used in caution in people with clotting disorders.

Some forms of chondroitin are produced from bovine (usually tracheal) cartilage, so it is theoretically possible that it may be a source of transmission of bovine spongiform encephalopathy (mad cow disease) and other diseases. This transmission has not been demonstrated and is deemed unlikely.

PREGNANCY USE

Insufficient reliable information available to advise on safety in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Chondroitin is a naturally occurring building block of joint tissue and cartilage. Supplements are made from shark cartilage or bovine tracheal cartilage.
- Chondroitin is generally considered effective in treating the pain and disability of osteoarthritis and may act to slow disease progression, although it may take some weeks before a clinical effect is evident.
- It is considered extremely safe and may reduce the need for NSAIDs, which can have serious side-effects.
- There may be benefits in taking chondroitin in conjunction with glucosamine for treating arthritis.
- Patients undergoing anticoagulant therapy or with clotting disorders should have their blood clotting monitored while taking chondroitin.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Multiple scientific studies have shown that chondroitin sulfate reduces symptoms of OA and may also reduce further progression of the condition. Some people find that they do not require NSAIDs as often when taking it.

When will it start to work?

Symptom relief takes 2–4 months to reach maximal effect, but protection effects on the joints occur only with long-term use of several years.

Are there any safety issues?

Generally considered a very safe treatment and far safer than pharmaceutical anti-inflammatory drugs; however, it should be used with caution by people with clotting disorders or taking anticoagulants.

REFERENCES

Abdellatif M, Reda DJ. A Paradox-based data collection and management system for multi-center randomized clinical trials. Comput Methods Programs Biomed 73(2) (2003): 154-64.

Adebowale A et al. The bioavailability and pharmacokinetic of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs. Biopharm Drug Dispos 23(6) (2002): 217-25.

Bourgeois P et al. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 × 400 mg/day vs placebo. Osteoarthritis Cartilage 6(A) (1998): 25-30.

Bucci LR et al. P196 Comparison between glucosamine with chondroitin sulfate and glucosamine with chondroitin sulfate and hyaluronate for symptoms of knee osteoarthritis. Osteoarthritis Cartilage 13(Suppl 1) (2005): S99.

Bucsi L, Poor G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. Osteoarthritis Cartilage 6(A) (1998): 31-6.

Caraglia M et al. Alternative therapy of earth elements increases the chondroprotective effects of chondroitin sulfate in mice. Exp Mol Med 37(5) (2005): 476-81.

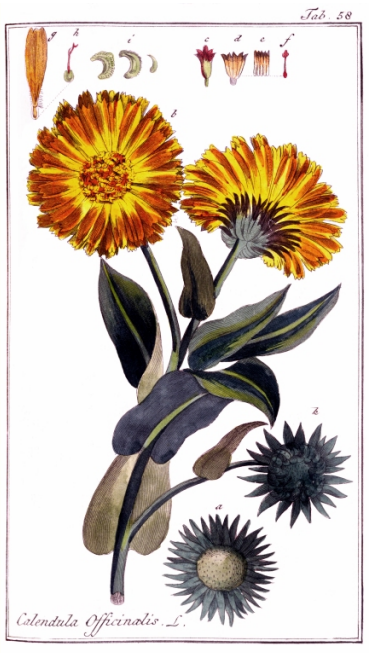
Chan PS et al. Glucosamine and chondroitin sulfate regulate gene expression and synthesis of nitric oxide and prostaglandin E2 in articular cartilage explants. Osteoarthritis Cartilage 13(5) (2005): 387-94.

Chavez ML. Glucosamine sulfate and chondroitin sulfates. Hosp Pharm 32(9) (1997): 1275-85.
Chou MM et al. Effects of chondroitin and glucosamine sulfate in a dietary bar formulation on inflammation, interleukin-1-beta, matrix metalloprotease-9, and cartilage damage in arthritis. Exp Biol Med 230(4) (2005): 255-62.
Clegg DO et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 354(8) (2006): 795-808.
Clegg DO et al. P145 Chondroitin sulfate may have differential effects on OA symptoms related to degree of radiographic involvement. Osteoarthritis Cartilage 13(Suppl 1) (2005): S76-7.
Cohen M et al. A randomized double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol 30 (2003): 523-8.
Conrozier T. Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6). Presse Medicale (Paris, France: 1983) 27(36) (1998): 1862-5.
Consumer-labs (2). Product Review: Glucosamine and chondroitin.
Conte A et al. Metabolic fate of exogenous chondroitin sulfate in man. Arzneimittelforschung 41(7) (1991): 768-72.
Conte A et al. Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. Arzneimittelforschung 45(8) (1995): 918-25.
Das A Jr, Hammad TA. Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis Cartilage 8(5) (2000): 343-50.
Dechant JE et al. Effects of glucosamine hydrochloride and chondroitin sulphate, alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explant metabolism. Equine Vet J 37(3) (2005): 227-31.
Du J et al. The bioavailability and pharmacokinetics of glucosamine hydrochloride and chondroitin sulfate after oral and intravenous single dose administration in the horse. Biopharm Drug Dispos 25(3) (2004): 109-16.
Fioravanti A et al. Clinical efficacy and tolerance of galactosoaminoglucuronoglycan sulfate in the treatment of osteoarthritis. Drugs Exp Clin Res 17(1) (1991): 41-4.
Ha BJ. Oxidative stress in ovariectomy menopause and role of chondroitin sulfate. Arch Pharm Res 27(8) (2004): 867-72.
Krane SM, Goldring MB Clinical implications of cartilage metabolism in arthritis. Eur J Rheumatol Inflamm 10(1) (1990): 4-9.
Larson RS et al. Viscoelastic agents. Contact Lens Assoc Ophthalmol J 15(2) (1989): 151-60.
Lazebnik L. Efficacy of chondroitin sulphate in the treatment of elderly patients with gonarthrosis and coxarthrosis. Terapevtich Arkhiv 77(8) (2005): 64-9.
Leeb BF et al. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. J Rheumatol 27(1) (2000): 205-11.
Leffler CT et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. Military Med 164(2) (1999): 85-91.
Lenclud CCP et al. Effects of chondroitin sulfate on snoring characteristics: a pilot study. Curr Ther Res 59(4) (1998): 234-43.
Liesegang T J. Viscoelastic substances in ophthalmology. Surv Ophthalmol 34(4) (1990): 268-93.
Limberg MB et al. Topical application of hyaluronic acid and chondroitin sulfate in the treatment of dry eyes. Am J Ophthalmol 103(2) (1987): 194-7.
Mazieres B et al. Chondroitin sulfate in osteoarthritis of the knee: A prospective, double blind, placebo controlled multicenter clinical study. J Rheumatol 28(1) (2001): 173-81.
Mazieres B, Hucher M, Zaim M. P140 Chondroitin sulfate in the treatment for knee osteoarthritis: A randomized, double blind, multicenter, placebo-controlled trial. Osteoarthritis Cartilage 13(Suppl 1) (2005): S74.

McAlindon TE et al. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 283(11) (2000): 1469-75.
Michel BA et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 52(3) (2005): 779-86.
Morreale P et al. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol 23(8) (1996): 1385-91.
Morrison LM. Response of ischemic heart disease to chondroitin sulfate-A. J Am Geriatr Soc 17(10) (1969): 913-23.
Morrison LM. Reduction of ischemic coronary heart disease by chondroitin sulfate A. Angiology 22(3) (1971): 165-74.
Morrison LM, Enrick NL. Coronary heart disease: reduction of death rate by chondroitin sulfate-A. Angiology 24(5) (1973): 269-87.
Morrison LM et al. The prevention of coronary arteriosclerotic heart disease with chondroitin sulfate A: preliminary report. Exp Med Surg 27(3) (1969): 278-89.
National Institutes of Health (NIH) (2002). National Centre for Complementary and Alternative Medicine GAIT Study.
Nguyen P et al. A randomized double-blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorders: a pilot study. Cranio 19(2) (2001): 130-9.
Oliviero U et al. Effects of the treatment with matrix on elderly people with chronic articular degeneration. Drugs Exp Clin Res 17(1) (1991): 45-51.
Pipitone V. Chondroprotection with chondroitin sulfate. Drugs Exp Clin Res 17(1) (1991): 3-7.
Pipitone V et al. A multicenter, triple-blind study to evaluate galactosaminoglucuronoglycan sulfate versus placebo in patients with femorotibial gonarthritis. Curr Ther Res 52(4) (1992): 608-38.
Pothacharoen P et al. Raised chondroitin sulfate epitopes and hyaluronan in serum from rheumatoid arthritis and osteoarthritis patients. Osteoarthritis Cartilage 14(3) (2006): 299-301.
Rai J et al. Efficacy of chondroitin sulfate and glucosamine sulfate in the progression of symptomatic knee osteoarthritis: A randomized, placebo-controlled, double blind study. Bull Postgrad Inst Med Ed Res Chandigarh 38(1) (2004): 18-22.
Raoudi M et al. P152 Effect of chondroitin sulfate on hyaluronan synthesis and expression of udp-glucose dehydrogenase and hyaluronan synthases in synoviocytes and articular chondrocytes. Osteoarthritis Cartilage 13(Suppl 1) (2005): S79-80.
Ronca G, Conte A. Metabolic fate of partially depolymerized shark chondroitin sulfate in man. Int J Clin Pharmacol Res 13(Suppl) (1993): 27-34.
Ross I. A submission to the Complementary Medicines Evaluation Committee concerning chondroitin sulfate. Complementary Healthcare Council of Australia, 2000.
Rovetta G. Galactosaminoglycuronoglycan sulfate (matrix) in therapy of tibiofibular osteoarthritis of the knee. Drugs Exp Clin Res 17(1) (1991): 53-7.
Rovetta G et al. Chondroitin sulfate in erosive osteoarthritis of the hands. Int J Tissue React 24(1) (2002): 29-32.
Sasada T et al. Role of chondroitin sulfate on mechanical behavior of articular cartilage. Rep Chiba Inst Technol (52) (2005): 91-7.
Sumino T et al. P163 Effect of long term oral administration of glucosamine hydrochloride and chondroitin sulfate on the progression of cartilage degeneration in a guinea pig model of spontaneous osteoarthritis. Osteoarthritis Cartilage 13(Suppl 1) (2005): S84.
Uebelhart D et al. Protective effect of exogenous chondroitin 4,6-sulfate in the acute degradation of articular cartilage in the rabbit. Osteoarthritis Cartilage 6(A) (1998a): 6-13.
Uebelhart DE et al. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: A pilot study. Osteoarthritis Cartilage 6(A) (1998b): 39-46.
Uebelhart D et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: A one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage 12(4) (2004): 269-76.

Verbruggen G et al. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint OA. Osteoarthritis Cartilage 6(A) (1998): 37-8.
Verges J et al. Clinical and histopathological improvement of psoriasis in patients with osteoarthritis treated with chondroitin sulfate: Report of 3 cases. Med Clin 123(19) (2004): 739-42.
Verges J et al. P156 Chondroitin sulfate: A novel symptomatic treatment for psoriasis. report of eleven cases. Osteoarthritis Cartilage 13(Suppl 1) (2005): S81.
Volpi N. Oral absorption and bioavailability of ichthyic origin chondroitin sulfate in healthy male volunteers. Osteoarthritis Cartilage 11(6) (2003): 433-41.
Volpi N. Chondroitin sulphate for the treatment of osteoarthritis. Curr Med Chem Anti-Inflamm Anti-Allergy Agents 4(3) (2005): 221-34.

Chromium



Historical note In the 1950s, researchers identified the role of chromium in insulin and glucose control (Shwarz & Mertz 1959). The importance of chromium was validated in 1977 when a woman on long-term TPN, without chromium, developed symptoms of diabetes that could not be controlled by insulin. After further investigation it was noted that she was deficient in chromium and when $< 50\ \mu g$ was added to her TPN solution, symptoms resolved. This led to the US FDA listing chromium as an essential trace nutrient (Edmonson 2002). However, problems in elucidating the effects of chromium supplementation persist, due to a lack of practical methods for diagnosing deficiency (Mertz 1998).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Absorption of chromium occurs by passive diffusion and is inversely related to dietary intake (e.g. from a dose of 10 μg, 2% is absorbed; from a dose of 40 μg, 0.5% is absorbed) (Anderson & Kozlovsky 1985). Absorption may be inhibited by zinc (Hahn & Evans 1975) and phytates, and enhanced by oxalate (Bryson & Goodall 1983) and ascorbic acid (Offenbacher 1994). In regard to supplements, chromium picolinate appears to be the most absorbable form as the complexation of picolinic acid with chromium increases its bioavailability (Edmonson 2002, Press et al 1990).

Chromium is transported around the systemic circulation primarily by transferrin (Campbell et al 1997) potentially competing with iron, and accumulates in kidney, muscle and liver (Hepburn & Vincent 2003). It is excreted primarily in urine, but small amounts are lost in hair, perspiration and faeces.

CHEMICAL COMPONENTS

Chromium exists mostly in two valence states in nature: hexavalent chromium (chromium (VI)) and trivalent chromium (chromium (III)). The hexavalent form is used in industry and is associated with toxicity. Trivalent chromium is an essential trace element in the human body and approved as a supplement.

Supplemental forms used in trials include organic chromium complexes such as chromium picolinate and chromium nicotinate and inorganic salts such as chromium chloride. Nicotinic acid is also a metabolite of tryptophan improving its absorption; however, the picolinate form is the one surrounded by the most controversy.

FOOD SOURCES

Brewer's yeast, wholegrain breads and cereals, cheese, eggs, bananas, spinach, mushrooms, broccoli, organ meats and processed meat products.

DEFICIENCY SIGNS AND SYMPTOMS

PRIMARY DEFICIENCY

Symptoms of weight loss, glucose intolerance and neuropathy have been noted in patients on TPN deficient in chromium (Verhage et al 1996). Deficiency may also be a precursor to the development of insulin resistance, and thus associated with hyperglycaemia, hypoglycaemia and obesity. Up to 90% of USA diets have been found to be below the minimum suggested safe and adequate daily intake for chromium of 50 μg/day (Anderson & Kozlovsky 1985).

SECONDARY DEFICIENCY

Factors that may exacerbate deficiency, generally by increasing requirements for or urinary excretion of chromium, include pregnancy, excessive exercise, infection, physical trauma and stress (Anderson 1986). Diets high in simple sugars have been found to increase urinary chromium excretion up to 30-fold, thereby increasing the risk of deficiency (Kozlovsky et al 1986). Corticosteroids also increase urinary losses of chromium (Kim et al 2002).

Clinical note — Problems testing for chromium deficiency

Currently, testing for chromium deficiency involves serum testing. This is problematic as it is still uncertain whether serum levels correlate with tissue levels and, therefore, are truly representative of nutritional status. Studies have shown that subjects with widely varying plasma chromium levels respond favourably to chromium supplementation, suggesting that this marker is misleading (Bahijri 2000). As a consequence, serum tests should not be solely relied upon, leaving the diagnosis of marginal deficiency up to a practitioner's clinical suspicion. Other tests have been proposed such as toenail chromium concentration (Guallar et al 2005) and urinary chromium response to glucose load (Bahijri & Mufti 2002), as conditions that increase circulating glucose and insulin concentrations increase urinary chromium output (Vincent 2004); however, further research is required to confirm the validity of these tests.

MAIN ACTIONS

IMPORTANT COFACTOR IN MANY BIOCHEMICAL REACTIONS

Chromium is an essential trace mineral required for carbohydrate, lipid, protein and corticosteroid metabolism (Kim et al 2002). It is a key constituent of glucose tolerance

factor, together with nicotinic acid and the amino acids cysteine, glycine and glutamic acid.

IMPROVES BLOOD SUGAR CONTROL (CARBOHYDRATE METABOLISM AND INSULIN SENSITIVITY)

Trivalent chromium is an essential trace element for normal carbohydrate metabolism and insulin sensitivity (Wilson & Gondy 1995), aiding the transport of glucose into cells. Rather than increasing insulin secretion, chromium appears to improve glycaemic control by enhancing the action of insulin; improving the ability of insulin to bind to cells; enhancing beta-cell sensitivity; increasing the number of insulin receptors; and activating insulin receptor kinase, thus increasing insulin sensitivity (Anderson 1997, Edmonson 2002). Additionally, in vitro studies have shown that chromium inhibits the secretion of TNF-alpha, a cytokine known to reduce the sensitivity and action of insulin, and that this appears to be mediated by its antioxidant effects (Jain & Kannan 2001).

LIPID-LOWERING ACTIVITY

Although the mechanism of action is yet to be fully explained, studies show that chromium supplementation may decrease triglyceride levels, total and LDL-cholesterol and modestly increase HDL-cholesterol (Bahijri 2000, Lee & Reasner 1994, Press et al 1990, Preuss et al 2000).

ANTIDEPRESSANT/NEUROTRANSMITTER EFFECTS

Depression is often associated with insulin resistance, owing to cortisol overproduction (McCarty 1994). The reputed antidepressant effects of chromium may be explained by improvements in insulin sensitivity (Davidson et al 2003) and related increases in tryptophan availability and/or noradrenaline release (McLeod & Golden 2000). Chromium has also been shown to lower the cortisol response to challenge with 5-hydroxy-L-tryptophan (5-HTP) and decrease the sensitivity of 5-HT_{2A} receptors (Attenburrow et al 2002).

OTHER ACTIONS

IMMUNOMODULATION

A review detailing the effects of chromium on the immune system found that chromium has both immunostimulatory and immunosuppressive effects, as shown by its effects on T and B lymphocytes, macrophages and cytokine production (Shrivastava et al 2002).

BONE DENSITY PROTECTION

It has been suggested that modulation of insulin by chromium may have positive effects on bone density, reducing bone resorption and promoting collagen production by osteoblasts (McCarty 1995). One placebo-controlled study using chromium picolinate (equivalent to 200 μg chromium/day for 60 days) has shown a 47% reduction in the urinary hydroxyproline:creatinine ratio, indicating a decrease in calcium excretion and a potential role in the prevention of osteoporosis (Evans et al 1995).

ANTIOXIDANT

A placebo controlled trial using 1000 μg/day of chromium (as chromium yeast) for 6 months found chromium supplementation an effective treatment in reducing oxidative stress in type 2 diabetes patients with severe hyperglycaemia (HbA1c >8.5%); however, it may act as a pro-oxidant in euglycaemic people (Cheng et al 2004).

INCREASES DEHYDROEPIANDROSTERONE

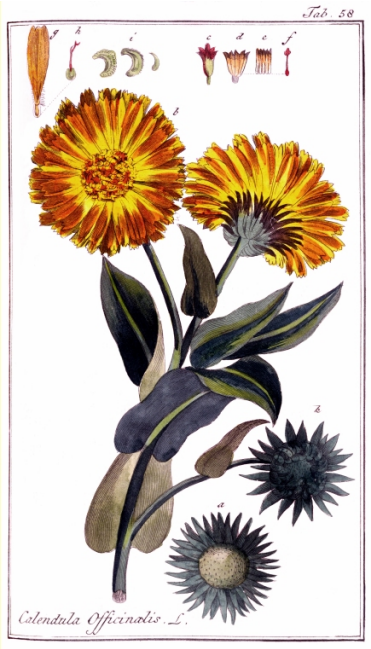
In a placebo-controlled trial, chromium picolinate (equivalent to 200 μg chromium/day for 60 days) increased dehydroepiandrosterone by 24% in postmenopausal women (Evans et al 1995).

CLINICAL USE

Supplemental forms used in trials include organic chromium complexes, such as chromium picolinate and chromium nicotinate, and inorganic salts such as chromium chloride. Considering chromium is known to improve insulin sensitivity, a theoretical basis exists for its use in conditions associated with insulin resistance such as type 2 diabetes mellitus, gestational diabetes, hypoglycaemia, polycystic ovarian syndrome, obesity, and syndrome X. For many of these indications, controlled studies are not yet available. However, there has been investigation into its use in diabetes, hypoglycaemia, hyperlipidaemia and obesity.

DEFICIENCY STATES — PREVENTION AND TREATMENT

Although chromium deficiency is uncommon (Vincent 2004) and mostly described in relation to the use of TPN without chromium, subclinical deficiency states also exist and should respond to supplementation (Verhage 1996). Chromium supplementation is also used in cases at risk of deficiency, such as long-term corticosteroid use (Kim et al 2002) or people with a high sugar intake (Kozlovsky et al 1986).



DIABETES

Results of RCT on the use of varying forms of chromium for glucose and insulin regulation in healthy subjects and in individuals with glucose intolerance or type 2 diabetes have produced contradictory results (Althuis et al 2002, Frauchiger et al 2004, Gunton et al 2005). Overall, it appears that positive results are more likely in persons with known glycaemic aberrations rather than in healthy subjects; however, the response to chromium is difficult to predict.

Although it is uncertain why this is the case, the varying responses of glucose and lipid regulation may be partly explained by variations in pretreatment chromium and iron status, and phenotypic characteristics of the studied individuals.

Type 2 diabetes mellitus (non-insulin-dependent) Results have shown that chromium supplementation appears to be more effective in patients with type 2 diabetes than type 1 (Ravina & Slezack 1993). A 2003 review determined that 'chromium appears to be a safe supplement and may have a role as adjunctive therapy for treatment of type 2 diabetes' (Ryan et al 2003).

Patients with early-stage type 2 diabetes of less than 2 years' duration were found to have lower chromium plasma levels (33%) and increased chromium excretion (100%) compared with healthy controls. Over a period of time this may contribute to the development of the insulin resistance seen in these patients (Morris et al 1999).

The most promising RCT to date tested chromium picolinate at doses of both 200 and 1000 μg/day in subjects with type 2 diabetes who were instructed to maintain their current medications, diet and lifestyle habits. HbA_{1c} values (a marker of long-term glycaemic control) improved significantly in the higher treatment group after 2 months and in both groups after 4 months' treatment. Fasting glucose was lower in the 1000 μg group after 2 and 4 months (4-month values: 7.1 $\pm$ 0.2 mmol/L vs placebo 8.8 $\pm$ 0.3 mmol/L). Two-hour glucose values were also significantly lower in the 1000 μg group after both 2 and 4 months (4-month values: 10.5 $\pm$ 0.2 mmol/L vs placebo 12.3 $\pm$ 0.4 mmol/L). Fasting and 2-hour insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased in the subjects receiving 1000 μg chromium after 4 months (Anderson et al 1997). A double-blind, placebo-controlled crossover study using 400 μg for 12 weeks in diabetics known to have lower serum chromium levels than the healthy controls (Ghosh et al 2002) produced positive results, but a shorter randomised, double-blind placebo-controlled study using 1000 μg for only 8 weeks was not positive (Amato et al 2000). These results not only suggest that improvements are dose-related but are also affected by treatment duration and possibly initial chromium status. A controlled trial of elderly patients with diabetes

(average age 73 years) reported that supplementation with chromium (200 μg twice daily) for 3 weeks improved fasting blood glucose, HbA_{1c}, and total cholesterol levels (Rabinovitz et al 2004), suggesting lower doses may be effective in older patients.

Studies using chromium nicotinic acid have proven more promising with higher doses of nicotinic acid (100 mg/day) (Urberg & Zemel 1987) than those with low-dose nicotinic acid (1.8 mg) (Thomas & Gropper 1996), demonstrating a synergistic effect with chromium (200 μg/day).

Type 1 diabetes mellitus (insulin-dependent) As chromium appears to improve insulin sensitivity rather than secretion its use in type 1 diabetes is probably limited (Edmondson 2002). One study did show reduced requirements for medication in 33.6% of patients with type 1 diabetes taking 200 μg chromium/day (Ravina & Slezack 1993), and another showed a 30% reduction in insulin requirements in 71% of subjects at the same dose (Ravina et al 1995), but as yet it is unclear which patients might respond to treatment.

Gestational diabetes Pregnancy can be described as an increased insulin resistance state, which may result in gestational diabetes if the pancreas is unable to increase insulin levels to maintain blood glucose balance (Jovanovic & Peterson 1996). As such, the beneficial effect of chromium on insulin sensitivity provides a theoretical basis for its use in this condition. A small placebo-controlled trial using 4 or 8 μg/kg of chromium daily in gestational diabetes found a significant dose-dependent improvement in fasting insulin, 1-hour insulin and glucose, and postprandial glucose levels after 8 weeks' supplementation (Jovanovic et al 1999).

Corticosteroid-induced diabetes mellitus Human trials have shown that corticosteroid use significantly increases urinary chromium excretion. Supplementation with chromium picolinate (equivalent to 600 μg chromium/day) in patients experiencing steroid-induced diabetes resulted in decreased fasting blood glucose values (from > 13.9 mmol/L to < 8.3 mmol/L). Furthermore, hypoglycaemic medications were also reduced by 50% in all patients within 1 week (Ravina et al 1999).

Prevention of long-term diabetic complications Both QTc interval prolongation and chronic hyperinsulinaemia have been associated with atherosclerosis progression and increased cardiovascular morbidity in patients with type 2 diabetes. In a crossover trial of 60 subjects, chromium picolinate (1000 μg/day) for 3 months was shown to reduce both QTc interval duration and plasma insulin levels (Vrtovec et al 2005), probably by reducing the adrenergic activation of the sympathetic nervous system due to hyperinsulinaemia. Benefits were most significant in obese patients with higher peripheral insulin resistance (Vrtovec et al 2005).

Animal studies have found that chromium supplementation in mice with type 2 diabetes reduces the symptoms of hyperglycaemia and improves the renal function by recovering renal chromium concentration (Mita et al 2005, Mozaffari et al 2005) which may hold promise for human trials investigating the potential role of chromium in reducing the incidence of diabetic nephropathy.

HYPOGLYCAEMIA

Eight patients with reactive hypoglycaemia were given chromium chloride (equivalent to 200 μg chromium) for 3 months in a double-blind crossover study. Chromium supplementation significantly improved blood sugar regulation, insulin binding to receptors and red blood cells, and alleviated symptoms of hypoglycaemia (Anderson et al 1987).

A double-blind crossover study using chromium chloride (equivalent to 200 μg/day elemental chromium) for 8 weeks found a significant improvement in glycaemic control in subgroups where the 2-hour glucose level was > 10% above or below the fasting level (Bahijri 2000). In these subgroups chromium supplementation resulted in a 2-hour mean not significantly different to the fasting mean, suggesting an amphoteric effect on glycaemic control.

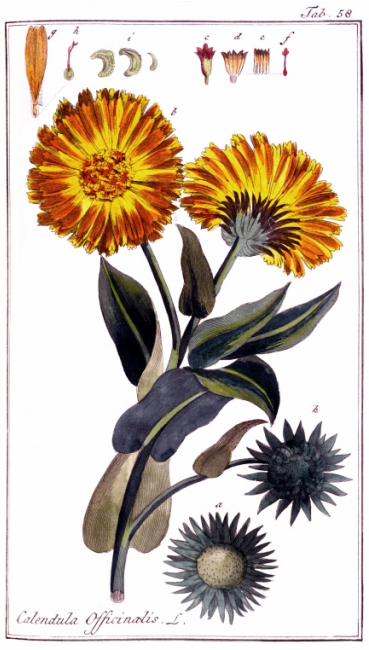
HYPERLIPIDAEMIA

Trials yielding both positive and negative results for supplemental chromium in hyperlipidaemia have been reported.

Currently, it is unclear what circumstances or conditions and type of subjects are most likely to respond to treatment, so in practice a treatment trial period is often used to establish usefulness in individual patients.

A placebo-controlled trial using chromium tripicolinate (equivalent to 200 μg chromium/day) for 42 days found a reduction in total cholesterol, LDL and apolipoprotein B (the major protein of the LDL fraction) with a slight increase in HDL and a significant increase in apolipoprotein A1 (the major protein of the HDL fraction) (Press et al 1990). Another RCT of 40 hypercholesterolaemic subjects found that chromium polynicotinate (equivalent to 200 μg elemental chromium) twice daily for 2 months decreased total (10%) cholesterol and LDL-cholesterol (14%) (Preuss et al 2000).

A prospective, double-blind, placebo-controlled crossover study was performed with 30 subjects with type 2 diabetes. Triglyceride levels were significantly reduced (17.4%) and HDL levels increased during the 2 months' chromium picolinate supplementation (Lee & Reasner 1994). This is further supported by other trials (Bahijri 2000).



Another double-blind, placebo-controlled randomised study of young, non-obese adults taking chromium nicotinate (equivalent to 220 μg elemental chromium) for 90 days found no statistically significant differences in lipid levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) at this dose (Wilson & Gondy 1995). Similar results were found in older, non-obese subjects taking 1000 μg chromium picolinate for 8 weeks (Amato et al 2000) suggesting that subjects without identified pre-existing hypercholesterolaemia or other conditions predisposing them to hypercholesterolaemia may not respond to treatment. However, a prospective, double-blind, placebo-controlled crossover study of mostly hispanic patients with type 2 diabetes also elicited disappointing results, finding that only triglyceride levels were significantly reduced (17.4%) (Lee & Reasner 1994).

OBESITY

As chromium has a role in maintaining carbohydrate and lipid metabolism, and potentiating insulin action, it has been suggested that chromium supplementation may have effects on body composition, including reducing fat mass and increasing lean body mass (Vincent 2003).

A meta-analysis of RCT concluded that chromium picolinate elicited a relatively small effect compared with placebo for reducing body weight (Pittler et al 2003). One study, however, did show promising results using 200 μg chromium bound to niacin three times daily (total 600 μg/day) with moderate exercise. At these high doses, while overall reduction in body weight was similar for both the chromium and placebo groups, total fat loss was more significant in the chromium group, suggesting a muscle sparing effect (Crawford et al 1999).

ATYPICAL DEPRESSION

A placebo-controlled double-blind study of chromium picolinate (600 μg/day) for 8 weeks was conducted in 15 patients with DSM-IV major depressive disorder, atypical type. Seven (70%) of 10 patients receiving chromium picolinate and none of the placebo group responded to treatment. Six subjects in the chromium group also experienced remission compared with none in the placebo group. However, a significant difference was not detected in the Hamilton Depression Scale at the end of treatment (Anon 2003, Davidson et al 2003).

OTHER USES

While controlled trials are yet to be conducted or are inconclusive in some cases, chromium is also used in the following conditions, based on a theoretical understanding of its pharmacological actions.

RESISTANCE TRAINING

Studies in female athletes have shown no effect on body composition or muscle strength following supplementation of 500 μg chromium picolinate daily during 6 weeks of resistance training (Livolsi et al 2001). In a clinical trial of older women a high-dose chromium picolinate supplement did not affect body composition, skeletal muscle size or maximal strength above that of resistance training alone (Campbell et al 2002). A meta-analysis of trials of dietary supplements for enhancing lean muscle mass and strength during resistance training did not support the use of chromium for this purpose (Nissen & Sharp 2002).

POLYCYSTIC OVARIAN SYNDROME

The relationship between PCOS and insulin resistance provides a theoretical basis for the use of chromium in this condition. A small study has found that chromium picolinate (200 μg/day) appears to improve glucose tolerance but not ovulatory frequency in women with polycystic ovary syndrome (Lucidi et al 2005). Larger studies are required to investigate the potential benefits of chromium supplementation in this population.

SYNDROME X

Syndrome X highlights the link between insulin resistance and lipid profiles. As a number of studies have proved promising in regard to both these factors, a theoretical basis exists for the use of chromium in this condition. Furthermore, the presence or absence of this syndrome may explain why studies have shown varying responses to treatment with chromium in the past and may provide direction for more consistent trial results in future studies.

PREVENTION OF MYOCARDIAL INFARCTION

In a population-based case–control study, toenail chromium concentration was inversely associated with the risk of a first myocardial infarction in men. Men with the highest levels of chromium were 35% less likely to have a heart attack than those with the lowest levels (Guallar et al 2005). Future studies are required to determine whether chromium supplementation may be beneficial for the prevention of cardiovascular incidents.

OSTEOPOROSIS

Effects on bone resorption, calcium excretion and collagen production suggest a role in the prevention of osteoporosis (Evans et al 1995, McCarty 1995); however, there are no controlled trials to determine clinical effectiveness.

DOSAGE RANGE

The ESADDI is 50–200 μg/day. The most common doses studied include 200, 400, 600 and 1000 μg daily. Doses in the upper range appear to produce more convincing trial results.

AUSTRALIAN ADEQUATE INTAKE

- Women: 25 μg/day
- Men: 35 μg/day

Chromium picolinate is the best absorbed form, although chromium nicotinate may have a better safety profile and the synergistic effects with nicotinic acid may have further benefits in some conditions, especially with regard to lipid profiles.

Clinical note — Does chromium picolinate cause cancer?

There has been some concern in the past over in vitro studies suggesting chromium picolinate exerts clastogenic effects in hamster ovary cells (Stearns et al 1995a, 2002) and possible DNA damage (Speetjens et al 1999). This has been refuted by a number of authors, suggesting the doses tested were several thousand times higher than equivalent human doses (McCarty 1997, Salmon 1996) and that chromium is relatively short lived so that the accumulated doses suggested by researchers (Stearns et al 1995a) were not feasible (Hepburn & Vincent 2003). It should also be noted that picolinic acid appears to be the source of the concern and other forms of chromium have not been implicated (Bagchi et al 2002, Stearns et al 1995b).

ADVERSE REACTIONS

It is important to differentiate between hexavalent chromium (Cr IV) and trivalent chromium (Cr III) when assessing toxicity. Cr IV is used in industry and is highly toxic, whereas Cr III is approved for use as a supplement and does not attract the same concerns. Recent in vitro studies suggest a possibility that Cr III may oxidise to Cr V, a potential carcinogen (Shrivastava et al 2005); however, this requires confirmation from in vivo studies.

Irritability and insomnia have been reported with chromium yeast supplementation (Schrauzer et al 1992).

A follow-up survey of the Anderson trial at 1 year found no side-effects for doses up to 1000 μg/day of chromium picolinate (Cheng et al 1999).

Of five anecdotal adverse reports attributed to chromium picolinate and reviewed by Lamson and Plaza (2002), only one reporting transient and vague symptoms was considered to be a possible adverse reaction (Huszonek 1993). Three could not be validated by the reviewers due to concurrent medications (Cerulli et al 1998, Martin & Fuller 1998, Wasser et al 1997), and another involved the inappropriate use of

potassium dichromate, a strong oxidising agent known to elicit reactions in a majority of people (Fowler 2000). A case report exists of toxic hepatitis and greatly elevated hepatic chromium levels (>10-fold normal) following 5 month ingestion of chromium polynicotinate in combination with vegetable extracts (Lanca et al 2002). Whether chromium supplementation was responsible for this incident is currently unclear.

NO ADVERSE EFFECTS ON IRON STATUS

As chromium competes with iron for binding to transferrin it has been suggested that high-dose chromium supplementation may adversely affect iron status. While some studies support this (Ani & Moshtaghie 1992), others show that serum iron concentrations and serum ferritin concentrations are unaffected by chromium picolinate supplementation (Campbell et al 1997). It would appear that iron does not use all available transferrin and therefore this situation is unlikely under normal conditions.

SIGNIFICANT INTERACTIONS

CORTICOSTEROIDS

Corticosteroids increase urinary losses of chromium, and chromium supplementation has been shown to aid in recovery from steroid-induced diabetes mellitus. Therefore a beneficial interaction may be possible (Kim et al 2002).

HYPOGLYCAEMIC MEDICINES

Chromium may reduce requirements for hypoglycaemic agents (Ravina & Slezack 1993, Ravina et al 1995). While a beneficial interaction is possible, this combination should be used with caution and drug requirements monitored and adjusted if necessary by a healthcare professional.

LIPID-LOWERING MEDICINES

Additive effects are theoretically possible as some clinical studies have indicated lipid-lowering effects. Observe patients taking this combination and monitor drug requirements.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to chromium.

PREGNANCY USE

Oral ingestion of doses typically found in the diet are likely to be safe. Taken under professional supervision, supplements are also likely to be safe and may be beneficial in the prevention and treatment of gestational diabetes (Jovanovic & Peterson 1996, Jovanovic et al 1999).

PRACTICE POINTS/PATIENT COUNSELLING

- Chromium is an essential trace mineral required for carbohydrate, lipid, protein and corticosteroid metabolism.
- Dietary intakes are generally below the minimum suggested safe and adequate levels, and factors such as high-sugar diets, corticosteroid use, excessive exercise, infection, physical trauma and psychological stress further increase the risk of deficiency.
- Chromium supplements are used in the treatment of type 2 diabetes, hypoglycaemia, gestational diabetes and hyperlipidaemia. However, inconsistent results have been obtained from clinical studies.
- It is also used in the treatment of obesity, atypical depression, syndrome X, PCOS and osteoporosis, and in resistance training.
- Supplemental forms used in trials include organic chromium complexes, such as chromium picolinate and chromium nicotinate, and inorganic salts such as chromium chloride.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Chromium is essential for health and wellbeing. It may also have beneficial effects in type 2 diabetes, gestational diabetes, hypoglycaemia and elevated cholesterol and triglyceride levels in some people, although scientific research has produced mixed results.

When will it start to work?

Effects in diabetes and elevated cholesterol or triglyceride levels require 8–12 weeks to establish.

Are there any safety issues?

Used under professional supervision, chromium supplements are considered safe.

REFERENCES

Althuis MD, Jordan NE, Ludington EA, Wittes JT. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. Am J Clin Nutr 76(1) (2002): 148-55.

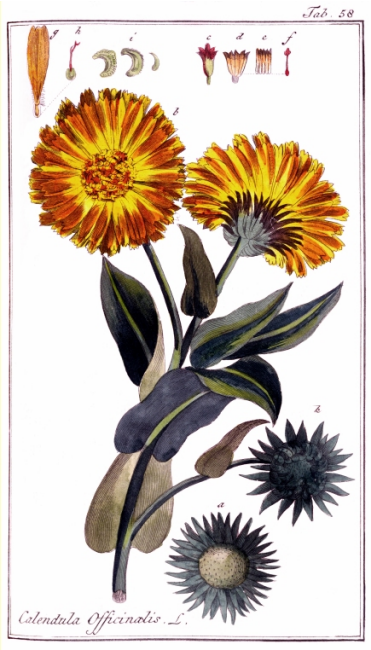
Amato P, Morales AJ, Yen SS. Effects of chromium picolinate supplementation on insulin sensitivity, serum lipids, and body composition in healthy, nonobese, older men and women. J Gerontol A Biol Sci Med Sci 55(5) (2000): M260-3.

Anderson RA. Chromium metabolism and its role in disease processes in man. Clin Physiol Biochem 4 (1986): 31-41 [cited in Salmon B. The truth about chromium. What science knows won't kill you. Let's Live Apr 1996].

Anderson RA. Nutritional factors influencing the glucose/insulin system: chromium. J Am Coll Nutr 16(5) (1997): 404-10.

Anderson RA, Kozlovsky AS. Chromium intake, absorption and excretion of subjects consuming self-selected diets. Am J Clin Nutr 41(6) (1985): 1177-83.

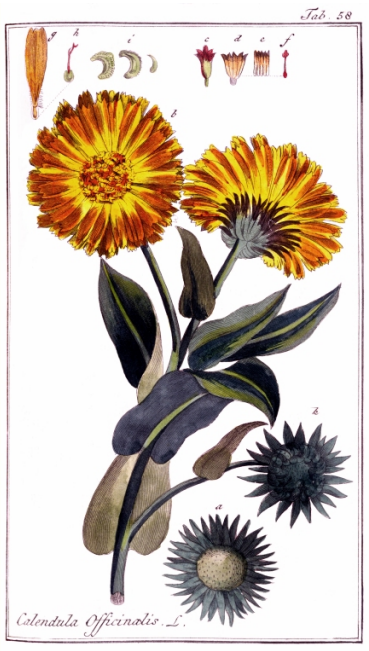
Anderson RA, Polansky MM, Bryden NA, Bhathena SJ, Canary JJ. Effects of supplemental chromium on patients with symptoms of reactive hypoglycemia. Metabolism 36(4) (1987): 351-5.
Anderson RA et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 46(11) (1997): 1786-91.
Ani M, Moshtaghie AA. The effect of chromium on parameters related to iron metabolism. Biol Trace Elem Res Jan-Mar; 32 (1992): 57-64.
Anon. Chromium, atypical depression. (Clinical Capsules – supplement improves symptoms) (Brief Article). Family Practice News 33 (2003): 23.
Attenburrow MJ, Odontiadis J, Murray BJ, Cowen PJ, Franklin M. Chromium treatment decreases the sensitivity of 5-HT2A receptors. Psychopharmacology (Berl) 159(4) (2002): 432-6 [Epub 2001, Nov 28].
Bagchi D, Stohs SJ, Downs BW, Bagchi M, Preuss HG. Cytotoxicity and oxidative mechanisms of different forms of chromium. Toxicology 180(1) (2002): 5-22.
Bahijri SM. Effect of chromium supplementation on glucose tolerance and lipid profile. Saudi Med J 21(1) (2000): 45-50.
Bahijri SM, Mufti AM. Beneficial effects of chromium in people with type 2 diabetes, and urinary chromium response to glucose load as a possible indicator of status. Biol Trace Elem Res 85(2) (2002): 97-109.
Bryson WG, Goodall CM. Differential toxicity and clearance kinetics of chromium III or IV in mice. Carcinogenesis 4 (1983): 1535-9.
Campbell WW, Beard JL, Joseph LJ, Davey SL, Evans WJ. Chromium picolinate supplementation and resistive training by older men: effects on iron-status and hematologic indexes. Am J Clin Nutr 66(4) (1997): 944-9.
Campbell WW, Joseph LJ, Anderson RA, Davey SL, Hinton J, Evans WJ. Effects of resistive training and chromium picolinate on body composition and skeletal muscle size in older women. Int J Sport Nutr Exerc Metab 12(2) (2002): 125-35.
Cerulli J et al. Chromium picolinate toxicity. Ann Pharmacother 32 (1998): 428-31.
Cheng N, Xixing Z, et al. Follow-up survey of people in China with type-II diabetes mellitus consuming supplemental chromium. J Trace Elem Exper Med 12 (1999): 55-60.
Cheng HH, Lai MH, Hou WC, Huang CL. Antioxidant effects of chromium supplementation with type 2 diabetes mellitus and euglycemic subjects. J Agric Food Chem 52(5) (2004): 1385-9.
Crawford V, Scheckenbach R, Preuss HG. Effects of niacin-bound chromium supplementation on body composition in overweight African-American women. Diabetes Obes Metab 1(6) (1999): 331-7.
Davidson JR, Abraham K, Connor KM, McLeod MN. Effectiveness of chromium in atypical depression: a placebo-controlled trial. Biol Psychiatry 53(3) (2003): 261-4.
Edmondson C. Can chromium be used for diabetes? Drug Utilization Rev 18(11) (2002): 5.
Evans GW, Swensen G, Walters K. Chromium picolinate decreases calcium excretion and increases dehydroepiandrosterone [DHEA] in postmenopausal women. FASEB J 9 (1995): A449.
Fowler JF Jr. Systemic contact dermatitis caused by oral chromium picolinate. Cutis 65 (2000): 116.
Frauchiger MT, Wenk C, Colombani PC. Effects of acute chromium supplementation on postprandial metabolism in healthy young men. J Am Coll Nutr 23(4) (2004): 351-7.
Ghosh D, Bhattacharya B, et al. Role of chromium supplementation in Indians with type 2 diabetes mellitus. J Nutr Biochem 13(11) (2002): 690-7.
Guallar E et al. Low toenail chromium concentration and increased risk of nonfatal myocardial infarction. Am J Epidemiol 162(2) (2005): 157-64.
Gunton JE et al. Chromium supplementation does not improve glucose tolerance, insulin sensitivity, or lipid profile: a randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance. Diabetes Care 28(3) (2005): 712-13.
Hahn CJ, Evans GW. Absorption of trace minerals in zinc-deficient rats. Am J Physiol 228 (1975): 1020-3.
Hepburn DD, Vincent JB. Tissue and subcellular distribution of chromium picolinate with time after entering the bloodstream. J Inorg Biochem 94(1-2) (2003): 86-93.
Huszonek J. Over-the-counter chromium picolinate. Am J Psychiatry 150 (1993): 1560-1.



Jain SK, Kannan K. Chromium chloride inhibits oxidative stress and TNF-alpha secretion caused by exposure to high glucose in cultured U937 monocytes. Biochem Biophys Res Commun 289(3) (2001): 687-91.
Jovanovic L, Peterson CM. Vitamin and mineral deficiencies which may predispose to glucose intolerance of pregnancy. J Am Coll Nutr 15(1) (1996): 14-20.
Jovanovic L, Gtierrez M, Peterson CM. Chromium supplementation for women with gestational Diabetes mellitus. J Trace Elem Exp Med 12 (1999): 91-7.
Kim DS, Kim TW, Park IK, Kang JS, Om AS. Effects of chromium picolinate supplementation on insulin sensitivity, serum lipids, and body weight in dexamethasone-treated rats. Metabolism 51(5) (2002): 589-94.
Kozlovsky AS, Moser PB, Reiser S, Anderson RA. Effects of diets high in simple sugars on urinary chromium losses. Metabolism 35(6) (1986): 515-18.
Lamson DW, Plaza SM. The safety and efficacy of high-dose chromium. Alt Med Rev 7(3) (2002): 218-35.
Lanca S, Alves A, Vieira AI, Barata J, de Freitas J, de Carvalho A. Chromium-induced toxic hepatitis. Eur J Int Med 13(8) (2002): 518-20.
Lee NA, Reasner CA. Beneficial effect of chromium supplementation on serum triglyceride levels in type 2 diabetes. Diabetes Care 17(12) (1994): 1449-52.
Livolsi JM, Adams GM, Laguna PL. The effect of chromium picolinate on muscular strength and body composition in women athletes. J Strength Cond Res 15(2) (2001): 161-6.
Lucidi RS, Thyer AC, Siler-Khodr TM, Holden AE, Schenken RS, Brzyski RG. The effect of chromium supplementation on insulin resistance and ovarian/menstrual cyclicity in women with polycystic ovary syndrome. Fertil Steril 84(Suppl 1) (2005): S427-8.
Martin WR, Fuller RE. Suspected chromium picolinate-induced rhabdomyolysis. Pharmacotherapy 18 (1998): 860-2.
McCarty MF. Enhancing central and peripheral insulin activity as a strategy for the treatment of endogenous depression: an adjuvant role for chromium picolinate? Med Hypotheses 43(4) (1994): 247-52.
McCarty MF. Anabolic effects of insulin on bone suggest a role for chromium picolinate in preservation of bone density. Med Hypotheses 45(3) (1995): 241-6.
McCarty MF. Subtoxic intracellular trivalent chromium is not mutagenic: implications for safety of chromium supplementation. Med Hypotheses 49(3) (1997): 263-9.
McLeod MN, Golden RN. Chromium treatment of depression. Int J Neuropsychopharmacol 3(4) (2000): 311-14.
Mertz W. Chromium research from a distance: from 1959 to 1980. J Am Coll Nutr 17(6) (1998): 544-7.
Micromedex. Chromium. Thomsen 2003. www.micromedex.com.
Mita Y, Ishihara K, Fukuchi Y, Fukuya Y, Yasumoto K. Supplementation with chromium picolinate recovers renal Cr concentration and improves carbohydrate metabolism and renal function in type 2 diabetic mice. Biol Trace Elem Res 105(1-3) (2005): 229-48.
Morris BW, MacNeil S, Hardisty CA, et al. Chromium homeostasis in patients with type II (NIDDM) diabetes. J Trace Elem Med Biol 13(1-2) (1999): 57-61.
Mozaffari MS, Patel C, Ballas C, Schaffer SW. Effects of chronic chromium picolinate treatment in uninephrectomized rat. Metabolism 54(9) (2005): 1243-9.
Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J Appl Physiol 94(2) (2003): 651-9 [Epub ahead of print 2002].
Offenbacher EG. Promotion of chromium absorption by asccorbic acid. Trace Elem Electrolytes 11 (1994): 178.
Pittler MH, Stevinson C, Ernst E. Chromium picolinate for reducing body weight: meta-analysis of randomized trials. Int J Obes Relat Metab Disord 27(4) (2003): 522-9.
Press RI, Geller J, Evans GW. The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. West J Med 152(1) (1990): 41-5.
Preuss HG et al Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. J Med 31(5-6) (2000): 227-46.

Rabinovitz H, Friedensohn A, Leibovitz A, Gabay G, Rocas C, Habot B. Effect of chromium supplementation on blood glucose and lipid levels in type 2 diabetes mellitus elderly patients. Int J Vitam Nutr Res 74(3) (2004): 178-82.
Ravina A, Slezack L. Chromium in the treatment of clinical diabetes mellitus. Harefuah 125(5-6) (1993): 142-45, 191 [in Hebrew].
Ravina A et al. Clinical use of the trace element chromium III in the treatment of diabetes mellitus. J Trace Elem Exp Med 8 (1995): 183-90.
Ravina A, Slezack L, Mirsky N, Bryden NA, Anderson RA. Reversal of corticosteroid-induced diabetes mellitus with supplemental chromium. Diabet Med 16(2) (1999): 164-7.
Ryan GJ, Wanko NS, Redman AR, Cook CB. Chromium as adjunctive treatment for type 2 diabetes. Ann Pharmacother 37(6) (2003): 876-85.
Salmon B. The truth about chromium: What science knows won't kill you. Let's Live Apr 1996.
Schrauzer GN, Shrestha KP & Arce MF: Somatopsychological effects of chromium supplementation. J Nutr Med 3(1) (1992): 43-8.
Schwarz K, Mertz W. Chromium(III) and the glucose tolerance factor. Arch Biochem Biophys 85 (1959): 292-5.
Shrivastava R, Upreti RK, Seth PK, Chaturvedi UC. Effects of chromium on the immune system. FEMS Immunol Med Microbiol 34(1) (2002): 1-7.
Shrivastava HY, Ravikumar T, Shanmugasundaram N, Babu M, Unni Nair B. Cytotoxicity studies of chromium(III) complexes on human dermal fibroblasts. Free Rad Biol Med 38(1) (2005): 58-69.
Speetjens JK, Collins RA, Vincent JB, Woski SA. The nutritional supplement chromium(III) tris(picolinate) cleaves DNA. Chem Res Toxicol 12(6) (1999): 483-7.
Stearns DM, Belbruno JJ, Wetterhahn KE. A prediction of chromium (III) accumulation in humans from chromium dietary supplements. FASEB J 9(15) (1995a): 1650-7.
Stearns DM, Wise JP Sr, Patierno SR, Wetterhahn KE. Chromium(III) picolinate produces chromosome damage in Chinese hamster ovary cells. FASEB J 9(15) (1995b): 1643-8.
Stearns DM, Silveira SM, Wolf KK, Luke AM. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. Mutat Res 513(1-2) (2002): 135-42.
Thomas VL, Gropper SS. Effect of chromium nicotinic acid supplementation on selected cardiovascular disease risk factors. Biol Trace Elem Res 55(3) (1996): 297-305.
Urberg M, Zemel MB. Evidence for synergism between chromium and nicotinic acid in the control of glucose tolerance in elderly humans. Metabolism 36(9) (1987): 896-9.
Verhage AH, Cheong WK, Jeejeebhoy KN. Neurologic symptoms due to possible chromium deficiency in long-term parenteral nutrition that closely mimic metronidazole-induced syndromes. J Parenter Enteral Nutr 20(2) (1996): 123-7.
Vincent J. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. Sports Med 33(3) (2003): 213-30.
Vincent JB. Recent advances in the nutritional biochemistry of trivalent chromium. Proc Nutr Soc 63(1) (2004): 41-7.
Vrtovec M, Vrtovec B, Briski A, Kocijancic A, Anderson RA, Radovancevic B. Chromium supplementation shortens QTc interval duration in patients with type 2 diabetes mellitus. Am Heart J 149(4) (2005): 632-6.
Wasser WG, Feldman NS, Agnati VD. Chronic renal failure after ingestion of over-the-counter chromium picolinate. Ann Intern Med 126 (1997): 410.
Wilson BE, Gondy A. Effects of chromium supplementation on fasting insulin levels and lipid parameters in healthy, non-obese young subjects. Diabetes Res Clin Pract 28(3) (1995): 179-84.

Cinnamon



Historical note Cinnamon has been used since ancient times for a variety of uses and was considered a precious commodity. In ancient Egypt, it was used as a flavouring for beverages, in combination with other spices for embalming, and as a medicinal agent. Ancient Chinese herbals mention it as a medicinal treatment as early as 2700 BC (Castleman 1991). In medieval Europe, cinnamon was a common ingredient in cooking, often used together with ginger. Due to the high demand for cinnamon, discovering lands where it grew was a primary motive for a number of explorers' enterprises in the 15th and 16th centuries. Today, two main types of cinnamon are cultivated, *Cinnamomum verum*, also known as Ceylon cinnamon, and *Cinnamomum cassia*, also known as Chinese cinnamon.

OTHER NAMES

Cinnamomum verum: cannelle de ceylan, Ceylon celonzimi cinnamon, Ceylon cinnamon, cinnamon bark, cortex cinnamomi ceylanici, dalchini, ecorce de cannelier de Ceylan, echter, gujerati-dalchini, kannel, kuei-pi, kurundu, kulit kayumanis, ob choei, tamalpatra, wild cinnamon

Cinnamomum cassia Blume: cassia, Chinese cinnamon, dalchini, guipi, kannan keihi, keishi, lavanga-pattai, lurundu, macrophyllos cassia bark tree, rou gui, Saigon cinnamon, saleekha, taj, toko keihi, Viet Nam cinnamon

BOTANICAL NAME/FAMILY

Cinnamomum verum J.S. Presl (also known as *C. zeylanicum* Nees) and *C. cassia* Blume (family Lauraceae)

PLANT PARTS USED

Dried inner bark of the shoots grown on cut stock of *Cinnamomum verum* or of the trunk bark, freed from the underlying parenchyma; outer cork of *C. cassia* Blume.

CHEMICAL COMPONENTS

Both forms of cinnamon contain an essential oil that consists primarily of cinnamaldehyde (up to 80% in *C. verum* and 90% in *C. cassia*) and differ primarily in their eugenol and coumarin content. The volatile oil from *C. verum* contains 10% eugenol whereas the oil from *C cassia* contains only trace amounts and *C. cassia* contains coumarin, which is not found substantially in *C. verum*. The bark of *C. verum*

contains caryophyllene, cinnamyl acetate and linalool whereas the bark of *C. cassia* contains catechin and 1,8 cineole.

MAIN ACTIONS

The cinnamaldehyde constituent in cinnamon is attributed with producing most of the herb's biological effects. This component is found in large amounts in both forms of cinnamon. More recently, several other constituents have also been tested in isolation and found to exert significant pharmacological effects.

ANTIBACTERIAL AND FUNGICIDAL EFFECTS

Several in vitro studies have identified broad-spectrum antibacterial and fungicidal effects for both forms of cinnamon. This has been chiefly attributed to cinnamaldehyde although other constituents such as eugenol, carophyllene and 1,8 cineole also exhibit antimicrobial properties.

Cinnamomum verum demonstrated activity against a wide range of bacteria and fungi including *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisia*, *Candida albicans*, *L. monocytogenes* and *Salmonella enterica* (De et al 1999, Friedman et al 2002, Matan et al 2006, Simic et al 2004, Tampieri et al 2005).

Cinnamomum cassia extracts significantly inhibited *Helicobacter pylori* in vitro and produced zones of inhibition greater than or equal to commonly used antibiotics (Tabak et al 1999). The essential oil of *C. cassia* also exhibited strong antifungal properties in vitro (Giordani et al 2006). When tested with amphotericin, a reduced amount of drug was required for adequate antifungal effects.

Antibacterial activity for the oil has also been demonstrated against antibiotic-resistant *E. coli* and *Staphylococcus aureus* (Friedman et al 2004).

Fungi in bakery products Antifungal activity against the more common fungi causing spoilage of bakery products, *Eurotium amstelodami*, *E. herbariorum*, *E. repens*, *E. rubrum*, *Aspergillus flavus*, *A. niger* and *Penicillium corylophilum*, was demonstrated for cinnamon oil in vitro (Guynot et al 2003).

Respiratory tract pathogens An in vitro study of the antibacterial activity of essential oils and their major components against the major bacteria causing respiratory tract infection indicated that cinnamon bark oil was effective against *Haemophilus influenzae*, *Streptococcus pneumoniae* and *S. pyogenes* (Inouye et al 2001).

Oral pathogens According to in vitro research, cinnamon bark oil is an effective inhibitor of bacteria causing dental caries and periodontal disease (Saeki et al 1989).

CARMINATIVE

The essential oil exhibits carminative activity and decreases smooth muscle contractions in guinea-pig trachea and ileum, and in dog ileum, colon and stomach (WHO 2004). The oil has also demonstrated antifoaming activity in a foam generator model for flatulence (ESCOP 2003). The active antispasmodic constituent is considered to be cinnamaldehyde.

ENHANCED INSULIN SENSITIVITY

Water soluble compounds extracted from *C. cassia* potentiate insulin activity, as measured by glucose oxidation in the rat epididymal fat cell assay. The most active compound, methylhydroxy chalcone polymer (MHCP), increased glucose metabolism approximately 20-fold and was an effective mimetic of insulin according to an in vitro study. When combined with insulin, the responses were greater than additive, indicating synergism between the two compounds (Jarvill-Taylor et al 2001). According to Anderson, MHCP is actually a water-soluble polyphenolic type-A polymer that increases insulin sensitivity by activating the key enzymes that stimulate insulin receptors, while inhibiting the enzymes that deactivate them. More specifically, extracts of cinnamon activate insulin receptor kinase and inhibit dephosphorylation of the insulin receptor, leading to maximal phosphorylation of the insulin receptor.

The United States Agricultural Research Service has filed a patent application on the active substances.

OTHER ACTIONS

Antioxidant and anti-inflammatory activity for cinnamon bark oil has been demonstrated in vitro and for the dry ethanolic extract in vivo (ESCOP 2003, Jarvill-Taylor et al 2001, Lee et al 2003, Mathew & Abraham 2006). Antinociceptive activity has been demonstrated when administered orally to mice in the hot plate and acetic acid writhing induced tests.

Cinnamomum cassia also possesses antipyretic activity (Kurokawa et al 1998) and reduced the occurrence of ulcers in rats in a dose-dependent manner in a study that administered an aqueous extract (Tanaka et al 1989).

Besides antispasmodic and broad-spectrum antibacterial and fungicidal activities, cinnamaldehyde also exhibits antitumor effects (Kwon et al 1998) and cytotoxicity (Moon & Pack 1983).

CLINICAL USE

Cinnamon has not been significantly studied in controlled trials, so evidence is mainly derived from in vitro and in vivo research and traditional usage.

DYSPEPSIA AND RELATED SYMPTOMS

Cinnamon bark oil and crushed cinnamon bark is used in the treatment of dyspeptic conditions, such as mild spastic conditions of the gastrointestinal tract, fullness and flatulence, loss of appetite and diarrhoea. Although controlled studies are unavailable, evidence of antispasmodic and antifoaming activity in animal models and a long tradition of use provide some support for its use in these indications.

Cinnamon bark and Chinese cinnamon are approved by the German Commission E for the treatment of loss of appetite and dyspeptic complaints such as mild gastrointestinal spasms, bloating, and flatulence (Blumenthal et al 1998).

Helicobacter pylori infection According to a placebo-controlled study of 15 volunteers with documented *H. pylori* infection, an ethanolic extract of cinnamon was ineffective at eradicating the infection when used at a dose of 40 mg twice daily for 4 weeks (Nir et al 2000). Considering this is an extremely low dose, further investigation is required using therapeutic doses in order to adequately test its effectiveness for this indication.

DIABETES

A randomised, placebo-controlled study of type 2 diabetes demonstrated that cinnamon exerts clinically significant glucose- and lipid-lowering effects (Khan et al 2003). The study involved 60 people who were divided into six groups. Groups 1–3 consumed 1, 3 or 6 g of cinnamon daily whereas groups 4–6 were given the equivalent number of placebo capsules and acted as controls. The volunteers were not using insulin therapy and had a fasting blood glucose reading between 140 and 400 mg/dL. After 40 days of treatment, all three doses of cinnamon reduced mean fasting serum glucose by18% to 29%, triglycerides by 23% to 30%, LDL-cholesterol by 7% to 27%, and total cholesterol by 12% to 26%. No significant changes were observed in the placebo groups. The effect on glucose and lipid levels was sustained 20 days after treatment had ceased, suggesting that cinnamon would not need to be consumed every day. The cinnamon used was *C. cassia*, which was finely ground and put into capsules.

More recently, a 6-week placebo-controlled study was conducted in 25 postmenopausal women with type 2 diabetes and produced different results (Vanschoonbeek et al 2006). Researchers assessed the effects of cinnamon supplementation (*C. cassia*, 1.5 g/day) on fasting blood glucose, insulin, and glycosylated haemoglobin concentrations, indices of oral glucose tolerance and whole-body insulin sensitivity, and fasting blood lipid profiles. During the trial, volunteers maintained their normal dietary and physical activities and continued all medication. After 6 weeks, cinnamon supplementation had no significant effect on fasting plasma

glucose or insulin concentrations, whole-body oral glucose tolerance, or blood lipid profiles in this sample.

It is not clear why positive results should be observed in the first study and not in the second. The dose of cinnamon used was within the range expected to be active and the same form was used. Vanschoonbeek et al report that baseline values of fasting glucose and triglycerides were different for subjects participating in the two studies and discrepant results may be accounted for by this difference and lack of nutritional standardisation in the study by Khan et al.

Gestational diabetes A randomised, double-blind placebo controlled study of 51 women with gestational diabetes found that 6 weeks of treatment with 1 g of cinnamon daily produced a trend towards decreased insulin requirements (53.85% cinnamon vs 44% placebo, $P = 0.58$); however, this did not reach significance (Graham et al 2005). The cinnamon used was *C. cassia*. The researchers suggested that a longer duration of treatment may be required to produce better results.

OTHER USES

TRADITIONAL USES

Cinnamon has been traditionally used by ancient healers from many backgrounds for stomach cramps, flatulence, nausea, vomiting, diarrhoea, infant colic, common infections and also female reproductive problems such as dysmenorrhoea, menorrhagia, lactation, and pain in childbirth. It has also been used as an ingredient in topical preparations for pain and inflammation. Cinnamon is often used in combination with other herbs and spices for most of these indications. In TCM it is considered to warm the kidneys and fortify yang, so is used for impotence among other indications.

NATURAL FOOD PRESERVATIVE

Spices such as cinnamon have been used traditionally for the preservation of food products. The considerable antimicrobial, fungicidal and antioxidant properties of cinnamon provide a theoretical basis for its use.

DOSAGE RANGE

GENERAL GUIDE

- Dried bark (crushed cinnamon): 1.5–4 g taken up to four times daily.
- Fluid extract 1:1: 0.5–1.0 mL taken up to three times daily.
- Tea: ½ to ¾ teaspoon of powdered cinnamon in a cup of boiling water taken 2–3 times daily with meals.
- Essential oil: 0.05–0.2 mL diluted in carrier oil.

ACCORDING TO CLINICAL STUDIES

- Diabetes: 1–6 g daily of powdered cinnamon (*C. cassia*) administered in capsules.

TOXICITY

The oral LD_{50} for cinnamon bark oils in rats is 4.16 g/kg and 3.4 mL/kg body weight.

ADVERSE REACTIONS

When the powdered herb is ingested orally, it is generally well tolerated; however, when cinnamon oil is applied topically, allergic reactions are possible as cinnamaldehyde may cause allergic contact dermatitis (Cheung et al 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are based on evidence of activity and are largely theoretical and speculative.

HYPOGLYCAEMIC AGENTS

Oral ingestion of cinnamon capsules may reduce blood glucose levels, therefore theoretically, an additive effect is possible with concurrent use — observe; potential beneficial interaction under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Cinnamon is contraindicated in people with an allergy to cinnamon or Peru balsam, in cases of fever of unknown origin, active stomach or duodenal ulcers (WHO 2004).

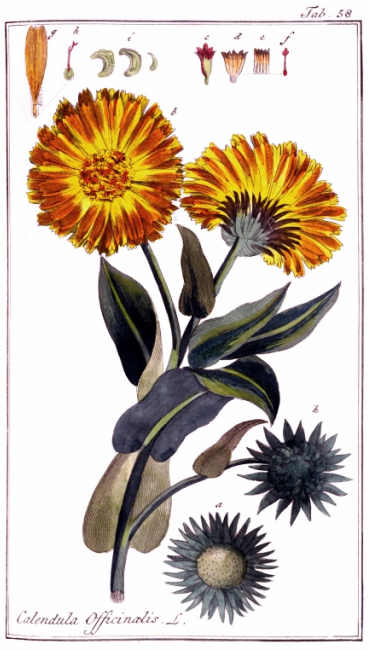
PREGNANCY USE

Cinnamomum cassia or *C. zeylanicum/verum* should not be used in pregnancy; however, usual dietary intakes are likely to be safe. Currently, evidence of teratogenicity from animal studies is contradictory.

PRACTICE POINTS/PATIENT COUNSELLING

- Cinnamon has been used since ancient times as a flavouring and medicinal agent.
- It is a natural food preservative with antioxidant and wide ranging antimicrobial and antifungal properties.
- It has been used traditionally to treat dyspepsia, nausea, flatulence, poor appetite, stomach cramps and diarrhoea. Some evidence suggests it may be effective for some of these indications.
- Ground cinnamon (*C. cassia*) may reduce blood glucose and lipid levels and be useful for people with type 2 diabetes; however, this has yet to be clearly established because inconsistent results have been obtained in controlled studies.

- Cinnamon oil can cause allergic contact dermatitis when used topically and should be avoided by people with allergies to cinnamon or Peru balsam, pregnancy or those with active gastrointestinal ulcers.



ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Cinnamon is a natural food preservative with wide ranging antimicrobial and antifungal properties. It may improve digestion and ease symptoms of dyspepsia, flatulence and nausea. Its effect on blood glucose, total cholesterol and triglyceride levels remains to be established as inconsistent test results have been reported.

When will it start to work?

The effects on digestion should start rapidly; however, effects on blood glucose and lipid levels may take 1 month or more.

Are there any safety issues?

Cinnamon oil can cause allergic contact dermatitis when used topically and should be avoided by people with allergies to cinnamon or Peru balsam, pregnant women or those with active gastrointestinal ulcers.

REFERENCES

Anderson RA et al. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem 52 (2004): 65-70.

Blumenthal M et al. The Complete German Commission E monographs: Therapeutic Guide to Herbal Medicines. Austin, TX: The American Botanical Council, 1998.

Castleman M. Cinnamon. In: The Healing Herbs. Melbourne: Schwartz Books, 1991, 115-18.

Cheung C, Hotchkiss SA, Pease CK. Cinnamic compound metabolism in human skin and the role metabolism may play in determining relative sensitisation potency. J Dermatol Sci 31(1) (2003): 9-19.

De M, Krishna DA, Banerjee AB. Antimicrobial screening of some Indian spices. Phytother Res 13(7) (1999): 616-18.

European Scientific Co-operative On Phytomedicine (ESCOP). Cinnamomi cortex. In: ESCOP Monographs, 2nd edn. Stuttgart: Thieme, 2003, 92-7

Friedman M, Henika PR, Mandrell RE. Bactericidal activities of plant essential oils and some of their isolated constituents against Campylobacter jejuni, Escherichia coli, Listeria monocytogenes, and Salmonella enterica. J Food Prot 65(10) (2002): 1545-60.

Friedman M, Buick R, Elliott CT. Antibacterial activities of naturally occurring compounds against antibiotic-resistant Bacillus cereus vegetative cells and spores, Escherichia coli, and Staphylococcus aureus. J Food Prot 67(8) (2004): 1774-8.

Giordani R et al. Potentiation of antifungal activity of amphotericin B by essential oil from Cinnamomum cassia. Phytother Res 20(1) (2006): 58-61.

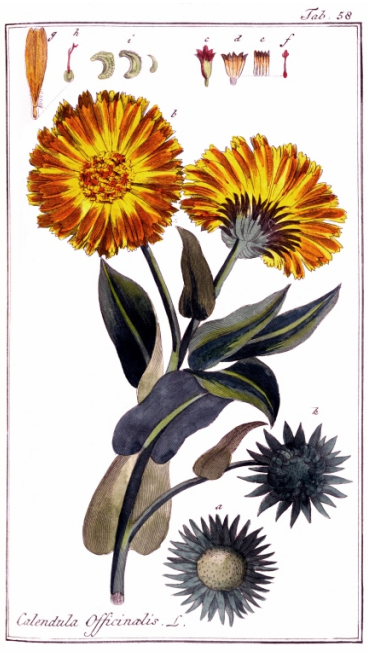
Graham F et al. Cinnamon for glycemic control in gestational diabetes: A randomized double-blind placebo controlled pilot study. Am J Obst Gynecol 193(6) (Suppl 1) (2005): S91.

Guynot ME, Ramos AJ, Seto L, Purroy P, Sanchis V, Marin S. Antifungal activity of volatile compounds generated by essential oils against fungi commonly causing deterioration of bakery products. J Appl Microbiol 94(5) (2003): 893-9.

Inouye S, Yamaguchi H, Takizawa T. Screening of the antibacterial effects of a variety of essential oils on respiratory tract pathogens, using a modified dilution assay method. J Infect Chemother 7(4) (2001): 251-4.

Jarvill-Taylor KJ, Anderson RA, Graves DJ. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll Nutr 20(4) (2001): 327-36.
Khan A et al. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care 26(12) (2003): 3215-18.
Kurokawa M et al. Antipyretic activity of cinnamyl derivatives and related compounds in influenza virus-infected mice. Eur J Pharmacol 348(1) (1998): 45-51.
Kwon BM et al. Synthesis and in vitro cytotoxicity of cinnamaldehydes to human solid tumor cells. Arch Pharm Res 21(2) (1998): 147-52.
Lee SE et al. Screening of medicinal plant extracts for antioxidant activity. Life Sci 73(2) (2003): 167-79.
Matan N et al. Antimicrobial activity of cinnamon and clove oils under modified atmosphere conditions. Int J Food Microbiol 107(2) (2006): 180-5.
Mathew S, Abraham TE. Studies on the antioxidant activities of cinnamon (Cinnamomum verum) bark extracts, through various in vitro models. Food Chem 94(4) (2006): 520-8.
Moon KH, Pack MY. Cytotoxicity of cinnamic aldehyde on leukemia L1210 cells. Drug Chem Toxicol 6(6) (1983): 521-35.
Nir Y et al. Controlled trial of the effect of cinnamon extract on Helicobacter pylori. Helicobacter 5(2) (2000): 94-7.
Saeki Y et al. Antimicrobial action of natural substances on oral bacteria. Bull Tokyo Dent Coll 30(3) (1989): 129-35.
Simic A et al. The chemical composition of some Lauraceae essential oils and their antifungal activities. Phytother Res 18(9) (2004): 713-17.
Tabak M, Armon R, Neeman I. Cinnamon extracts' inhibitory effect on Helicobacter pylori. J Ethnopharmacol 67(3) (1999): 269-77.
Tampieri MP et al. The inhibition of Candida albicans by selected essential oils and their major components. Mycopathologia 159(3) (2005): 339-45.
Tanaka S et al. Antiulcerogenic compounds isolated from Chinese cinnamon. Planta Med 55(3) (1989): 245-8.
Vanschoonbeek K et al. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J Nutr 136(4) (2006): 977-80.
World Health Organization. Cortex Cinnamomi. In: WHO Monographs on Selected Medicinal Plants. Geneva: WHO, 2004.

Citrus aurantium



Historical note The root word for orange is the Arabic, *narandj* (Sellar 1992). The orange is a symbol of innocence and fertility. Some scholars believe the 'golden apple' Paris presented to Venus was actually an orange. In return, Venus bestowed Helen on Paris as a reward for selecting her in a beauty contest, which eventually caused the Trojan War. The tree is indigenous to eastern Africa, Arabia and Syria and it is believed that the crusaders may have introduced the orange to Europe when they returned from the crusades. Unripe dried fruits and the fruit peel are incorporated into various products, including foods such as marmalade, alcoholic beverages such as Curacao and medicinal products. The essential oil is used in perfumes, cosmetics and aromatherapy (Leung & Foster 1996), and also used as food flavouring and to disguise the unpleasant taste of medicines. Orange blossom water has been used for centuries in Mediterranean countries to flavour cakes and beverages (Jeannot et al 2005).

COMMON NAME
Orange

OTHER NAMES
Bitter orange, *Citrus sinensis*, green orange, Seville orange, Zhi Shi

BOTANICIAL NAME/FAMILY
Citrus aurantium var. *dulcis* (sweet orange) and *Citrus aurantium* var. *amara* (bitter orange) (family Rutaceae).

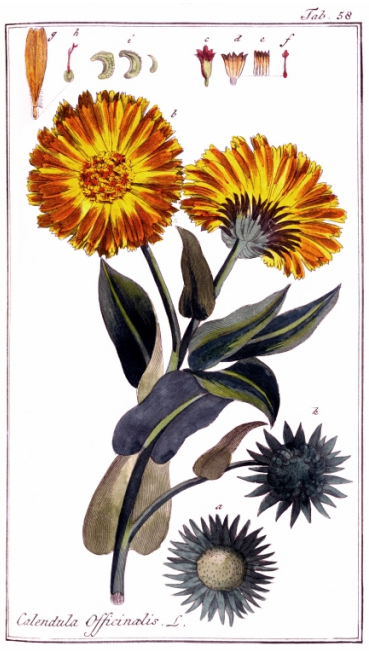
PLANT PARTS USED
Fruit, dried outer peel of the ripe fruit, and essential oils and floral water (orange blossom water).

Clinical note — Three different essential oils
C. aurantium var. *dulcis* (sweet orange) and *C. aurantium* var. *amara* (bitter orange) are obtained from the peel and are usually expressed oils.

Neroli essential oil is obtained from the flowers of *C. aurantium* var. *amara* by steam distillation and very occasionally enfleurage and is known as Neroli Bigarade, which is said to be the best Neroli essential oil available. Neroli essential oil obtained from *C. aurantium* var. *dulcis* is known as Neroli of Portugal.

Petitgrain is obtained from the leaves of *C. aurantium* var. *amara* by steam distillation.

Each of these oils has a different chemical profile and therefore different uses. Distilled essential oils are used more in food flavourings and expressed essential oils in aromatherapy and perfumes because of their stronger fragrance (Tisserand & Balacs 1995). This monograph concentrates on expressed sweet orange and bitter orange essential oils.



CHEMICAL COMPONENTS

BITTER ORANGE PEEL

Essential oil (0.2–0.5%), monoterpenes linalyl acetate, pinene, limonene, linalool, nerol, geraniol, bitter substances, flavonoids and methyl anthranilate, the alkaloid synephrine and n-methyltyramine (Blumenthal et al 2000, Pellati et al 2002). Synephrine is structurally similar to epinephrine.

ESSENTIAL OILS

Essential oil species	Major components	Minor components
Citrus aurantium var. *dulcis*	Limonene 89%	Linalool
	Myrcene 1.7%	Neral
	Beta-bisabolene 1.29%	Geranial, neral, citronellal, sabinene, myracene
Citrus aurantium var. *amara*	*d*-limonene 89–96%	Nerol, geraniol, linalyl acetate
		Bergaptene 0.069–0.073%
		Furanocoumarins (not in steam distilled oils)

Price & Price 1995, Sellar 1992

Terpeneless/deterpenated or concentrated orange oil is sometimes available. Although the terpenes are removed, terpeneless orange oils retain all their other chemical components, including the furanocoumarins, which are in larger amounts, and this increases their phototoxic potential. Therefore, the safe concentration in blends containing terpeneless oils is less than 0.2% (Tisserand & Balacs 1995).

Methyl anthranilate is an important compound that may give orange flowers their aroma (Jeannot et al 2005).

The composition of orange essential oils is described by the International Standards Organisation (ISO) under the following standard numbers 1340: 2005

9844: 1991	bitter orange *C. aurantium* var. *amara*
8901: 2003	*C. aurantium* (petitgrain)
3517: 2002	*C. aurantium* var. *amara* (neroli)
4735: 2002	Oils of citrus.

MAIN ACTIONS

SYMPATHOMIMETIC

Considering *C. aurantium* contains biologically active adrenergic amines, it may exert sympathomimetic activity.

An in vivo study found no significant effects on blood pressure when two concentrations of *C. aurantum* tincture (standardised to 4% synephrine or 6% synephrine) were administered (Calapai et al 1999). However, analysis of myocardial electrical activity showed ECG alterations such as ventricular arrhythmias with enlarged QRS complex. The effect was present after 5 days of treatment and became significant at day 10 and was still evident after 15 days. These effects may be explained by the positive chronotropic activity of synephrine, which has been observed on isolated atria from reserpinised guinea pigs due to beta-$_1$-adrenoceptor agonist activity, but could also be due to other constituents.

APPETITE SUPPRESSANT

Synephrine produces effects on human metabolism, which could be useful for reducing fat mass in obese humans because it stimulates lipolysis, raises metabolic rate and fat oxidation through increased thermogenesis (Pellati et al 2002). A controlled in vivo study of *C. aurantium* fruit hydro-alcoholic extracts standardised to synephrine 4% (Ci.au. 4%) and 6% (Ci.au. 6%) found repeated administration of the extract significantly and dose-dependently reduced food intake and body weight gain (Calapai et al 1999).

ANTIBACTERIAL

Seville orange has strong in vitro antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (Melendez & Capriles 2006).

ANTIVIRAL

The fruit of *C. aurantium* has a potent inhibitory activity on rotavirus infection (Kim et al 2000). The active components are neohesperidin and hesperidin.

ANTIFUNGAL

Bitter orange essential oil has been shown to be effective in treating resistant fungal skin conditions (Ramadan et al 1996).

DIGESTIVE EFFECTS

The essential oil of *C. aurantium* var. *dulcis* is believed to aid digestion by stimulating the flow of gastric juice and has antispasmodic and carminative actions. The essential oil of *C. aurantium* var. *amara* is considered to be a liver stimulant, reduces gastric spasm and relieves symptoms of indigestion (Price & Price 1995, Wichtl & Bisset 1994). It is also thought to lower cholesterol.

AROMATHERAPY EFFECTS

The essential oil of *C. aurantium* var. *dulcis* is considered to convey warmth and happiness and improve mood (Battaglia 2003), reduce stress, aid sleep by reducing stress (Miyake et al 1991), and aid concentration (Baron & Thomley 1994). The essential oil of *Citrus aurantium* var. *amara* is considered to have a calming effect (Price & Price 1995, Wichtl & Bisset 1994).

OTHER ACTIONS

ANTIOXIDANT

Natural antioxidants obtained from 'citrus oils' have been shown to inhibit oxidation of LDL-cholesterol in in vitro studies (Takahashi et al 2003), possibly due to the gamma-terpinene content. Terpinolene and alpha-terpinene also showed antioxidant properties. Takahashi et al suggested gamma-terpinene could be added to foods and beverages to prevent oxidation. Sellar (1992) suggested sweet orange oil aids the absorption of vitamin C.

CYP3A4 INHIBITION

Bergamottin and 6',7'-dihydroxybergamottin found in Seville oranges inactivate intestinal CYP3A4, as demonstrated clinically. Other furanocoumarins, including bergapten, could also be involved (Malhotra et al 2001).

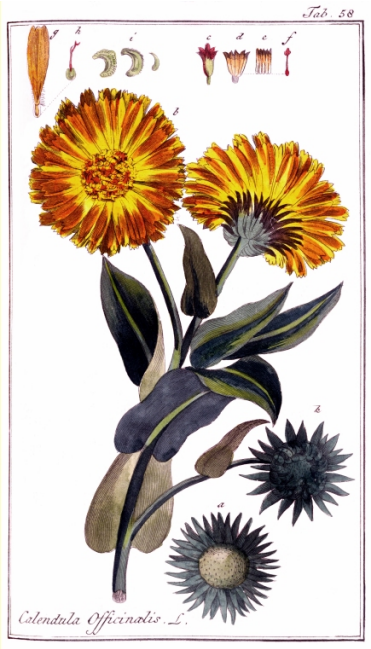
CLINICAL USE

HEARTBURN AND DYSPEPTIC SYMPTOMS

The primary indication for bitter orange tincture or extract is heartburn (Blumenthal et al 2000). The dried peel is officially listed in the British Pharmacopoeia (1983) as a bitter tonic and empirical evidence suggests it acts as a carminative agent. Commission E approves the use of cut peel for loss of appetite and dyspeptic symptoms (Blumenthal et al 2000).

WEIGHT LOSS

Citrus aurantium extract is growing increasingly popular as an ingredient in weight loss products, substituting for the banned ephedra in the United States. The main ingredient, synephrine, produces effects on human metabolism that could be useful



for reducing fat mass in obese humans because it stimulates lipolysis, rises metabolic rate and fat oxidation through increased thermogenesis.

Currently, only two small clinical studies have been published and both suggest possible weight reduction (Preuss et al 2002); more research is required to confirm effectiveness and safety.

SUPERFICIAL DERMATOPHYTE INFECTION

The oil of bitter orange (*C. aurantium* var. *amara*) was an effective topical treatment in treatment-resistant superficial dermatophyte infection according to a study of 60 patients (Ramadan et al 1996). Patients with tinea corporis, cruris or pedis were treated with one of three treatments based on oil of bitter orange and cure was assessed by clinical and mycological examinations. One group used a 25% emulsion of oil three times daily, the second group used 20% oil in alcohol three times daily and the third group applied pure oil once daily. Treatment with the 25% oil emulsion was most successful and resulted in 80% of patients being cured after 1–2 weeks and 20% in 2–3 weeks. The group using the 20% oil in alcohol preparation also experienced substantial cure rates, but it took longer to achieve. Application of the undiluted oil successfully cured 33% of subjects within the first week, 60% within 1–2 weeks and 7% in 2–3 weeks. The only side-effect reported was mild irritation when the undiluted oil was used.

AROMATHERAPY

Citrus aurantium var. dulcis The essential oil is used to convey warmth and happiness and improve mood (Battaglia 2003), reduce stress, and promote sleep (Miake et al 1991), and aid concentration (Baron & Thomley 1994). It is traditionally known as 'the oil of communication and happiness'. It is also used to improve digestion and as a carminative to relieve gastric cramping and discomfort.

Citrus aurantium var. amara The essential oil is used to reduce anxiety, muscle tension and promote relaxation. It is used in cosmetics to repair broken capillaries, stimulate cell regeneration and to manage acne-prone skin.

OTHER USES

Distilled orange oil is often added to foods and beverages to enhance their flavour and to medicines to reduce the unpleasant taste.

Orange blossom water or hydrosol contains small proportions of essential oils and is used on the skin as an astringent and orally as a gastrointestinal carminative (Jeannot et al 2005). There are no terpenes in orange hydrosol, so the likelihood of causing skin irritation is significantly reduced. It is also used topically as an astringent

for acne-prone skin and to calm babies and induce sleep (Bellakhdar 1997, Hmamouchi 1999).

The essential oil of *C. aurantium* var. *amara* is used as an ingredient in perfumes.

DOSAGE RANGE

BITTER ORANGE PEEL PRODUCTS

- General dose information: 4–6 g daily of cut peel for teas or other galenical preparations used for oral administration.
- Infusion: 2 g of cut peel in 150 mL boiling water taken three times daily.
- Weight loss: bitter orange 975 mg (used with caffeine 528 mg and St John's wort 900 mg in a small double-blind study).

ESSENTIAL OILS

- Oral LD_{50} dose: 5 g/kg (rat)
- Dermal LD_{50} dose: >5 g/kg (rabbit) (Citrus and Allied Essences 2004).
- Oral LD_{50} dose for a 15 kg child: 83 g/kg
- Oral LD_{50} dose for a 70 kg adult: 389 g/kg
- Oral doses in teas and other preparations: 4–6 g/day or 2 g in 150 mL of boiled water as an infusion (American Botanical Council 1999).
  The inhalation LD_{50} dose has not been established.
- Topical application dose of bitter orange to skin exposed to UV rays: 1.4% of a blend.

ADVERSE REACTIONS

SKIN SENSITISATION

Both *C. sinesis* and *C. amara* are mild skin irritants, but are considered to be low risk. Skin reactions are more likely if undiluted oils are applied directly to the skin or when used on broken or inflamed skin or when other skin pathology is present. Skin reactions are idiosyncratic and can be difficult to predict. Skin sensitisation due to topically applied orange oil is largely due to the components citral and cinnamic acid and is dose-dependent (Tisserand & Balacs 1995).

PHOTOSENSITISATION

Expressed *C. sinensis* essential oil is not normally phototoxic (Tisserand & Balacs 1995), whereas *C. amara* oil is moderately phototoxic due to its furanocoumarin content, although the risk is considered low unless higher than recommended concentrations are used or more than one potentially phototoxic oil is combined in a blend. The risk may be increased in fair-skinned individuals. Other phototoxic essential oils include *Citrus bergamia* (bergamot) and *Citrus limon* (lemon). Sensitivity to

sunlight or UVB light after topical application increases in the first hour after application and declines over the following 8 hours. A general caution is to avoid UV exposure for at least 12 hours after topical application and use a sunscreen during this period. An early study (Zaynoun 1977) ($n = 63$) showed no significant differences in phototoxic reactions to bergamot oil for eye colour, age, gender or tanning, but smaller amounts of oil produced an effect in light-skinned people. It is not clear whether this also applies to orange essential oil.

GASTROINTESTINAL SYMPTOMS

Abdominal pain, nausea, vomiting, diarrhoea, and dizziness have been reported with oral dosing (Citrus and Allied Essences 2004).

CARDIOTOXICITY

Bitter orange, standardised to 4–6% synephrine, demonstrated cardiovascular toxicity (ventricular arrhythmias with enlargement of QRS complex) and mortality in rats (Calapai et al 1999). The clinical significance of this finding remains unknown.

SIGNIFICANT INTERACTIONS

There are no known interactions between the essential oils and conventional medicines; however, interactions may occur with the fruit and fruit products.

Theoretically, an interaction exists for CYP 3A and P-gp substrates as human studies indicate that juice made from *C. aurantium* (Seville orange) inhibits CYP3A and possibly P-glycoprotein (Di Marco et al 2002, Malhotra et al 2001) — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS

Do not apply essential oils to eyes or undiluted to mucous membranes. Orange essential oil is flammable and should not be vapourised near sources of heat or open flames. Therefore, candle vapourisers are not recommended. Skin sensitisation and phototoxicity are possible with the essential oils, so exposure to UV light sources should be avoided for at least 12 hours after dermal application. The risk is increased in fair-skinned individuals and when a blend that also contains other phototoxic essential oils is used.

PREGNANCY USE

Bitter orange peel and associated products is not recommended for use in pregnancy (Blumenthal et al 2000).

Orange essential oil used in recommended doses is generally safe in pregnancy, but general safety precautions apply.

PRACTICE POINTS/PATIENT COUNSELLING

- Bitter orange peel and associated products are used to improve digestion, relieve dyspeptic symptoms and improve appetite.
- *Citrus aurantium* extract is growing increasingly popular as an ingredient in weight loss products; however, controlled studies are required to determine its safety and effectiveness.
- The oil of bitter orange (*Citrus aurantium* var. *amara*) was an effective topical treatment in treatment-resistant superficial dermatophyte infection according to one study.
- Topical application of orange oil and bitter orange oil can induce skin sensitisation, which is more likely to occur if old orange essential oil is used because of its tendency to oxidise. Appropriate storage reduces oxidation. A patch test is recommended for atopic people or those who have a tendency to skin reactions to fragrance compounds, cosmetics or essential oils.
- Topical application of orange oil and bitter orange oil can induce photosensitivity in some individuals. After topical application, exposure to sunlight or UVB light should be avoided for at least 12 hours. The risk of photoxicity increases if high concentrations of phototoxic essential oils are used or a blend contains several phototoxic essential oils or if used by fair-skinned people.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Orange essential oil can be used in a vapouriser or massage to aid focus and concentration and facilitate communication. It is also used to reduce stress and promote sleep and relaxation. In teas and tinctures, cut peel may aid digestion and relieve dyspeptic symptoms. There is some evidence that the oil may be an effective treatment for treatment-resistant fungal skin infections.

When will it start to work?

When used in aromatherapy, it usually acts soon after inhalation. When the oil or oil products are applied topically to fungal infections, results may be seen within 1–2 weeks; however, 3–4 weeks of treatment may be required. Used internally, bitter orange peel products should provide dyspeptic symptom relief quickly.

Are there any safety issues?

Skin irritation and phototoxicity (chemical burn) is possible after topical application of the oil if the skin is exposed to UV light such as sunlight. Use in recommended doses and do not use more than 15% of orange essential oil in a blend. Oral use of bitter orange peel products is not recommended in pregnancy and Seville orange juice can induce multiple drug interactions.

REFERENCES

American Botanical Council. Complete German E Commission Monographs: Therapeutic Guide to Herbal Medicines. Austin, TX: American Botanical Council, 1999.

Bellakhdar J. La Pharmacopee Marocaine Traditionnele. Casablanca: Le Fennec, 1997.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000, 287-9.

British Herbal Medicine Association Scientific Committee. 1983. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA.

Calapai G et al. Antiobesity and cardiovascular toxic effects of Citrus aurantium extracts in the rat: a preliminary report. Fitoterapia 70 (1999): 586-92.

Citrus and Allied Essences. 2004. Material Safety Data Sheet IOIIII. Lake Success, NY: Citrus and Allied Essences Ltd.

Di Marco MP et al. The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: The role of gut CYP3A and P-glycoprotein. Life Sci 71 (2002): 1149-60.

Hmamouchi M. Les plantes medicinales et aromatiques marocaines. Imprimerie de Fedala Mohammedia, 2000.

Jeannot V et al. Quantification and determination of chemical composition of the essential oil extracted from natural orange blossom water (Citrus aurantium L. ssp. Aurantium). Int J Aromather 15 (2005): 95-7.

Kim DH et al. Inhibitory effect of herbal medicines on rotavirus infectivity. Biol Pharm Bull 23 (2000): 356-8.

Leung A, Foster S. Encyclopaedia of Common Natural Products used in Food, Drugs and Cosmetics. New York (1996): John Wiley & Sons.

Malhotra S et al. Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furanocoumarins. Clin Pharmacol Ther 69 (2001): 14-23.

Melendez PA, Capriles VA. Antibacterial properties of tropical plants from Puerto Rico. Phytomedicine 13 (2006): 272-6.

Miyake Y, Nakagawa M, Asakura Y. Effects of odours on humans (1): Effects on sleep latency. Chem Senses 16 (1991): 183.

Pellati F et al. Determination of adrenergic agonists from extracts and herbal products of Citrus aurantium L. var. amara by LC. J Pharm Biomed Anal 29 (2002): 1113-19.

Preuss HG et al. Citrus aurantium as a thermogenic, weight-reduction replacement for ephedra: an overview. J Med 33 (2002): 247-64.

Price S, Price L. Aromatherapy for Health Professionals. Edinburgh, 1995: Churchill Livingstone.

Ramadan W et al. Oil of bitter orange: new topical antifungal agent. Int J Dermatol 35(6) (1996): 448-9

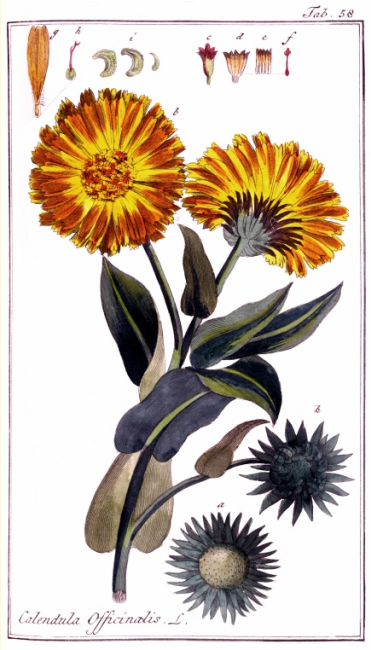
Sellar W. The Directory of Essential Oils. Essex UK, 1992: Saffron Walden.

Takahashi Y et al. Antioxidant effect of citrus essential oil components on human low-density lipoprotein in vitro. Biosci Biotechnol Biochem 67 (2003): 195-7.

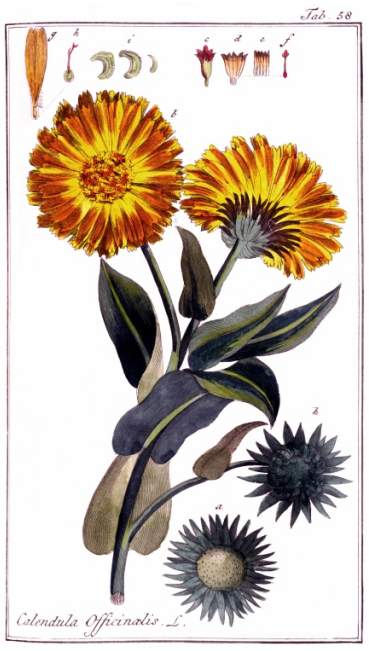
Tisserand R, Balacs T. Essential Oil Safety: A Guide for Health Professionals. Edinburgh, 1995: Churchill Livingstone.

Wichtl M, Bisset W (eds). Herbal Drugs and Phytopharmaceuticals. Stuttgart, 1994: Medpharm Scientific Publishers.

Zaynoun S. A study of bergamot and its importance as a phototoxic agent. Contact Dermatitis 3 (1977): 225-39.



Cloves



Historical note Spices such as cloves have been used as food preservatives, disinfectants and antiseptics for centuries (De et al 1999). Modern research has confirmed that cloves are an effective preservative that inhibit the growth of many food-poisoning and food-spoiling bacteria.

COMMON NAME
Cloves

OTHER NAMES
Oil of cloves, Oleum caryophylli
Eugenia carylophyllata, Eugenia aromatica, Caryophyllus aromaticus, Myrtaceae

SCIENTIFIC NAME
Syzygium aromaticum (family Myrtaceae)

PLANT PART USED
Dried flower buds (clove oil is distilled from this plant part).

CHEMICAL COMPONENTS
The main constituent of clove oil is eugenol. Others include beta-caryophyllene, acetyl eugenol, isoeugenol, eugenine, kaemferol, tannins, gallic acid, vitamin C, minerals (boron, calcium, chromium, iron, manganese, magnesium, potassium, phosphorus) (US Department of Agriculture 2002).

MAIN ACTIONS
Because of cloves' significant eugenol content, most pharmacological activity is based on studies involving eugenol.

LOCAL ANALGESIC, LOCAL ANAESTHETIC AND ANTI-INFLAMMATORY
The local analgesic and anti-inflammatory activity of clove oil is mainly due to the eugenol component. Eugenol acts on contact to depress nociceptors, the sensory receptors involved in pain perception (Brodin & Roed 1984). Eugenol also inhibits prostaglandin biosynthesis through potent cyclo-oxygenase-1 and -2 inhibitory activity (Huss et al 2002, Kelm et al 2000). Although eugenol is chiefly responsible, other constituents are also involved (Ghelardini et al 2001a). Beta-caryophyllene, another key component of clove oil, exhibits significant anti-inflammatory and rapid local anaesthetic activity in several animal models (Ghelardini et al 2001b,

Muruganandan et al 2001). Local anesthetic effects develop within 5 minutes of application and diminish after about 15 minutes.

ANTISEPTIC — FUNGICIDAL, ANTIBACTERIAL, ANTIVIRAL

Clove oil has an inhibitory effect against yeasts in vitro (Arora & Kaur 1999). Antibacterial activity has been demonstrated against Gram-negative anaerobic periodontal oral pathogens, including *Porphyromonas gingivalis* and *Prevotella intermedia* (Cai & Wu 1996). Activity has also been demonstrated against *Bacillus subtilis, Listeria monocytogenes, Salmonella enterica, Escherichia coli* and *Saccharomyces cerevisiae* (De et al 1999, Dorman & Deans 2000, Friedman et al 2002). In vitro assays have identified inhibitory effects on hepatitis C virus protease (Hussein et al 2000) and human cytomegalovirus (Shiraki et al 1998, Yukawa et al 1996). An animal model confirmed significant activity against herpes simplex virus type 1 (Kurokawa et al 1998).

Cloves are also effective against species belonging to the *Eurotium, Aspergillus* and *Penicillium* genera in vitro (Guynot et al 2003).

OTHER ACTIONS

ANTIHISTAMINE

Clove bud extracts inhibit histamine release from mast cells in vivo and in vitro (Kim et al 1997, Kim et al 1998, Shakila et al 1996).

ANTIOXIDANT

Several constituents within the flower have antioxidant activity, such as eugenol (US Department of Agriculture 2002).

ANTISPASMODIC

Both beta-caryophyllene and eugenol have antispasmodic activity (Duke 2002).

ANTIPLATELET

Eugenol inhibits platelet aggregation in vitro (Srivastava 1993, Srivastava & Malhotra 1991). It was more potent than aspirin in several experimental models and equivalent to indomethacin in one (Srivastava 1993).

CLINICAL USE

The clinical effects of cloves and clove oil have not been significantly investigated; however, an understanding of the herb's pharmacological activity suggests a role in the treatment of several conditions.

TOOTHACHE AND RELIEF OF DRY SOCKET PAIN

Clove oil and dried clove buds are used in dentistry to relieve dental pain and reduce infection. Based on the evidence available, Commission E has approved cloves for use as a local anaesthetic and antiseptic (Blumental et al 2000).

ORAL HYGIENE

Used as an antiseptic and antibacterial agent for the oral mucosa, clove is used as an ingredient in mouth rinses and gargles. Its established antiseptic activity provides a theoretical basis for efficacy.

HERPES SIMPLEX VIRUS TYPE 1

One study using a combination of acyclovir and cloves administered orally found this to be superior to acyclovir alone in the treatment of herpes simplex virus type 1 infection (Kurokawa et al 1995). The combination significantly reduced the development of skin lesion and/or prolonged survival times of infected mice and reduced viral loads.

HEADACHE (AS PART OF A COMBINATION)

Tiger balm is a popular OTC preparation that contains clove oil, menthol, cassia oil, camphor, cajuput oil and sometimes peppermint oil. It is generally used to relieve the symptoms of sore muscles, but a randomised double-blind study found that it is also as effective as paracetamol in reducing headache severity (Schattner & Randerson 1996). Although encouraging, the role of cloves in this combination is difficult to assess from the study.

OTHER USES

Cloves have been investigated as an agent to protect harvests from fungal contamination (Ranasinghe et al 2002).

DOSAGE RANGE

- Powder: 120–300 mg as a single dose
- Oil: 0.05–0.2 mL as a single dose
- Toothache or gum inflammation: oil of clove is applied directly to the site.
- Dry socket: the area is packed with dried flower buds steeped in oil.
- Headache: 1 drop of oil massaged into each temple or area of pain.

ADVERSE REACTIONS

According to one review, contact dermatitis has been reported, and local application may cause irritation to mucous membranes in sensitive individuals. Oral use of the oil can cause nervous system depression, seizures, hepatic dysfunction and irritation to mucosal tissues.

SIGNIFICANT INTERACTIONS
None known.

CONTRAINDICATIONS AND PRECAUTIONS
None known.

PREGNANCY USE
Safety unknown.

PRACTICE POINTS
- Clove flower buds and clove oil has antiseptic, analgesic, anti-inflammatory and local anaesthetic properties.
- It is directly applied to relieve the symptoms of toothache and dry socket.
- Clove oil is also used in mouth rinses and gargles to improve oral hygiene.
- Massaging one drop of oil into the temples has been used to treat headache.
- This herb and its essential oil should not be taken internally.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Clove flower buds and clove oil have antiseptic, anti-inflammatory, analgesic, and local anaesthetic properties that are useful in the treatment of toothache, dry socket and common mouth infections. Massaging one drop of the oil into the temples may relieve the symptoms of headache.

When will it start to work?
Research suggests that effects are almost immediate, although short lasting.

Are there any safety issues?
Clove buds and clove oil should not be taken internally, and only applied externally.

REFERENCES
Arora DS, Kaur J. Antimicrobial activity of spices. Int J Antimicrob Agents 12.3 (1999): 257-62.
Blumenthal M et al. Herbal Medicine: Expanded Commission E Monographs. American Botanical Council, 2000.
Brodin P, Roed A. Effects of eugenol on rat phrenic nerve and phrenic nerve-diaphragm preparations. Arch Oral Biol 29.8 (1984): 611-15.
Cai L, Wu CD. Compounds from Syzygium aromaticum possessing growth inhibitory activity against oral pathogens. J Nat Prod 59.10 (1996): 987-90.
De M, Krishna De A, Banerjee AB. Antimicrobial screening of some Indian spices. Phytother Res 13.7 (1999): 616-18.
Dorman HJ, Deans SG. Antimicrobial agents from plants: antibacterial activity of plant volatile oils. J Appl Microbiol 88.2 (2000): 308-16.
Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD (accessed Oct 11 2002): www.ars-grin.gov/duke.

Friedman M, Henika PR, Mandrell RE. Bactericidal activities of plant essential oils and some of their isolated constituents against Campylobacter jejuni, Escherichia coli, Listeria monocytogenes, and Salmonella enterica. J Food Prot 65.10 (2002): 1545-60.
Ghelardini C, Galeotti N, Mazzanti G. Local anaesthetic activity of monoterpenes and phenylpropanes of essential oils. Planta Med 67.6 (2001a): 564-6.
Ghelardini C et al. Local anaesthetic activity of beta-caryophyllene. Farmaco 56.5-7 (2001b): 387-9.
Guynot ME et al. Antifungal activity of volatile compounds generated by essential oils against fungi commonly causing deterioration of bakery products. J Appl Microbiol 94.5 (2003): 893-9.
Huss U et al. Screening of ubiquitous plant constituents for COX-2 inhibition with a scintillation proximity based assay. J Nat Prod 65.11 (2002): 1517-21.
Hussein G et al. Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytother Res 14.7 (2000): 510-16.
Kelm MA et al. Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomedicine 7.1 (2000): 7-13.
Kim HM et al. Antianaphylactic properties of eugenol. Pharmacol Res 36.6 (1997): 475-80.
Kim HM et al. Effect of Syzygium aromaticum extract on immediate hypersensitivity in rats. J Ethnopharmacol 60.2 (1998): 125-31.
Kurokawa M et al. Efficacy of traditional herbal medicines in combination with acyclovir against herpes simplex virus type 1 infection in vitro and in vivo. Antiviral Res 27.1-2 (1995): 19-37.
Kurokawa M et al. Purification and characterization of eugeniin as an anti-herpesvirus compound from Geum japonicum and Syzygium aromaticum. J Pharmacol Exp Ther 284.2 (1998): 728-35.
Muruganandan S et al. Anti-inflammatory activity of Syzygium cumini bark. Fitoterapia 72.4 (2001): 369-75.
Ranasinghe L, Jayawardena B, Abeywickrama K. Fungicidal activity of essential oils of Cinnamomum zeylanicum (L.) and Syzygium aromaticum (L.) against crown rot and anthracnose pathogens isolated from banana. Lett Appl Microbiol 35.3 (2002): 208-11.
Schattner P, Randerson D. Tiger Balm as a treatment of tension headache: A clinical trial in general practice. Aust Fam Physician 25.2 (1996): 216, 218, 220.
Shakila RJ, Vasundhara TS, Rao DV. Inhibitory effect of spices on in vitro histamine production and histidine decarboxylase activity of Morganella morganii and on the biogenic amine formation in mackerel stored at 30 degrees C. Z Lebensm Unters Forsch 203.1 (1996): 71-6.
Shiraki K et al. Cytomegalovirus infection and its possible treatment with herbal medicines. Nippon Rinsho 56.1 (1998): 156-60.
Srivastava KC. Antiplatelet principles from a food spice clove (Syzygium aromaticum L) [corrected]. Prostaglandins Leukot Essent Fatty Acids 48.5 (1993): 363-72.
Srivastava KC, Malhotra N. Acetyl eugenol, a component of oil of cloves (Syzygium aromaticum L.) inhibits aggregation and alters arachidonic acid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids 42.1 (1991): 73-81.
Yukawa TA et al. Prophylactic treatment of cytomegalovirus infection with traditional herbs. Antiviral Res 32.2 (1996): 63-70.

Cocoa

Historical note Cocoa originates from Mexico where the Mayas, Incas, and Aztecs considered it the food of the gods. Chocolate, mixed with vanilla and sugar, was first introduced as a beverage to Europe by Colombus and was considered an aphrodisiac and a symbol of wealth and power. The phenolics in chocolate prevent the fat becoming rancid, decreasing the need for added preservatives. This quality was exploited during World War II when at times US troops were rationed three chocolate bars per day during heavy combat as their sole source of nourishment (Waterhouse et al 1996).

COMMON NAME
Chocolate, Cocoa, cocoa liquor, cocoa mass, baking chocolate

BOTANICAL NAME/FAMILY
Theobroma cacao (family Sterculiaceae)

PLANT PARTS USED
Cocoa is produced through a process of fermenting the seeds from the pods of the cacao tree *Theobroma cacao*. The beans are dried, roasted, and crushed to produce high-fat, unsweetened chocolate, which is also called baking chocolate. This intermediate is pressed and alkalised to form cocoa powder, which is then homogenised with sugar and cocoa butter, and sometimes milk, to ultimately form chocolate. Dark chocolate generally contains more than 50% cocoa, whereas mass-produced milk chocolate only contains around 10% cocoa. White chocolate is based on cocoa butter (or theobroma oil) without the cocoa solids.

Although many different types of cocoa beans grow throughout the world, three varieties of cocoa beans are mainly used to make chocolate products: (a) criollo (meaning 'native'), distributed to the north and west of the Andes, (b) forastero (meaning 'foreign'), found mainly in the Amazon basin, and (c) trinitario (meaning 'sent from heaven') (Bruinsma & Taren 1999).

CHEMICAL COMPONENTS
Cocoa is among the most concentrated sources of the flavanols, catechin and epicatechin, with four times the catechin content of tea (Arts et al 1999). Chocolate also contains additional flavonoids not found in tea, with high concentrations of oligomeric procyanidins (Lazarus et al 1999). Post-harvesting and processing pro-

cedures can have a striking influence on the flavanol content of chocolate and cocoa (Hollenberg et al 2004). Dark chocolate has the highest total catechin content with approximately 53.5 mg/100 g, whereas milk chocolate contains approximately 15.9 mg/100 g (Arts et al 1999). White chocolate primarily contains cocoa butter with minimal levels of polyphenols. Cocoa also contains the methylxanthines, caffeine and theobromine, the biogenic amines phenylethylamine, phenylalanine and tyrosine (Bruinsma & Taren 1999) and the cannabinoid-like fatty acid anandanine analogs, *N*-oleoylethanolamine and *N*-linoleoylethanolamine (Di Tomaso et al 1996). Chocolate is also a rich source of minerals, including magnesium, calcium, iron, copper, phosphorus, potassium and zinc (Steinberg et al 2003).

MAIN ACTIONS

Both in vitro and in vivo studies indicate that cocoa flavanols have antioxidant effects and decrease LDL-cholesterol oxidation, reduce platelet aggregation, and enhance endothelial function. There is, however, tremendous variability in cocoa processing, flavonoid content and measurement of flavonoids, and questions remain around bioavailability and dosing frequency (Fisher & Hollenberg 2005). A feeding study demonstrated that procyanidins were remarkably stable in the stomach environment and thus most ingested procyanidins reach the small intestine intact and are available for absorption or metabolism (Rios et al 2002). Epicatechin and its metabolites reach maximal levels 2 hours after either chocolate or cocoa intake, with rapid excretion in the urine (Baba et al 2000) and dimeric procyanidins have been detected in human plasma as early as 30–60 minutes after the consumption of flavanol-rich beverages providing 0.25–0.50 g/kg cocoa/kg body weight (Holt et al 2002, Zhu et al 2005).

ANTIOXIDANT

Cocoa has been found to have much higher levels of total phenolics and flavonoids, with a corresponding higher antioxidant capacity per serving, than black tea, green tea or red wine (Lee et al 2003). It has been suggested that the antioxidant capacity of cocoa polyphenols is greater than synthetic antioxidants and that they have the potential to complement or replace synthetic antioxidants in aqueous and oil-based food applications (Osman et al 2004).

Human studies have confirmed that the polyphenols in chocolate are indeed bioavailable and able to increase the antioxidant capacity of plasma, with one study reporting that ingestion of 80 g of procyanidin-rich chocolate increased plasma epicatechin concentrations 12-fold, significantly increased plasma total antioxidant capacity by 31% and significantly decreased 2-thiobarbituric acid reactive substances

by 40% after 2 hours, with levels returning to normal within 6 hours (Rein et al 2000a).

Cocoa has also been consistently shown to inhibit LDL oxidation both in vitro (Sies et al 2005, Waterhouse et al 1996) and in vivo (Kondo et al 1996). In a crossover study in 23 healthy subjects cocoa powder and dark chocolate was seen to modestly reduce LDL oxidation susceptibility while increasing serum total antioxidant capacity and HDL-cholesterol concentrations (Wan et al 2001), and another cross-over trial of 25 healthy subjects found that supplementation with 36.9 g of dark chocolate (30 g of cocoa powder drink) for 6 weeks reduced LDL oxidisability (Mathur et al 2002). Similar results were seen in a randomised, double-blind crossover trial that found that a high-flavanol cocoa drink providing 187 mg flavan-3-ols/100 mL significantly reduced lipid peroxidation, compared with a low-flavanol cocoa drink providing only 14 mg/100 mL (Wiswedel et al 2004).

A further randomised, double-blind, placebo-controlled study of 21 healthy adults, however, found that intake of high-flavonoid (213 mg procyanidins, 46 mg epicatechin) dark chocolate bars for 2 weeks did not alter resistance to LDL oxidation, total antioxidant capacity, 8-isoprostanes, blood pressure, lipid parameters, body weight or BMI, despite increasing plasma epicatechin concentrations and improving endothelium-dependent flow-mediated dilation of the brachial artery (Engler et al 2004).

In addition to reducing lipid oxidation, consumption of a flavanol-rich cocoa beverage has been shown to reduce susceptibility of erythrocytes to haemolysis and to increase their ability to buffer free radicals (Zhu et al 2005).

There is evidence that the polyphenols are not the only antioxidants in chocolate, as suggested by a study that found that consumption of chocolate containing 200 mg of polyphenols, as well as chocolate with less than 10 mg of polyphenols, reduced faecal free radical production (Record et al 2003). Furthermore, similar reductions in markers of lipid peroxidation have been observed after daily consumption of 75 g of dark chocolate and dark chocolate enriched with cocoa polyphenols, as well as with white chocolate, which contains very little polyphenols (Mursu et al 2004).

EFFECTS ON MICROCIRCULATION AND NITRIC OXIDE

A double blind, dose-finding study found that flavanol-rich cocoa increased circulating NO species in the plasma of male smokers, with maximal effects seen with ingestion of 176–185 mg flavanols (Heiss et al 2005). Another double-blind trial found that ingestion of a high-flavanol cocoa drink, but not a low-flavanol one, enhanced NO bioactivity and increased plasma concentrations of nitroso compounds

and flow-mediated dilation of the brachial artery (Sies et al 2005). Similarly, ingestion of flavanol-rich cocoa is associated with acute elevations in levels of circulating NO species, enhanced flow-mediated dilatation response of conduit arteries, and an augmented microcirculation, with these effects being mimicked by ingestion of chemically pure epicatechin. Moreover, chronic consumption of a cocoa-flavanol-rich diet has been associated with augmented urinary excretion of NO metabolites (Schroeter et al 2006).

LIPID-LOWERING

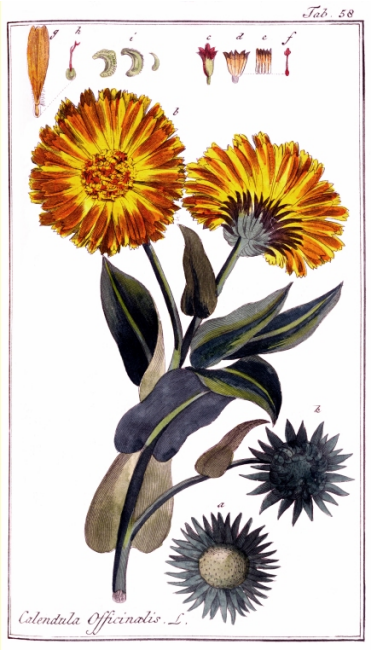
A 3-week clinical supplementation trial of 45 non-smoking, healthy volunteers consuming high-polyphenol chocolate found a significant increase in serum HDL-cholesterol with dark and high polyphenol chocolate (11.4% and 13.7%, respectively), whereas white chocolate consumption resulted in a small decrease in HDL. Markers of lipid peroxidation decreased 11.9% in all three study groups with no changes occurring in the total antioxidant capacity of plasma, in the oxidation susceptibility of serum lipids or VLDL and LDL, or in the concentration of plasma F2-isoprostanes or hydroxy fatty acids. This suggests that while cocoa polyphenols may increase the concentration of HDL-cholesterol, chocolate fatty acids may modify the fatty acid composition of LDL, making it more resistant to oxidative damage (Mursu et al 2004).

INHIBIT PLATELET FUNCTION

Numerous dietary intervention studies in humans and animals indicate that flavanol-rich foods and beverages might exert cardioprotective effects with respect to vascular function and platelet reactivity (Keen et al 2005). Acute doses of flavanols and oligomeric procyanidins from cocoa have been observed to inhibit platelet activation (Pearson et al 2002, Rein et al 2000b) and have an aspirin-like effect on primary hemostasis 2 and 6 hours after consumption (Hermann et al 2006, Pearson et al 2002, Rein et al 2000b), with the effects being similar to, but less profound than, aspirin (Pearson et al 2002). Similar results have been observed in longer studies with lower doses of cocoa flavanols, with a double-blind, controlled trial demonstrating significantly lower platelet aggregation and significantly higher plasma ascorbic acid concentrations after supplementation with cocoa flavanols (234 mg cocoa flavanols and procyanidins/day) over 28 days (Murphy et al 2003).

In another randomised trial of 30 healthy volunteers 100 mg of dark chocolate, but not white or milk chocolate, were found to significantly inhibit collagen-induced platelet aggregation (Innes et al 2003). The alteration of eicosanoid synthesis has been suggested as a plausible mechanism by which procyanidins can decrease

platelet activation, and has been observed in an in vitro study of the effect of procyanidin on aortic endothelial cells, as well as in a randomised, blinded, crossover study of high procyanidin chocolate (4.0 mg/g) (Schramm et al 2001).



PSYCHOLOGICAL EFFECTS

Chocolate is purported to have a range of psychological effects, including enhanced arousal and cognitive function, stimulation of feelings of wellbeing and euphoria, as well as initiating cravings. The orosensory aspects of chocolate, including its taste, smell and texture, certainly contribute to chocolate's positive appeal. Chocolate contains large amounts of fat in the form of cocoa butter, which melts at body temperature producing a pleasurable melt-in-the-mouth experience. Chocolate also often contains large amounts of sugar and thus satisfies the seemingly innate preference for sweet, high-fat, foods (Bruinsma & Taren 1999).

In addition to unique sensory properties, chocolate also contains many pharmacologically active substances. Several endogenous biogenic amines with sympathomimetic properties are found in chocolate, most notably tyramine and phenylethylamine (Hurst 1982). Phenylethylamine is an amphetamine analogue structurally related to methylenedioxymethamphetamine that may act to potentiate dopaminergic and noradrenergic neurotransmission and modulate mood (Bruinsma & Taren 1999).

Cocoa is also known to contain methylxanthines, including caffeine and theobromine, both of which are stimulants. Although the stimulatory and sympathomimetic effects of caffeine are well documented the psychological effects of theobromine are less certain.

A group of biologically active constituents, including *N*-oleoylethanolamine and *N*-linoleoylethanolamine, have been identified in chocolate and appear to be related to anandamide, the 'internal bliss' chemical, which is the endogenous lipoprotein that binds cannabinoid receptors within the brain (Di Tomaso 1996). Although is has been suggested that these compounds may elicit heightened sensitivity and euphoria by directly activating cannabinoid receptors or by increasing anandamide levels (Bruinsma & Taren 1999), measurements have suggested that their amounts in cocoa is several orders of magnitude below those required to reach the blood and cause observable central effects (Di Marzo et al 1998).

Chocolate craving, which is reported to be the most common food craving (Weingarten & Elston 1991), is more common in women, with fluctuations occurring with hormonal changes just before and during the menses (Rozin et al 1991). The basis for chocolate craving, however, remains undetermined, but it is suggested that aroma, sweetness, texture and calorie content are likely to play a more important role

in chocolate cravings than pharmacological factors (Bruinsma & Taren 1999, Michener & Rozin 1994, Rozin et al 1991, Smit et al 2004).

MODULATION OF IMMUNE FUNCTION AND INFLAMMATION

The procyanidin fraction from cocoa demonstrates immunomodulatory function in vitro, with stimulation of TNF-alpha (Mao et al 2002) and modulation of the secretion of the cytokine transforming growth factor (TGF-beta-1) (Mao et al 2003), as well as inhibiting induced nuclear transcription of human IL-1B (Mao et al 2000a), phytohemagglutinin-induced stimulation of IL-2 (Mao et al 1999) and mitogen-stimulated secretion of IL-4 (Mao et al 2000b) in peripheral blood mononuclear cells in vitro.

Cocoa polyphenols have also been shown to reduce leukotriene synthesis through inhibition of human 5-lipoxygenase (Sies et al 2005).

ALTERED CELLULAR SIGNALLING

Flavonoids have been shown to modulate tumour pathology in vitro and in animal models, and the pentameric procyanidin fraction isolated from cocoa is reported to slow the growth of cultured human aortic endothelial cells (Kenny et al 2004a), as well as inhibit the proliferation of human dermal microvascular endothelial cells in vitro through inhibition of tyrosine kinase ErbB2 expression. This has led to the suggestion polyphenols may influence endothelial growth signaling in vitro, with potential beneficial effects for specific neoplasias in which cells over-express ErbB2 (Kenny et al 2004b).

INHIBITION OF DENTAL CARIES

Cocoa contains substances that protect against dental caries (Palenik et al 1977, s'Gravenmade et al 1977) and in vitro experiments have shown that monomeric polyphenols and tannins from cocoa may interfere with glucosyltransferase activity of *Streptococcus mutans* and reduce plaque formation (Kashket et al 1985). Similar results were reported in hamsters, with a marked caries-inhibitive effect found with a water-extract of cocoa (Stralfors 1966). Cocoa bean husk, while not used in cocoa or chocolate, demonstrates antibacterial properties attributed to its unsaturated fatty acids and antiglucosyltransferase activities attributed to epicatechin polymers, as well as being shown both in vitro and in vivo to possess significant antiplaque activity (Matsumoto et al 2004).

ANTITUSSIVE

It has been suggested that theobromine, a methylxanthine derivative present in cocoa, may form the basis for a new class of antitussive drugs, as it has been shown

to effectively inhibit citric acid-induced cough in guinea-pigs in vivo, as well as suppress capsaicin-induced cough in a human double-blind trial. The observation that theobromine inhibits capsaicin-induced sensory nerve depolarisation of the guinea-pig and human vagus nerve suggests that its antitussive action may be mediated peripherally through an inhibitory effect on afferent nerve activation (Usmani et al 2005).

OTHER ACTIONS

The major flavonoids of cocoa, epicatechin and catechin, protected cellular membrane from amyloid beta-protein-induced neurotoxicity in vitro, suggesting that cocoa may have anti-neurodegenerative effects (Heo & Lee 2005).

CLINICAL USE

CARDIOVASCULAR DISEASE

Epidemiologic studies have shown inverse associations between dietary polyphenols and mortality from coronary heart disease. Small, short-term, intervention studies have indicated that cocoa-containing foods may provide many cardiovascular benefits including reducing blood pressure, inhibiting platelet function, preventing lipid oxidation, reducing LDL, increasing HDL, improving endothelial function, increasing insulin sensitivity, reducing insulin resistance and reducing inflammation.

Dark chocolate, but not white chocolate, was observed to significantly improve endothelial and platelet function in healthy smokers, with increased flow-mediated dilatation, increased total antioxidant status and reduced shear stress dependent platelet function seen 2–8 hours after ingestion (Hermann et al 2006). Dark chocolate has also been shown to increase insulin sensitivity and decrease blood pressure in healthy people (Grassi et al 2005a). Similar results were obtained in a RCT using 100 g of dark chocolate containing approximately 500 mg polyphenols which was consumed daily for 15 days. Chocolate was found to decrease DBP by -11.9 ± 7.7 mmHg, decrease serum LDL-cholesterol from 3.4 to 3.0 mmol/L, improve flow-mediated dilation, and reduce insulin resistance and increase insulin sensitivity in patients with newly diagnosed essential hypertension (Grassi et al 2005b). Similarly, a study of male soccer players found that consumption of 105 g of flavanol-containing milk chocolate (168 mg of flavanols) for 14 days decreased DBP (–5 mmHg), mean blood pressure (–5 mmHg), plasma cholesterol (–11%), LDL-cholesterol (–15%), malondialdehyde (–12%), urate (–11%) and lactate dehydrogenase activity (–11%), and increased vitamin E/cholesterol (+12%) (Fraga et al 2005).

As yet there are no published long-term RCT or intervention studies of cocoa with hard clinical end-points (Maron 2004). The cardiovascular benefits of cocoa are

supported, however, in a 15-year epidemiological study of 470 elderly men, which found that cocoa intake was inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality. This study found a 50% reduction in cardiovascular-related death and all-cause mortality in the highest tertile of cocoa intake compared to the lowest tertile, suggesting that the pharmacological actions described for cocoa do, in fact, translate into clinical benefits (Buijsse et al 2006).

HYPERLIPIDAEMIA

The lipid content of chocolate is relatively high, yet around one-third of the lipid in cocoa butter is composed of the fat, stearic acid, which exerts a neutral cholesterolaemic response in humans by an unknown mechanism (Kris-Etherton et al 1993, Steinberg et al 2003). Cocoa butter, however, is considered a high calorie fat because it has a high digestibility with a digestible energy value of 37 kJ/g in humans (Shahkhalili et al 2000). The results of a randomised, double-blind crossover design supplementation study suggest that the addition of calcium to chocolate can significantly reduce the absorption of cocoa butter, thus reducing the absorbable energy value of the chocolate by approximately 9% while at the same time reducing the plasma LDL-cholesterol level and leaving the plasma HDL-cholesterol level and taste of the chocolate unchanged (Shahkhalili et al 2001).

Although there are some short-term studies demonstrating that cocoa flavanols can reduce serum LDL (Fraga et al 2005, Grassi et al 2005) and increase HDL (Mursu et al 2004, Wan et al 2001), long-term clinical trials are needed to determine its role in the clinical treatment of hypercholesterolaemia.

Cocoa bran may also have a use in hypercholestrolaemia, as well as constipation, because this low-fat, high-fibre material has been shown in a randomised, controlled, double-blind study to increase faecal bulk similarly to wheat bran and reduce the LDL/HDL-cholesterol ratio, with no effect on LDL-cholesterol oxidation (Jenkins et al 2000).

PREMENSTRUAL SYNDROME

Magnesium deficiency may contribute to the symptomology of PMS, which may be improved by chocolate or cocoa powder, which contain a high concentration of magnesium (≈100 mg/100 g in chocolate and 520 mg/100 g in cocoa powder). There is also some evidence to suggest that serotonin levels are low premenstrually, and it is possible that premenstrual chocolate cravings are the body's attempt to raise CNS concentrations of serotonin (Bruinsma & Taren 1999).

ENHANCED COGNITIVE FUNCTION

The results of a double-blind, placebo-controlled study suggests that both milk and dark chocolate, but not white chocolate, improve cognitive function. A second double-blind study suggests that this improvement is due to the methylxanthin content of chocolate, with 11.6 g of cocoa powder producing identical improvements in cognitive function and the mood construct 'energetic arousal' as a mixture of caffeine (19 mg) and theobromine (250 mg) (Smit et al 2004).

Consumption of a 65 g chocolate bar was shown to significantly increase driving accuracy and reduce collisions compared to an equicaloric snack of cheese and biscuits or no snack in a controlled trial of 12 volunteers (Smith & Rich 1998).

FOOD SOURCE

Cocoa and chocolate are nutritious foods that contribute to caloric as well as trace mineral intake (Steinberg et al 2003). Milk chocolate has a relatively low glycaemic index of approximately 40 (Foster-Powell et al 2002) and this is attributed to the fat in chocolate slowing gastric emptying and thus the rate of subsequent digestion and absorption. The glycaemic effect of milk chocolate can be further reduced by replacing the sucrose with fructose or isomalt (Gee et al 1991). Foods containing cocoa have been shown to lead to a greater postprandial insulin secretion in healthy young adults than foods with alternative flavourings, despite having a similar glycaemic index. It is suggested that specific insulinogenic amino acids or greater cephalic phase insulin release may explain this finding, although the clinical implications are uncertain (Miller et al 1995).

Milk chocolate has also been shown to be a cheap, effective and palatable form of fatty meal for producing gall bladder contraction prior to cholecystography (Harvey 1977).

OTHER USES

Chocolate consumption 15 minutes before exercise has been shown to enhance exercise capacity, spare glycogen stores, delay fatigue, and contribute to the recovery of glycogen repletion in healthy subjects (Chen et al 1996).

Cocoa may also be of use in lactose intolerance, with a feeding study of 35 subjects finding that the addition of cocoa significantly reduced breath hydrogen levels, as well as bloating and cramping, with the result being independent of the presence of sucrose and carrageenan (Lee & Hardy 1989).

Cocoa butter is used in the formation of suppositories and pessaries, as well as preparations for rough or chafed skin, chapped lips, sore nipples, and various cosmetics (Raintree Nutrition 1996).

DOSAGE RANGE

There is enormous variability in the polyphenol content of cocoa and chocolate. Trials suggest that effective doses are approximately 40–100 g of dark chocolate or 15–30 g of cocoa powder, providing approximately 200–500 mg polyphenols.

TOXICITY

Cocoa contains caffeine, which is a mild CNS stimulant that can be profoundly toxic in large doses, resulting in arrhythmia, tachycardia, vomiting, convulsions, coma and death. The caffeine content of cocoa is variable, being approximately 0.009% by weight (Kondo et al 1996), with a typical milk chocolate bar containing approximately 10 mg of caffeine, compared to a cup of coffee, which contains approximately 100 mg (Bruinsma & Taren 1999). Fatal caffeine overdoses in adults have been reported, but are rare and typically require ingestion of more than 5 g of caffeine or more than 50 kg of chocolate (Kerrigan & Lindsey 2005).

ADVERSE REACTIONS

It is believed that chocolate is a trigger for migraine, yet there is inconsistent support for this. In one small double-blind, parallel-group study of 12 patients who believed that chocolate could provoke their attacks, chocolate ingestion was more likely than placebo to trigger a typical migraine episode, with the median time until the onset of the attack of 22 hours (Gibb et al 1991). Three other double-blind placebo-controlled trials suggest that chocolate on its own rarely precipitates migraine (Marcus et al 1997, Moffett et al 1974), with the results of one trial suggesting that chocolate was no more likely to provoke headache than was carob in typical migraine, tension-type, or combined headache sufferers (Marcus et al 1997).

Allergy to cocoa has been documented (Taibjee et al 2004) and it has been suggested that workers employed in the processing of cocoa and flour may be at a high risk for the development of allergic sensitisation and respiratory impairment (Zuskin et al 1998). One case report of cocoa aspiration causing severe aspiration pneumonitis in a 4-year-old has been documented (Lopatka et al 2004).

There is no evidence that chocolate contributes to acne (Ravenscroft 2005).

SIGNIFICANT INTERACTIONS

Polyphenols may reduce iron absorption, with a cocoa beverage containing 100–400 mg total polyphenols per serving having been shown to reduce iron absorption by approximately 70% (Hurrell et al 1999).

PREGNANCY USE

Cocoa and chocolate can be considered safe to use in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Cocoa has many potential benefits for the cardiovascular system and may reduce blood pressure, inhibit platelet function, and improve the serum cholesterol profile, as well as having beneficial effects on insulin sensitivity. However, further research is required to confirm the benefits.
- The most active agents in cocoa are the polyphenols, which are present in high amounts in dark chocolate, with lesser amounts in milk chocolate and minimal amounts in white chocolate.
- Cocoa powder contains minimal fat while dark chocolate contains less fat and sugar than milk or white chocolate. Beneficial effects are more likely to result from the use of cocoa powder or dark chocolate containing more than 50–60% cocoa mass.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Cocoa is a nutritious food that appears to have beneficial effects on blood pressure, cholesterol, blood clotting, and psychological well-being.

When will it start to work?

Psychological effects of chocolate consumption may be evident immediately, whereas beneficial effects on blood pressure and cholesterol may be evident after 2–4 weeks.

Are there any safety issues?

Cocoa powder and dark chocolate are extremely safe and are unlikely to precipitate migraine or dental caries or produce adverse effects from the caffeine content.

REFERENCES

Arts CI et al. Chocolate as a source of tea flavonoids. Lancet 354(9177) (1999): 488.

Baba S et al. Bioavailability of (-)-epicatechin upon intake of chocolate and cocoa in human volunteers. Free Radic Res 33(5) (2000): 635-41.

Bruinsma K, Taren DL. Chocolate: food or drug? J Am Diet Assoc 99(10) (1999): 1249-56.

Buijsse B et al. Cocoa intake, blood pressure, and cardiovascular mortality: The Zutphen Elderly Study. Arch Intern Med 166 (2006): 411-17.

Chen J et al. The effect of a chocolate bar supplementation on moderate exercise recovery of recreational runners. Biomed Environ Sci 9(2-3) (1996): 247-55.

Di Marzo V et al. Trick or treat from food endocannabinoids? Nature 396(6712) (1998): 636-7.

Di Tomaso E et al. Brain cannabinoids in chocolate. Nature 382 (1996): 677-8.

Engler MB et al. Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. J Am Coll Nutr 23(3) (2004): 197-204.

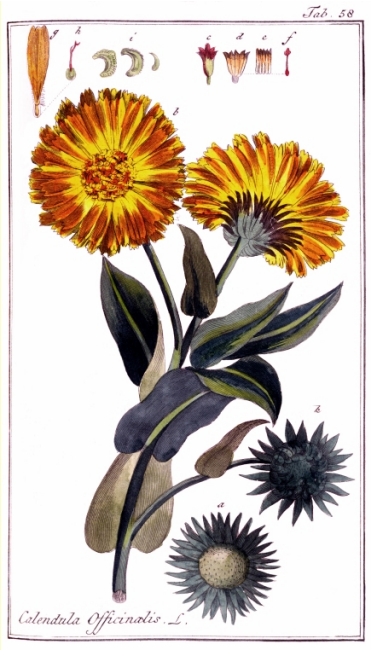
Fisher NDL, Hollenberg NK. Flavanols for cardiovascular health: The science behind the sweetness. J Hypertens 23(8) (2005): 1453-9.

Foster-Powell K et al. International table of glycemic index and glycemic load values. Am J Clin Nutr 76 (2002): 5-56.

Fraga CG et al. Regular consumption of a flavanol-rich chocolate can improve oxidant stress in young soccer players. Clin Dev Immunol 12(1) (2005): 11-17.

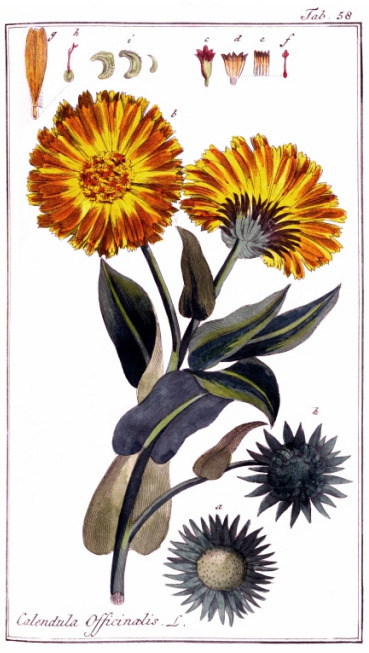
Gee JM et al. Effects of conventional sucrose-based, fructose-based and isomalt-based chocolates on postprandial metabolism in non-insulin-dependent diabetics. Eur J Clin Nutr 45(11) (1991): 561-6.
Gibb CM et al. Chocolate is a migraine-provoking agent. Cephalalgia 11(2) (1991): 93-5.
Grassi D et al. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. Am J Clin Nutr 81(3) (2005a): 611-14.
Grassi D et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 46(2) (2005b): 398-405.
Harvey IC. Milk chocolate as the fatty meal in oral cholecystography. Clin Radiol 28(6) (1977): 635-6.
Heiss C et al. Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers. J Am Coll Cardiol 46(7) (2005): 1276-83.
Heo HJ, Lee CY. Epicatechin and catechin in cocoa inhibit amyloid beta protein induced apoptosis. J Agric Food Chem 53(5) (2005): 1445-8.
Hermann FL et al. Dark chocolate improves endothelial and platelet function. Heart 92(1) (2006): 119-20.
Hollenberg NK et al. Cocoa, flavanols and cardiovascular risk. Br J Cardiol 11(5) (2004): 379-86.
Holt RR et al. Procyanidin dimer B2 [epicatechin-(4-Beta-8)-epicatechin] in human plasma after the consumption of a flavanol-rich cocoa. Am J Clin Nutr 76(4) (2002): 798-804.
Hurrell RF et al. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. Br J Nutr 81(4) (1999): 289-95.
Hurst WJ et al. Biogenic amines in chocolate: a review. Nutr Rep Int 26 (1982): 1081-6.
Innes AJ et al. Dark chocolate inhibits platelet aggregation in healthy volunteers. Platelets 14(5) (2003): 325-7.
Jenkins DJ et al. Effect of cocoa bran on low-density lipoprotein oxidation and fecal bulking. Arch Intern Med 160(15) (2000): 2374-9.
Kashket S et al. In-vitro inhibition of glucosyltransferase from the dental plaque bacterium Streptococcus mutans by common beverages and food extracts. Arch Oral Biol 30(11-12) (1985): 821-6.
Keen CL et al. Cocoa antioxidants and cardiovascular health. Am J Clin Nutr 81(1) (2005): 298-303S.
Kenny TP et al. Cocoa procyanidins inhibit proliferation and angiogenic signals in human dermal microvascular endothelial cells following stimulation by low-level H_2O_2. Exp Biol Med 229(8) (2004a): 765-71.
Kenny TP et al. Pentameric procyanidins isolated from Theobroma cacao seeds selectively downregulate erbb2 in human aortic endothelial cells. Exp Biol Med 229(3) (2004b): 255-63.
Kerrigan S, Lindsey T. Fatal caffeine overdose: two case reports. Forensic Sci Int 153(1) (2005): 67-9.
Kondo K et al. Inhibition of LDL oxidation by cocoa. Lancet 348(9040) (1996): 1514.
Kris-Etherton P et al. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. Metab Clin Exp 42(1) (1993): 121-9.
Lazarus SA et al. Chocolate contains additional flavonoids not found in tea. Lancet 354(9192) (1999): 1825.
Lee CM, Hardy CM. Cocoa feeding and human lactose intolerance. Am J Clin Nutr 49(5) (1989): 840-4.
Lee KW et al. Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. J Agric Food Chem 51(25) (2003): 7292-5.
Lopatka J et al. Cocoa powder aspiration. Clin Pediatr 43(1) (2004): 111-14.
Mao TK et al. Influence of cocoa procyanidins on the transcription of interleukin-2 in peripheral blood mononuclear cells. Int J Immunother 15(1) (1999): 23-9.
Mao T et al. Cocoa procyanidins and human cytokine transcription and secretion. J Nutr 130(8) (2000a): 2093-9S.
Mao TK et al. Effect of cocoa procyanidins on the secretion of interleukin-4 in peripheral blood mononuclear cells. J Med Food 3(2) (2000b): 107-14.
Mao TK et al. Modulation of TNF-alpha; secretion in peripheral blood mononuclear cells by cocoa flavanols and procyanidins. Dev Immunol 9(3) (2002): 135-41.
Mao TK et al. Cocoa flavonols and procyanidins promote transforming growth factor-beta1 homeostasis in peripheral blood mononuclear cells. Exp Biol Med 228(1) (2003): 93-9.

Marcus DA et al. A double-blind provocative study of chocolate as a trigger of headache. Cephalalgia 17(8) (1997): 855-62, discussion 800.
Maron DJ. Flavonoids for reduction of atherosclerotic risk. Curr Atheroscler Rep 6(1) (2004): 73-8.
Mathur S et al. (2002). Cocoa products decrease low density lipoprotein oxidative susceptibility but do not affect biomarkers of inflammation in humans. J Nutr 132(12): 3663-7.
Matsumoto M et al. Inhibitory effects of cacao bean husk extract on plaque formation in vitro and in vivo. Eur J Oral Sci 112(3) (2004): 249-52.
Michener W, Rozin P. Pharmacological versus sensory factors in the satiation of chocolate craving. Physiol Behav 56(3) (1994): 419-22.
Miller JB et al. The glycaemic index of foods containing sugars: Comparison of foods with naturally-occurring added sugars. Br J Nutr 73(4) (1995): 613-23.
Moffett AM et al. Effect of chocolate in migraine: a double blind study. J Neurol Neurosurg Psychiatr 37(4) (1974): 445-8.
Murphy KJ et al. Dietary flavanols and procyanidin oligomers from cocoa (Theobroma cacao) inhibit platelet function. Am J Clin Nutr 77(6) (2003): 1466-73.
Mursu J et al. Dark chocolate consumption increases HDL cholesterol concentration and chocolate fatty acids may inhibit lipid peroxidation in healthy humans. Free Radic Biol Med 37(9) (2004): 1351-9.
Osman H et al. Extracts of cocoa (Theobroma cacao L.) leaves and their antioxidation potential. Food Chem 86(1) (2004): 41-6.
Palenik CJ et al. Studies of antiplaque substances derived from cocoa. J Dent Res 56(Spec. B) (1977): 272.
Pearson DA et al. The effects of flavanol-rich cocoa and aspirin on ex vivo platelet function. Thromb Res 106(4-5) (2002): 191-7.
Raintree Nutrition. Tropical Plant Database: Database File for Chocolate (Theobroma Cocao). Carson City, 1996: Raintree Nutrition, Inc.
Ravenscroft J. Evidence based update on the management of acne. Arch Dis Child Educ Pract 90 (2005): ep98-101.
Record IR et al. Chocolate consumption, fecal water antioxidant activity, and hydroxyl Radic production. Nutr Cancer 47(2) (2003): 131-5.
Rein D et al. Epicatechin in human plasma: In vivo determination and effect of chocolate consumption on plasma oxidation status. J Nutr 130(8) (2000a): 2109-14S.
Rein D et al. Cocoa inhibits platelet activation and function. Am J Clin Nutr 72(1) (2000b): 30-5.
Rios LY et al. Cocoa procyanidins are stable during gastric transit in humans. Am J Clin Nutr 76(5) (2002): 1106-10.
Rozin P et al. Chocolate craving and liking. Appetite 17(3) (1991): 199-212.
Schramm DD et al. Chocolate procyanidins decrease the leukotriene-prostacyclin ratio in humans and human aortic endothelial cells. Am J Clin Nutr 73(1) (2001): 36-40.
Schroeter H et al. (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. Proc Ntl Acad Sci USA 103(4) (2006): 1024-9.
s'Gravenmade EJ et al. A potential cariostatic factor in cocoa beans. Caries Res 11(2) (1977): 138.
Shahkhalili Y et al. Digestibility of cocoa butter from chocolate in humans: a comparison with corn-oil. Eur J Clin Nutr 54(2) (2000): 120-5.
Shahkhalili Y et al. Calcium supplementation of chocolate: effect on cocoa butter digestibility and blood lipids in humans. Am J Clin Nutr 73(2) (2001): 246-52.
Sies H et al. Cocoa polyphenols and inflammatory mediators. Am J Clin Nutr 81(1) (2005): 304-12S.
Smit HJ et al. Methylxanthines are the psycho-pharmacologically active constituents of chocolate. Psychopharmacologia 176(3-4) (2004): 412-19.
Smith AP, Rich N. Effects of consumption of snacks on simulated driving. Percept Motor Skills 87(3 Pt 1) (1998): 817-18.
Steinberg FM et al. Cocoa and chocolate flavonoids: implications for cardiovascular health. J Am Diet Assoc 103(2) (2003): 215-23.



Stralfors A. Effect on hamster caries by dialysed, detanned or carbon-treated water-extract of cocoa. Arch Oral Biol 11(6) (1966): 609-15.
Taibjee SM et al. Orofacial granulomatosis worsened by chocolate: Results of patch testing to ingredients of Cadbury's chocolate. Br J Dermatol 150(3) (2004): 595.
Usmani OS et al. (2005). Theobromine inhibits sensory nerve activation and cough. FASEB J 19(2): 231-3.
Wan Y et al. Effects of cocoa powder and dark chocolate on LDL oxidative susceptibility and prostaglandin concentrations in humans. Am J Clin Nutr 74(5) (2001): 596-602.
Waterhouse AL et al. Antioxidants in chocolate. Lancet 348(9030) (1996): 834.
Weingarten HP, Elston D. Food cravings in a college population. Appetite 17 (1991): 167-75.
Wiswedel I et al. Flavanol-rich cocoa drink lowers plasma F(2)-isoprostane concentrations in humans. Free Radic Biol Med 37(3) (2004): 411-21.
Zhu QY et al. Influence of cocoa flavanols and procyanidins on free Radic-induced human erythrocyte hemolysis. Clin Dev Immunol 12(1) (2005): 27-34.
Zuskin E et al. Respiratory function and immunological status in cocoa and flour processing workers. Am J Indust Med 33(1) (1998): 24-32.

Coenzyme Q10



OTHER NAMES

Ubiquinone, ubidecarenone, ubiquinol

BACKGROUND AND RELEVANT PHARMACOKINETICS

Coenzyme Q10 (CoQ10) is an endogenous enzyme cofactor produced in humans from tyrosine through a cascade of reactions that itself requires eight vitamin coenzymes: tetrahydrobiopterin, vitamins B6, C, B2, B12, folic acid, niacin, and pantothenic acid (Folkers et al 1990). CoQ10 is also a fat-soluble antioxidant vitamin that plays an indispensable role in intracellular energy production.

Absorption occurs in the small intestine and tends to be poor, and is influenced by the presence of food and drink. CoQ10 is better absorbed in the presence of a fatty meal and is primarily bound to VLDL- and LDL- cholesterol. As such, serum levels of CoQ10 depend mostly on the amount of CoQ10-containing lipoproteins in circulation.

After incorporation into lipoproteins in the liver, CoQ10 is subsequently concentrated in various tissues, including the adrenals, spleen, kidneys, lungs and myocardium. Physical activity markedly reduces muscle tissue levels of CoQ10, which do not correlate to serum levels, suggesting they are independently regulated (Laaksonen et al 1995a, Overvad et al 1999).

CHEMICAL COMPONENTS

The basic structure of ubiquinones is a benzoquinone head and terpinoid tail. The number of isoprenoid units in the tail portion varies among coenzymes. CoQ10 contains one quinine group and 10 isoprenyl units (Overvad et al 1999). Ubiquinones have been found in microorganisms, plants and animals but the CoQ10 form is the most common type found in mammals and humans.

FOOD SOURCES

Meat and fish products are the most concentrated sources of CoQ10, although lesser quantities are found in boiled broccoli, cauliflower, nuts, spinach and soy.

DEFICIENCY SIGNS AND SYMPTOMS

No RDI levels have been established but there has been some speculation as to possible deficiency signs and symptoms. These include fatigue, muscle aches and pains and chronic gum disease.

Based on biopsy and/or serum samples, it has been observed that relative CoQ10 deficiency is associated with:

- congestive heart failure (Sole & Jeejeebhoy 2002, Spigset 1994a)
- cardiomyopathy (Mortensen et al 1990)
- hypertension (Karlsson et al 1991)
- ischaemic heart disease (Karlsson et al 1991)
- hyperthyroidism (Bianchi et al 1999)
- breast cancer (Folkers et al 1997).

At this stage it is still unclear whether an observation of relative deficiency in a particular disease state can be interpreted as part of the aetiology of that disease or whether lowered levels are a consequence of disease. In heart failure the situation is somewhat clearer, as patients with more advanced heart failure have significantly lower CoQ10 levels than those with less advanced conditions (Mortensen 1993).

A deficiency state may result from:

- impaired or reduced synthesis due to nutritional deficiencies, advancing age or medication use
- interactions with drugs — there is clinical evidence that lovastatin, pravastatin and simvastatin reduce CoQ10 status in humans, which may in part explain the incidence of side-effects, particularly myopathy, associated with their use (Bargossi et al 1994a, b, Folkers et al 1990, Mortensen et al 1997). Clinical evidence also suggests that use of gemfibrozil and other fibric acid derivatives reduce CoQ10 levels (Aberg et al 1998). In vitro evidence suggests that other drugs, such as clonidine, hydralazine, hydrochlorothiazide, methyldopa, metoprolol and propranolol, may also decrease endogenous production of CoQ10 (Kishi et al 1975). Other sources cite tricyclic antidepressants as further medicines that can reduce CoQ10 status (Pelton et al 1999)
- genetic or acquired defects in synthesis or utilisation
- inadequate intake or biosynthesis to meet increased requirements resulting from illness or excess physical exertion.

MAIN ACTIONS

ANTIOXIDANT

Being a vital electron and proton carrier, CoQ10 supports adenosine triphosphate synthesis in the mitochondrial inner membrane and stabilises cell membranes, preserving cellular integrity and function. It also reconstitutes vitamin E back into its antioxidant form (Kaikkonen et al 2002).

CARDIOPROTECTIVE

CoQ10 may offer myocardial protection during cardiac surgery, as suggested by some clinical trials that observed improved postoperative cardiac function and reduced myocardial structural damage with pre-surgery administration of CoQ10.

ANTIHYPERTENSIVE

In the 1970s Yamagami et al observed a deficiency in CoQ10 in patients with hypertension (1975, 1976) and suggested that correction of the deficiency could result in hypertensive effects. Small studies were initially conducted with hypertensive patients identified as CoQ10 deficient. Since then, significant antihypertensive activity has been observed in several clinical studies (Burke et al 2001, Digiesi et al 1994, Langsjoen et al 1994), however, not all have identified the subjects' baseline CoQ10 plasma levels and whether oral administration restored levels to within the normal range. It has been suggested that CoQ10 supplementation is associated with a decrease in total peripheral resistance, possibly because of action as an antagonist of vascular superoxide, either scavenging or suppressing its synthesis (McCarty 1999).

IMMUNOSTIMULANT ACTIVITY

Several models of immune function have demonstrated the immunostimulant activity of CoQ10 (Folkers & Wolaniuk 1985).

ENDOTHELIAL FUNCTION

A randomised study involving 40 dyslipidaemic patients with type 2 diabetes mellitus found that oral CoQ10 (200 mg daily) taken over 12 weeks improved the endothelial function of conduit arteries of the peripheral circulation (Watts et al 2002). Another study of 80 subjects using the same dose for the same treatment period failed to improve endothelial forearm vasodilator function when given alone, although when combined with fenofibrate, the effectiveness was significant (Playford et al 2003). Both research groups suggested that the effect may be due to an increase in the bioactivity of and/or responses to endothelium-derived relaxing factors, including nitric oxide.

OTHER ACTIONS

Tests in animal models have demonstrated that CoQ10 protects against doxorubicin cardiotoxicity, possibly via antioxidant activity and restoring depleted nutrient status (Combs et al 1977, Folkers et al 1978).

Recent research has identified that CoQ10 affects the expression of genes involved in human cell signalling, metabolism and transport (Groneberg et al 2005). This mechanism may account for some of the pharmacological effects observed with

CoQ10 supplementation. Additionally, CoQ10 inhibits the formation of beta-amyloid protein in vitro (Ono et al 2005).

CLINICAL USE

CARDIOVASCULAR DISEASES

In 1972 Folkers and Littaru from Italy documented a deficiency of coenzyme Q10 in human heart disease (Ernster & Dallner 1995).

Since those early reports, a steady stream of research articles have been published and clinical experience in its use as an adjunct to conventional treatment in various forms of heart disease has accumulated. Data from laboratory studies have also accumulated and generally provide a supportive basis for its use.

A review by Langsjoen and Langsjoen of over 34 controlled studies and additional open studies concluded that CoQ10 supplementation goes beyond the correction of a simple deficiency state with strong evidence to show it has the potential to reduce the risk of cardiovascular disease by the maintenance of optimal cellular and mitochondrial function in cardiomyocytes.

Although investigation into specific cardiovascular diseases has been undertaken, the results of an open study of 424 patients suggested that CoQ10 may have widespread benefits. The study found that CoQ10 supplementation produced clinically significant improvements in cardiac function and reduced medication requirements in patients with a range of cardiovascular disorders, including ischaemic cardiomyopathy, dilated cardiomyopathy, primary diastolic dysfunction, hypertension, mitral valve prolapse and valvular heart disease (Langsjoen et al 1994).

A recent review by Langsjoen and Langsjoen (1999) of more than 34 controlled studies and additional open studies concluded that CoQ10 supplementation goes beyond the correction of a simple deficiency state, with strong evidence to show it has the potential to reduce the risk of cardiovascular disease by the maintenance of optimal cellular and mitochondrial function in cardiomyocytes.

Congestive heart failure CoQ10 has been reported to improve symptoms of congestive heart failure (CHF) and QOL, and to reduce hospitalisation, and is used as standard therapy for CHF in some parts of Europe, Russia and Japan.

At the cellular level, oxidative stress, mitochondrial dysfunction and energy starvation are believed to play important roles in the aetiology of CHF (Overvad et al 1999). As such it has been suggested that low CoQ10 levels identified in patients with CHF may play a role in disease development (Jeejeebhoy et al 2002) and that restoring myocyte nutrition with vitamin supplementation, including CoQ10, produces significant improvement (Sole & Jeejeebhoy 2002). Furthermore, an inverse

relationship has been found between the severity of CHF and CoQ10 levels in blood from endocardial biopsies.

Clinical studies Currently, over 15 RCTs involving subjects with heart failure have been published in addition to numerous open-trials (Bhagavan & Chopra 2005).

One meta-analyses of 8 RCT found that adjunctive therapy with CoQ10 led to significant improvements in total work capacity, cardiac index, cardiac output and stroke volume (Soja & Mortensen 1997). The subjects had cardiomyopathy and CHF of varying aetiologies (idiopathic, dilated, ischaemia, hypertension, valvular heart disease and congenital heart disease).

In 1994, the results were published of a large multicentre trial of 2664 subjects with New York Heart Association (NYHA) classes II and III that had studied the effects of oral CoQ10 (predominantly 100 mg/day) over 3 months (Baggio et al 1994). The percentages of patients experiencing improvements in clinical signs and symptoms of heart failure were: 78% for cyanosis, 79% for oedema, 72% jugular reflux, 53% dyspnoea, 75% palpitations, 80% sweating, 63% subjective arrhythmia, 63% insomnia, 73% vertigo and 54% nocturia. Improvements in at least three symptoms were reported by 54% of subjects.

Currently, the largest controlled trial in adult cardiomyopathy and CHF was reported in 1993 (Morisco et al) and involved 641 patients with NYHA classes III and IV. The double-blind placebo-controlled study used a dose of 2 mg CoQ10 per kg daily over 1 year and found that active treatment significantly improved arrhythmias and episodes of pulmonary oedema, as well as reducing the number of hospitalisations and overall mortality rate. The same researchers conducted a smaller double-blind crossover study that again produced positive results. Oral CoQ10 (150 mg/day) taken for 4 weeks significantly improved ejection fraction (EF), stroke volume and cardiac output in chronic heart failure patients (Morisco et al 1994). A controlled crossover study of 79 subjects with chronic cardiomyopathy and congestive heart failure showed that 3 months treatment with CoQ10 (100 mg/day) significantly improved volume load EF, arteriovenous oxygen difference and QOL assessment (Hofman-Bang et al 1995). Another randomised, double-blind study of 22 heart failure patients (NYHA classes II and III) found treatment for 12 weeks with 200 mg coenzyme Q10 daily improved left ventricular EF (Munkholm et al 1999).

More recently, a double blind, placebo-controlled study involving 39 patients with a NYHA class II or III heart failure due to ischaemic or dilated cardiomyopathy found that despite the small sample size, 150 mg oral CoQ10 taken for 3 months resulted in significant improvement of 0.5 class compared with placebo (Keogh et al 2003). Other parameters that showed significant improvements were Specific Activities Scale

class and the 6-minute walk-test distance, and there was a significant correlation between the increase in exercise time and the increase in serum CoQ10 level. Of note, patients were also receiving maximal non-beta-blocker therapy.

Although CoQ10 is generally studied in heart failure patients (NYHA class II and III), a double-blind, placebo-controlled, randomised study published in 2004 (Berman et al) describes its effects in end-stage heart failure among patients awaiting heart transplantation. The study of 32 subjects compared Ultrasome CoQ10 (60 mg/day) to placebo over 3 months as an adjunct to conventional therapy. Significant improvements in functional status, clinical symptoms and QOL were reported for CoQ10; however, no significant changes in the echocardiography parameters (dimensions and contractility of cardiac chambers) or ANF and TNF blood levels were observed.

These results are clearly encouraging; however, three controlled studies in CHF have failed to demonstrate an additional improvement with CoQ10 above that achieved for pharmaceutical therapy (Khatta 2000, Permanetter et al 1989, Watson et al 1999). One theory proposes that the most profound effects on myocardial function occur when supplementation is given shortly after the diagnosis of CHF and before the development of irreversible myocyte loss and fibrosis. Some commentators have suggested that the sample sizes, severity and duration of disease, treatment dose and duration of treatment may have contributed to the neutral effects observed (Langsjoen 2000). An important issue that often fails to be considered is the measurement of plasma and myocyte CoQ10 concentrations and whether supplementation has achieved levels that are within the range likely to produce clinical results.

The review by Langsjoen and Langsjoen in 1999 suggests that maximal effects on the mitochondrial bioenergetics of the heart muscle appear to require above normal plasma levels.

HYPERTENSION AND CHOLESTEROL LOWERING

CoQ10 has been studied both as stand-alone and adjunctive treatment in hypertension. According to a review of 8 studies, supplemental CoQ10 results in a mean decrease in systolic blood pressure of 16 mmHg and in diastolic blood pressure of 10 mmHg (Rosenfeldt et al 2003). The effect on blood pressure has been reported within 10 weeks of treatment at doses usually starting at 100 mg daily. One small 10-week open study of 26 subjects with essential hypertension study found that an oral dose of 50 mg taken twice daily also reduced total serum cholesterol levels with a modest increase in serum HDL-cholesterol (Digiesi et al 1994).

CARDIAC SURGERY

The use of CoQ10 supplementation before cardiac surgery has been studied since the early 1980s. Since that time, growing evidence suggests that CoQ10 can reduce reperfusion injury after coronary artery bypass surgery, reduce surgical complications, accelerate recovery times and possibly shorten hospital stays (Chello et al 1996, Chen et al 1994, Judy et al 1993, Rosenfeldt et al 2002, Taggart et al 1996, Tanaka et al 1982, Zhou et al 1999). In general, the studies that achieved positive results had provided supplements for 1–2 weeks prior to surgery.

One study observed that continuing to administer CoQ10 for 30 days after surgery hastened the recovery course to 3–5 days without complications, compared with a 15–30-day recovery period for a control group, which did experience complications (Judy et al 1993, Rosenfeldt et al 2002).

The most recent randomised, double-blind trial investigated the effects of preoperative high-dose CoQ10 therapy (300 mg/day) in patients undergoing elective cardiac surgery (mainly coronary artery bypass graft surgery or valve replacement) (Rosenfeldt et al 2005). Approximately 2 weeks of active treatment resulted in significantly increased CoQ10 levels in the serum, atrial myocardium and mitochondria compared with placebo, but no significant change in the duration of hospital stay. Active treatment also improved subjective assessment of physical QOL (+13%) compared with placebo; however, the authors point out that physical QOL does not necessarily indicate improved cardiac pump function and further studies are required with larger sample sizes to clarify the role of CoQ10 in cardiac surgery.

The use of CoQ10 as preoperative treatment may hold special significance for older patients, who generally experience poorer recovery of cardiac function after cardiac surgery than their younger counterparts. One explanation gaining support is that the aged myocardium has less homeostatic reserve and so is more sensitive to both aerobic and physical stress and less well equipped to deal with cardiac surgery. Two studies have confirmed this theory, demonstrating an age-related deficit in myocardial performance after aerobic and ischaemic stress and the capacity of CoQ10 treatment to correct age-specific diminished recovery of function (Rosenfeldt et al 1999).

Besides improving cardiac resilience, CoQ10 has been found to reduce skeletal muscle reperfusion injury after clamping and declamping by reducing the degree of peroxidative damage (Chello et al 1996).

ANGINA PECTORIS

Based on the observation of relative CoQ10 deficiency in patients with ischaemic heart disease, and in animal models showing that it prevents reperfusion injury,

several randomised clinical trials have been performed in angina pectoris. The doses used have varied from 60 mg to 600 mg daily, and the time frames for use varied from 4 days to 4 weeks. Overall, CoQ10 appears to delay signs of oxygen deficiency in the myocardium, increases patients' stamina on a treadmill or during exercise and delays the onset of angina (Overvad et al 1999), as well as reducing nitroglycerin consumption (Kamikawa et al 1985).

STATIN DRUG USE

The mechanism of action of the statin group of drugs is inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase, an enzyme involved in the biosynthesis of cholesterol from acetyl-CoA. Inhibition of this enzyme also adversely effects the intrinsic biosynthesis of CoQ10, as demonstrated in laboratory animals and humans and reduces plasma and myocardial levels of CoQ10 (Bargossi et al 1994b, Folkers et al 1990, Rosenfeldt et al 2005). Studies have indicated that reductions of 20–30% in circulating coenzyme Q10 concentrations may be expected in response to treatment with statins (Nawarskas 2005); however, it is uncertain whether reduced serum levels are of clinical consequence. It is more likely that reduced muscle CoQ10 concentrations are of greater concern because they may be associated with impaired cardiac function. The results obtained by Folkers et al (1990) and Silver et al (2004) provide some support for this rationale; however, a study by Colquhoun et al (2005) casts doubt on this relationship. Folkers et al showed that oral administration of CoQ10 to five hospitalised patients with cardiac disease made worse with lovastatin, produced an improvement in cardiac function (1990). Silver et al found that left ventricular diastolic function worsened in 10 of 14 patients after atorvastatin therapy, as observed with Doppler echocardiography (2004). When CoQ10 (300 mg/day) was administered to 9 of these patients, 8 experienced a reversal of diastolic abnormality. In contrast, Colquhoun et al (2005) studied left ventricular EF in 21 hypercholesterolaemic subjects with normal function receiving simvastatin over 6 months. After 1 month, EF significantly decreased; however, no significant changes were observed after 3 or 6 months and washout of simvastatin. No association was found between the size of the reduction in EF and the reduction in plasma CoQ10 level after 1 month.

There has been some suggestion that the side-effects of myalgia, fatigue and rhabdomyolisis associated with statin treatment may be dependent on CoQ10 depletion. A recent study identified that statin-induced myopathy can be associated with a mild decrease in muscle CoQ10 concentration, providing some support for this theory (Lamperti et al 2005). Numerous anecdotal reports suggest that some patients using statin therapy long-term and experiencing fatigue find benefit with CoQ10

supplementation; however, controlled trials are unavailable to determine the significance of these observations. A case study by Walravens et al (1989) illustrates the point.

A 48-year-old physician was taking lovastatin 20 mg/day for moderate hypercholesterolaemia and he also jogged three times a week, with occasional high-altitude cycling. After 2–3 weeks of lovastatin treatment, exercise became difficult because of muscle soreness and fatigue and at 7 weeks he had severe cramps while cycling. Soreness and weakness continued for 6 months, after which he began taking CoQ10 (30 mg daily). After a few days' treatment, muscle fatigue after exercise ceased and the severe cramps did not recur. Restarting lovastatin 10 mg 5–6 times weekly did not result in muscle cramping while CoQ10 was taken.

Currently it is still not clear whether CoQ10 supplementation should be considered a necessary adjunct to all patients taking statin drugs; however, those patients considered at risk of deficiency may benefit, in particular, patients with a family history of heart failure, elevated cholesterol levels and who are over 65 years of age and taking statin drugs long-term (Levy & Kohlhaas 2006).

ARRHYTHMIAS

A small open study of 27 volunteers showed that CoQ10 exerts antiarrhythmic effects in some individuals (Fujioka et al 1983).

SPORTS SUPPLEMENT/ERGOGENIC AID

Because CoQ10 is essential for energy metabolism, researchers have speculated that it may improve athletic performance. Eight clinical studies investigating the effects of CoQ10 supplementation on physical capacity were located, generally showing negative results (Bonetti et al 2000, Braun et al 1991, Laaksonen et al 1995, Malm et al 1997, Nielsen et al 1999, Porter et al 1995, Snider et al 1992, Weston et al 1997, Ylikoski et al 1997). Test doses of CoQ10 varied between 60 mg to 150 mg daily over time periods of 28 days to 8 weeks. Of these eight studies, only one double-blind crossover trial produced positive results on both objective and subjective parameters of physical performance (Ylikoski et al 1997). In that study 94% of athletes felt that CoQ10 had improved their performance and recovery times, compared with the 33% receiving placebo.

Of the others, one study found that 150 mg CoQ10 taken over 2 months had no effect on maximal oxygen consumption, lactate thresholds or forearm blood flow, although it did improve the subjective perceived level of vigour (Porter et al 1995). Another study demonstrated that CoQ10 did not alter physiological or metabolic parameters measured as part of cardiopulmonary exercise testing; however, it did

extend the time and the workload required to reach muscular exhaustion (Bonetti et al 2000). Five further clinical trials produced negative results.

One retrospective study found that muscle CoQ10 levels were positively related to exercise capacity and/or marathon performance, suggesting that runners with the highest levels performed better than those with lower levels (Karlsson et al 1996).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

At least two clinical trials have investigated the use of CoQ10 supplementation in COPD (Fujimoto et al 1993, Satta et al 1991). In one study, 20 patients with COPD were randomly assigned CoQ10 (50 mg) or placebo as part of their pulmonary rehabilitation program (Satta et al 1991). Treatment resulted in a 13% increase in maximum oxygen consumption and a 10% increase in maximum expired volume, both significant improvements. A dose of CoQ10 (90 mg) daily over 8 weeks was studied in a smaller trial of patients with COPD (Fujimoto et al 1993). Significantly elevated serum CoQ10 levels were associated with improved hypoxaemia at rest, but pulmonary function was unchanged.

PERIODONTAL DISEASE

CoQ10 is used both topically and internally for the treatment of chronic periodontal disease. Topical application has been shown to improve adult peridontitis (Hanioka et al 1994) and a small open study has shown that oral CoQ10 supplementation can produce dramatic results within 5–7 days, making location of baseline biopsy sites impossible (Wilkinson et al 1975).

PARKINSON'S DISEASE

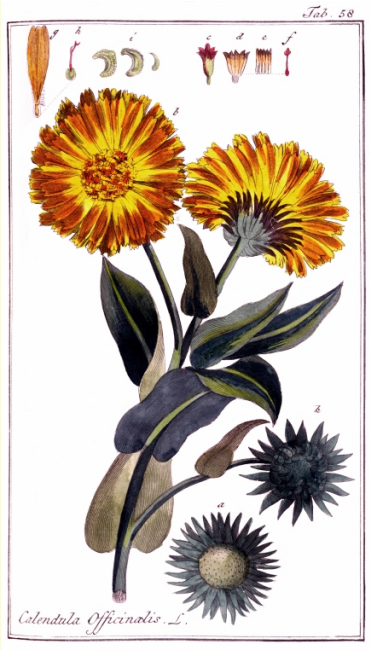
There is currently much speculation about the aetiology of Parkinson's disease. Recent experiments suggest that mitochondrial impairment may play a role in the degeneration of nigrostriatal dopaminergic neurons (Ebadi et al 2001, Gotz et al 2000). Additionally, oxidative damage and inflammation are now considered contributing factors.

A number of preclinical studies using in vitro and in vivo models of Parkinson's disease have demonstrated that CoQ10 can protect the nigrostriatal dopaminergic system, and levels of CoQ10 have been reported to be decreased in blood and platelet mitochondria from subjects with Parkinson's disease (Shults 2005). As a result, a multicentre study was conducted to determine whether CoQ10 supplementation would exert beneficial effects in the disease.

The randomised, placebo-controlled double-blind study compared three different doses of CoQ10 (300 mg, 600 mg or 1200 mg) with placebo in 80 subjects with early Parkinson's disease. After 9 months of treatment, subjects taking 1200 mg CoQ10

daily experienced significant improvements in disability compared with the placebo group. CoQ10 was also well tolerated at the dosages studied (Shults et al 2002). In 2003, results were published of a double-blind placebo controlled study that showed that even a relatively low dose CoQ10 (360 mg/day) taken for a short period (4 weeks) produced a significant mild benefit on Parkinson's disease symptoms and significantly improved visual function compared with placebo (Muller et al 2003).

The safety and tolerability of high dose CoQ10 in subjects with Parkinson's disease was investigated in an open study of 17 patients (Shults et al 2004). The study used an escalating dosage of 1200, 1800, 2400, and 3000 mg/day administered together with vitamin E (alpha-tocopherol) 1200 IU/day and failed to identify any serious adverse effects with CoQ10 administration. It also identified that plasma CoQ10 levels reached a plateau at 2400 mg/day, suggesting that higher treatment doses are not required.



ALZHEIMER'S DEMENTIA

Similarly to Parkinson's disease, mitochondrial dysfunction and oxidative damage appear to play a role in the pathogenesis of Alzheimer's dementia and therefore CoQ10 supplementation has been investigated as a possible treatment. Currently, evidence is limited to test tube and animal studies and is far from definitive.

Recently, CoQ10 was shown to inhibit beta amyloid formation in vitro (Ono et al 2005) and protect against brain mitochondrial dysfunction induced by a neurotoxic beta-peptide in a study using brain mitochondria isolated from diabetic rats (Moreira et al 2005). McDonald et al (2005) conducted two studies with test animals and found that supplemental CoQ10 (123 mg/kg/day) taken with alpha-tocopherol acetate (200 mg/kg/day) improved age related learning deficits; however, supplementation of CoQ10 alone at this dose, or higher doses of 250 or 500 mg/kg/day, failed to produce comparable effects.

MIGRAINE

An open-labelled trial investigated the effects of oral CoQ10 supplementation (150 mg/day) over 3 months in 32 volunteers with a history of episodic migraine with or without aura. CoQ10 significantly reduced both the frequency of attacks and the number of days with migraine after 3 months' treatment (Rozen et al 2002). In 2005, Sandor et al investigated the effects of CoQ10 (300 mg/day) taken over 3 months in 42 migraine subjects in a double-blind, randomised, placebo controlled study. 47.6% of CoQ10 treated patients responded to treatment compared with 14.4% for placebo, experiencing a (50% or less) reduction in migraine frequency (number needed to treat, 3). Active treatment was superior to placebo for reducing attack

frequency, headache days and days with nausea in the third treatment month and was well tolerated.

OTHER USES

CANCER

Currently, controlled studies are not available to determine the clinical effectiveness of CoQ10 in cancer; however, there have been several case reports of CoQ10 (390 mg/day) successfully reducing metastases or eliminating tumours entirely (Lockwood et al 1994, 1995). An in vivo study found that CoQ10 enhances the effects of immunochemotherapy (Kokawa et al 1983).

There is some evidence that CoQ10 supplementation protects the mitochondria of the heart from anthracycline-induced damage. A systematic review of six studies (three randomised) in which patients in five of the six studies received anthracyclines concluded that CoQ10 provides some protection against cardiotoxicity or liver toxicity during cancer treatment; however, the results were not conclusive and further research is required (Roffe et al 2004).

MITOCHONDRIAL MYOPATHY

An open multicentre study involving 44 volunteers with mitochondrial myopathies showed that treatment with CoQ10 (2 mg/kg/daily) over 6 months decreased post-exercise lactate levels by at least 25% in 16 patients. Of those responding, a further 3 months' treatment with either CoQ10 or placebo produced no significant differences (Bresolin et al 1990).

HUNTINGTON'S CHOREA

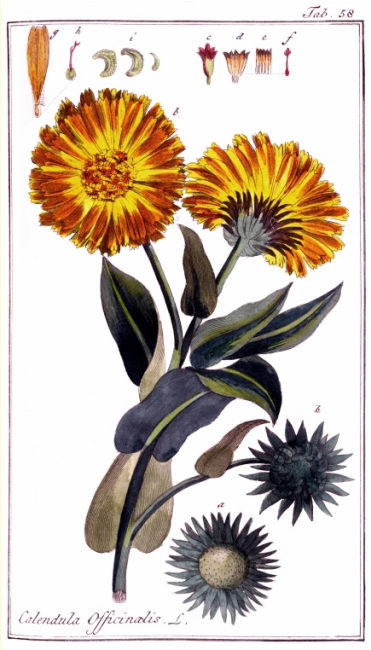
A randomised double-blind study involving 347 patients with early Huntington's chorea showed that a dose of CoQ10 (600 mg/day) taken over 30 months produced a trend towards slow decline as well as beneficial trends in some secondary measures; however, changes were not significant at this dosage level (Huntington's Study Group 2001).

DOSAGE RANGE

ACCORDING TO CLINICAL STUDIES

- Generally 100–150 mg/day has been used for conditions such as congestive cardiac failure (Mortensen et al 1990), hypertension, neurological disease, performance enhancement, periodontal disease (Wilkinson et al 1975).
- As preparation for cardiac surgery: 100–300 mg/day for 2 weeks before surgery followed by 100 mg/day for 1 month after surgery has been used (Judy et al 1993,

Rosenfeldt et al 2002, 2005); 30–60 mg taken for 6 days before surgery has also been found to be effective (Tanaka et al 1982).
- Angina pectoris: 60–600 mg daily
- Chronic obstructive pulmonary disease: 50–90 mg daily
- Huntington's chorea: 600 mg daily
- Migraine: 150–300 mg daily
- Parkinson's disease (<12,000 mg/day) (Shults et al 2002)



ADVERSE REACTIONS

CoQ10 appears relatively safe and non-toxic and is extremely well tolerated. Dizziness, nausea, epigastric discomfort, anorexia, diarrhoea, photophobia, irritability and skin rash occur in less than 1% of patients. This tends to occur with higher doses (>200 mg/day).

SIGNIFICANT INTERACTIONS

When controlled studies are not available, interactions are based on evidence of pharmacological activity, case reports and other evidence and are largely theoretical.

The following pharmaceutical drugs are suspected to reduce CoQ10 levels, so increased CoQ10 intake may be required with long-term drug therapy:
- beta-adrenergic antagonists
- clonidine
- gemfibrozil
- HMG-CoA-reductase inhibitors: simvastatin, pravastatin and lovastatin reduce both endogenous synthesis of CoQ10 and the serum concentration (Overvad et al 1999). Supplementation with CoQ10 may counter this effect without adversely affecting HMG-CoA-reductase inhibitor efficacy (Bargossi et al 1994a, b, Mortensen et al 1997).
- hydralazine
- hydrochlorothiazide
- methyldopa
- tricyclic antidepressants

WARFARIN

There are three case reports suggesting that CoQ10 may decrease the INR in patients previously stabilised on anticoagulants (Spigset 1994b). However, a double-blind crossover study involving 24 outpatients on stable long-term warfarin found that oral CoQ10 (100 mg) daily had no significant effect on INR or warfarin levels (Engelson 2003). Observe patients using high CoQ10 doses and taking warfarin.

DOXORUBICIN
Contradictory evidence exists as to whether oral CoQ10 supplementation reduces the cardiotoxicity of doxorubicin — potentially beneficial interaction (Combs et al 1977, Zhou 2002).

TIMOLOL
Eye drops — oral CoQ10 reduced the vascular side-effects of timolol without affecting eye pressure (Takahashi 1989) — beneficial interaction.

VITAMIN E
Reconstitutes oxidised vitamin E to its unoxidised form — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS
Insufficient reliable evidence — unknown.

PREGNANCY USE
Safety has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING
- CoQ10 is a safe antioxidant vitamin used in supplement form for a wide range of cardiovascular diseases, such as heart failure, hypertension and angina, with generally positive evidence supporting its use.
- Preliminary research has shown that presurgical supplementation has positive effects in cardiac surgery and improves recovery.
- There is also some clinical evidence suggesting a role in migraine headache, Huntington's chorea, mitochondrial myopathy, COPD, periodontal disease and slowing the progression of Parkinson's disease.
- Several common medicines, such as statins, have been found to reduce serum CoQ10 status. Although still speculative, case reports show that CoQ10 supplements have reversed some side-effects associated with statin drugs.

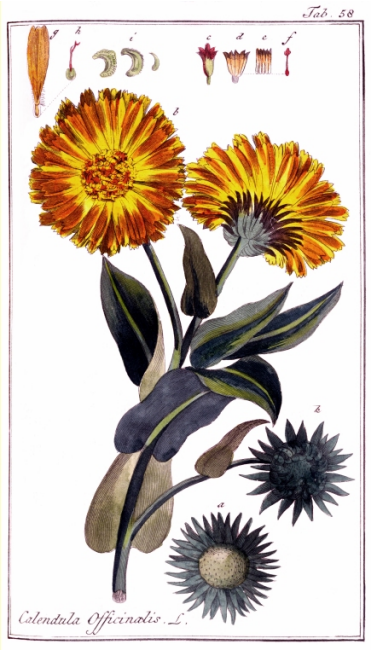
ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this vitamin do for me?
CoQ10 is an antioxidant vitamin used in every cell of the body. It is necessary for healthy function and can improve heart function, lower blood pressure and reduce angina. Taken before cardiac surgery it has been shown to reduce complications and hasten recovery in some studies. It may also provide benefits in periodontal disease, migraine headache, Huntington's chorea, mitochondrial myopathy, COPD and slow the progression of Parkinson's disease.

When will it start to work?

This depends on the indication. For heart conditions and to reduce migraine, 10–12 weeks may be required. To delay the progression of Parkinson's disease, one study found that effects started after 9 months' use.

Are there any safety issues?

Medical monitoring is required in patients taking warfarin and starting high dose CoQ10 supplements; however, even high dose supplements are well tolerated and considered safe.



REFERENCES

Aberg F et al. Gemfibrozil-induced decrease in serum ubiquinone and alpha- and gamma-tocopherol levels in men with combined hyperlipidaemia. Eur J Clin Invest 28.3 (1998): 235-42.

Baggio E et al. Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. CoQ10 Drug Surveillance Investigators. Mol Aspects Med 15 (Suppl) (1994): S287-94.

Bargossi AM et al. Exogenous CoQ10 preserves plasma ubiquinone levels in patients treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Int J Clin Lab Res 24.3 (1994a): 171-6.

Bargossi AM et al. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Mol Aspects Med 15 Suppl (1994b): S187-93.

Berman M et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation. a randomized, placebo-controlled study. Clin Cardiol 27 (2004): 295-9.

Bhagavan HN, Chopra RK. Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy. Clin Nutr 24 (2005): 331-8.

Bianchi G et al. Oxidative stress and anti-oxidant metabolites in patients with hyperthyroidism: effect of treatment. Horm Metab Res 31.11 (1999): 620-4.

Bliznakov EG. Cardiovascular diseases, oxidative stress and antioxidants: the decisive role of coenzyme Q10. Cardiovasc Res 43.1 (1999): 248-9.

Bonetti A et al. Effect of ubidecarenone oral treatment on aerobic power in middle-aged trained subjects. J Sports Med Phys Fitness 40.1 (2000): 51-7.

Braun B et al. Effects of coenzyme Q10 supplementation on exercise performance, VO2max, and lipid peroxidation in trained cyclists. Int J Sport Nutr 1.4 (1991): 353-65.

Bresolin N et al. Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. J Neurol Sci 100.1-2 (1990): 70-8.

Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. South Med J 94.11 (2001): 1112-17.

Chello M et al. Protection by coenzyme Q10 of tissue reperfusion injury during abdominal aortic cross-clamping. J Cardiovasc Surg (Torino) 37.3 (1996): 229-35.

Chen YF, Lin YT, Wu SC. Effectiveness of coenzyme Q10 on myocardial preservation during hypothermic cardioplegic arrest. J Thorac Cardiovasc Surg 107 (1994): 242-7.

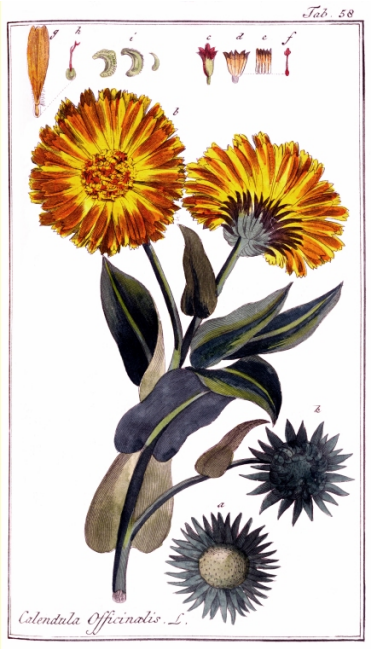
Colquhoun DM et al. Effects of simvastatin on blood lipids, vitamin E, coenzyme Q10 levels and left ventricular function in humans. Eur J Clin Invest 35 (2005): 251-8.

Combs AB et al. Reduction by coenzyme Q10 of the acute toxicity of adriamycin in mice. Res Commun Chem Pathol Pharmacol 18.3 (1977): 565-8.

Digiesi V et al. Coenzyme Q10 in essential hypertension. Mol Aspects Med 15 (Suppl) (1994): S257-63.

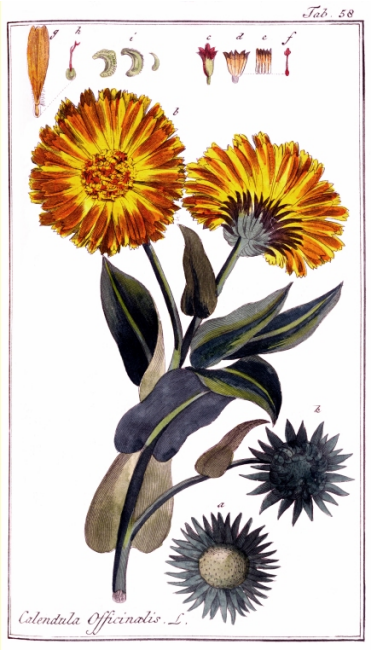
Ebadi M et al. Ubiquinone (coenzyme q10) and mitochondria in oxidative stress of parkinson's disease. Biol Signals Recept 10.3-4 (2001): 224-53.

Engelson J, Nielson JD, Hansen KF. Effect of coenzyme Q10 and Ginkgo biloba on warfarin dosage in patients on long-term warfarin treatment: A randomized, double-blind, placebo-controlled cross-over trial. Ugeskr Laeger 165.18 (2003): 1868-71.
Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta 1271.1 (1995): 195-204.
Folkers K. Relevance of the biosynthesis of coenzyme Q10 and of the four bases of DNA as a rationale for the molecular causes of cancer and a therapy. Biochem Biophys Res Commun 224.2 (1996): 358-61.
Folkers K, Wolaniuk A. Research on coenzyme Q10 in clinical medicine and in immunomodulation. Drugs Exp Clin Res 11.8 (1985): 539-45.
Folkers K, Choe JY, Combs AB. Rescue by coenzyme Q10 from electrocardiographic abnormalities caused by the toxicity of adriamycin in the rat. Proc Natl Acad Sci USA 75.10 (1978): 5178-80.
Folkers K et al. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA 87.22 (1990): 8931-4.
Folkers K et al. Activities of vitamin Q10 in animal models and a serious deficiency in patients with cancer. Biochem Biophys Res Commun 234.2 (1997): 296-99.
Fujimoto S et al. Effects of coenzyme Q10 administration on pulmonary function and exercise performance in patients with chronic lung diseases. Clin Invest 71.8 (Suppl) (1993): S162-6.
Fujioka,T, Sakamoto Y, Mimura G. Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report): antiarrhythmic action of coenzyme Q10 in diabetics. Tohoku J Exp Med 141 (Suppl) (1983): 453-63.
Gotz ME et al. Altered redox state of platelet coenzyme Q10 in Parkinson's disease. J Neural Transm 107.1 (2000): 41-8.
Groneberg DA et al. Coenzyme Q10 affects expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. Int J Biochem Cell Biol 37 (2005): 1208-18.
Hanioka T et al. Effect of topical application of coenzyme Q10 on adult periodontitis. Mol Aspects Med 15 (Suppl) (1994): S241-8.
Hofman-Bang C et al. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure: The Q10 Study Group. J Card Fail 1 (1995): 101-7.
Huntington's Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. Neurology 57.3 (2001): 397-404.
Jeejeebhoy F et al. Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. Am Heart J 143.6 (2002): 1092-100.
Judy WV, Stogsdill WW, Folkers K. Myocardial preservation by therapy with coenzyme Q10 during heart surgery. Clin Invest 71.8 (Suppl) (1993): S155-61.
Kaikkonen J et al. Coenzyme Q10: absorption, antioxidative properties, determinants, and plasma levels. Free Radic Res 36.4 (2002): 389-97.
Kamikawa T et al. Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. Am J Cardiol 56.4 (1985): 247-51.
Karlsson J et al. Muscle fibre types, ubiquinone content and exercise capacity in hypertension and effort angina. Ann Med 23.3 (1991): 339-44.
Karlsson J et al. Muscle ubiquinone in healthy physically active males. Mol Cell Biochem 156.2 (1996): 169-72.
Keogh A et al. Randomised double-blind, placebo-controlled trial of coenzyme Q10 therapy in class II and III systolic heart failure. Heart Lung Circ 12 (2003): 135-41.
Khatta M et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 132 (2000): 636-40.
Kishi H, Kishi T, Folkers K. Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs. Res Commun Chem Pathol Pharmacol 12.3 (1975): 533-40.



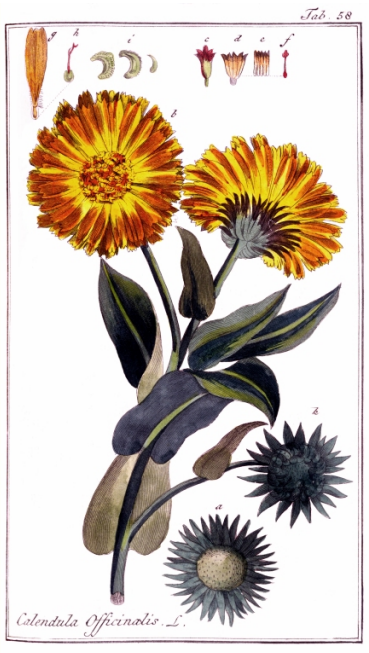
Kokawa T et al. Coenzyme Q10 in cancer chemotherapy: experimental studies on augmentation of the effects of masked compounds, especially in the combined chemotherapy with immunopotentiators. Gan To Kagaku Ryoho 10.3 (1983): 768-74.
Laaksonen R et al. Serum and muscle tissue ubiquinone levels in healthy subjects. J Lab Clin Med 125.4 (1995a): 517-21.
Laaksonen R et al. Ubiquinone supplementation and exercise capacity in trained young and older men. Eur J Appl Physiol Occup Physiol 72.1-2 (1995b): 95-100.
Lamperti C et al. Muscle coenzyme Q10 level in statin-related myopathy. Arch Neurol 62 (2005): 1709-12.
Langsjoen H et al. Usefulness of coenzyme Q10 in clinical cardiology: a long-term study. Mol Aspects Med 15 (Suppl) (1994): S165-75.
Langsjoen P et al. Treatment of essential hypertension with coenzyme Q10. Mol Aspects Med 15 (Suppl) (1994): S265-72.
Langsjoen PH. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. J Am Coll Cardiol 35.3 (2000): 816-17.
Langsjoen PH, Langsjoen AM. Overview of the use of CoQ10 in cardiovascular disease. Biofactors 9 (1999): 273-84.
Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme q10 during statin therapy. Ann Pharmacother 40 (2006): 290-4.
Lockwood K, Moesgaard S, Folkers K. Partial and complete regression of breast cancer in patients in relation to dosage of coenzyme Q10. Biochem Biophys Res Commun 199.3 (1994): 1504-8.
Lockwood K et al. Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases. Biochem Biophys Res Commun 212.1 (1995): 172-7.
Malm C et al. Effects of ubiquinone-10 supplementation and high intensity training on physical performance in humans. Acta Physiol Scand 161.3 (1997): 379-84.
McCarty MF. Coenzyme Q versus hypertension: does CoQ decrease endothelial superoxide generation? Med Hypotheses 53.4 (1999): 300-4.
McDonald SR, Sohal RS, Forster MJ. Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice. Free Radic Biol Med 38 (2005): 729-36.
Moreira PI et al. CoQ10 therapy attenuates amyloid beta-peptide toxicity in brain mitochondria isolated from aged diabetic rats. Exp Neurol 196 (2005): 112-19.
Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure. a long-term multicenter randomized study. Clin Invest 71 (1993): S134-6.
Morisco C et al. Noninvasive evaluation of cardiac hemodynamics during exercise in patients with chronic heart failure. effects of short-term coenzyme Q10 treatment. Mol Aspects Med 15 (Suppl) (1994): S155-63.
Mortensen SA et al. Coenzyme Q10: clinical benefits with biochemical correlates suggesting a scientific breakthrough in the management of chronic heart failure. Int J Tissue React 12.3 (1990): 155-62.
Mortensen SA. Perspectives on therapy of cardiovascular diseases with coenzyme Q10 (ubiquinone). Clin Invest 71.8 (Suppl) (1993): S116-23.
Mortensen SA et al. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med 18 (Suppl) (1997): S137-44.
Muller T et al. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neurosci Lett 341 (2003): 201-4.
Munkholm H, Hansen HH, Rasmussen K. Coenzyme Q10 treatment in serious heart failure. Biofactors 9 (1999): 285-9.
Nawarskas JJ. HMG-CoA reductase inhibitors and coenzyme Q10. Cardiol Rev 13 (2005): 76-9.
Nielsen AN et al. No effect of antioxidant supplementation in triathletes on maximal oxygen uptake, 31P-NMRS detected muscle energy metabolism and muscle fatigue. Int J Sports Med 20.3 (1999): 154-8.
Ono K et al. Preformed beta-amyloid fibrils are destabilized by coenzyme Q10 in vitro. Biochem Biophys Res Commun 330 (2005): 111-16.
Overvad K et al. Coenzyme Q10 in health and disease. Eur J Clin Nutr 53.10 (1999): 764-70.

Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Lexi-Comp. Inc., 1999.
Permanetter B et al. Lack of effectiveness of coenzyme Q10 (ubiquinone) in long-term treatment of dilated cardiomyopathy. Z Kardiol 78.6 (1989): 360-5.
Playford DA et al. Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type 2 diabetes. Atherosclerosis 168 (2003): 169-79.
Porter DA et al. The effect of oral coenzyme Q10 on the exercise tolerance of middle-aged, untrained men. Int J Sports Med 16.7 (1995): 421-7.
Roffe L, Schmidt K, Ernst E. Efficacy of coenzyme Q10 for improved tolerability of cancer treatments. a systematic review. J Clin Oncol 22 (2004): 4418-24.
Rosenfeldt F et al. Coenzyme Q10 improves the tolerance of the senescent myocardium to aerobic and ischemic stress: studies in rats and in human atrial tissue. Biofactors 9.2-4 (1999): 291-9.
Rosenfeldt F et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. J Thorac Cardiovasc Surg 129 (2005): 25-32.
Rosenfeldt F et al. The effects of ageing on the response to cardiac surgery: protective strategies for the ageing myocardium. Biogerontology 3 (2002): 37-40.
Rosenfeldt F et al. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. Biofactors 18 (2003): 91-100.
Rozen TD et al. Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia 22.2 (2002): 137-41.
Sandor PS et al. Efficacy of coenzyme Q10 in migraine prophylaxis. a randomized controlled trial. Neurology 64 (2005): 713-15.
Satta A et al. Effects of ubidecarenone in an exercise training program for patients with chronic obstructive pulmonary diseases. Clin Ther 13.6 (1991): 754-7.
Shults CW. Therapeutic role of coenzyme Q(10) in Parkinson's disease. Pharmacol Ther 107 (2005): 120-30.
Shults CW et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 59.10 (2002): 1541-50.
Shults CW et al. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. Exp Neurol 188 (2004): 491-4.
Silver MA et al. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. Am J Cardiol 94 (2004): 1306-10.
Snider IP et al. Effects of coenzyme athletic performance system as an ergogenic aid on endurance performance to exhaustion. Int J Sport Nutr 2.3 (1992): 272-86.
Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med 18 Suppl (1997): S159-68.
Sole MJ, Jeejeebhoy KN. Conditioned nutritional requirements: therapeutic relevance to heart failure. Herz 27.2 (2002): 174-8.
Spigset O. Coenzyme Q10 (ubiquinone) in the treatment of heart failure. Are any positive effects documented? Tidsskr Nor Laegeforen 114.8 (1994a): 939-42.
Spigset, O. Reduced effect of warfarin caused by ubidecarenone. Lancet 344 (1994b): 1372-3.
Taggart DP et al. Effects of short-term supplementation with coenzyme Q10 on myocardial protection during cardiac operations. Ann Thorac Surg 61 (1996): 829-33.
Takahashi N et al. Effect of coenzyme Q10 on hemodynamic response to ocular timolol. J Cardiovasc Pharmacol 14.3 (1989): 462-8.
Tanaka J et al. Coenzyme Q10: the prophylactic effect on low cardiac output following cardiac valve replacement. Ann Thorac Surg 33.2 (1982): 145-51.
Walravens PA, Greene C, Freeman FE. Lovastatin, isoprenes, and myopathy. Lancet 2 (1989): 1097-8.
Watson PS et al. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. J Am Coll Cardiol 33.6 (1999): 1549-52.
Watts GF et al. Coenzyme Q(10) improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. Diabetologia 45 (2002): 420-6.



Weston SB et al. Does exogenous coenzyme Q10 affect aerobic capacity in endurance athletes? Int J Sport Nutr 7.3 (1997): 197-206.
Wilkinson EG et al. Bioenergetics in clinical medicine. II. Adjunctive treatment with coenzyme Q in periodontal therapy. Res Commun Chem Pathol Pharmacol 12.1 (1975): 111-23.
Yamagami T, Shibata N, Folkers K. Bioenergetics in clinical medicine: Studies on coenzyme Q10 and essential hypertension. Res Commun Chem Pathol Pharmacol 11 (1975): 273-88.
Yamagami T, Shibata N, Folkers K. Bioenergetics in clinical medicine. VIII. Adminstration of coenzyme Q10 to patients with essential hypertension. Res Commun Chem Pathol Pharmacol 14 (1976): 721-7.
Ylikoski T et al. The effect of coenzyme Q10 on the exercise performance of cross-country skiers. Mol Aspects Med 18 (Suppl) (1997): S283-90.
Zhou M et al. Effects of coenzyme Q10 on myocardial protection during cardiac valve replacement and scavenging free radical activity in vitro. J Cardiovasc Surg (Torino) 40 (1999): 355-61.
Zhou Q, Chowbay B. Effect of coenzyme Q10 on the disposition of doxorubicin in rats. Eur J Drug Metab Pharmacokinet 27.3 (2002): 185-92.

Colostrum



BACKGROUND AND RELEVANT PHARMACOKINETICS

Colostrum is the milk produced by female mammals towards the end of pregnancy and secreted from the mammary gland in the first 2 days after giving birth. It is a very complex fluid, rich in nutrients, antibodies, growth factors, vitamins and minerals (Uruakpa et al 2002). The antibodies provide passive immunity to the newborn, and the growth factors stimulate development of the gastrointestinal tract.

CHEMICAL COMPONENTS

Colostrum contains macronutrients, such as protein and carbohydrate, micronutrients, such as vitamins and minerals, together with cytokines, including IL-1-beta, IL-6, trypsin inhibitors, protease inhibitors and oligosaccharides. It also contains growth factors such as insulin-like growth factor (IGF)-I and -II, transforming growth factor-alpha and -beta, lactoferrin, epidermal growth factor and others. Several different antimicrobial factors are also present, such as immunoglobulin (Ig) A, secretory IgA, IgG-1, IgG-2 and IgM, lactoferrin, lactoperoxidase and lysozyme, which produce both specific and non-specific bacteriostatic and bacteriocidal effects on many pathological microorganisms, including bacteria, viruses and fungi. IgG-1 is the principal immunoglobulin type in colostrums, and IgM, IgA and IgG-2 are present in lower amounts (Mach & Pahud 1971).

FOOD SOURCES

Bovine colostrums (BC) is derived from cows, and hyperimmune BC is derived from cows that have been exposed to organisms that can cause disease in humans.

Clinical note – Hyperimmune bovine colostrum

Bovine colostrum contains a variety of Ig, but the specific Ig present varies and is influenced by previous immune system challenges. Hyperimmune BC, in which the concentration of specific antibodies is raised, can be produced by immunising cows with either specific pathogens or their antigens. For example, BC from cows exposed to rotavirus might contain a relatively high neutralising Ig titre against the virus (as well as many other pathogenic microorganisms), whereas BC collected from cows never exposed to rotavirus is less likely to have specific neutralising Ig against rotavirus. This is an important distinction, because much of the research on BC as prophylaxis or treatment for infectious disease, has focused on products that are, as

a consequence of specific immune provocation, immunologically unique (Kelly 2003).

MAIN ACTIONS

IMPARTS PASSIVE IMMUNITY AND STIMULATES GROWTH OF THE NEONATAL GASTROINTESTINAL TRACT

Just as the immunoglobulins of human colostrum impart passive immunity to the newborn child, so too BC provides protection against microbial infections and confers passive immunity to the newborn calf until its own immune system matures (Korhonen et al 2000). Studies with targeted hyperimmune BC suggest that passive immunity may prevent or treat infectious diseases that affect the entire length of the gastrointestinal tract (Pacyna et al 2001).

ANTIBACTERIAL AND ANTIVIRAL EFFECTS

Targeted hyperimmune BCs have proven effective in prophylaxis against various human infectious diseases such as rotavirus, *Shigella flexneri, Escherichia coli, Clostridium difficile, Streptococcus mutans, Cryptosporidium parvum* and *Helicobacter pylori* (Korhonen et al 2000). It is suspected that colostrum may modulate the interaction of *H. pylori* and other adhesin-expressing pathogens with their target tissues, chiefly due to phosphatidylethanolamine and its derivatives rather than to an antibody response (Bitzan et al 1998).

IMPROVES GUT PERMEABILITY

Studies with agents known to disrupt gut permeability indicate that BC has a preventive effect that is likely to be a result of more than one growth factor present in the colostrum.

REDUCES NSAID-INDUCED INTESTINAL DAMAGE

Defatted BC had major beneficial effects in preventing NSAID-induced gut injury in a variety of well-validated in vivo and in vitro models (Kim et al 2005a,b, Playford et al 1999). BC improves the integrity of intestinal villi and prevents NSAID-induced increases in small intestine permeability. More specifically, the studies indicate that it stimulates both cell migration and proliferation, thereby enhancing the natural repair mechanisms that occur during acute mucosal injury. One of the studies by Kim et al (2005a) identified that when BC is administered together with glutamine, gastrointestinal protection is greater than when either agent is used alone. The other study further found that the overgrowth of enteric aerobic bacteria seen with NSAID administration did not occur to the same extent with BC (Kim et al 2005b).

OTHER ACTIONS

The high nutritional content of BC makes it an excellent source of many macro- and micronutrients.

CLINICAL USE

The use of BC as a dietary supplement has increased substantially over the past 2 decades. Unlike other dietary supplements, the composition of BC is not precisely defined and varies greatly according to the breed and health status of the cow, feeding practices, previous exposure to infectious organisms and time collected post-parturition (Kelly 2003).

PREVENTION AND TREATMENT OF INFECTION

Targeted hyperimmune BC products have proven effective in prophylaxis against various infectious diseases in humans.

INFECTIOUS DIARRHOEA

Rotavirus infection The clinical evidence available suggests hyperimmune BC is a promising agent in the prophylaxis and treatment of infectious diarrhoea caused by rotavirus. One Australian study using BC containing high titres of antibody to all four human rotavirus serotypes found that administration successfully prevented symptomatic infection in 100% of children treated with the preparation (Davidson et al 1989). It also reduced the duration of rotavirus excretion, which may have implications for preventing cross-infection. A double-blind study of 75 boys aged 6–24 months with rotavirus diarrhoea compared ordinary BC to hyperimmune BC (100 mL three times daily for 3 days) from cows immunised with four serotypes of human rotavirus (Mitra et al 1995). Diarrhoea ceased within 48 hours in 50% of children receiving hyperimmune BC whereas 100% of children receiving ordinary BC continued to have diarrhoea. Total stool output (g/kg) between admission and cessation of diarrhoea was also reduced in the group receiving hyperimmune BC compared with ordinary BC. Another double-blind study also found that treatment with anti-rotavirus immunoglobulin of BC origin is effective in the management of children with acute rotavirus diarrhoea (Sarker et al 1998). A double-blind study of children aged 6–30 months found treatment with hyperimmune BC (100 mL solution four times daily for 4 days) lead to improved weight gain, decreased duration of diarrhoea and resulted in fewer stools, although the differences were not statistically significant compared to ordinary colostrum or placebo (Ylitalo et al 1998).

Studies using hyperimmune BC in young children have identified rotavirus antibodies as early as 8 hours after ingestion and up to 72 hours after consumption has ceased, with a strong relation between the titre of rotavirus antibody adminis-

tered and the level of antibody activity detected in the faeces (Pacyna et al 2001). This suggests that passive immunity is imparted to the entire length of the gastrointestinal tract.

Shigella infection According to one small study, hyperimmune BC with a high titre of anti-*Shigella flexneri* 2a lipopolysaccharide prevented the incidence of shigella infection in 10 of 10 volunteers whereas 5 of 11 volunteers administered a control substance went on to develop the infection (Tacket et al 1992).

HIV-induced diarrhoea BC has also been investigated as a potential treatment in HIV-induced diarrhoea, a symptom that occurs in most patients infected with AIDS. A BC product (Lactobin, Biotest, Dreieich, Germany) containing high titres of antibodies against a wide range of bacterial, viral and protozoal pathogens, as well as against various bacterial toxins, was tested in a multicentre pilot study involving 29 HIV-infected patients (Rump et al 1992). An oral dose of 10 g/day produced a transient (10 days) or long-lasting (>4 weeks) normalisation of the stool frequency in 21 patients. Mean daily stool frequency decreased from 7.4 to 2.2 at the end of the treatment. Some success was also obtained 1 year later in a prospective, open, uncontrolled study of 25 HIV patients with chronic refractory diarrhoea and either confirmed cryptosporidiosis ($n = 7$) or absence of demonstrable pathogenic organisms ($n = 18$) (Plettenberg et al 1993). An oral dose of 10 g/day of an immunoglobulin preparation from BC over a period of 10 days led to complete remission of cryptosporidiosis infection in 3 of 7 subjects and 2 had partial remission. Complete remission was also seen in 7 of 18 patients with diarrhoea and negative stool culture and a further 4 had partial remission. Of those subjects not responding to treatment, doubling of the dose to 20 g/day led to partial remission in four more patients and complete remission in one.

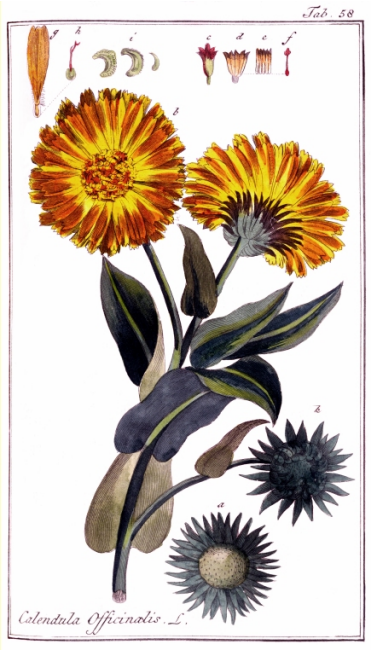
A BC product designed for slow passage through the gastrointestinal tract (ColoPlus) was tested over 4 weeks in an open-label study of 30 people with HIV-associated diarrhoea (Floren et al 2006). Treatment resulted in a dramatic decrease in daily stool evacuations (from 7.0 ± 2.7 to 1.3 ± 0.5), a mean increase of 7.3 kg of body weight, a 125% increase in $CD4^+$ count and a substantial decrease in self-estimated fatigue.

REDUCING INCIDENCE OF URTI

IgA is found in saliva and acts as a major barrier preventing pathogens entering the body via the oral route. As such, the level of secretory IgA has been found to correlate with resistance to some viral infections. According to two clinical studies, BC (20 g/day) increases salivary IgA levels, a factor that could feasibly increase the host's resistance to infection (Crooks et al 2006, Mero et al 2002). In the study by Crooks et

al, secretory IgA levels were elevated by 79% after 12 weeks of BC administration in athletes. The presence of numerous immune factors in BC further provides a theoretical basis for its use; however, little clinical investigation has been conducted to confirm its preventive effects.

In 2003, results of a randomised, double-blind, placebo-controlled trial were published, providing some support for its use as a prophylactic agent (Brinkworth & Buckley 2003). The study of 174 physically active young males compared colostrum powder (60 g/day; intact™, Numico Research Australia Pty Ltd) to concentrated whey powder over 8 weeks. During the test period, a significantly fewer proportion of subjects taking BC reported URTI symptoms than the control group; however, BC did not alter the duration of URTI once infection was established. Due to the self-reporting method used in this study, results should be viewed as preliminary and require further confirmation.



IMPROVED PHYSICAL PERFORMANCE AND PRESERVATION OF MUSCLE MASS

BC has been used by athletes mainly as a natural source of IGF-I because it has an anabolic effect and is involved in the regulatory feedback of growth hormone. It is taken in the belief that protein catabolism will be reduced during intense training periods and physical performance will improve.

A double-blind crossover study of nine male athletes confirmed that ingestion of BC (125 mL/day; Bioenervie, Viable Bioproducts) resulted in elevated concentrations of IGF-I; however, no significant effects were reported for serum IgG or saliva IgA concentrations (Mero et al 1997). Several years later in a larger study of athletes, under double-blind study conditions, the researchers confirmed that BC ingestion produced significant increases in serum IGF-I (Mero et al 2002). The dose of 20 g/day of BC (Dynamic supplement) was used during a 2-week training period. The study further found saliva IgA levels increased with this particular treatment.

GASTROINTESTINAL PROTECTION AGAINST NSAID-INDUCED DAMAGE

BC has also been investigated in a small randomised, crossover study as prophylaxis against NSAID-induced gastrointestinal damage (Playford et al 2001). A spray-dried, defatted colostrum (125 mL three times daily) was co-administered with indomethacin (50 mg three times daily) for 5 days in the first phase, then the effect of 7 days treatment with the colostral solution on gut permeability was determined in subjects taking NSAID long-term. Indomethacin (150 mg/day) caused a threefold increase in gut permeability after 5 days, whereas no change was observed when colostrum was co-administered, suggesting a protective effect. In contrast, no

protective effect was seen in subjects who had been using NSAIDs long-term and then administered colostrum for 1 week.

OTHER USES

Due to its effects on gut permeability, BC is used in a variety of other conditions, such as inflammatory bowel disease, coeliac disease, food allergies, intestinal infection and inflammatory joint diseases. It has also been used to restore normal gut permeability in people using chemotherapy. In some instances, it is used with glutamine for these indications.

DOSAGE RANGE

ACCORDING TO CLINICAL STUDIES

- Diarrhoea due to rotavirus: 100 ml three times daily for 3 days of BC from cows immunised with the four serotypes of human rotavirus.
- HIV-induced diarrhoea: 10 g/day (Lactobin, Biotest, Dreieich, Germany).
- Prevention of URTI: 60 g/day (intact™, Numico Research Australia Pty Ltd).
- Increasing serum IGF-I levels: 125 ml/day (Bioenervie, Viable Bioproducts) or 20 g/day (Dynamic supplement).
- Prevention of NSAID-induced gastrointestinal damage: 125 mL three times daily of spray-dried, defatted BC.

TOXICITY

Not known.

ADVERSE REACTIONS

Not known.

SIGNIFICANT INTERACTIONS

Not known.

CONTRAINDICATIONS AND PRECAUTIONS

Only BC products produced under strict quality control guidelines should be used. They typically contain lactose, so should be avoided by people with lactose intolerance.

PREGNANCY USE

Likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Colostrum is a very complex fluid that is rich in nutrients, antibodies, growth factors, vitamins and minerals.

- Targeted hyperimmune BC products have proven effective in prophylaxis against various infectious diseases in humans, notably infectious diarrhoea.
- BC is a popular supplement among athletes and used mainly as a natural source of IGF-I because it has an anabolic effect and is involved in the regulatory feedback of growth hormone.
- Preliminary evidence suggests BC may prevent NSAID-induced gastrointestinal damage and improve gut permeability.
- Most studies use hyperimmune BC in which the concentration of specific antibodies is raised.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Bovine colostrum contains nutrients, antibodies, growth factors, vitamins and minerals, and has a variety of effects on the gastrointestinal tract, immune function and the ability to fight some infections, and may possibly reduce muscle catabolism.

When will it start to work?

Studies with infectious diarrhoea have reported benefits within 3–4 days, and improvement in gut permeability within 5 days.

Are there any safety issues?

Bovine colostrum produced under quality control guidelines is a safe substance; however, it should be avoided by people with lactose intolerance.

REFERENCES

Bitzan MM et al. Inhibition of Helicobacter pylori and Helicobacter mustelae binding to lipid receptors by bovine colostrum. J Infect Dis 177 (1998): 955-61.

Brinkworth GD, Buckley JD. Concentrated bovine colostrum protein supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. Eur J Nutr 42 (2003): 228-32.

Crooks CV et al. The effect of bovine colostrum supplementation on salivary IgA in distance runners. Int J Sport Nutr Exerc Metab 16 (2006): 47-64.

Davidson GP et al. Passive immunisation of children with bovine colostrum containing antibodies to human rotavirus. Lancet 2 (1989): 709-712.

Floren CH et al. ColoPlus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea. Scand J Gastroenterol 41 (2006): 682-6.

Kelly GS. Bovine colostrums: a review of clinical uses. Altern Med Rev 8 (2003): 378-94.

Kim JW et al. Combined effects of bovine colostrum and glutamine in diclofenac-induced bacterial translocation in rat. Clin Nutr 24 (2005a): 785-93.

Kim JW et al. Protective effects of bovine colostrum on non-steroidal anti-inflammatory drug induced intestinal damage in rats. Asia Pac J Clin Nutr 14 (2005b): 103-7.

Korhonen H, Marnila P, Gill HS. Bovine milk antibodies for health. Br J Nutr 84 (Suppl 1) (2000): S135-46.

Mach JP, Pahud JJ. Secretory IgA, a major immunoglobulin in most bovine external secretions. J Immunol 106 (1971): 552-63.

Mero A et al. Effects of bovine colostrum supplementation on serum IGF-I, IgG, hormone, and saliva IgA during training. J Appl Physiol 83 (1997): 1144-51.

Mero A et al. IGF-I, IgA, and IgG responses to bovine colostrum supplementation during training. J Appl Physiol 93 (2002): 732-9.
Mitra AK et al. Hyperimmune cow colostrum reduces diarrhoea due to rotavirus: a double-blind, controlled clinical trial. Acta Paediatr 84 (1995): 996-1001.
Pacyna J et al. Survival of rotavirus antibody activity derived from bovine colostrum after passage through the human gastrointestinal tract. J Pediatr Gastroenterol Nutr 32 (2001): 162-7.
Playford RJ et al. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. Gut 44 (1999): 653-8.
Playford RJ et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clin Sci (Lond) 100 (2001): 627-33.
Plettenberg A et al. A preparation from bovine colostrum in the treatment of HIV-positive patients with chronic diarrhoea. Clin Invest 71 (1993): 42-5.
Rump JA et al. Treatment of diarrhoea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum. Clin Invest 70 (1992): 588-94.
Sarker SA et al. Successful treatment of rotavirus diarrhoea in children with immunoglobulin from immunized bovine colostrum. Pediatr Infect Dis J 17 (1998): 1149-54.
Tacket CO et al. Efficacy of bovine milk immunoglobulin concentrate in preventing illness after Shigella flexneri challenge. Am J Trop Med Hyg 47 (1992): 276-83.
Uruakpa FO et al. Colostrum and its benefits: a review. Nutr Res 22 (2002): 755-67.
Ylitalo S et al. Rotaviral antibodies in the treatment of acute rotaviral gastroenteritis. Acta Paediatr 87 (1998): 264-7.

Cranberry

Historical note Native American Indians have used cranberries as both a food and a treatment for bladder and kidney diseases. In the mid 1800s, German scientists suggested that cranberry juice had antibacterial activity, supporting its use as a treatment for bladder infections. Recent investigation has confirmed its usefulness in the prevention of urinary tract infections.

COMMON NAME
Cranberry

OTHER NAMES
Kronsbeere, marsh apple, moosbeere, preisselbeere

BOTANICAL NAME/FAMILY
Vaccinium oxycoccus, *Vaccinium macrocarpon* (family Ericaceae)

PLANT PART USED
Fruit

CHEMICAL COMPONENTS
Catechin, flavone glycosides, fructose, organic acids, proanthocyanidins, vitamin C.

Cranberry has a high flavonol content (100–263 mg/kg) (Hakkinen et al 1999) — higher than commonly consumed fruits and vegetables.

MAIN ACTIONS

BACTERIOSTATIC

The adhesion of pathogenic organisms to a tissue surface is required to initiate most infectious diseases (Sharon & Ofek 2002). Cranberry is a potent inhibitor of *Escherichia coli* adhesion, thereby influencing the initiation of disease without exerting bactericidal activity. One in vitro study found that cranberry juice inhibited adhesion of 46 different *E. coli* isolates by 75% (Sobota 1984): when administered to mice for 14 days, adherence of *E. coli* to uroepithelial cells was inhibited by 80%. Significant inhibition of adherence was also observed in samples of human urine 1–3 hours after subjects drank a cranberry drink.

It appears that the anti-adhesion effects are a result of irreversible inhibition of the expression of P-fimbriae of *E. coli* (Ahuja et al 1998). Electron micrographic evidence suggests that cranberry juice acts either on the cell wall, preventing proper

attachment of the fimbrial subunits, or as a genetic control preventing the expression of normal fimbrial subunits, or both.

This inhibitory effect has not only been seen with *E. coli* and uroepithelial tissues, but also in the adhesion of *Helicobacter pylori* to human gastrointestinal cells (Burger et al 2002) and in the co-aggregation of oral bacteria and *Streptococcus mutans* counts in saliva (Sharon & Ofek 2002, Weiss et al 1998).

Earlier hypotheses that cranberry juice prevents UTI by acidification of urine or by its hippuric acid content have not been substantiated.

ANTIOXIDANT

In vitro tests with whole fruit and isolated flavonol glycosides found in cranberry showed free radical scavenging activity comparable or superior to that of vitamin E (Yan et al 2002).

INCREASES SECRETION OF OXALIC ACID AND URIC ACID

According to an open study, a dose of 330 mL cranberry juice can increase the excretion of oxalic acid and uric acid (Kessler et al 2002).

ALTERATIONS TO URINARY pH

Results from human studies are contradictory, but overall suggest no significant change to urinary pH at doses less than 330 mL daily. A crossover study of 27 patients with indwelling urinary catheters and chronic bacteriuria showed no change to urinary pH (Nahata et al 1982), as did a double-blind study of 153 women (Avorn et al 1994). One small, open study involving 12 healthy subjects found that 330 mL cranberry juice reduced urinary pH (Kessler et al 2002).

OTHER ACTIONS

In vitro tests using four different *Vaccinium* spp. found that the proanthocyanidin fraction of cranberry exhibits potential anticarcinogenic activity (Bomser et al 1996).

CLINICAL USE

PREVENTION OF UTI

Several human studies support the use of cranberry in solid-dose form and cranberry juice drink for preventing UTI.

A recent Cochrane systematic review considered results from seven randomised clinical trials (four crossover design and three parallel group) that compared the effects of cranberry juice (or cranberry–lingonberry juice) to placebo or cranberry tablets to placebo in elderly men or women, subjects with a history of recurring UTI or subjects needing intermittent catheterisation (e.g. children with neuropathic bladder) (Jepson et al 2004). The final meta-analysis was performed using results from two

good quality studies (Kontiokari et al 2001, Stothers 2002) and showed that cranberry products significantly reduced the incidence of UTI at 12 months compared with placebo/control in women and there was no significant difference in the incidence of UTI between cranberry juice versus cranberry capsules. One trial used 7.5 g cranberry concentrate daily (in 50 mL) whereas the other used a 1:30 concentrate given either in 250 mL juice or in tablet form. Additionally, Stothers showed that cranberry tablets provided the most cost-effective prevention for UTI when compared with organic cranberry juice (Stothers 2002). The five studies not included in the meta-analysis were omitted due to methodological flaws or lack of available data.

Spinal cord injuries Patients with spinal cord injuries are a high-risk group for UTI, so cranberry products are popular in this group. An open, pilot study involving 15 volunteers with spinal cord injuries showed that three glasses of cranberry juice daily significantly reduced adhesion of Gram-negative and Gram-positive bacteria to uroepithelial cells (Reid 2002).

Children Cranberry use is popular for children with renal disease. An anonymous survey of 117 parents of children seen in a hospital paediatric nephrology clinic identified that 29% gave cranberry products to their children, to treat as well as prevent diverse renal problems (Super et al 2005). Most parents felt it was beneficial and only one reported a side-effect (nausea).

Two studies conducted with children managed by clean intermittent catheterisation found no clinical or statistical difference in the number of symptomatic UTI observed in either the cranberry or placebo groups (Foda et al 1995, Schlager et al 1999). Foda et al used a dose of 5 mL/kg/day of cranberry cocktail for 6 months and the dose used by Schlager was 2 ounces (≈55 g) of cranberry concentrate.

TREATMENT OF UTI

Although cranberry may be a viable adjunctive treatment in UTI when antibiotic resistance is encountered, there is no reliable evidence that it is an effective sole treatment in diagnosed UTI (Ulbricht & Basch 2005).

URINARY DEODORISING ACTIVITY

Cranberry juice and solid-dose forms are popular in nursing homes as urinary deodorising agents in older adults with incontinence. Although no clinical study is available to confirm efficacy, numerous anecdotal reports suggest that it is useful when used on a regular basis.

OTHER USES

GOUT

Cranberry juice has been used to treat gout. Evidence of increased uric acid excretion in humans provides a theoretical basis for the indication, although studies in patients with gout are not available to confirm effectiveness (Kessler et al 2002).

ORAL HYGIENE

The anti-adhesion effect of cranberry on oral microbial flora has been demonstrated in vitro, suggesting a possible role in oral hygiene; however, the high sugar content of commercial cranberry juice makes this use unsuitable (Weiss et al 1998).

PREVENTION AND TREATMENT OF HELICOBACTER INFECTION

Cranberry inhibits the adhesion of *H. pylori* to human gastrointestinal cells in vitro; however, no clinical evidence is available to confirm significance in humans (Burger et al 2002).

DOSAGE RANGE

PREVENTING UTI

- According to clinical studies:
  Adults: 30–300 mL daily or 400 mg capsule daily
  Children: 15 mL/kg to 300 mL daily
  In practice, much higher doses are being used in an attempt to achieve quicker results (e.g. cranberry capsules or tablets 10,000 mg/day for prevention).

TREATING UTI

- Cranberry capsules or tablets up to 10,000 mg 3–4 times daily (according to Australian manufacturers).

ADVERSE REACTIONS

At high doses (3 L or greater), gastrointestinal discomfort and diarrhoea can occur (Ulbricht & Basch 2005).

SIGNIFICANT INTERACTIONS

PROTON-PUMP INHIBITORS

Cranberry juice increases the absorption of vitamin B12 when used concurrently with PPI medicines (Saltzman et al 1994) — beneficial interaction.

WARFARIN

Although a preliminary report suggested that cranberry juice may increase the INR in patients taking warfarin (Grant 2004) a recent study casts doubt on a pharmacokinetic interaction (Greenblatt et al 2006) — caution.

CONTRAINDICATIONS AND PRECAUTIONS

Patients with diabetes should take care when using commercially prepared cranberry juices because of the high sugar content.

If symptoms of UTI become more severe while cranberry is being administered, other treatment may be required and medical advice is recommended.

People with a history of oxalate kidney stones should limit their intake of cranberry juice.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Cranberry preparations are widely used to prevent and treat minor UTI.
- Overall, clinical testing suggests that the juice and solid-dose forms may have significant beneficial effects for UTI management.
- Cranberry exerts bacteriostatic effects by reducing bacterial adhesion to host tissues.
- Overall, evidence suggests no significant alteration to urinary pH at doses less than 330 mL daily.
- Cranberry products have also been used to treat gout and to deodorise urine in people with incontinence.
- Preliminary research suggests a possible role in preventing conditions such as *Helicobacter pylori* infection and dental plaque formation.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Cranberry products appear to reduce the risk of developing UTI and may be useful as a treatment in minor UTI.

When will it start to work?

Studies using 1–2 glasses of cranberry juice suggest that 4–8 weeks' continual use is required; however, faster effects using concentrated tablets or capsules have been reported.

Are there any safety issues?

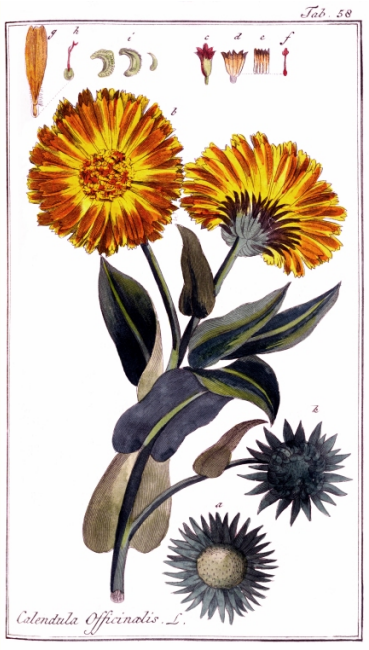
If fever or pain exists or symptoms of UTI become more severe, seek medical advice.

REFERENCES

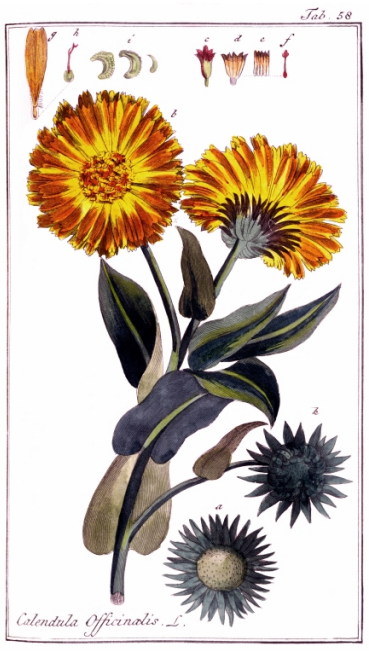
Ahuja S, Kaack B, Roberts J. Loss of fimbrial adhesion with the addition of Vaccinium macrocarpon to the growth medium of P-fimbriated Escherichia coli. J Urol 159.2 (1998): 559-62.

Avorn J et al. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 271.10 (1994): 751-4.

Bomser J et al. In vitro anticancer activity of fruit extracts from Vaccinium species. Planta Med 62.3 (1996): 212-16.
Burger O et al. Inhibition of Helicobacter pylori adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. Crit Rev Food Sci Nutr 42.3 [Suppl] (2002): 279-84.
Foda MM et al. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. Can J Urol 2.1 (1995): 98-102.
Grant P. Warfarin and cranberry juice: an interaction? J Heart Valve Dis 13.1 (2004): 25-6.
Greenblatt DJ et al. Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: in vitro and clinical studies. Clin Pharmacol Ther 79.1 (2006): 125-33.
Hakkinen SH et al. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. J Agric Food Chem 47.6 (1999): 2274-9.
Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2 (2004): CD001321.
Kessler T, Jansen B, Hesse A. Effect of blackcurrant-, cranberry- and plum juice consumption on risk factors associated with kidney stone formation. Eur J Clin Nutr 56.10 (2002): 1020-3.
Kontiokari T et al. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ 322.7302 (2001): 1571.
Nahata MC et al. Effect of urinary acidifiers on formaldehyde concentration and efficacy with methenamine therapy. Eur J Clin Pharmacol 22.3 (1982): 281-4.
Reid G. The role of cranberry and probiotics in intestinal and urogenital tract health. Crit Rev Food Sci Nutr 42.3 (Suppl) (2002): 293-300.
Saltzman JR et al. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B12 absorption. J Am Coll Nutr 13.6 (1994): 584-91.
Schlager TA et al. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. J Pediatr 135.6 (1999): 698-702.
Sharon N, Ofek I. Fighting infectious diseases with inhibitors of microbial adhesion to host tissues. Crit Rev Food Sci Nutr 42.3 (Suppl) (2002): 267-72.
Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. J Urol 131.5 (1984): 1013-16.
Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol 9.3 (2002): 1558-62.
Super EA et al. Cranberry use among pediatric nephrology patients. Ambul Pediatr 5.4 (2005): 249-52.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Weiss EI et al. Inhibiting interspecies coaggregation of plaque bacteria with a cranberry juice constituent. J Am Dent Assoc 129.12 (1998): 1719-23 [published erratum J Am Dent Assoc 130.1 (1999): 36 and 130.3 (1999): 332].
Yan X et al. Antioxidant activities and antitumor screening of extracts from cranberry fruit (Vaccinium macrocarpon). J Agric Food Chem 50.21 (2002): 5844-9.



Creatine



Historical note Creatine was first discovered in 1832 when it was identified in meat. The word creatine is derived from the Greek *kreas* for flesh, similar to the word 'creature'. About 15 years later, the meat from foxes killed in the wild were found to have 10-fold more creatine than meat from domesticated foxes, suggesting that physical exercise must influence the amount of creatine that accumulates in muscles. Early last century orally consumed creatine was shown to be partly retained in the body and able to increase creatine content in muscles, leading some to suspect this could influence the performance of muscles. Nowadays, creatine monohydrate enjoys enormous popularity as a sports supplements and is being recommended to elite athletes by respected sporting bodies such as the Australian Institute of Sport (AIS).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Creatine is a naturally occurring nitrogenous compound produced in the human liver, pancreas and kidneys at a rate of 1–2 g daily. It is synthesised from the amino acids glycine, arginine and methionine and stored primarily in skeletal muscle, where it is in dynamic equilibrium with phosphocreatine and is a precursor to adenosine triphosphate (ATP), the main source of energy for muscle activity and many other biological functions. Orally ingested creatine is absorbed from the small intestine, then distributed via creatine transporters around the body to muscles and nerves (Persky et al 2003). These transporters also serve as a clearance mechanism because of creatine 'trapping' by skeletal muscle. It is ultimately converted to creatinine and excreted by the kidneys.

CHEMICAL COMPONENTS

Creatine is known chemically as N-(aminoiminomethyl)-N-methyl glycine.

FOOD SOURCES

Animal protein and fish. It has been estimated that approximately 1–2 g are ingested daily from the diet by non-vegetarians (Hendler et al 2001).

DEFICIENCY SIGNS AND SYMPTOMS

Several rare inborn errors of metabolism that result in a lack of creatine and phosphorylcreatine in the brain and severe mental retardation have been identified. Other symptoms and signs, such as involuntary extrapyramidal movements, speech

disability, epilepsy, muscular hypotonia and weakness, and, in older patients, autism with self-injurious behaviour have also been reported (Wyss & Schulze 2002).

People involved in intense physical activity, vegetarians and those with muscle diseases may have lowered creatine levels.

MAIN ACTIONS

ENERGY PRODUCTION

Although the exact mechanism is unknown, much is known about the biochemistry of endogenous creatine. In skeletal muscle tissue, it is used for the production of phosphocreatine, an important form of high-energy phosphate. Phosphocreatine is broken down into phosphate and creatine during high intensity exercise lasting 15–30 seconds. During the process, energy is released and is used to regenerate ATP, the primary source of energy.

Supplemental creatine Oral supplementation with creatine has been shown to increase phosphocreatine levels in muscles, and as such, has been described as 'fuelling up' natural energy stores. Increased creatine stores leads to faster regeneration of ATP, thereby making more energy immediately available to muscles. Theoretically, increased free creatine allows depleted stores to replenish more quickly, thus shortening recovery times during repeated bouts of intense exercise. Increased muscle creatine may also buffer the lactic acid produced during exercise, delaying muscle fatigue and soreness.

It has been estimated that short-term supplementation over 5–7 days with a daily dose of 20 g creatine increases total creatine content by 10–30% and phosphocreatine stores by 10–40% (Kreider 2003).

In clinical studies, the effect of creatine on performance, endurance, strength and recovery is variable.

NEUROPROTECTIVE

Creatine supplementation has displayed neuroprotective effects in several animal models of neurological disease, such as Huntington's disease, Parkinson's disease, or motor neurone disease (MND) (also known as amyotrophic lateral sclerosis) (Andreassen et al 2001, Dedeoglu et al 2003, Ferrante et al 2000, Wyss & Schulze 2002) and is currently being evaluated in early stage trials in Parkinson's disease and MND (Beal 2003). A number of theories of a possible mechanism for neuroprotection have been put forward. One theory proposes that creatine exerts antioxidant activity and mitochondrial stabilising effects, two mechanisms of benefit in neurodegenerative diseases, which are characterised by mitochondrial dysfunction and oxidative damage (Shefner et al 2004).

OTHER ACTIONS

It has been suggested that daily creatine supplementation may indirectly reduce coronary heart disease and cerebrovascular disease by suppressing normal creatine synthesis and therefore inhibiting a major production process of homocysteine (McCarty 2001). Research in animal models has shown it inhibits the growth of some solid tumours and also exhibits antioxidant activity (Lawler et al 2002).

CLINICAL USE

Creatine monohydrate is the form generally used and tested. In practice, this is available in three different forms, which differ according to particle size (granular, powder and micronised), in the belief that smaller particles are more fully absorbed and cause less gastric distress.

ERGOGENIC AID

Creatine supplementation has become one of the most widely used supplements taken by athletes and is touted by some as the only truly effective ergogenic aid besides carbohydrate loading. It is used by athletes engaged in sprint disciplines (e.g. 100 m run or 50 m swim), strength disciplines (e.g. weight lifting) or high-intensity, repetitive burst exercise (e.g. tennis, hockey, football, soccer) separated by short bouts of recovery. Its use is based on the assumption that supplementation at doses above dietary levels will increase energy and power output and also enhance recovery.

Hundreds of small studies have attempted to evaluate the effects of creatine supplementation on exercise capacity and muscle physiology in various populations.

A 2003 review of the literature concluded that approximately 300 studies have evaluated its potential as an ergogenic aid, with about 70% of studies reporting statistically significant positive results (Kreider 2003).

Who will respond? The observation that not every athlete responds to creatine supplementation with improved strength, performance and recovery has prompted investigation into identifying key features of responders. One study identified that responders had the lowest initial levels of muscle creatine, greatest percentage of type 2 fibres, greatest preload muscle fibre cross-sectional area and fat free mass in comparison to non-responders (Syrotuik & Bell 2004). Other factors that are likely to influence an individual's response to creatine include training status, diet, age and the bioavailability of the creatine supplement being used. Not taking these factors into account may partly explain the inconsistent results obtained in randomised studies.

Short duration, high-intensity exercise Most, but not all, controlled studies have shown that supplementation improves performance and delays muscle fatigue (Balsom et al 1995, Becque et al 2000, Burke et al 1996, Cox et al 2002, Finn et al 2001, Gilliam et al 2000, Kreider et al 1998, Maganaris & Maughan 1998, Mujika &

Padilla 1997, Mujika et al 2000, Tarnopolsky & MacLennan 2000, Williams & Branch 1998). Studies have been conducted in a variety of athletes, such as sprint cyclists, soccer players and sprint swimmers, and generally used a dose of 20 g daily.

Lean body mass Creatine increases exercise-related gains in lean body mass (Chrusch et al 2001, Jowko et al 2001, Stone et al 1999), although some of these apparent gains may actually represent water retention in the muscles.

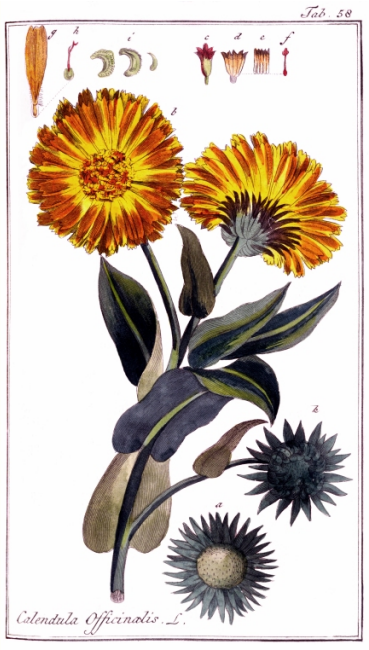
Enhanced power Many studies show that creatine supplementation in conjunction with resistance training augments gains in muscle strength and size, although the effect is not consistent for everybody (Spriet & Gibala 2004, Volek & Rawson 2004). Creatine supplementation increases muscle fibre hypertrophy, myosin heavy chain expression and swelling of myocytes, which may in turn affect carbohydrate and protein metabolism. Supplementation also increases acute weightlifting performance and training volume, which may allow for greater overload and adaptation to training.

A 2003 review of 22 studies estimated that the average increase in muscle strength following creatine supplementation as an adjunct to resistance training was 8% greater than for placebo (20% vs 12%) (Rawson & Volek 2003). Similarly, the average increase in weightlifting performance (maximal repetitions at a given percentage of maximal strength) following creatine supplementation plus resistance training was 14% greater than placebo (26% vs 12%).

Reducing strength decline in the elderly The effects of supplemental creatine in older adults has been investigated in a few studies, overall producing positive results (Brose et al 2003, Chrusch et al 2001, Kreider et al 1998). One randomised, double-blind study involving 30 older men (>70 years) showed that resistance training combined with creatine supplementation produced significantly greater increases in lean tissue mass, leg strength, endurance and average power than placebo (Chrusch et al 2001). The dose regimen used was 0.3 g/kg for the first 5 days followed by 0.07 g/kg thereafter. Another double-blind study in 28 men and women aged over 65 years showed that creatine supplementation (5 g daily) combined with resistance training enhanced the increase in total and fat-free mass, and gains in several indices of isometric muscle strength (Brose et al 2003).

Cervical level spinal cord injury According to a randomised, double-blind, placebo controlled crossover trial, creatine supplementation enhances upper extremity work capacity in subjects with complete cervical-level spinal cord injury (Jacobs et al 2002).

Clinical note — The Australian Institute of Sport Supplement Program
The AIS is world renowned for its professionalism and high-quality training programs. In 2000, a project called the AIS Sports Supplement Program was developed to ensure that athletes use supplements correctly and confidently, and receive 'cutting edge' advice on nutritional practices. In order to streamline the information available, a panel of experts categorised some of the most popular sports supplements into various classes to clarify which are approved or recommended and which are directly banned by international doping rules. Some of the approved supplements recommended for use include creatine, antioxidants (vitamins C and E), multivitamins, iron, calcium supplements and sports drinks.



MUSCULAR DYSTROPHY

A number of muscle diseases are associated with a decrease in intracellular creatine concentration, which could theoretically contribute to muscle weakness and degeneration of muscle tissue (Wyss et al 1998). As a result, testing with creatine supplementation in a variety of muscle diseases has started.

One double-blind, crossover study of 36 patients with various muscle diseases found that creatine supplementation over 8 weeks produced a mild but significant improvement in muscle strength and daily-life activities on Medical Research Council scales and the Neuromuscular Symptom Score (Walter et al 2000). A single-blind placebo-controlled trial of 21 volunteers with different neuromuscular disorders found that creatine supplementation (10 g daily for 5 days followed by 5 g daily for 5–7 days) produced significant improvements in body weight, handgrip, dorsiflexion, and knee extensor strength (Tarnopolsky et al 1997).

CONGESTIVE HEART FAILURE

Muscle fatigue due to loss of skeletal muscle mass and strength, decreased oxidative capacity and other abnormalities of muscle metabolism have been associated with congestive heart failure. As a result, creatine supplementation has been suggested as a possible therapeutic agent in this condition.

A dose of 10 g creatine daily for 7 days significantly increased exercise capacity and muscle strength compared to placebo in a double-blind study involving 17 men with congestive heart failure (Gordon et al 1995). However, creatine supplementation did not alter ejection fraction at rest or at work. Muscle endurance during handgrip exercises was also seen to improve in another double-blind, crossover study of 20 men given 5 g creatine four times daily for 5 days (Andrews et al 1998).

NEUROLOGICAL DEGENERATIVE DISEASES

Over the past few years, a considerable body of scientific evidence has given support to the idea that creatine supplementation may alleviate some of the clinical symptoms of neurological disease and delay disease progression (Wyss & Schulze 2002). Studies conducted in both animal models of neurodegenerative disease and humans have produced mixed results.

Huntington's disease A number of studies conducted with experimental animal models of Huntington's disease have identified a possible role for creatine supplementation (Andreassen et al 2001, Dedeoglu et al 2003, Ferrante et al 2000). Creatine was shown to increase survival, delay onset of symptoms and exert neuroprotective effects in vivo.

Motor neuron disease A preliminary study demonstrated that creatine supplementation of 20 g daily for 7 days followed by 3 g daily for 3 and 6 months produced temporary increases in maximal isometric power in patients with MND (Mazzini et al 2001). More recently, two randomised, double blind, placebo-controlled studies have been conducted with MND patients, with both finding no change to disease progression with creatine monohydrate supplementation at doses of 5–10 g daily (Groeneveld et al 2003, Shefner et al 2004). Study periods varied from 6 to 12 months. The study by Shefner et al used creatine monohydrate at a loading dose of 20 g/day for 5 days, followed by 5 g/day. It must be noted that this study was powered only to detect a 50% or greater change, so the failure to show a significant positive effect of treatment might have limited clinical significance.

REDUCES MENTAL FATIGUE

Creatine supplement (8 g/day for 5 days) reduced mental fatigue when examined under double-blind placebo-controlled conditions in 24 healthy volunteers (Watanabe et al 2002).

OTHER USES

GYRATE ATROPHY

Doses of 1.5 g/day for 1 year resulted in improvement of the skeletal muscle abnormality that accompanies gyrate atrophy, a genetically acquired form of blindness (Feldman 1999).

DOSAGE RANGE

There are two common dosing regimens.

LOADING

Creatine loading protocols have been well studied.

- Rapid loading: A dose of 5 g is taken four times daily for 5–7 days as a loading phase, followed by 2–10 g daily as maintenance for 1 week to 6 months (Bemben & Lamont 2005). This is followed by a 4-week break and then restarted in a process known as 'cycling'.
- Slower loading: A similar effect can be achieved by taking 3 g daily over 28 days.

Concurrent ingestion of carbohydrate (50–100 g) may improve creatine uptake. Once muscles have become saturated, it takes approximately 4 weeks to return to baseline levels.

NON-LOADING

- Daily dose of 3 g.

In practice, creatine is often taken with simple carbohydrates, such as glucose or fruit juice, in order to increase creatine accumulation within muscle.

Clinical note — Interview with Steve Brown — Mr Australia and personal trainer

In practice, micronised forms of creatine monohydrate provide superior results to powders or granules and have less gastrointestinal side-effects, particularly when taken with glucose or dark grape juice, according to Steve Brown (pers. commun. 2003). The loading regimen typically increases the ability to lift heavier weights for greater repetitions within 2–4 weeks and occurs quite suddenly. Also, creatine increases alertness and mental sharpness, effects that are obvious after the first week. Although there is a slight weight gain due to water retention, lean body mass also increases, because the body is able to work harder and for longer with creatine. Once supplementation stops, the physical effects on performance quickly reduce and are noticeable after the first week.

ADVERSE REACTIONS

Side-effects include gastrointestinal distress with nausea and vomiting, diarrhoea, muscle fatigue, pain and cramping, dehydration and heat intolerance. The effects may be reduced when micronised forms of creatine are taken together with glucose or simple carbohydrates. Fluid retention is commonly observed during the loading phase of supplementation.

SIGNIFICANT INTERACTIONS

Controlled studies are not available and there is insufficient reliable evidence to determine interaction potential.

CONTRAINDICATIONS AND PRECAUTIONS

Use of high-dose creatine is contraindicated in individuals with renal failure.

Creatine supplementation for up to 8 weeks has not been associated with major health risks, but the safety of more prolonged creatine supplementation has not been established (Williams & Branch 1998).

PREGNANCY USE

Insufficient reliable data are available, but it is generally not recommended in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Creatine is a very popular sports supplement and is not a substance banned by the International Olympic Committee. Although scientific evidence supports its use in high-intensity, repetitive burst exercise, not every individual will respond. Investigation is underway to determine key characteristics of athletes most likely to respond.
- Creatine is also used in the treatment of numerous conditions involving fatigue or muscle weakness, but little evidence is available yet to determine its effectiveness.
- Creatine is used in the production of ATP, the main source of energy for muscle activity and many other biological functions.
- In practice, creatine is often taken in high doses for 5–7 days, followed by lower maintenance doses for up to 8 weeks. This is called 'loading'.
- High-dose creatine is contraindicated in renal failure.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Creatine enhances physical power and recovery in most cases. It may also reduce mental fatigue and have a protective effect on nerves.

When will it start to work?

The physical effects generally develop within 1–4 weeks of use.

Are there any safety issues?

It should not be taken in high doses by people with kidney disease and its long-term safety has not been established.

REFERENCES

Andreassen OA et al. Creatine increases survival and delays motor symptoms in a transgenic animal model of Huntington's disease. Neurobiol Dis 8(3)(2001): 479-91.

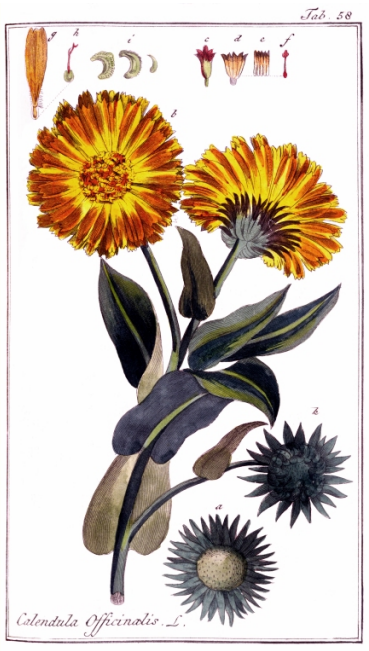
Andrews R et al. The effect of dietary creatine supplementation on skeletal muscle metabolism in congestive heart failure. Eur Heart J 19(4) (1998): 617-22.

Australian Institute of Sport (AIS). Sports Supplement Program project 2000. Available from: AIS PO Box 176, Belconnen ACT 2616, Australia.

Balsom PD et al. Skeletal muscle metabolism during short duration high-intensity exercise: influence of creatine supplementation. Acta Physiol Scand 154(3) (1995): 303-10.
Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. Ann Neurol 53(Suppl 3) (2003): S39-47.
Becque MD, Lochmann JD, Melrose DR. Effects of oral creatine supplementation on muscular strength and body composition. Med Sci Sports Exerc 32(3) (2000): 654-8.
Bemben MG, Lamont HS. Creatine supplementation and exercise performance: recent findings. Sports Med 35(2) (2005): 107-25.
Brose A et al. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. J Gerontol A Biol Sci Med Sci 58(1) (2003a): 11-19.
Burke LM, Pyne DB, Telford RD. Effect of oral creatine supplementation on single-effort sprint performance in elite swimmers. Int J Sport Nutr 6(3) (1996): 222-33.
Chrusch MJ et al. Creatine supplementation combined with resistance training in older men. Med Sci Sports Exerc 33(12) (2001): 2111-17.
Cox G et al. Acute creatine supplementation and performance during a field test simulating match play in elite female soccer players. Int J Sport Nutr Exerc Metab 12(1) (2002): 33-46.
Dedeoglu A et al. Creatine therapy provides neuroprotection after onset of clinical symptoms in Huntington's disease transgenic mice. J Neurochem 85(6) (2003): 1359-67.
Feldman EB. Creatine: a dietary supplement and ergogenic aid. Nutr Rev 57(2) (1999): 45-50.
Ferrante RJ et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci 20(12) (2000): 4389-97.
Finn JP et al. Effect of creatine supplementation on metabolism and performance in humans during intermittent sprint cycling. Eur J Appl Physiol 84(3) (2001): 238-43.
Gilliam JD et al. Effect of oral creatine supplementation on isokinetic torque production. Med Sci Sports Exerc 32(5) (2000): 993-6.
Gordon A et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. Cardiovasc Res 30(3) (1995): 413-18.
Groeneveld JG et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. Ann Neurol 53(4) (2003): 437-45.
Hendler S. PDR for Nutritional Supplements. Montvale: Thomson Healthcare. 2001.
Jacobs PL et al. Oral creatine supplementation enhances upper extremity work capacity in persons with cervical-level spinal cord injury. Arch Phys Med Rehabil 83(1) (2002): 19-23.
Jowko E et al. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition 17(7-8) (2001): 558-66.
Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem 244(1-2) (2003): 89-94.
Kreider RB et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc 30(1) (1998): 73-82.
Lawler JM et al. Direct antioxidant properties of creatine. Biochem Biophys Res Commun 290(1) (2002): 47-52.
Maganaris CN, Maughan RJ. Creatine supplementation enhances maximum voluntary isometric force and endurance capacity in resistance trained men. Acta Physiol Scand 163(3) (1998): 279-87.
Mazzini L et al Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. J Neurol Sci 191(1-2) (2001): 139-44.
McCarty MF. Supplemental creatine may decrease serum homocysteine and abolish the homocysteine 'gender gap' by suppressing endogenous creatine synthesis. Med Hypotheses 56(1) (2001): 5-7.
Mujika I, Padilla S. Creatine supplementation as an ergogenic acid for sports performance in highly trained athletes: a critical review. Int J Sports Med 18(7) (1997): 491-6.
Mujika I et al. Creatine supplementation and sprint performance in soccer players. Med Sci Sports Exerc 32(2) (2000): 518-25.

Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet 42(6) (2003): 557-74.
Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. J Strength Cond Res 17(4) (2003): 822-31.
Shefner JM et al. A clinical trial of creatine in ALS. Neurology 63(9) (2004): 1656-61.
Spriet LL, Gibala MJ. Nutritional strategies to influence adaptations to training. J Sports Sci 22(1) (2004): 127-41.
Stone MH et al. Effects of in-season (5 weeks) creatine and pyruvate supplementation on anaerobic performance and body composition in American football players. Int J Sport Nutr 9(2) (1999): 146-65.
Syrotuik DG, Bell GJ. Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs nonresponders. J Strength Cond Res 18(3) (2004): 610-17.
Tarnopolsky MA, MacLennan DP. Creatine monohydrate supplementation enhances high-intensity exercise performance in males and females. Int J Sport Nutr Exerc Metab 10(4) (2000): 452-63.
Tarnopolsky MA, Roy BD, MacDonald JR. A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 20(12) (1997): 1502-9.
Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. Nutrition 20(7-8) (2004): 609-14.
Walter MC et al. Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study. Neurology 54(9) (2000): 1848-50.
Watanabe A, Kato N, Kato T. Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. Neurosci Res 42(4) (2002): 279-85.
Williams MH, Branch JD. Creatine supplementation and exercise performance: an update. J Am Coll Nutr 17(3) (1998): 216-34.
Wyss M, Schulze A. Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience 112(2) (2002): 243-60.
Wyss M et al. The therapeutic potential of oral creatine supplementation in muscle disease. Med Hypotheses 51(4) (1998): 333-6.

Damiana



Historical note Damiana is a wild deciduous shrub found in the arid and semi-arid regions of South America, Mexico, United States and West Indies. It is believed that Mayan Indians used damiana to prevent giddiness, falling and loss of balance, and as an aphrodisiac. It has also been used during childbirth, and to treat colic, stop bed wetting and bring on suppressed menses. Today its leaves are used for flavouring in food and beverages, and infusions and other preparations are used for a variety of medicinal purposes.

COMMON NAME
Damiana

OTHER NAMES
Herba de la pastora, Mexican damiana, miziboc, old woman's broom, shepherd's herb, stag's herb

BOTANICAL NAME/FAMILY
Turnera diffusa, *Damiana aphrodisiaca*, *Turnera aphrodisiaca* (family Turneraceae)

PLANT PARTS USED
Dried leaves and stems

CHEMICAL COMPONENTS
Sesquiterpenes, alkaloids, essential oils containing caryophyllene, delta-cadinene, beta-elemene and 1–8 cineol and other lesser constituents, tetraphylin B (a cyanogenic glycoside, 0.26%), resin, tannins, gum, mucilage, starch, a bitter element and possibly caffeine. Damiana also contains a flavone and at least five flavonoids including arbutin (Piacente et al 2002).

MAIN ACTIONS
The pharmacological actions of damiana have not been significantly investigated, so traditional use and in vitro and in vivo evidence is used.

HORMONAL EFFECTS
One study that investigated the effects of over 150 herbs for their relative capacity to compete with oestradiol and progesterone binding to intracellular receptors identified damiana as a herb that binds to intracellular progesterone receptors, exerting a neutral effect and also exerting weak oestrogen agonist activity (Zava et al 1998). It

has been reported that delta-cadinene is a testosterone inducer and 1,8-cineole is a testosterone hydroxylase inducer (Duke 2006). A study analysing the constituents of the essential oils found in various damiana samples identified that fresh and dry samples contained both compounds, but wild plants contained more delta-cadinene than cultivated plants (Alcaraz-Melendez et al 2004). The action of these constituents may support the common belief that damiana is useful as an aphrodisiac.

ANTI-INFLAMMATORY ACTIVITY

Significant anti-inflammatory activity was identified for the aqueous and ethanolic fractions of damiana in an experimental model (Antonio & Brito 1998). Antiplatelet activity was not observed.

HYPOGLYCAEMIC AGENT

A decoction of dried damiana leaves caused a significant reduction of the hyperglycaemic peak, exerting a hypoglycaemic effect comparable to that of tolbutamide in an experimental model (Alarcon-Aguilara et al 1998).

CLINICAL USE

Damiana has not been significantly investigated under clinical trial conditions; therefore, evidence is derived from traditional use, in vitro and animal studies and clinical significance is unknown.

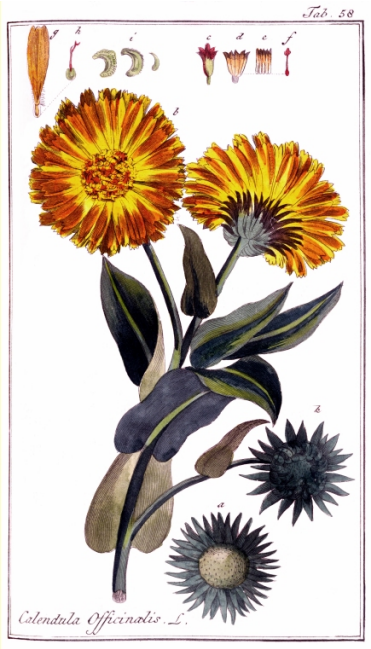
SEXUAL DYSFUNCTION OR DECREASED LIBIDO

Damiana has been used traditionally for sexual dysfunction or as an aphrodisiac to enhance sexual activity. Scientific studies in experimental models provide preliminary support for its use in these conditions, but controlled trials are lacking. One in vivo study established that damiana fluid extract significantly improves the copulatory performance of sexually sluggish animals, but has no effect on normally functioning ones (Arletti et al 1999). The effect appears to be dose-dependent as positive results were only obtained when the highest dose (1 mL/kg) was administered.

One clinical study of unknown design compared a herbal combination product consisting of ginseng, ginkgo, damiana, l-arginine and a variety of vitamins and minerals with placebo in 77 female volunteers. After 4 weeks, 73.5% of the women in the treatment group reported an increase in sexual satisfaction compared with 37.2% receiving placebo (Ito et al 2001). Although promising, the role of damiana in achieving this result is unknown.

DIABETES

Although in vivo studies suggest significant hypoglycaemic activity, no clinical studies are available to determine whether the effects are clinically significant.



WEIGHT LOSS

No controlled studies are available to determine the effectiveness of damiana as a stand-alone treatment in weight loss; however, one study that used a combination of herbs that included damiana has produced positive results. The randomised double-blind study involving 47 overweight subjects tested a herbal combination product known as 'YGD' (*Yerbe mate*, *Paullinia cupana* and damiana) for weight loss activity. Treatment resulted in a prolonged gastric emptying time and a body weight reduction of 5.1 ± 0.5 kg compared with 0.3 ± 0.08 kg after placebo over 45 days. A 12-month follow-up revealed that weight loss was maintained in the active treatment group (Andersen & Fogh 2001). Until studies using damiana as sole therapy are conducted, the effectiveness of this herb in weight loss is still unknown.

OTHER USES

In practice, damiana is sometimes used to treat anxiety and depression associated with hormonal changes (e.g. menopause) or where there is a sexual factor involved. It is also used as a mild stimulant, aphrodisiac, to enhance stamina generally, nervous dyspepsia and constipation.

DOSAGE RANGE

- Dried leaf: 2–4 g taken three times daily.
- Infusion: pour a cup of boiling water onto 1 teaspoonful of the dried leaves and let infuse for l0–l5 minutes. Drink 3 cups daily.
- Liquid extract (1:2) or solid dose equivalent: 20–40 mL per week or 3–6 mL/day.

ADVERSE REACTIONS

There is insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

HYPOGLYCAEMIC AGENTS

Additive effects are theoretically possible, with unknown clinical significance — observe patients.

CONTRAINDICATIONS AND PRECAUTIONS

Traditionally, the herb is not recommended for people with overactive sympathetic nervous system activity.

PREGNANCY USE

Safety in pregnancy has not been scientifically evaluated however no increase in fetal abnormalities has been observed from limited use in women (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Damiana is a herb with a traditional reputation as being an aphrodisiac, stimulant, mood enhancer and general tonic.
- Currently, evidence to support its use as an aphrodisiac is limited to research in animals, which has produced some positive results.
- In vivo studies have identified significant anti-inflammatory and hypoglycaemic activity, although human studies are still required to determine clinical significance.
- It is also suspected that the herb exerts some degree of hormonal activity.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Damiana has not been significantly tested in human studies, so much information is taken from traditional sources or preliminary research in animals. According to these sources, it may increase sexual function and libido in some cases of dysfunction, lower blood glucose levels and exert anti-inflammatory actions.

When will it start to work?

There is insufficient evidence to predict when effects may develop.

Are there any safety issues?

A long history of use suggests it is generally safe. However, scientific testing has not been conducted.

REFERENCES

Alarcon-Aguilara FJ et al. Study of the anti-hyperglycemic effect of plants used as antidiabetics. J Ethnopharmacol 61.2 (1998): 101-10.

Alcaraz-Melendez L, Delgado-Rodriguez J, Real-Cosio S: Analysis of essential oils from wild and micropropagated plants of damiana (Turnera diffusa). Fitoterapia 75 (2004): 696-701.

Andersen T, Fogh J. Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. J Hum Nutr Diet 14.3 (2001): 243-50.

Antonio MA, Souza Brito ARM. Oral anti-inflammatory and anti-ulcerogenic activities of a hydroalcoholic extract and partitioned fractions of Turnera ulmifolia (Turneraceae). J Ethnopharmacol 61 (1998): 215-28 (as cited in MicroMedex 2003).

Arletti R et al. Stimulating property of Turnera diffusa and Pfaffia paniculata extracts on the sexual behavior of male rats. Psychopharmacology (Berl) 143.1 (1999): 15-19.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. (accessed 2006) www.ars-grin.gov/duke/

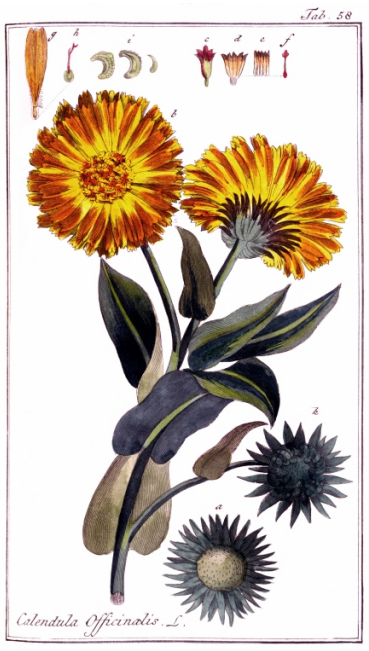
Fetrow CW, Avila JR. Professionals Handbook of Complementary and Alternative medicines. Springhouse, PA: Springhouse, 1999.

Hoffman DL. Damiana. www.healthy.net.com 2003.

Ito TY, Trant AS, Polan ML. A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. J Sex Marital Ther 27.5 (2001): 541-9.
Micromedex. Damiana. Thomson 2003. www.micromedex.com
Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis, MO: Churchill Livingstone, 2005.
Piacente S et al. Flavonoids and arbutin from Turnera diffusa. Z Naturforsch [C] 57.11-12 (2002): 983-5.
Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217.3 (1998): 369-78.

Dandelion

Historical note Dandelion grows throughout the world as a weed and has a long history of medicinal and culinary use. Dandelion leaves are added to salads, providing a good source of minerals, and the roasted root is used as a coffee substitute. Dandelion leaves are traditionally used as a diuretic, and the root is used as a liver tonic.



OTHER NAMES

Blowball, cankerwort, common dandelion, lion's tooth, priest's crown, puffball, swine snout, taraxacum, wild endive, white endive

BOTANICAL NAME/FAMILY

Taraxacum officinale; synonyms: *Leontodon taraxacum*, *Taraxacum vulgare* (family Compositae [Asteraceae])

PLANT PARTS USED

Leaf and root

CHEMICAL COMPONENTS

Dandelion leaf and root contain slightly different constituents.

Overall, dandelion is a rich source of minerals, particularly potassium (Hook et al 1993), as well as iron, magnesium, zinc, potassium, manganese, copper, choline, selenium, calcium, boron and silicon (Queralt et al 2005), and a rich source of vitamins A, C, D and B complex (US Department of Agriculture 2003). The relatively high protein, fibre and linoleic acid content of dandelion leaves has led to suggestions that dandelion is a nutritious and underutilised food source (Escudero et al 2003). Dandelion's constituents also include triterpenes, flavonoid glycosides and various phenolic acids, as well as phytosterols, sugars and mucilage (Blumenthal et al 2000). The many phenolic acids and flavonoids include chicoric acid (dicaffeoyltartaric acid) and quercetin glycosides (Schutz et al 2005).

MAIN ACTIONS

DIURETIC

Dandelion leaf has been found to have a greater diuretic effect than the roots, with activity comparable to that of frusemide, without causing potassium loss because of the leaves' high potassium content (Newall et al 1996). A study using an infusion of

dandelion root found that dandelion did not significantly increase diuresis in rats (Grases et al 1994), and no secondary metabolites showing major diuretic activity were found (Hook et al 1993).

CHOLERETIC

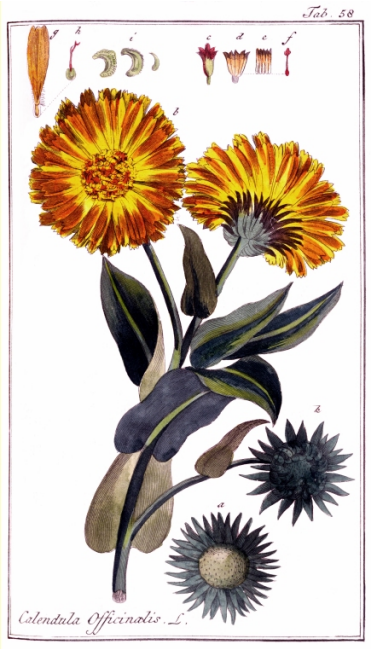
The bitter constituents in dandelion root are believed to be responsible for increasing bile production and flow, as well as contributing to the root's mild laxative effects.

HEPATIC ENZYME INDUCTION

In vivo studies have demonstrated decreased activity of CYP1A2 and CYP2E enzymes and dramatic increases in levels of the phase II detoxifying enzyme UDP-glucuronosyl transferase in liver microsomes of rats receiving dandelion tea (Maliakal & Wanwimolruk 2001). The same study found that dandelion tea had no effect on the activities of CYP2D and CYP3A.

ANTI-INFLAMMATORY AND ANTIOXIDANT ACTIVITY

Dandelion extract was shown to exhibit a mild analgesic and anti-inflammatory effect in mice (Tito et al 1993), and an aqueous dandelion extract was found to prevent diabetic complications due to lipid peroxidation and free radicals in diabetic rats (Cho et al 2002). Dandelion extract has also been found to have a protective effect against CCK octapeptide-induced acute pancreatitis in rats (Seo et al 2005) and dandelion flower extract demonstrated marked antioxidant activity that has been attributed to its phenolic content, with suppression of reactive oxygen species and nitric oxide (Hu & Kitts 2003, 2005, Kery et al 2004). Extracts of dandelion flowers, roots and stem have been found to have significant OH-radical scavenging activity (Kaurinovic et al 2003).



OTHER ACTIONS

There is preliminary scientific evidence from animal and in vitro studies that suggests the roots of *Taraxacum japonicum* may have a cancer preventative effect. The extract has been shown to induce cytotoxicity through TNF-alpha and IL-1-alpha secretion in vitro.

Traditionally, dandelion root is understood to have laxative activity and to stimulate digestion, whereas dandelion leaf has antirheumatic effects. Dandelion root infusion, which contains oligofructans, has been found to stimulate the growth of multiple strains of bifidobacteria, suggesting its use as a probiotic (Trojanova et al 2004).

Dandelion may have antidiabetic actions, because ethanolic extracts of whole dandelion exhibited insulin secretagogue activity (Hussain et al 2004) and dandelion

in conjunction with various other herbal extracts has been shown to have an antihyperglycaemic effect in mice (Petlevski et al 2003).

CLINICAL USE

The therapeutic effectiveness of dandelion has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

DIURETIC

Dandelion has a long history of use as a diuretic in well-established systems of traditional medicines; however, the scientific and clinical evidence to support this use is limited to animal studies (see above). The high potassium content of dandelion is considered to be partly responsible for any diuretic activity (Hook et al 1993).

A double-blind randomised study of 57 women with recurrent cystitis found that a commercial preparation known as Uva-E (a combination of *Arctostaphylos* leaves and dandelion root) significantly reduced the frequency of recurrence of cystitis compared with placebo. At the end of 12 months, none of the patients taking Uva-E had had a recurrence of cystitis, compared with 23% recurrence in the control group ($P < 0.05$) (Larsson et al 1993). The role of dandelion in achieving this result is unknown; however, the researchers suggested that its diuretic effect was likely to have contributed to the positive results.

LIVER TONIC

Dandelion has a long history of use as a liver tonic (Macia et al 2005); however, the scientific and clinical evidence to support this use is limited. Preliminary studies suggest that dandelion root stimulates the flow of bile.

Commission E approves the use of dandelion root and herb for disturbances in bile flow, loss of appetite and dyspepsia (Blumenthal et al 2000).

OTHER USES

Dandelion has been used traditionally as a source of minerals and for treating diabetes, rheumatic conditions, heartburn, bruises and for recurrent hives, urticaria and eczema. It has also been used to treat various digestive complaints such as dyspepsia, lack of appetite and constipation (Newall et al 1996), as well as treating warts (Guarrera 2005) and for breast and uterine cancers (Koo et al 2004).

DOSAGE RANGE

LEAF

- Infusion of dried herb: 4–10 g three times daily.
- Fluid extract (25%): 4–10 mL three times daily.

- Fresh juice: 10–20 mL three times daily.

ROOT

- Decoction of dried root: 2–8 g three times daily.
- Tincture (1:5): 5–10 mL three times daily.
- Fluid extract (30%): 2–8 mL three times daily.
- Juice of fresh root: 4–8 mL three times daily.

ADVERSE REACTIONS

Dandelion is generally considered safe when consumed in amounts commonly found in foods. Cross-reactivity may exist between dandelion and other members of the Compositae (Asteraceae) family, such as ragweed, mugwort, sunflower, daisy and chamomile (Cohen et al 1979, Fernandez et al 1993, Jovanovic et al 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

DIURETIC AGENTS

Dandelion leaf may theoretically interact with other diuretics, although the clinical significance of this is unknown — observe patient.

QUINOLONE ANTIBIOTICS

The high mineral content of dandelion may result in the formation of chelate complexes with quinolone antibiotics and reduce their absorption and bioavailability. This has been demonstrated in rats with *Taraxacum mongolicum* (Chinese dandelion) (Zhu et al 1999). While the clinical significance of this is unknown, it is recommended to avoid concomitant use of these substances or to separate their dosing.

CONTRAINDICATIONS AND PRECAUTIONS

It is recommended that dandelion not be used by people with obstruction of the bile ducts or other serious diseases of the gall bladder (Blumenthal et al 2000).

PREGNANCY USE

Based on a long history of use in traditional medicine, dandelion is generally considered safe in pregnancy and lactation (Blumenthal et al 2000, McGuffin et al 1997).

PRACTICE POINTS/PATIENT COUNSELLING

- Dandelion leaf and root have a long tradition of culinary and medicinal use.

- Dandelion has been traditionally used as a diuretic and liver tonic. It has also been used to treat various digestive complaints such as dyspepsia, lack of appetite and constipation.
- The therapeutic effectiveness of dandelion has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.
- Dandelion is generally considered to be safe and non-toxic, but may cause allergy in people allergic to ragweed and daisies.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this do for me?

In practice, dandelion is used to improve digestion and detoxification, as a diuretic and laxative and to treat diabetes, rheumatic conditions, heartburn, bruises and for recurrent hives, urticaria and eczema. Controlled studies are not available to determine its effectiveness in these conditions.

When will it work?

Stimulation of digestive processes is thought to occur rapidly after one dose.

Are there any safety issues?

Dandelion is generally considered to be safe and non-toxic but may cause allergy in people allergic to ragweed and daisies.

REFERENCES

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Cho SY et al. Alternation of hepatic antioxidant enzyme activities and lipid profile in streptozotocin-induced diabetic rats by supplementation of dandelion water extract. Clin Chim Acta 317.1-2 (2002): 109-17.

Cohen SH et al. Acute allergic reaction after composite pollen ingestion. J Allergy Clin Immunol 64.4 (1979): 270-4.

Escudero NL et al. Taraxacum officinale as a food source. Plant Foods Hum Nutr 58.3 (2003): 1-10.

Fernandez Martin-Esteban CM et al. Analysis of cross-reactivity between sunflower pollen and other pollens of the Compositae family. J Allergy Clin Immunol 92.5 (1993): 660-7.

Grases F et al. Urolithiasis and phytotherapy. Int Urol Nephrol 26.5 (1994): 507-11.

Guarrera PM. Traditional phytotherapy in Central Italy (Marche, Abruzzo, and Latium). Fitoterapia 76.1 (2005): 1-25.

Hook I et al. Evaluation of dandelion for diuretic activity and variation in potassium content. Int J Pharmacog 31.1 (1993): 29-34.

Hu C, Kitts DD. Antioxidant, prooxidant, and cytotoxic activities of solvent-fractionated dandelion (Taraxacum officinale) flower extracts in vitro. J Agric Food Chem 51.1 (2003): 301-10.

Hu C, Kitts DD. Dandelion (Taraxacum officinale) flower extract suppresses both reactive oxygen species and nitric oxide and prevents lipid oxidation in vitro. Phytomedicine 12.8 (2005): 588-97.

Hussain ZA et al. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. Phytother Res 18.1 (2004): 73-7.

Jovanovic MA et al. Sesquiterpene lactone mix patch testing supplemented with dandelion extract in patients with allergic contact dermatitis, atopic dermatitis and non-allergic chronic inflammatory skin diseases. Contact Dermatitis 51.3 (2004): 101-10.
Kaurinovic B et al. Effects of Calendula officinalis L. and Taraxacum officinale Weber (Asteraceae) extracts on the production of OH radicals. Fresenius Environ Bull 12.2 (2003): 250-3.
Kery A et al. Free radical scavenger and lipid peroxidation inhibiting effects of medicinal plants used in phytotherapy. Acta Pharm Hung 74.3 (2004): 158-65.
Koo H-N et al. Taraxacum officinale induces cytotoxicity through TNF-[alpha] and IL-1[alpha] secretion in Hep G2 cells. Life Sci 74.9 (2004): 1149-57.
Larsson B, Jonasson A, Fianu S. Prophylactic effect of Uva-E in women with recurrent cystitis: a preliminary report. Curr Ther Res 53.4 (1993): 441-3.
Macia MJ, et al. An ethnobotanical survey of medicinal plants commercialized in the markets of La Paz and El Alto, Bolivia. J Ethnopharmacol 97.2 (2005): 337-50.
Maliakal PP, Wanwimolruk S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol 53.10 (2001): 1323-9.
McGuffin M et al (eds). American Herbal Products Association's Botanical Safety Handbook. Boca Raton, FL: CRC Press, 1997: 114.
Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.
Petlevski R et al. Glutathione S-transferases and malondialdehyde in the liver of NOD mice on short-term treatment with plant mixture extract P-9801091. Phytother Res 17.4 (2003): 311-14.
Queralt I et al. Quantitative determination of essential and trace element content of medicinal plants and their infusions by XRF and ICF techniques. X-Ray Spectrometry 34.3 (2005): 213-17.
Schutz K et al. Characterization of phenolic acids and flavonoids in dandelion (Taraxacum officinale WEB. ex WIGG.) root and herb by high-performance liquid chromatography/electrospray ionization mass spectrometry. Rapid Commun Mass Spectrometry 19.2 (2005): 179-86.
Seo S-W et al. Taraxacum officinale protects against cholecystokinin-induced acute pancreatitis in rats. World J Gastroenterol 11.4 (2005): 597-9.
Takasaki M et al: Anti-carcinogenic activity of Taraxacum plant II. Biol Pharm Bull 22.6 (1999): 606-10.
Tito B et al. Taraxacum officinale W: pharmacological effect of ethanol extract. Pharmacol Res 27 (Supp 1) (1993): 23-4.
Trojanova I et al. The bifidogenic effect of Taraxacum officinale root. Fitoterapia 75.7-8 (2004): 760-3.
US Department of Agriculture. Phytochemical Database. Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003.
Zhu M et al. Effects of Taraxacum mongolicum on the bioavailability and disposition of ciprofloxacin in rats. J Pharmaceut Sci 88.6 (1999): 632-4.

Devil's claw

Historical note The botanical name *Harpagophytum* means 'hook plant' in Greek, after the hook-covered fruits of the plant. Devil's claw is native to southern Africa and has been used traditionally as a bitter tonic for digestive disturbances, febrile illnesses, allergic reactions and to relieve pain (Mills & Bone 2000). It has been used in Europe for the treatment of rheumatic conditions for over 50 years, and was first cited in the literature by Zorn at the University of Jena, Germany, who described his observations on the antiphlogistic and anti-arthritic effects after administration of oral aqueous extracts prepared from the secondary roots of *H. procumbens* in patients suffering from arthritides (Chrubasik et al 2006).

COMMON NAMES

Devil's claw root, grapple plant, harpagophytum, wood spider

BOTANICAL NAME/FAMILY

Harpagophytum procumbens (family Pedaliaceae)

PLANT PART USED

Dried tuber/root

CHEMICAL COMPONENTS

The major active constituent is considered to be the bitter iridoid glucoside, harpagoside, which should constitute not less than 1.2% of the dried herb. Other iridoid glycosides include harpagide and procumbide. About 50% of the herb consists of sugars. There are also triterpenes, phytosterols, plant phenolic acids, flavonol glycosides and phenolic glycosides. *Harpagophytum zeyheri*, which has a lower level of active compounds, may be partially substituted for *H. procumbens* in some commercial preparations (Stewart & Cole 2005). The extraction solvent (e.g. water, ethanol) has a major impact on the active principle of the products (Chrubasik 2004a)

MAIN ACTIONS

ANTI-INFLAMMATORY/ANALGESIC

There is good in vitro and in vivo pharmacological evidence of the anti-inflammatory and analgesic properties of devil's claw, although some negative findings have also

been reported (McGregor et al 2005). Overall, greatest activity appears to be in semi-chronic rather than acute conditions.

Devil's claw exerted significant analgesic effects against thermally and chemically induced nociceptive pain stimuli in mice and significant dose-related reduction of experimentally induced acute inflammation in rats (Mahomed & Ojewole 2004), as well as reducing pain and inflammation in Freund's adjuvant-induced arthritis in rats (Andersen et al 2004).

The iridoids, particularly harpagoside, are thought to be the main active constituents responsible for the anti-inflammatory activity, although the mechanism of action is unknown and devil's claw is also rich in water-soluble antioxidants (Betancor-Fernandez et al 2003).

It has been suggested that the suppression of matrix metalloproteinases in chondrocytes via the inhibition of inflammatory cytokine synthesis, demonstrated in vitro, could explain its therapeutic effect in arthritic inflammation (Kundu et al 2005). In vitro evidence also suggests that the anti-inflammatory effect may be due to effects on TNF-alpha (Fiebich et al 2001) or antioxidant activity (Langmead et al 2002). Additionally, inhibition of leukotriene synthesis has been observed in vitro, which appears to relate to the amount of harpagoside present (Loew et al 2001).

Contradictory evidence exists as to whether devil's claw affects prostaglandin (PG) synthesis. Early in vitro and in vivo studies suggest that it does not inhibit PG synthesis (Whitehouse et al 1983) and this is supported by studies of PG production in humans (Moussard et al 1992). However, more recent investigations have suggested that its anti-inflammatory and analgesic activities are due to suppression of PGE_2 synthesis and nitric oxide production and that the herb may suppress expressions of COX-2 and iNOS (Jang et al 2003). More recently, methanoloic extracts of devil's claw have been shown to inhibit COX-2 in vivo (Kundu et al 2005, Na et al 2004).

In vivo experiments have determined that the method of administration of devil's claw affects its anti-inflammatory properties. Intraperitoneal and intraduodenal administration was shown to reduce carrageenan-induced oedema, whereas oral administration had no effect, suggesting that exposure to stomach acid may reduce its anti-inflammatory activity (Soulimani et al 1994). This is supported by a study that found a loss of anti-inflammatory activity after acid treatment (Bone & Walker 1997).

In vitro studies on rat mesangial cells suggest that devil's claw may be used as an anti-inflammatory agent in the treatment of glomerular inflammatory diseases (Kaszkin et al 2004a). Devils claw extract produced a concentration-dependent suppression of nitrite formation in rat mesangial cells in vitro due to an inhibition of iNOS expression through interference with the transcriptional activation of iNOS. It

was found that this activity was due to harpagoside, together with other constituents that possibly have strong anti-oxidant activity (Kaszkin et al 2004b).

CHONDROPROTECTIVE

In-vitro data suggests that the active principles of *H. procumbens* inhibit not only inflammatory mediators but also mediators of cartilage destruction, such as TNF-alpha, IL-1-beta, matrix metalloproteinases, NO and elastase (Boje et al 2003, Fiebich et al 2001, Huang et al 2006, Schulze-Tanzil et al 2004). A study using an animal model confirmed a chondroprotective effect in which the tissue inhibitor of metalloproteinase-2 is involved (Chrubasik et al 2006).

HYPOGLYCAEMIC

Devil's claw extract produced a dose-dependent, significant reduction in the blood glucose concentrations of both fasted normal and fasted diabetic rats (Mahomed & Ojewole 2004).

OTHER ACTIONS

In vitro and in vivo evidence suggests that harpagoside may exhibit cardiac affects and lower blood pressure, heart rate and reduce arrhythmias (Fetrow & Avila 1999). As an extremely bitter herb, devil's claw is thought to increase appetite and bile production.. Diterpenes extracted from the roots and seeds of devil's claw exhibited selective antiplasmodial activity in vitro (Clarkson et al 2003), which may have future relevance in view of the increasing resistance to conventional antimalarials.

CLINICAL USE

ARTHRITIS

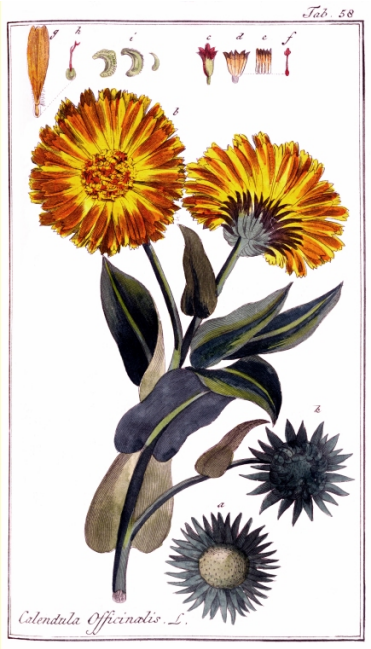
Overall, current evidence from clinical trials suggest that devil's claw may be a useful treatment for arthritis; however, it is suggested, as with many herbal medicines, that evidence of effectiveness is not transferrable from product to product and that the evidence is more robust for products that contain at least 50 mg of harpagoside in the daily dosage (Chrubasik et al 2003a, Gagnier et al 2004).

An observational study of 6 months' use of 3–9 g/day of an aqueous extract of devil's claw root reported significant benefit in 42–85% of the 630 people suffering from various arthritic complaints (Bone & Walker 1997). In a 12-week uncontrolled multicentre study of 75 patients with arthrosis of the hip or knee, a strong reduction in pain and the symptoms of osteoarthritis were observed in patients taking 2400 mg of devil's claw extract daily, corresponding to 50 mg harpagoside (Wegener & Lupke 2003). Similar results were reported in a 2-month observational study of 227 people with osteoarthritic knee and hip pain and non-specific low back pain (Chrubasik et al

2002) and a double-blind study of 89 subjects with rheumatic complaints using powdered devil's claw root (2 g/day) for 2 months, which also provided significant pain relief, whereas another double-blind study of 100 people reported benefit after 1 month (Bone & Walker 1997). A case report suggests that devil's claw relieved strong joint pain in a patient with Crohn's disease (Kaszkin et al 2004).

Comparisons with standard treatment have also been investigated. In 2000, encouraging results of a randomised double-blind study comparing the effects of treatment with devil's claw 2610 mg/day with diacerhein 100 mg/day were published (Leblan et al 2000). The study involved 122 people with osteoarthritis of the hip and/or knee and was conducted over 4 months. It found that both treatment groups showed similar considerable improvements in symptoms of osteoarthritis; however, those receiving devil's claw required fewer rescue analgesics.

One double-blind, randomised, multicentre clinical study of 122 patients with osteoarthritis of the knee and hip found that treatment with Harpadol (6 capsules/day, each containing 435 mg of cryoground powder of *H. procumbens*) given over 4 months was as effective as diacerhein (an analgesic) 100 mg/day (Chantre et al 2000). However, at the end of the study, patients taking Harpadol were using significantly fewer NSAIDs and had a significantly lower frequency of adverse events. In a 6-week study of only 13 subjects, similar benefits for devil's claw and indomethacin were reported (Newall et al 1996). A recent preliminary study comparing the proprietary extract Doloteffin with the COX-2 inhibitor, rofecoxib, reported a benefit with the herbal treatment but suggested that larger studies are still required (Chrubasik et al 2003b). The herb is Commission E approved as supportive therapy for degenerative musculoskeletal disorders (Blumenthal et al 2000) and ESCOP approved for painful osteoarthritis (ESCOP 2003).



BACK PAIN

Several double-blind studies have reported benefit with devil's claw in people with back pain. A double-blind study of 117 people with back pain reported decreased pain and improved mobility after 8 weeks' treatment with devil's claw extract LI 174, known commercially as Rivoltan (Laudahn & Walper 2001). Use of the same extract provided significant pain relief after 4 weeks in another randomised, double-blind placebo-controlled study of 63 subjects with muscle stiffness (Gobel et al 2001). Similar results were reported in two double-blind studies of 118 people (Chrubasik et al 1996) and 197 people (Chrubasik et al 1999) with chronic lower back pain.

Devil's claw appears to compare favourably to conventional treatments. A 6-week double-blind study of 88 subjects comparing devil's claw to rofecoxib found equal improvements in both groups (Chrubasik et al 2003b) A follow-up of the subjects

from that study who were all given devil's claw for 1 year found that it was well tolerated and improvements were sustained (Chrubasik et al 2005). In an open, prospective study, an unspecific lower back pain treatment with *Harpagophytum* extract and conventional therapy were found to be equally effective (Schmidt et al 2005).

Devil's claw root is approved for relief of low back pain by ESCOP (ESCOP 2003).

DYSPEPSIA

Traditionally, devil's claw has also been used to treat dyspepsia and to stimulate appetite (Fisher and Painter 1996). The bitter principles in the herb provide a theoretical basis for its use in these conditions, although controlled studies are not available to determine effectiveness. The herb is Commission E (Blumenthal et al 2000) and ESCOP (2003) approved for dyspepsia and loss of appetite.

OTHER USES

Traditionally, the herb is also used internally to treat febrile illnesses, allergic reactions and to induce sedation, and topically for wounds, ulcers, boils and pain relief (Fisher & Painter 1996, Mills & Bone 2000), as well as for diabetes, hypertension, indigestion and anorexia (Van Wyk 2000).

DOSAGE RANGE

MUSCULOSKELETAL CONDITIONS

- Dried root or equivalent aqueous or hydroalcoholic extracts: 2–6 g daily for painful arthritis; 4.5–9 g daily for lower back pain.
- Liquid extract (1:2): 6–12 mL/day.
- Tincture (1:5): 2–4 mL three times daily.

It is suggested that devil's claw extracts with at least 50 mg harpagoside in the daily dosage should be recommended for the treatment of pain (Chrubasik 2004a, b).

DIGESTIVE CONDITIONS (E.G. DYSPEPSIA)

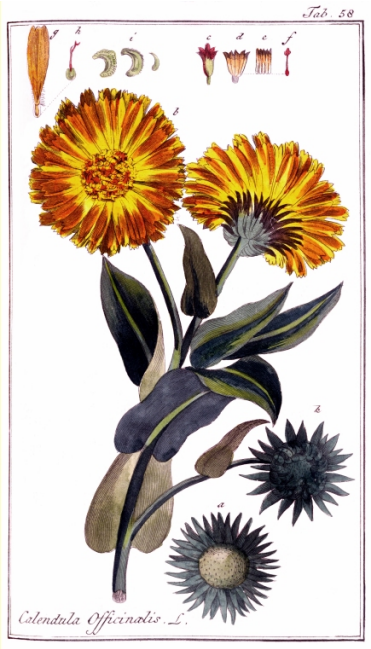
- Dosages equivalent to 1.5 g/day dried herb are used (Blumenthal et al 2000). It is suggested that devil's claw preparations be administered between meals, when gastric activity is reduced.

TOXICITY

The acute LD_{50} of devil's claw was more than 13.5 g/kg according to one study (Bone & Walker 1997).

ADVERSE REACTIONS

Diarrhoea was reported in one clinical study.



SIGNIFICANT INTERACTIONS

Devil's claw has been found to moderately inhibit cytochrome P450 enzymes in vitro (Unger & Frank 2004), however, the clinical relevance of this is yet to be determined.

WARFARIN

Rare case reports suggest that devil's claw may potentiate the effects of warfarin, requiring caution and possible dose adjustments (Argento et al 2000, Heck et al 2000); however, clinical testing is required to confirm this — use caution in patients receiving warfarin.

ANTIARRYTHMIC DRUGS

Theoretical interaction exists when the herb is used in high doses; however, clinical testing is required to determine significance — observe patients taking concurrent antiarrythmics (Fetrow & Avila 1999).

CONTRAINDICATIONS AND PRECAUTIONS

Use cautiously in patients with gastric and duodenal ulcers, gallstones or acute diarrhoea, as devil's claw may cause gastric irritation (Blumenthal et al 2000).

Suspend use of concentrated devil's claw preparations 1 week before major surgery to avoid increased risk of bleeding.

PREGNANCY USE

Devil's claw is not recommended in pregnancy, as it has exhibited oxytocic activity in animals.

PRACTICE POINTS/PATIENT COUNSELLING

- Devil's claw reduces pain and inflammation and is a useful treatment in arthritis and back pain, according to controlled studies.
- The anti-inflammatory action appears to be different to that of NSAIDs and has not been fully elucidated. There is also preliminary evidence of a chondroprotective effect.
- Preliminary research suggests that it is best to take devil's claw between meals, on an empty stomach.
- Devil's claw appears to be relatively safe but should not be used in pregnancy and should be used with caution in people with ulcers or gall stones or in those taking warfarin.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Devil's claw is a useful treatment for arthritis and back pain. It may also increase appetite and improve digestion and dyspepsia.

When will it start to work?

Results from studies suggest that pain-relieving effects will start within 4–12 weeks.

Are there any safety issues?

Devil's claw should be used cautiously by people with gallstones, diarrhoea, stomach ulcers and those taking the drug warfarin. It is also not recommended in pregnancy.

REFERENCES

Andersen ML et al. Evaluation of acute and chronic treatments with Harpagophytum procumbens on Freund's adjuvant-induced arthritis in rats. J Ethnopharmacol 91.2-3 (2004): 325-30.

Argento AE et al. Oral anticoagulants and medicinal plants: An emerging interaction. Ann Ital Med Intern 15.2 (2000): 139-43.

Betancor-Fernandez A et al. Screening pharmaceutical preparations containing extracts of turmeric rhizome, artichoke leaf, devil's claw root and garlic or salmon oil for antioxidant capacity. J Pharm Pharmacol 55.7 (2003): 981-6.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Boje K, Lechtenberg M, Nahrstedt A. New and known iridoid- and phenylethanoid glycosides from Harpagophytum procumbens and their in vitro inhibition of human leukocyte elastase. Planta Med 69 (2003): 820-5.

Bone K, Walker M. Devil's claw. MediHerb Professional Review. Australia: Mediherb Pty Ltd (February 1997).

Chantre P et al. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine 7.3 (2000): 177-83.

Chrubasik JE et al. Potential molecular basis of the chondroprotective effect of Harpagophytum procumbens. Phytomedicine (2006) [Epub ahead of print].

Chrubasik S. Devil's claw extract as an example of the effectiveness of herbal analgesics. Der Orthopade 33.7 (2004a): 804-8.

Chrubasik S. Salix and Harpagophytum for chronic joint and low back pain: From evidence-based view herbal medicinal products are recommended. Schweiz Z GanzheitsMed 16.6 (2004b): 355-9.

Chrubasik S et al. Effectiveness of Harpagophytum procumbens in treatment of acute low back pain. Phytomedicine 3.1 (1996): 1-10.

Chrubasik S et al. Effectiveness of Harpagophytum extract WS 1531 in the treatment of exacerbation of low back pain: a randomized, placebo-controlled, double-blind study. Eur J Anaesthesiol 16.2 (1999): 118-29.

Chrubasik S et al. Comparison of outcome measures during treatment with the proprietary Harpagophytum extract doloteffin in patients with pain in the lower back, knee or hip. Phytomedicine 9.3 (2002): 181-94.

Chrubasik S et al. The quality of clinical trials with Harpagophytum procumbens. Phytomedicine 10.6-7 (2003a): 613-23.

Chrubasik S et al. A randomized double-blind pilot study comparing Doloteffin(R) and Vioxx(R) in the treatment of low back pain. Rheumatology 42.1 (2003b): 141-8.

Chrubasik S et al. A randomized double-blind pilot study comparing Doloteffin and Vioxx in the treatment of low back pain. Rheumatology 42.1 (2003c): 141-8.

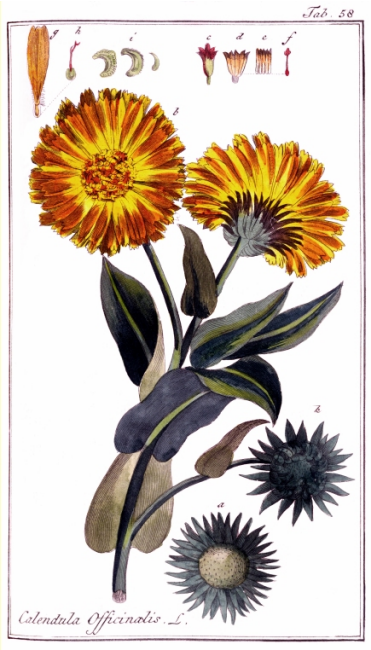
Chrubasik S et al. A 1-year follow-up after a pilot study with Doloteffin(R) for low back pain. Phytomedicine 12.1-2 (2005): 1-9.

Clarkson C et al. In vitro antiplasmodial activity of abietane and totarane diterpenes isolated from Harpagophytum procumbens (Devil's Claw). Planta Med 69.8 (2003): 720-4.

European Scientific Co-operative On Phytomedicine (ESCOP), 2nd edn. Stuttgart: Thieme, 2003.

Fetrow CW, Avila JR. Professionals' Handbook of Complementary and Alternative Medicines. Springhouse, PA: Springhouse Publishing, 1999.

Fiebich BL et al. Inhibition of TNF-alpha synthesis in LPS-stimulated primary human monocytes by Harpagophytum extract SteiHap 69. Phytomedicine 8.1 (2001): 28-30.
Fisher C, Painter G. Materia Medica for the Southern hemisphere. Auckland: Fisher-Painter Publishers, 1996.
Gagnier JJ et al. Harpgophytum procumbens for osteoarthritis and low back pain: a systematic review. BMC Complement Altern Med 4 (2004): 13.
Gobel HA et al. Effects of Harpagophytum procumbens LI 174 (devil's claw) on sensory, motor and vascular muscle reagibility in the treatment of unspecific back pain. Schmerz 15.1 (2001): 10-18.
Heck AM et al. Potential interactions between alternative therapies and warfarin. Am J Health-System Pharm 57.13 (2000): 1221-7; quiz 1228-30.
Huang TH et al. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-kappaB activation. J Ethnopharmacol 104 (2006): 149-55.
Jang MH et al. Harpagophytum procumbens suppresses lipopolysaccharide-stimulated expressions of cyclooxygenase-2 and inducible nitric oxide synthase in fibroblast cell line L929. J Pharmacol Sci 93.3 (2003): 367-71.
Kaszkin M et al. Downregulation of iNOS expression in rat mesangial cells by special extracts of Harpagophytum procumbens derives from harpagoside-dependent and independent effects. Phytomedicine 11.7-8 (2004a): 585-95.
Kaszkin M et al. High dosed Harpagophytum special extract for maintenance of remission in patients with Crohn's disease: A case report. Arztezeitschr Naturheilverfahr 45.2 (2004b): 102-6.
Kundu JK et al. Inhibitory effects of the extracts of Sutherlandia frutescens (L.) R. Br. and Harpagophytum procumbens DC. on phorbol ester-induced COX-2 expression in mouse skin: AP-1 and CREB as potential upstream targets. Cancer Lett 218.1 (2005): 21-31.
Langmead L et al. Antioxidant effects of herbal therapies used by patients with inflammatory bowel disease: an in vitro study. Aliment Pharmacol Ther 16.2 (2002): 197-205.
Laudahn D, Walper A. Efficacy and tolerance of Harpagophytum extract LI 174 in patients with chronic non-radicular back pain. Phytother Res 15.7 (2001): 621-4.
Leblan D, Chantre P, Fournie B. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis: Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. Joint Bone Spine 67.5 (2000): 462-7.
Loew D et al. Investigations on the pharmacokinetic properties of Harpagophytum extracts and their effects on eicosanoid biosynthesis in vitro and ex vivo. Clin Pharmacol Ther 69.5 (2001): 356-64.
Mahomed IM, Ojewole JAO. Analgesic, antiinflammatory and antidiabetic properties of Harpagophytum procumbens DC (Pedaliaceae) secondary root aqueous extract. Phytother Res 18.12 (2004): 982-9.
McGregor GB et al. Devil's claw (Harpagophytum procumbens): An anti-inflammatory herb with therapeutic potential. Phytochem Rev 4.1 (2005): 47-53.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Moussard CD et al. A drug used in traditional medicine, Harpagophytum procumbens: no evidence for NSAID-like effect on whole blood eicosanoid production in human. Prostaglandins Leukot Essent Fatty Acids 46.4 (1992): 283-6.
Na HK et al. Inhibition of phorbol ester-induced COX-2 expression by some edible African plants. BioFactors (Oxford) 21.1-4 (2004): 149-53.
Newell CA, Anderson LA, Phillipson JD. Herbal medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.
Schmidt A et al. Effectiveness of Harpagophytum procumbens in treatment of unspecific low back pain. Physikal Med Rehabilitationsmed Kurortmed 15.5 (2005): 317-21.
Schulze-Tanzil G, Hansen C, Shakibaei M. Effect of a Harpagophytum procumbens DC extract on matrix metalloproteinases in human chondrocytes in vitro. Arzneimittelforschung 54 (2004): 213-20.
Soulimani R et al. The role of stomachal digestion on the pharmacological activity of plant extracts, using as an example extracts of Harpagophytum procumbens. Can J Physiol Pharmacol 72.12 (1994): 1532-6.



Stewart KM, Cole D. The commercial harvest of devil's claw (Harpagophytum spp.) in southern Africa: The devil's in the details. J Ethnopharmacol 100.3 (2005): 225-36.
Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. Rapid Commun in Mass Spectrometry 18.19 (2004): 2273-81.
Van Wyk BE, Gericke N. People's Plants: A Guide to Useful Plants of Southern Africa. Pretoria: Briza Publications, 2000.
Wegener T, Lupke N-P. Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (Harpagophytum procumbens DC). Phytother Res 17.10 (2003): 1165-72.
Whitehouse LW et al. Devil's claw (Harpagophytum procumbens): no evidence for anti-inflammatory activity in the treatment of arthritic disease. Can Med Assoc J 129.3 (1983): 249-51.

Dong quai

Historical note Dong quai is an aromatic herb commonly used in TCM. Its reputation is second to that of ginseng and is regarded as a 'female' remedy, or women's ginseng. Used in combination with other herbs, dong quai is used to treat numerous menstrual disorders and menopausal symptoms, as well as abdominal pain, migraine headache, rheumatism and anaemia (Murray 1995). Dong quai *(Angelica sinensis)* is closely related to the European *Angelica archangelica*, a common garden herb and the flavouring in Benedictine and Chartreuse liqueurs.

COMMON NAME
Dong quai

OTHER NAMES
Chinese angelica, dang gui, women's ginseng, tang kuei

BOTANICAL NAME/FAMILY
Angelica sinensis (synonym: *Angelica polymorpha sinensis*) (family Apiaceae [Umbelliferae] — carrot family)

PLANT PART USED
Root

CHEMICAL COMPONENTS
Dong quai contains essential oil (0.4–0.7%) consisting of 45% ligustilide, n-butylphthalide, cadinene, carvacrol, safrole and isosafrol. The root also contains sucrose (40%) and various lactones and vitamins, together with phytosterols, ferulic acid and coumarins, including osthole, psoralen and bergapten (Micromedex 2003). Ferulic acid and ligustilide are considered to be the main active components (Dong et al 2005) and it has been suggested that assessment of total ferulic acid content provides a good measure of herbal quality (Lu et al 2005).

MAIN ACTIONS
Nearly all studies investigating the pharmacological effects of dong quai have been conducted in vitro or in animals, so it is difficult to predict whether the observed effects are clinically significant.

HORMONE MODULATION AND UTERINE EFFECTS

Studies on the uterine effects of dong quai have produced variable results. A uterine relaxant effect has been attributed to the volatile oil, whereas a uterine stimulant effect has been attributed to an aqueous extract (Mills & Bone 2000). Animal experiments report that dong quai produces increased uterine excitability, with initial irregular, fast contractions, later slowing and becoming more regular (Zhu 1987).

Studies of dong quai's oestrogenic activity have also produced contradictory results. In vitro reports suggest that dong quai has weak oestrogen-receptor-binding activity, producing up-regulation of progesterone-receptor mRNA (Liu et al 2001), and stimulating oestrogen-dependent breast cancer cells independent of oestrogenic activity (Amato et al 2002). An aqueous extract of dong quai was found to stimulate the growth of both oestrogen-receptor-positive and -negative breast cancer cells in vitro, suggesting both a weak oestrogen-agonistic activity and activity independent of oestrogen-receptor-mediated pathways (Lau et al 2005). This is contrasted by a study using several different in vitro bioassays that found that dong quai did not have oestrogenic activity (Klein et al 2003), oestrogen-receptor-binding activity or stimulate the growth of oestrogen-positive breast cancer cells and that it had neutral progestin activity (Zava & Blen 1998). Dong quai has also been reported to have anti-oestrogenic activity and anti-androgenic activity in vitro (Rosenberg et al 2001).

IMMUNOSTIMULANT EFFECT

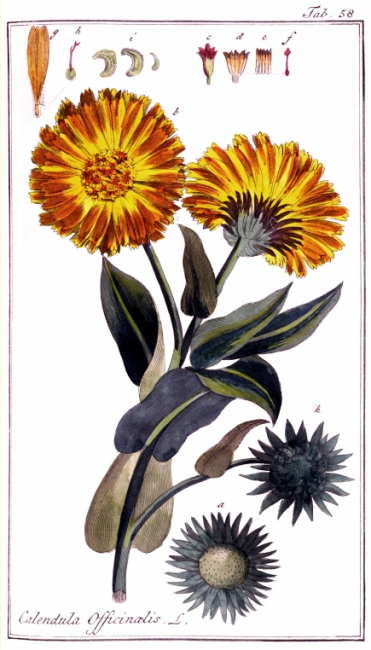
It is reported that dong quai can counter the immunosuppressive effects of hydrocortisone in vivo (Mills & Bone 2000). Immunostimulation is further suggested by in vitro studies demonstrating enhanced cell mediated immunity (Yang et al 2005a) and upregulation of IL-2 and IFN-gamma (Yang et al 2005a), as well as non-specific lymphoproliferation (Wilasrusmee et al 2002). A polysaccharide from dong quai has also been found to enhance non-specific immunity while suppressing humoral immunity (Yang et al 2003).

HEPATOPROTECTION

Dong quai is said to improve abnormal protein metabolism in people with chronic hepatitis or hepatic cirrhosis. Evidence comes from an in vivo study in which 5% dong quai was added to the daily diet of rats, resulting in enhanced metabolism, increased hepatic oxygen utilisation, and increased glutamic acid and cysteine oxidation (Micromedex 2003). Dong quai has been found to have antioxidant activity (Wu et al 2004), as well as antiproliferative and pro-apoptotic activities in hepatic stellate cells in vitro, suggesting a potential antifibrotic action (Chor et al 2005).

CARDIAC PROTECTION

Dong quai is reported to have a quinidine-like action, prolonging the cardiac refractory period and correcting atrial fibrillation (Fetrow & Avila 1999). An in vitro study of dong quai in conjunction with *Astragalus membranaceus* demonstrated protection against myocardial ischaemia-reperfusion injury (Yim et al 2000), while in vivo studies report prevention of atherosclerosis, dilation of coronary vessels and increased coronary blood flow (Mills & Bone 2000). A combined extract of dong quai and *Ligusticum chuanxiong* has been found to inhibit vascular smooth muscle cell proliferation in vitro (Hou et al 2005).



ANTICOAGULANT AND ANTIPLATELET EFFECTS

Dong quai has been shown to have potent anticoagulant effects, as well as haemostatic effect related to promoting platelet aggregation (Yang T et al 2002). In a controlled trial an IV preparation of dong quai was found to prolong prothrombin times significantly more than IV dextran in a group of 96 patients admitted with ischaemic stroke (Micromedex 2003). Dong quai has also been shown to significantly inhibit platelet activation, relieve vascular endothelial cell injury, and improve microcirculation in patients with ulcerative colitis (Dong et al 2004). Ferulic acid, found in dong quai, has been reported to inhibit the aggregation of platelets in blood and retard platelet release of serotonin and adenosine diphosphate. *Angelica sinensis* has a lower coumarin content than other *Angelica* species.

ANTICARCINOGENIC

Polysaccharides from dong quai have been shown to possess antitumour effects in experimental in vivo tumour models and inhibitory effects on invasion and metastasis of in vitro hepatocellular carcinoma cells (Shang et al 2003). An acetone extract of dong quai was found to inhibit proliferation of human cancer cells in vitro via induction of cell cycle arrest and apoptosis (Cheng et al 2004). There is evidence to suggest that a chloroform extract of dong quai suppresses growth of malignant brain tumour cells in vitro, as well as suppressing growths of malignant brain tumours of rat and human origin and shrinking the volumes of in situ glioblastoma multiforme, significantly prolonging survivals in vivo (Tsai et al 2005).

NEUROPROTECTION

Dong quai has been found to be effective in treating acute cerebral infarction. In a case series of 1404 patients with acute cerebral infarction, of whom 692 were treated with dong quai injection, 390 with compound salvia and 322 with low-molecular dextran injection, the group treated with dong quai were found to have significantly

better neurological function and a larger reduction of infarcted area than the other groups (Liu Y-M et al 2004).

Bak Foong Pills, a combination Chinese herbal formula that contains dong quai and other herbs such as *Panax ginseng* and *Glycyrrhiza uralensis*, have been found to have a neuroprotective action, suggesting these herbs may have a use in the treatment of neurodegenerative diseases, such as Parkinson's disease (Jia et al 2005, Rui et al 2005). A multi-herbal formula (Guibi-tang) containing dong quai has also been shown to improve learning and memory, and to increase the proliferation of hippocampal cells in rats (Oh et al 2005). An aqueous extract of three herbs, including dong quai, has been found to have a neuroprotective action and improve cognitive function in an animal model of vascular dementia (Lin et al 2005) and a multi-herbal combination (Danggui-Shaoyao-san) has been found to improve memory and modulate monoamine neurotransmitter metabolism suggesting a possible use for treating senile dementia and Alzheimer's disease (Kou et al 2005).

GASTROPROTECTION

Polysaccharides derived from dong quai have been found to have a protective effect on colon injury in acetic acid-induced rat colitis, through promotion of growth factors, decreasing oxygen free radicals and some anti-inflammatory effects (Liu et al 2004), as well as relieving the inflammation reaction and colon injury in immunological colitis in rats (Liu et al 2003a,b). A polysaccharide containing extract of dong quai was also shown to promote migration and proliferation of normal gastric epithelial cells and enhance gastric ulcer healing in animal models (Ye et al 2003).

OTHER ACTIONS

A preparation containing polysaccharides extracted from dong quai has been shown to have a radioprotective effect in mice (Mei 1988, Sun et al 2005), as well as an analgesic action in rats (Yue et al 2002).

An in vivo study has shown that dong quai in conjunction with astragalus reduced the deterioration of renal function and histologic damage in an animal model of nephrotic syndrome (Wang et al 2004). Dong quai has also been found to alleviate bleomycin-induded pulmonary fibrosis in rats (Chai et al 2003).

Dong quai promotes melanocytic proliferation, melanin synthesis and tyrosinase activity, suggesting a use in the treatment of skin pigmentation (Deng & Yang 2003).

An aqueous extract of dong quai has also been found to directly stimulate the proliferation and activity of human osteoprecursor cells in a dose-dependent manner in vitro (Yang et al 2002).

The essential oil of dong quai has been found to have an anxiolytic action similar to diazepam in a mouse model of anxiety (Chen et al 2004).

Various other in vitro and in vivo studies provide some evidence for antispasmodic, anti-allergic and anti-anaemic effects (Micromedex 2003).

CLINICAL USE

GYNAECOLOGICAL USE

Orally, dong quai has been traditionally used in combination with other herbs for gynaecological ailments including menstrual cramps, irregularity, retarded flow, weakness during the menstrual period, and symptoms of menopause (Fisher & Painter 1996). Very little clinical research has been conducted to determine its effectiveness as sole treatment in these indications.

In a 12-week randomised, placebo-controlled trial in 55 postmenopausal women, a combination of dong quai and chamomile was found to significantly reduce hot flushes and improve sleep disturbances and fatigue. Another double-blind, randomised, placebo-controlled clinical trial of 71 women using dong quai as a single agent (4.5 g/day) found no differences between groups in the number of vasomotor flushes, endometrial thickness, or vaginal cells over a 24-week period (Hirata et al 1997).

It is suggested that dong quai may have some efficacy for premenstrual syndrome when used in traditional Chinese multi-herbal formulas (Hardy 2000), and an uncontrolled trial has suggested the possible benefit of uterine irrigation with dong quai extract for infertility due to tubal occlusion (Hardy 2000).

OTHER USES

In TCM, dong quai is used to strengthen the heart, lung and liver meridians and harmonise the blood. It is used to regulate menstruation, treat amenorrhoea, dysmenorrhoea, headache, constipation, abdominal pain and palpitations.

Traditionally, dong quai is considered a 'hot' herb and is not used in conditions associated with 'heat', according to these prescribing systems.

DOSAGE RANGE

- Decoction of dried root: 4.5–9 g/day.
- Liquid extract (1:2): 4.5–8.5 mL/day.

ADVERSE REACTIONS

Furanocoumarins, such as bergapten and psoralen, which are in dong quai have been widely studied for their phototoxicity; however, only *Angelica gigas* (Korean angelica) has been demonstrated to cause photodermatitis.

Safrole, found in the volatile oil, is a potential carcinogen; however, no specific cases of carcinogenesis have been reported (Micromedex 2003).

High doses of dong quai volatile oil have been reported to cause nephrosis in rats but there are no reports in humans (Zhu 1987).

SIGNIFICANT INTERACTIONS

WARFARIN

Case reports suggest the elevations in prothrombin and INR may occur when dong quai is used with warfarin (Heck et al 2000, Page & Lawrence 1999) — use caution if used concurrently with warfarin.

CONTRAINDICATIONS AND PRECAUTIONS

Because dong quai may have oestrogenic effects, women with hormone-sensitive tumours, endometriosis and uterine fibroids should avoid using dong quai.

Traditional contraindications include diarrhoea due to weak digestion, haemorrhagic disease, heavy periods, first trimester of pregnancy, and acute infection such as colds or flu (Zhu 1987).

PREGNANCY USE

Dong quai may stimulate uterine contractions and is therefore contraindicated in pregnancy (Mills & Bone 2000).

PRACTICE POINTS/PATIENT COUNSELLING

- Dong quai is a popular Chinese medicine used widely to relieve menopausal symptoms; however, controlled trials in humans are lacking. In practice, dong quai is prescribed together with other herbs and may be effective when used in this way.
- Evidence of oestrogenic activity is contradictory.
- Care is required in people using drugs that affect blood clotting.
- Dong quai is generally safe when used appropriately.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Dong quai has a long history of use as a women's tonic. Although conclusive evidence is lacking, dong quai is used in conjunction with other herbs to assist in menopausal and menstrual complaints, and may be effective when used in this way.

When will it start to work?

It is difficult to predict from the available scientific research.

Are there any safety issues?

Dong quai appears to be relatively safe but care should be taken in people using drugs that affect blood clotting or in pregnancy and conditions that are hormone sensitive.

REFERENCES

Amato P et al. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 9(2) (2002): 145-50.

Chai W-S et al. The effects of Angelica sinensis on pulmonary fibrosis in rats. Chin Pharmacoll Bull 19(7) (2003): 819-22.

Chen SW et al. The effects of angelica essential oil in three murine tests of anxiety. Pharmacol Biochem Behav 79(2) (2004): 377-82.

Cheng Y-L et al. Acetone extract of Angelica sinensis inhibits proliferation of human cancer cells via inducing cell cycle arrest and apoptosis. Life Sci 75(13) (2004): 1579-94.

Chor SY et al. Anti-proliferative and pro-apoptotic effects of herbal medicine on hepatic stellate cell. J Ethnopharmacol 100(1-2) (2005): 180-6.

Deng Y, Yang L. Effect of Angelica sinensis (Oliv.) on melanocytic proliferation, melanin synthesis and tyrosinase activity in vitro. Di Yi Jun Yi Da Xue Xue Bao [Acad J First Med Coll PLA] 23(3) (2003): 239-41.

Dong W-G et al. Abnormal function of platelets and role of Angelica sinensis in patients with ulcerative colitis. World J Gastroenterol 10(4) (2004): 606-9.

Dong ZB et al. Hypothesis of potential active components in Angelica sinensis by using biomembrane extraction and high performance liquid chromatography. J Pharm Biomedl Anal 38(4) (2005): 664-9.

Fetrow CW, Avila JR. Professionals' Handbook of Complementary and Alternative Medicines. Springhouse, PA: Springhouse Publishing, 1999.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Hardy ML. Herbs of special interest to women. J Am Pharm Assoc 40(2) (2000): 234-42; quiz 327-29.

Heck AM et al. Potential interactions between alternative therapies and warfarin. Am J Health-System Pharm 57(13) (2000): 1221-7; quiz 1228-30.

Hirata JD et al. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil Steril 68(6) (1997): 981-6.

Hou Y-Z et al. Inhibition of rat vascular smooth muscle cell proliferation by extract of Ligusticum chuanxiong and Angelica sinensis. J Ethnopharmacol 100(1-2) (2005): 140-4.

Jia RR et al. Anti-apoptotic activity of Bak Foong Pills and its ingredients on 6-hydroxydopamine-induced neurotoxicity in PC12 cells. Cell Biol Int 29(10) (2005): 835-42.

Klein KO et al. Estrogen bioactivity in Fo-Ti and other herbs used for their estrogen-like effects as determined by a recombinant cell bioassay. J Clin Endocrinol Metab 88(9) (2003): 4077-9.

Kou J et al. Neuroprotective effects of the aqueous extract of the Chinese medicine Danggui-Shaoyao-san on aged mice. J Ethnopharmacol 97(2) (2005): 313-18.

Lau CBS et al. Use of dong quai (Angelica sinensis) to treat peri- or postmenopausal symptoms in women with breast cancer: Is it appropriate? Menopause 12(6) (2005): 734-40.

Lin Z et al. Protective effects of FBD: An experimental Chinese traditional medicinal formula on memory dysfunction in mice induced by cerebral ischemia-reperfusion. J Ethnopharmacol 97(3) (2005): 477-83.

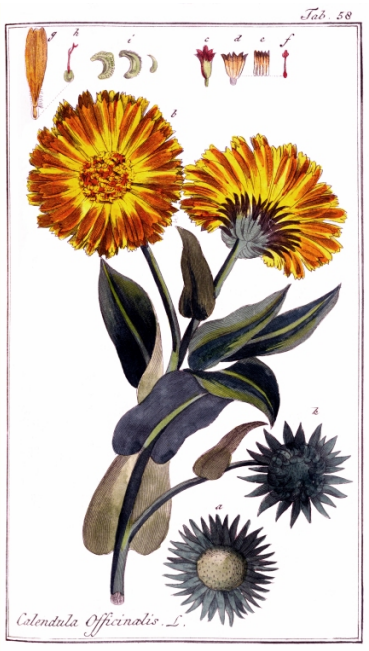
Liu J et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 49(5) (2001): 2472-9.

Liu S-P et al. Protective effect of angelica sinensis polysaccharide on experimental immunological colon injury in rats. World J Gastroenterol 9(12) (2003a): 2786-90.

Liu S-P et al. Study on the protective effects of Angelica sinensis polysaccharides on the colon injury in immunological colitis rats. Chin Pharmacol Bull 19(6) (2003b): 693-6.

Liu S-P et al. Protective effects of Angelica sinensis polysaccharides on acetic acid-induced rat colitis. World Chin Digestol 12(2) (2004): 367-70.
Liu Y-M et al. Observation on clinical effect of Angelica injection in treating acute cerebral infarction. Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi [Chinese J Integr Trad West Med/Zhongguo Zhong Xi Yi Jie He Xue Hui, Zhongguo Zhong Yi Yan Jiu Yuan Zhu Ban] 24(3) (2004): 205-8.
Lu G-H et al. Assay of free ferulic acid and total ferulic acid for quality assessment of Angelica sinensis. J Chromatogr A 1068(2) (2005): 209-19.
Mei QB. Effects of Angelica sinensis polysaccharides on hemopoietic stem cells in irradiated mice. Chung Kuo YaoLI Hsueh Pao 9 (1988): 279-82.
Micromedex. Dong Quai. Thomson 2003. www.micromedex.com
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Murray M. The Healing Power of Herbs. Rocklin, CA: Prima Health, 1995,
Oh MS et al. The multi-herbal formula Guibi-tang enhances memory and increases cell proliferation in the rat hippocampus. Neurosci Lett 379(3) (2005): 205-8.
Page RL 2nd, Lawrence JD. Potentiation of warfarin by dong quai. Pharmacotherapy 19(7) (1999): 870-6.
Rosenberg Z et al. Effects of natural products and nutraceuticals on steroid hormone-regulated gene expression. Clin Chim Acta 312(1-2) (2001): 213-19.
Rui RJ et al. Anti-apoptotic activity of Bak Foong Pills and its ingredients on 6-hydroxydopamine-induced neurotoxicity in PC12 cells. Cell Biol Int 29(10) (2005): 835-42.
Shang P et al. Experimental study of anti-tumor effects of polysaccharides from Angelica sinensis. World J Gastroenterol 9(9) (2003): 1963-7.
Sun Y et al. Water-soluble polysaccharides from Angelica sinensis (Oliv.) Diels: Preparation, characterization and bioactivity. Int J Biol Macromol 36(5) (2005): 283-9.
Tsai N-M et al. The antitumor effects of Angelica sinensis on malignant brain tumors in vitro and in vivo. Clin Cancer Res 11(9) (2005): 3475-84.
Wang H et al. Antifibrotic effect of the Chinese herbs, Astragalus mongholicus and Angelica sinensis, in a rat model of chronic puromycin aminonucleoside nephrosis. Life Sci 74(13) (2004): 1645-58.
Wilasrusmee C et al. In vitro immunomodulatory effects of herbal products. Am Surg 68(10) (2002): 860-4.
Wu S-J et al. Antioxidant activities of some common ingredients of traditional chinese medicine, Angelica sinensis, Lycium barbarum and Poria cocos. Phytother Res 18(12) (2004): 1008-12.
Yang Q et al. Effect of Angelica sinensis on the proliferation of human bone cells. Clin Chim Acta 324(1-2) (2002): 89-97.
Yang T et al. Effects of Angelica polysaccharide on blood coagulation and platelet aggregation. Zhong Yao Cai [Zhongyaocai/J Chin Med Mater] 25(5) (2002): 344-5.
Yang T et al. Immunoloregulation effect of Angelica polysaccharide isolated from Angelica sinensis. Chin Pharmacol Bull 19(4) (2003): 448-51.
Yang T et al. Effects of Angelica sinensis polysaccharide on cell-mediated immuneity. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi [Chin J Cell Mol Immunol] 21(6) (2005a): 782-3.
Yang T et al. Effect of Angelica sinensis polysaccharide on lymphocyte proliferation and cytokine induction. Zhong Yao Cai [Zhongyaocai/J Chin Med Mater] 28(5) (2005b): 405-7.
Ye YN et al. Effect of polysaccharides from Angelica sinensis on gastric ulcer healing. Life Sci 72(8) (2003): 925-32.
Yim TK et al. Myocardial protection against ischaemia-reperfusion injury by a Polygonum multiflorum extract supplemented with 'Dang-Gui decoction for enriching blood', a compound formulation, ex vivo. Phytother Res 14(3) (2000): 195-9.
Yue J et al. Experimental studies on analgesic effect of Angelica sinensis polysaccharide. Chin Pharm J 37(10) (2002): 746-8.
Zava DT, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217(3) (1998): 369-78.
Zhu DP. Dong quai. Am J Chin Med 15(3-4) (1987): 117-25.

Echinacea



Historical note Echinacea was first used by Native American Sioux Indians centuries ago as a treatment for snakebite, colic, infection and external wounds, among other things. It was introduced into standard medical practice in the USA during the 1800s as a popular anti-infective medication, which was prescribed by eclectic and traditional doctors until the 20th century. Remaining on the national list of official plant drugs in the USA until the 1940s, it was produced by pharmaceutical companies during this period. With the arrival of antibiotics, echinacea fell out of favour and was no longer considered a 'real' medicine for infection. Its use has re-emerged, probably because we are now in a better position to understand the limitations of antibiotic therapy and because there is growing public interest in self-care. The dozens of clinical trials conducted overseas have also played a role in its renaissance.

COMMON NAME
Echinacea

OTHER NAMES
E. angustifolia — American coneflower, black sampson, black susans, coneflower, echinaceawurzel, Indian head, kansas snakeroot, purple coneflower, purpursonnenhutkraut, racine d'echinacea, *Rudbeckia angustifolia* L., scurvy root, snakeroot

E. purpurea — *Brauneria purpurea* (L.) Britt., combflower, purple cone flower, red sunflower

Rudbeckia purpurea L. — *E. pallida*, *Brauneria pallida* (Nutt.) Britt., pale coneflower, *Rudbeckia pallida* Nutt.

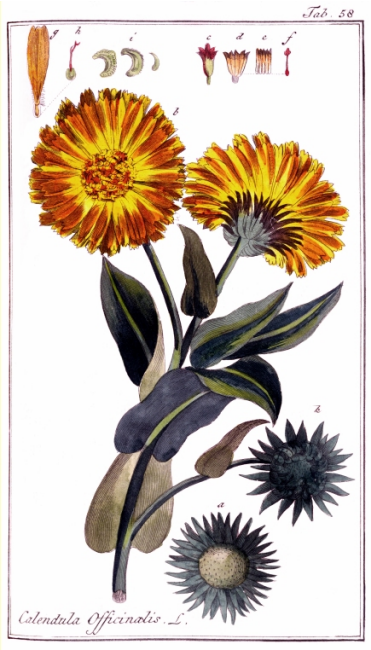
BOTANICAL NAME/FAMILY
Echinacea species (family Asteraceae [Compositae])

The name 'echinacea' generally refers to several different plants within the genus — *E. purpurea*, *E. pallida* and *E. angustifolia*.

PLANT PARTS USED
Root, leaf and aerial parts

CHEMICAL COMPONENTS

The most important constituents in regard to pharmacological activity are the polysaccharides, caffeic acid derivatives, alkylamides, essential oils and polyacetylenes, although there are other potentially active constituents, as well as a range of vitamins, minerals, fatty acids, resins, glycoproteins and sterols (Pizzorno & Murray 2006). Constituent concentrations vary depending on the species, plant part and growing conditions. In regards to the final chemical composition of an *Echinacea*-containing product, the drying and extraction processes further alter chemical composition.



MAIN ACTIONS

Due to the wide assortment of chemical constituents found in Echinacea, it has varied pharmacological effects.

IMMUNOSTIMULANT AND IMMUNOMODULATOR

The immunostimulant activity of echinacea has been the subject of countless studies. Overall, the fresh-pressed leaf juice of *E. purpurea* and alcoholic extracts of the roots of *E. pallida*, *E. angustifolia* and *E. purpurea* have been shown to act mainly on non-specific cellular immunity (Blumenthal et al 2000). Macrophage activation has been well demonstrated, as has stimulation of phagocytosis (Barrett 2003, Bauer et al 1988). Orally administered root extracts of echinacea have produced stronger effects on phagocytosis than aerial parts, with *E. purpurea* roots producing the greatest effect, followed by that of *E. angustifolia* and *E. pallida* (Pizzorno & Murray 2006).

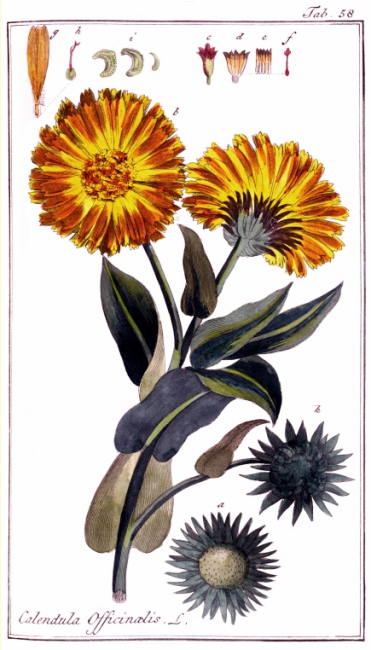
Activation of polymorphonuclear leukocytes and NK cells has been reported and increased numbers of T-cell and B-cell leukocytes. Research in human subjects has produced conflicting results, with some studies showing that echinacea stimulates non-specific immunity and others showing no significant effect (Roesler et al 1991, Schwarz et al 2002).

It is currently believed that no one single constituent is responsible for the herb's immunomodulating action, with the most important elements being polysaccharides, glycoproteins, alkamides and flavonoids (Ernst 2002).

ANTI-INFLAMMATORY

Echinacea purpurea has demonstrated anti-inflammatory activity in vitro and in vivo (Raso et al 2002). More specifically, alkamides from the roots of *E. purpurea* partially inhibit both COX-1 and COX-2 isoenzymes (Clifford et al 2002). In vivo tests identify anti-inflammatory effects also for *E. angustifolia* and *E. pallida* when applied topically (Speroni et al 2002, Tragni et al 1985, Tubaro et al 1987).

Recent research has further identified that alkamides from echinacea modulate TNF-alpha mRNA expression in human monocytes/macrophages via the cannabinoid type 2 (CB2) receptor (Raduner et al 2006). Two alkamides that bind to the CB2 receptor more strongly than the endogenous cannabinoids have been identified. They also bind to CB1. Alkamides also potently inhibit lipopolysaccharide-induced inflammation in human whole blood and exert modulatory effects on cytokine expression in vitro. Cytokine modulation was also observed for two different echinacea extracts in a study using cytokine antibody arrays to investigate the changes in the proinflammatory cytokines and chemokines released from a cultured line of human bronchial epithelial cells exposed to rhinovirus 14 (Sharma et al 2006). Virus infection stimulated the release of at least 31 cytokine-related molecules, an effect that was reversed by simultaneous exposure to either of the two echinacea extracts, although the patterns of response were different for the two extracts.



ANTIVIRAL

Extracts of eight taxa of the genus *Echinacea* were found to have antiviral activity against HSV-1 in vitro when exposed to visible and UVA light (Binns et al 2002).

ANTIFUNGAL ACTIVITY

Hexane extracts of echinacea have phototoxic antimicrobial activity against fungi (Binns et al 2000). The extracts inhibited growth of yeast strains of *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatulytica* and *C. tropicalis*.

OTHER ACTIONS

ANTIOXIDANT

Free radical scavenging activity can be attributed to numerous antioxidant constituents found in echinacea, such as vitamin C, beta carotene, flavonoids, selenium and zinc. Herbalists consider it also to have lymphatic, blood cleansing and wound healing actions.

ANAESTHETIC

The alkylamides exert a mild anaesthetic activity, which is typically experienced as a tingling sensation on the tongue (Pizzorno & Murray 2006).

APOPTOSIS

Apoptosis, or programmed cell death, is a physiological, active cellular suicide process that can be modulated by various stimuli, including hormones, cytokines, growth factors, and some chemotherapeutic agents. According to one study, *E. purpurea* was able to regulate the process of apoptosis in vivo (Di Carlo et al 2003).

CYTOCHROMES

Contradictory results have been obtained by two research groups testing the effects of echinacea on cytochrome P (CYP) activity in human volunteers. One study found that echinacea had no significant effect on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 activity (Gurley et al 2004), whereas the other identified a significant effect on CYP3A and CYP1A2 (Gorski et al 2004).

CHEMOPREVENTION

Several experimental studies with mice have found that treatment with echinacea reduces the incidence of tumour development (Brousseau & Miller 2005, Hayashi et al 2001, Miller 2005). Most research has been conducted with *E. purpurea*.

CLINICAL USE

Clinical trials using echinacea have used various preparations, such as topical applications, homeopathic preparations, injectable forms and oral dose forms, characteristics that should be noted when reviewing the data available. Overall, the majority of clinical studies performed in Europe have involved a commercial product known as Echinacin (Madaus, Germany), which contains the fresh-pressed leaf juice of *E. purpurea* stabilised in ethanol.

UPPER RESPIRATORY TRACT INFECTIONS

Overall, clinical studies support the use of echinacea in URTIs, such as bacterial sinusitis, common cold, influenza-like viral infections and streptococcal throat. Evidence is strongest for use of echinacea in adults as an acute treatment; however, results in children have been disappointing.

A 1999 review of 13 clinical trials consisting of 9 treatment studies and 4 prevention studies concluded that 8 of 9 treatment trials produced positive results whereas 3 of 4 prevention trials suggested modest effects (Barrett et al 1999). In other words, current evidence is stronger for supporting the use of echinacea as acute treatment in URTIs than as prophylactic treatment. In 2000, a Cochrane review was published that had assessed the evidence available from 16 clinical trials (8 treatment and 8 prevention) involving a total of 3396 subjects (Melchart et al 2000), and it concluded that some echinacea preparations may be better than placebo, with a majority of studies reporting favourable effects. Unfortunately, due to variations in the type of echinacea preparations tested, it is still difficult to confidently determine which one is superior.

Since 2000, numerous other randomised double-blind studies have been published, with varied results.

Adult studies Schulten et al (2001) recruited 80 adults experiencing the first signs of a cold and randomly assigned treatment with *E. purpurea* (Echinacin, EC31J0) or placebo. The results revealed that treatment with echinacea shortened the duration of illness by 3 days compared with placebo and was well tolerated. Barrett et al (2002) used a very different echinacea product, an encapsulated mixture of unrefined *E. purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%). One hundred and forty-eight students with recent-onset colds took either placebo or echinacea capsules in 1 g doses six times on the first day, then three times on each subsequent day for a maximum of 10 days. The results did not produce a statistically significant treatment effect. No significant effects on total cold symptom scores, mean individual symptoms or time to resolution of symptoms were observed in a double-blind, placebo-controlled trial of 128 subjects conducted by Yale and Liu (2004) using a standardised preparation of *E. purpurea* (freeze-dried pressed juice of the aerial portion). Subjects were enrolled within 24 hours of cold symptom onset and given 100 mg three times daily of active treatment or placebo. In contrast, a double-blind, placebo-controlled trial of 282 adults, which used a highly standardised formulation of freshly harvested *E. purpurea*, found that it significantly reduced the total daily symptom scores by 23% compared to placebo (Goel et al 2004). That study used *E. pupurea* containing alkamides, cichoric acid, and polysaccharides at concentrations of 0.25, 2.5, and 25 mg/mL, respectively and commercially available as Echinilin (Natural Factors Nutritional Products, Inc., Vancouver, BC, Canada). Subjects were instructed to start treatment at the onset of the first symptom related to a cold, consuming 10 doses the first day and 4 doses per day on subsequent days for 7 days.

A crucial factor in the investigation of any cold treatment is the time of treatment initiation. For best effects, treatment must be commenced at the first signs of infection, because later use is less likely to induce benefits (Schoop et al 2006). With regard to echinacea research, the time of initiation has varied between studies and is one possible explanation for the contradictory results obtained. Variations in the product's chemical composition, the clinical setting and study populations are further confounding variables. Between 2000 and 2005, three studies have used artificial rhinovirus inoculation as a means of standardising 'time to treatment initiation', together with standardised echinacea extracts (Sperber et al 2004, Turner et al 2000, 2005). The two earlier studies used *E. purpurea*, whereas the most recent one used two different concentrations of an alcoholic extract of *E. angustifolia*. According to these studies, echinacea inhibited the onset and severity of symptoms; however, this was not significantly superior to placebo.

In response to these negative findings, Schoop et al (2006) conducted a meta-analysis to determine whether the results were a consequence of inadequate efficacy or inadequate sample size. Based on the analysis, the likelihood of experiencing a clinical cold was 55% higher with placebo than with echinacea treatment; however, there was no significant difference between groups for total symptom scores.

A recently published Cochrane systematic review analysed results from 16 randomised, double-blind studies (Linde et al 2006), only 5 of which had been included in a previous Cochrane review. Studies that investigated the effectiveness of combination echinacea products or *E. purpurea* preparations compared to placebo in the prevention of experimentally induced rhinovirus infections were not included. The authors concluded that overall assessment was difficult to make because of the great heterogeneity of preparations tested and variability of trial approaches and methods for cold assessment. Even so, they concluded that there is some evidence that preparations based on the aerial parts of *E. purpurea* might be effective for the early treatment of colds in adults, although results are not completely consistent. Beneficial effects of other echinacea preparations, and their use for preventative purposes, might exist, but have not been shown in independently replicated, rigorous randomised trials.

It is hoped that future research will include full disclosure of the chemical analysis of the echinacea preparation being tested. Systematic reviews will then be able to use this information to separately assess the effects of each echinacea species, rather than combining them under the umbrella term of 'Echinacea'.

Paediatric studies Four randomised studies published after 2000 were conducted with children and generally produced disappointing results (Cohen et al 2004, Spasov et al 2004, Taylor et al 2003, Weber et al 2005). Taylor et al (2003) studied the effects of *E. purpurea* (dried pressed juice of the aerial portions) mixed into a syrup in healthy children aged 2–11-years-old who were advised to start treatment at the onset of cold symptoms and continue for a maximum of 10 days or until symptoms resolved. Treatment with *E. purpurea* failed to reduce the duration of the URTI or severity of symptoms compared with placebo. There was no difference in the rate of adverse events reported by both groups, although rash occurred in 7.1% of children using echinacea compared with 2.7% with placebo. Spasov et al (2004) compared the effects of *E. purpurea* extract to placebo and a herbal combination treatment (Kan Jang) in 130 children aged between 4 and 11 years over a period of 10 days. They found that treatment with Kan Jang was more effective than echinacea for reducing symptom severity and reducing symptom duration when started at the early stage of uncomplicated common colds. In contrast, *E. purpurea* appeared to reduce the

incidence of subsequent URTIs in a double-blind, placebo-controlled study of 401 children (Weber et al 2005).

A combination product was investigated in the study by Cohen et al (2004), which involved 430 children aged 1–5 years. The preparation (Chizukit, Hadas Corp., Israel) contained 50 mg/mL of echinacea (aerial parts of *E. purpurea* and roots of *E. angustifolia*), 50 mg/mL of propolis and 10 mg/mL of vitamin C and was administered twice daily for 12 weeks. Active treatment resulted in a significant reduction in illness episodes (55% reduction), number of episodes per child (50% reduction) and number of days with fever per child (2.1 vs 5.4; 62% reduction). The total number of illness days and duration of individual episodes were also significantly lower in the treatment group.

Commission E approves the use of *E. purpurea* herb as an immune system support in cases of respiratory and lower urinary tract infection, and *E. pallida* root as supportive treatment in influenza-like infections (Blumenthal et al 2000).

Clinical note — Common cold symptoms: what is usual?

The pathogenesis of the common cold involves a complex interplay between replicating viruses and the host's inflammatory response (Heikkinen & Jarvinen 2003). The onset of cold symptoms after viral incubation varies considerably and depends on the causative virus. In experimental rhinovirus infections, the onset of symptoms has been reported to occur as soon as 10–12 hours after intranasal inoculation. Generally, the severity of the symptoms increases rapidly, peaks within 2–3 days after infection, and decreases soon after. The mean duration of the common cold is 7–10 days, but in a proportion of patients some symptoms can still be present after 3 weeks. Symptoms typically start with a sore throat, which is soon accompanied by nasal stuffiness and discharge, sneezing and cough. The soreness of the throat usually disappears quickly, whereas the initial watery rhinorrhoea becomes thicker and more purulent over time and can be accompanied by fever, most usually in children. Other symptoms associated with the cold syndrome include hoarseness, headache, malaise and lethargy.

WOUND HEALING

Several uncontrolled clinical studies support the topical use of echinacea to enhance wound healing. A trial involving 4598 people investigated the effects of a preparation consisting of the juice of the aerial parts of *E. purpurea* on various wounds, burns, skin infections and inflammatory skin conditions (Kinkel et al 1984). Topical application of echinacea produced a 85% overall success rate, and the key constituent

responsible for enhancing wound healing appears to be echinacoside (Speroni et al 2002).

Commission E approves the external use of *E. purpurea* herb for poorly healing wounds and chronic ulcerations (Blumenthal et al 2000).

HERPES INFECTION

Based on the herb's antiviral activity against HSV-1 in vitro, it is also used in the treatment of herpes infections.

Genital herpes A prospective, double-blind, placebo-controlled crossover trial conducted over 1 year investigated the effects of an extract of the plant and root of *E. purpurea* (Echinaforce 800 mg twice daily) on the incidence and severity of genital herpes outbreaks in 50 patients (Vonau et al 2001). The study found no statistically significant benefit compared with placebo after 6 months of therapy.

REDUCING CHEMOTHERAPY SIDE-EFFECTS

Results from a small, open, prospective study of subjects with advanced gastric cancer suggests that intravenous administration of a polysaccharide fraction isolated from *E. purpurea* may be effective in reducing chemotherapy-induced leucopenia (Melchart et al 2002). Test subjects had advanced gastric cancer and were undergoing palliative chemotherapy with etoposide, leucovorin and 5-fluorouracil. The median number of leukocytes 14–16 days after chemotherapy was 3630/microL (range 1470–5770) in the patients receiving herbal treatment compared with 2370/microL (870–3950) in the patients of the historical control group ($P = 0.015$).

RADIATION-ASSOCIATED LEUCOPENIA

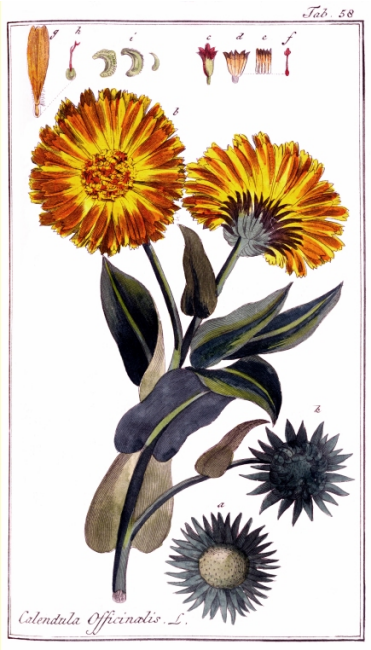
Equivocal evidence exists for the use of echinacea in radiation-induced leucopenia, according to a small number of randomised studies (Ulbricht & Basch 2006). The product tested was Esberitox, which contains ethanolic extracts of three herbs, including root of echinacea.

RECURRENT CANDIDIASIS

The herb is used to treat recurrent candidiasis, chiefly because of its antifungal and immunostimulant properties. Controlled studies are unavailable to determine effectiveness in this condition.

OTHER USES

Echinacea has also been used to treat UTI, allergies, acne and abscesses, and as adjunctive therapy in cancer (Mills & Bone 2000). It has also been used to prevent exercise-induced immunosuppression (Gleeson et al 2001). In practice, it is prescribed with other herbs to treat common infections and to prevent infections generally.



DOSAGE RANGE

GENERAL GUIDE

- Dried herb: 3 g/day of either *E. angustifolia* or *E. purpurea*.
- Liquid extract (1:2): 3–6 mL/day of either *E. angustifolia* or *E. purpurea*. This dose may be increased to 10–20 mL/day in acute conditions. Treatment is usually started at the first sign of URTI and continued for 7–14 days.

SPECIFIC GUIDE

- *E. angustifolia* dried root: 1–3 g/day.
- *E. purpurea* dried root: 1.5–4.5 g/day.
- *E. purpurea* dried aerial parts: 2.5–6.0 g/day.
- *E. purpurea* expressed juice of fresh plant: 6–9 mL/day.
- *E. pallida* ethanolic extract of root: 2–4 mL/day.

Although controversy still exists over which part of the plant and which particular plant has the strongest pharmacological activity, it appears that the cold-pressed juice of *E. purpurea* is the most studied preparation for URTIs.

ADVERSE REACTIONS

Oral dose forms and topical preparations tend to be well tolerated, although allergic reactions are possible in rare cases (mainly to the aerial parts, in contact dermatitis). One study using *E. purpurea* in children found that rash occurred in 7.1% of children using echinacea compared with 2.7% with placebo (Taylor et al 2003).

There is no clear evidence from basic science or human studies to show that echinacea causes liver toxicity (Ulbricht & Basch 2006).

Clinical note — Safety of echinacea

The safety of echinacea has come into question in recent years due to two different articles that were poorly described in the press. One was a case report of suspected anaphylaxis reported in the *Medical Journal of Australia* (Mullins 1998). On closer inspection, the article describes an atopic woman who had taken nearly a dozen supplements at once, as well as double the recommended dose of a liquid echinacea product, before experiencing symptoms suggestive of anaphylaxis. Successful treatment consisted of oral promethazine and no other intervention. After the event, hypersensitivity was confirmed by skin prick and RAST testing, suggesting that an allergic response did occur.

In 2002, a second report described in detail five allergic reactions to different echinacea preparations and further stated that 51 adverse reaction reports involving echinacea had been made to ADRAC (Mullins & Heddle 2002). Unfortunately, this time the media omitted the important fact that these cases were reported over a

21-year period. Once again, a closer look at the article finds approximately half of those reports were of suspected allergic responses and of those, only two could certainly be linked to echinacea use, with 10 classified as probable and 12 as possible. Considering an estimated 200 million doses of echinacea are used by Australians each year, the relative lack of adverse reports is impressive.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

IMMUNOSUPPRESSION AGENTS

Theoretically, there may be an antagonistic pharmacodynamic interaction with immunosuppressive medication, but the clinical relevance is unclear. Exercise caution when using immunosuppressive agents and echinacea concurrently.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with allergies to the Compositae family of plants (e.g. chamomile, ragweed).

Commission E warns against using echinacea in cases of autoimmune disorders, such as multiple sclerosis, SLE and RA, as well as tuberculosis or leukocytosis (Blumenthal et al 2000). This is based on theoretical considerations and has not been tested in controlled trials. In practice, echinacea has been successfully used by herbalists in autoimmune disease without mishap (Mills & Bone 2005).

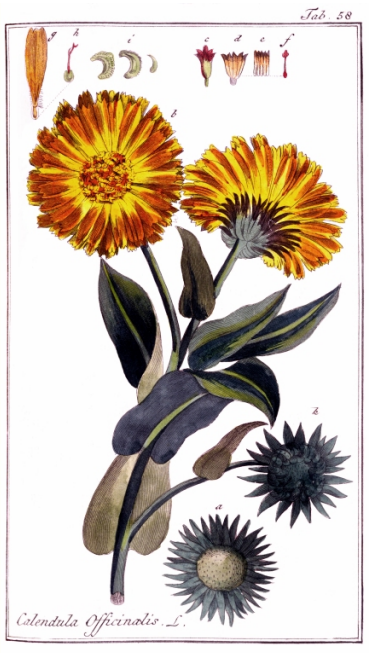
Duration of use Based on evidence that parenterally administered echinacea reversibly depresses immune parameters, Commission E has recommended that echinacea should not be used for more than 8 weeks. However, in a study in which it was taken orally for up to 6 months, no changes in immune parameters were detected (Vonau et al 2001). As such, no conclusive evidence demonstrates that long-term use is detrimental.

PREGNANCY USE

Although safety in pregnancy has not been categorically established, results from a prospective study of 206 women who had inadvertently taken echinacea during their pregnancy found that gestational use is not associated with an increased risk for major malformations (Gallo et al 2000). Oral use of echinacea is considered safe in pregnancy when used in recommended doses (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Different types of echinacea have demonstrated immunostimulant, anti-inflammatory, antifungal, antiviral and antioxidant activity.



- Overall, clinical studies support the use of echinacea in URTIs, such as bacterial sinusitis, common cold, influenza-like viral infections and streptococcal throat. Current evidence is strongest for supporting its use as acute treatment in URTIs rather than as prophylactic treatment.
- Several uncontrolled clinical studies support the topical use of echinacea to enhance wound healing.
- Echinacea is also used to treat UTI, allergies, acne and abscesses, as adjunctive therapy in cancer, herpes virus infections and candidiasis.
- Although controversy still exists over which part of the plant and which particular plant has the strongest pharmacological activity, it appears that the cold-pressed juice of *E. purpurea* is the most studied preparation for URTIs.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Echinacea stimulates immune function and may also have antifungal, antiviral and anti-inflammatory activity. Scientific research generally supports its use as an acute treatment for URTIs in adults. Applied to the skin, it may also enhance wound healing and be useful for chronic wounds. It also has anti-inflammatory actions.

When will it start to work?

As an acute treatment for URTI, it has effects within the first week of treatment.

Are there any safety issues?

Echinacea is well tolerated, although allergic reactions are possible in rare cases.

REFERENCES

Barrett B. Medicinal properties of Echinacea: a critical review. Phytomedicine 10.1 (2003): 66-86.

Barrett B, Vohmann M, Calabrese C. Echinacea for upper respiratory infection. J Fam Pract 48.8 (1999): 628-35.

Barrett BP et al. Treatment of the common cold with unrefined Echinacea: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 137.12 (2002): 939-46.

Bauer VR et al. Immunologic in vivo and in vitro studies on Echinacea extracts. Arzneimittelforschung 38.2 (1988): 276-81.

Binns SE et al. Light-mediated antifungal activity of Echinacea extracts. Planta Med 66.3 (2000): 241-4.

Binns SE et al. Antiviral activity of characterized extracts from echinacea spp. (Heliantheae: Asteraceae) against herpes simplex virus (HSV-I). Planta Med 68.9 (2002): 780-3.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Brousseau M, Miller SC. Enhancement of natural killer cells and increased survival of aging mice fed daily Echinacea root extract from youth. Biogerontology 6.3 (2005): 157-63.

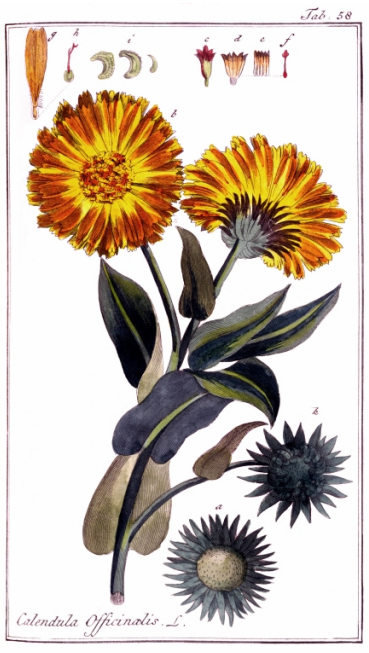
Clifford LJ et al. Bioactivity of alkamides isolated from Echinacea purpurea (L.) Moench. Phytomedicine 9.3 (2002): 249-53.

Cohen HA et al. Effectiveness of an herbal preparation containing echinacea, propolis, and vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled, multicenter study. Arch Pediatr Adolesc Med 158.3 (2004): 217-21.

Di Carlo G et al. Modulation of apoptosis in mice treated with Echinacea and St John's wort. Pharmacol Res 48.3 (2003): 273-7.
Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med 136.1 (2002): 42-53.
Gallo M et al. Pregnancy outcome following gestational exposure to echinacea: a prospective controlled study. Arch Intern Med 160.20 (2000): 3141-3.
Gleeson M, Lancaster GI, Bishop NC. Nutritional strategies to minimise exercise-induced immunosuppression in athletes. Can J Appl Physiol 26 (Suppl) (2001): S23-35.
Goel V et al. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther 29.1 (2004): 75-83.
Gorski JC et al. The effect of Echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther 75.1 (2004): 89-100.
Gurley BJ et al. In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: Citrus aurantium, Echinacea purpurea, milk thistle, and saw palmetto. Clin Pharmacol Ther 76.5 (2004): 428-40.
Hayashi I et al. Effects of oral administration of Echinacea purpurea (American herb) on incidence of spontaneous leukemia caused by recombinant leukemia viruses in AKR/J mice. Nihon Rinsho Meneki Gakkai Kaishi 24.1 (2001): 10-20.
Heikkinen T, Jarvinen A. The common cold. Lancet 361.9351 (2003): 51-9.
Kinkel HJ, Plate M, Tullner HU. Effect of Echinacin ointment in healing of skin lesions. Med Klin 1984; 79: 580-4; as cited in Micromedex Thomson 2003. www.micromedex.com.
Linde K et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev 1 (2006): CD000530.
Melchart D et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev 2 (2000): CD000530.
Melchart D et al. Polysaccharides isolated from Echinacea purpurea herba cell cultures to counteract undesired effects of chemotherapy: a pilot study. Phytother Res 16.2 (2002): 138-42.
Miller SC. Echinacea: a miracle herb against aging and cancer? Evidence in vivo in mice. Evid Based Complement Altern Med 2.3 (2005): 309-14.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis, MO: Churchill Livingstone, 2005.
Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. Ann Allergy Asthma Immunol 88.1 (2002): 42-51.
Mullins RJ. Echinacea-associated anaphylaxis. Med J Aust 168.4 (1998): 170-1.
Pizzorno J, Murray M. Textbook of Natural Medicine. St Louis: Elsevier, 2006.
Raduner S et al. Alkylamides from Echinacea are a new class of cannabinomimetics: Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. J Biol Chem 281.20 (2006): 14192-206.
Raso GM et al. In-vivo and in-vitro anti-inflammatory effect of Echinacea purpurea and Hypericum perforatum. J Pharm Pharmacol 54.10 (2002): 1379-83.
Roesler J et al. Application of purified polysaccharides from cell cultures of the plant Echinacea purpurea to test subjects mediates activation of the phagocyte system. Int J Immunopharmacol 13.7 (1991): 931-41.
Schoop R et al. Echinacea in the prevention of induced rhinovirus colds: a meta-analysis. Clin Ther 28.2 (2006): 174-83.
Schulten B et al. Efficacy of Echinacea purpurea in patients with a common cold: A placebo-controlled, randomised, double-blind clinical trial. Arzneimittelforschung 51.7 (2001): 563-8.
Schwarz E et al. Oral administration of freshly expressed juice of Echinacea purpurea herbs fail to stimulate the nonspecific immune response in healthy young men: results of a double-blind, placebo-controlled crossover study. J Immunother 25.5 (2002): 413-20.
Sharma M et al. Echinacea extracts modulate the pattern of chemokine and cytokine secretion in rhinovirus-infected and uninfected epithelial cells. Phytother Res 20.2 (2006): 147-52.

Spasov AA et al. Comparative controlled study of Andrographis paniculata fixed combination, Kan Jang and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children. Phytother Res 18.1 (2004): 47-53.
Sperber SJ et al. Echinacea purpurea for prevention of experimental rhinovirus colds. Clin Infect Dis 38.10 (2004): 1367-71.
Speroni E et al. Anti-inflammatory and cicatrizing activity of Echinacea pallida Nutt. root extract. J Ethnopharmacol 79.2 (2002): 265-72.
Taylor JA et al. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. JAMA 290.21 (2003): 2824-30.
Tragni E et al. Evidence from two classic irritation tests for an anti-inflammatory action of a natural extract, Echinacina B. Food Chem Toxicol 23.2 (1985): 317-19.
Tubaro A et al. Anti-inflammatory activity of a polysaccharidic fraction of Echinacea angustifolia. J Pharm Pharmacol 39.7 (1987): 567-9.
Turner RB, Riker DK, Gangemi JD. Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. Antimicrob Agents Chemother 44.6 (2000): 1708-9.
Turner RB et al. An evaluation of Echinacea angustifolia in experimental rhinovirus infections. N Engl J Med 353.4 (2005): 341-8.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Vonau B et al. Does the extract of the plant Echinacea purpurea influence the clinical course of recurrent genital herpes? Int J STD AIDS 12.3 (2001): 154-8.
Weber W et al. Echinacea purpurea for prevention of upper respiratory tract infections in children. J Altern Complement Med 11.6 (2005): 1021-6.
Yale SH, Liu K. Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med 164.11 (2004): 1237-41.

Eucalyptus



Historical note Indigenous Australians traditionally used eucalyptus to treat fevers and respiratory infections, accounting for its name 'fevertree'. European settlers also recognised the medicinal qualities of eucalyptus and surgeon Consiglen is credited with producing the first essential oil sample in 1788. Bosisto investigated oils from several Australian plants and in 1854 eventually produced essential oils commercially in association with Müeller, a pharmacist. Bosisto and Müeller concentrated on oils rich in 1,8-cineole, which includes *Eucalyptus* species. In the late 1800s, articles about its medicinal use appeared in medical journals such as *The Lancet*, focusing on its potential in scarlet fever and diphtheria.

COMMON NAME

Eucalyptus

OTHER NAMES

Aetheroleum Eucalypti, cineole, *Oleum Eucalypti*, *Essence of eucalyptus rectifiee*

Common names include Australian fever tree leaf, blue gum, eucalyptol, fever tree, gum tree, red gum, stringy bark tree

BOTANICAL NAME/FAMILY

Eucalyptus species (family Myrtaceae)

The species most commonly used in health care are:

- *Eucalyptus globulus* (blue gum)
- *Eucalyptus citriodora* (lemon scented gum)
- *Eucalyptus dives* (broad leaf peppermint)
- *Eucalyptus polybractea*

There are over 500 species of eucalyptus trees and shrubs native to Australia, but many species are cultivated in other parts of the world.

PLANT PARTS USED

The essential oil is extracted by steam distillation from fresh twigs and leaves. Modern eucalyptus essential oils are primarily extracted from *E. polybractea*, *E. dives*, *E. leucoxylon*, *E. sideroxylon*, and *E. radiata* in Australia, but other species are used in other countries (Lassak & McCarthy 2001).

CHEMICAL COMPONENTS

The major chemical constituents under the general heading 'eucalyptus' consist of oxides and hydroterpenes, primarily 1,8-cineole, which is the most significant constituent and ranges from 54–95%, citronellal camphone, fenchone, limonene, phellandrene and pinene depending on the species (Clarke 2002).

The exact chemical composition of an oil depends on the particular species from which it was extracted. There are small amounts of alpha-pinene (2.6%), alpha-cymene (2.7%), aromadendrene, ciminaldehyde, globulol and pinocarveol and *d*-limonene, alpha-phellandrene, camphene and alpha-terpinene (Bisset 1994, Bruneton 1995).

MAIN ACTIONS

The main reported actions are expectorant, antitussive (Misawa & Kizawa 1990), nasal decongestant (Burrows 1983, FDA 1994), analgesic (Gobel 1995) and antispasmodic in animal and human studies. Antimicrobial and anti-inflammatory activity has also been reported in animal and human studies.

ANTITUSSIVE

Antitussive effects were compared with codeine in guinea pigs in which cough was mechanically stimulated. Essential oil 5% in normal saline was administered by inhalation and had a significant antitussive effect relative to codeine ($P < 0.05$) (Misawa & Kizawa 1990).

NASAL DECONGESTANT

Two clinical studies have demonstrated that inhalation of eucalyptus oil reduces nasal congestion (Burrows 1983, FDA 1994), and one study showed topical application to the forehead and temples was ineffective (Gobel 1995).

ANTIMICROBIAL

Previous studies indicate eucalyptus has antimicrobial activity in vitro against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Eschehria coli* (Kurrerath & Mundulaldo 1954).

ANTI-INFLAMMATORY

Eucalyptus inhibits prostaglandin synthesis in vitro (Wagner 1986) at a concentration of 37 micromol/L. Anti-inflammatory and antinociceptive effects have been demonstrated in animal models (Ulbricht & Basch 2005). Alternatively, a study in which 1,8-cineole was injected into the rat hind-paw demonstrated that eucalyptus induced oedema, most likely due to the release of mast cell mediators (Santos & Rao 1997). The clinical implications of this finding for topically applied eucalyptus oil require

further investigation. Anti-inflammatory activity of *E. radiata* has been demonstrated in patients with dry and weeping dermatitis, most probably due to inhibition of inflammatory markers such as TNF-alpha, COX enzymes, 5-lipoxygenase and other leukotrines, and it could be an alternative to topical steroid medicines (Hadji-Minglou & Bolcato 2005, Santos & Raos 2000).

OTHER ACTIONS

Eucalyptus oil is metabolised in the liver; however, evidence is contradictory as to whether it induces the cytochrome P450 enzyme system. One study conducted with an animal model demonstrated a slight increase in CYP4A expression (Ngo et al 2003), whereas 1,8-cineole has demonstrated CYP 450 induction in vitro and animal studies (Ulbricht & Basch 2005).

CLINICAL USE

Eucalyptus oil has been investigated in numerous forms; however, there is a lack of controlled, clinical studies.

RESPIRATORY CONDITIONS

Eucalyptus oil is used as symptomatic treatment in obstructive respiratory conditions such as bronchitis, asthma, the common cold and other conditions associated with catarrh of the upper respiratory tract. Although it is used internally and externally in Europe for these indications, in Australia the oil is generally used externally in vapourisers, chest rubs and nasal inhalations.

Nasal decongestant properties were assessed in 31 healthy volunteers using inhalations of 10 mL of essential oil for 5 minutes. There was no effect on nasal resistance to air flow, but there was a stimulant effect on the cold receptors in the nose and the majority of subjects reported being able to breathe more easily (FDA 1994). A single-blind, parallel clinical trial ($n = 234$) was conducted to assess whether vapourised essential oil reduced nasal congestion compared with steam. The essential oil was significantly more effective ($P < 0.02$), but only in the first hour after inhalation. Other researchers found no significant differences in nasal decongestion compared with placebo (Burrows 1983). There was no significant difference between placebo and topically applied *E. piperita* to the forehead and temples to treat headache in a randomised, double crossover trial ($n = 32$); however, cognitive performance and muscle and mental relaxation were greater in the essential oil group (Gobel 1995).

AROMATHERAPY

Eucalyptus, as it is traditionally used in aromatherapy, has not been systematically investigated under clinical trial conditions. Therefore, most evidence is derived from traditional sources.

Aromatherapists use eucalyptus for its mentally uplifting and stimulating effects and to aid concentration. It is also used in massage and vapourisers to relieve respiratory symptoms, treat minor skin infections and acne, and relieve headache and muscular aches and pain. Usually eucalyptus oil is included in a blend of 3–5 essential oils for a massage but may be used alone for an inhalation.

OTHER USES

Eucalyptus oil is often included in OTC medicines and other medicines in formulations, such as rubs, mouthwashes, cleansing products, inhalers, soaps and insect repellents in which the 1,8-cineole content is standardised to 80–90%. Bosisto's Eucalyptus Oil is commonly sold in supermarkets and has an Aust R label (10908). It is not used in aromatherapy and is dispensed in a ribbed poison bottle with a childproof cap.

DUST MITE REMOVAL

Eucalyptus oil can be formulated with a kitchen detergent concentrate to form an inexpensive acaricidal wash that reduces the number of live mites found in blankets during normal machine washing (Tovey & McDonald 1997). When compared with detergent concentrate alone, a 30-minute pre-wash soak of woollen blankets with the eucalyptus oil/detergent formula reduced the number of live mites that could be recovered by 97%. This eliminates the need for very hot water and may maintain low allergen levels in bedding for longer than normal laundering alone because mites are adversely affected by low concentrations of eucalyptus oil vapour, which lingers for 2–3 days. In this study, the dishwashing liquid detergent concentrate (Kit, L&K, Rexona, Sydney, Australia) was used to form an emulsion in water because the essential oil is not soluble in water.

CLEANING AGENT

Washing in diluted eucalyptus oil is also used as a method of removing stains from fabric; however, it does leave a faint characteristic odour for 2–3 days despite rinsing and drying, and some people may find this irritating.

MALODOROUS NECROTIC ULCERS

These ulcers are a major concern for cancer patients and can lead to social isolation and reduced QOL because current treatments inadequately reduce the foul smell to acceptable levels. A paper recently published reported that rinsing the ulcers twice a

day with an antibacterial essential oil mixture (mainly eucalyptus oil) resulted in complete disappearance of odour by day 3 or 4 in all patients ($n = 30$) (Warnke et al 2006). The eucalyptus was used in combination with a standard course of antibiotics. A number of beneficial secondary findings were anti-inflammatory activity, promotion of healing and complete re-epithelialisation, and emotional relief on resolution of the condition.

DOSAGE RANGE

Dose recommendations vary, but generally low doses are used. Internal formulations may take longer to show an effect than conventional medicines.

- Inhalation: 12 drops in 150 mL of boiling water or 5 drops in a nebuliser, which delivers approximately 35 mg (unpubl. data: Harris & Harris – Aromatic Medicine: The Interfaces of Absorption, seminar course notes, Melbourne, 2003). High doses are not recommended because they can irritate the eyes and mucus membranes and may trigger an asthma-like attack.
- Mouth wash: 20 mL (0.91 mg/mL) solution gargled twice daily.
- Massage: traditionally aromatherapists use essential oils as 3.5–5% in a carrier substance but doses between 5% and 20% are used for adults and much lower doses for children and older people.
- Ointments, creams, gels and poultices: 5–10% in a carrier substance such as beeswax.
- Internal use: 0.3–0.6 mL/day essential oil 1–4 times daily; capsules 100–200 mg; lozenges 0.2–15.0 mg dissolved slowly in the mouth every 30–60 minutes.

Most Australian aromatherapists do not currently administer essential oils via the internal route (oral, vaginal and rectal), but they are administered via these routes in other countries, especially France.

TOXICITY

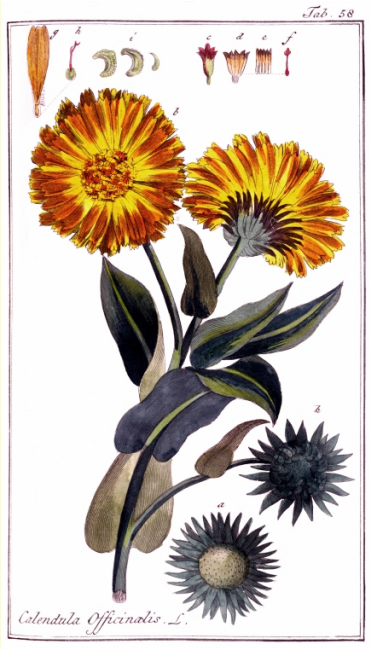
Toxicity symptoms occur rapidly, but may be delayed for hours and include altered conscious state, drowsiness and unconsciousness, which are dose-dependent. Symptoms reported in other studies include epigastric burning, nausea, vomiting, dizziness, muscular weakness, delirium and convulsions.

The acute oral LD_{50} dose of 1,8-cineole in rats is 2.48 g/kg and the dermal LD_{50} dose in rabbits is >5 g/kg.

Fatal poisoning has occurred in children after accidental ingestion of whole or diluted eucalyptus oil in amounts ranging from 2 to 10 mL. Tibballs (1995) reported 109 children who were admitted to hospital for eucalyptus oil poisoning in an 11-year period; 27 had been accidentally poisoned when an adult administered the oil

orally by mistake and most of the remaining 82 children had ingested the oil from a vapouriser. Another review of 41 cases of eucalyptus oil poisoning (Webb & Pitt 1993) indicated that 80% were asymptomatic. There was no relationship between the amount of oil ingested and the presence and severity of symptoms.

The Victorian Poisons Information Centre (see Appendix 3) recommends all patients who ingest ≥1 mL of eucalyptus oil be assessed in an emergency department. The Centre attributes the toxicity to the cineole, terpene and phellandrene content and indicates that although hydrocyanic acid is only present in small amounts it may be responsible for most of the toxicity.



ADVERSE REACTIONS

Eucalyptus oil is generally safe when used externally in an appropriate manner.

A number of adverse reactions are reported for topical application, including systemic toxicity in a 6-year-old girl, and urticaria, contact dermatitis and skin irritation in other cases (Darben 1988). However, when considering the risks of topical application of eucalyptus oil the state of the skin must be considered as well as the individual's susceptibility to atopic conditions such as eczema and asthma.

Allergic reactions to lozenges have also been reported anecdotally.

Inhalations may irritate the eyes and mucus membranes.

SIGNIFICANT INTERACTIONS

Due to the lack of clinical evidence, interactions are theoretical and speculative.

CNS DEPRESSANTS

Oral ingestion of eucalyptus has been associated with CNS depression, therefore additive effects are theoretically possible — caution.

DRUGS METABOLISED BY CYP 450

Some evidence suggests CYP induction is possible; however, it is not known which CYP enzymes are affected, thus making recommendations difficult. Interactions are unlikely when used topically or inhaled, but could theoretically occur when used internally (Springhouse 2001) — caution.

HYPOGLYCAEMIC AGENTS

If used in combination with oral glucose-lowering conventional or complementary medicines it may contribute to hypoglycaemia (oral doses) — blood glucose levels should be monitored (Springhouse 2001).

CONTRAINDICATIONS AND PRECAUTIONS

Essential oils are not recommended in the first 3 months of life because the barrier function of the skin is not fully developed. *Eucalyptus globulus* may cause skin allergy

in susceptible individuals (those prone to asthma, allergies, and previous reaction to eucalyptus).

Eucalyptus oil should not be administered internally to children or people with inflammatory gastrointestinal tract disease or impaired liver function, or during pregnancy.

Eucalyptus oil should not be applied to the face, especially of infants and young children because of the risk of bronchospasm and irritation.

The oil should be stored out of the reach of children and confused people.

Vapourisers containing eucalyptus essential oils should also be placed out of reach. Poisoning has occurred following ingestion from vapourisers.

Oily carrier fluids should not be used for nasal spays because they inhibit protective nasal ciliary movements and could cause lipid pneumonia.

The essential oil is highly flammable and represents a fire risk when used in candle vapourisers.

PREGNANCY USE

No studies have been undertaken. The essential oil is not teratogenic in animal studies, but doses of 500 mg/kg cross the placenta in large enough amounts to stimulate (Jori & Briatico 1973) hepatic activity in rodents. Aromatherapists do not use eucalyptus essential oil during pregnancy, especially in the first trimester.

PRACTICE POINTS/PATIENT COUNSELLING

- Eucalyptus essential oils are steam distilled from a number of *Eucalyptus* species, and have different chemical composition depending on the species. Most contain a large proportion of 1,8-cineole, which appears to be responsible for the action on the respiratory system.
- Eucalyptus is primarily used in aromatherapy as an inhalation to relieve nasal congestion and in massage to relieve muscular aches and pain, as well as in ointments, gels, and compresses, and via a vapouriser for mental stimulation and to aid concentration.
- It is used internally in lozenges, tinctures and conventional medicines.
- When used topically in an appropriate manner, eucalyptus oil is considered safe; however, several cautions exist to reduce the risk of adverse reactions and toxicity. People using eucalyptus essential oil should be monitored for allergies and it should not be applied to the face of children. Eucalyptus should not be used internally unless it is diluted and used in the recommended doses and dose intervals.

- Signs of poisoning usually occur rapidly and include confusion, irritability, respiratory distress, hypotension, nausea and vomiting. If poisoning is suspected medical care should be sought urgently. Do not induce vomiting. Use charcoal and monitor consciousness.
- Several drug interactions are theoretically possible; however, their clinical significance is unknown.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this essential oil do for me?

Eucalyptus essential oil can be used in a vapouriser or on tissues to help clear the nose and make breathing easier in the presence of URTI. It can also increase mental alertness. In a massage blend eucalyptus can help relieve muscular and arthritic pain.

Eucalyptus oil can be added to the washing machine to help kill dust mites in human clothes and animal bedding. Dust mites are responsible for many respiratory conditions, such as asthma.

When will it start to work?

Inhaled eucalyptus oil usually acts quickly and provides symptomatic relief quickly. Oral doses and massage blends usually take longer to have an effect.

Are there any safety issues?

Ingested eucalyptus oil has caused poisoning especially in children and therefore any source of the oil, including vapourisers, should be placed out of reach.

Eucalyptus can irritate the eyes and mucus membranes. It should be kept away from the face, especially of children.

Ingested eucalyptus oil could affect the action of some medicines such as antidepressants, sedatives and anaesthetic agents. It increases absorption of nicotine.

REFERENCES

Bisset N. Herbal Drugs and Pharmaceuticals. Boca Raton, CA, CRC Press, 1994.
Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants. Paris: Lavoisier, 1995.
Burrows A. The effects of camphor, eucalyptus and menthol vapour on nasal resistance to airflow and nasal sensation. Acta Otolaryngol 96 (1983): 157-61.
Clarke S. Essential Oil Chemistry for Safe Aromatherapy. Edinburgh: Churchill Livingstone, 2002.
Darben T. Topical Eucalyptus oil poisoning. Aust J Dermatol 39 (1988): 265-7.
Food and Drug Administration. Over the Counter Drugs: Monograph for OTC Nasal Decongestant Drug Products. Fed Reg 41 (1994): 38408-9.
Gobel H. Essential plant oils and headache mechanisms. Phytomedicine 2 (1995): 93-102.
Hadji-Minaglou A, Bolcato O. The potential role of specific essential oils in replacement of dermocorticoid drugs (strong, medium, weak) in the treatment of acute dry or weeping dermatitis. Int J Aromather 15.2 (2005): 66-73.
Jori A, Briatico G. Effects of eucalyptol on microsomal enzyme activity of foetal and newborn rats. Biochem Pharmacol 22 (1973): 543-4.

Kurrerath F, Mundulaldo G. The activity of some preparations containing essential oils in tuberculosis. Fitoterpia 25 (1954): 483-5.
Lassak E, McCarthy T. Australian Medicinal Plants. Sydney: Reed New Holland, 2001.
Misawa M, Kizawa M. Antitussive effects of several volatile oils especially cedar leaf oil in guinea pigs. Pharmacometrics 39 (1990): 81-7.
Ngo SNT et al. The effects of Eucalyptus terpenes on hepatic cytochrome P450 CYP4A, peroxisomal Acyl CoA oxidase (AOX) and peroxisome proliferator activated receptor alpha (PPAR[alpha]) in the common brush tail possum (Trichosurus vulpecula). Comp Biochem Physiol C Toxicol Pharmacol 136.2 (2003): 165-73.
Santos F, Raos V. Antiinflammatory and antinociceptive effects of 1,8-cineole and terpenoid oxide present in many plant essential oils. Phytother Res 14 (2000): 240-4.
Santos FA, Rao VSN. Mast cell involvement in the rat paw oedema response to 1,8-cineole, the main constituent of eucalyptus and rosemary oils. Eur J Pharmacol 331.2-3 (1997): 253-8.
Springhouse Corporation. Nursing Drug Handbook Series: Herbal Medicine. Springhouse, PA: Springhouse Corporation. 2001
Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. Med J Aust 163 (1995): 177-80.
Tovey ER, McDonald LG. A simple washing procedure with eucalyptus oil for controlling house dust mites and their allergens in clothing and bedding. J Allergy Clin Immunol 100.4 (1997): 464-6.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Wagner H. In vitro inhibition of prostaglandin biosynthesis by essential oils and phenolic compounds. Planta Med 3 (1986): 184-7.
Warnke PH et al. Antibacterial essential oils in malodorous cancer patients: Clinical observations in 30 patients. Phytomedicine (in press), 2006.
Webb N, Pitt W. Eucalyptus and poisoning in childhood: 41 cases in South East Queensland. J Paediatr Child Health 29 (1993): 368-71.

Evening primrose oil

OTHER NAMES

EPO, primrose oil, butter rose, cow slip, fever plant, huile d'onagre, king's cure all, mayflower, Our Lady's key, palsywort, sundrop

BOTANICAL NAME/FAMILY

Oenothera biennis (family Onagraceae)

PLANT PART USED

Fixed oil from the seed. A suitable extract must be obtained from cold-pressing rather than heat extraction to avoid damaging the oil.

CHEMICAL COMPONENTS

Evening primrose oil contains essential fatty acids (EFAs). EFAs are polyunsaturated fatty acids containing two or more double bonds. EPO contains about 70% linoleic acid (LA) and 9% gamma-linolenic acid (GLA) (Horrobin 2000), as well as oleic, palmitic, and stearic acids, campesterol and beta-sitosterol. Due to the position of its double bonds EPO is classified as an omega-6 (n-6) fatty acid.

Borage seeds (18–26%) and blackcurrant oil (15–20%) also contain high amounts of GLA; however, research suggests that they are not necessarily any more potent on a gram-for-gram basis and it has been postulated that this is possibly due to other biologically active components of EPO or the minor stereodimensional differences in the GLA contained within the different oils (Fan & Chapkin 1992)

MAIN ACTIONS

The two main actions of EFAs are related to their roles in the structures of membranes and in the synthesis of a wide variety of derivatives that regulate numerous aspects of cellular activity. In regard to EPO, its main actions relate to its EFA content, GLA in particular.

ANTI-INFLAMMATORY

Although GLA is a theoretical precursor for arachidonic acid (AA) and as such could also generate pro-inflammatory eicosanoids, such as the 2-series PGs, 4-series leukotrienes and platelet activating factor, the evidence to date suggests that GLA can encourage uptake of dihomo-GLA (DGLA) into cell membranes and this in turn inhibits the synthesis of AA metabolites. In addition to this, the direct metabolites of DGLA include PGE_1, which has been shown to inhibit inflammation, regulate immunity, cause vasodilation and reduce blood pressure, improve flexibility of red

blood cell membranes, induce insulin receptors and inhibit platelet aggregation and thrombosis (Horrobin 1990). Consequently the net effect of this omega-6 oil is anti-inflammatory, which distinguishes it clearly from other non-GLA n-6 oils (Fan & Chapkin 1998).

GLA and DGLA have been shown to reduce inflammation and excessive immune reactivity in experimental models of arthritis, autoimmune disease, allergic and chronic inflammatory disorders (Godfrey et al 1986, Kunkel et al 1981a, b, Mertin 1984, Tate et al 1988).

Dermatological effects The anti-inflammatory effect of EPO has been most extensively studied in relation to skin disorders. In addition, n-6 fatty acids are involved in maintaining the integrity of the water impermeability barrier of the skin. Both LA and GLA, but not other EFAs, seem to be capable of this (Horrobin 1990).

ANTITHROMBOTIC ACTIVITY

GLA is metabolised to DGLA, which is a precursor to the 1-series of PGs. Increases in PGE_1 production results in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation. Additionally, red cell membranes deficient in EFAs become stiffer than normal, resulting in reduced capacity of red cells to flow through the capillaries and, therefore, adequately oxygenate target tissues (Horrobin 1990).

OTHER ACTIONS

Bone metabolism Oral GLA and eicosapentaenoic (EPA) acid in the ratio 3:1 have been shown to significantly increase intestinal calcium absorption, calcium balance and bone calcium in rats, compared with controls that consumed LA (sunflower oil) and alpha-LA (linseed oil) acids (3:1) or a commercially available rat chow (Claassen et al 1995).

Hypotensive effects Vegetable oils, including sunflower oil, linseed oil and EPO, have been shown to enhance the effects of several antihypertensive drugs, including dihydralazine, clonidine and captopril in rats under experimental conditions (Hoffmann et al 1984).

A study examining the effects of salt-loading on blood pressure development in borderline hypertensive rats found that dietary sunflower and fish oils abolished the pressor response, reducing blood pressure below control levels (Mills et al 1989).

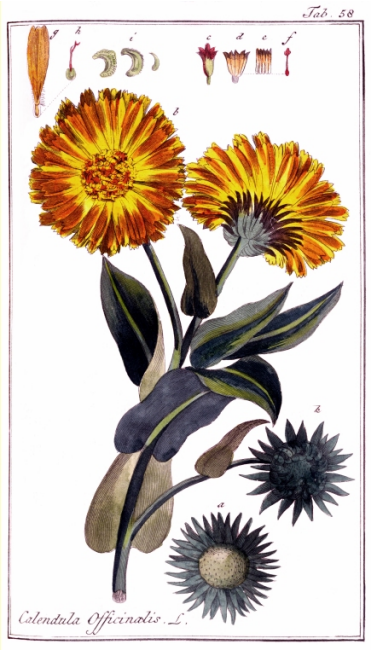
Antidiabetic effects Several studies have indicated that treatment with EPO can prevent or reverse diabetic neuropathy in animals. The effect does not seem to be mediated by regulating the sorbitol or other polyol levels in peripheral nerves, nor by having any effect on the control of blood sugar. The interval between oral intake of

EPO and its effect in peripheral nerves of rats was studied 35 days after induction of diabetes. EPO did not affect nerve conduction velocity in the first 12 hours of its administration, but significantly increased it 24 hours later. Nerve conduction needed 10 days to stabilise. The latency suggests that neuroactivity of EPO may be mediated by its metabolic products synthesised in the body, and not by constituents of the oil (Julu 1996). In another experiment, diabetic rats not receiving EPO showed highly significant elevations of nerve sorbitol and fructose combined with a depletion of nerve myo-inositol. The rats had increased immunoreactivity and reduced nerve conductivity. Treatment of other diabetic rats with EPO attenuated conduction deficiency and in some cases completely prevented the development of the motor nerve conduction velocity deficit (Tomlinson et al 1989).

Alcohol metabolism Many reports have now confirmed the teratogenic potential of alcohol in humans and in laboratory animals. A characteristic pattern of congenital anomalies is present in infants born to mothers with chronic alcoholism. Chronic consumption of ethanol causes a depletion of EFAs, partly by blocking GLA formation and partly by depleting DGLA. Treatment of pregnant rats with ethanol and EPO (Efamol), a rich source of GLA, led to a significant reduction in the embryopathic activity of ethanol (Varma & Persaud 1982).

Renal effects Evening primrose oil, safflower oil and salmon oil have all shown a favourable effect on progression of renal failure in partially nephrectomised rats compared with controls that were fed beef tallow. The regulation of thrombotic and inflammatory mediators may explain the protective role of these oils (Barcelli et al 1986). Further studies showed that EPO and safflower oil may help prevent diabetic nephropathy (Barcelli et al 1990). Compared with beef tallow the oils appeared to have a clear beneficial effect on proteinuria, glomerular sclerosis and tubular abnormalities in diabetic rats. The effect was mediated via PG and thromboxane metabolism. No significant changes in plasma lipid composition were observed. Fish oils did not have an effect on renal disease, but decreased plasma lipids and inhibited eicosanoid synthesis by platelets and kidney cortex.

Diets containing fish oils, EPO or a combination all lowered plasma triglyceride and total cholesterol levels compared with diets containing beef tallow in experimentally induced nephritic syndrome in rats. However, only the combination of EPO and fish oil (75:25) affected HDL-cholesterol levels. The combination prevented the 10-fold suppression of aortic 6-keto-PGF_{1alpha} caused by the fish oils. These changes in plasma lipids and eicosanoid production are potentially anti-atherogenic and may prevent glomerular sclerosis. The combination of EPO and fish oils may offer



advantages over either family of fatty acids in nephrotic syndrome (Barcelli et al 1988).

Metabolites of EPA and GLA have been shown to slow or modulate the development of experimentally induced glomerulonephritis in rats (Papanikolaou 1987).

Antitumour effect Excess dietary fat has been identified as a risk factor in the development of human breast carcinoma. However, the quality of fat may be more important than the overall quantity. Animals treated with EFAs from EPO and fish oils developed tumours that were significantly smaller than two control groups treated with dietary olive oil or normal laboratory feed (Pritchard et al 1989).

CLINICAL USE

Although this review focuses primarily on GLA, evidence now suggests that n-6 fatty acid intake must be considered in relation to concurrent omega-3 (n-3) fatty acid intake to have a more consistent anti-inflammatory effect. As such, many studies are now using combination supplements or dietary changes that alter the ratio of n-3 to n-6 EFAs.

For more information about the n-3:n-6 fatty acid balance, which has implications in cardiovascular disease and cancer, refer to the monograph on Fish oils.

DEFICIENCY

Like other essential nutrients, EFAs must be supplied by the diet. Unlike other essential nutrients, however, it has not yet been possible to identify a minimal daily requirement and a minimum daily intake for GLA has not been determined. Besides insufficient intake, secondary deficiency states are also possible due to faulty EFA metabolism.

The first step in EFA metabolism is the desaturation of LA. The reaction requires delta-6-desaturase and other enzymes, and it is the rate-limiting reaction of dietary LA metabolism. A deficiency or significant inhibition of the desaturase enzyme due to other dietary or lifestyle factors could lead to a deficiency of GLA. Excessive consumption of LA could also lead to a relative deficiency of GLA. In any case, direct supplementation with GLA may be clinically beneficial in these situations (Horrobin 1990).

It is now suspected that a number of common conditions, such as dermatitis, may be aggravated by or in part caused by an imbalance between n-3 and n-6 EFAs and relative lack of GLA.

DERMATITIS AND PSORIASIS

Research from the 1930s to the 1950s established that a deficit of n-6 EFAs leads to an inflammatory skin condition in both animals and humans. More recently, it has been established that there is no deficit of LA in atopic eczema. Instead, concentrations of LA tend to be elevated in blood, milk and adipose tissue of patients with atopic eczema, whereas concentrations of LA metabolites are substantially reduced. This suggests reduced conversion of LA to GLA (i.e. delta-6-desaturase) is responsible. In most studies, but not all, administration of GLA has been found to improve the clinically assessed skin condition, the objectively assessed skin roughness, and the elevated blood catecholamine concentrations of patients with atopic eczema. Atopic eczema may be a minor inherited abnormality of EFA metabolism in some cases (Horrobin 2000).

Clinical studies While early results appear promising, including a meta-analysis published in 1998 that found that oral EPO provided significant improvement for patients with atopic eczema (Morse et al 1989), more recent studies appear to have reached an almost unanimous negative conclusion.

Evening primrose oil, as well as its combination with fish oils, taken for 16 weeks failed to improve symptoms of atopic dermatitis compared with placebo in another double-blind study of 102 adults (Berth-Jones & Graham-Brown 1993). Another study (Oliwiecki & Burton 1994) found that a combination of EPO and fish oil was ineffective in the treatment of psoriasis, and another found it also to be ineffective in atopic eczema, apart from a certain subgroup who failed to show increased erythrocyte DGLA levels and for whom adherence to inclusion criteria and the study protocol were questionable (Henz et al 1999).

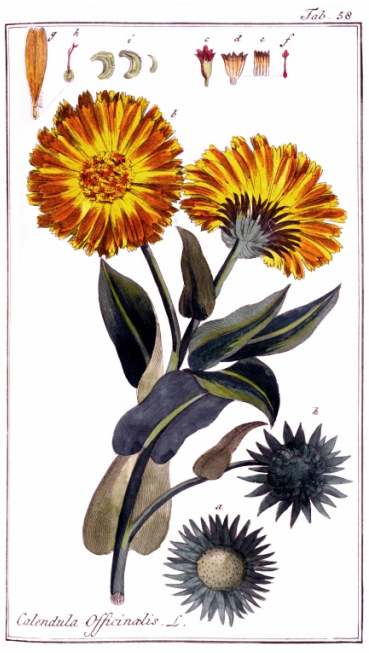
In 2000 a substantial review was conducted by the NHS Health Technology Assessment Programmes, looking at more than 15 studies involving either EPO or borage oil in the treatment of atopic dermatitis, and it was concluded that the largest and best reported studies showed no convincing effect (Hoare et al 2000). Most recently a randomised, double blind, placebo-controlled parallel group trial of 151 patients treated with high-dose borage oil (920 mg GLA) found in favour of the placebo (Takwale et al 2003).

The effects of EPO supplementation in children with atopic eczema has also been investigated, producing both positive and negative results once again (Bamford et al 1985, Biagi et al 1988, Hederos & Berg 1996, Wright & Burton 1982).

Clinical note — Company interest bias in the evidence?

The research into the efficacy of EPO has attracted much criticism from different members of the scientific community. In particular, attention has been paid to the

contrast between early 'strikingly' positive findings and the negative conclusions currently being drawn as a result of more in-depth analysis regarding the efficacy of EPO in the treatment of some conditions. While some may justifiably argue that as with all research it is due to the improvement in techniques, design etc. one editorial published in 2003 in the *British Medical Journal* implies that research funding from the manufacturers, selective inclusion of positive only studies in previous reviews and meta-analyses as well as partial suppression of negative findings has had a part to play (Williams 2003).



FEMALE REPRODUCTIVE SYSTEM DISORDERS

Without doubt, the most popular use for EPO supplements is conditions relating to the female reproductive system.

Premenstrual syndrome Interest in EPO supplements as a potential treatment for PMS began in the early 1980s, largely as a result of investigational work published by David Horrobin. In the *Journal of Reproductive Medicine* he reported on positive results obtained in three double-blind placebo-controlled studies and two open trials in women with premenstrual syndrome (Horrobin 1983).

Shortly afterwards, results from a study conducted by Brush et al provided a rationale for considering EPO supplementation for PMS. This study found that levels of LA in the phospholipids of women with PMS were significantly above normal, yet the concentrations of all metabolites were significantly reduced (Brush et al 1984). Based on these findings, researchers suggested that some women with PMS may not be able to adequately convert LA to GLA and as a result, sensitivity to luteal phase prolactin and steroids may be increased. As such, supplementation directly with GLA (found in EPO oil) would bypass the problem and potentially normalise sensitivity and result in reduced symptoms.

For a time, these results stood unquestioned, until in 1990 another double-blind placebo-controlled trial involving 38 women failed to show evidence of efficacy over six cycles (Khoo et al 1990).

A comprehensive review published in 1996 identified seven placebo-controlled trials, although in two the randomisation was not clearly indicated. The two most well controlled studies failed to detect a benefit for EPO supplements; however, as they were small, modest benefits cannot be excluded (Budeiri et al 1996). Interestingly, in one of these studies the only significant benefit noted by subjects was a mild reduction in breast pain.

Mastalgia An early review on treatments for mastalgia produced by the Cardiff Mastalgia Clinic concluded that danazol was the most effective drug treatment, with

bromocriptine and EPO having equivalent efficacy. Additionally, they state that patients treated with EPO reported much fewer adverse events than those using danazol or bromocriptine (Gateley et al 1992a). Interestingly, treatment with EPO was found to improve the fatty acid profiles towards normal, although this was not always associated with a clinical response (Gateley et al 1992b).

A more recent 6-month, randomised double-blind trial did not find that EPO, EPA or a combination of the two were significantly better than placebo in reducing the symptoms of mastalgia. Corn oil and corn oil with wheatgerm oil were used as control oils. The decrease in days with pain was 12.3% for EPO and 13.8% for its control oil; the decrease in days with pain was 15.5% for fish oil and 10.6% for its control oil (Blommers et al 2002).

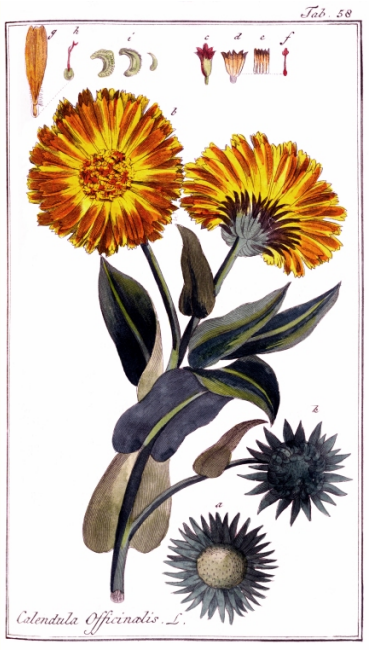
Evening primrose oil has also been assessed for its ability in preventing fibro-adenomas. A small study of 21 patients found that EPO had no significant influence over the natural history of breast fibro-adenomas (Kollias et al 2000). A more recent study has also yielded negative results when compared with topical NSAIDs, with significantly reduced efficacy, more reported adverse effects and ratings of less acceptability by the patients (Quereshi & Sultan 2005).

Endometriosis A combination of GLA and EPA is better than placebo in relieving the symptoms of endometriosis according to one placebo-controlled study. Of those in the treatment group, 90% reported relief of symptoms compared with 10% of those in the placebo group (Horrobin 1990).

Oedema and hypertension during pregnancy In a partially double-blind, placebo-controlled clinical trial, a combination of EPO, fish oil and magnesium oxide was found to be superior to placebo in lowering the incidence of oedema ($P = 0.004$) in pregnant women. Significantly fewer women developed hypertension in the group receiving the oils and magnesium oxide. The three cases of eclampsia all occurred in the control group (D'Almeida et al 1992).

Menopausal hot flushes According to one randomised, double-blind placebo-controlled study EPO supplementation significantly reduces the maximum number of night-time flushes, although other symptoms failed to respond. The study used a dose of four capsules daily (each containing 500 mg EPO and 10 mg vitamin E) over 6 months (Chenoy et al 1994).

A position statement of the North American Menopause Society (2004) concluded that evidence was lacking to warrant the use of EPO in the treatment of vasomotor symptoms of menopause.



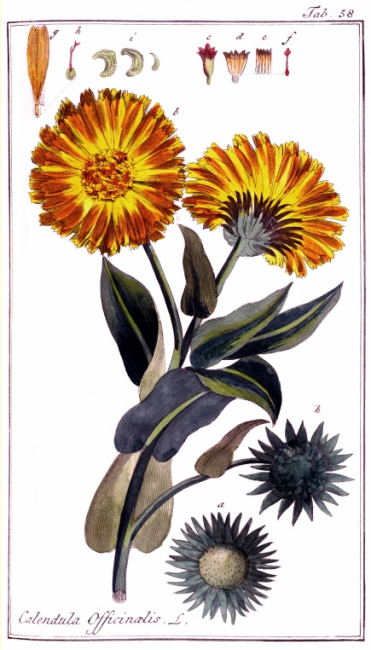
DIABETES

The activity of delta-6-desaturase enzyme is compromised in patients with type 1 and type 2 diabetes mellitus, which can decrease the production of PGE_1, therefore possibly contributing to an overall inflammatory excess in these conditions, as demonstrated by increased levels of PGE_2 (Halat & Dennehey 2003).

The first randomised, double-blind placebo-controlled study investigating EPO as a treatment agent in type 1 and type 2 diabetes mellitus involved 22 patients with mild distal diabetic neuropathy. Patients were administered 360 mg/day of GLA or placebo for 6 months. Patients receiving GLA had statistically significant improvements in all measures of nerve function, wrist and ankle heat threshold values, as well as overall symptom scores. As there was no change in HbA_{1c} in the patients receiving EPO, improvements in symptoms were deemed to be independent of any effect on glucose control.

A subsequent larger, randomised, double-blind placebo-controlled study involved 111 patients with type 1 or 2 diabetes and mild or moderate neuropathy. Patients received either placebo or 480 mg/day of GLA for 1 year. At 1 year, patients who received GLA had a statistically significant increase in 13 of 16 neural function measurements compared with placebo, including a variety of motor conductivity, action potential and sensory tests. Greater benefits were observed in those patients who had glycohaemoglobin values less than 10% at baseline (Jamal & Carmichael 1990).

Currently, there is a need for more conclusive research; however, the evidence to date appears promising for EPO supplementation in mild to moderate neuropathy, even as an adjunct to conventional treatments.



RHEUMATOID ARTHRITIS

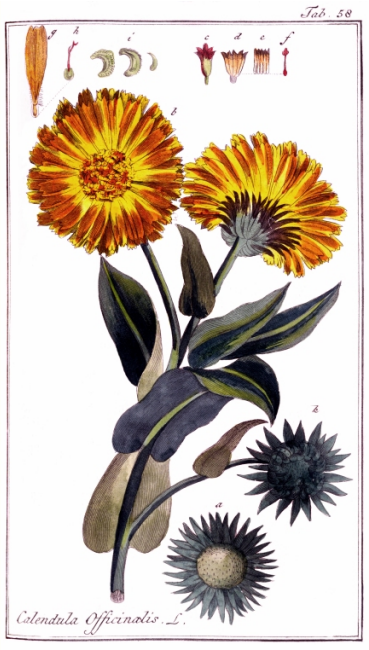
Evening primrose oil supplementation leads to an elevation of DGLA, which is a competitive inhibitor of pro-inflammatory PGs and leukotrienes, and therefore results in a reduced inflammatory response (Belch & Hill 2000). As such, EPO supplements have been investigated in the management of RA, with both negative and positive results (Belch et al 1988, Brzeski et al 1991, Hansen et al 1983, Jantti et al 1989, Veale et al 1994, Zurier et al 1996).

In one study, 16 patients with RA were given 540 mg GLA/day (EPO), 15 patients 240 mg EPA and 450 mg GLA/day (EPO/fish oil) and 18 patients an inert oil (placebo). The initial 12-month treatment period was followed by 3 months' placebo for all groups. Results at 12 months showed a significant subjective improvement for EPO and EPO/fish oil compared with placebo. Additionally, within 12 months the patients receiving EPO and EPO/fish oil had significantly reduced their NSAID intake. After

3 months' placebo, those receiving active treatment had relapsed. Despite the decrease in NSAIDs, measures of disease activity did not worsen. It is suggested that EPO and EPO/fish oil produce a subjective improvement and allow some patients to reduce or stop treatment with NSAIDs. There is, however, no evidence that they act as disease-modifying agents (Belch et al 1988).

In a randomised, single-blind placebo-controlled trial (Zurier et al 1996), treatment with 2.8 g/day GLA resulted in a significant and clinically relevant reduction in RA symptoms and signs of disease activity. GLA therapy demonstrated a significant improvement in swollen joint count and score, tender joint count and score, duration of morning stiffness, patient's global assessment, patient's assessment of pain and degree of disability compared with baseline (measured by Health Assessment Questionnaire score). Not all of these parameters were significantly improved compared with placebo, but this may be due to the choice of safflower oil as a placebo. Olive oil, which contains oleic acid, also found in safflower oil, has been reported in other studies to benefit patients with RA (Brzeski et al 1991).

In one group of patients who were treated with GLA for 12 months, 16 of 21 showed meaningful improvement and 7 patients were able to decrease their NSAID and/or prednisolone dosage. GLA does not have a disease-modifying effect and supplementation must be long term. After 3 months without GLA supplementation, most patients were experiencing an exacerbation of symptoms. GLA was well tolerated during the trial with only three minor adverse reactions reported. Complete blood count and platelet count did not show abnormal results (Zurier et al 1996).



CARDIOVASCULAR DISEASES

Hypertension A double-blind, placebo-controlled study with a crossover design found that the combination of EPO and fish oils significantly lowered blood pressure in 25 non-obese black patients with mild–moderate uncomplicated essential hypertension after 8–12 weeks compared with placebo (sunflower and linseed oil) (Venter et al 1988). Other smaller studies have found a similar beneficial effect in hypertensive patients. A combination of 4 g GLA and DHA daily for 6 weeks reduced blood pressure in nine mildly hypertensive patients compared with placebo (sunflower oil) (Deferne & Leeds 1992).

EPO (1.3 g/day) significantly lowered blood pressure in mildly hypertensive but otherwise healthy subjects in a small placebo-controlled, double-blind short-term trial. EPO treatment led to a group reduction of systolic pressure (8.98 mmHg) and diastolic pressure (12.25 mmHg). The authors suggest that the effect may be mediated via GLA's effects on PG metabolism (Leeds et al 1990).

A study conducted in 2001 in mice demonstrated that consumption of a GLA-based diet significantly reduced aortic vessel wall medial layer thickness and reduced atherosclerotic lesion size. These results were reported by the researchers to indicate that dietary GLA can suppress smooth muscle cell proliferation in vivo and potentially retard the development of atherosclerotic plaques. Human trials are now required to confirm this effect (Fan et al 2001).

OTHER USES

ALCOHOLISM

Essential fatty acids are major structural components of the brain and through their effects on membrane properties are essential for the proper actions of neurotransmitters and nerve conduction. Ethanol has three main known actions on EFA and PG metabolism: it reduces blood LA levels and induces or exaggerates EFA deficiency states; it blocks metabolism of LA to EFA metabolites, which are known to be important in brain structure; and it enhances conversion of DGLA to PGE_1 (Horrobin 1987).

Small clinical studies have found EPO somewhat beneficial in the treatment of alcoholism. In a double-blind placebo-controlled clinical trial EPO significantly reduced the severity of the withdrawal syndrome and improved liver function during the early weeks of withdrawal from alcohol. Relapse rates over 6 and 12 months did not improve, but in those who did not relapse certain parameters of cerebral function improved significantly (Horrobin 1990).

MIGRAINE

Gamma-linolenic acid may be beneficial in the prevention of migraine headache when used in combination with other nutritional supplements and as part of an overall management plan, according to an open, prospective, uncontrolled trial involving 168 migraine patients. In the study, patients took a combination of GLA and alpha-LA (1800 mg/day), other vitamins, coenzymes and antioxidants, and were instructed to lower their arachidonic acid intake. They were also instructed on correct techniques of self-medication and in stress-reduction and progressive relaxation techniques. Of the 129 patients who were evaluated after 6 months, 86% reported an improvement, with 22% of the total being free from migraine, while 14% were not able to implement the self-management of progressive relaxation and stress reduction techniques. Severity and frequency of attacks were decreased in patients reporting a positive response. Significant reduction in nausea and vomitting was reported in all groups except the failure group (Wagner & Nootbaar-Wagner 1997).

Although encouraging, further research using GLA as a stand-alone treatment is required to determine its role in achieving these impressive results.

SCHIZOPHRENIA

A 2000 review of clinical trials concluded that although EPA (from fish oils) may help up to one-third of people avoid initiation of standard treatment with antipsychotic drugs, but there is no clear evidence of any benefit from EPO, and in fact it may lower seizure threshold in some patients (Halat & Dennehey 2003, Joy et al 2000).

RAYNAUD'S SYNDROME

Prostaglandin E_1 and prostacyclin have been used in Raynaud's syndrome, but as these compounds are unstable and require intravenous administration, other treatments that increase the body's own production of these chemicals have been sought, for example, by administration of the precursor EFA. A small, double-blind, placebo-controlled study of 21 patients with Raynaud's phenomenon found that EPO significantly reduced the number of attacks as the weather worsened compared with placebo. Visual analogue scales assessing the severity of attacks and coldness of hands improved in the EPO group, but no changes were seen in either group for objective measures of blood flow although changes in platelet behaviour and blood prostanoids were observed (Belch et al 1985).

DOSAGE RANGE

- Like other essential nutrients, EFAs must be supplied by the diet. Unlike other essential nutrients, it has not yet been possible to identify a minimum daily requirement.
- To reduce the risk of rancidity, EPO is mostly administered in sealed soft gel capsules that are taken orally and should be cold-pressed form of the oil.

ACCORDING TO CLINICAL STUDIES

- Diabetic neuropathy 360–480 mg GLA, which is approximately 4–6 1-g capsules per day (Halat & Dennehy 2003).
- Alcoholism, cardiovascular and inflammatory disorders: 0.5–2.8 g GLA/day (approximately 5.0–28.0 g EPO/day) (Belch & Hill 2000, Leeds et al 1990, Zurier et al 1996).
- EPO may be applied topically in the treatment of skin disorders.

ADVERSE REACTIONS

Mild gastrointestinal symptoms, such as nausea, flatulence, loose bowels and bloating have been reported (Bamford et al 1985). High doses of 5–10 mL/kg/day

administered in animal models failed to detect toxic effects or carcinogenicity (Everett et al 1988).

SIGNIFICANT INTERACTIONS

PHENOTHIAZINES

Several case reports suggest that EPO may reduce seizure threshold and reduce drug effectiveness in patients with schizophrenia treated with phenothiazines (Vaddadi 1981). Avoid concomitant use.

ORAL ANTICOAGULANTS

Due to the antithrombotic effect of EPO, concomitant use may theoretically increase the risk of bleeding — use caution and monitor bleeding time and signs and symptoms of excessive bleeding.

ANTIPLATELET DRUGS

Concomitant use may theoretically increase risk of bleeding, but enhanced anti-inflammatory effects may also develop, making this a useful combination — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

There is mixed evidence for EPO lowering the seizure threshold in people with epilepsy (Spinella 2001). Until safety can be better established, EPO should be used with caution by people with a history of partial complex seizure disorders such as temporal lobe epilepsy. Schizophrenics treated with neuroleptic drugs (phenothiazides) should also use this supplement with caution as it may lower seizure threshold. Suspend use of high doses 1 week before major surgery.

PREGNANCY USE

Safety has not yet been established in pregnancy, although studies with experimental models suggest it is safe. Furthermore, EPO combined with fish oils has been used successfully to reduce the incidence of pre-eclampsia (D'Almeida et al 1992).

PRACTICE POINTS/PATIENT COUNSELLING

- Evening primrose oil contains a number of EFAs, most notably GLA, which is thought to be the most important for exerting pharmacological activity.
- It is suspected that GLA supplementation results in increased production of useful metabolites such as PGE_1, which inhibits inflammation, regulates immunity, causes vasodilation and reduces blood pressure, improves flexibility of red blood cell membranes, induces insulin receptors and inhibits platelet aggregation and thrombosis.

- Evening primrose oil appears beneficial in the treatment of diabetic neuropathy, RA and cardiovascular disease.
- In many disorders, EPO is combined with fish oils (EPA) for best results.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What is EPO?

Evening primrose oil is the oil from the seed of the plant known as evening primrose. A similar oil is made from borage seeds. The oil contains high amounts of GLA, which is the main active compound.

What will this supplement do for me?

Current evidence supports the use of EPO in the treatment of diabetic neuropathy, RA and cardiovascular disease.

When will it start to work?

Beneficial effects have been reported in some studies within 2–4 weeks' continuous use. However, long-term use is necessary for chronic diseases such as RA.

Are there any safety issues?

Evening primrose oil is generally well tolerated. Only minor gastrointestinal upset may occur. Should this happen it is recommended the capsules be taken with meals. EPO should be avoided by some people taking anti-epileptic medicines and blood thinning medicines.

REFERENCES

Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). J Am Acad Dermatol 13.6 (1985): 959-65.

Barcelli UO et al. Beneficial effects of polyunsaturated fatty acids in partially nephrectomized rats. Prostaglandins 32.2 (1986): 211-19.

Barcelli UO et al. A diet containing n-3 and n-6 fatty acids favorably alters the renal phospholipids. eicosanoid synthesis and plasma lipids in nephrotic rats. Lipids 23.11 (1988): 1059-63.

Barcelli UO et al. High linoleic acid diets ameliorate diabetic nephropathy in rats. Am J Kidney Dis 16.3 (1990): 244-51.

Belch JJ, Hill A. Evening primrose oil and borage oil in rheumatologic conditions. Am J Clin Nutr 71.1 (Suppl) (2000): 352-6S.

Belch JJ et al. Evening primrose oil (Efamol) in the treatment of Raynaud's phenomenon: a double blind study. Thromb Haemost 54.2 (1985): 490-4.

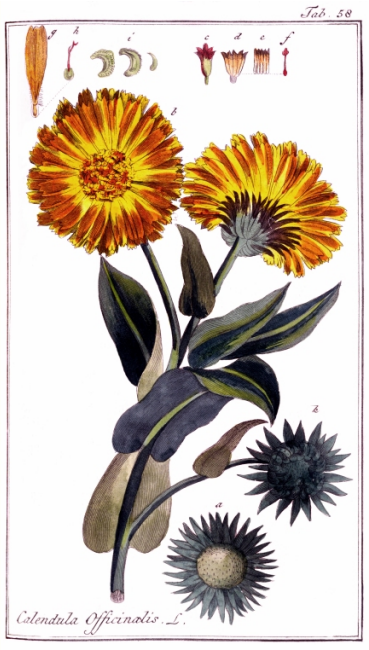
Belch JJ et al. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. Ann Rheum Dis 47.2 (1988): 96-104.

Berth-Jones J, Graham-Brown RA. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. Lancet 341.8860 (1993): 1557-60.

Biagi PL et al. A long-term study on the use of evening primrose oil (Efamol) in atopic children. Drugs Exp Clin Res 14.4 (1988): 285-90.

Blommers J et al. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. Am J Obstet Gynecol 187.5 (2002): 1389-94.

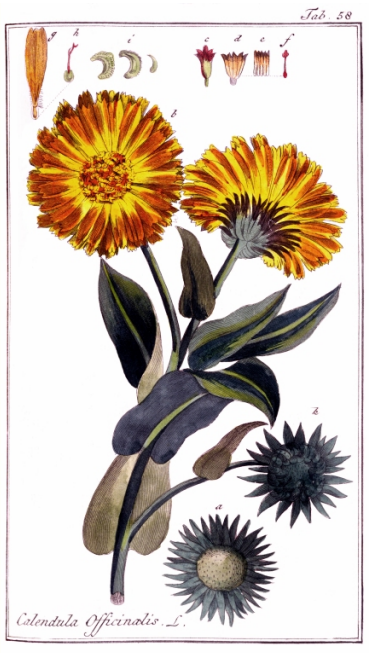
Brush MG et al. Abnormal essential fatty acid levels in plasma of women with premenstrual syndrome. Am J Obstet Gynecol 150.4 (1984): 363-6.
Brzeski M, Madhok R, Capell HA. Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. Br J Rheumatol 30.5 (1991): 370-2.
Budeiri D, Li Wan PA, Dornan JC. Is evening primrose oil of value in the treatment of premenstrual syndrome? Control Clin Trials 17.1 (1996): 60-8.
Chenoy R et al. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ 308.6927 (1994): 501-3.
Claassen N et al. Supplemented gamma-linolenic acid and eicosapentaenoic acid influence bone status in young male rats: effects on free urinary collagen crosslinks, total urinary hydroxyproline, and bone calcium content. Bone 16.4 [Suppl.] (1995): 385-92S.
D'Almeida A et al. Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia. Women Health 19.2-3 (1992): 117-31.
Deferne J, Leeds A. The antihypertensive effect of dietary supplementation with a 6-desaturated essential fatty acid concentrate as compared with sunflower seed oil. J Hum Hypertens 6.2 (1992): 113-19.
Everett DJ, Perry CJ, Bayliss P. Carcinogenicity studies of Efamol evening primrose oil in rats and mice. Med Sci Res 16.16 (1988): 865–6.
Fan Y-Y, Chapkin RS. Mouse peritoneal macrophage prostaglandin E_1 synthesis is altered by dietary γ-linolenic acid. J Nutr 122 (1992):1600-6.
Fan Y-Y, Chapkin RS. Importance of dietary γ-linolenic acid in human health and nutrition. J Nutr 128.9 (1998): 1411-14.
Fan Y-Y, Ramos KS, Chapkin RS. Dietary γ-linolenic acid suppresses aortic smooth muscle cell proliferation and modifies atherosclerotic lesions in apolipoprotein e knockout mice. J Nutr 131 (2001):1675-81.
Gateley CA et al. Drug treatments for mastalgia: 17 years experience in the Cardiff Mastalgia Clinic. J R Soc Med 85.1 (1992a): 12-15.
Gateley CA et al. Plasma fatty acid profiles in benign breast disorders. Br J Surg 79.5 (1992b): 407-9.
Godfrey DG et al. Effects of dietary supplementation on autoimmunity in the MRL/lpr mouse: a preliminary investigation. Ann Rheum Dis 45.12 (1986): 1019-24.
Halat KM, Dennehy CE. Botanicals and dietary supplements in diabetic peripheral neuropathy. J Am Board Fam Pract 16 (2003): 47-57.
Hansen TM et al. Treatment of rheumatoid arthritis with prostaglandin E1 precursors cis-linoleic acid and gamma-linolenic acid. Scand J Rheumatol 12.2 (1983): 85-8.
Hederos CA, Berg A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. Arch Dis Child 75.6 (1996): 494-7.
Henz BM et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. Br J Dermatol 140.4 (1999): 685-8.
Hoare C et al. Systematic review of treatments for atopic eczema. Health Technol Assess 4 (2000): 37.
Hoffmann P, Taube C, Bartels T. Cardiovascular effects of antihypertensive drugs as affected by dietary polyunsaturates. Biomedica Biochimica Acta 43.8-9 (1984): S195-8.
Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. J Reprod Med 28.7 (1983): 465-8.
Horrobin DF. Essential fatty acids, prostaglandins, and alcoholism: an overview. Alcohol Clin Exp Res 11.1 (1987): 2-9.
Horrobin DF. Gamma linolenic acid. Rev Contemp Pharmacother 1.1 (1990): 1-45.
Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. Am J Clin Nutr 71.1 [Suppl] (2000): 367-72S.
Jamal GA, Carmichael H. The effect of gamma-linolenic acid on human diabetic peripheral neuropathy: a double-blind placebo-controlled trial. Diabet Med 7.4 (1990): 319-23.



Jantti J et al. Evening primrose oil and olive oil in treatment of rheumatoid arthritis. Clin Rheumatol 8.2 (1989): 238-44.
Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid (fish or evening primrose oil) for schizophrenia. Cochrane Database Syst Rev 2 (2000): CD001257.
Julu PO. Latency of neuroactivity and optimum period of treatment with evening primrose oil in diabetic rats. J Lipid Mediat Cell Signal 13.2 (1996): 99-113.
Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. Med J Aust 153.4 (1990): 189-92.
Kleijnen J. Evening primrose oil. BMJ 309.6958 (1994): 824-5.
Kollias J et al. Effect of evening primrose oil on clinically diagnosed fibroadenomas. Breast 9.1 (2000): 35-6.
Kunkel SL et al. Suppression of chronic inflammation by evening primrose oil. Prog Lipid Res 20 (1981a): 885-8.
Kunkel SL et al. Modulation of inflammatory responses by prostaglandins and essential fatty acids. Federation Proc 40.3 I (1981b): 632.
Leeds A, Gray I, Ahmad M. Effects of n-6 essential fatty acids as evening primrose oil in mild hypertension. In Horrobin D (ed). Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine. New York: Alan R Liss, 1990; 157-71.
Mertin J. Omega-6 and omega-3 polyunsaturates and the immune system. Br J Clin Pract Suppl 31 (1984): 111-14.
Mills DE et al. Dietary N-6 and N-3 fatty acids and salt-induced hypertension in the borderline hypertensive rat. Lipids 24.1 (1989): 17-24.
Morse PF et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. Br J Dermatol 121.1 (1989): 75-90.
North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement. Menopause 11.1 (2004): 11-33.
Oliwiecki S, Burton JL. Evening primrose oil and marine oil in the treatment of psoriasis, Clin Exp Dermatol 19.2 (1994): 127-9.
Papanikolaou N. Alteration of mercuric chloride-induced autoimmune glomerulonephritis in brown-Norway rats by herring oil, evening primrose oil and OKY-046 a selective TXA-synthetase inhibitor. Prostaglandins Leukot Med 27.2-3 (1987): 129-49.
Pritchard GA, Jones DL, Mansel RE. Lipids in breast carcinogenesis. Br J Surg 76.10 (1989): 1069-73.
Qureshi S, Sultan N. Topical nonsteroidal anti-inflammatory drugs versus oil of evening primrose in the treatment of mastalgia. Surgeon 3.1 (2005): 7-10.
Spinella M. Herbal medicines and epilepsy: the potential for benefit and adverse effects. Epilepsy Behav 2.6 (2001): 524-32.
Takwale A et al. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. BMJ 327 (2003): 1385-7.
Tate GA et al. Suppression of monosodium urate crystal-induced acute inflammation by diets enriched with gamma-linolenic acid and eicosapentaenoic acid. Arthritis Rheum 31.12 (1988): 1543-51.
Tomlinson DR et al. Essential fatty acid treatment-effects on nerve conduction, polyol pathway and axonal transport in streptozotocin diabetic rats. Diabetologia 32.9 (1989): 655-9.
Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. Prostaglandins Med 6.4 (1981): 375-9.
Varma PK, Persaud TV. Protection against ethanol-induced embryonic damage by administering gamma-linolenic and linoleic acids. Prostaglandins Leukot Med 8.6 (1982): 641-5.
Veale DJ et al. A double-blind placebo controlled trial of Efamol Marine on skin and joint symptoms of psoriatic arthritis. Br J Rheumatol 33.10 (1994): 954-8.
Venter CP, Joubert PH, Booyens J. Effects of essential fatty acid on mild to moderate essential hypertension. Prostaglandins Leukot Essential Fatty Acids 33.1 (1988): 49-51.

Wagner W, Nootbaar-Wagner U. Prophylactic treatment of migraine with gamma-linolenic and alpha-linolenic acid. Cephalalgia 17.2 (1997): 127-30.
Williams HC. Evening primrose oil for atopic dermatitis. BMJ 327 (2003): 1358-9.
Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. Lancet 2.8308 (1982): 1120-2.
Zurier RB et al. Gamma-Linolenic acid treatment of rheumatoid arthritis: a randomized placebo-controlled trial. Arthritis Rheum 39.11 (1996): 1808-17.

Fenugreek



Historical note Fenugreek's seeds and leaves are used not only as food but also as an ingredient in traditional medicine. It is indigenous to Western Asia and Southern Europe, but is now mainly cultivated in India, Pakistan, France, Argentina and North African countries. In ancient times it was used as an aphrodisiac by the Egyptians and, together with honey, for the treatment of rickets, diabetes, dyspepsia, rheumatism, anaemia and constipation. It has also been described in early Greek and Latin pharmacopoeias for hyperglycaemia and was used by Yemenite Jews for type 2 diabetes (Yeh et al 2003). In India and China it is still widely used as a therapeutic agent. In the United States, it has been used since the 19th century for postmenopausal vaginal dryness and dysmenorrhea (Ulbricht & Basch 2005).

COMMON NAME
Fenugreek

OTHER NAMES
Trigonella seeds, bird's foot, Greek hay, hu lu ba, methi, trigonella

BOTANICAL NAME/FAMILY
Trigonella foenum graecum (family Leguminosae)

PLANT PARTS USED
Dried mature seed, although leaves are used less commonly.

CHEMICAL COMPONENTS
The main chemical constituents are fibre, tannic acid, fixed and volatile oils and a bitter extractive, steroidal saponins, flavonoids, polysaccharides, alkaloids, trigonelline, trigocoumarin, trigomethyl coumarin, mucilage (up to 30%), seven essential amino acids and vitamins A, C, D, B1, B2 and B3 (Bin-Hafeez et al 2003, Fisher & Painter 1996, Shang et al 1998, Zia et al 2001).

MAIN ACTIONS

HYPOGLYCAEMIC
The hypoglycaemic effect of fenugreek seeds has been demonstrated in numerous studies involving experimentally induced diabetes (both type 1 and type 2) in rats, dogs, mice, rabbits and humans (Alarcon-Aguilara et al 1998, Madar et al 1988, Raju

et al 2001, Ribes et al 1984, 1986, Riyad et al 1988, Sharma et al 1990, Vats et al 2002), and the effect has been described as slow but sustained (Puri et al 2002). Interestingly, no reduction of fasting or postprandial blood sugar levels were observed in a placebo-controlled study in non-diabetic people who used a dose of 5 g/day over 3 months (Bordia et al 1997).

Fenugreek exerts its hypoglycaemic effect by delaying glucose absorption and enhancing its utilisation (Al Habori et al 2001). Results from in vivo experiments suggest that fenugreek may increase the sensitivity of tissues to available insulin (Puri et al 2002). The active component responsible for this activity is associated with a de-fatted part (non-lipid extract), rich in fibre-containing steroidal saponins and proteins (Ribes et al 1986, Valette et al 1984).

ANTIULCEROGENIC ACTIVITY

Both an aqueous extract and a gel fraction isolated from the seeds demonstrated significant ulcer-protective effects in vivo (Pandian et al 2002). The seed fractions given orally to test animals provided dose-dependent gastric protection against the effects of ethanol that was as potent as that of omeprazole. Furthermore, histological studies found that the soluble gel fraction was significantly more protective than omeprazole. Preliminary research suggests that the polysaccharide composition and/or flavonoid components of the gel are responsible for the gastroprotective and antisecretory activities of the seeds.

HYPOCHOLESTEROLAEMIC EFFECT

Significant cholesterol-lowering activity has been demonstrated in several animal studies and human studies with diabetic volunteers (Gupta et al 2001, Petit et al 1995, Rao et al 1996, Stark & Madar 1993, Sharma et al 1990, Sowmya & Rajyalakshmi 1999). Although the mechanism of action is still unclear, it appears that the fibre and steroidal saponin content are important for activity.

IMMUNOSTIMULANT ACTIVITY

Enhanced humoral immunity, significant increases in macrophage activity and a stimulatory effect on lymphoproliferation have been demonstrated in vivo (Bin-Hafeez et al 2003). Stimulatory effects were observed at 100 mg/kg and in some cases at 250 mg/kg.

ANTI-INFLAMMATORY AND ANTIPYRETIC ACTIVITY

Potent anti-inflammatory activity was demonstrated in an animal model for both single-dose and chronic-dose applications of a dried leaf decoction of fenugreek (Ahmadiani et al 2001). The effectiveness of the 1000 mg/kg dose of the extract was

relatively equal to 300 mg/kg sodium salicylate for single dosing; however, chronic administration was more effective than sodium salicylate. Additionally, the fenugreek decoction demonstrated stronger antipyretic activity than that of sodium salicylate.

ANTINOCICEPTIVE EFFECTS

Two studies in animal models have identified antinociceptive activity for fenugreek (Ahmadiani et al 2001, Javan et al 1997). This seems to be mediated through central and peripheral mechanisms. According to Javan et al (1997), the antinociceptive effects of 2000 mg/kg of the extract were more potent than 300 mg/kg sodium salicylate.

EFFECT ON THYROID HORMONES

Administration of fenugreek seed extract for 15 days to both mice and rats significantly decreased serum triiodothyronine (T_3), suggesting that thyroxine (T_4)-to-T_3 conversion is inhibited and leads to increases in T_4 levels (Panda et al 1999).

STIMULATES DIGESTION

Traditionally, fenugreek is used to improve digestion. In vivo studies have identified that it enhances the activity of pancreatic and intestinal lipase, and sucrase and maltase thereby providing support to this traditional use (Platel & Srinivasan 1996, 2000).

OTHER ACTIONS

Antineoplastic activity has been observed for fenugreek in the Ehrlich ascites carcinoma model in mice (Sur et al 2001). Protodioscin, purified from fenugreek, has also exhibited antineoplastic activity on human leukaemia cell lines in vitro (Hibasami et al 2003). Although fenugreek contains coumarin constituents, a placebo-controlled study found that it does not affect platelet aggregation, fibrinolytic activity or fibrinogen (Bordia et al 1997). Traditionally it is thought to promote lactation in nursing mothers and act as a general tonic.

CLINICAL USE

DYSPEPSIA AND LOSS OF APPETITE

Although controlled studies are unavailable, the increased activity of pancreatic and intestinal lipase seen in animal studies provides a theoretical basis for its use in dyspepsia.

Commission E approved the internal use of fenugreek seed for loss of appetite (Blumenthal et al 2000).

ELEVATED LIPID LEVELS

Several clinical studies conducted in people with and without diabetes have identified significant lipid-lowering activity with different fenugreek preparations, such as de-fatted fenugreek, germinated seed and hydro-alcoholic extracts (Bordia et al 1997, Gupta et al 2001, Sharma et al 1990, Sowmya & Rajyalakshmi 1999). As can be expected, the dose used and type of preparation tested has an influence over results.

An open study using a daily dose of 18.0 g germinated fenugreek seed in healthy volunteers demonstrated significant reductions in total cholesterol and LDL-cholesterol levels. A placebo-controlled study found no effect after 3 months with a lower dose of 5 g seed daily (Bordia et al 1997, Sowmya & Rajyalakshmi 1999), suggesting that higher intakes may be required for lipid-lowering activity to become significant.

DIABETES

Fenugreek is a popular natural treatment used to aid blood sugar regulation in diabetes. Overall, results from clinical studies have produced positive results however trials have used diverse preparations, various dosage regimens and outcome measures.

In one open study involving 60 people with type 2 diabetes, 25 g fenugreek seed powder taken together with lunch and dinner for 24 weeks produced significant reductions to fasting blood sugar levels and symptoms of diabetes, and improved glucose tolerance (Sharma et al 1996). A shorter 10-day randomised study of people with type 1 diabetes found that de-fatted fenugreek seed powder (50 g twice daily) significantly reduced fasting blood sugar level and improved glucose tolerance (Sharma et al 1990). More recently, a double-blind, placebo-controlled study involving 25 volunteers with mild to moderate type 2 diabetes showed that 1 g/day hydro-alcoholic extract of fenugreek seeds for 2 months improved insulin resistance and increased insulin sensitivity but had no effect on fasting blood glucose level at this low dose (Gupta et al 2001).

Studies with de-fatted fenugreek seed (100 g/day) in patients with type 1 diabetes identified significant reductions in total cholesterol, LDL- and VLDL-cholesterol and triglyceride levels but no changes to HDL-cholesterol under randomised conditions (Sharma et al 1990). Similar results were obtained with an ethanolic extract of de-fatted fenugreek seeds in vivo, which produced an 18–26% reduction in plasma cholesterol level (Stark & Madar 1993).

A placebo-controlled study using a lower dose of 2.5 g unaltered fenugreek seed twice daily over 3 months found this was ineffective in type 1 diabetes but did have a lipid-lowering effect in patients with diabetes and coronary artery disease (Bordia et al

1997). In this population, total cholesterol and triglyceride levels were significantly reduced.

Although high doses of fenugreek seeds are required, a 2001 double-blind placebo-controlled study found that a dose of 1 g ethanolic extract of fenugreek was able to significantly decrease serum triglyceride levels and increase HDL-cholesterol in mild to moderate type 2 diabetes mellitus (Gupta et al 2001).

PROMOTING LACTATION

Although fenugreek has been used traditionally for centuries to increase milk production and improve lactation, no controlled studies are available to confirm effectiveness.

EXTERNALLY — TO REDUCE LOCAL INFLAMMATION

Although controlled studies are not available, evidence of anti-inflammatory and antinociceptive activity provides a theoretical basis for this indication.

Commission E approves the external use of fenugreek as a poultice for local inflammation (Blumenthal et al 2000).

OTHER USES

In Ayurvedic and Unani systems of medicine, fenugreek is used for treating epilepsy, paralysis, gout, dropsy, chronic cough and piles. The seeds are reported to have nutritive properties and to stimulate digestive processes, and have been used to treat a range of gastrointestinal disorders in the Indian system of medicine. It is also used as a general tonic, mixed with milk and sugar to promote lactation and to lower lipid and glucose levels.

DOSAGE RANGE

INTERNAL USE

According to clinical studies

- General dose range: liquid extract (1:2): 2–6 mL/day.
- Diabetes: 50–100 g seed daily taken in divided doses with meals, or 1 g/day ethanolic seed extract.
- Lipid-lowering activity: according to the above studies, 18.0 g germinated fenugreek or 100 g de-fatted seeds daily taken in divided doses with meals.

EXTERNAL USE

- As a poultice: 50 g powdered seed in 0.5–1 L hot water applied topically to affected area.

TOXICITY

Safety studies indicate that fenugreek is extremely safe. When consumed as 20% of the diet, it did not produce toxic effects in animal tests.

ADVERSE REACTIONS

One clinical study found that a dose of 50 g taken twice daily produced mild gastrointestinal symptoms, such as diarrhoea and flatulence, which subsided after 3–4 days. Allergic reactions have been reported, but are rare.

SIGNIFICANT INTERACTIONS

Where controlled studies are not available, interactions are speculative and based on evidence of pharmacological activity and case reports.

HYPOGLYCAEMIC AGENTS

Additive effects are theoretically possible in diabetes — monitor concomitant use and monitor serum glucose levels closely — potentially beneficial interaction.

IRON

Frequent use of fenugreek can inhibit iron absorption — separate doses by 2 hours.

WARFARIN

Although there is a theoretical concern that concomitant use could increase bleeding risk due to the herb's coumarin content, this is unlikely. A placebo-controlled study found that fenugreek does not affect platelet aggregation, fibrinolytic activity or fibrinogen (Bordia et al 1997).

CONTRAINDICATIONS AND PRECAUTIONS

Fenugreek is contraindicated in people with allergy to the herb, which has been observed in several case reports (Patil et al 1997), or those with allergy to chickpeas, because of possible cross-reactivity (Ulbricht & Basch 2005). Monitor patients with thyrotoxicosis when using this herb at doses above usual dietary intake.

PREGNANCY USE

When taken in usual dietary amounts, fenugreek is likely to be safe; however, the safety of larger doses has not been scientifically evaluated.

PRACTICE POINTS/PATIENT COUNSELLING

- Fenugreek's seeds and leaves are used not only as food but also as an ingredient in traditional medicine systems.
- Clinical studies have identified significant hypoglycaemic and lipid-lowering activity; however, dosage forms and treatment regimens varied.

- In animal studies fenugreek has been shown to exert immunostimulant, anti-inflammatory and antinociceptive activity, stimulate digestive enzyme production and provide significant antiulcerogenic effects.
- In practice it is used to manage blood sugar levels in patients with diabetes, to lower cholesterol levels, to provide symptom relief in dyspepsia and to promote lactation.
- Externally it is made into a poultice with hot water and used as an anti-inflammatory application.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Fenugreek can lower blood sugar levels in patients with diabetes, reduce cholesterol levels and stimulate digestion. It may also protect the gastrointestinal tract from ulcers, stimulate immune function and provide anti-inflammatory and antipyretic effects. Traditionally, it has also been used to promote lactation.

When will it start to work?

Studies suggest that blood sugar effects can be seen within 10 days in type 1 diabetes, whereas lipid-lowering effects can take up to 3 months to establish. Traditionally, digestive effects are thought to occur soon after ingestion of the seeds.

Are there any safety issues?

Used as a food, fenugreek appears extremely safe but may interact with blood-thinning medicines. When used in high doses as a medicine, it may cause flatulence, diarrhoea and mild stomach discomfort. Allergies to fenugreek are possible. When used with diabetic medicine, it may increase sugar-lowering activity and safety should be monitored.

REFERENCES

Ahmadiani A et al. Anti-inflammatory and antipyretic effects of Trigonella foenum-graecum leaves extract in the rat. J Ethnopharmacol 75.2-3 (2001): 283-6.

Al Habori M et al. In vitro effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase A. Int J Exp Diabetes Res 2.2 (2001): 91-9.

Alarcon-Aguilara FJ et al. Study of the anti-hyperglycemic effect of plants used as antidiabetics. J Ethnopharmacol 61.2 (1998): 101-10.

Bin-Hafeez B et al. Immunomodulatory effects of fenugreek (Trigonella foenum graecum L.) extract in mice. Int Immunopharmacol 3.2 (2003): 257-65.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bordia A Verma SK, Srivastava KC. Effect of ginger (Zingiber officinale Rosc.) and fenugreek (Trigonella foenumgraecum L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 56.5 (1997): 379-84.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Gupta A, Gupta R, Lal B. Effect of Trigonella foenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. J Assoc Physicians India 49 (2001): 1057-61.
Hibasami H et al. Protodioscin isolated from fenugreek (Trigonella foenumgraecum L.) induces cell death and morphological change indicative of apoptosis in leukemic cell line H-60, but not in gastric cancer cell line KATO III. Int J Mol Med 11.1 (2003): 23-6.
Javan M et al. Antinociceptive effects of Trigonella foenum-graecum leaves extract. J Ethnopharmacol 58.2 (1997): 125-9.
Lambert JP, Cormier A. Potential interaction between warfarin and boldo-fenugreek. Pharmacotherapy 21.4 (2001): 509-12.
Madar Z et al. Glucose-lowering effect of fenugreek in non-insulin dependent diabetics. Eur J Clin Nutr 42.1 (1988): 51-4.
Panda S, Tahiliani P, Kar A. Inhibition of triiodothyronine production by fenugreek seed extract in mice and rats. Pharmacol Res 40.5 (1999): 405-9.
Pandian RS, Anuradha CV, Viswanathan P. Gastroprotective effect of fenugreek seeds (Trigonella foenum graecum) on experimental gastric ulcer in rats. J Ethnopharmacol 81.3 (2002): 393-7.
Patil SP, Niphadkar PV, Bapat MM. Allergy to fenugreek (Trigonella foenum graecum). Ann Allergy Asthma Immunol 78.3 (1997): 297-300.
Petit PR et al. Steroid saponins from fenugreek seeds: extraction, purification, and pharmacological investigation on feeding behavior and plasma cholesterol. Steroids 60.10 (1995): 674-80.
Platel K, Srinivasan K. Influence of dietary spices or their active principles on digestive enzymes of small intestinal mucosa in rats. Int J Food Sci Nutr 47.1 (1996): 55-9.
Platel K, Srinivasan K. Influence of dietary spices and their active principles on pancreatic digestive enzymes in albino rats. Nahrung 44.1 (2000): 42-6.
Puri D, Prabhu KM, Murthy PS. Mechanism of action of a hypoglycemic principle isolated from fenugreek seeds. Indian J Physiol Pharmacol 46.4 (2002): 457-62.
Raju J et al. Trigonella foenum graecum (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes. Mol Cell Biochem 224.1-2 (2001): 45-51.
Rao P, Sesikeran B, Rao P, Naidu M, Rao V, Ramachandran EP. Short term nutritional and safety evaluation of fenugreek. Nutr Res 16.9 (1996): 1495-505.
Ribes G et al. Effects of fenugreek seeds on endocrine pancreatic secretions in dogs. Ann Nutr Metab 28.1 (1984): 37-43.
Ribes G et al. Antidiabetic effects of subfractions from fenugreek seeds in diabetic dogs. Proc Soc Exp Biol Med 182.2 (1986): 159-66.
Riyad MA, Abdul-Salam SA, Mohammad SS. Effect of fenugreek and lupine seeds on the development of experimental diabetes in rats. Planta Med 54.4 (1988): 286-90.
Shang M, Cai S, Wang X. Analysis of amino acids in Trigonella foenumgraecum seeds. Zhong Yao Cai 21.4 (1998): 188-90.
Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr 44.4 (1990): 301-6.
Sharma RD et al. Use of fenugreek seed powder in the management of non-insulin dependent diabetes mellitus. Nutr Res 16(8) (1996): 1331-9.
Sowmya P, Rajyalakshmi P. Hypocholesterolemic effect of germinated fenugreek seeds in human subjects. Plant Foods Hum Nutr 53.4 (1999): 359-65.
Stark A, Madar Z. The effect of an ethanol extract derived from fenugreek (Trigonella foenum-graecum) on bile acid absorption and cholesterol levels in rats. Br J Nutr 69.1 (1993): 277-87.
Sur P et al. Trigonella foenum graecum (fenugreek) seed extract as an antineoplastic agent. Phytother Res 15.3 (2001): 257-9.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.

Valette G et al. Hypocholesterolaemic effect of fenugreek seeds in dogs. Atherosclerosis 50.1 (1984): 105-11.
Vats V, Grover JK, Rathi SS. Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonella foenum-graecum Linn, Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanized diabetic rats. J Ethnopharmacol 79.1 (2002): 95-100.
Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 26.4 (2003): 1277-94.
Zia T, Hasnain SN, Hasan SK. Evaluation of the oral hypoglycaemic effect of Trigonella foenum-graecum L. (methi) in normal mice. J Ethnopharmacol 75.2-3 (2001): 191-5.

Feverfew

Historical note Feverfew has been used for centuries in Europe to treat headaches, arthritis and fever and used as an emmenagogue and anthelmintic agent. In the 1970s it was 'rediscovered' by the medical establishment and subjected to clinical studies, which produced encouraging results that suggested feverfew was an effective prophylactic medicine for migraine headache.

OTHER NAMES
Altamisa, bachelor's button, camomile grande, featherfew, featherfoil, chrysanthemum parthenium, mutterkraut, matrem, tanaceti parthenii herba/folium

BOTANICAL NAME/FAMILY
Tanacetum parthenium (family [Asteraceae] Compositae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
The leaves and flowering tops contain many monoterpenes and sesquiterpenes as well as sesquiterpenes lactones (chrysanthemolide, chrysanthemonin, 10-epi-canin, magnoliolide and parthenolide), reynosin, santamarin, tanaparthins and other compounds. Until recently, the sesquiterpene lactone parthenolide was thought to be the major biologically active constituent. However, in vitro and in vivo research suggests others are also present (Brown et al 1997, Pugh & Sambo 1988).

Clinical note – Natural variations in parthenolide content
The amount of parthenolide present in commercial preparations of feverfew leaves varies significantly, with some exhibiting levels as high as 1,7% dry weight and others as low as 0.01% to non-detectable (Cutlan et al 2000). The study by Cutlan et al measured the parthenolide content in plants produced from seeds taken from over 30 different sources and germinated under identical conditions. According to this study, feverfew collected from the wild and distributed by botanical gardens or US Department of Agriculture seed banks yielded plants with the highest mean parthenolide value, and plants with yellow leaves also had significantly higher parthenolide levels than those with green leaves.

MAIN ACTIONS

ANTI-INFLAMMATORY AND ANALGESIC

Several in vivo studies have identified anti-inflammatory and antinociceptive activity for feverfew extracts and parthenolide. When feverfew extracts were orally administered, or pure parthenolide was injected IP, significant dose-dependent anti-inflammatory and antinociceptive effects were observed in animal models (Jain & Kulkarni 1999). Similarly, when feverfew extracts and parthenolide from *Tanacetum vulgare* was administered orally in a rat model, gastric ulcer index was significantly reduced (Tournier et al 1999).

The mechanisms responsible for these effects are not well elucidated. Jain and Kulkarni (1999) demonstrated that the antinociceptive effect was not mediated through the opiate pathway and was not associated with sedation. In regards to the anti-inflammatory effect, several mechanisms appear to be responsible.

Two in vitro studies have found evidence of COX and lipoxygenase inhibition (Capasso 1986, Pugh & Sambo 1988), while other tests reveal no effect on COX (Collier et al 1980, Makheja & Bailey 1982). Inhibition of phospholipase A_2 has also been suggested (Heptinstall 1988). Direct binding and inhibition of I-kappa B kinase beta, an important subunit involved in cytokine-mediated signalling, has been demonstrated for parthenolide in test tube studies (Kwok et al 2001). Parthenolide also inhibits NO production, an important regulator and inducer of various inflammatory states (Wong & Menendez 1999). More recently, results from an in vivo study confirm that parthenolide inhibits proinflammatory cytokine responses, although the authors propose that proinflammatory mediators including chemokines (MIP-2), plasma enzyme mediators (complement, kinin and clotting systems) and lipid mediators (COX, PG, platelet-activating factor) are also likely to be involved (Smolinski & Pestka 2003).

The essential oil constituent of feverfew, chrysanthenyl acetate, inhibits PG synthetase in vitro and also seems to possess analgesic properties (Pugh & Sambo 1988).

ANTISPASMODIC

The results from several in vitro studies generally indicate that feverfew decreases vascular smooth muscle spasm (Barsby et al 1992, Barsby et al 1993a, b, Collier et al 1980).

INHIBITS SEROTONIN RELEASE AND BINDING

Parthenolide and several other sesquiterpene lactone constituents inhibit serotonin release but do not bind to $5HT_1$ receptors, according to in vivo data (Groenewegen &

Heptinstall 1990, Marles et al 1992, Weber et al 1997a). Some tests with $5HT_{2A}$ receptors show parthenolide is a low-affinity antagonist (Weber et al 1997b), whereas other tests found no effect on $5HT_{2A}$ or $_{2B}$ receptors. Feverfew extract potently and directly blocked $5HT_{2A}$ and $_{2B}$ receptors and neuronally released 5HT, suggesting that feverfew powder or extracts are more effective than isolated parthenolide (Mittra et al 2000).

OTHER ACTIONS

INHIBITS PLATELET AGGREGATION

Evidence is contradictory as to whether feverfew inhibits platelet aggregation. Several test tube studies and animal models have observed inhibition of platelet aggregation (Heptinstall et al 1988, Jain & Kulkarni 1999, Makheja & Bailey 1982). However, no significant effects were seen in a clinical study of 10 patients receiving feverfew (Biggs et al 1982).

MAST-CELL STABILISATION

Tests with rat mast cells indicate that feverfew extract inhibits histamine release, but the mechanism of action is different to cromoglycate and quercetin (Hayes & Foreman 1987).

CLINICAL USE

PROPHYLAXIS OF MIGRAINE HEADACHE

The first double-blind study investigating feverfew in migraine prophylaxis was published in 1985 and involved 17 patients who had been chewing fresh feverfew leaves on a daily basis (Johnson et al 1985). Therapeutic effect was maintained when capsules containing freeze-dried feverfew powder were continued, whereas those allocated placebo capsules experienced a significant increase in the frequency and severity of headache, nausea, and vomiting during the early months of withdrawal.

Since then, numerous clinical studies have been conducted to determine the role of feverfew in the prevention of migraine headache.

In 2000, Ernst and Pittler published a systematic review of six randomised, placebo-controlled double-blind trials of feverfew as a prophylactic treatment and concluded that the current evidence favours feverfew as an effective preventative treatment against migraine headache, and is generally well tolerated.

Clinical note — Migraine

Migraine is a common episodic familial headache disorder characterised by a combination of headache and neurologic, gastrointestinal, and autonomic symp-

toms. It has a 1-year prevalence of approximately 18% in women, 6% in men, and 4% in children before puberty (Silberstein 2004). Several underlying mechanisms are considered responsible for the onset of migraine.

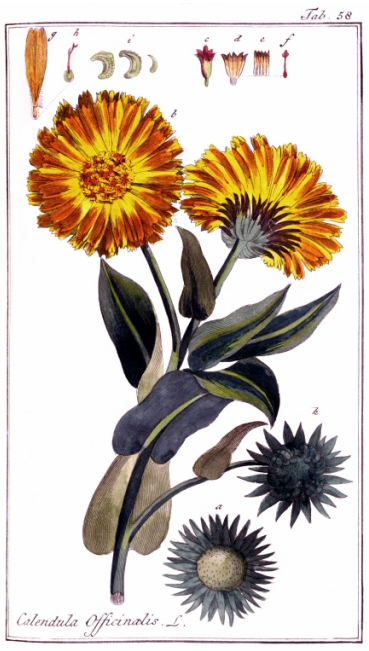
One of the genes linked to migraine is associated with dysfunction in P-type neuronal calcium channels, which mediate 5-HT and excitatory neurotransmitter release. This dysfunction can impair release of 5-HT and predispose patients to migraine attacks or impair their self-aborting mechanism (Silberstein 2004). Additionally, NO may be involved in the initiation and maintenance of migraine headache (Ferrari 1998). Migraine aura is now thought to be caused by neuronal dysfunction, not ischaemia, and headache begins while cortical blood flow is reduced.

In clinical practice, the three goals of migraine-preventive therapy are to reduce attack frequency, severity, and duration, improve responsiveness to treatment of acute attacks, and improve function and reduce disability. Ultimately, choice of treatment should be based on efficacy, adverse effects and coexistent conditions with a full therapeutic trial taking 2–6 months.

A more recent Cochrane systematic review of five placebo-controlled, randomised, double-blind trials ($n = 343$) concluded that there was insufficient evidence to determine whether feverfew was superior to placebo in reducing migraine frequency or incidence, severity of nausea or severity of migraines (Pittler & Ernst 2004). A closer look at the studies reveals that results were mixed, methodological quality varied and various dosage regimens, administration forms and extracts were used. One study used three different dosing regimens for a CO_2 extract, two studies used an alcoholic and CO_2 extract, three studies used dried feverfew leaves for 8–24 weeks and one study used an alcoholic extract for 8 weeks. Interpretation of test results is made even more difficult when one considers the naturally occurring chemical variations among the preparations.

The authors have offered several explanations for the inconsistent clinical findings and point out that previous negative studies used extracts standardised for parthenolide concentration; however, it is possible that other compounds found in whole-leaf preparations may also be important for pharmacological activity. In vivo studies support this view (Mittra et al 2000). Additionally, the negative results obtained by some studies may be due to under-dosing.

Since then, positive results were obtained for a CO_2-extract of feverfew in a randomised, double-blind, placebo-controlled, multicentre study of 170 patients (Diener et al 2005). Active treatment with feverfew (MIG-99) at a dose of 6.25 mg,



three times daily, significantly reduced the frequency of migraine headache episodes over a 16-week period.

ARTHRITIC CONDITIONS

Although traditionally used as a treatment for inflammatory joint conditions, the results of a randomised, double-blind study involving 41 patients with symptoms of RA found no difference between chopped dried feverfew (70–86 mg) or placebo after 6 weeks' treatment (Pattrick et al 1989).

OTHER USES

DERMATOLOGY

Parthenolide-free feverfew extract is being investigated in various dermatological conditions. One study found that the formulation protected skin against inflammation and UV-induced damage (Finkey et al 2005). When the pathenolide-free feverfew extract was topically applied, it significantly reduced the loss of cell viability, the increase in proinflammatory mediator release and the induction of DNA damage induced by solar simulated UV radiation in a human epidermal model. It also exhibited potent antioxidant activity in vitro. Other in vitro tests have revealed that parthenolide-free feverfew extract reduces inflammation through several mechanisms and is being investigated further as a novel non-steroidal extract for irritated skin (Martin et al 2005).

ONCOLOGY

In vitro tests suggest that parthenolide may have potential as a radiation sensitiser. According to the study, parthenolide inhibits NF-kappa-B activity, slows cell growth, and synergistically enhances cell killing after moderate doses of radiation (Mendonca et al 2003).

TRADITIONAL USE

Feverfew has been used traditionally to treat coughs and colds, fevers, atonic dyspepsia, worm infestation, menstrual disorders, nervous debility, joint pain and headaches.

DOSAGE RANGE

- Dried leaf: 50 mg to 200 mg daily
- Fresh plant tincture (1:1): 0.7–2.0 mL/day.
- Dried plant tincture (1:5): 1–3 mL/day.
- Prevention of migraine headaches (based on clinical studies): 125–250 mg/day of powder, standardised to contain a minimum parthenolide content of 0.2%, or

400 μg, which should be taken for at least 4 months. It is still controversial as to whether standardised extracts are best for migraine prophylaxis or not.

TOXICITY
Unknown, although no major safety issues have been identified (Ernst & Pittler 2000).

ADVERSE REACTIONS
According to a Cochrane systematic review of five studies (Pittler & Ernst 2004), feverfew is well tolerated and adverse events are generally mild and reversible. Symptoms were most frequently reported by long-term users and were predominantly mouth ulceration and gastrointestinal symptoms. Contact dermatitis, mouth soreness and lip swelling has also been reported when leaves are chewed.

SIGNIFICANT INTERACTIONS
Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

ANTICOAGULANTS
Theoretically, feverfew may increase bruising and bleeding; however, although feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in a clinical study (Biggs et al 1982) — observe patients taking this combination.

ANTIPLATELET DRUGS
Theoretically, feverfew may increase bruising and bleeding; however, contradictory evidence exists — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS
Hypersensitivity to plants in the Asteraceae (Compositae) (daisy) family (e.g. chamomile, ragweed).

PREGNANCY USE
Contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING
- Although early studies were positive and showed a preventative effect for migraine headache, not all studies have been positive, which may be related to variations in preparations and dosing. Further research is required to determine its place in practice for this indication.
- Of the studies that have produced positive results for migraine therapy, feverfew reduced severity of symptoms such as vomiting and visual disturbances, but did not alter the duration of an episode.

- Tincture or solid-dose preparations may be better tolerated than chewing the fresh leaves, which have been associated with mouth ulcers and lip swelling in some individuals.
- Traditionally, feverfew has also been used to treat coughs and colds, fevers, atonic dyspepsia, worm infestation, menstrual disorders, nervous debility, joint pain and headaches.
- Use is contraindicated in pregnancy.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

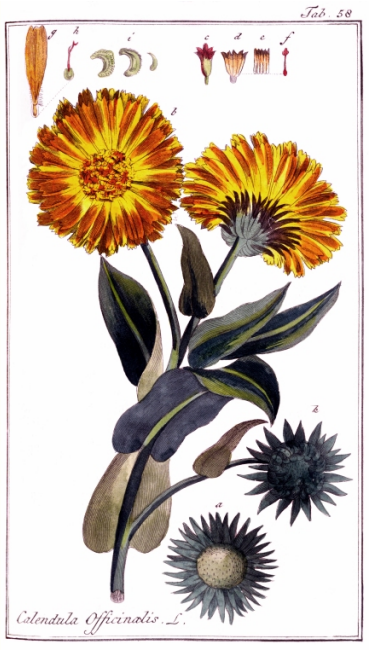
Some evidence suggests that feverfew may reduce the frequency and severity of migraine headaches; however, test results are inconsistent.

When will it start to work?

Of those studies producing positive results, it appears that approximately 4 months' continual use may be required; however, in practice, some patients experience benefits within the first 4 weeks.

Are there any safety issues?

Feverfew should not be used in pregnancy. It may increase tendency to bruising and bleeding in patients taking warfarin.



REFERENCES

Barsby RW et al. Feverfew extracts and parthenolide irreversibly inhibit vascular responses of the rabbit aorta. J Pharm Pharmacol 44.9 (1992): 737-40.

Barsby RW, Knight DW, McFadzean I. A chloroform extract of the herb feverfew blocks voltage-dependent potassium currents recorded from single smooth muscle cells. J Pharm Pharmacol 45.7 (1993a): 641-5.

Barsby RW et al. Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. Planta Med 59.1 (1993b): 20-5.

Biggs MJ et al. Platelet aggregation in patients using feverfew for migraine. Lancet 2.8301 (1982): 776.

Brown AM et al. Pharmacological activity of feverfew (Tanacetum parthenium (L.) Schultz-Bip.): assessment by inhibition of human polymorphonuclear leukocyte chemiluminescence in-vitro. J Pharm Pharmacol 49.5 (1997): 558-61.

Capasso F. The effect of an aqueous extract of Tanacetum parthenium L. on arachidonic acid metabolism by rat peritoneal leucocytes. J Pharm Pharmacol 38.1 (1986): 71-2.

Collier HO et al. Extract of feverfew inhibits prostaglandin biosynthesis. Lancet 2.8200 (1980): 922-3.

Cutlan AR et al. Intra-specific variability of feverfew: correlations between parthenolide, morphological traits and seed origin. Planta Med. 66.7 (2000): 612-17.

Diener HC et al. Efficacy and safety of 6.25 mg t.i.d. feverfew CO_2-extract (MIG-99) in migraine prevention: a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia 25(11) (2005): 1031-41.

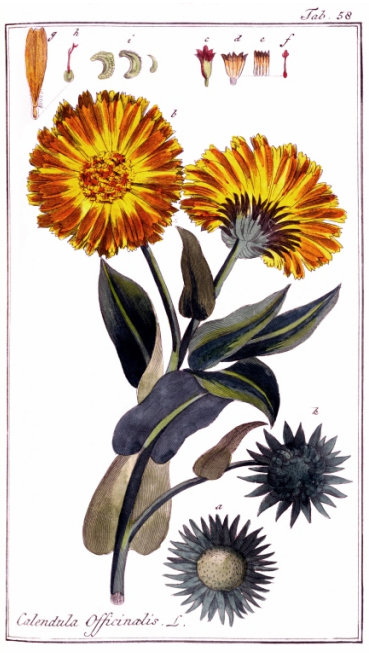
Ernst E, Pittler MH. The efficacy and safety of feverfew (Tanacetum parthenium L.): an update of a systematic review. Public Health Nutr 3.4A (2000): 509-14.

Ferrari MD. Migraine. Lancet 351.9108 (1998): 1043-51.

Finkey MB et al. Parthenolide-free feverfew extract protects the skin against UV damage and inflammation. J Am Acad Dermatol 52.3 (2005): 93.

Groenewegen WA, Heptinstall S. A comparison of the effects of an extract of feverfew and parthenolide, a component of feverfew, on human platelet activity in-vitro. J Pharm Pharmacol 42.8 (1990): 553-7.
Hayes NA, Foreman JC. The activity of compounds extracted from feverfew on histamine release from rat mast cells. J Pharm Pharmacol 39.6 (1987): 466-70.
Heptinstall S. Feverfew: an ancient remedy for modern times? J R Soc Med 81.7 (1988): 373-4.
Heptinstall S et al. Inhibition of platelet behaviour by feverfew: a mechanism of action involving sulphydryl groups. Folia Haematol Int Mag Klin Morphol Blutforsch 115.4 (1988): 447-9.
Jain NK, Kulkarni SK. Antinociceptive and anti-inflammatory effects of Tanacetum parthenium L. extract in mice and rats. J Ethnopharmacol 68.1-3 (1999): 251-9.
Johnson ES et al. Efficacy of feverfew as prophylactic treatment of migraine. BMJ (Clin Res Ed) 291.6495 (1985): 569-73.
Kwok BH et al. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IkappaB kinase. Chem Biol 8.8 (2001): 759-66.
Makheja AN, Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew (Tanacetum parthenium). Prostaglandins Leukot Med 8.6 (1982): 653-60.
Marles RJ et al. A bioassay for inhibition of serotonin release from bovine platelets. J Nat Prod 55.8 (1992): 1044-56.
Martin K et al. Pathenolide-free feverfew: an extract with effective anti-irritant activity in vitro. J Am Acad Dermatol 52.3 (2005): 93.
Mendonca MS et al. Inhibition of constitutive NF[kappa]B activity by the anti-inflammatory sesquiterpene, parthenolide slows cell growth and increases radiation sensitivity. Int J Radiat Oncol Biol Physics 57.2 (Suppl 1) (2003): S354.
Mittra S, Datta A, Singh SK, Singh A. 5-hydroxytryptamine-inhibiting property of feverfew: role of parthenolide content. Acta Pharmacol Sin; 21(12) (2000): 1106-14.
Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. Lancet 2.8604 (1988): 189-92.
Pattrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. Ann Rheum Dis 48.7 (1989): 547-9.
Pittler M, Ernst E. Feverfew for preventing migraine. Cochrane Database Syst Rev 1 (2004): CD 002286.
Pugh WJ, Sambo K. Prostaglandin synthetase inhibitors in feverfew. J Pharm Pharmacol 40.10 (1988): 743-5.
Silberstein SD. Migraine. Lancet 363.9406 (2004): 381-91.
Smolinski AT, Pestka JJ. Modulation of lipopolysaccharide-induced proinflammatory cytokine production in vitro and in vivo by the herbal constituents apigenin (chamomile), ginsenoside Rb1 (ginseng) and parthenolide (feverfew). Food Chem Toxicol 41.10 (2003): 1381-90.
Tournier H et al. Effect of the chloroform extract of Tanacetum vulgare and one of its active principles, parthenolide, on experimental gastric ulcer in rats. J Pharm Pharmacol 51.2 (1999): 215-19.
Weber JT et al. Rabbit cerebral cortex 5HT1a receptors. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 117.1 (1997a): 19-24.
Weber JT et al. Activity of Parthenolide at 5HT2A receptors. J Nat Prod 60.6 (1997b): 651-3.
Wong HR, Menendez IY. Sesquiterpene lactones inhibit inducible nitric oxide synthase gene expression in cultured rat aortic smooth muscle cells. Biochem Biophys Res Commun 262.2 (1999): 375-80.

Fish oils



BACKGROUND AND RELEVANT PHARMACOKINETICS

One of the two fats identified as being essential for humans to consume is alpha-linolenic acid (ALA or 18:3n-3) which, due to the position of its first double bond, is classified as an omega-3 essential fatty acid (n-3 EFA). Although mammals have the ability to introduce double bonds into most positions of the fatty acid chain in fat metabolism, therefore creating a variety of unsaturated metabolites, they lack the capacity to insert double bonds at the n-3 and n-6 position. Consequently, linoleic acid (LA) and alpha-linolenic acid (ALA), which already have the double bond at the n-3 or n-6 position, respectively, are considered essential and must be consumed in the diet. When the EFAs are consumed in this precursor state they follow a pathway of further elongation and desaturation via the action of delta-6- and delta-5-desaturase until they form the 'active' fatty acids: eicosapentaenoic acid (20:5 n-3) (EPA) and docosahexaenoic acid (DHA) (22:6 n-3).

Fish oils, also known as marine oils, are rapidly absorbed from the gastrointestinal tract and compete with arachidonic acid (AA) for incorporation into phospholipids, particularly of platelets, erythrocytes, neutrophils, monocytes and liver cells (Simopoulos 1999). When stimulated, the cell membranes release polyunsaturated fatty acids (PUFAs), which are then converted into 20-carbon eicosanoids, which have important and extensive physiological effects. The most active of these metabolites are prostaglandins, prostacyclins and thromboxanes, which affect blood chemistry, muscle contraction, immune function and inflammation. Dietary fats not used in this way are stored in adipose tissue and ultimately oxidised to produce energy. The FA cell membrane profile of different tissues will have varying ratios of EPA and DHA, but generally DHA is considered the major component of phospholipids in the retina, brain, male reproductive tissue, and myocardium (Groff & Gropper 2004).

Supplements based on fish liver oils, such as cod and halibut, contain EPA and DHA together with high levels of vitamins A and D. As such, they have additional actions and safety issues besides those found with traditional marine lipid supplements. This review will focus on the research surrounding those fish oils that are not liver extractions.

CHEMICAL COMPONENTS

Dietary fish contains a number of nutrients important for health, such as several types of vitamin B, vitamin E, calcium, magnesium and potassium and are an excellent

source of protein with a low saturated fat content. Importantly, they also contain the two PUFAs: EPA and DHA. EPA has 20 carbon atoms and 5 double bonds, and DHA has 22 carbon atoms and 6 double bonds. Both are derived from ALA and are considered conditionally essential.

FOOD SOURCES

Most dietary EPA and DHA are consumed in the form of fish or seafood. Deep sea cold water fish, such as salmon, mackerel, halibut and herring, provide the most concentrated sources. Current Australian estimates of intake indicate inadequate consumption according to WHO standards (Meyer et al 2003).

Clinical note — Are ALA-rich oils a worthy substitute for fish oils?
Both EPA and DHA are derived from ALA, so food sources containing ALA are seen as indirect dietary sources. ALA is commonly found in non-hydrogenated canola oil, linseed oil, soyabean oil, flaxseed, pumpkin and walnuts. Studies investigating the effects of ALA supplementation have not consistently produced the same positive results as for fish oils, most likely due to inefficient conversion of ALA into EPA and DHA. This is reportedly poor in healthy individuals, with only 5–10% of ALA converted to EPA and 2–5% of ALA converted to DHA (Davis & Kris-Etherton 2003). Consequently, the few foods that contain both EPA and DHA in their preformed state offer a significant advantage over other sources. The most concentrated dietary source of both EPA and DHA is fish oil.

DEFICIENCY SIGNS AND SYMPTOMS

Based on epidemiological studies the low levels of n-3 PUFAs are associated with:

- fetal alcohol syndrome (DHA) (Horrocks & Yeo 1999)
- attention deficit hyperactivity disorder (DHA) (Horrocks & Yeo 1999)
- learning deficits (DHA) (Horrocks & Yeo 1999)
- cystic fibrosis (DHA) (Horrocks & Yeo 1999)
- phenylketonuria (DHA) (Horrocks & Yeo 1999)
- cardiovascular disease including an increased risk of sudden death due to heart disease (Siscovick et al 2003).
- inflammatory disorders
- rheumatoid arthritis (Navarro et al 2000)
- unipolar depression (DHA) (Horrocks & Yeo 1999)
- senile dementia.

In addition to these symptoms, lack of dietary EFAs has been implicated in the development or aggravation of numerous diseases such as breast cancer, prostate

cancer, RA, asthma, pre-eclampsia, depression and schizophrenia (Yehuda et al 2005).

PRIMARY DEFICIENCY

Full-term babies fed a skim-milk formula low in ALA are at risk of primary deficiency. In the past, patients fed long-term with fat-free TPN solutions were at risk, but fat emulsions are now in general use and prevent deficiency. Studies have demonstrated lower plasma levels of EPA and DHA in vegetarians and vegans, suggesting they may be at risk of deficiency; however, the findings of a recent cross-sectional study comparing the dietary intakes and plasma levels of 196 meat-eating, 231 vegetarian, and 232 vegan men in the United Kingdom did not suggest there is cause for alarm (Rosell et al 2005). Vegans and vegetarians had significantly lower levels of these fatty acids; however, they remained steady and there is evidence of some conversion of ALA into EPA and DHA.

There is much discussion regarding the inadequate intake of EPA and DHA generally in the Western diet. Recent Australian data, based on dietary intake records from the 1995 National Nutrition Survey, have estimated the average daily intake at 0.008 g EPA and 0.015 g DHA. If correct, this indicates that the majority of Australians are failing to meet recommended amounts (Meyer et al 2003).

SECONDARY DEFICIENCY

People with fat malabsorption syndromes, serious trauma or burns are at risk of reduced PUFA levels (Beers et al 2003). A secondary deficiency may also manifest as a result of abnormal or compromised activity of the delta-6 and delta-5 desaturase enzymes, such as in diabetics and patients with a variety of metabolic disorders and those individuals with increased dietary saturated fats, *trans* fatty acids, alcohol, and the elderly (Davis & Kris-Etherton 2003, Houston 2005).

MAIN ACTIONS

As precursors of eicosanoids, PUFAs found in fish oils exert a wide influence over many important physiological processes.

CARDIOVASCULAR EFFECTS

Fish oils exert myriad different effects on the heart and vessels, which have been demonstrated in both experimental models and human studies. It is suspected that the summation of many small protective risk factor effects of omega-3 fatty acids adds up to a larger protective effect on mortality and/or cardiovascular events.

Prevent malignant cardiac arrhythmias Dietary fish or fish oil intake has been shown to prevent cardiac arrhythmias and associated sudden death in numerous animal studies (Billman et al 1999, 1997, Kang & Leaf 1996, 2000, McLennan et al

1988, 1990). This has been achieved using intakes below those required to alter plasma lipids or blood pressure. It appears that the myocardial membrane phospholipid content of DHA increases with fish intake, but not always EPA. The preferential accumulation of DHA affords protection against ventricular fibrillation induced under a variety of conditions such as ischaemia and reperfusion (McLennan 2001).

Inadequate DHA in myocyte membranes have been reported to be associated with altered sodium, calcium and potassium ion channel functions, mitochondrial function and increased arrhythmia susceptibility with an increased prevalence of sudden cardiac death (Siscovick et al 2003). One in vivo study suggests fish oils electrically stabilise myocytes, increasing the electrical impulse required to produce an action potential by approximately 50% and prolonging the refractory time by 150% (Kang & Leaf 2000).

Triglyceride-lowering activity Human studies have revealed the potent ability of EPA and DHA to reduce circulating levels of blood triglyceride levels significantly, which is of interest because only moderate elevations in triglyceride levels have been associated with a progressively increased risk of ischaemic heart disease, independent of other major risk factors including HDL-cholesterol (Jeppesen et al 1998).

Lipoprotein effects Concerns raised previously about increased levels of the long-chain PUFAs in lipoproteins increasing the susceptibility to oxidation of the LDLs have recently been moderated, with a demonstrable difference between EPA and DHA on this outcome. While increased levels of EPA (4.8 g/day) did increase the LDL susceptibility to damage, DHA supplementation (4.9 g/day) had no effect on the oxidation process (Mesa et al 2004).

Improved endothelial function Studies have indicated that fish oils can improve endothelial relaxation by enhancing NO- and non-NO-induced vasodilatation (Holub 2002).

A double-blind study conducted by Mori et al (2000) showed that relative to placebo, DHA, but not EPA, enhances vasodilator mechanisms and attenuates constrictor responses in the forearm microcirculation.

Reduce blood pressure Two meta-analyses have concluded that fish oils exert a significant blood pressure-lowering effect in hypertensive people; however, the effects can only be described as modest, between 2 and 5 mmHg (Geleijnse et al 2002, Morris et al 1993). Hypotensive activity appears to be dose-dependent and DHA may have greater effect than EPA. Alternately, a 2006 Cochrane review found no significant changes to SBP or DBP with n-3 EFA consumption (Hooper et al 2006). The

review assessed studies that used both plant-and fish-based n-3 fatty acids, dietary sources and supplements.

The mechanism responsible is unknown; however, current theories include EPA stimulation of prostacyclin synthesis and increased NO production, both vasodilators. An additional action may be improved autonomic nervous system function, and inhibition of the adrenal activation (Din et al 2004, Ross 2005). Of the n-3 EFAs, hypotensive activity is attributed to DHA.

Reduce and possibly reverse atherogenesis Omega-3 fatty acids alter eicosanoid synthesis and inhibit smooth muscle cell proliferation, suggesting a role in reducing atherosclerotic development (Holub 2002). One controlled study demonstrated that fish oil ingestion had a clinically significant influence on atherosclerosis (von Schacky et al 2001). This randomised double-blind study of 223 patients found that a dose of 1.5 g n-3 fatty acids reduced progression and increased regression of established coronary artery disease as assessed by coronary angiography.

ANTITHROMBOTIC AND ANTIPLATELET

Dietary omega-3 EFAs produce a state of enhanced anti-aggregatory and anti-adhesive platelet activity. This is achieved by inducing increased production of the platelet-anti-aggregatory substance prostacyclin I_3 and suppressing synthesis of the chemotactic platelet adhesion-promoting substance leukotriene B4 (Kinsella 1987). In animal models of arterial thrombosis, fish-oil-enriched diets have been shown to have an antithrombotic effect; however, there is evidence suggesting that this is most likely to occur when associated with reduced saturated fat intake (Hornstra 1989).

Clinical observations of Eskimos have found lowered platelet counts, inhibition of platelet aggregation and prolonged bleeding times compared with age- and sex-matched Danes. However, intervention studies using fish oil supplements have produced conflicting results (Hellsten et al 1993, Kristensen et al 1989, Radack et al 1990) and overall no significant effect is consistently seen at doses below 10 g.

ANTI-INFLAMMATORY

Fish oils induce a series of chemical changes in the body that ultimately produce an anti-inflammatory effect. They partially replace AA in inflammatory cell membranes, and compete with it for the enzymes cyclo-oxygenase (COX) and lipoxygenase (LOX), leading to reduced production of pro-inflammatory metabolites such as 2-series PGs and 4-series leukotrienes (Calder 2002, 2003, Cleland et al 2003).

Besides this, fish oils suppress the production of pro-inflammatory cytokines, according to both animal and human studies and reduce the expression of cell

adhesion molecules, which are critical in recruiting circulating leucocytes to the vascular endothelium (Calder 2002, Din et al 2004).

According to new research, it appears that anti-inflammatory activity may vary among different sources of fish oils due to variations in EPA/DHA content (Bhattacharya et al 2006).

NEUROLOGICAL EFFECTS

Fatty acids are major components of the brain and are found in high concentrations in two structural components: the neuronal membrane and the myelin sheath. About 50% of the neuronal membrane is composed of fatty acids (1/3 from the omega-3 family), while in the myelin sheath lipids constitute about 70% (Yehuda et al 2005). The lipid component has a relatively high turnover, in contrast to the protein component, which is especially stable.

Essential fatty acids play an active role in neuronal membrane function and fluidity and the control of neuronal growth factors. Essential fatty acids also potentially influence each step in biogenic amine function, including neurotransmitter synthesis, degradation, release, reuptake and binding (Bruinsma & Taren 2000). Studies indicate that dietary PUFAs may influence noradrenergic and serotonergic neurotransmission and receptor function in the nervous system and, thereby, have a direct effect on function, mood and behaviour. Other actions at the neuronal cell membrane includes suppression of the phosphatidyl-associated signal transduction pathways, blocking of the calcium ion influx through L-calcium channels and direct inhibition of protein kinase C, which are similar actions to those exhibited by pharmaceutical mood stabilisers.

Prenatal and postnatal neurological development DHA plays an important, if not critical, role in the growth and functional development of the brain during the third trimester and the early postnatal period when maximal growth occurs (Horrocks & Yeo 1999). Given that 15% of brain growth occurs during infancy, much attention has been paid to the consequences of variable omega-3 levels during late pregnancy and early infancy. It also plays an important role in retinal development, where DHA constitutes 60% of total PUFAs.

CHEMOPREVENTATIVE EFFECTS

Marine fatty acids, particularly EPA and DHA, have been consistently shown to inhibit the proliferation of breast and prostate cancer cell lines in vitro and to reduce the risk and progression of these tumours in animal experiments (Bagga et al 2002, Terry et al 2003). Similar effects have also been observed for colorectal and prostate cancers (Calder et al 1998, Llor et al 2003, Stoll 2002).

Chemopreventative actions demonstrated by n-3 EFAs include suppression of neoplastic transformation, cell growth inhibition and enhanced apoptosis, and anti-angiogenicity (Rose & Connolly 1999). The proposed mechanisms for these are extensive, including the suppression of n-6 eicosanoid synthesis; influences on transcription factor activity, gene expression, and signal transduction pathways; effects on oestrogen metabolism; increased or decreased production of free radicals and reactive oxygen species, and influences on both insulin sensitivity and membrane fluidity (Larsson et al 2004). Ongoing research is attempting to elucidate the specific chemopreventative mechanisms of fish oils with the individual cancer cell lines.

CLINICAL USE

Hundreds of randomised studies have been conducted in various populations to determine the clinical consequences of eating fish regularly or taking fish oil supplements. Some studies have focused on n-3 fatty acids intake as a whole and included vegetable sources together with marine-based sources. As with many reviews, inconsistent results are often seen. Sometimes this may be explained because the oils used as placebo are not necessarily inert, such as olive oil (Pizzorno & Murray 2006). It is important to note that few studies or reviews have considered the effect of variations in EPA/DHA, the ratio of n-3 FA:n-6 FA or the possible adverse effects relating to heavy metal contamination of fish sources.

PREVENTION OF MORBIDITY AND MORTALITY OF CARDIOVASCULAR DISEASE

For over 25 years, fish and fish oils have been linked to cardiovascular health. This association was first recognised when significantly lower death rates from acute myocardial infarction (MI) were found among Greenland's Inuit population, despite only moderate differences between the Inuits' blood cholesterol levels and those of other populations (Holub 2002). A high dietary omega-3 fatty acid intake in the form of marine mammals (seal, whale) and various fish were thought responsible for the protective effect (Bang et al 1980). In 1989, results from the first large, randomised, clinical trial investigating the effects of fatty fish consumption on survival and risk of secondary MI confirmed a link to cardiovascular health (Burr et al 1989). The DART (Diet and Reinfarction study) found a modest intake of 2–3 portions weekly of fatty fish reduced mortality in men who had previously experienced a MI and produced a relative reduction in total mortality of 29% during the 2-year follow-up, attributed mainly to a reduction in deaths from coronary heart disease (CHD). Increased consumption of fish (RR = 0.66 for 5 or more times per week) was further confirmed in the Nurses Study as significantly reducing risk in both CHD and CHD mortality independent of the cardiovascular status (Hu et al 2002).

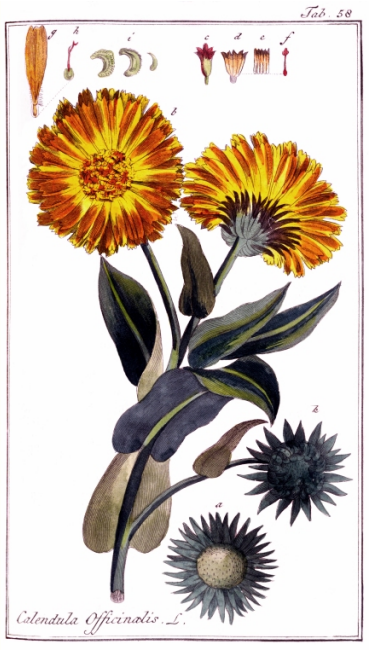
Various intervention studies have also been conducted to investigate whether similar or superior effects could be obtained with concentrated fish oil supplements. The largest of these is known as the GISSI trial, which involved 11,324 survivors of MI, and showed that a low-dose fish oil supplement significantly reduced the risk of all-cause death, non-fatal MI, and non-fatal stroke (Stone 2000). This study was re-analysed and subsequently published again in 2002 (Marchioli et al 2002). This time it specifically showed the reduction in risk of sudden cardiac death was nearly significant at 3 months, accounting for 67% of the overall mortality benefit, became significant at 4 months, and was highly significant at 3.5 years, the end of the study, when it accounted for 59% of the n-3 PUFA advantage in mortality. The reduction observed in all-cause mortality and in cardiovascular mortality resulted mainly from the prevention of sudden cardiac death by the n-3 fatty acids.

Meta-analyses In 2002, a high-quality systematic review of 11 RCT on the effect of fish-based dietary or supplemental omega-3 fatty acids on cardiovascular morbidity and mortality in people with CHD found a strongly significant benefit (Bucher et al 2002); however, a 2006 Cochrane review came to a different conclusion (Hooper et al 2006). The review assessed 48 studies that compared at least 6 months of omega-3 fats (vegetable- and fish-based) with placebo or control and used data involving 36 913 participants. Meta-analysis of the studies assessing the effects of increased omega-3 fats on total mortality or combined cardiovascular events found strongly significant statistical heterogeneity. When randomised studies considered to be at medium or high risk of bias were removed, there was no significant effect of omega-3 fats on total mortality; the relative risk was 0.87 (95% confidence interval 0.73 to 1.03, with significant heterogeneity) whereas the cohort studies suggested significant protection, the relative risk was 0.65 (95% confidence interval 0.48 to 0.88, no significant heterogeneity).

It is important to note that until the publication of the DART-2 trial in 2003 (Burr et al 2003), the evidence showed that omega-3 from oily fish or supplements reduced the risks of fatal MI, sudden death, and overall mortality among people with existing disease. Inclusion of the DART-2 trial in the Cochrane review had a major influence on the conclusion, as removing it produced relative risks similar to those in the Bucher review (fatal MI: RR 0.70, 95% confidence interval 0.54 to 0.91; sudden death: RR 0.68, 95% confidence interval 0.42 to 1.10; overall mortality: RR 0.83 (95% confidence interval 0.75 to 0.91). The DART-2 trial included 3114 men with stable angina and tested the hypothesis that the main benefit of omega-3 fat is derived from its anti-arrhythmic action in the presence of chronic disease. Surprisingly, it did not confirm this, showing an excess of sudden and total cardiac deaths most clearly in

participants taking fish oil capsules rather than eating oily fish. Authors of the Cochrane review report that something about the DART-2 study is different from the other included studies; however, further investigation has failed to clarify the issue.

It is possible that, based on this latest review, the effect of omega-3 fats on CVD is smaller than previously thought or that effects in people who have had a MI are protective of death, but the effects in men with angina and no MI are not.



Clinical note — The n-3:n-6 fatty acid balance: implications in cardiovascular disease and cancer

In recent years, attention has been drawn to the importance of not only n-3 fatty acid intake but also its relation to concurrent n-6 fatty acid intake. When there is increased n-3 PUFA in the diet and in our bodies, a shift in AA metabolism occurs, which results in the production of metabolites that have beneficial effects on cardiovascular physiology and cancer incidence and promotion (Leaf 2002). For example, when EPA is available to compete with AA, production of thromboxane A2 (a potent vasoconstrictor and platelet activator) is reduced and production of thromboxane B3 results, which is only weakly active. Additionally, several forms of research implicate n-6 PUFAs as stimulating processes that promote human cancer development and progression, whereas n-3 PUFAs have the opposite effect (Weisburger 1997). Once again, competition with AA is thought to be involved, although several other protective mechanisms have also been identified. Overall, it seems that in order to obtain maximal cardiovascular and chemopreventative benefits, intake of n-3 PUFAs should be increased and intake of n-6 PUFAs must be reduced.

It has been estimated that the ratio of n-6 to n-3 essential fatty acids in the Western diet is some 15:1 to 20:1 or higher, whereas the optimal ratio appears to be closer to 2:1 or 1:1 (Leaf 2002, Simopoulos 1999).

ELEVATED TRIGLYCERIDE LEVELS

DHA and EPA supplementation significantly reduces triglyceride levels and is used as sole therapy in cases of elevation or as adjunctive therapy with cholesterol-lowering medication when indicated. According to Din et al, omega-3 fatty acids reduce triglyceride concentrations in a dose-dependent manner, with intakes of about 4 g/day lowering serum triglycerides by 25–30% (Din et al 2004).

Overall, it appears that the smallest amount of omega-3 PUFA needed to lower serum triglyceride levels significantly is approximately 1 g/day, as provided by a fish diet, or as little as 0.21 g EPA and 0.12 g DHA/day for those with hyperlipidaemia (Weber & Raederstorff 2000).

HYPERTENSION

According to two meta-analyses fish oils have a significant but modest effect dose-dependent, on blood pressure in hypertension (Geleijnse et al 2002, Morris et al 1993). The DHA component is likely to have stronger effects than EPA. In contrast, a 2006 Cochrane review found no significant changes to SBP or DBP with n-3 EFA consumption of vegetable or fish origin (Hooper et al 2006).

The first meta-analysis was of 31 placebo-controlled trials involving 1356 subjects and detected a statistically significant dose–response effect on blood pressure when studies were grouped by omega-3 fatty acid dose: –1.3/–0.7 mmHg at doses ≤3 g/day, –2.9/–1.6 mmHg at 3.3–7 g/day, and –8.1/–5.8 mmHg at 15 g/day (Morris et al 1993). The hypotensive effect was strongest in hypertensive subjects and those with clinically evident atherosclerotic disease or hypercholesterolaemia, whereas no effect was detected in healthy subjects.

The 2002 meta-regression analysis considered the results from 36 trials, of which 22 had a double-blind design, to determine whether fish oil had a significant effect on blood pressure (Geleijnse et al 2002). Fish oil intake (median dose: 3.7 g/day) was found to reduce SBP by 2.1 mmHg and DBP by 1.6 mmHg when all trials were considered. When restricted to double-blind studies only, effects were not as large, but still apparent. Overall, the effects of fish oil on blood pressure tended to be greater in older people (>45 years) and in hypertensive populations (BP ≥140/90 mmHg).

In contrast, the 2006 Cochrane review discussed at length in the previous section failed to detect a significant hypotensive effect for n-3 fatty acids of vegetable or fish origin (Hooper et al 2006).

Would you like methylmercury with that?

There has been increasing public awareness and concern regarding mercury exposure due to the consumption of fish in the diet. This has been partly in response to the health warnings issued by Food Standards Australia and New Zealand (FSANZ) in March 2004 regarding maximal intake of select species of fish during pregnancy and childhood (Bambrick & Kjellstrom 2004). Interestingly, while the main public concern relates to neurodevelopmental toxicity, emerging data shows a relationship between increasing methylmercury (MeHg) exposure and cardiovascular disease, in particular MI (Stern 2005). Mechanisms postulated for this effect include the known oxidative stress and reactive oxygen species observed with in vitro exposures to MeHg, as well as impaired calcium homeostasis and kidney function.

MeHg concentrations in fish and shellfish species, which represent 80–90% of the mercury present, range from <0.1 ppm for shellfish, such as oysters and

mussels, to multiple parts per million in large predatory fish such as tuna, marlin, swordfish and shark. Consequently, MeHg intake depends on the species of fish consumed, as well as the quantity of fish eaten. Previous American data determined that adults consumed an average of 18 μg MeHg/day, with 80–90% coming from fish and shellfish (Mahaffey et al 2004).

In contrast to the beliefs of many, it is the organic form of mercury, which is a natural geological product and not an industry byproduct, that is toxic to human beings. Inorganic mercury is readily excreted in the urine whereas MeHg accumulates in erythrocytes across a wide range of exposures (Mahaffey et al 2004). Multiple international studies have assessed levels of MeHg exposure to reveal that approximately 10% of the samples have high blood levels. American studies have identified populations who appear to be at greater risk, among them a subpopulation consuming a substantial amount of fish in pursuit of health benefits. Blood MeHg analysis revealed blood mercury levels up to 90 μg/L (Hightower & Moore 2003). This is of concern because levels >5 μg/L have been reported as potentially detrimental in women of childbearing age.

Some researchers propose that the potentially cardiotoxic effects of MeHg is countered by the presence of the omega-3 oils also found within fish, and interestingly there is some overlap between those species with the highest concentrations of both (Bambrick & Kjellstrom 2004). However, there is also concern that the converse is true and MeHg could counteract the health-giving benefits of fish.

While there remains little doubt that the discriminating inclusion of fish is an important and healthy part of the diet, more research is required to better weigh up the risks and benefits of dietary fish. In contrast to the concerns of some consumers, fish oil supplements are not a major source of mercury and as such there is no need to restrict their intake (FSANZ 2004).

NEUROLOGICAL EFFECTS

There is evidence that alterations to n-3 fatty acid metabolism and the composition of the phospholipids in serum and membranes are involved in the pathogenesis of some neurological disorders (Ulbricht & Basch 2006). As a result, there has been much interest in understanding the effects of supplemental n-3 fatty acids in neurological development, cognitive function, depression, schizophrenia, and behavioural problems.

Cognitive function Low serum DHA level is considered a significant risk factor for the development of Alzheimer's dementia (Conquer et al 2000). Additionally, both

DHA and total n-3 fatty acid levels are significantly lower in cognitively impaired but non-demented people and people with other dementias. One of the first interventional studies was a small RCT of 4.3 g/day DHA in 20 elderly nursing home residents, assessing the efficacy of fish oil in the treatment of vascular dementia. DHA supplementation resulted in a small improvement in dementia rating scores within 3 months of treatment (Terano et al 1994).

The results from numerous animal studies, demonstrating neuroprotection from the n-3 EFAs and some slowing of neurodegeneration, appear promising (Hashimoto et al 2005, Mucke & Pitas 2004); however, more clinical trials are required to confirm these positive findings.

Alzheimer's dementia A 2003 prospective study conducted with a random sample of 815 older volunteers (aged 65–94 years) who initially were unaffected by Alzheimer's dementia (AD) found that consumption of fish once weekly was associated with a 60% reduced risk of developing the disease compared with those who rarely or never ate fish, after adjustment for age and other risk factors (Morris et al 2003). A review of the evidence prepared for the US Department of Health and Human Services in 2005 concluded that there is a significant correlation between fish consumption and reduced incidence of AD. Total n-3 EFA and DHA consumption correlated with this risk reduction; however, ALA and EPA did not (Maclean et al 2005). A recent Cochrane review came to a similar conclusion and reported that there is a growing body of evidence from biological, observational and epidemiological studies to suggest a protective effect of omega-3 PUFAs against dementia; however, further research is required before firm conclusions can be made (Lim et al 2006).

Pregnancy, breast feeding and infants Despite numerous studies demonstrating a positive relationship in mothers and infants consuming greater amounts of EFAs on subsequent cognitive development and IQ of their offspring (Cohen et al 2005, Helland et al 2003, Williams et al 2001), the findings of the Evidence Report/Technology Assessment prepared for the Agency of Healthcare Research and Quality US Department of Health and Human Services concludes that based on the small number of current well-designed studies there is no conclusive evidence of any benefit Lauritzen et al 2001 (Moher 2005). It makes the observation that studies observing a positive relationship between omega-3 oils and cognition are those which assessed children under 1 year of age, whereas studies of older children did not maintain a significant statistical relationship.

According to the WHO and FAO the pregnant woman should take at least 2.6 g of n-3 EFAs, incorporating 100–300 mg of DHA, daily to look after the needs of the fetus (Bambrick & Kjellstrom 2004). Postnatal deficiencies have been associated with

reduced visual acuity, poor neurodevelopment and ill effects on behaviour. Breast-fed infants generally receive sufficient DHA if the maternal diet is adequate, but it is not known whether formula-fed infants receive adequate amounts if their formula does not contain PUFAs.

Depression The balance between n-6 and n-3 fatty acids influences the metabolism of biogenic amines, an interaction that may be relevant to changes in mood and behaviour (Bruinsma & Taren 2000). In several observational studies, low concentrations of n 3 PUFAs predicted impulsive behaviours and greater severity of depression. Additionally early research by Horrobin et al (1999) revealed that almost all studies on depression have found increased PG_2 series or related thromboxanes and there is evidence that the older antidepressants (i.e. MAOIs and TCAs) either inhibit PFG synthesis or are powerful antagonists of their actions. Going one step further are the findings of a number of studies showing a correlation between low erythrocyte n-3 EFAs and suicide attempts; one of these demonstrated an eightfold difference in suicide attempt risk between the lowest and highest RBC EPA level quartiles (Huan et al 2004). Researchers from Belgium have also speculated about a seasonal variation in EFA status that correlates with seasonal patterns of suicide (De Vriese et al 2004); however, studies on larger populations of depressed people are required to confirm this link.

In spite of a plethora of epidemiological data correlating n-3 status with a range of depressive disorders, including major depression, postpartum depression and seasonal affective disorder, there are very few interventional studies. One conducted in 2005 involved 77 patients with depression who were randomly assigned to receive either 8 g/day of DHA-enriched (1.23%) fish oil or olive oil, in addition to existing medication, over 12 weeks. Interestingly, the fish oil group did not show significant improvement over the olive oil group, but both groups improved in mood over baseline. This was significant at 2 weeks and remained so throughout the study (Silvers et al 2005).

In response to a lack of demonstrated benefit, the authors of this trial note that previous successful interventions have predominantly used purified fish oil preparations, particularly ethyl-EPA, and therefore variable make-up of standard fish oil preparations may explain the inconsistency of results. Adding to the riddle is a question over optimal dosage and whether olive oil was in fact an inert placebo devoid of activity (2002).

A randomised study was conducted of 28 children aged between 6 and 12 years who were diagnosed as having depression according to the Children's Depression Rating Scale (CDRS), Children's Depression Inventory (CDI), and Clinical Global

Impression (CGI) (Nemets et al 2006). After 1 month of treatment, omega-3 fatty acid supplementation was shown to have highly significant effects on symptoms using the above three scales.

Aggressive behaviour The DHA component of fish oils has been used to reduce aggressive behaviour in children and adolescents. One placebo-controlled study of 42 college students showed that DHA supplementation (1.5–1.8 g/day) prevented an increase in aggression toward others at times of mental stress (Hamazaki et al 1996); however, another placebo-controlled trial found that DHA supplementation had no effect on aggressive behaviour under non-stressful conditions (Hamazaki et al 1998).

Attention-deficit hyperactivity disorder It has been reported that many children with ADHD have EFA deficiency (mainly n-3 FA) with a high correlation between severity of symptoms and severity of deficiency (Yehuda et al 2005). Deficiency may be due to insufficient dietary intake or inefficient conversion of EFA to longer chain fatty acids. Several studies have investigated the effects of supplemental fatty acids to children with ADHD with mixed results; however, interpretation of findings is difficult because of the use of different treatments, measurements and subject selection (Richardson & Puri 2000).

Schizophrenia According to a 2003 review, four out of five placebo-controlled double-blind trials of EPA in the treatment of schizophrenia have produced positive results (Peet 2003).

CANCER

It is well established that dietary fat has an influence on human cancer development and progression. Several forms of research implicate n-6 PUFAs as stimulators of these reactions, whereas n-3 PUFAs have the opposite effect and have been shown to inhibit development and progression (Leitzmann et al 2004, Weisburger 1997). Therefore, it is the ratio of n-3 to n-6 PUFAs intake that appears to be an important factor influencing cancer incidence and progression.

This observation is supported by both animal and epidemiologic studies. The largest to date involved 24 European countries and identified a significant inverse correlation with fish and fish oil consumption, when expressed as a proportion of total or animal fat, for both male and female colorectal cancer and for female breast cancer (Caygill et al 1996). Importantly, the protective effects were only detected in countries with a high animal fat intake, suggesting that fish oil protects against the promotional effects of animal fat in carcinogenesis.

Breast and prostate cancer A 2003 review has found that overall the evidence remains unclear as to whether dietary fish or fish oil consumption exerts a protective effect against the development of breast and prostate cancers (Terry et al 2003). The

assessment of EPA and DHA intake and their relation to n-6 fatty acid intake and cancer incidence still requires further examination before conclusions can be confidently made. An updated review conducted by the same researchers in 2004 (Terry et al 2004) also reached a similar conclusion; however, they also observed that those studies that assess omega-3 intake concomitant with the omega-6 consumption were most likely to yield a statistically significant inverse relationship between fish oils and breast and prostate cancers. Once again this reinforces the understanding that the fats due to interrelated metabolism and actions should not be viewed independently.

A prospective cohort study in the USA of 47 866 men aged 40–75 years with no cancer history were assessed using a 131-item semiquantitative food-frequency questionnaire administered annually over 14 years, as part of the Health Professionals Follow-Up study. Nutrient intake data from this trial suggests an association between ALA and advanced prostate cancer, but an inverse relationship with the ALA metabolites, EPA and DHA. Earlier studies investigating the relationship between ALA and prostate cancer have had mixed results while the inverse relationship with EPA/DHA appears to be largely supported. Again the authors demonstrate that ratios of omega 3:6 appear to be highly influential in conveyed risk (Leitzmann 2004).

Colorectal cancer Both EPA and DHA and their main dietary source, fish oil, have been shown to exert antineoplastic effects in colorectal cancer (Llor et al 2003). Fish oil supplementation, in one study, providing 4.1 g EPA and 3.6 g DHA per day in patients with sporadic adenomatous colorectal polyps was reported to reduce the percentage of cells in the S-phase in the upper crypt of the rectal mucosa (Anti et al 1992). The evidence to date as reviewed in 2004 by Roynette et al suggests a primary preventative effect but some residual ambiguity over the safety of n-3 PUFAs with respect to secondary tumour formation.

DIABETES

Increasing the intake of n-3 FAs has been shown to be both preventative in a healthy population and beneficial in people with diabetes (Montori et al 2000, Nettleton & Katz 2004, Sirtori and Galli 2002, Sirtori et al 1997). Although there have been random reports of improved glucose control with fish oil supplementation, a review published in 2004 cites two large meta-analyses of trials with n-3 long-chain PUFAs or fish oil in subjects with diabetes, which confirmed no adverse or positive effect on glucose control or impact on glycated haemoglobin.

A meta-analysis of 18 trials found that fish oil supplementation lowers plasma triglyceride levels in type 2 diabetic subjects; however, a possible rise in plasma LDL-cholesterol may occur (Montori et al 2000). Additionally, no significant effect occurs

on glycaemic control, total cholesterol or HDL-cholesterol. In addition to this, more recent studies reveal an average of 7.4% increase in HDL levels concomitant with a 25% reduction in tryglycerides in response to 203 g of EPA/DHA supplementation over 6 months (Sirtori et al 1998). Such findings are supported by the results of other trials in the diabetic population (Nettleton & Katz 2005).

WEIGHT REDUCTION

To date there is only limited evidence that n-3 EFAs may be associated with reduced incidence of obesity, ease of weight loss, and maintenance of body weight in this population (Nettelton & Katz 2004).

INFLAMMATORY DISEASES

Numerous clinical trials have investigated the effects of fish oil supplementation in several inflammatory and autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, lupus erythematosus and migraine headaches (Belluzzi 2002, Belluzzi et al 1996, Miura et al 1998, Simopoulos 2002). Although not all trials have produced positive results, many of the placebo-controlled trials reveal significant benefit in chronic disease, including decreased disease activity and sometimes, reduced requirement for anti-inflammatory medicines (Adam et al 2003).

Rheumatoid arthritis Of the inflammatory diseases, the use of fish oil supplementation is most widely seen in RA. According to multiple randomised, controlled studies, fish oil supplements have been consistently shown to reduce symptoms in RA, such as the number of tender joints on physical examination and the amount of morning stiffness (Adam et al 2003, Cleland et al 2003, Kremer 2000, Ulbricht & Basch 2006, Volker et al 2000). Generally, supplements are taken daily as adjuncts to standard therapy with clinical effects appearing after 12 weeks. A dose ranging from 30 mg to 40 mg/kg of EPA and DHA daily has been used successfully, although some studies have found a minimum of 3 g/day is required.

Results from a double-blind crossover study suggest that the beneficial effects obtained from fish oil capsules is further enhanced when combined with an anti-inflammatory diet providing less than 90 mg/day of AA (Adam et al 2003).

Although the anti-inflammatory activity of fish oil supplementation is thought to be chiefly responsible for symptom relieving effects, there is also evidence that n-3 fatty acids can modulate the expression and activity of degradation factors that cause cartilage destruction (Curtis et al 2000).

In spite of these positive findings, an evidence report conducted for the US Department of Health and Human Services in 2004 concludes that, upon meta-analysis of the trials to date, there is little evidence of statistically significant relief of

either objective or subjective features of RA, including swollen joint count and erythrocyte sedimentation rate, with the use of fish oils (MacLean et al 2004). While the studies incorporated met the strict methodological inclusion criteria of the review committee, it is important to note that the studies selected are all of reasonably small sample size and were conducted in the early 1990s, with more recent evidence failing to be incorporated.

A 2005 randomised study published after the above report was released has found that fish oil supplements (3 g/day), whether taken alone or in combination with olive oil (9.6 mL) produced a statistically significant improvement ($P < 0.05$) compared to placebo on several clinical parameters in RA (Berbert et al 2005). Significant improvements were observed for joint pain intensity, right and left handgrip strength after 12 and 24 weeks, duration of morning stiffness, onset of fatigue, Ritchie's articular index for pain joints after 24 weeks, ability to bend down to pick up clothing from the floor, and getting in and out of a car after 24 weeks. The group using a combination of oils showed additional improvements with respect to duration of morning stiffness after 12 weeks, patient global assessment after 12 and 24 weeks, ability to turn taps on and off after 24 weeks, and rheumatoid factor after 24 weeks. In addition, this group showed a significant improvement in patient global assessment compared with fish oils alone after 12 weeks.

Based on these results, it appears that while fish oils will not improve all parameters of RA, overall they have demonstrated symptomatic relief in the majority and result in significantly reduced use of anti-inflammatory and corticosteroid use, a fact MacLean et al (2004) acknowledges and which is confirmed by a 2005 review by Stamp et al. There appears to be little evidence of sustained improvements following cessation of the supplements.

A large prospective cohort study ($n = 57,053$) investigating the association between dietary factors and risk of RA found that each increase in intake of 30 g fatty fish (≥8 g fat/100 g fish) per day was associated with 49% reduction in the risk of RA ($P = 0.06$); however, a medium intake of fatty fish (3–7 g fat/100 g fish) was associated with significantly increased risk of RA (Pedersen et al 2005). No associations were found between risk of RA and intake of a range of other dietary factors, including long-chain fatty acids, olive oil, vitamins A, E, C and D, zinc, selenium, iron, and meat. The authors caution that due to the limited number of patients who developed RA during follow up, it is not yet possible to make firm conclusions.

ASTHMA

Because n-3 PUFAs exhibit anti-inflammatory activity and epidemiological evidence has demonstrated a correlation between fish intake and a decreased risk of asthma and improved lung function, they have been used in the management of asthma (Wong 2005). Recent evidence suggests this protective effect may extend back as far as adequate fetal n-3 EFA exposure and a reduced incidence of asthma in the offspring (Salam et al 2005).

A 2002 Cochrane review of nine RCT conducted between 1986 and 2001 concluded that there was no consistent effect on any of the analysable outcomes: forced expiratory volume in 1 second, peak flow rate, asthma symptoms, asthma medication use or bronchial hyperreactivity (Woods et al 2002). One of the RCTs, conducted with children, showed that when fish oil supplementation was combined with dietary changes, positive results were obtained, as evidenced by improved peak flow and reduced asthma medication use.

Since then, a number of positive studies have been published. The equivocal nature of the results in asthma trials, as documented by a review in the *Journal of the American Dietetic Association* (Wong 2005) may be clarified in future with the identification of a subtype of asthma more likely to respond to EFA manipulation. Interestingly in recent years the attention has moved away from investigating atopic asthma towards other populations such as athletes.

One randomised, double-blind, crossover study of 16 non-atopic asthmatic patients with documented exercise-induced broncoconstriction (EIB) compared the effects of 3.2 g of EPA and 2.0 g DHA per day and placebo capsules for 3 weeks. During treatment with fish oils, subjects demonstrated improved pulmonary function to below the diagnostic EIB threshold, which was associated with a concurrent reduction in bronchodilator use. Measurement of leukotriene B(4) and B(5) levels also confirmed a significant reversal of the inflammatory picture (Mickleborough et al 2006).

DERMATITIS

Atopic dermatitis A double-blind multicentre study involving 145 patients with moderate to severe atopic dermatitis showed that n-3 fatty acids (6 g/day) improved clinical symptom scores by 30% after 4 months' treatment (Soyland et al 1994). The results were confirmed by the total subjective clinical score reported by the patients. An earlier, 12-week, prospective double-blind study produced similar results with a dose of 10 g/day (fish oil) improving overall severity of atopic dermatitis and reducing scaling (Bjorneboe et al 1989).

OTHER USES

Fish oil supplements are also used in the management of acute respiratory distress syndrome, psoriasis, multiple sclerosis, osteoporosis and dysmenorrhoea, and in children with dyslexia.

DOSAGE RANGE

- Fish should be considered part of a healthy diet for everybody and be consumed at least twice a week. Care should be taken to avoid intake of fish known or suspected to contain higher levels of mercury.
- Additional administration of n-3 PUFA supplements should be considered in specific groups.
- Fish meals should consist of deep sea oily fish, whereas fried or processed fish containing partially hydrogenated fats and salted or pickled fish should be avoided.

CARDIOVASCULAR DISEASE

Secondary prevention trials after MI indicate that consumption of 0.5–1.8 g/day of EPA and DHA from fish or fish oil supplements may be beneficial. Intake of marine-derived omega-3 fatty acids can be increased through diet or with fish oil supplements.

- An expert US panel of nutrition scientists has recommended an intake of 0.65 g/day whereas the British Nutrition Foundation's recommendation is 1.2 g/day (Din et al 2004).
- National Heart Foundation/Cardiac Society of Australia and New Zealand: >2 serves/week.
- Patients who have experienced coronary artery bypass surgery with venous grafts: 4 g/day of n-3 PUFA.
- Moderate hypertension: 4 g/day of fish oils.
- Elevated triglyceride levels: 1–4.6 g/day of fish oils.

OTHER CONDITIONS

- Aggression induced by mental stress: DHA supplementation, 1.5–1.8 g/day.
- Atopic dermatitis: 6 g/day fish oils.
- Colorectal cancer: 4.1 g EPA + 3.6 g DHA daily
- Dementia: DHA supplementation, 4.32 g/day.
- Exercise-induced asthma in non-atopic individuals: 3.2 g EPA + 2.0 g DHA daily
- Pregnancy: According to the WHO and FAO the pregnant woman should take at least 2.6 g of n-3 EFAs, incorporating 100–300 mg of DHA daily to look after the needs of the fetus.
- Rheumatoid arthritis: 30–40 mg/kg body weight of EPA and DHA daily.

ADVERSE REACTIONS

Fish oil supplementation is generally safe and well tolerated. The few side-effects reported are usually mild and can include gastrointestinal discomfort and loose bowels, halitosis, and a fishy odour of the skin and urine.

SIGNIFICANT INTERACTIONS

ANTIPLATELET AGENTS

Theoretically, concomitant use with antiplatelet agents may increase the risk of bleeding; however, one study has suggested that the combined effects may be beneficial (Engstrom et al 2001) — observe patients taking this combination.

ANTICOAGULANTS

Bleeding time is increased at very high doses of 12 g/day according to one clinical study Doses <12 g should be used with caution and very high doses >12 g avoided unless under medical supervision.

NSAIDS

Additional anti-inflammatory effects are theoretically possible with concurrent use of fish oil supplements, suggesting a beneficial interaction. Drug dosage may require modification.

PRAVASTATIN

Low-dose pravastatin combined with fish oil supplementation is more effective than pravastatin alone for changing the lipid profile after renal transplantation, according to one clinical study — potential beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

One area of concern is the growing problem of heavy metal contamination found in fish, specifically mercury. In areas where contamination is possible, fish oil supplements may represent a safer option. According to the *Australia New Zealand Food Standards Code* fish with higher levels of mercury include: swordfish, southern bluefin tuna, barramundi, ling, orange roughy, rays and shark. Fish considered to have lower levels of mercury include: mackerel, silver warehou, atlantic salmon, canned salmon and canned tuna in oil, herrings and sardines.

People with bleeding disorders should take fish oil supplements under medical supervision. Suspend use of high dose supplements (>10 g) 1 week before major surgery.

PREGNANCY USE

Fish oils appear to be safe during pregnancy at dietary doses.

PRACTICE POINTS/PATIENT COUNSELLING

- As precursors of eicosanoids, polyunsaturated fatty acids found in fish oils exert a wide influence over many important physiological processes.
- They have demonstrated anti-inflammatory, immunological, neurological, antiplatelet and chemopreventative effects, and a range of beneficial actions within the cardiovascular system.
- Daily ingestion of at least 1 g EPA and DHA (equivalent to fish eaten at least twice weekly) may result in a reduction in total mortality, cardiovascular mortality and morbidity.
- Trials generally support the use of supplements in a range of inflammatory and autoimmune diseases, such as rheumatoid arthritis and atopic dermatitis, elevated triglycerides, hypertension and other cardiovascular conditions, poor cognitive function and diabetes. Preliminary research suggests a possible role in depression.
- People with bleeding disorders should take fish oil supplements under medical supervision and high doses should be avoided 1 week prior to major surgery.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Regular consumption of fish oils may reduce total mortality, cardiovascular mortality, and morbidity. Additionally, beneficial effects have been demonstrated in a wide variety of conditions.

When will it start to work?

This will depend on the dosage taken and indication for use.

Are there any safety issues?

People with bleeding disorders or taking blood thinning drugs should take fish oil supplements under medical supervision. High-dose fish oil supplements should be avoided prior to major surgery to avoid risk of excessive bleeding.

REFERENCES

Adam O et al. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. Rheumatol Int 23.1 (2003): 27-36.

Anti M et al. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. Gastroenterology 103 (1992): 883-91.

Bagga D et al. Long-chain n-3 to n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer. Nutr Cancer 42.2 (2002): 180-5.

Bambrick HJ, Kjellstrom TE. Good for your heart but bad for your baby? Revised guidelines for fish consumption in pregnancy. Med J Aust 181.2 (2004): 61-2.

Bang HO et al. The composition of the Eskimo food in north western Greenland. Am J Clin Nutr 33.12 (1980): 2657-61.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Rahway, NJ: Merck and Co. Inc., 2003.

Belluzzi A. N-3 fatty acids for the treatment of inflammatory bowel diseases. Proc Nutr Soc 61.3 (2002): 391-5.

Belluzzi A et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 334.24 (1996): 1557-60.
Berbert AA et al. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 21.2 (2005): 131-6.
Bhattacharya A et al. Different ratios of eicosapentaenoic and docosahexaenoic omega-3 fatty acids in commercial fish oils differentially alter pro-inflammatory cytokines in peritoneal macrophages from C57BL/6 female mice. J Nutr Biochem (2006) [Epub ahead of print].
Billman GE et al. Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs. Lipids 32.11 (1997): 1161-8.
Billman GE et al. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. Circulation 99.18 (1999): 2452-57.
Bjorneboe A et al. Effect of n-3 fatty acid supplement to patients with atopic dermatitis. J Intern Med Suppl 225.731 (1989): 233-6.
Bruinsma KA, Taren DL. Dieting, essential fatty acid intake, and depression. Nutr Rev 58.4 (2000): 98-108.
Bucher HC et al. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med 112.4 (2002): 298-304.
Burr ML et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 2.8666 (1989): 757-61.
Burr ML et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr 57.2 (2003): 193-200.
Calder PC. Dietary modification of inflammation with lipids. Proc Nutr Soc 61.3 (2002): 345-58.
Calder PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids 38.4 (2003): 343-52.
Calder PC et al. Dietary fish oil suppresses human colon tumour growth in athymic mice. Clin Sci (Lond) 94.3 (1998): 303-11.
Caygill CP et al. Fat, fish, fish oil and cancer. Br J Cancer 74.1 (1996): 159-64.
Cleland LG et al. The role of fish oils in the treatment of rheumatoid arthritis. Drugs 63.9 (2003): 845-53.
Cohen JT et al. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. Am J Prev Med 29.4 (2005): 366.e1-e12.
Conquer JA et al. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 35.12 (2000): 1305-12.
Curtis CL et al. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. J Biol Chem 275.2 (2000): 721-4.
Davis BC, Kris-Etherton PM. Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications. Am J Clin Nutr 78.3 (2003): 640-6S.
De Vriese SR et al. In humans, the seasonal variation in poly-unsaturated fatty acids is related to the seasonal variation in violent suicide and serotonergic markers of violent suicide. Prostaglandins Leukot Essent Fatty Acids 71.1 (2004): 13-18.
Deck C, Radack K. Effects of modest doses of omega-3 fatty acids on lipids and lipoproteins in hypertriglyceridemic subjects. A randomized controlled trial. Arch Intern Med 149.8 (1989): 1857-62.
Din JN et al. Omega 3 fatty acids and cardiovascular disease: fishing for a natural treatment. BMJ 328 (2004): 30-5.
Engstrom K et al. Effect of low-dose aspirin in combination with stable fish oil on whole blood production of eicosanoids. Prostaglandins Leukot Essent Fatty Acids 64.6 (2001): 291-7.
Erkkila AT et al. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin Nutr 78.1 (2003): 65-71.
Food Standards Australia New Zealand (FSANZ). Available at: www.foodstandards.gov.au (accessed 18-03-04).
Geleijnse JM et al. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens 20.8 (2002): 1493-9.

Hamazaki T et al. The effect of docosahexaenoic acid on aggression in young adults: A placebo-controlled double-blind study. J Clin Invest 97.4 (1996): 1129-33.
Hamazaki T et al. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions: A randomized, placebo-controlled, double-blind study. Lipids 33.7 (1998): 663-7.
Hashimoto M et al. Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid beta-infused rats. J Nutr 135.3 (2005): 549-55.
Helland IB et al. Maternal supplementation with very-long chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 111.1 (2003): e39-44.
Hellsten G et al. Effects on fibrinolytic activity of corn oil and a fish oil preparation enriched with omega-3-polyunsaturated fatty acids in a long-term study. Curr Med Res Opin 13.3 (1993): 133-9.
Hightower JM, Moore D. Mercury levels in high-end consumers of fish. Environ Health Perspect 111 (2003): 604-8.
Holub BJ. Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care. Can Med Assoc J 166.5 (2002): 608-15.
Hooper L et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ 332.7544 (2006): 752-60.
Hornstra G. Influence of dietary fish oil on arterial thrombosis and atherosclerosis in animal models and in man. J Intern Med Suppl 225.731 (1989): 53-9.
Horrocks LA, Yeo YK. Health benefits of docosahexaenoic acid (DHA). Pharmacol Res 40.3 (1999): 211-25.
Houston MC. Nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. Progr Cardiovasc Dis 47.6 (2005): 396-449.
Hu FB et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 287 (2002): 1815-21.
Jeppesen J et al. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 97.11 (1998): 1029-36.
Kang JX, Leaf A. The cardiac antiarrhythmic effects of polyunsaturated fatty acid. Lipids 31 [Suppl] (1996): S41-4.
Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. Am J Clin Nutr 71.1 [Suppl] (2000): 202-7S.
Kinsella JE. Effects of polyunsaturated fatty acids on factors related to cardiovascular disease. Am J Cardiol 60.12 (1987): 23-32G.
Kremer JM. n-3 fatty acid supplements in rheumatoid arthritis. Am J Clin Nutr 71.1 [Suppl.] (2000): 349-51S.
Kristensen SD et al. Dietary supplementation with n-3 polyunsaturated fatty acids and human platelet function: a review with particular emphasis on implications for cardiovascular disease. J Intern Med [Suppl] 225.731 (1989): 141-50.
Larsson SC et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 79.6 (2004): 935-45.
Lauritzen L et al. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. Progr Lipid Res 40.1-2 (2001): 1-94.
Leaf A. On the reanalysis of the GISSI-Prevenzione. Circulation 105.16 (2002): 1874-5.
Leitzmann MF et al. Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80.1 (2004): 204-16.
Lemaitre RN et al. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 77.2 (2003): 319-25.
Lim WS et al. Omega 3 fatty acid for the prevention of dementia. Cochrane Database Syst Rev 1 (2006): CD005379.
Llor X et al. The effects of fish oil, olive oil, oleic acid and linoleic acid on colorectal neoplastic processes. Clin Nutr 22.1 (2003): 71-9.

MacLean CH et al. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evid Rep Technol Assess (Summ) 89 (2004): 1-4.
Mahaffey KR et al. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environ Health Perspect 112.5 (2004): 562-70.
Marchioli R et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione Circulation 105 (2002): 1897-903.
McLennan PL. Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. Lipids 36 [Suppl] (2001): S111-14.
McLennan PL et al. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. Am Heart J 116.3 (1988): 709-17.
McLennan PL et al. Reversal of the arrhythmogenic effects of long-term saturated fatty acid intake by dietary n-3 and n-6 polyunsaturated fatty acids. Am J Clin Nutr 51.1 (1990): 53-8.
Meyer BJ et al. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. Lipids 38.4 (2003): 391-8.
Mickleborough TD et al. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. Chest 129.1 (2006): 39-49.
Miura S et al. Modulation of intestinal immune system by dietary fat intake: relevance to Crohn's disease. J Gastroenterol Hepatol 13.12 (1998): 1183-90.
Montori VM et al. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. Diabetes Care 23.9 (2000): 1407-15.
Mori TA et al. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. Circulation 102.11 (2000): 1264-9.
Morris MC et al. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 88.2 (1993): 523-33.
Morris MC et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 60.7 (2003): 940-6.
Mucke L, Pitas RE. Food for thought: essential fatty acid protects against neuronal deficits in transgenic mouse model of AD. Neuron 43.5 (2004): 596-9.
Navarro E et al. Abnormal fatty acid pattern in rheumatoid arthritis. A rationale for treatment with marine and botanical lipids. J Rheumatol 27.2 (2000): 298-303.
Nemets H et al. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. Am J Psychiatry 163.6 (2006): 1098-100.
Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: A review. J Am Diet Assoc 105.3 (2005): 428-40.
Pedersen M et al. Diet and risk of rheumatoid arthritis in a prospective cohort. J Rheumatol 32.7 (2005): 1249-52.
Peet M. Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. Prostaglandins Leukot Essent Fatty Acids 69.6 (2003): 477-85.
Pizzorno J, Murray M. Textbook of Natural Medicine. St Louis: Elsevier, 2006.
Radack K et al. The comparative effects of n-3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. J Am Coll Nutr 9.4 (1990): 352-7.
Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. Prostaglandins Leukot Essent Fatty Acids 63.1-2 (2000): 79-87.
Rose DP, Connolly JM. Omega-3 fatty acids as cancer chemopreventive agents. Pharmacol Ther 83.3 (1999): 217-44.
Rosell MS et al. Long-chain n-3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. Am J Clin Nutr 82.2 (2005): 327-34.
Ross CM. Fish oil, adrenal activation, and cardiovascular health [Letter]. Thromb Res 116.3 (2005): 273.

Salam MT et al. Maternal fish consumption during pregnancy and risk of early childhood asthma. J Asthma 42.6 (2005): 513-18.
Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr 70.3 [Suppl] (1999): 560-9S.
Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr 21.6 (2002): 495-505.
Sirtori CR, Galli C. N-3 fatty acids and diabetes. Biomed Pharmacother 56.8 (2002): 397-406.
Sirtori CR et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance: Italian Fish Oil Multicenter Study. Am J Clin Nutr 65.6 (1997): 1874-81.
Siscovick DS et al. The fish story: a diet-heart hypothesis with clinical implications: n-3 polyunsaturated fatty acids, myocardial vulnerability, and sudden death. Circulation 107.21 (2003): 2632-4.
Soyland E et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis: A double-blind, multicentre study. Br J Dermatol 130.6 (1994): 757-64.
Stark KD et al. Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial. Am J Clin Nutr 72.2 (2000): 389-94.
Stern AH. A review of the studies of the cardiovascular health effects of methylmercury with consideration of their suitability for risk assessment. Environ Res 98.1 (2005): 133-42.
Stoll BA. N-3 fatty acids and lipid peroxidation in breast cancer inhibition. Br J Nutr 87.3 (2002): 193-8.
Stone NJ. The Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardio (GISSI)-Prevenzione Trial on fish oil and vitamin E supplementation in myocardial infarction survivors. Curr Cardiol Rep 2.5 (2000): 445-51.
Terano T et al. Docosahexanoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular disease. Lipids 34 [Suppl] (1994): S345-6.
Terry PD et al. Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence. Am J Clin Nutr 77.3 (2003): 532-43.
Terry PD et al. Long-chain (n-3) fatty acid intake and risk of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. J Nutr 134 (2004): 3412-20S.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Volker D et al. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. J Rheumatol 27.10 (2000): 2343-6.
von Schacky C. The role of omega-3 fatty acids in cardiovascular disease. Curr Atheroscler Rep 5.2 (2003): 139-45.
von Schacky C et al. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. Lipids 36 [Suppl] (2001): S99-102.
Weber P, Raederstorff D. Triglyceride-lowering effect of omega-3 LC-polyunsaturated fatty acids: a review. Nutr Metab Cardiovasc Dis 10.1 (2000): 28-37.
Weisburger JH. Dietary fat and risk of chronic disease: mechanistic insights from experimental studies. J Am Diet Assoc 97.7 [Suppl] (1997): S16-23.
Williams C et al. Stereo acuity at age 3-5 years in children born full term is associated with pre-natal and post-natal dietary factors: a report from a population-based cohort study. Am J Clin Nutr 73 (2001): 316-22.
Wong KW. Clinical efficacy of n-3 fatty acid supplementation in patients with asthma. J Am Diet Assoc 105.1 (2005): 98-105.
Woods RK et al. Dietary marine fatty acids (fish oil) for asthma in adults and children. Cochrane Database Syst Rev 3 (2002): CD001283.
Yehuda S et al. Essential fatty acids and the brain: From infancy to aging. Neurobiol Aging 26.1 [Suppl 1] (2005): 98-102.

Flaxseed oil

Historical note For over 5000 years flaxseed in its various forms has been a part of the diet of people in Asia, Africa and Europe. It has a long history of use as both a food and a medicine, with the seed being most commonly used. The oil was also popular and has been a traditional food of the Egyptians from the time of the Pharaohs to the present day. The oil is also consumed by the Chinese, who documented its medicinal properties in the Pen-T's AO, the Great Chinese Pharmacopeia (Judd 1995). Its Latin name *usitatissimum* means 'most useful', suggesting its various uses have been recognised for centuries (Kolodziejczyk & Fedec 1995). Interestingly research into its nutritional properties and effects on human health were not studied in earnest until the 1980s (Cunane & Thompson 1995). In Australia in 1981, cultivation of a low alpha-linolenic acid variety, now known as Linola, was pioneered in an attempt to improve the stability of the oil and increase its commercial viability as a cooking oil. Such modifications were successful and resulted in ALA content $<3.0\%$ and a higher concentration of linoleic acid than the naturally occurring form (Bhatty 1995). These modified oils are not used for medicinal purposes.

OTHER NAMES

Flax oil and linseed oil.

Internationally it is accepted that 'flaxseed' refers to products for human consumption whereas 'linseed oil' refers to products that have been denatured, made unfit for human consumption, and used in commercial products, such as paints and varnishes.

BOTANICAL NAME/FAMILY

Linium usitatissimum (family Linaceae)

PLANT PART USED

Fixed oil is derived from the seeds of the plant. Due to the highly polyunsaturated nature of the oil (≈73%), extracts are obtained by cold-pressing rather than heat extraction. Flaxseed oil (FSO) is highly susceptible to photo-oxygenation, so it is packaged in opaque bottles. It is also susceptible to auto-oxidation, resulting in the production of hydroperoxides and aldehydes that can give a rancid flavour.

Encapsulated FSO is considered more stable, particularly when anti-oxidants are added (Kolodziejczyk & Fedec 1995).

CHEMICAL COMPONENTS

Flaxseed oil contains several types of fatty acids (FAs). It contains a high concentration of alpha-linolenic acid (ALA), ranging from 40% to 60%, and is the most concentrated plant source of omega-3 FA identified to date.

FSO also contains unsaturated FAs, such as linolenic, linolenic acid, linoleic acid and oleic acid. Linoleic acid (LA or C18:2n-6) and oleic acid each contribute 15% to the total FA content of the oil. Due to the range of FA present, it contains precursors for the omega-3, -6 and -9 families. FSO may also contain varying amounts of the lignan, secoisolariciresinol diglycoside (SDG), which is a precursor to enterodiol and enterolactone.

Flax seeds contain 41% fat, 28% dietary fibre, 21% protein and significantly higher amounts of lignans, which behave as phytoestrogens (Morris 2001).

However, this review focuses on FSO.

Clinical note — Is FSO equivalent to the fish oils?

Flaxseed oil has been commercially promoted as the vegetarian or vegan alternative to fish oils, with many of the health benefits ascribed to fish oils also being attributed to the oil. A review of the literature suggests that FSO is unlikely to be equipotent with fish oils in the treatment of a variety of conditions.

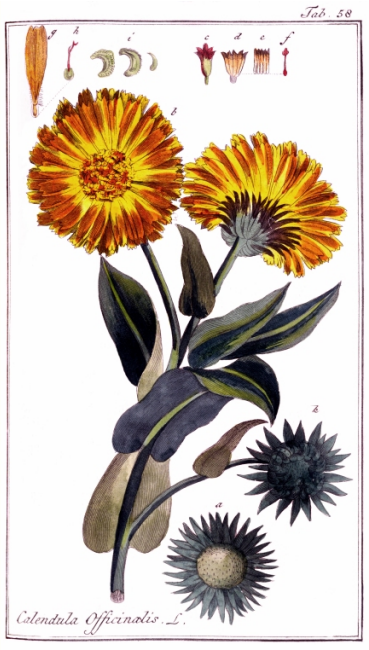
The ALA present in FSO can theoretically undergo desaturation and elongation to synthesise eicosapentanoic acid (EPA) and docosahexaenoic (DHA), which are found in fish oil; however, most studies using oral FSO intake demonstrate only moderate increases in EPA and DHA remains unchanged (Allman et al 1995, Kelley et al 1993, Mantzioris et al 1994, Nestel et al 1997). Although results from one early study suggest that increases in DHA levels may be achieved with long-term supplementation (Cunnane et al 1993), more recent studies fail to confirm this result (Harper et al 2006, Hussein et al 2005).

Conversion rates of ALA to EPA and docosapentaenoic acid (DPA) are reported to be $<10\%$ (Harris et al 1997) and approximately 8%, respectively, whereas the DHA yield ranges from 0% to 0.5%. One explanation for this is that DHA synthesis is under separate regulatory control, a hypothesis supported by enzymatic studies (Burdge 2004). This means a 20 mL serve of FSO, providing 11.1 g of ALA, would result in a maximum of 880 mg DPA and 5 mg of DHA.

Adding to this puzzle is a wide range of other variables that can inhibit the conversion of ALA into its metabolites. For instance, high dietary intake of linoleic

acid (LA), common in Western cultures, inhibits both the uptake of ALA and its conversion to long-chain metabolites. An interesting study conducted in 1998, which used radioactively labelled ALA, showed that a diet high in omega-6 fats reduced conversion by 40–50% (Gerster 1998). This adds weight to the argument that the ratios of FAs may have the primary influence on their resultant health benefits. The authors of this study suggest that the ratio of omega-6:omega-3 should not exceed 4.

Other studies have reported abnormal or compromised activity of the delta-6 and delta-5 desaturase enzymes in the elderly, diabetics and patients with a variety of metabolic disorders, as well as those individuals with increased dietary intake of saturated fats, *trans*-fatty acids and alcohol (David & Kris-Etherton 2003). Studies using radioisotopes of ALA have revealed significant gender differences in conversion capability, with women demonstrating higher levels of FA metabolites. It is believed this is due to their higher oestrogen levels, a theory supported by the increased conversion capacity evident in women taking synthetic oestrogens and speculated as representing a physiological adaptation that ensures adequate EFA delivery to the foetus in pregnancy (Burdge 2004).



MAIN ACTIONS

The main actions of FSO have been attributed to its high ALA content. ALA is subject to three different metabolic fates: (a) incorporation into structural, transport or storage pools, (b) beta-oxidation as an energy source and (c) elongation and further desaturation to form EPA, DPA and DHA. It appears that all three contribute to the biological effects of this oil.

ALA's direct role in cell membrane structure is likely to be minor, with ALA representing less than 0.5% of the total FA in cell membranes and blood lipids in healthy adults. However, its limited propensity to generate the n-3 metabolites, EPA and DHA, the major FAs in cell membranes, could represent an indirect effect via this mechanism (Burdge 2004).

Studies exploring the metabolism of ALA have revealed that 22% of ALA undergoes beta-oxidation in women and 33% in men. Once broken down the carbon chain can be used as fuel or in the synthesis of cholesterol and other fatty acids such as palmitic, palmitoleic, stearic and oleic acids de novo (Burdge 2004). FSO also influences the eicosanoid production cascade via conversion of the n-3 and n-6 parent FAs in FSO to their respective metabolites.

It is also thought that some of the actions of FSO may be independent of its FA content and can be attributed to the lignan SDG. This has been partly supported by research conducted by Prasad et al in 1998 and again in 1999.

ANTI-INFLAMMATORY

Metabolites of ALA and LA act as substrates for the formation of the anti-inflammatory eicosanoids, comprising prostaglandins, thromboxanes, and leukotrienes (Gerster 1998). ALA suppresses AA production by interfering with the conversion of LA to AA, and reduces the biosynthesis of inflammatory eicosanoids, although not to the same extent as EPA and DHA (Morris 2001). Cytokines, another important group of inflammatory mediators, are generated in response to these eicosanoids and are influenced by changes in the n-3:n-6 ratios in cell membranes (James et al 2000). In one study, ingestion of FSO (equivalent to 13.7 g/day ALA) for 4 weeks by healthy male subjects resulted in a 30% reduction in TNF-alpha, 31% reduction in IL-1-beta, 29% reduction in eicosanoids thromboxane B(2) and 30% reduction in PGE_2 (Caughey et al 1996).

In animal models ALA has consistently demonstrated eicosanoid-mediated anti-inflammatory effects; however, the extent of these has been dependent on the levels of both ALA and LA in the diet, duration of use and type of tissue studied (Cunnane & Thompson 1995).

IMMUNE EFFECTS

Evidence of ALA deficiency has been reported in patients on prolonged TPN, which resulted in reduced T-helper cells to below the normal range and impaired proliferation of peripheral blood mononuclear cells. Although supplementation with small doses of ALA corrected these abnormalities, the effect of ALA on human immune cells appears to be paradoxical, with evidence of immune function inhibition at higher doses (≥40 mL/day FSO) (Kelley 1995).

CARDIOVASCULAR EFFECTS

FSO and ALA have been studied as possible agents in the prevention or treatment of cardiovascular disease because ALA can be converted to long-chain (n-3) PUFA in humans and may potentially reproduce the beneficial effects of fish oils on risk factors. The numerous studies available have suggested that FSO and ALA exert a myriad of different mechanisms in the body, which can be beneficial in cardiovascular disease; however, inconsistent results have meant that much is still unknown and more research is required.

ANTITHROMBOTIC AND ANTIPLATELET ACTIVITY

The question of whether supplementation with ALA affects platelet aggregation remains unclear. A major determinant appears to be the degree of conversion to EPA (Garg et al 1989). When there is an increase in total EPA and reduced AA, due to ALA inhibition of LA conversion, the result is EPA replacing AA in the cell membrane and a decrease in thromboxane synthesis. In addition, SDG, another component of FSO, is metabolised to enterolactone and enterodiol and these substances may have antiplatelet-activating factor activity. Due to the variable lignan content of FSO it is difficult to determine the clinical significance of this (Prasad 1999). Studies assessing the actual anti-aggregatory effect of FSO in humans have produced mixed results.

REDUCED ENDOTHELIAL INFLAMMATION

A number of studies have confirmed that consumption of high-dose FSO reduces endothelium inflammation. One study assessing the cardiovascular effects of a diet in which 6.5% of total kilocalorie intake was contributed by ALA and compared with the Standard American Diet (SAD) showed that the ALA-enriched diet produced a 75% reduction in C-reactive protein, a 19% reduction in cellular adhesion molecule, and a 15.6% reduction in vascular cellular adhesion molecule (VCAM) (Zhao et al 2004). An earlier study had reported these findings, demonstrating a 28% reduction in VCAM with additional reductions in soluble E-selectin (17%) (Thies et al 2001).

LIPID-LOWERING

Whole flaxseed is the form most commonly investigated in lipid-lowering studies, because the high fibre content and ALA appear to act synergistically, whereas there are few studies using FSO. Those that have been conducted with FSO have produced conflicting results with an almost 50/50 weighting of research showing no effect or a positive one. At worst FSO has resulted in increases in fasting triacylglycerol concentrations and lower HDL-cholesterol (Bemelmans et al 2002, Finnegan et al 2003, Wilkinson et al 2005) and at best it has been described in earlier studies as having comparable effects with bio-equivalent doses of fish oils (Harris 1997, Singer et al 1986). The reality probably lies somewhere in between; however, further investigation is required. The results of the small study of 57 men by Wilkinson et al (2005), who substituted 45 g of fat per day with 15 g/day ALA derived from FSO over 12 weeks adds to the puzzle. While confirming the mixed cardiovascular effects noted above, this treatment group also demonstrated a reduction of total cholesterol by 12.3% in comparison to a reduction of 7.3% in the group receiving equivalent LA.

The same equivocal trend is evident from studies assessing the effects of FSO on lipoproteins. Zhao's trial (2004) using an ALA-enriched diet showed that this change resulted in a reduction in apololipoproteins A1 and B, the latter by almost 10%.

ANTI-ARRHYTHMIC

Three recent studies have identified an anti-arrhythmic effect mediated by ALA (Albert et al 2005, Ander et al 2004, Christensen et al 2005) although one meta-analysis concluded otherwise (Mathan et al 2005). Although the majority of research has been conducted in animals, one of the most interesting human trials involved 106 women with a mean age of 59.5 years referred for coronary angiography due to suspected coronary artery disease. Following adipose sampling for ALA levels and monitoring of 24-hour heart rate variability (HRV), it was concluded that a positive and independent association was present between ALA in adipose tissue and HRV, which was even stronger in smokers (Christensen et al 2005).

ANTI-ATHEROGENIC

Earlier positive findings and recent promising epidemiological data have been substantially challenged by RCTs of FSO in atherosclerosis. Following earlier positive outcomes in cardiovascular disease trials with whole flaxseed, a 1999 study showed that a low-ALA variety could produce comparable results with the earlier trials, suggesting that the anti-atherogenic properties of flaxseed are independent of its ALA content (Prasad 1999).

More recent large-scale epidemiological studies continue to suggest a relationship between higher ALA intake and reduced coronary artery calcification (Djousse et al 2005); however, there is ongoing criticism that important variables have not been sufficiently accounted for, such as corresponding reductions in *trans*-FAs (Harris 2005, Wilkinson et al 2005).

ANTIPROLIFERATIVE

ALA has demonstrated the capacity to inhibit tumour progression in animal models of mammary tumour (Chen et al 2002, Cognault et al 2000); however, the clinical significance of these findings needs to be examined further. An immunostimulant action, which is both eicosanoid and non-eicosanoid mediated, has been suggested as one possible mechanism of action. Another theory suggests that through ALA's competitive inhibition of LA, tumour cells may not receive sufficient LA, which would inhibit further cell growth (Johnston 1995). It is interesting to observe that higher dietary ALA intake is associated with a reduction in cancer deaths; however, this is not seen with higher EPA/DHA intakes, suggesting that the protective effect is not reliant on the conversion of ALA to EPA/DHA (Cunnane 1995). In addition, results from

epidemiological studies show an association between low ALA consumption in humans and increased cancer deaths in general (Dolecek 1992).

Animal studies testing SDG and its metabolites from the seeds have produced promising results and suggest that they may act as selective oestrogen receptor modulating agents and therefore play a protective role against oestrogen-dependent cancers (Kitts et al 1999, Wang et al 2005).

INSULIN SENSITISING

Preliminary animal studies suggest a protective role for ALA against the development of insulin resistance and an ability to counter the associated oxidative stress (Ghafoorunissa & Natarajan 2005, Suresh & Das 2003). Clinical trials are required to determine the significance of these findings.

CLINICAL USE

REDUCED MORTALITY IN CORONARY HEART DISEASE

The most likely mechanism by which ALA may prevent coronary heart disease (CHD) mortality is by reducing cardiac arrhythmia. In Western populations, almost 50% of all deaths from cardiovascular disease can be attributed to sudden cardiac death and the majority of sudden deaths are directly caused by acute ventricular arrhythmia (Brouwer et al 2004). A review in 2001 (Lanzmann-Petithory) and a meta-analysis of three studies in 2004 (Brouwer et al) both found in favour of a protective effect from increased ALA consumption against fatal CHD (RR 0.24). The dose associated with this trend was small; only 1–3 g/day ALA higher than controls (Brouwer et al 2004). A study published in 2005, which derived data from the Nurses' Health Study (Albert et al), found that women consuming ALA in the highest two quintiles had a 38–40% lower risk of sudden cardiac death than women in the lowest quintile; however, the protective effect did not extend to other fatal forms of CHD or non-fatal myocardial infarction.

Much criticism has been directed at those researchers wanting to extrapolate prescriptive advice from these findings. An editorial by Harris (2005) notes that only one primary prevention study with ALA in CHD has been conducted and that was in the 1960s. The 1-year trial involved 13,578 Norwegian men and compared 10 g of FSO (providing 5.5 g/day ALA) with a sunflower seed placebo. In the analysis there was no demonstrable difference in end-points between the two groups. Recent attempts to explain this lack of effect, such as high baseline n-3 consumption by this population, appear to be well founded (Mozaffarian et al 2005).

There is an urgent need for RCTs using FSO in suitable populations to clarify the relationship between ALA and CHD mortality.

ANTICLOTTING

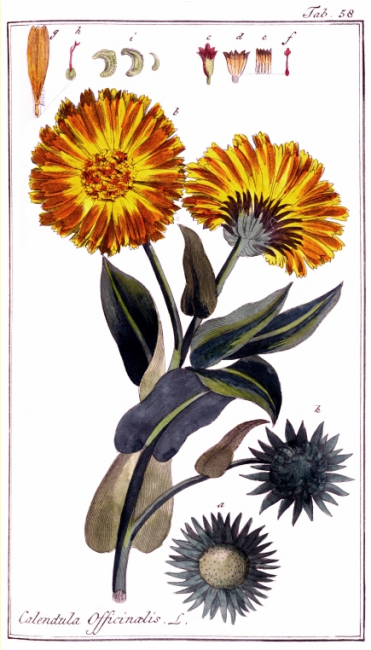
There has been a surprising number of studies investigating the influence of ALA from FSO on coagulation and fibrinolysis, and enormous variation in results. Methodological issues have plagued the overall quality of evidence, with small sample sizes, inconsistent methodologies and diverse sample characteristics making interpretation difficult.

One early study compared different dietary ratios of n-6 and n-3 EFAs in relation to prostanoid production in a group of normolipidaemic men (Kelley et al 1993). The high ALA dietary intervention constituted an overall n-6:n-3 ratio of 2.7 versus control ratios of up to 27.4. Following the 18 days of the intervention, groups showed significant differences in measured outcomes, notably, that 6-keto-$PGF_{1\text{-alpha}}$ was significantly higher following the high ALA diet but no evidence of significant effect on bleeding time or thromboxane B2 production. A second study published in the same year also failed to show an effect on clotting; however, the dose of FSO used was only 4.3 g/day (Kelley et al 1993). In contrast, the results of a study using a much larger dose of 40 g/day of FSO over 23 days in 11 healthy men showed that FSO significantly reduced collagen-induced aggregation response when compared to 40 g/day sunflower seed oil (Allman et al 1995).

A follow-up study of 29 healthy males that was conducted over 6 weeks investigated the effects of a diet in which approximately 7% of the total kilocalories from polyunsaturated fat was made up of either an ALA-rich (n-3:n-6 = 1:1.2) or LA-rich diet (n-3:n-6 = 1:21). The ALA-enriched diet resulted in triple the EPA phospholipid levels compared to the LA-enriched diet, but had no demonstrable effect on coagulation or fibrinolysis, other than an increase in the ratio of activated protein C. The authors speculated that the latter finding may still prove significant, but suggest that future studies should be conducted in patients with vascular pathology, as healthy clotting profiles may have obscured the true effects of FSO (Allman-Farinelli et al 1999).

In the same year another group of Australian researchers published the results of their study of 17 vegetarian men who were assigned to either a low- or high-ALA diet (derived from FSO) for 28 days following a run-in baseline diet for 14 days. Again there were no significant differences in prothrombin time, activated partial thromboplastin time, or plasminogen activities with the different ALA diets, despite increases in EPA and DPA levels (Li et al 1999).

Since 1994 Mutanen and Freese have conducted many studies assessing the effect of ALA and LA:ALA ratios on haemostatic factors (Freese & Mutanen 1997, Freese et al 1994, Mutanen & Freese 2001). Their 1997 study was the largest and involved a



sample of 46 subjects who were given FSO to provide 5.9 g/day ALA or a fish/sunflower oil combination equal to 5.2 g/day EPA/DHA over 4 weeks. Extensive analysis of the sample throughout the intervention, as well as at the 12-week follow-up, revealed no difference in collagen-induced platelet aggregation, thromboxane production or bleeding time between the two groups, suggesting equivalent anticoagulant effects for FSO and fish oil when consumed in comparable quantities This was despite smaller increases in EPA levels in the platelets of the subjects taking FSO.

The largest and most recent trial (Finnegan et al 2003) compared the effects of small increases in ALA (4.5 or 9.5 g/day) and EPA and DHA (0.8 or 1.7 g/day EPA+DHA) intake on blood coagulation and fibrinolytic factors over 6 months. The randomised, placebo-controlled, parallel study of 150 moderately hyperlipidaemic subjects found no significant differences in coagulation or fibrinolysis for any intervention.

Currently the evidence is equivocal, but may indicate a minor anti-aggregatory role for FSO in high doses. Further research, with more heterogeneous designs, is required to form any valid conclusion.

ENDOTHELIAL FUNCTION

In one 12-week study of healthy subjects aged 55–75 years, low levels of ALA (equivalent to approximately 5 mL/day of FSO) were shown to decrease some markers of endothelial activation (Thies et al 2001). More specifically, ALA decreased the plasma concentrations of soluble VCAM-1 by 16% and soluble E-selectin by 23%.

LIPID-LOWERING

The largest and most recent trial involved over 150 moderately hyperlipidaemic patients in a double-blind placebo-controlled 5-arm parallel design conducted over 6 months. Two groups received FSO at different doses (equivalent to 4.5 g/day and 9.5 g/day of ALA), two groups received bioequivalent levels of EPA/DHA and one group received LA and served as a control group. Although the higher ALA dose induced comparable changes in serum and cell membrane EPA levels to the fish oil group, ALA failed to significantly lower lipid levels, whereas EPA and DHA reduced triacylglycerides (Finnegan et al 2003).

Alternatively, a shorter study of only 2 weeks supplementing with much higher doses of FSO (60 mL/day) or sunflower oil or 130 g/day of mackerel in hypertensive males produced positive results. Subjects taking either FSO or consuming fish experienced an equal decrease in serum triglycerides, total cholesterol, and LDL-cholesterol (Singer et al 1986). Interestingly, FSO intake resulted in only marginal

increases in EPA levels, suggesting lipid-lowering activity is not reliant on conversion to EPA.

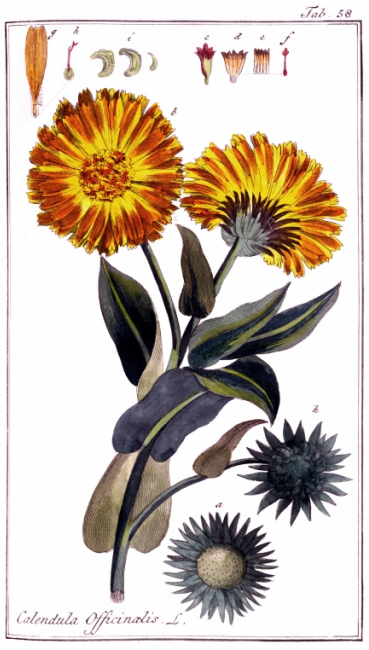
One possible explanation for this comes from the results of a number of trials conducted by Prasad (Prasad 1997, 1999, Prasad et al 1998), who investigated low-ALA FSO and later isolated extracts of the lignan SDG and found significant lipid-lowering effects in animal models. In rabbits, administration of the lignan at high doses produced significant changes to blood lipids, including a 33% reduction in total cholesterol, 35% reduction in LDL-cholesterol and an astonishing increase of over 140% in HDL-cholesterol by week 8 (Prasad 1999). As exciting as these results are, it is difficult to determine the clinical significance of these findings because the lignan content of FSO is variable. It is possible that the high dose of FSO (60 mL/day used by Singer 1986) contained a substantial amount of SDG, which could explain the effects seen; however, this is speculation.

Clinical Note — Are vegetarians at risk of omega-3 deficiency?

Omnivores can obtain n-3 long-chain PUFAs in two ways: from the partial conversion of dietary ALA or directly through the consumption of fish, eggs, or animal products (Li et al 1999). Lacto-ovovegetarians obtain n-3 EFAs from the conversion of plant-based ALA and a limited amount of preformed EPA and DHA from milk, dairy products, and eggs; however, their EFA content is highly dependent upon the animals' diet. In contrast, strict vegetarians and vegans are at risk of inadequate n-3 EFA, DHA and EPA intake because they are solely reliant on plant-based ALA, which has poor conversion to n-3 EFA metabolites in the body and they have no dietary intake of preformed DHA or EPA.

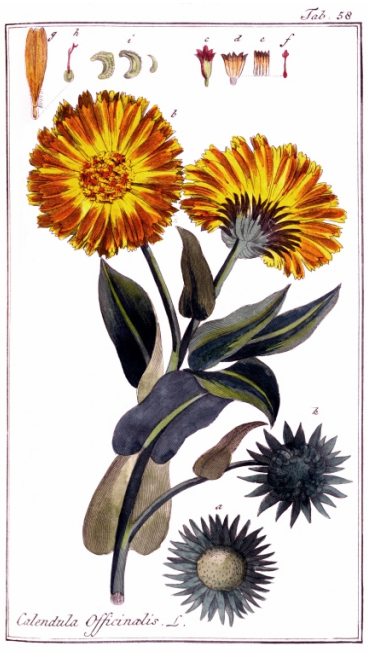
This has been demonstrated in studies in which lower plasma and platelet levels of n-3 EFAs have been identified in vegetarians compared with omnivores, together with lower EPA and DHA levels. For vegetarians and vegans, increased consumption and conversion of ALA has been proposed as a strategy to ensure omega-3 adequacy; however, the evidence to date suggests this is not effective (Burdge 2004, Phinney et al 1990).

Average daily intake of ALA has been estimated at 1.5 g in the general population and may be lower in vegetarians and vegans. Based on current conversion calculations, general consumption levels already fall short of EPA and DHA requirements. Studies investigating increased ALA consumption at 9.5 g/day, the equivalent of approximately 17 mL FSO, found this increased EPA and DPA, yet failed to improve DHA concentrations, which is further proof that ALA is not an effective substitute for animal-derived omega-3 EFAs (Burdge 2004).



To complicate matters, there is evidence suggesting that high intakes of ALA downregulate the delta-6-desaturase enzyme, therefore inhibiting its own conversion (Gerster 1998). Vegetarian diets are also notoriously rich in the n-6 EFA, LA, which if consumed in significantly higher quantities than omega-3 will further retard conversion of ALA (Kris-Etherton & Skulas 2005).

Vegans and vegetarians are recommended to consume additional sources of ALA, such as algae, that may contain some preformed EPA and DHA in an attempt to reduce risk of deficiency (Kris-Etherton & Skulas 2005, Li et al 1999).



INSULIN SENSITIVITY/METABOLIC SYNDROME

It has been proposed that FSO may be of benefit in insulin resistance (IR) based on its possible cardioprotective activities; however, direct evidence of improved insulin sensitivity remains elusive. One small study published in 1997 demonstrated improved systemic arterial compliance in 12 subjects with suspected IR, fed a high dose of ALA over 12 weeks, although an additional finding in this study was evidence of slight deterioration in insulin sensitivity (Nestel 1997). Another study using relatively low-dose FSO (1.7 g/day ALA) in normoglycaemic adults found no changes in glycaemic response (Curran et al 2002). Further investigation using higher doses of FSO and ALA is required to determine whether there is a role for FSO in this condition.

ANTICANCER EFFECTS

Breast and colon cancer Bougnoux et al (1994) made an important observation when they demonstrated an inverse relationship between ALA levels in breast tissue and risk of lymph node involvement and visceral metastases in breast cancer. This has been followed up with larger studies of similar design (Klein et al 2000, Maillard et al 2002) and one meta-analysis, all yielding comparable results (Saadatian-Elahi et al 2004). The data indicate that those women with the highest breast tissue concentrations of ALA have a relative risk of breast cancer between 0.36 and 0.39, while other FA levels fail to exhibit a statistically significant relationship. Interestingly, an epidemiological study has identified an association between low consumption of ALA in humans and increased cancer deaths in general (Dolecek 1992). Currently the only evidence from interventional studies using FSO as a chemoprotective agent is provided by animal trials, which demonstrate that dietary FSO is effective in preventing colon tumour development and malignant mammary tumours (Dwivedi et al 2005).

Prostate cancer There is much debate surrounding research into the hypothesised link between ALA and the risk of prostate cancer. Giovannucci, a prolific prostate cancer researcher, has contributed to numerous papers on this topic, deriving data

from large epidemiological or prospective cohort studies including The Health Professionals Follow-Up, The Physician's Health Study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Gann et al 1994, Giovannucci et al 1993, Leitzmann et al 2004, Mannisto et al 2003). The conclusions oscillate between a positive independent association between increased ALA intake and prostate cancer risk (Gann et al 1994, Giovannucci et al 1993, Leitzmann et al 2004) to no significant association (Mannisto et al 2003). Further support of ALA as a risk factor has come from a large Norwegian epidemiological study (Harvei et al 1997), a review by Astorg and a meta-analysis by Brouwer et al in 2004. Although the majority of published data appear to implicate ALA as a prostate cancer risk factor, it is worthy of note that none of the trials were interventional and many rely exclusively on food frequency questionnaires rather than independent biochemical indices of ALA. Other researchers have also presented sound arguments against this theory, such as those articulated by de Lorgeril and Salen (2004), which query the quality of evidence being considered, the exclusion of trials that demonstrated minor risk reduction with increased ALA intake (Schuurman et al 1999) and other weaknesses of the study designs. Additional criticisms include the lack of distinction in the sources of dietary ALA, with red meat, an independent risk factor for prostate cancer, being a major dietary source of ALA in some studies (Brouwer et al 2004). Until interventional trials are conducted a resolution on the matter is not possible.

DOSAGE RANGE

- Anticlotting: 5.9 g/day ALA
- Improved endothelial function: 2 g/day ALA
- Lipid-lowering: 60 mL/day FSO
- Reduced CHD mortality: 1–3 g/day ALA

A key consideration with FSO supplementation is product quality. Due to the high potential for FSO to become oxidised, ingestion of inadequately manufactured or preserved FSO could result in higher intakes of peroxides. It is recommended that only refrigerated FSO packaged in opaque containers be used. Once opened, the product should be consumed within a few weeks of opening and kept stored in the fridge.

ADVERSE REACTIONS

Flaxseed oil may cause loose stools in some individuals. There is a report of an allergic reaction to FSO, with a 40-year-old woman experiencing ocular pruritis and weeping followed by generalised urticaria and nausea, and vomiting within 10 minutes of taking a spoonful of linseed oil. A subsequent skin prick test produced a positive response to linseed. It remains unclear, however, whether this patient consumed FSO

or linseed oil, which is denatured and unfit for human consumption (Alonso et al 1996).

SIGNIFICANT INTERACTIONS

None known

CONTRAINDICATIONS AND PRECAUTIONS

- Hypersensitivity to flaxseed/linseed
- Prostate cancer

There are a number of studies that link increased ALA intake with a higher risk of prostate or aggressive prostate cancer. Although the evidence is preliminary and widely debated, it is recommended that at-risk individuals avoid high dose consumption of FSO and only consume FSO that is packaged in opaque containers and refrigerated.

PREGNANCY USE

There is no evidence to suggest safety concerns for FSO.

PRACTICE POINTS/PATIENT COUNSELLING

- Good quality, cold-pressed FSO is a good source of the essential fatty acid alpha-linolenic acid (ALA), which is often deficient in the Western diet.
- The polyunsaturated fatty acids found in FSO, particularly ALA, are precursors of eicosanoids and influence many important physiological processes. Additional actions may be attributed to the variable amount of lignan present in FSO, but which is found in higher concentrations in the actual seed.
- FSO has demonstrated anti-inflammatory, immunological, minor antiplatelet and chemopreventive effects and a range of beneficial actions within the cardiovascular system; however, large RCTs are still required to determine the role of FSO in clinical practice.
- FSO is not an adequate substitute for animal sources of n-3 EFAs. Most studies of oral FSO demonstrate only moderate increases in EPA, while DHA remains unchanged. Strict vegetarians and vegans using FSO as n-3 EFA substitute may be at risk of EPA and DHA deficiency.
- There is some evidence to suggest that daily ingestion of an additional 1–3 g of ALA (equivalent to 5 mL FSO) may reduce the incidence of some cancers and coronary heart disease mortality; however, this remains speculative.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Regular consumption of flaxseed oil, in the presence of balanced linoleic acid (omega-6) intake, may reduce cardiovascular mortality and possibly reduce the risk of some cancers; however, this remains speculative.

When will it start to work?

This will depend on the dosage taken and indication for use.

Are there any safety issues?

Long-term high doses may compromise immune function in susceptible individuals.

Preliminary evidence suggests a possible link between high ALA intake and increased risk of prostate cancer; however, this is controversial.

REFERENCES

Albert CM et al. Dietary alpha-linolenic acid intake and risk of sudden cardiac death and coronary heart disease. Circulation 112(21) (2005): 3232-8.

Allman MA et al. Supplementation with flaxseed oil versus sunflowerseed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. Eur J Clin Nutr 49(3) (1995): 169-78.

Allman-Farinelli MA et al. Comparison of the effects of two low fat diets with different alpha-linolenic: linoleic acid ratios on coagulation and fibrinolysis. Atherosclerosis 3 (1999): 159-68.

Alonso L et al. Anaphylaxis caused by linseed (flaxseed) intake. J Allergy Clin Immunol 98(2) (1996): 469-70.

Ander BP et al. Dietary flaxseed protects against ventricular fibrillation induced by ischemia-reperfusion in normal and hypercholesterolemic rabbits. J Nutr 134(12) (2004): 3250-6.

Astorg P. Dietary N-6 and N-3 polyunsaturated fatty acids and prostate cancer risk: a review of epidemiological and experimental evidence. Cancer Causes Control 15 (2004): 367-86.

Bemelmans WJE et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean Alpha-linolenic Enriched Groningen Dietary Intervention (MARGARIN) study. Am J Clin Nutr 75(2) (2002): 221-7.

Bhatty RS. Nutrient composition of whole flaxseed and flaxseed meal. In: Cunnane SC, Thompson LU (eds). Flaxseed in Human Nutrition. Illinois: ACOS Press, 1995: 22-42.

Bougnoux P et al. alpha-Linolenic acid content of adipose breast tissue: a host determinant of the risk of early metastasis in breast cancer. Br J Cancer 70(2) (1994): 330-4.

Brouwer IA et al. Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis. J Nutr 134(4) (2004): 919-22.

Burdge G. [alpha]-Linolenic acid metabolism in men and women: nutritional and biological implications [Lipid metabolism and therapy]. Curr Opin Clin Nutr Metab Care 7(2) (2004): 137-44.

Caughey GE et al. The effect on human tumor necrosis factor alpha and interleukin 1-beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. Am J Clin Nutr 63(1) (1996): 116-22.

Chan JK et al. Effect of dietary alpha-linolenic acid and its ratio to linoleic acid on platelet and plasma fatty acids and thrombogenesis. Lipids 28(9) (1993): 811-17.

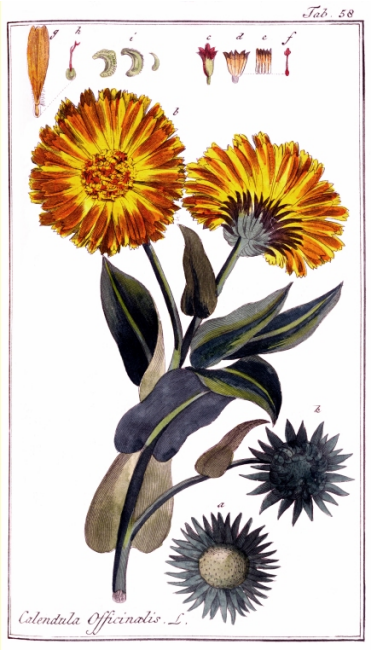
Christensen JH et al. Alpha-linolenic acid and heart rate variability in women examined for coronary artery disease. Nutr Metab Cardiovasc Dis 15(5) (2005): 345-51.

Cunnane SC et al. High alpha-linolenic acid flaxseed (Linum usitatissimum): some nutritional properties in humans. Br J Nutr 69(2) (1993): 443-53.

Cunnane SC, Thompson LU (eds). Flaxseed in Human Nutrition. Illinois: AOCS Press, 1995.

Curran RRD et al. Influence of flaxseed oil administration on glycemic response in active, healthy adults. Topics Clin Nutr 17(5) (2002): 28-35.

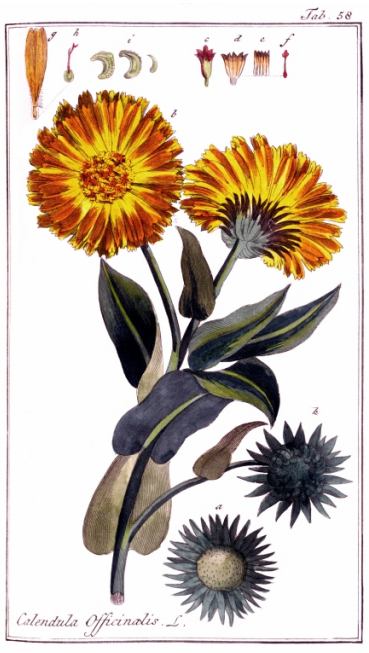
Das UN. A defect in the activity of delta6 and delta5 desaturases may be a factor predisposing to the development of insulin resistance syndrome. Prostagland Leukot Essent Fatty Acids 72(5) (2005): 343-50.
David BC, Kris-Etherton PM. Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications (Review). Am J Clin Nutr 78(3 Suppl) (2003): 640-6S.
de Lorgeril M, Salen P. Alpha-Linolenic acid, coronary heart disease, and prostate cancer. J Nutr 134 (2004): 3385.
Djousse L et al. Dietary linolenic acid is inversely associated with calcified atherosclerotic plaque in the coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. Circulation 111 (2005): 2921-6.
Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proc Soc Exp Biol Med 1992; (2002): 177-82.
Dwivedi C et al. Chemopreventive effects of dietary flaxseed oil on colon tumor development. Nutr Cancer 51(1) (2005): 52-8.
Finnegan YE et al. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. Am J Clin Nutr 77(4) (2003): 783-95.
Freese R, Mutanen M. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. Am J Clin Nutr 66(3) (1997): 591-8.
Freese R et al. Comparison of the effects of two diets rich in monounsaturated fatty acids differing in their linoleic/alpha-linolenic acid ratio on platelet aggregation. Thromb Haemost 71(1) (1994): 73-7.
Gann PH et al. Prospective study of plasma fatty acids and risk of prostate cancer. J Natl Cancer Inst 86(4) (1994): 281-6.
Garg ML et al. Dietary saturated fat level alters the competition between alpha-linolenic and linoleic acid. Lipids 24(4) (1989): 334-9.
Gerster H. Can adults adequately convert alpha-linolenic acid (18: 3n-3) to eicosapentaenoic acid (20: 5n-3) and docosahexaenoic acid (22: 6n-3)? Int J Vitam Nutr Res 68(3) (1998): 159-73.
Ghafoorunissa, IA, Natarajan S. Substituting dietary linoleic acid with alpha-linolenic acid improves insulin sensitivity in sucrose fed rats. Biochim Biophys Acta 1733(1) (2005): 67-75
Giovannucci E et al. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 85(19) (1993): 1571-9.
Guil JL et al. Identification of fatty acids in edible wild plants by gas chromatography. J Chromatogr A 719(1) (1996): 229-35.
Harper CR et al. Flaxseed oil increases the plasma concentrations of cardioprotective (n-3) fatty acids in humans. J Nutr 136(1) (2006): 83-7.
Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 65(5 Suppl) (1997): 1645-54S.
Harris WS. Alpha-linolenic acid: a gift from the land? (Editorial) Circulation 111(22) (2005): 2872-4.
Harvei S et al. Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. Int J Cancer 71(1997): 545-51.
Hussein N et al. Long-chain conversion of [13C] linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in men. J Lipid Res 46(2) (2005): 269-80.
James MJ et al. Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr 71(1) (2000): 343-8s.
Johnston PV. Alpha-Linolenic acid and carcinogenesis. In: Cunnane SC, Thompson LU (eds). Flaxseed in Human Nutrition. ACOS Press, 1995: 207-18.
Judd A. Flax: some historical considerations. In: Cunnane SC, Thompson LU (eds). Flaxseed in Human Nutrition. ACOS Press, 1995: 1-10.
Kelley DS et al. Dietary alpha-linolenic acid alters tissue fatty acid composition, but not blood lipids, lipoproteins or coagulation status in humans. Lipids 28(6) (1993): 533-7.



Klein V et al. Low alpha-linolenic acid content of adipose breast tissue is associated with an increased risk of breast cancer. Eur J Cancer 36(3) (2000): 335-40.
Kolodziejczyk PP, Fedec P. Processing flaxseed for human consumption. In: Cunnane SC, Thompson LU (eds). Flaxseed in Human Nutrition. ACOS Press, 1995: 261-80.
Kris-Etherton P, Skulas A. Essential fatty acids and vegetarians: the missing link in long-chain omega-3 fatty acid recommendations. Nutr MD 31(8) (2005): 1-4.
Lanzmann-Petithory D. Alpha-linolenic acid and cardiovascular diseases (Review). J Nutr Health Aging 5(3) (2001): 179-83.
Leitzmann MF et al. Dietary intake of n–3 and n–6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80(1) (2004): 204-16.
Li D et al. Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. Am J Clin Nutr 69(5) (1999): 872-82.
Maillard V et al. N-3 and N-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France. Int J Cancer 98(1) (2002): 78-83.
Mannisto S et al. Fatty acids and risk of prostate cancer in a nested case-control study in male smokers. Cancer Epidemiol Biomarkers Prev 12(12) (2003): 1422-8.
Mantzioris E et al. Dietary substitution with an alpha-linolenic acid-rich vegetable oil increases eicosapentaenoic acid concentrations in tissues. Am J Clin Nutr 59(6) (1994): 1304-9.
Matthan NR et al. A systematic review and meta-analysis of the impact of omega-3 fatty acids on selected arrhythmia outcomes in animal models. Metabolism 54(12) (2005): 1557-65.
Morris D. Essential nutrients and other functional compounds in flaxseed. Nutr Today 36(3) (2001): 159-62.
Mozaffarian D et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation 111 (2005): 157-64.
Mutanen M, Freese R. Fats, lipids and blood coagulation. Curr Opin Lipidol 12(1) (2001): 25-9.
Nestel PJ et al. Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability. Arterioscler Thromb Vasc Biol 17(6) (1997): 1163-70.
Phinney SD et al. Reduced arachidonate in serum phospholipids and cholesteryl esters associated with vegetarian diets in humans. Am J Clin Nutr 51(3) (1990): 385-92.
Prasad K. Dietary flaxseed in prevention of hypercholesterolemic atherosclerosis. Atherosclerosis 132 (1997): 69-76.
Prasad K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Circulation 99(10) (1999): 1355-62.
Prasad K et al. Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. Atherosclerosis 136 (1998): 367-75.
Saadatian-Elahi M et al. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer 111(4) (2004): 584-91.
Schuurman AG et al. Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. Cancer 86 (1999): 1019-27.
Simopoulos AP. Omega-3 fatty acids and antioxidants in edible wild plants. Biol Res 37(2) (2004): 263-77.
Singer P et al. Slow desaturation and elongation of linoleic and alpha-linolenic acids as a rationale of eicosapentaenoic acid-rich diet to lower blood pressure and serum lipids in normal, hypertensive and hyperlipemic subjects. Prostaglandins Leukot Med 24(2-3) (1986): 173-93.
Suresh Y, Das UN. Long-chain polyunsaturated fatty acids and chemically induced diabetes mellitus: Effect of omega-3 fatty acids. Nutrition 19(3) (2003): 213-28.
Thies F et al. Influence of dietary supplementation with long-chain n-3 or n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. Lipids 36(11) (2001): 1183-93.
Wilkinson P et al. Influence of alpha-linolenic acid and fish oil on cardiovascular risk with an atherogenic lipoprotein phenotype. Atherosclerosis 181(1) (2005): 115-24.

Zhao G et al. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr 134 (2004): 2991-7.

Folate



Historical note Folic acid was isolated from spinach leaves in 1941 and synthesised in 1946, hence its name comes from the Latin *folium*, which means leaf.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Folate is the generic term for a large family of chemically similar trace compounds that fall within the vitamin B group. Folate is also known as folacin and vitamin B9. Folic acid (pteroylmonoglutamic acid or PGA) is the most oxidised and stable form of folate and the one most often used in supplements and food fortification. Folate found in animal sources is present in a 'free form' and is readily absorbed; however, aside from the organ meats, animal products are notoriously poor sources. Folic acid found in plant foods exists in a conjugated form, which has to be converted in the gut prior to absorption. This deconjugation process requires a zinc-dependent intracellular enzyme (Kelly 1998), which then makes folate available for absorption in the small intestine. This is inhibited by chronic alcohol ingestion and some foods, including oranges and legumes (Gropper et al 2005).

The average bioavailability of natural folate is between 50% and 66%, although synthetic forms, such as those found in fortified foods or supplements, show almost a twofold increase in bioavailability (Carmel 2006, Kelly 1998). Small amounts of folacin are endogenously produced by bacteria in the intestines, but this appears to be predominantly lost via faeces (Gropper et al 2005). Conversion into folate's active forms is a multistep pathway beginning within the intestinal cell wall and finishing in the liver. Secretion into the bile of these tetrahydrofolate (THF) derivatives and their subsequent reabsorption through the enterohepatic circulation enables redistribution throughout the body. Distribution of folate appears to be regulated via an unknown mechanism, ensuring increased availability to those tissues demonstrating rapid cell division (Gropper et al 2005). Although many of the biochemical pathways in which folate is involved act to regenerate the nutrient, there is still a significant amount that is broken down and eliminated, chiefly in the urine.

CHEMICAL COMPONENTS

Folate derived from the diet requires a complicated conversion to a variety of THF derivatives. In contrast, the synthetic form of folate, known as folic acid or PGA, is used in food fortification and supplements because it is more stable and offers better

bioavailability. A pharmaceutical form known as folinic acid (5-formyl-THF) acts as an immediate precursor to the primary metabolite (Kelly 1998).

Clinical note — Is synthetic folate the superior form?

Given its profound instability in processing, poor bioavailability, and complex conversion to active forms, adequate folate appears more difficult to achieve with the natural form than with synthetic forms, because the latter are comparatively stable and some act as an immediate precursor to the primary metabolite (Kelly 1998). Importantly, when synthetic folate is taken with food, it offers a higher bioavailability than dietary forms, 85–100% compared with 50–66% respectively. As such, both supplementation and fortification of grains and cereals may actually be a more reliable manner of increasing tissue levels. Accurate assessment of an individual's folate status may therefore require an adjustment made for increased bioavailability of synthetic forms using the equation:

1 dietary folate equivalent	= 1 μg of dietary folate
	= 0.6 μg of folic acid from a fortified source or supplement taken with food
	= 0.5 μg of folic acid from a supplement taken on an empty stomach (NHMRC 2005).

One residual concern regarding high dose exposure to folic acid is due to the passive diffusion of unmodified PGA across the epithelium and into the bloodstream. This monoglutamate form is not naturally seen in human blood and the discovery of high levels in supplemented patients has raised questions regarding its biological effects (Lucock 2004). Until further research is conducted in this area, the implications are unclear.

FOOD SOURCES

Good dietary sources are fresh green leafy vegetables, such as cabbage and spinach, asparagus, broccoli, sprouts, mushrooms, legumes, nuts and fortified cereals, and organ meats.

Food preparation and processing can destroy up to 100% of the naturally occurring folate, as it is sensitive to light and air but especially heat; therefore, raw foods, as well as fortified foods, are considered superior sources, which in Australia provide 100 μg per serve (Gropper et al 2005, Hickling et al 2005).

Clinical note — Food fortification with folate: still not enough for pregnant women?

In 1995, legislation allowing voluntary fortification of Australian foods with folate was introduced with the goal of improving the population's folate status, especially that of pregnant women without putting certain groups at risk of masked pernicious anaemia. In the years following the introduction of fortification, a study evaluating mean serum levels of folate in over 20,000 Australian women aged 14–45 years found that although a mean increase in serum concentrations of 19% was evident, the prevalence of poor folate status in this age group was only reduced from 8.5% to 4.1% (Metz et al 2002). More recently, a smaller study conducted in Perth found a 38% increase in mean serum folate in subjects post-fortification, which correlates with a 30% reduction in the incidence of neural tube defect in Western Australia (Hickling et al 2005).

Although food fortification provides some measure of protection for women of reproductive age, it is still insufficient and personal supplementation is required. Unfortunately, widespread public health campaigns have had limited success and many women remain unaware of the need to take folic acid supplements prior to pregnancy or are aware but still fail to use supplements (Metz et al 2002). In a systematic review of 52 studies, in approximately 20 (mainly Western) countries between 1992 and 2001, the reported periconceptional supplement use ranged from 0.5% to 52% (Ray et al 2004). The situation is similar in Australia, with research demonstrating that only 36% and 46% of new mothers in Victoria and New South Wales, respectively, took folate supplements, with even lower rates reported for women of low socioeconomic or non-English speaking backgrounds (Watson et al 2006).

DEFICIENCY SIGNS AND SYMPTOMS

Folate deficiency is not uncommon and can develop within only 4 months of an inadequate diet (Carmel 2006, Gropper et al 2005, Wilson et al 1991).

In light of folate's fundamental role in DNA synthesis, deficiency of this nutrient will predictably impact most on those cells and tissues that exhibit a high turnover (e.g. blood and the cells in the gastrointestinal tract), which also applies to those stages of development with increased rates of growth, such as pregnancy and fetal tissue development.

SIGNS AND SYMPTOMS OF DEFICIENCY

- Macrocytic/megaloblastic anaemia.
- Fatigue.

- Psychological symptoms such as irritability and depression (Reynolds 2002).
- Headache.
- Hair loss.
- Nausea.
- Insomnia (Pelton et al 2000).
- Peripheral neuropathy.
- Tendon hyperreflexivity.
- Diarrhoea.
- Weight loss.
- Cerebral disturbances (Botez 1976) and cognitive decline.
- Increased blood levels of homocysteine.

PRIMARY DEFICIENCY

This develops in response to inadequate dietary intake and can be caused by a diet generally lacking in fresh, lightly cooked vegetables. Risk is increased in patients with MTHFR (N5,10-methylenetetrahydrofolate reductase) deficiency or 677C→T polymorphisms of the *MTHFR* gene, in people receiving TPN, chronic alcoholics, phenylketonuria patients on restricted diets, patients with sickle cell anemia and the institutionalised elderly (Carmel 2006, Wahlqvist et al 2002).

SECONDARY DEFICIENCY

This is caused by compromised absorption, increased excretion or increased demands or losses. Inadequate absorption can occur in malabsorption syndromes such as coeliac and Crohn's disease, with long-term use of certain medications such as phenytoin, sulfasalazine, cimetidine, antacids and OCP, in congenital malabsorption states and in blind loop syndrome (Beers et al 2003), especially when combined with suboptimal dietary intake (Carmel 2006). Significantly impaired absorption has also been observed in HIV patients (Revell et al 1991).

Besides impaired absorption, inadequate use can occur with concurrent vitamin B12 or C deficiency or chronic alcoholism. A genetic variation in folate requirement has also been identified, as a congenital enzyme deficiency exists in approximately 13% of the Western population (Ma et al 1994). In these cases, total or partial absence of the enzyme responsible for the final step in converting folate to its major active metabolite (methylene tetrahydrofolate reductase) results in decreased plasma levels (Kumar & Clarke 2002). Therefore, these individuals have a higher folate requirement than others without this congenital enzyme deficiency and display increased susceptibility to folate deficiency.

A number of pharmaceutical drugs, such as folic acid antagonists (e.g. methotrexate), can affect folic acid status by interfering with absorption, use and conversion to its active forms. In such cases, oral folic acid supplements are sometimes given to reduce side-effects, although it may marginally reduce drug efficacy (Kumar & Clarke 2002, Strober & Menon 2005).

Additionally, there are several subpopulations with increased demands for folic acid, such as pregnant and lactating women, the elderly and patients with malignancies, haemolytic anaemias such as sickle cell disease, chronic exfoliative skin disorders, or achlorhydria (Gropper et al 2005). Extra losses have also been reported in haemodialysis patients.

MAIN ACTIONS

COENZYME

The primary role of folate and its active derivatives in the body is related to its capacity to act as a methyl donor in multiple biochemical pathways. In this way, it is involved in a variety of reactions important for the metabolism of amino acids and nucleic acids.

DNA and RNA synthesis Folate plays an essential part in the production of purines and pyrimidines that make up DNA, making it a critical nutrient in relation to cell division and repair of genetic material, and is generally required for genomic stability. Subsequently, folate plays an indirect role in the synthesis of transfer RNA.

Production of the active form of B12 Folate and B12 are closely interwoven; for example, the conversion of B12 into methylcobalamin is dependent upon the presence of a THF coenzyme.

Reduction of homocysteine levels Folate, in the presence of B12, primes the homocysteine molecule for methylation by an activated B12. With the additional assistance of B6, together they effectively lower homocysteine levels in the blood through regeneration of methionine.

Synthesis of *S*-adenosyl-L-methionine (SAMe) A THF derivative is critical for the regeneration of methionine from homocysteine. The methyl group donated in this process is taken up by SAMe, which provides it with the ability to become a carbon donor in multiple transmethylation reactions throughout the body including the synthesis of adrenaline, melatonin and creatine (Hendler & Rorvik 2001).

Amino acid metabolism Folate is involved in the synthesis of some of the non-essential amino acids such as serine and glycine. It is also required for the conversion of histidine into glutamate (Gropper et al 2005).

CLINICAL USE

The conditions for which folate is indicated as a potential treatment are primarily due to an existing deficiency, through either primary or secondary pathways. Research has focused particularly on those conditions in which folate deficiency is a consequence of medication use and benefits of improved folate status.

PREVENTION AND TREATMENT OF DEFICIENCY

Commonly, folic acid supplements are used to correct identifiable deficiency states, such as macrocytic anaemia, or given as preventative treatment to those patients at risk of deficiency, such as in malabsorption syndromes or taking long-term folate antagonist medication. Increased oral intake of folate has been found to be effective even in cases of malabsorption due to the passive diffusion evident with pharmacological doses (Carmel 2006).

PRECONCEPTION AND DURING PREGNANCY

Poor folate status either 1 month before conception or during the first trimester of pregnancy is an independent risk factor for neural tube defects (NTD) in the newborn. One study has suggested the increased risk could be as high as 10-fold (Daly et al 1995).

Intervention trials for pregnancy have routinely used 400 μg folic acid/day; however, there is some suggestion that routine ingestion of only 100 μg folate from fortified food would prevent the majority of NTDs. Studies have also been conducted on women with a previous NTD birth, with benefits demonstrated at doses of 4 mg/day. There is a general consensus among researchers and health authorities that due to the inconsistent nature of natural food sources, taking a supplement or incorporating fortified foods is the only reliable way to increase levels sufficiently (Cuskelly et al 1996).

Our understanding of folate's role in healthy pregnancies has progressed significantly in the last several years, with the ongoing identification of associated birth defects including Down syndrome (Eskes 2006) and cleft lip and/or palate (Blieka et al 2006). Higher folate levels are linked to the prevention of miscarriages, decreased risk of intrauterine growth retardation, increased birth weight in the offspring of smoking mothers (Sram et al 2005) and increased rates of twin pregnancies, from both natural and IVF conception (Haggarty et al 2006).

OCP-INDUCED FOLATE DEFICIENCY

Long-term use of the oral contraceptive pill (>5 years) has historically been associated with a progressive decrease in serum folate levels, of up to 40%, which could feasibly result in changes to cognition and mood, increased risk of macrocytic anaemia and

increased risk of NTD in newborns once use has ceased. Results from recent studies suggest this last concern may be unfounded (Lussanaa et al 2003, Sütterlin et al 2003).

There are a number of proposed mechanisms for folate depletion with OCP use, including concurrent depletion of B12, which is involved in the regeneration pathway of THF (Bielenberg 1991), and impaired folate resorption (Sütterlin et al 2003).

HYPERHOMOCYSTEINAEMIA

Together with vitamins B12 and B6, folic acid has been shown to reduce high plasma levels of homocysteine. Of the three, folate appears to have the strongest activity (Voutilainen et al 2001). Although elevated homocysteine has been implicated as a risk factor in cardiovascular disease (including atherosclerosis and coronary artery disease), cerebrovascular disease, peripheral vascular disease and venous thromboembolism (Clarke et al 1991, den Heijer 1996, Malinow et al 1989, Selhub 1995), exudative age-related macular degeneration, noise-related hearing loss, cognitive dysfunction, and adverse pregnancy outcomes (Gok et al 2004, Nowak et al 2005), cognitive dysfunction, and adverse pregnancy outcomes (Bjorke Monsen & Ueland 2003), clinical trials are currently underway to determine the clinical relevance of this association.

Cardiovascular protection Although folate adequacy remains protective against primary cardiovascular disease it may not be a useful intervention in those patients with established disease. In spite of promising results from earlier studies (Hendler & Rorvik 2001, Verhaar et al 2002), lowering homocysteine levels failed to exert a significant protective effect against cardiovascular events in a large study of 3749 men and women post-infarction. Combinations of 800 μg of folate, 400 μg B12 and 40 mg B6 were used in the 40-month study and appeared to increase risk (RR 1.22) (Bønaa et al 2006).

Alzheimer's dementia and impaired cognitive function in the elderly Findings such as the prevalence of folate deficiency in the elderly, increasing homocysteine levels with age and evidence of an inverse relationship total plasma homocysteine levels and cognitive function have attracted attempts to link the phenomena and provide an explanation for neuropsychiatric disorders in this population.

Currently, an abundance of epidemiological evidence and a limited number of studies have shown a positive correlation between folate status and dementia. For example, a 2002 review has estimated that 71% of medical patients admitted acutely to hospital with severe folate deficiency have been observed with organic brain syndrome compared with 31% of controls (Reynolds 2002).

A 2003 Cochrane review examined the effects of folic acid supplementation, with or without vitamin B12, in elderly healthy and demented people, in preventing cognitive impairment or retarding its progress (Malouf et al 2003). The review analysed data from four RCT and concluded that there was no beneficial effect of 750 μg of folic acid/day on measures of cognition or mood in older healthy or cognitively impaired people. It also noted that the available studies are limited in size and scope and more studies are needed.

Renal transplant recipients Combination vitamin B treatment (folate, B12 and B6) may be of benefit in renal transplant patients, according to a RCT of 56 renal transplant patients, which found that vitamin supplementation with folic acid (5 mg/day), vitamin B6 (50 mg/day) and vitamin B12 (400 μg/day] for 6 months reduced the progression of atherosclerosis, as evidenced by a significant decrease in carotid intima-media thickness. Additionally, a significant decrease in homocysteine levels was observed (Marcucci et al 2003).

Restenosis after percutaneous coronary intervention A RCT found that treatment with vitamin B12 (cyanocobalamin 400 μg/day), folic acid (1 mg/day) and vitamin B6 (pyridoxine hydrochloride 10 mg/day) for 6 months significantly decreased the incidence of major adverse events, including restenosis, after percutaneous coronary intervention (Schnyder et al 2002). In contrast, a more recent trial demonstrated an increased risk of in-stent restenosis in those patients intravenously administered 1 mg of folic acid, 5 mg of vitamin B6, and 1 mg of vitamin B12 followed by daily oral doses of 1.2 mg of folic acid, 48 mg of vitamin B6, and 60 μg of vitamin B12 for 6 months (Lange et al 2004). Further research with more consistent study designs are required to elucidate the true effects.

Recurrent spontaneous miscarriage Maternal hyperhomocysteinemia and poor folate status are risk factors for recurrent embryo loss and for a first early embryo loss (George et al 2002). There has also been conflicting evidence in relation to the role of *MTHFR* polymorphism and pregnancy, although many studies point towards increased risk of recurrent spontaneous abortion. One explanation for the discrepant results may be that the numbers of study participants have been relatively small (Zetterberg 2004). Although researchers encourage the periconceptional use of both folate and B12 to reduce these risks, there is a lack of interventional studies in this area.

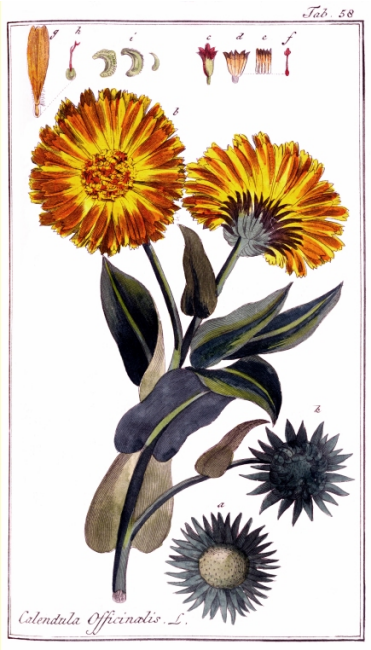
CARDIOVASCULAR DISEASE PROTECTION INDEPENDENT OF HOMOCYSTEINE STATUS

In the absence of a causal relationship between homocysteine and cardiovascular disease, what remains most promising for folate are studies illustrating its protective

effects, mediated through other mechanisms. This has led some researchers to suggest that folate deficiency may be the primary cause of an increased vascular risk and that elevated homocysteine levels should principally be considered a marker for low folate status rather than a pathogenetic marker (Verhaar et al 2002).

Demonstrations of in vitro antioxidant activity, effects on cofactor availability and direct and indirect interactions with the endothelial NO synthase enzyme have been proposed as plausible mechanisms, through which folate may prevent endothelial dysfunction (Das 2003, Verhaar et al 2002).

Several studies show the cardiovascular protective effects of folic acid, including the predictive value of low folate status on stroke risk (Verhaar et al 2002, Bazzano et al 2002). Few interventional studies have been conducted and on the whole results have been disappointing, which may be because the trials are commonly looking at folate in secondary prevention rather than primary. One such study was an open label trial of 500 μg/day folate over 2 years in 593 patients, which failed to reduce cardiovascular events (Liem et al 2003).



ANTICONVULSANT-INDUCED FOLATE DEFICIENCY

Anticonvulsant medications such as phenytoin, carbamazepine and valproate reduce serum folate status. Individual studies have estimated an incidence of 15% folate deficiency in this group, compared with 2% for control groups (Froscher et al 1995). However, the figure may be as high as 97% with long-term phenytoin therapy (Rivey et al 1984). This may be due to increased use of folate in drug metabolism and/or decreased mucosal absorption (Berg et al 1992, Pelton et al 2000). Sometimes, folic acid supplements are recommended to avoid deficiency, but this requires close supervision to ensure drug efficacy is not substantially reduced (Rivey et al 1984).

PSYCHIATRIC ILLNESS

Over the past three decades, a vast number of case reports, open studies and, to a lesser extent, case–control studies have been published on the topic of psychopathology and folate deficiency. Many report a high incidence of serum folate deficiency in patients with symptoms of depression and various psychiatric disorders, particularly in geriatric populations (Reynolds 2002). For instance, one review identified that serum folate deficiency varied between 8% and 50% in patients with various psychiatric disorders including depression and schizophrenia (Young and Ghadirian 1989). Two large studies involving over 350 patients diagnosed with acute psychiatric presentations identified low folate levels or frank deficiency (31% and 12% respectively). The patients with the most marked deficiency were also the group with the highest percentage of inpatients (Carney et al 1990). Recently, another study of

similar design found 30% of 224 newly admitted psychiatric patients had low serum folate (<3.5 ng/mL) compared to only 2.4% of controls and that patients with low folate were 3.5-fold more likely to present with depressive features (Lerner et al 2006). Disturbingly the researchers also identified a significant trend between folate deficiency and hospital readmissions.

DEPRESSION

The relationship between folate and depression has been linked to hyperhomocysteinaemia, as well as its role in neurotransmitter synthesis and methylation, independent of homocysteine (Bottiglieri et al 2005, Lerner et al 2006). Overall, it has been estimated that between 15% and 38% of depressed people also have a folate deficiency (Alpert & Fava 1997). Studies have demonstrated that dietary folate consumption below the median (256 μg/day) (Tolmunen et al 2004), serum folate <3.5 ng/mL (Lerner et al 2006) and a *MTHFR* C677T genotype are all independently associated with an increased risk of depression (Kelly et al 2004). Preliminary evidence from a study of geropsychiatric patients has found evidence of neuropathology in the absence of frank folate deficiency prompting a reassessment of the currently accepted 'healthy range' for this subpopulation (Scott et al 2004).

A Cochrane systematic review of three controlled trials involving 247 depressed people suggested that, on the evidence available, folate shows potential, but whether its effectiveness is restricted to only those patients with an existing deficiency remains unclear (Taylor 2003). The studies assessed used 500 μg folic acid, 15 mg methyltetrahydrofolate and 50 mg methyltetrahydrofolate once daily and lasted from 8 weeks to 6 months. Two studies used folate as an adjunct to standard therapy.

Given the volume of evidence linking folate with depression it is surprising that so few clinical trials have been conducted using folic acid.

Affects response to standard antidepressants Research investigating folate's effects on the success of antidepressant treatment has escalated in recent years and there is now evidence of a reduced response to fluoxetine with declining folate levels, from 44.7% in subjects with normal serum folate to 7.1% of patients with folate deficiency (<2.5 ng/mL) (Papakostas et al 2004a,b). Reduced folate levels have also been associated with reduced response to sertraline (Alpert et al 2003). In addition to this, poor folate status appears to negatively impact response time (+1.5 weeks) (Papakostas et al 2005) and relapse rates during continuation of fluoxetine (42.9% relapse in patients with low folate levels vs 3.2%) (Papakostas et al 2004a,b), independent of B12 and homocysteine levels.

SCHIZOPHRENIA

Folate has been implicated in the causality of schizophrenia since the 1950s and aberrations of one-carbon metabolism were proposed as a distinct hypothesis at around the same time (Regland 2005). With our current knowledge linking the two there has been renewed interest in the role of folate in this disorder. One key issue relates to a controversial association between low folate levels and schizophrenia incidence (Muntjewerff & Blom 2005). A review of seven case-control studies concluded that three of these demonstrated a relationship, although overall the evidence was undermined by methodological shortcomings (Muntjewerff & Blom 2005). In spite of this, elevated homocysteine and a high incidence of the *MTHFR* C677T genotype are reportedly frequent findings in this population (Kemperman et al 2006, Regland 2005), with several case reports of success using 15–30 mg folate in combination with B12 injections (1 mg every 10 days) and N-acetyl cysteine (200 mg twice daily) (Regland 2005).

CHEMOPREVENTATIVE ROLE

Epidemiological, animal and human studies all suggest that folate status affects the risk of developing cancers in selected tissues. The exact nature of this relationship continues to elude researchers (Bollheimer et al 2005, Powers 2005). Previously, high folate intake was purported to have a protective effect, although there were some anomalies. An extensive review of the role of the *MTHFR* C677T polymorphism in cancer risk concluded that, in spite of the poor folate status and activity associated with this polymorphism, many studies identify it as protective against a range of cancers (Sharp & Little 2004). To add to this a group of Swedish researchers have demonstrated that the relationship between serum folate and colorectal cancer follows a bell-shaped curve distribution (Van Guelpen et al 2006). Speculation regarding the role of additional co-factors involved in folate activity has also emerged (Powers 2005).

However, folate's actions still represent a plausible modulator of cancer risk due to its critical role in the production, methylation and repair of DNA, regulation of cell turnover and suppression of excessive proliferation (Choi et al 2000, 2002).

Colon cancer The link between folate status and colorectal cancer was first suggested in the 1990s when clinical studies identified an inverse association between folate and colorectal carcinogenesis. Subsequent rodent studies further strengthened the theory when chemically induced colorectal carcinogenesis was shown to be tremendously enhanced under dietary folate deprivation and reduced with folate administration (Cravo et al 1992, Kim et al 1996).

In 2005, a major review of in vitro, animal and various clinical and epidemiological studies concluded that high folate intake does not lead to an independent, overall chemopreventative effect on colorectal carcinogenesis, although results from two large studies suggest that folate deficiency might have a particular impact on proximal colon cancer in females (Bollheimer et al 2005).

Since then, a recent study demonstrated improved response in patients with adenomatous polyps using a combination of 100 μg of folate and 5 mg riboflavin over folate alone (Powers 2005).

Cervical cancer The potential role of folate in the prevention of cervical cancer has been equivocal and results from intervention studies on cervical cancer have been inconsistent (Henao et al 2005, Kwanbunjan et al 2005, Sedjo et al 2003). Many of these studies have methodological limitations, including a lack of information on high-risk human papillomavirus (HR-HPV) infection, a risk factor for cervical cancer. This is notable as folate deficiency may increase the risk of cervical cancer in individuals infected with HR-HPV (Piyathilake et al 2004).

The most promising RCT involved 47 patients taking an OCP who demonstrated mild to moderate intraepithelial dysplasia. A dose of 10 mg folic acid daily over 3 months resulted in significantly lower biopsy scores in the treatment group and a significant reduction in cytology scores from baseline (Butterworth et al 1982). Other studies have shown that folic acid treatment does not alter the course of disease in patients with pre-established cervical dysplasia (Childers et al 1995).

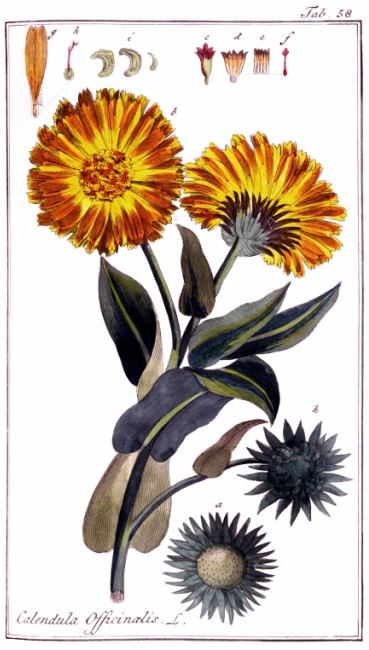
PERIODONTAL DISEASE

A series of RCTs has shown that rinsing with a solution of folate (5 mg/dose) twice daily alleviates gingival inflammation in all age groups and in pregnant and non-pregnant women (Pack 1984, Thomson & Pack 1982). Treatment results in a significant reduction in inflammation without altering plaque levels or folate serum status and appears to be more successful than oral supplements (Vogel et al 1976).

Preliminary evidence suggests that topical folate may also have a role in controlling gingival hyperplasia associated with long-term phenytoin use (Drew et al 1987).

METHOTREXATE TOXICITY

Methotrexate is a cytotoxic drug with folate antagonist properties. In part, its efficacy is dependent on this effect, but severe deficiency symptoms such as macrocytic anaemia are sometimes induced (Lambie et al 1985). Co-administration of folic acid or folinic acid has been investigated as preventative treatment, with both forms capable of reducing drug side-effects (Ortiz et al 1998, Strober & Menon 2005).



SICKLE CELL ANAEMIA

In the past, folate supplements were recommended to patients with sickle cell anaemia, but more recent studies show that clinically significant folate deficiency occurs in a very small percentage of these patients and other nutrients may be indicated (Reed et al 1987).

VITILIGO

Although a number of uncontrolled studies testing combination treatments have been promising, folate has never been assessed as a sole treatment. As such, it is difficult to determine its role in the treatment of this condition. In previous studies, a combination of oral folic acid and vitamin B12, together with increased sun exposure, has produced response rates in the vicinity of 50% (Juhlin & Olsson 1997). A more recent controlled study by a different group of researchers found that exposure to a specific band width of UV radiation produced repigmentation in 92% of subjects, irrespective of vitamin supplementation (Tjioe et al 2002).

DOSAGE RANGE

AUSTRALIAN RDI

- 400 μg/day for adults; up to 1 mg/day in deficiency states (NMMRC 2005).
- 600 μg/day in pregnancy.
- 500 μg/day during lactation.

ACCORDING TO CLINICAL STUDIES

- Preconception care or early pregnancy supplementation: 400–600 μg /day.
- Preconception and pregnancy supplementation in women with a previous NTD birth: 4 mg/day.
- Anticonvulsant-induced deficiency: 15 mg/day (under supervision).
- Prevention of cervical cancer: 800–10 000 μg/day.
- Prevention of colorectal cancer in ulcerative colitis patients: 1–5 mg/day.
- Alzheimer's dementia and cognitive changes in the elderly: doses adequate to correct deficiency if present.
- Depression: 50 mg methylfolate daily.
- Acute psychiatric presentation: 15–30 mg methylfolate daily in combination with standard psychotropic treatment.
- Hyperhomocysteinaemia: 500–5000 μg/day.
- Methotrexate toxicity: 5 mg/week.
- OCP-induced folate deficiency: 2 mg/day.
- Periodontal disease: rinse mouth with a solution of folate (5 mg/dose) twice daily.

- Prevention of restenosis after percutaneous coronary intervention: 1 mg in combination with vitamin B12 (400 μg) and vitamin B6 (10 mg) daily.
- Sickle cell anaemia: 1 mg/day.
- Ulcerative colitis: 15 mg/day.
- Vitiligo: 2–10 mg/day.

ADVERSE REACTIONS

Adverse reactions appear to be limited to oral doses greater than 5 mg/day. Reactions include a generalised urticaria associated with an allergic response, nausea, flatulence and bitter taste in the mouth, irritability and excitability.

SIGNIFICANT INTERACTIONS

ANTACIDS

Reduce folic acid absorption — separate doses by 2–3 hours.

GASTRIC ACID INHIBITORS (PROTON-PUMP INHIBITORS)

Reduced folic acid absorption — separate doses by 2–3 hours.

ZINC

At high doses (>15 mg/day), minor zinc depletion may develop (Carmel 2006, Kelly 1998) — observe patients for signs and symptoms of zinc deficiency.

CHOLESTYRAMINE (E.G. QUESTRAN)

Reduced folate absorption — observe patient for signs and symptoms of folate deficiency and separate doses by at least 4 hours.

ANTICONVULSANTS (PHENYTOIN)

Reduced folate levels frequently develop with long-term use, but macrocytic anaemia is rare (Lambie et al 1985). Supplementation can reduce toxicity, which is a beneficial interaction, although medical supervision is advised.

ORAL CONTRACEPTIVES

Folate levels are reduced with long-term use of the OCP, particularly those with high oestrogen content; therefore, increased intakes may be required for women undertaking long-term use.

METHOTREXATE

Methotrexate is a folate antagonist drug. Folate supplementation can reduce toxicity, which is a beneficial interaction; however, it may reduce the efficacy of methotrexate — medical supervision advised.

PANCREATIN
Reduced folate absorption (Kelly 1998) — separate doses by 2–3 hours.

PYRIMETHAMINE (E.G. MALOPRIM)
Impairs the use of folate and, as such, supplementation with folinic acid may be beneficial.

SULFASALAZINE
Folic acid can reduce drug absorption — separate doses by 2–3 hours.

TRIMETHOPRIM
Trimethoprim is a folate antagonist drug. Supplementation can reduce toxicity, which is a beneficial interaction — medical supervision advised.

CONTRAINDICATIONS AND PRECAUTIONS
Use of folate supplements may mask a B12 deficiency state by correcting an apparent macrocytic anaemia without altering progression of neurological damage. It is recommended that patients be screened for vitamin B12 deficiency.

PREGNANCY USE
According to the Australian Drug Evaluation Committee (1999), folate is considered to be safe to take in both pregnancy and lactation. Retrospective analysis of a trial of folate in pregnancy in the 1960s has suggested a possible increase in all-cause mortality and breast cancer in pregnant women taking 5 mg/day folate; however, this finding could be due to a number of factors unrelated to folate (Bland 2005, Charles et al 2004). The only context requiring special consideration is those pregnant women taking anticonvulsant medication (see Significant Interactions).

PRACTICE POINTS/PATIENT COUNSELLING
- Folate is involved in a number of important biochemical pathways required for health and wellbeing, in particular development and cell growth.
- Folate supplements are often given to correct deficiencies or prevent deficiency in people at risk, such as those with malabsorption syndromes (e.g. coeliac disease and Crohn's disease), long-term use of certain medications such as phenytoin, sulfasalazine, cimetidine, antacids and the OCP, in congenital malabsorption states and blind loop syndrome, chronic alcoholism, the institutionalised elderly, pregnant and lactating women and HIV infection.
- It is considered to be the most important supplement to be taken by women in the weeks leading up to conception and during the first 12 weeks of pregnancy, in order to significantly reduce the risk of NTD in newborns. Food fortification is not considered sufficient.

- Other uses for folic acid supplements include reducing homocysteine levels (often in combination with vitamins B12 and B6), reducing primary cardiovascular disease risk and cancer risk in general, periodontal disease (as a topical application), depression and vitiligo, but only in patients who exhibit a deficiency.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Folic acid is essential for health and wellbeing. Supplements have a critical role in preventing NTD in newborns and may also reduce the risk of primary cardiovascular disease, improve brain function in Alzheimer's dementia and non-Alzheimer's dementia and depression. It can also reduce the toxic effects of some medicines and may reduce the risk of developing some forms of cancer.

When will it start to work?

This depends on the indication.

Are there any safety issues?

The major concern with high doses of folate is that it may mask an underlying vitamin B12 deficiency and allow it to progress unnoticed, which means that a vitamin B12 deficiency should be excluded. It also interacts with some drugs in both a potentially harmful and beneficial way.

REFERENCES

Alpert JE, Fava M. Nutrition and depression: the role of folate. Nutr Rev 55.5 (1997): 145-9.

Alpert M et al. Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant. J Clin Psychopharmacol 23 (2003): 309-13.

Australian Drug Evaluation Committee. Prescribing Medicines in Pregnancy, 4th edn. Canberra: TGA Publications, 1999.

Bazzano LA et al. Dietary intake of folate and risk of stroke in US men and women: NHANES1 epidemiological follow-up study. Stroke 33 (2002): 1183-9.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Berg MJ et al. Phenytoin pharmacokinetics: before and after folic acid administration. Epilepsia 33.4 (1992): 712-20.

Bielenberg J. Folic acid and vitamin deficiency caused by oral contraceptives. Med Monatsschr pharm 14.8 (1991): 244-7.

Bjorke Monsen AL, Ueland PM. Homocysteine and methylmalonic acid in diagnosis and risk assessment from infancy to adolescence. Am J Clin Nutr 78.1 (2003): 7-21.

Bland J. Taking folate in pregnancy and risk of maternal breast cancer. What's in a name? BMJ 330 (2005): 600.

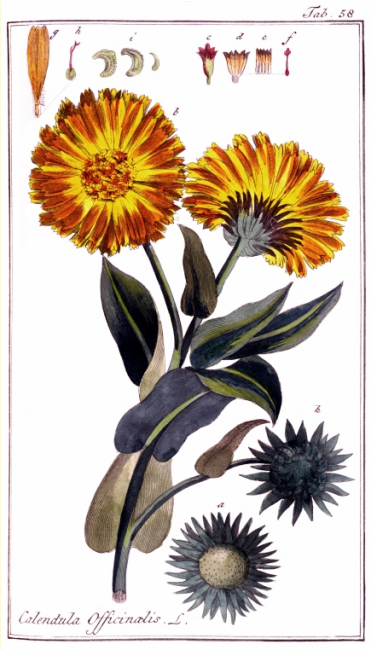
Blieka J, Rothenberg S, Steegers-Theunissen R. Maternal folate receptor autoantibodies and cleft lip and/or palate. Int J Gynecol Obstet 93.2 (2006): 142-3.

Bollheimer L et al. Folate and its preventative potential in colorectal carcinogenesis. How strong is the biological and epidemiological evidence? Crit Rev Oncol Hematol 55 (2005): 13-36.

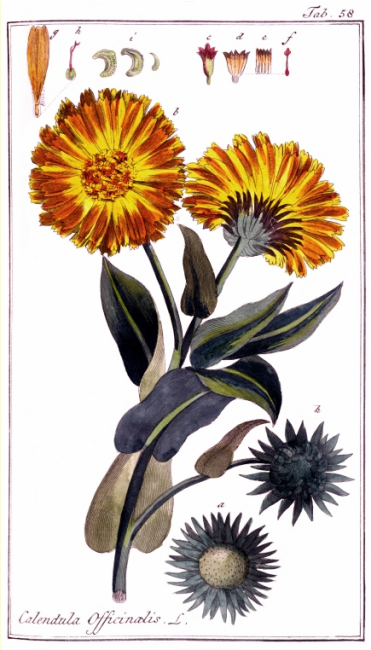
Bønaa K et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 354 (2006): 1578-88.

Botez MI. Folate deficiency and neurological disorders in adults. Med Hypotheses 2 (1976): 135-240.

Bottiglieri T. Homocysteine and folate metabolism in depression. Progr Neuro-psychopharmacol Biol Psychiatry 29 (2005): 1103-12.
Butterworth CE Jr et al: Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. Am J Clin Nutr 35.1 (1982): 73-82.
Carmel R. Folic acid. In: Shils M et al (eds). Modern Nutrition in Health and Disease. Baltimore: Lippincott Williams & Wilkins, 2006; 470-81.
Carney MW et al. Red cell folate concentrations in psychiatric patients. J Affect Disord 19.3 (1990): 207-13.
Charles D et al. Taking folate in pregnancy and risk of maternal breast cancer. BMJ 329 (2004): 1375-6.
Childers JM et al. Chemoprevention of cervical cancer with folic acid: phase III (Southwest Oncology Group Intergroup Study). Cancer Epidemiol Biomarkers Prev 4.2 (1995): 155-9.
Choi S et al. Folate and carcinogenesis: An integrated scheme. J Nutr 130 (2000): 129-32.
Choi S et al. Folate status: Effects on pathways of colorectal carcinogensis. J Nutr 132 (2002): 2413–18S.
Clarke R et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 324 (1991): 1149-55.
Cravo ML et al. Folate deficiency enhances the development of colonic neoplasia in dimethylhydrazine-treated rats. Cancer Res 52.18 (1992): 5002-6.
Cuskelly GJ, McNulty H, Scott JM. Effect of increased dietary folate on red-cell folate: implications for the prevention of neural tube defects. Lancet 47.9002 (1996): 657-9.
Daly LE et al. Folate levels and neural tube defects. Implications for prevention. JAMA 274 (1995): 1698-702.
Das U. Folic acid says NO to vascular diseases. Nutrition 19.7-8 (2003): 686-92.
den Heijer M et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 334 (1996): 759-62.
Drew HJ et al. Effect of folate on phenytoin hyperplasia. J Clin Periodontal 14.6 (1987): 350-6.
Eskes T. Abnormal folate metabolism in mothers with Down syndrome offspring: Review of the literature. Eur J Obstet Gynecol Reprod Biol 124 (2006): 130-3.
Food and Agriculture Organization of the United Nations/World Health Organization. FAO/WHO Expert Consultation 2000: Folate and Folic Acid, Ch. 4. Rome: FAO, 2000.
Froscher W et al. Folate deficiency, anticonvulsant drugs, and psychiatric morbidity. Clin Neuropharmacol 18.2 (1995): 165-82.
George L et al. Plasma folate levels and risk of spontaneous abortion. JAMA 288.15 (2002): 1867-73.
Gok U et al. Comparative analysis of serum homocysteine, folic acid and vitamin B12 levels in patients with noise-induced hearing loss. Auris Nasus Larynx 31.1 (2004): 19-22.
Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism. Belmont, CA: Wadsworth, 2000.
Gropper S, Smith J, Groff J. Advanced Nutrition and Human Metabolism, 4th edn. Belmont, CA: Wadsworth Thomson Learning, 2005.
Haggarty P et al. Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet 367 (2006): 1513-19.
Henao O et al. Women with polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS) are less likely to have cervical intraepithelial neoplasia (CIN) 2 or 3. Int J Cancer 113.6 (2005): 991-7.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Hickling S et al. Impact of voluntary folate fortification on plasma homocysteine and serum folate in Australia from 1995 to 2001: a population based cohort study. J Epidemiol Community Health 59 (2005): 371-6.
Juhlin L, Olsson M J. Improvement of vitiligo after oral treatment with vitamin B12 and folic acid and the importance of sun exposure. Acta Derm Venereol 77.6 (1997): 460-2.
Kelly GS. Folate supplemental forms and therapeutic applications. Altern Med Rev 3 (1998): 208-20.
Kelly C et al. The MTHFR C677T polymorphism is associated with depressive episodes in patients from Northern Ireland. J Psychopharmacol 18.4 (2004): 567-71.
Kemperman R et al. Low essential fatty acids and B-vitamin status in a subgroup of patients with schizophrenia and its response to dietary supplementation. Prostaglandins Leukot Essent Fatty Acids 74 (2006): 75-85.



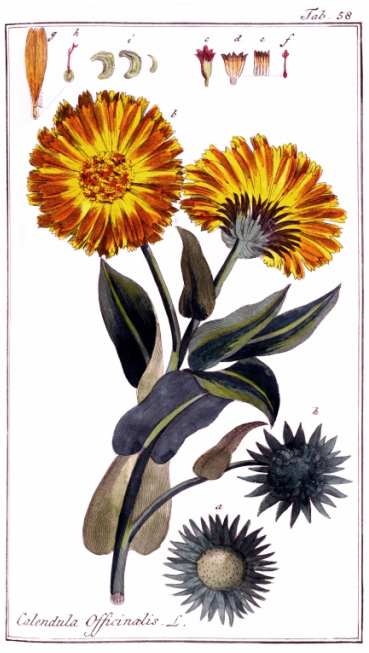
Kim YI et al. Dietary folate protects against the development of macroscopic colonic neoplasia in a dose responsive manner in rats. Gut 39.5 (1996): 732-40.
Kumar P, Clarke M. Clinical Medicine, 5th edn. London: WB Saunders, 2002.
Kwanbunjan K et al. Low folate status as a risk factor for cervical dysplasia in Thai women. Nutr Res 25 (2005): 641-54.
Lambie DG, Johnson RH. Drugs and folate metabolism. Drugs 30.2 (1985): 145-55.
Lange H et al. Folate therapy and in-stent restenosis after coronary stenting. N Engl J Med 350 (2004): 2673-81.
Lerner V et al. Vitamin B12 and folate serum levels in newly admitted psychiatric patients. Clin Nutr 25 (2006): 60-7.
Liem A et al. Secondary prevention with folic acid: effects on clinical outcomes. J Am Coll Cardiol 41.12 (2003): 2105-13.
Lucock M. Is folic acid the ultimate functional food component for disease prevention? BMJ 328 (2004): 211-14.
Lussanaa F et al. Blood levels of homocysteine, folate, vitamin B6 and B12 in women using oral contraceptives compared to non-users. Thromb Res 112.1-2 (2003): 37-41.
Ma J et al. Methylenetertahydrofolate reductase polymorphism, plasma folate, homocysteine, and risk of myocardial infarction in US physicians. Circulation 1994.10 (1996): 2410-16.
Malinow MR et al. Prevalence of hyperhomocyst(e)inemia in patients with peripheral arterial occlusive disease. Circulation 79 (1989): 1180-8.
Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 4 (2003): CD004514.
Marcucci R et al. Vitamin supplementation reduces the progression of atherosclerosis in hyperhomocysteinemic renal-transplant recipients. Transplantation 75.9 (2003): 1551-5.
Metz J et al. Changes in serum folate concentrations following voluntary food fortification in Australia. Med J Aust 176.2 (2002): 90-1.
Muntjewerff J-W, Blom H. Aberrant folate status in schizophrenic patients: What is the evidence? Prog Neuro-psychopharmacol Biol Psychiatry 29.7 (2005): 1133-9.
National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Canberra: Department of Health and Ageing, 2005: 87-94.
Nowak M et al. Homocysteine, vitamin B12, and folic acid in age-related macular degeneration. Eur J Ophthalmol 15.6 (2005): 764-7.
Oritz Z et al. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis: A metaanalysis of randomized controlled trials. J Rheumatol 25.1 (1998): 36-43.
Pack ARC. Folate mouthwash: effects on established gingivitis in periodontal patients. J Clin Periodontol 11.9 (1984): 619-28.
Papakostas G et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder. Part 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry 65.8 (2004a): 1090-5.
Papakostas G et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder. Part 2: predictors of relapse during the continuation phase of pharmacotherapy. J Clin Psychiatry 65.8 (2004b): 1096-8.
Papakostas G et al. The relationship between serum folate, vitamin B12, and homocysteine levels in major depressive disorder and the timing of improvement with fluoxetine. Int J Neuro-psychopharmacol 8.4 (2005): 523-8.
Passeri M et al. Oral 5-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicentre study. Aging Clin Exp Res 5 (1993): 63-71.
Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.
Piyathilake C et al. Folate is associated with the natural history of high-risk human papillomaviruses. Cancer Res 64 (2004): 8788-93.



Powers H. Interaction among folate, riboflavin, genotype, and cancer, with reference to colorectal and cervical cancer. J Nutr 135 (2005): 2960-6S.
Procter A. Enhancement of recovery from psychiatric illness by methylfolate. Br J Psychiatry 159 (1991): 271-2.
Ray JG, Singh G, Burrows RF. Evidence for suboptimal use of periconceptional folic acid supplements globally. Br J Obstet Gynaecol 111.5 (2004): 399-408.
Reed JD et al. Nutrition and sickle cell disease. Am J Hematol 24.4 (1987): 441-55.
Regland B. Schizophrenia and single-carbon metabolism. Prog Neuro-psychopharmacol Biol Psychiatry 29 (2005): 1124-32.
Revell P et al. Folic acid absorption in patients infected with human immunodeficiency virus. J Intern Med 230 (1991): 227-31.
Reynolds EH. Folic acid, ageing, depression and dementia. BMJ 324 (2002): 1512-15.
Rivey MP, Schottelius DD, Berg MJ. Phenytoin-folic acid: a review. Drug Intell Clin Pharm 18.4 (1984): 292-301.
Schnyder G et al. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. JAMA 288.8 (2002): 973-9.
Scott T et al. Homocysteine and B vitamins relate to brain volume and white-matter changes in geriatric patients with psychiatric disorders. Am J Geriatr Psychiatry 12.6 (2004): 631-8.
Sedjo R et al. Folate, vitamin B12, and homocysteine status. findings of no relation between human papillomavirus persistence and cervical dysplasia. Nutrition 19.6 (2003): 497-502.
Selhub J et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 332 (1995): 286-91.
Seshadri S et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 346 (2002): 476-83.
Sharp L, Little J. Polymorphisms in genes involved in folate metabolism and colorectal neoplasia: a HuGE review. Am J Clin Epidemiol 159.5 (2004): 423-43.
Sram R et al. The impact of plasma folate levels of mothers and newborns on intrauterine growth retardation and birth weight. Mutat Res 591 (2005): 302-10.
Strober B, Menon K. Folate supplementation during methotrexate therapy for patients with psoriasis. J Am Acad Dermatol 53 (2005): 652-9.
Sütterlin M et al. Serum folate and vitamin B12 levels in women using modern oral contraceptives (OC) containing 20 µg ethinyl estradiol. Eur J Obstet Gynecol Reprod Biol 107.1 (2003): 57-61.
Taylor MJ et al. Folate for depressive disorders. Cochrane Database Syst Rev 2 (2003).
Thomson ME, Pack ARC. Effects of extended systemic and topical folate supplementation on gingivitis of pregnancy. J Clin Periodontol 9.3 (1982): 275-80.
Tjioe M et al. Treatment of vitiligo with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. Acta Derm Venereol 82.5 (2002): 369-72.
Tolmunen T et al. Dietary folate and the risk of depression in Finnish middle-aged men: A prospective follow-up study. Psychother Psychosom 73.6 (2004): 334-9.
Van Guelpen B et al. Low folate levels may protect against colorectal cancer. Gut (2006) [Epub ahead of print].
Verhaar MC, Stroes E, Rabelink TJ. Folates and cardiovascular disease. Arterioscler Thromb Vasc Biol 22 (2002): 6.
Vogel RI et al: The effect of folic acid on gingival health. J Periodontol 47.11 (1976): 667-8.
Voutilainen S et al. Low dietary folate intake is associated with and excess incidence of acute coronary events. Circulation 103 (2001): 2674.
Wahlqvist ML (ed.) Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Watson L, Brown S, Davey M. Use of periconceptional folic acid supplements in Victoria and New South Wales, Australia. Aust NZ J Public Health 30.1 (2006): 42-9.
Wilson JD et al. Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991.

Young SN, Ghadirian AM. Folic acid and psychopathology. Prog Neuro-psychopharmacol Biol Psychiatry 13.6 (1989): 841-63.
Zetterberg H. Methylenetetrahydrofolate reductase and transcobalamin genetic polymorphisms in human spontaneous abortion: biological and clinical implications. Reprod Biol Endocrinol 2.7 (2004): 1-8.

Garlic



Historical note Garlic has been used as both a food and a medicine since antiquity. Legend has it that garlic was used in ancient Egypt to increase workers' resistance to infection and later used externally to prevent wound infection. Other ancient civilizations have also used it medicinally. Sanskrit records document the use of garlic approximately 5000 years ago and the Chinese have been using it for over 3000 years. One of the uses of garlic was as a treatment for tumours, a use which extends back to the Egyptian Codex Ebers of 1550 BC (Hassan 2004). Louis Pasteur was one of the first scientists to confirm that garlic had antimicrobial properties. Garlic was used to prevent gangrene and treat infection in both world wars. Traditionally, garlic has been used as a warming and blood cleansing herb to prevent and treat colds and flu, coughs, menstrual pain and expel worms and other parasites.

COMMON NAME
Garlic

OTHER NAMES
Ail, ajo, allium, camphor of the poor, da-suan, knoblauch, la-juan, poor man's treacle, rustic treacle, stinking rose

BOTANICAL NAME/FAMILY
Allium sativum (family Liliaceae)

PLANT PART USED
Bulb, and oil from the bulb

CHEMICAL COMPONENTS
Garlic bulbs contain organosulfur compounds, protein (mainly alliinase), amino acids (such as arginine, lysine, threonine and tryptophan), fibre, lipids, phytic acid, saponins, beta-sitosterol and small quantities of vitamins and minerals such as vitamin C, vitamin E, beta-carotene, chromium, iron and selenium (Duke 2003).

Of the numerous constituents present, it is the alliin component and resultant degradation products, such as allicin and ajoene, that produce much of the herb's pharmacological activity. These are formed when garlic is crushed or chewed and alliin is exposed to the enzyme alliinase.

According to Commission E, 1 mg of alliin produces 0.458 mg of allicin (Blumenthal et al 2000).

MAIN ACTIONS

ANTIOXIDANT

Garlic has strong antioxidant activity and is capable of directly scavenging free radicals, and indirectly by enhancing endogenous antioxidant systems such as glutathione, superoxide dismutase, catalase and glutathione peroxidase (Wei & Lau 1998).

INHIBITS PLATELET AGGREGATION AND ANTITHROMBOTIC EFFECTS

It appears that the method of garlic preparation has a great influence over its antiplatelet activity in humans (Lawson et al 1992, Rahman & Billington 2000). Additionally, antithrombotic activity has been identified under clinical conditions (Ali & Thomson 1995).

STIMULATES FIBRINOLYSIS

A significant increase in fibrinolysis has been observed in several clinical tests for both raw and fried garlic (Bordia et al 1998, Chutani & Bordia 1981, Gadkari & Joshi 1991).

REDUCES SERUM CHOLESTEROL LEVELS

A 2000 meta-analysis of 13 clinical trials concluded that garlic is superior to placebo in reducing total cholesterol levels, exerting a modest effect (Stevinson et al 2001). The mechanism of action involves inhibition of cholesterol synthesis by deactivating HMG-CoA reductase via enhanced phosphorylation, but not changing the amount of the enzyme, according to in vitro research (Liu & Yeh 2002). The compounds containing an allyl-disulfide or allyl-sulfhydryl group are most likely responsible for the inhibition of cholesterol synthesis by garlic and that this inhibition is likely to be mediated at sterol 4-alpha-methyl oxidase (Singh & Porter 2006). Clinical evidence also suggests it raises HDL levels and reduces triglyceride levels (Bordia et al 1998).

ANTIHYPERTENSIVE ACTIVITY

Numerous clinical studies have identified antihypertensive activity with garlic (Andrianova et al 2002, Silagy & Neil 1994). Although the mechanism of action has not been fully elucidated, evidence from in vivo research suggests that both the renin–angiotensin system and the NO system are responsible for this activity (Mohamadi et al 2000).

ANTIMICROBIAL AND IMMUNE-ENHANCING ACTIVITY

Garlic appears to exert both direct and indirect effects against various pathogens, as it enhances macrophage and T-lymphocyte function (Lau et al 1991) and has direct antibacterial, antifungal, antiviral and antiparasitic activity.

Allicin is believed to be chiefly responsible for garlic's antimicrobial activity. More specifically, it has been found to exert antibacterial activity against a wide range of Gram-negative and Gram-positive bacteria, including multidrug-resistant enterotoxicogenic strains of *Escherichia coli, Staphylococcus aureus, Mycobacterium tuberculosis*, *Proteus* spp., *Streptococcus faecalis* and *Pseudomonas aeruginosa*; antifungal activity particularly against *Candida albicans*; antiparasitic activity against some of the major human intestinal protozoan parasites such as *Entamoeba histolytica* and *Giardia lamblia*; and antiviral activity (Ankri & Mirelman 1999). Ajoene is another important antimicrobial constituent, with greater antiviral activity than allicin, according to one in vitro test (Weber et al 1992).

***Helicobacter pylori* infection** Several in vitro and in vivo tests have shown that garlic has activity against *H. pylori* (Chung et al 1998, Jonkers et al 1999, O'Gara et al 2000); however, results from clinical studies are equivocal. Two studies found that a combination of garlic and omeprazole produced synergistic effects against *H. pylori* (Cellini et al 1996, Jonkers et al 1999).

ANTINEOPLASTIC AND CHEMOPREVENTATIVE EFFECTS

Many studies have reported antineoplastic effects of both oil and water soluble allyl sulfur compounds from garlic, but the effect is generally greater for the lipid-soluble compounds (Knowles & Milner 2001). Diallyl disulfide, one of the most studied oil-soluble organosulfur compounds in garlic, has demonstrated antineoplastic activity against both hormone-dependent and hormone-independent breast cancer cell lines (Nakagawa et al 2001). It also inhibits the proliferation of human tumour cell lines for colon, lung and skin cancer (Sundaram & Milner 1996). Garlic derivatives inhibit proliferation of human prostate cancer cell lines and human breast cancer cell lines (Pinto & Rivlin 2001). In vitro results also show ajoene induces apoptosis in human leukaemic cells (Dirsch et al 2002), whereas allicin, but not its precursor alliin, inhibits proliferation of human mammary, endometrial, and colon cancer cells (Hirsch et al 2000).

Several mechanisms appear to be involved. Notable among these is a depression in nitrosamine formation and a reduction in carcinogen bioactivation (Milner 2001). This is thought to involve an inhibitory effect on CYP2E1, one of the isoenzymes responsible for the activation of a number of carcinogens (Yang et al 2001). Some of the organosulfur compounds may also aid detoxification by enhancing glutathione S-

transferases, thereby reducing carcinogen loads (Bianchini & Vainio 2001). Suppression of proliferation associated with a depression in cell cycle progression and the induction of apoptosis has also been observed (Knowles & Milner 2001).

ANTIATHEROSCLEROTIC ACTIVITY

Evidence from in vitro, animal and human research has shown that garlic supplementation significantly reduces the atherosclerotic process (Campbell et al 2001, Durak et al 2002, Ferri et al 2003, Koscielny et al 1999, Kwon et al 2003, Orekhov et al 1995). More specifically, garlic significantly decreased aortic tissue cholesterol as determined biochemically, fatty streak formation and the size of atherosclerotic plaque, compared with controls in an animal model (Campbell et al 2001).

Similar results have been obtained using ultrasound techniques in a randomised, double-blind, placebo-controlled clinical trial, involving 152 people (Koscielny et al 1999). Not only did high-dose garlic powder significantly reduce arteriosclerotic plaque volume, it also induced a slight regression in plaque spread within the 4-year test period. Later, these results were found to be significant only in females.

Results from several recently published animal studies further confirm antiatherogenic effects and have investigated the mechanisms responsible (Durak et al 2002, Ferri et al 2003, Kwon et al 2003). One in-vivo study found that garlic activated antioxidant systems and decreased peroxidation in aortic tissue (Durak et al 2002) whereas ajoene inhibited smooth muscle cell proliferation in another (Ferri et al 2003).

OTHER ACTIONS

HYPOGLYCAEMIC ACTIVITY

Over a decade ago, one double-blind study reported that 800 mg garlic powder taken daily for a period of 4 weeks reduced blood glucose concentrations by 11.6% (Kiesewetter et al 1993). However, a more recent study using a higher dose of 3 g/day over 26 weeks found no effects (Ali & Thomson 1995).

ANTI-INFLAMMATORY ACTIVITY

Fresh garlic extracts and garlic oil have been shown to inhibit COX activity in test tube and animal studies (Bordia et al 1996, Thomson et al 2000).

HEPATOPROTECTIVE EFFECTS

Aged garlic extract has a glutathione-sparing effect in the liver and specifically elevates reduced glutathione content, thereby enhancing endogenous protective mechanisms, according to in vitro tests (Wang et al 1999).

ENHANCES MICROCIRCULATION

Jung et al (1991) found that 5 hours after the administration of garlic powder (Kwai: total dose 900 mg garlic powder) a significant increase in capillary skin perfusion (55%) occurred in the healthy volunteers, whereas Kiesewetter et al (1993) showed a 48% increase with a dose of 800 mg garlic.

MODULATES CYTOCHROME P450

Garlic may have the potential to alter CYP450 enzymes; however, results from in vitro, animal and human studies are confusing. Garlic oil induced CYP450 according to one animal study (Dalvi 1992), whereas in vitro tests failed to identify an inhibitory effect on cytochrome P450 (2C9*1, 2C19, 3A4, 3A5 and 3A7) (Foster et al 2001). Other researchers using human volunteers found that garlic oil reduced CYP2E1 activity by 39%, but had no effect on CYP1A2, CYP2D6 or CYP3A4 activity (Gurley et al 2002).

Recently, an interaction between saquinivir and garlic has been reported, suggestive of a CYP induction effect, but human tests do not support this theory (Piscitelli et al 2002).

CLINICAL USE

Most studies have used a non-enteric coated dehydrated garlic powder preparation standardised to 1.3% alliin content (Kwai, Lichtwer Pharma) or an aged garlic extract (Kyolic, Wakunaga of America).

CARDIOVASCULAR DISEASE

Epidemiologic studies show an inverse correlation between garlic consumption and progression of CVD in general (Rahman & Lowe 2006).

This review will consider the evidence for garlic in the management of specific risk factors such as hypertension and hyperlipidaemia. Additionally, investigation into the effects of garlic directly on the atherosclerotic and arteriosclerotic processes is presented.

Hypertension A meta-analysis of seven clinical trials using a garlic preparation, produced commercially as Kwai, found that three showed a significant reduction in SBP and four in DBP (Silagy & Neil 1994). Kwai was used in these studies in the dosage of 600–900 mg daily. Garlic treatment resulted in a mean reduction in SBP of 7.7 mmHg and 5.0 mmHg in DBP compared with placebo.

In 2000, the Agency for Health Care Research and Quality analysed results from 27 randomised, placebo-controlled trials and reported that results were mixed (Mulrow et al 2000). When significant reductions in blood pressure were observed, these were small.

Several newer trials have since been published further confirming that the effect on blood pressure is small and sometimes non-significant (Andrianova et al 2002, McMahon & Vargas 1993, Zhang et al 2001a).

Atherosclerosis and arteriosclerosis Garlic indirectly affects atherosclerosis by reduction of hyperlipidaemia, hypertension, and prevention of thrombus formation.

Koscielny et al conducted a randomised, double-blind, placebo-controlled clinical trial involving 152 volunteers to determine whether garlic powder supplements (Kwai 900 mg daily) directly alter plaque volumes in carotid and/or femoral arteries (Koscielny et al 1999). After 4 years' treatment, garlic intake significantly reduced the expected increase in arteriosclerotic plaque volume by 5–18%, with a slight regression also observed. A subsequent re-evaluation of the results found that significant effects were limited to women only (Siegel & Klussendorf 2000).

Hyperlipidaemia In 2000, a meta-analysis of 13 clinical trials concluded that garlic reduces total cholesterol levels significantly more than placebo; however, the effects can only be described as modest (Stevinson et al 2001). The same year, a systematic review and meta-analysis were published by the Agency for Health Care Research and Quality, which analysed results from 44 studies with lipid outcomes (Mulrow et al 2000a). Most studies involved fewer than 100 volunteers and randomisation techniques were unclear in 82% of studies. Pooled data from the placebo-controlled trials reporting changes in total cholesterol levels found a significant average reduction in total cholesterol levels of 7.2 mg/dL after 4–6 weeks using any form of garlic and a reduction of 17.1 mg/dL at 8–12 weeks. Results at 20–24 weeks were not significant and thought to be due to low statistical power, fewer long-term studies or a time-dependant effect of garlic.

Since then several new studies have been published, with most showing no significant reduction to total cholesterol levels (Gardner et al 2001, Kannar et al 2001, Peleg et al 2003, Turner et al 2004, Zhang et al 2001b, Ziaei et al 2001). According to one review, non-enteric coated tablets containing dehydrated garlic powder (standardised to 1.3% allicin) produce the most consistent results (Ulbricht & Basch 2005).

Comparative studies Two clinical studies have compared different garlic preparations with pharmaceutical cholesterol-lowering medicines. Garlic taken as 300 mg three times daily (Kwai) produced similar lipid-lowering effects to 200 mg bezafibrate (a hypolipidaemic fibrate) three times daily in subjects with primary hyperlipidaemia (Holzgartner et al 1992) whereas clofibrate 500 mg was more effective than an essential oil extract of 50 g raw garlic (Arora & Arora 1981).

Commission E approves the use of garlic as an adjunct to dietary changes in the treatment of hyperlipidaemia (Blumenthal et al 2000).

Diabetics with hyperlipidaemia A 12-week placebo-controlled, single-blind, randomised study of 70 patients with type 2 diabetes and newly diagnosed dyslipidaemia found that treatment with a garlic tablet (Garlex-Bosch Pharmaceuticals: 300 mg, containing 1.3% allicin) twice daily, together with a diet and exercise plan, resulted in a significant reduction in total cholesterol of 28 mg/dL (12.03%) compared to placebo (Ashraf et al 2005).

Clinical note — Not all garlic preparations are the same

One of the difficulties encountered when interpreting the research available for garlic is comparing the effects of different preparations, which often have not been tested for the presence of important constituents or allicin-releasing potential. It is known that fresh garlic and dried garlic powder contain alliin and the enzyme allinase required for biotransformation, but some other forms may only contain alliin, and not the necessary alliinase component, thus compromising allicin-releasing potential. An example of the manufacturing process affecting potency has been suggested for a commercial garlic product known as Kwai, which has often been used in cholesterol research (Lawson et al 2001). According to a 2001 experiment, substantial differences were found between tablets manufactured before 1993 (the years when all but one of the positive trials were conducted) and those manufactured after 1993 (the years when all of the negative trials were conducted). Kwai products manufactured after 1993 released only one-third as much allicin as older preparations. Those preparations from before 1993 disintegrated more slowly, protecting alliinase from acid exposure and inactivation.

Antiplatelet effects Antiplatelet effects of garlic are well recognised, but the dose at which this becomes significant remains uncertain. Results from a 2001 double-blind study have identified a dose of 7.2 g/day of aged garlic extract as significantly inhibiting platelet aggregation and adhesion (Steiner et al 1996).

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

In 2000, Mulrow et al reported on two double-blind, placebo-controlled trials in participants with atherosclerotic lower extremity disease (Mulrow et al 2000b). One study of 64 participants showed that pain-free walking increased by approximately 40 metres with standardised dehydrated garlic (Kwai 800 mg daily) compared with approximately 30 metres with placebo over 12 weeks. Cochrane reviewers report that the effect was not significant (Jepson et al 2000). The other study of 100 participants (Mulrow et al 2000b) showed that a combination treatment of garlic oil macer-

ate/soya lecithin/hawthorn oil/wheat germ oil significantly increased the maximum walking distance (114%) compared to placebo (17%) ($P < 0.05$).

INFECTION

Garlic oil is effective against numerous bacteria, viruses and fungi including *Staphylococcus aureus*, MRSA, and several species of *Candida, Aspergillus* and *Cryptococcus neoformans* in vitro (Davis et al 1994, Tsao & Yin 2001, Yoshida et al 1987). As such, it has been used both internally and externally to treat various infections and prevent wound infection.

Tinea pedis, tinea corporis, tinea cruris A trial comparing the effects of three different strengths of ajoene cream (0.4%, 0.6% and 1%) with 1% terbinafine applied twice daily found the cure rate to be 72% for 0.6% ajoene, 100% for 1% ajoene, and 94% for 1% terbinafine after 60 days (Ledezma et al 2000).

Vaginitis Taken internally as a 'natural antibiotic' or applied topically in a cream base, garlic is used to treat vaginitis. The considerable antibacterial activity of garlic provides a theoretical basis for its use in this condition, but controlled studies are not available to determine effectiveness.

Common cold prevention A 12-week, double-blind randomised study involving 146 people demonstrated that allicin-containing garlic preparations significantly reduce the incidence of colds and accelerate recovery compared with placebo (Josling 2001). More specifically, the number of symptom days in the placebo group was 5.01 compared with 1.52 days in the garlic treated group. Additionally, garlic reduced the incidence of developing a second cold whereas placebo did not.

***Helicobacter pylori* infection** It has been suggested that gastrointestinal lesions, such as gastric ulcers, duodenal ulcers and gastric cancers, are strongly associated with *H. pylori* infection (Scheiman & Cutler 1999). Medical treatment consisting of 'triple therapy' has a high eradication rate, yet is associated with side-effects and has started to give rise to antibiotic resistance. Since garlic intake has been associated with a lowered incidence of stomach cancer, researchers have started investigating whether garlic has activity against *H. pylori*. Several in vitro and in vivo tests have shown garlic to be effective against *H. pylori* (see MAIN ACTIONS). However, to date only a few small clinical trials have been conducted with disappointing and controversial results (Aydin et al 2000, Graham et al 1999, McNulty et al 2001).

A small pilot study of dyspeptic patients with confirmed *H. pylori* infection found that treatment with 4 mg garlic oil capsules taken four times daily with meals for 14 days did not alter symptoms or lead to *H. pylori* eradication (McNulty et al 2001). Another small study using garlic oil 275 mg three times a day (allicin 800 μg/capsule) either as stand-alone treatment or in combination with omeprazole (20 mg twice

daily) found that both treatments produced similar results (Aydin et al 2000). These results were confirmed in another small clinical study (Graham et al 1999).

PROTECTIVE EFFECTS AGAINST CANCER

A 2001 critical review of the epidemiological evidence suggests a preventive effect for garlic consumption in stomach and colorectal cancers, but not other cancers (Fleischauer & Arab 2001). In regard to gastric cancer protection, case-control studies suggested a protective effect for raw and/or cooked garlic when eaten at least once a week whereas protective effects against colorectal cancer seem to require at least two servings of garlic per week. A similar view was reported in a 2003 review by Ernst, which stated that the weight of evidence to support the use of allium vegetables, such as garlic, in cancer is clearly positive.

Intervention study in colorectal cancer A preliminary double-blind, randomised clinical trial in patients with colorectal adenomas–precancerous lesions of the large bowel produced promising results with the use of high-dose aged garlic extract (AGE 2.4 mL/day) (Tanaka et al 2006). The study of 51 patients measured the number and size of adenomas at baseline and at 6 and 12 months and found that AGE significantly suppressed both the size and the number of colon adenomas in patients after 1 year of treatment ($P = 0.04$). In comparison, the number of adenomas increased linearly in the control group from the beginning.

OTHER USES

Some early research suggests that it may prevent the incidence of altitude sickness (Fallon et al 1998, Kim-Park & Ku 2000) and reduce mosquito numbers (Jarial 2001). It has also been used to assist in heavy metal detoxification. Studies with experimental animal models provide some support for its use in this way (Bone & Morgan 2005).

DOSAGE RANGE

GENERAL GUIDE

- Fresh garlic: 2–5 g/day (ensure it is bruised, crushed or chewed).
- Dried powder: 0.4–1.2 g/day.
- Aged-garlic extracts have been studied in amounts ranging from 2.4 to 7.2 g/day.
- Oil: 2–5 mg/day.
- Garlic preparations that will provide 4–12 mg alliin daily.
- Fluid extract (1:1): 0.5–2 mL three times daily.

ACCORDING TO CLINICAL STUDIES

- Hypertension: 600–900 mg/day in divided doses (delivering approximately 5000–6000 μg allicin potential).

- Hyperlipidaemia: 600–9000 mg/day.
- Fungal infection: topical 0.4–0.6% ajoene cream applied twice daily.
- Occlusive arterial disease: 600–800 mg/day.

It is important to be aware of the thiosulfinate content, in particular allicin-releasing ability, of any commercial product to ensure efficacy.

ADVERSE REACTIONS

INTERNAL USE

Breath and body odour, allergic reactions, nausea, heartburn, flatulence, abdominal discomfort and diarrhoea have been reported (Berthold et al 1998).

Headache, myalgia and fatigue were reported in one study using a dose of 900 mg garlic powder (standardised to 1.3% alliin) (Holzgartner et al 1992).

TOPICAL USE

An ajoene 0.6% gel produces a transient burning sensation after application, according to one study (Ledezma et al 1999). Contact dermatitis can occur — one study using patch testing found that 5.2% of volunteers had contact sensitisation (Lembo et al 1991).

SIGNIFICANT INTERACTIONS

SAQUINAVIR

A clinical study showed that garlic reduces blood levels of saquinavir and therefore may reduce efficacy of drug — avoid using concurrently (Piscitelli et al 2002).

ANTICOAGULANTS

Potentiation effects are possible when using garlic at high doses (>4 g) in excess of usual dietary amounts. Avoid high doses in patients taking anticoagulants unless under professional supervision.

ANTIPLATELET DRUGS

Potentiation effects are possible when using garlic at high doses in excess of usual dietary amounts. Use high doses with caution in patients taking antiplatelet drugs.

ANTIHYPERTENSIVE AGENTS

Theoretically, potentiation effects are possible when using garlic at high doses in excess of usual dietary amounts.

ANTIHYPERLIPIDAEMIC AGENTS

Theoretically, potentiation effects are possible when using garlic at high doses in excess of usual dietary amounts however the effect is likely to be minimal — observe.

HELICOBACTER PYLORI TRIPLE THERAPY

Additive effects are theoretically possible. While it is prudent to observe the patient for adverse reactions, the interaction may be beneficial.

HEPATOTOXIC DRUGS

Garlic may exert hepatoprotective activity against liver damage induced by drugs according to in vitro tests, which suggests a beneficial interaction.

PARACETAMOL

In vivo protection from garlic and ajoene on paracetamol-induced hepatotoxicity has been observed (Hsu et al 2006) — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Patients with bleeding abnormalities should avoid therapeutic doses of garlic. Although usual dietary intakes are likely to be safe prior to major surgery, suspend the use of high-dose garlic supplements 1 week before, as garlic may increase bleeding risk.

If being used as part of a topical application, a test patch is advised before more widespread application.

PREGNANCY USE

Garlic is not recommended at doses greater than usual dietary intakes.

PRACTICE POINTS/PATIENT COUNSELLING

- Garlic is both a food and a therapeutic medicine capable of significant and varied pharmacological activity.
- It has antioxidant, antimicrobial, antiplatelet, antithrombotic, antihypertensive, lipid-lowering, anti-atherosclerotic and vasoprotective activity.
- It also enhances microcirculation and may have hypoglycaemic, anti-inflammatory and immunostimulant activity.
- Garlic is used as a treatment for many common infections, to reduce the incidence of colds, improve peripheral circulation and manage hyperlipidaemia and hypertension.
- Increased consumption of garlic has been associated with a decreased risk of stomach and colorectal cancer, according to a review of the epidemiological evidence.
- Several important drug interactions are possible with garlic (refer to significant interactions).

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

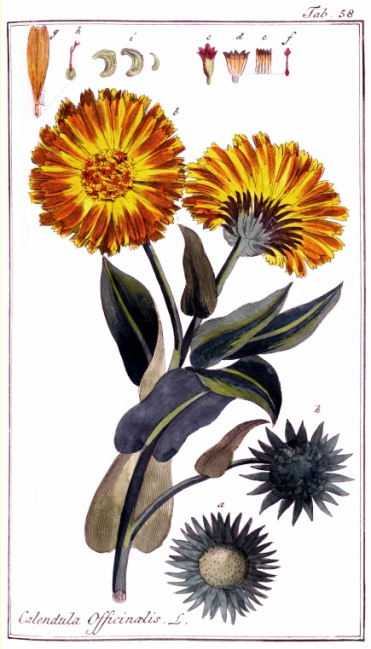
Garlic has many different actions in the body and is used to treat conditions such as elevated blood pressure, cholesterol levels, poor peripheral circulation and common infections such as the common cold, flu and athletes foot. Research suggests it may be effective in all of these conditions; however, in some cases, the effect is small.

When will it start to work?

This varies greatly, depending on the reason for use. For example, garlic has been shown to improve microcirculation within 5 hours of ingestion, whereas slowing down of the atherosclerotic process or cancer protective effects are likely to require several years' continuous use.

Are there any safety issues?

When garlic is taken at doses above the usual dietary levels, it may interact with a number of medications. Also, it should not be taken by people with bleeding disorders and use should stop at least 2 weeks before major surgery.



REFERENCES

Ali M, Thomson M. Consumption of a garlic clove a day could be beneficial in preventing thrombosis. Prostaglandins Leukot Essent Fatty Acids 53.3 (1995): 211-12.

Andrianova IV, Fomchenkov IV, Orekhov AN. [Hypotensive effect of long-acting garlic tablets allicor (a double-blind placebo-controlled trial)]. Ter Arkh 74.3 (2002): 76-8.

Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic. Microbes Infect 1.2 (1999): 125-9.

Arora RC, Arora S. Comparative effect of clofibrate, garlic and onion on alimentary hyperlipidemia. Atherosclerosis 39.4 (1981): 447-52.

Ashraf R, Aamir K, Shaikh AR, Ahmed T. Effects of garlic on dyslipidemia in patients with type 2 diabetes mellitus. J Ayub Med Coll Abbottabad 17.3 (2005): 60-4.

Aydin A et al. Garlic oil and Helicobacter pylori infection. Am J Gastroenterol 95.2 (2000): 563-4.

Berthold HK, Sudhop T, von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. JAMA 279.23 (1998): 1900-2.

Bianchini F, Vainio H. Allium vegetables and organosulfur compounds: do they help prevent cancer? Environ Health Perspect 109.9 (2001): 893-902.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bone K, Morgan M. Herbs to assist heavy metal detoxification [abstract]. In: Herbs to Assist Heavy Metal Detoxification: A Phytotherapist's Perspective, Vol. 49, 2005.

Bordia A, Verma SK, Srivastava KC. Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 58.4 (1998): 257-63.

Bordia T et al. An evaluation of garlic and onion as antithrombotic agents. Prostaglandins Leukot Essent Fatty Acids 54.3 (1996): 183-6.

Campbell JH et al. Molecular basis by which garlic suppresses atherosclerosis. J Nutr 131.3s (2001): 1006-9S.

Cellini L et al. Inhibition of Helicobacter pylori by garlic extract (Allium sativum). FEMS Immunol Med Microbiol 13.4 (1996): 273-7.

Chung JG et al. Effects of garlic compounds diallyl sulfide and diallyl disulfide on arylamine N-acetyltransferase activity in strains of Helicobacter pylori from peptic ulcer patients. Am J Chin Med. 26.3-4 (1998): 353-64.

Chutani SK, Bordia A. The effect of fried versus raw garlic on fibrinolytic activity in man. Atherosclerosis 38.3-4 (1981): 417-21.
Dalvi RR. Alterations in hepatic phase I and phase II biotransformation enzymes by garlic oil in rats. Toxicol Lett 60.3 (1992): 299-305.
Davis LE, Shen J, Royer RE. In vitro synergism of concentrated Allium sativum extract and amphotericin B against Cryptococcus neoformans. Planta Med 60.6 (1994): 546-9.
Dirsch VM et al. Ajoene, an experimental anti-leukemic drug: mechanism of cell death. Leukemia 16.1 (2002): 74-83.
Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. www.ars-grin.gov/duke.
Durak I et al. Effects of garlic extract on oxidant/antioxidant status and atherosclerotic plaque formation in rabbit aorta. Nutr Metab Cardiovasc Dis 12.3 (2002): 141-7.
Ernst E. The current position of complementary/alternative medicine in cancer. Eur J Cancer 39.16 (2003): 2273-7.
Fallon MB et al. Garlic prevents hypoxic pulmonary hypertension in rats. Am J Physiol 275.2 (1998): L283-7.
Ferri N et al. Ajoene, a garlic compound, inhibits protein prenylation and arterial smooth muscle cell proliferation. Br J Pharmacol 138.5 (2003): 811-18.
Fleischauer AT, Arab L. Garlic and cancer: a critical review of the epidemiologic literature. J Nutr 131.3 [Suppl] (2001): 1032-40S.
Foster BC et al. An in vitro evaluation of human cytochrome P450 3A4 and P-glycoprotein inhibition by garlic. J Pharm Pharm Sci 4.2 (2001): 176-84.
Gadkari JV, Joshi VD. Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects. J Postgrad Med 37.3 (1991): 128-31.
Gardner CD, Chatterjee LM, Carlson JJ. The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. Atherosclerosis 154.1 (2001): 213-20.
Graham DY, Anderson SY, Lang T. Garlic or jalapeno peppers for treatment of Helicobacter pylori infection. Am J Gastroenterol 94.5 (1999): 1200-2.
Gurley BJ et al. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther 72.3 (2002): 276-87.
Hassan HT. Ajoene (natural garlic compound): a new anti-leukaemia agent for AML therapy. Leuk Res 28.7 (2004): 667-71.
Hirsch K et al. Effect of purified allicin, the major ingredient of freshly crushed garlic, on cancer cell proliferation. Nutr Cancer 38.2 (2000): 245-54.
Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. Arzneimittelforschung 42.12 (1992): 1473-7.
Hsu CC, Lin CC, Liao TS, Yin MC. Protective effect of s-allyl cysteine and s-propyl cysteine on acetaminophen-induced hepatotoxicity in mice. Food Chem Toxicol 44.3 (2006): 393-7.
Jarial MS. Toxic effect of garlic extracts on the eggs of Aedes aegypti (Diptera: Culicidae): a scanning electron microscopic study. J Med Entomol 38.3 (2001): 446-50.
Jepson RG, Kleijnen J, Leng GC. Garlic for peripheral arterial occlusive disease. Cochrane Database Syst Rev 2 (2000): CD000095.
Jonkers D et al. Antibacterial effect of garlic and omeprazole on Helicobacter pylori. J Antimicrob Chemother 43.6 (1999): 837-9.
Josling P. Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. Adv Ther 18.4 (2001): 189-93.
Jung EM et al. Influence of garlic powder on cutaneous microcirculation: A randomized placebo-controlled double-blind cross-over study in apparently healthy subjects. Arzneimittelforschung 41.6 (1991): 626-30.
Kannar D, Wattanapenpaiboon N, Savige GS, Wahlqvist ML. Hypocholesterolemic effect of an enteric-coated garlic supplement. J Am Coll Nutr 20.3 (2001): 225-31.

Kiesewetter H et al. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. Int J Clin Pharmacol Ther Toxicol 29.4 (1991): 151-5.
Kiesewetter H et al. Effects of garlic coated tablets in peripheral arterial occlusive disease. Clin Invest 71.5 (1993): 383-6.
Kim-Park S, Ku DD. Garlic elicits a nitric oxide-dependent relaxation and inhibits hypoxic pulmonary vasoconstriction in rats. Clin Exp Pharmacol Physiol 27.10 (2000): 780-6.
Knowles LM, Milner JA. Possible mechanism by which allyl sulfides suppress neoplastic cell proliferation. J Nutr 131.3 [Suppl] (2001): 1061-6S.
Koscielny J et al. The antiatherosclerotic effect of Allium sativum. Atherosclerosis 144.1 (1999): 237-49.
Kwon MJ et al. Cholesteryl ester transfer protein activity and atherogenic parameters in rabbits supplemented with cholesterol and garlic powder. Life Sci 72.26 (2003): 2953-64.
Lau BH, Yamasaki T, Gridley DS. Garlic compounds modulate macrophage and T-lymphocyte functions. Mol Biother 3.2 (1991): 103-7.
Lawson LD, Ransom DK, Hughes BG. Inhibition of whole blood platelet-aggregation by compounds in garlic clove extracts and commercial garlic products. Thromb Res 65.2 (1992): 141-56.
Lawson LD, Wang ZJ, Papadimitriou D. Allicin release under simulated gastrointestinal conditions from garlic powder tablets employed in clinical trials on serum cholesterol. Planta Med 67.1 (2001): 13-18.
Ledezma E et al. Ajoene in the topical short-term treatment of tinea cruris and tinea corporis in humans: Randomized comparative study with terbinafine. Arzneimittelforschung 49.6 (1999): 544-7.
Ledezma E et al. Efficacy of ajoene in the treatment of tinea pedis: a double-blind and comparative study with terbinafine. J Am Acad Dermatol 43.5 Pt 1 (2000): 829-32.
Lembo G et al. Allergic contact dermatitis due to garlic (Allium sativum). Contact Dermatitis 25.5 (1991): 330-1.
Liu L, Yeh YY. S-alk(en)yl cysteines of garlic inhibit cholesterol synthesis by deactivating HMG-CoA reductase in cultured rat hepatocytes. J Nutr 132.6 (2002): 1129-34.
McMahon FG, Vargas R. Can garlic lower blood pressure? A pilot study. Pharmacotherapy 13.4 (1993): 406-7.
McNulty CA et al. A pilot study to determine the effectiveness of garlic oil capsules in the treatment of dyspeptic patients with Helicobacter pylori. Helicobacter 6.3 (2001): 249-53.
Milner JA. Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation. Garlic and carcinogenesis. Adv Exp Med Biol 492 (2001): 69-81.
Mohamadi A et al. Effects of wild versus cultivated garlic on blood pressure and other parameters in hypertensive rats. Heart Dis 2.1 (2000): 3-9.
Mulrow C et al. Garlic: effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects. Evid Rep Technol Assess (Summ) 20 (2000): 1-4.
Nakagawa H et al. Growth inhibitory effects of diallyl disulfide on human breast cancer cell lines. Carcinogenesis 22.6 (2001): 891-7.
O'Gara EA, Hill DJ, Maslin DJ. Activities of garlic oil, garlic powder, and their diallyl constituents against Helicobacter pylori. Appl Environ Microbiol 66.5 (2000): 2269-73.
Orekhov AN et al. Direct anti-atherosclerosis-related effects of garlic. Ann Med 27.1 (1995): 63-5.
Peleg A, Hershcovici T, Lipa R, Anbar R, Redler M, Beigel Y. Effect of garlic on lipid profile and psychopathologic parameters in people with mild to moderate hypercholesterolemia. Israel Med Assoc J 5.9 (2003): 637-40.
Pinto JT, Rivlin RS. Antiproliferative effects of allium derivatives from garlic. J Nutr 131.3 [Suppl] (2001): 1058-60S.
Piscitelli SC et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 34.2 (2002): 234-8.
Pittler MH, Ernst E. Complementary therapies for peripheral arterial disease: systematic review. Atherosclerosis 181.1 (2005): 1-7.
Rahman K, Billington D. Dietary supplementation with aged garlic extract inhibits ADP-induced platelet aggregation in humans. J Nutr 130.11 (2000): 2662-5.

Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. J Nutr 136.3 [Suppl] (2006): 736-40S.
Scheiman JM, Cutler AF. Helicobacter pylori and gastric cancer. Am J Med 106.2 (1999): 222-6.
Siegel G, Klussendorf D. The anti-atherosclerotic effect of Allium sativum: statistics re-evaluated. Atherosclerosis 150.2 (2000): 437-8.
Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens 12.4 (1994): 463-8.
Singh DK, Porter TD. Inhibition of sterol 4alpha-methyl oxidase is the principal mechanism by which garlic decreases cholesterol synthesis. J Nutr 136.3 [Suppl] (2006): 759-64S.
Steiner M et al. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. Am J Clin Nutr 64.6 (1996): 866-70.
Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. Ann Intern Med 133.6 (2001): 420-9.
Sundaram SG, Milner JA. Diallyl disulfide inhibits the proliferation of human tumor cells in culture. Biochim Biophys Acta 1315.1 (1996): 15-20.
Tanaka S et al. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. J Nutr 136.3 [Suppl] (2006): 821-6S.
Thomson M, Mustafa T, Ali M. Thromboxane-B(2) levels in serum of rabbits receiving a single intravenous dose of aqueous extract of garlic and onion. Prostaglandins Leukot Essent Fatty Acids 63.4 (2000): 217-21.
Tsao SM, Yin MC. In-vitro antimicrobial activity of four diallyl sulphides occurring naturally in garlic and Chinese leek oils. J Med Microbiol 50.7 (2001): 646-9.
Turner B, Molgaard C, Marckmann P. Effect of garlic (Allium sativum) powder tablets on serum lipids, blood pressure and arterial stiffness in normo-lipidaemic volunteers: a randomised, double-blind, placebo-controlled trial. Br J Nutr 92.4 (2004): 701-6.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Wang BH et al. Treatment with aged garlic extract protects against bromobenzene toxicity to precision cut rat liver slices. Toxicology 132.2-3 (1999): 215-25.
Weber ND et al. In vitro virucidal effects of Allium sativum (garlic) extract and compounds. Planta Med 58.5 (1992): 417-23.
Wei Z, Lau BHS. Garlic inhibits free radical generation and augments antioxidant enzyme activity in vascular endothelial cells. Nutr Res 18 (1998): 61-70.
Yang CS et al. Mechanisms of inhibition of chemical toxicity and carcinogenesis by diallyl sulfide (DAS) and related compounds from garlic. J Nutr 131.3 (2001): 1041-5S.
Yoshida S et al. Antifungal activity of ajoene derived from garlic. Appl Environ Microbiol 53.3 (1987): 615-17.
Zhang XH et al. A randomized trial of the effects of garlic oil upon coronary heart disease risk factors in trained male runners. Blood Coagul Fibrinolysis 12.1 (2001a): 67-74.
Zhang XH et al. Gender may affect the action of garlic oil on plasma cholesterol and glucose levels of normal subjects. J Nutr 131.5 (2001b): 1471-8.
Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnants at high risk of preeclampsia. Eur J Obstet Gynecol Reprod Biol 99.2 (2001): 201-6.

Gentian

Historical note The genus *Gentiana* is derived from Gentius, king of ancient Ilyra who is attributed with the discovery of its therapeutic effects (Blumenthal et al 2000). In ancient Greece and Rome it was used to relieve common gastrointestinal symptoms, much as it is used today. It was first noted in the Chinese medical literature in 50 BC (Willard 1991).

OTHER NAMES
Gentiana, yellow gentian, wild gentian

BOTANICAL NAME/FAMILY
Gentiana lutea (family Gentianaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
Secoiridoid bitter glycosides, oligosaccharides, phenolic acids, phytosterols, polysaccharides (inulin and pectin), tannin, lupeol, beta-amyrin triterpenes, xanthones and essential oil.

MAIN ACTIONS
The active principals in gentian root are the bitter constituents, gentiopicroside and amarogentin.

DIGESTIVE STIMULANT
The bitter principals induce reflex excitation of taste receptors and increased saliva, gastric juice and bile secretion thereby stimulating appetite and digestion according to in vivo experiments. The small human study confirmed oral administration of gentian root extract increases gastric juice secretion and emptying of the gall bladder (ESCOP 2003).

OTHER ACTIONS
A gentian root preparation inhibited *Helicobacter pylori* in vitro (Mahady et al 2005).

Antioxidant activity has been observed in vitro for the ethyl acetate and chloroform fractions of gentian (Calliste et al 2001). Animal studies with amarogentin have identified antileishmanial properties (Medda et al 1999). Traditionally, gentian is

considered to have stomachic, anthelmintic, antiseptic, anti-inflammatory and tonic activity (Willard 1991).

CLINICAL USE

Gentian root preparations have not been significantly investigated under clinical trial conditions, so evidence is mainly derived from traditional, in vitro and animal studies.

DYSPEPSIA AND FLATULENCE

The considerable bitter taste of gentian provides a theoretical basis for its use in dyspepsia and flatulence for which increased saliva and gastric acid secretion would be beneficial. Commission E and ESCOP approve its use for this indication (Blumenthal et al 2000, ESCOP 2003).

LOSS OF APPETITE

The considerable bitter taste of gentian provides a theoretical basis for its use in anorexia when increased saliva and gastric acid secretion would be beneficial. Commission E and ESCOP approve its use for this indication (Blumenthal et al 2000, ESCOP 2003).

OTHER USES

Traditionally, gentian has also been used for gout, amenorrhea, diarrhoea and worms in the stomach and bowel (Willard 1991). Gentian is also used in alcoholic drinks such as brandy, medicinal wines and vermouth.

Clinical note — Herbs in alcoholic drinks

The maceration of herbs and spices in wine was common practice in antiquity, and the invention of aromatised wine, the ancestor of vermouth, has been attributed to Hippocrates (Liddle & Boero 2003). Herbs are still commonly used in alcoholic drink production today, either as flavourings, or as both fermentation substrates and flavouring agents. The volatile components of a herb will provide its distinctive odour, whereas non-volatile constituents can affect some gustatory reactions and produce a physiological effect. Herbs such as gentian are used for flavour, but also because they contain a significant amount of fermentable sugars that can be converted by strains of yeast into ethanol in an alcoholic fermentation process. Examples of other herbs that are used in brandies, flavoured spirits, liqueurs, medicinal wines and vermouth are anise, caraway, cardamom, coriander, dandelion, sage and yarrow (Veljkovic & Stankovic 2003).

DOSAGE RANGE

GENERAL GUIDE

- Cut root or dried extract : 2–4 g/day.
- Fluid extract (1:1): 1–2 mL taken 1 hour before meals up to three times daily.
- Tincture (1:5): 3–12 mL/day.
- Infusion: 1–2 g in 150 mL boiled water taken 1 hour before meals and up to three times daily

ADVERSE REACTIONS

Headaches have been reported (ESCOP 2003) and nausea and vomiting with high doses.

SIGNIFICANT INTERACTIONS

Interactions are unknown.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in gastric or duodenal ulcers and hyperacidity according to Commission E (Blumenthal et al 2000).

PREGNANCY USE

There is insufficient reliable information available to make a recommendation.

PRACTICE POINTS/PATIENT COUNSELLING

- Gentian root and its preparations are extremely bitter.
- Gentian preparations stimulate salivation, gastric juice and bile secretion.
- They are used to improve digestion, relieve flatulence and stimulate appetite.
- Little clinical investigation has been undertaken with the herb so evidence of efficacy relies on traditional and animal studies.
- It should not be used in cases of gastric or duodenal ulcer or hyperacidity.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Gentian preparations stimulate taste buds when taken orally, and increase gastric juice secretion, thereby improving digestion.

When will it start to work?

Effects are expected within several minutes of ingestion.

Are there any safety issues?

It should not be used by people with gastric or duodenal ulcers or with gastric hyperacidity.

REFERENCES

ESCOP. Gentianae Radix. In: European Scientific Co-operative On Phytomedicine (ESCOP), 2nd edn. Stuttgart: Thieme, 2003: 174-7.

Blumenthal M et al (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Calliste CA et al. Free radical scavenging activities measured by electron spin resonance spectroscopy and B16 cell antiproliferative behaviors of seven plants. J Agric Food Chem 49: (2001): 3321-7.

Liddle P, Boero L. Vermouth. In: Benjamin C (ed.) Encyclopedia of Food Sciences and Nutrition. Oxford: Academic Press, 2003: 5980-4.

Mahady GB et al. In vitro susceptibility of Helicobacter pylori to botanical extracts used traditionally for the treatment of gastrointestinal disorders. Phytother Res 19 (2005): 988-91.

Medda S et al. Evaluation of the in-vivo activity and toxicity of amarogentin, an antileishmanial agent, in both liposomal and niosomal forms. J Antimicrob Chemother 44 (1999): 791-4.

Veljkovic VB, Stankovic MZ. Herbs used in alcoholic drinks. In: Benjamin C (ed.) Encyclopedia of Food Sciences and Nutrition. Oxford: Academic Press, 2003: 3098-107.

Willard T. Gentian. In: The Wild Rose Scientific Herbal. Calgary: Wild Rose College of Natural Healing, 1991: 135-7.

Ginger

Historical note Ginger has been used as both a food and a medicine since ancient times. Confucius wrote about it in his Analects, the Greek physician, Dioscorides, listed ginger as an antidote to poisoning, as a digestive, and as being warming to the stomach in De Materia Medica, and the Koran, the Talmud and the Bible all mention ginger. Records suggest that ginger was highly valued as an article of trade and in 13th and 14th century England, one pound of ginger was worth the same as a sheep (Rosengarten 1969). Ginger is still extremely popular in the practice of phytotherapy, particularly in TCM, which distinguishes between the dried and fresh root. It is widely used to stimulate circulation, treat various gastrointestinal disorders and as a stimulant heating agent.

OTHER NAMES
African ginger, Indian ginger, Jamaica ginger, common ginger, rhizoma zingiberis, shokyo (Japanese)

BOTANICAL NAME/FAMILY
Zingiber officinale Roscoe (family Zingiberaceae)

PLANT PART USED
Rhizome

CHEMICAL COMPONENTS
The ginger rhizome contains an essential oil and resin known collectively as oleoresin. The composition of the essential oil varies according to the geographical origin, but the chief constituents, sesquiterpene hydrocarbons, which are responsible for the characteristic aroma, are fairly constant.

The oleoresin contains:

- sesquiterpenes: zingiberene, ar-curcumene, beta-sesquiphellandrene and beta-bisabolene
- pungent phenolic compounds: gingerols and their corresponding degradation products, shogaols, zingerone, and paradol. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products (Govindarajan 1982)

- other constituents: diarylheptanoids galanolactone (diterpenoid), 6-gingesulfonic acid), monoacyldigalactosylglycerols (Awang 1992, Bhattarai et al 2001, Charles et al 2000, Govindarajan 1982, Kikuzaki et al 1991, WHO 2003, Yamahara et al 1992, Yoshikawa et al 1992, 1993).

MAIN ACTIONS

ANTI-EMETIC

Ginger has demonstrated anti-emetic activity in both experimental models and human studies, the exact mechanism of which is still unknown although both shogaols and gingerols have been shown to have anti-emetic activity (Kawai et al 1994).

It appears that several key constituents and several different mechanisms are responsible. According to both animal and human studies, ginger reduces emesis due to a peripherally acting mechanism, acting on the gastrointestinal tract alone (Holtmann et al 1989). One constituent found in ginger, galanolactone, is a serotonin receptor antagonist, which may partly explain the anti-emetic effect (Huang et al 1991a, Mustafa et al 1993, Yamahara et al 1990). It also explains the inhibitory effect of ginger on serotonin-induced diarrhoea and antispasmodic effects on visceral and vascular smooth muscle.

Ginger has been shown to blunt gastric dysrhythmias and nausea evoked by acute hyperglycaemia in humans. The anti-arrhythmic and anti-emetic effects are thought to be due to a blockade of prostaglandins rather than inhibition of their release (Gonlachanvit 2001). Ginger has also been shown to reduce radiation-induced gastrointestinal distress and emesis in rat models, which is thought to be due at least in part to its antioxidant properties and the ability to scavenge free radicals and inhibit lipid peroxidation (Sharma et al 2005).

GASTROINTESTINAL ACTIVITY

Ginger exerts several effects in the gastrointestinal tract. It stimulates the flow of saliva, bile and gastric secretions (Platel & Srinivasan 1996, 2001, Yamahara et al 1985) and has been shown to increase gastrointestinal motility without affecting gastric emptying in several animal models and human studies (Gupta & Sharma 2001, Micklefield et al 1999, Phillips et al 1993). Ginger has also been observed to have prokinetic activity in mice in vivo and antispasmodic activity in vitro (Ghayur & Gilani 2005) These findings appear to support the traditional use of ginger in the treatment of gastrointestinal discomfort, colic, diarrhoea and bloating and its use as a carminative agent.

Anti-ulcer activity A number of in vivo studies have identified antiulcer activity for ginger extract and several of its isolated constituents. The orally administered acetone extract of ginger at a dose of 1000 mg/kg and zingiberene, the main terpenoid in this extract, at 100 mg/kg significantly inhibited gastric lesions by 97.5% and 53.6%, respectively. Additionally, the pungent principle, 6-gingerol at 100 mg/kg, significantly inhibited gastric lesions by 54.5%. These results suggest that both zingiberene and 6-gingerol are important constituents responsible for ginger's anti-ulcer activity (Yamahara et al 1988). Other constituents demonstrating antiulcer properties in gastric ulcer models in rats include beta-sesquiphellandrene, beta-bisabolene, arcurcumene and shogaol (Sertie et al 1992, Yoshikawa et al 1994).

In addition to direct anti-ulcer activity, ginger exerts synergistic effects with the antibiotic clarithromycin in inhibiting different *Helicobacter pylori* isolates independent of the organisms' susceptibility to clarithromycin (Nostro et al 2006).

HYPOLIPIDAEMIC

High doses of an aqueous extract of ginger (500 mg/kg) significantly reduced serum cholesterol according to an animal study that used oral doses of a raw aqueous extract of ginger administered daily for a period of 4 weeks (Thomson et al 2002).

Effects on triglyceride levels are more difficult to determine, as one study demonstrated that 250 μg ginger extract/day reduced serum triglyceride levels by 27% in mice (Fuhrman et al 2000), whereas another study using a high dose of 500 mg/kg found no significant effects (Thomson et al 2002).

An ex-vivo study found that 250 μg/day of a standardised ginger extract significantly reduced plasma LDL-cholesterol levels, the LDL basal oxidative state, as well as LDL-cholesterol and serum cholesterol's susceptibility to oxidation and aggregation, compared with placebo. Ginger also reduced aortic atherosclerotic lesions by 44% in atherosclerotic mouse aorta (Fuhrman et al 2000).

ANTI-INFLAMMATORY AND ANALGESIC

The anti-inflammatory effects of ginger may be due to its effects on the arachidonic acid cascade, as COX-1 and -2 and lipoxygenase inhibition has been shown in vitro (Kobayashi et al 1987) and high oral doses of an aqueous extract of ginger (500 mg/kg) significantly lowered serum PGE_2 and thromboxane B2 levels in rats (Thomson et al 2002).

Ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase, thus distinguishing ginger from NSAIDs. Additionally, ginger extract has been shown to inhibit thromboxane synthase (Langner et al 1998) and a ginger extract (EV.EXT.77) has been found to inhibit the induction of several genes involved in the inflammatory

response. These include genes encoding cytokines, chemokines, and the inducible enzyme COX-2, thus providing evidence that ginger modulates biochemical pathways activated in chronic inflammation (Grzanna et al 2005).

No one single constituent seems to be responsible for the anti-inflammatory effect of ginger. An acetone extract containing gingerols, shogaols and minor compounds like gingerenone A, [6]-gingerdiol, hexahydrocurcumin and zingerone have been shown synergistically to produce dose-dependent anti-inflammatory effects (Schuhbaum & Franz 2000). Other studies have identified the gingerols and diarylheptanoids and gingerdione as the key compounds responsible (Flynn et al 1986, Kiuchi et al 1992).

Gingerol and 8-gingerol have been found to evoke capsaicin-like intracellular Ca^{2+} transients and ion currents in vitro and it has been suggested that gingerols represent a novel class of naturally occurring vanilloid receptor agonists that contribute to ginger's medicinal properties (Dedov et al 2002). This is supported by the finding that topical application of ginger creams or compresses produce an analgesic capsaicin-like effect on the release of the immunoreactive substance P from primary afferent neurons (Onogi et al 1992). In an animal study of chemically induced inflammation, ginger extract reduced oedema that was partly caused by serotonin-receptor antagonism (Penna et al 2003). Additionally, ginger oil has shown anti-inflammatory activity, significantly suppressing both paw and joint swelling in severe adjuvant arthritis in rats (Sharma et al 1994).

ANTIPLATELET

It has been suggested that gingerols and their derivatives represent a potential new class of platelet activation inhibitors, with synthetic gingerols being found to inhibit the arachidonic acid-induced platelet release reaction in vitro in a similar dose range as aspirin possibly due to an effect on COX activity in platelets (Koo et al 2001, Lu 2005, Nurtjahja-Tjendraputra et al 2003, Tjendraputra et al 2001).

Powdered ginger exerted an antiplatelet activity when taken in very high doses of at least 10 g, according to one human study (Bordia et al 1997). A randomised double-blind study found that doses up to 2 g of dried ginger had no effect on bleeding time, platelet aggregation or platelet count (Lumb 1994). This lack of effect has been demonstrated in healthy volunteers (Janssen et al 1996) and those with type 1 diabetes mellitus or coronary artery disease (Bordia et al 1997).

ANTIMICROBIAL AND ANTIPARASITIC

Ginger extract and several of its main constituents exhibit antimicrobial activity in vitro and in vivo. Ginger extract has been shown to have an antibacterial effect against

Staphylococcus aureus, *Streptococcus pyogenes*, *S. pneumoniae* and *Haemophilus* collected from throat swaps of infected individuals. The minimum inhibitory concentration of ginger ranged from 0.0003–0.7 μg/mL, and the minimum bactericidal concentration ranged from 0.135–2.04 μg/mL (Akoachere et al 2002). Ginger has also shown antischistosomal activity. Gingerol (5.0 ppm) completely abolished the infectivity of *Schistosoma* spp. (blood flukes) in animal studies (Adewunmi et al 1990). Gingerol and shogaol exhibited potent molluscicidal activity in vivo.

Gingerols demonstrated antibacterial activity against *Bacillus subtilis* and *Escherichia coli* in vitro (Yamada et al 1992), and the essential oils of ginger have been shown to have antimicrobial activity against Gram-positive and Gram-negative bacteria, yeasts and filamentous fungi in vitro (Martins et al 2001). Shogaol and gingerol have demonstrated anti-nematode activities; 6.25 μg/mL 6-shogaol destroyed *Anisakis* larvae within 16 hours in vitro, whereas the antinematodal medication pyrantel pamoate had no lethal effect at 1 mg/mL (Goto et al 1990). Ginger constituents have also been shown to be antifungal and antiviral. Shogaol and zingerone strongly inhibited *Salmonella typhi*, *Vibrio cholerae* and *Tricophyton violaceum*. Aqueous extracts have also been shown to be effective against *Trichomonas vaginalis* (Henry & Piggott 1987). Several sesquiterpenes, but especially beta-sesquiphellandrene, isolated from ginger have also been shown to have antirhinoviral activity in vitro (Denyer et al 1994).

ANTIOXIDANT

According to in vivo research, ginger exerts significant direct and indirect antioxidant effects. Orally administered ginger significantly lowered levels of free radicals and raised the activities of endogenous antioxidants superoxide dismutase and catalase and had a sparing effect on vitamins C and E (Jeyakumar et al 1999).

IMMUNOMODULATION

In vitro and in vivo research suggests ginger extract exerts some degree of immunomodulatory activity and has been shown to significantly prolong the survival of cardiac allografts in mice (Wilasrusmee et al 2003). Ginger oil has also been shown to have immunomodulatory activity in mice, with dose-dependent inhibition of T lymphocyte proliferation and IL-1-alpha secretion in vitro and reduced delayed type of hypersensitivity response in vivo (Zhou et al 2006).

HEPATOPROTECTIVE

Ginger has significant hepatoprotective effects comparable to those of silymarin, according to research with experimental models of alcohol-induced liver damage (Bhandari et al 2003).

OTHER ACTIONS

ANTIHISTAMINE

Shogaols and certain gingerols exhibit dose-dependent inhibition of drug-induced histamine release from rat peritoneal mast cells in vitro (Yamahara et al 1995).

ANXIOLYTIC

A combination of ginger and *Ginkgo biloba* has been shown to reduce anxiety in an animal model (elevated plus-maze test). The effect was similar to diazepam (Hasenohrl et al 1996). A highly non-polar fraction of a ginger extract has been shown to possess anticonvulsant, anxiolytic and anti-emetic activities in animals (Vishwakarma et al 2002).

ANTIFIBROTIC

Supplementation with 5 g ginger not only prevented a decrease, but also significantly increased fibrinolytic activity in 30 healthy adult volunteers who consumed 50 g fat in a meal in an open clinical study (Verma & Bordia 2001).

APOPTOSIS

A pungent phenolic substance found in ginger (6-paradol) effectively inhibits tumour promotion in mouse skin carcinogenesis. 6-Paradol and structurally related derivatives have also been shown to induce apoptosis through a caspase-3-dependent mechanism (caspase is a 'suicidal' cell protein that, when activated, induces the cell to destroy itself) (Keum et al 2002).

POSITIVE INOTROPE

Gingerols and shogaols isolated from ginger have positive inotropic activity, as demonstrated on isolated heart muscle (Shoji et al 1982, Yamahara et al 1995). The effect of gingerol seems to be rather specific to SR Ca^{2+}–ATPase activity (Kobayashi et al 1987).

THERMOGENIC

Ginger helps to maintain body temperature and inhibit serotonin-induced hypothermia in vivo (Huang et al 1991b, Kano et al 1991). However, the addition of a ginger-based sauce to a meal did not produce any significant effect on metabolic rate in humans (Henry & Piggott 1987).

CLINICAL USE

Although ginger is used in many forms, including fresh ginger used in cooking or chai (Indian spicy tea), pickled or glazed ginger, ethanol extracts and concentrated powdered extracts, preparations made with the root are used medicinally. Depending

on the specific solvent used, the resultant preparation will contain different concentrations of the active constituents and may differ markedly from crude ginger. Although the great majority of research refers specifically to the species *Zingiber officinale*, there is the potential for confusion with other species or even with other genera (Canter 2004). Furthermore, there are reported to be wide variations in the quality of commercial ginger supplements with concentrations of gingerols ranging from 0.0 to 9.43 mg/g. As such, the results of specific research can not necessarily be extrapolated to different preparations (Schwertner et al 2006).

PREVENTION OF NAUSEA AND VOMITING

Many clinical studies have investigated the effects of ginger in the prevention and treatment of nausea and vomiting associated with different circumstances, including pregnancy (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Portnoi et al 2003, Smith et al 2004, Sripramote & Lekhyananda 2003, Vutyavanich et al 2001, Willetts et al 2003), the postoperative period (Arfeen et al 1995, Bone et al 1990, Phillips et al 1993b, Meyer et al 1995, Visalyaputra et al 1998), motion sickness (Grontved & Hentzer 1986, Lien et al 2003, Mowrey & Clayson 1982, Schmid et al 1994, Stewart et al 1991) and chemotherapy (Manusirivithaya et al 2004, Meyer et al 1995, Sontakke et al 2003).

A recent systematic review of 24 RCTs covering 1073 patients suggest that results for the treatment of nausea and vomiting in pregnancy are encouraging; however, results for postoperative nausea and vomiting and motion sickness are unclear and daily doses of up to 6 g of ginger seems to have few side-effects (Betz et al 2005). More recent reviews provide further encouragement and suggest that ginger may indeed be effective in nausea associated with pregnancy (Boone & Shields 2005) and the postoperative period (Chaiyakunapruk et al 2006).

Clinical note — Morning sickness

Nausea and vomiting are the most common symptoms experienced in early pregnancy, with nausea affecting between 70% and 85% of women. About half of pregnant women experience vomiting (Jewell 2002). Hyperemesis gravidarum is more severe and affects between 0.3% and 2% of all pregnant women. It is a multifactorial disease in which pregnancy-induced hormonal changes associated with concurrent gastrointestinal dysmotility and possible *Helicobacter pylori* infection function as contributing factors (Eliakim et al 2000).

Nausea of pregnancy There are many studies, including an observational study (Portnoi et al 2003) and at least six RCTs (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Portnoi et al 2003, Smith et al 2004, Sripramote & Lekhyananda 2003,

Vutyavanich et al 2001, Willetts et al 2003), as well as multiple systematic reviews, including a Cochrane review, that suggest that ginger powder or extract may be safe and effective in treating nausea and vomiting of pregnancy (Boone & Shields 2005, Borrelli et al 2005, Bryer 2005, Dib & El-Saddik 2004, Ernst & Pittler 2000, Jewell 2003). The most recent review, which considers six double-blind RCTs with a total of 675 participants, and a prospective observational cohort study of 187 women, suggest that ginger is superior to placebo and as effective as vitamin B6 in relieving pregnancy-related nausea and vomiting and that there is an absence of significant side-effects and adverse pregnancy outcomes (Borrelli et al 2005).

In three double-blind, placebo-controlled, randomised trials of ginger for pregnancy related-nausea and vomiting, including one trial on hyperemesis gravidarum, 1 g ginger in divided doses was significantly more effective than placebo in reducing nausea and vomiting (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Vutyavanich et al 2001). In a further double blind of 120 women, 25 mg of the ginger extract EV.EXT35 (equivalent to 1.5 g of dried ginger) four times daily was useful in patients experiencing nausea and retching, although no significant result was seen for vomiting (Willetts et al 2003).

In two further randomised, double-blind, controlled trials, one involving 138 women and the second 291 women, 1–1.5 g of ginger was found to be equivalent to vitamin B6 in helping to reduce pregnancy-related nausea, dry retching, and vomiting (Smith et al 2004, Sripramote & Lekhyananda 2003).

Postoperative nausea Ginger may be useful for the prevention of postoperative nausea; however, not all studies have produced positive results and as the ginger preparations used have not been standardised, it is difficult to directly compare studies. A recent meta-analysis of five randomised trials, however, including a total of 363 patients found that a fixed dose of at least 1 g of ginger was more effective than placebo for the prevention of postoperative nausea and vomiting (Chaiyakunapruk et al 2006).

Most of the studies on postoperative nausea and vomiting have been done on patients undergoing gynaecological surgery. In two such randomised, placebo-controlled, double-blind studies, ginger significantly reduced the incidence of postoperative nausea and vomiting (Bone et al 1990, Phillips et al 1993), although two further studies failed to show any benefit with ginger (Arfeen et al 1995, Eberhart et al 2003). A fifth study of 80 women undergoing gynaecological laparoscopy found that 1 g of ginger taken 1 hour before surgery was significantly superior to placebo in reducing the incidence of nausea 2–4 hours afterwards;

however, it failed to show statistical significance for an observed reduction in the incidence and frequency of vomiting (Pongrojpaw & Chiamchanya 2003).

Although other types of surgery have not been as extensively studied as gynaecological surgery, there is a report on 6 months of clinical anaesthetic experience that suggests that a nasocutaneously administered 5% solution of essential oil of ginger given pre-operatively, together with conventional therapies, to general anaesthesia patients at high risk for postoperative nausea and vomiting is a safe and cost-effective way of reducing nausea and vomiting post anaesthesia (Geiger 2005).

In the only double-blind, placebo-controlled study of postoperative nausea and vomiting in patients undergoing middle ear surgery, ginger was ineffective and the use of 1 g of ginger 1 hour before surgery was associated with significantly more postoperative nausea and vomiting than the use of ondansetron or placebo (Gulhas et al 2003).

Motion sickness Commission E approves the use of ginger root for the prevention of motion sickness (Blumenthal et al 2000) and several clinical studies have assessed its effects as either prophylaxis or treatment. An early double-blind, randomised, placebo-controlled study involving 80 naval cadets found that ginger was significantly superior to placebo in reducing symptoms of vomiting and cold sweats due to seasickness. Fewer symptoms of nausea and vertigo were also reported with ginger, but the difference was not statistically significant (Grontved & Hentzer 1986). In another randomised double-blind study of seasickness involving over 1700 tourists on a whale-watching safari 300 km north of the Arctic circle, 500 mg ginger was found to be as effective for the treatment of motion sickness as several common anti-emetic medications (cinnarizine, cyclizine, dimenhydrinate, domperidone, meclizine and scopolamine) with ginger preventing seasickness in 80% of the subjects during the 6-hour boat trip, although the incidence of severe vomiting did not differ significantly between treatment groups (Schmid et al 1994).

At least three studies have had mixed results from experimental models of motion sickness whereby subjects are seated in a rotating chair. The first study involving 28 volunteers found no significant protective effects for powdered ginger (500 mg or 1000 mg) or fresh ginger root (1000 mg) (Stewart et al 1991), whereas a second study involving 36 undergraduate men and women who reported very high susceptibility to motion sickness found that ginger was superior to dimenhydrinate (Mowrey & Clayson 1982). More recently, another double-blind, randomised, placebo-controlled crossover study showed positive benefits with ginger pretreatment on prolonging time before nausea, shortening recovery time and effectively reducing

nausea (Lien et al 2003). This study used pretreatment doses of 1000 mg and 2000 mg, which were also shown to reduce tachygastria and plasma vasopressin.

Chemotherapy-induced nausea In an open study, 1.5 g ginger was found to decrease psoralen-induced nausea in 11 patients treated with photopheresis for cutaneous T-cell lymphoma (Meyer et al 1995).

Powdered ginger root effectively reduced cyclophosphamide-induced nausea and vomiting in a randomised, prospective, crossover double-blind study, with the antiemetic effect of ginger being equal to metoclopramide (Sontakke et al 2003). Ginger was found to have similar efficacy to metoclopramide in reducing cisplatin-induced emesis in a randomised, double-blinded, crossover study of 48 gynaecologic cancer patients receiving chemotherapy (Manusirivithaya et al 2004).

MUSCULOSKELETAL DISORDERS

Ginger is described in Ayurvedic (traditional Indian) and Tibb (traditional Arabian) systems of medicine to be useful in inflammation and rheumatism and this traditional use is supported by modern studies demonstrating ginger's anti-inflammatory activity.

A randomised, double-blind, placebo-controlled, multicentre, parallel-group 6-week study of 261 patients found that a highly purified and standardised ginger extract (EV.EXT 77) moderately reduced the symptoms of OA of the knee (Altman & Marcussen 2001). Similarly, 250 mg of the ginger extract (Zintona EC) four times daily for 6 months was shown to be significantly more effective than placebo in reducing pain and disability in 29 OA patients in a double-blind, placebo-controlled, crossover study (Wigler et al 2003).

These studies are supported by an open retrospective study involving 56 patients (28 with RA, 18 with OA, 10 with muscular discomfort) that revealed that more than three-quarters experienced varying degrees of relief of pain and swelling from the long-term use of powdered ginger (Srivastava & Mustafa 1992). Further support comes from studies comparing ginger to NSAIDs.

In one double-blind, randomised, placebo-controlled trial involving 120 patients, 30 mg of an ethanolic ginger extract equivalent to 1 g of ginger and prepared from fresh ginger purchased from a local market in India was found to be significantly more effective than placebo and was as effective as 1.2 g of ibuprofen in the symptomatic treatment of OA (Haghighi et al 2005). In another double-blind crossover study 170 mg of the ginger extract EV.ext-33 with a standardised content of hydroxy-methoxy-phenyl compounds given twice daily was found to be significantly more effective than placebo but not as effective as ibuprofen in reducing pain and disability in 75 patients with OA before the crossover period, whereas no

statistical difference was seen between ginger and placebo in the analysis after the crossover period. The authors commented that the washout period may have been insufficient and that ginger might need to be administered for longer than 3 weeks, and possibly in a higher dosage, to be clinically effective (Bliddal et al 2000).

DYSPEPSIA

Ginger stimulates the flow of saliva, bile and gastric secretions and therefore is traditionally used to stimulate appetite, reduce flatulence and colic, gastrointestinal spasms and generally act as a digestive aid. Commission E approves the use of ginger root for the treatment of dyspepsia (Blumenthal et al 2000).

MIGRAINE

Ginger is used to prevent and treat migraine headache. Its ability to inhibit thromboxane A2 and exert antihistamine, anti-inflammatory and gastric actions makes it a theoretically attractive choice (Mustafa & Srivastava 1990b). This use is supported by an open-label study of 30 migraine sufferers that reported that treatment with a sublingual ginger and feverfew preparation (GelStat MigraineO) in the initial phase of a migraine resulted in most patients being satisfied with the therapy and being pain-free or only having mild headache post-treatment (Cady et al 2005).

OTHER USES

Ginger has been used orally to treat dysmenorrhoea, and ginger cream or compress is used externally for mastitis.

DOSAGE RANGE

The recommended dose ranges widely from 500 mg to 9 g/day dried root or equivalent; however, as there are wide variations in the gingerol concentrations in commercial ginger supplements (Schwertner et al 2006) the effective dosage will depend on the preparation and the indication for use.

- Liquid extract (1:2): 0.7–2.0 mL/day.
- Dried root: 1–3 g daily in divided doses or 1–2 g taken as a single dose for nausea and vomiting.
- Infusion: 4–6 slices of fresh ginger steeped in boiling water for 30 minutes.

ADVERSE REACTIONS

Gastric irritation, heartburn and bloating have been reported in clinical trials (Arfeen et al 1995). Contact dermatitis of the fingertips has also been reported (Seetharam & Pasricha 1987) with topical use.

SIGNIFICANT INTERACTIONS

Controlled studies are not available for many interactions; therefore they are based on evidence of activity and are largely theoretical and speculative.

WARFARIN

Due to the herb's antiplatelet effects there is a theoretical risk of increased bleeding at high doses (>10 g) although this is not evident clinically. There is no evidence of an interaction with warfarin at the usual dietary and therapeutic intakes (Jiang et al 2005, Stenton et al 2001, Vaes & Chyka 2000), and ginger has been shown not to alter prothrombin times in pooled human plasma collected from male volunteers between the ages of 18 and 57 years (Jones et al 2001). A standardised ginger extract, EV.EXT 33, has demonstrated no significant effect on coagulation parameters or on warfarin-induced changes in blood coagulation in rats (Weidner & Sigwart 2000) and ginger was found not to affect clotting status or the pharmacokinetics or pharmacodynamics of warfarin in healthy human subjects (Jiang et al 2005). Avoid high-dose supplements unless under medical supervision.

ANTIPLATELET DRUGS

Theoretically, increased antiplatelet and anti-inflammatory effects may occur with high-dose ginger preparations, but the clinical significance of this is unknown. Caution should be exercised with doses >10 g — possible beneficial effect.

CONTRAINDICATIONS AND PRECAUTIONS

Ginger in high doses is not recommended for children under 6 years of age due to the pungent nature of ginger. However, ginger lollies or ginger ale is sometimes used and a dose of 250 mg every 4 hours for motion sickness is safe.

Commission E suggests people with gallstones consult with their physician before using ginger. People with gastric ulcers or reflux should use this herb with caution. Suspend use of high dose supplements (> 10 g) 1 week before major surgery.

PREGNANCY USE

Although Commission E suggests that ginger is contraindicated in pregnancy, more recent research suggests that ginger is not contraindicated in pregnancy — doses up to 2 g/day of dried ginger root have been used safely.

No adverse effects on pregnancy were observed in multiple studies of ginger or nausea and vomiting (Boone & Shields 2005, Borrelli et al 2005, Bryer 2005, Dib & El-Saddik 2004, Ernst & Pittler 2000, Jewell 2003).

PRACTICE POINTS/PATIENT COUNSELLING

- Ginger is most often used for its anti-emetic, anti-inflammatory and gastrointestinal effects.
- There is clinical support for the use of ginger in the treatment of nausea and vomiting associated with motion sickness, the postoperative period, pregnancy and chemotherapy.
- Ginger is traditionally used for gastrointestinal disorders including dyspepsia, poor appetite, flatulence, colic, vomiting, diarrhoea and spasms, as well as a diaphoretic in the treatment of the common cold and influenza.
- Ginger is also used as an anti-inflammatory agent for arthritis, although large controlled studies have yet to produce strong support for this use.
- Although antiplatelet effects have been reported, this requires very large doses and is not likely to be significant in normal therapeutic doses and is not likely to be significant in normal therapeutic doses or dietary intake levels.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Ginger may be useful in the treatment of nausea and vomiting associated with motion sickness, postoperative nausea, vomiting in pregnancy and seasickness. It is also useful for treating symptoms of dyspepsia and may have symptom-relieving effects in arthritis, although this is less certain.

When will it start to work?

In the case of dyspepsia and motion sickness prevention, ginger will have an almost immediate effect, with improvement reported within 30 minutes. For motion sickness, 0.5–1.0 g ginger should be taken 30 minutes before travel and repeated 4 hourly. For nausea of pregnancy it should be taken for at least 4 days.

Are there any safety issues?

Ginger is well tolerated, although it should be used with caution by people with gallstones, gastric ulcers or reflux.

REFERENCES

Adewunmi CO, Oguntimein BO, Furu P. Molluscicidal and antischistosomal activities of Zingiber officinale. Planta Med 56.4 (1990): 374-6.

Akoachere JF et al. Antibacterial effect of Zingiber officinale and Garcinia kola on respiratory tract pathogens. East Afr Med J 79.11 (2002): 588-92.

Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum 44.11 (2001): 2531-8.

Arfeen Z et al. A double-blind randomized controlled trial of ginger for the prevention of postoperative nausea and vomiting. Anaesth Intensive Care 23.4 (1995): 449-52.

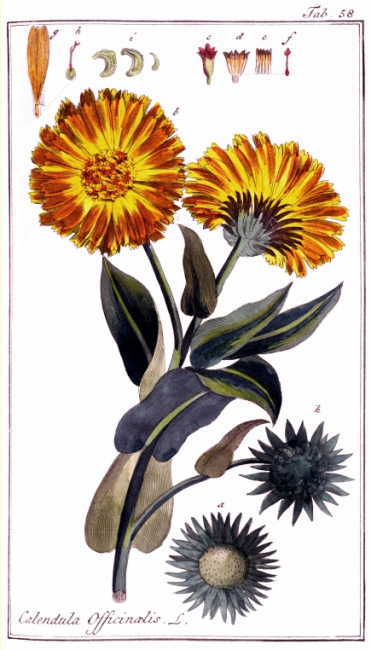
Awang DVC. Ginger. Can Pharm J 125.7 (1992): 309-11.

Betz O et al. Is ginger a clinically relevant antiemetic? A systematic review of randomized controlled trials. Forsch Komplementarmed Klassische Naturheilkunde 12.1 (2005): 14-23.

Bhandari U et al. Antihepatotoxic activity of ginger ethanol extract in rats. Pharm Biol 41.1 (2003): 68-71.

Bhattarai S, Tran VH, Duke CC. The stability of gingerol and shogaol in aqueous solutions. J Pharm Sci 90.10 (2001): 1658-64.
Bliddal H et al. A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis. Osteoarthritis Cartilage 8.1 (2000): 9-12.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Bone ME et al. Ginger root: a new antiemetic: The effect of ginger root on postoperative nausea and vomiting after major gynaecological surgery. Anaesthesia 45.8 (1990): 669-71.
Boone SA, Shields KM. Treating pregnancy-related nausea and vomiting with ginger. Ann Pharmacother 39.10 (2005): 1710-13.
Bordia A, Verma SK, Srivastava KC. Effect of ginger (Zingiber officinale Rosc.) and fenugreek (Trigonella foenumgraecum L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 56.5 (1997): 379-84.
Borrelli F et al. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. Obstet Gynecol 105.4 (2005): 849-56.
Bryer E. A literature review of the effectiveness of ginger in alleviating mild-to-moderate nausea and vomiting of pregnancy. J Midwifery Women's Health 50.1 (2005): e1-3.
Cady RK et al. Gelstat Migraine (sublingually administered feverfew and ginger compound) for acute treatment of migraine when administered during the mild pain phase. Med Sci Monitor Int Med J Exp Clin Res 11.9 (2005): PI65-9.
Canter PH. Ginger: Do we know what we are talking about? Focus Altern Complement Ther 9.3 (2004): 184-5.
Chaiyakunapruk N et al. The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. Am J Obstet Gynecol 194.1 (2006): 95-9.
Charles R, Garg SN, Kumar S. New gingerdione from the rhizomes of Zingiber officinale. Fitoterapia 71.6 (2000): 716-18.
Dedov VN et al. Gingerols: A novel class of vanilloid receptor (VR1) agonists. Br J Pharmacol 137.6 (2002): 793-8.
Denyer CV et al. Isolation of antirhinoviral sesquiterpenes from ginger (Zingiber officinale). J Nat Prod 57.5 (1994): 658-62.
Dib JG, El-Saddik RA. Ginger for nausea and vomiting in pregnancy. J Pharm Pract Res 34.4 (2004): 305-7.
Eberhart LHJ et al. Ginger does not prevent postoperative nausea and vomiting after laparoscopic surgery. Anesth Analg 96.4 (2003): 995-8.
Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: A current review. Am J Perinatol 17.4 (2000): 207-18.
Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. Br J Anaesth 84.3 (2000): 367-71.
Fischer-Rasmussen W et al. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 38.1 (1990): 19-24.
Flynn DL, Rafferty MF, Boctor AM. Inhibition of human neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds. Prostaglandins Leukot Med 24.2-3 (1986): 195-8.
Fuhrman B et al. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. J Nutr 130.5 (2000): 1124-31.
Geiger JL. The essential oil of ginger, Zingiber officinale, and anaesthesia. Int J Aromather 15.1 (2005): 7-14.
Ghayur MN, Gilani AH. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. Dig Dis Sci 50.10 (2005): 1889-97.
Gonlachanvit S et al. Ginger reduces hyperglycemia-evoked gastric dysrhythmias in healthy humans: possible role of endogenous prostaglandins. J Pharmacol Exp Ther 307(3) (2003): 1098-103.
Goto C et al. Lethal efficacy of extract from Zingiber officinale (traditional Chinese medicine) or [6]-shogaol and [6]-gingerol in Anisakis larvae in vitro. Parasitol Res 76.8 (1990): 653-6.

Govindarajan V. Ginger: chemistry, technology, and quality evaluation: part 2. Crit Rev Food Sci Nutr 17 (1982): 189-258.
Grontved A, Hentzer E. Vertigo-reducing effect of ginger root: A controlled clinical study. ORL 48.5 (1986): 282-6.
Grzanna R et al. Ginger: An herbal medicinal product with broad anti-inflammatory actions. J Med Food 8.2 (2005): 125-32.
Gulhas N et al. The effect of ginger and ondansetron on nausea and vomiting after middle ear surgery. Anestezi Dergisi 11.4 (2003): 265-8.
Gupta YK, Sharma M. Reversal of pyrogallol-induced delay in gastric emptying in rats by ginger (Zingiber officinale). Methods Find Exp Clin Pharmacol 23.9 (2001): 501-3.
Haghighi M et al. Comparing the effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis. Arch Iranian Med 8.4 (2005): 267-71.
Hasenohrl RU et al. Anxiolytic-like effect of combined extracts of Zingiber officinale and ginkgo biloba in the elevated plus-maze. Pharmacol Biochem Behav 53.2 (1996): 271-5.
Henry CJ, Piggott SM. Effect of ginger on metabolic rate. Hum Nutr Clin Nutr 41.1 (1987): 89-92.
Holtmann S et al. The anti-motion sickness mechanism of ginger. A comparative study with placebo and dimenhydrinate. Acta Oto-Laryngol 108.3-4 (1989): 168-74.
Huang Q et al. Anti-5-hydroxytryptamine3 effect of galanolactone, diterpenoid isolated from ginger. Chem Pharm Bull 39.2 (1991): 397-9.
Janssen PL et al. Consumption of ginger (Zingiber officinale roscoe) does not affect ex vivo platelet thromboxane production in humans. Eur J Clin Nutr 50.11 (1996): 772-4.
Jewell D. Nausea and vomiting in early pregnancy. Clin Evid 7 (2002): 1277-83.
Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 1 (2002): CD000145.
Jeyakumar SM, Nalini N, Menon VP. Antioxidant activity of ginger (Zingiber officinale Rosc) in rats fed a high fat diet. Med Sci Res 27.5 (1999): 341-4.
Jiang X et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 59.4 (2005): 425-32.
Jones SC, Miederhoff P, Karnes HT. The development of a human tissue model to determine the effect of plant-derived dietary supplements on prothrombin time. J Herbal Pharmacother 1.1 (2001): 21-34.
Kano Y, Zong QN, Komatsu K. Pharmacological properties of galenical preparation. XIV. Body temperature retaining effect of the Chinese traditional medicine, goshuyu-to and component crude drugs. Chem Pharm Bull (Tokyo) 39.3 (1991): 690-2.
Kawai T et al. Anti-emetic principles of Magnolia obovata bark and Zingiber officinale rhizome. Planta Med 60.1 (1994): 17-20.
Keating A, Chez RA. Ginger syrup as an antiemetic in early pregnancy. Altern Ther Health Med 8.5 (2002): 89-91.
Keum YS et al. Induction of apoptosis and caspase-3 activation by chemopreventive [6]-paradol and structurally related compounds in KB cells. Cancer Lett 177.1 (2002): 41-7.
Kikuzaki H, Usuguchi J, Nakatani N. Constituents of Zingiberaceae. I. Diarylheptanoids from the rhizomes of ginger (Zingiber officinale roscoe). Chem Pharm Bull 39.1 (1991): 120-2.
Kiuchi F et al. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull 40.2 (1992): 387-91.
Kobayashi M, Shoji N, Ohizumi Y. Gingerol, a novel cardiotonic agent, activates the Ca^{2+}-pumping ATPase in skeletal and cardiac sarcoplasmic reticulum. Biochim Biophys Acta Biomembranes 903.1 (1987): 96-102.
Koo KLK et al. Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. Thromb Res 103.5 (2001): 387-97.
Langner E, Greifenberg S, Gruenwald J. Ginger: History and use. Adv Ther 15.1 (1998): 25-44.
Lien HC et al. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection. Am J Physiol Gastrointest Liver Physiol 284.3 47-3 (2003): G481-9.

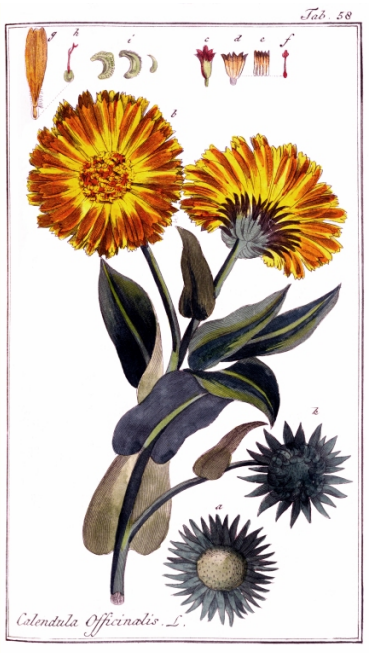


Lu CJ. Function of ginger on cerebrovascular disease and its gateway. Chin J Clin Rehab 9.45 (2005): 187-9.
Lumb AB. Effect of dried ginger on human platelet function. Thromb Haemost 71.1 (1994): 110-11.
Manusirivithaya S et al. Antiemetic effect of ginger in gynecologic oncology patients receiving cisplatin. Int J Gynecol Cancer 14.6 (2004): 1063-9.
Martins AP et al. Essential oil composition and antimicrobial activity of three Zingiberaceae from S.Tome e Principe. Planta Med 67.6 (2001): 580-4.
Meyer K et al. Zingiber officinale (ginger) used to prevent 8-Mop associated nausea. Dermatol Nurs 7.4 (1995): 242-4.
Micklefield GH et al. Effects of ginger on gastroduodenal motility. Int J Clin Pharmacol Ther 37.7 (1999): 341-6.
Mowrey D, Clayson D. Motion sickness, ginger and psychosis. Lancet 319.8273 (1982): 655-7.
Muller JL, Clauson KA. Pharmaceutical considerations of common herbal medicine. Am J Manage Care 3.11 (1997): 1753-70.
Mustafa T, Srivastava KC. Ginger (Zingiber officinale) in migraine headache. J Ethnopharmacol 29.3 (1990a): 267-73.
Mustafa T, Srivastava KC. Possible leads for arachidonic acid metabolism altering drugs from natural products. J Drug Develop 3.1 (1990b): 47-60.
Mustafa T, Srivastava KC, Jensen KB. Pharmacology of ginger, Zingiber officinale. J Drug Dev 6.11 (1993): 25-39.
Nostro A et al. Effects of combining extracts (from propolis or Zingiber officinale) with clarithromycin on Helicobacter pylori. Phytother Res 20.3 (2006): 187-90.
Nurtjahja-Tjendraputra E et al. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thromb Res 111.4-5 (2003): 259-65.
Onogi T et al. Capsaicin-like effect of (6)-shogaol on substance P-containing primary afferents of rats: A possible mechanism of its analgesic action. Neuropharmacology 31.11 (1992): 1165-9.
Penna SC et al. Anti-inflammatory effect of the hydralcoholic extract of Zingiber officinale rhizomes on rat paw and skin edema. Phytomedicine 10.5 (2003): 381-5.
Phillips S, Hutchinson S, Ruggier R. Zingiber officinale does not affect gastric emptying rate: A randomised, placebo-controlled, crossover trial. Anaesthesia 48.5 (1993a): 393-5.
Phillips S, Ruggier R, Hutchinson SE. Zingiber officinale (ginger): an antiemetic for day case surgery. Anaesthesia 48.8 (1993b): 715-17.
Platel K, Srinivasan K. Influence of dietary spices or their active principles on digestive enzymes of small intestinal mucosa in rats. Int J Food Sci Nutr 47.1 (1996): 55-9.
Platel K, Srinivasan K. Studies on the influence of dietary spices on food transit time in experimental rats. Nutr Res 21.9 (2001): 1309-14.
Pongrojpaw D, Chiamchanya C. The efficacy of ginger in prevention of post-operative nausea and vomiting after outpatient gynecological laparoscopy. J Med Assoc Thailand 86.3 (2003): 244-50.
Portnoi G et al. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol 189.5 (2003): 1374-7.
Rosengarten FJ. The Book of Spices. Wynnewood, PA: Livingston Publishing Co., 1969.
Schmid R et al. Comparison of seven commonly used agents for prophylaxis of seasickness. J Travel Med 1.4 (1994): 203-6.
Schuhbaum H, Franz G. Ginger: Spice and versatile medicinal plant. Z Phytother 21.4 (2000): 203-9 [in German].
Schwertner HA et al. Variation in concentration and labeling of ginger root dietary supplements. Obstet Gynecol 107.6 (2006): 1337-43.
Seetharam KA, Pasricha JS. Condiments and contact dermatitis of the finger-tips. Indian J Dermatol Venereol Leprol 53.6 (1987): 325-8.
Sertie JAA et al. Preventive anti-ulcer activity of the rhizome extract of Zingiber officinale. Fitoterapia 63.1 (1992): 55-9.

Sharma A et al. Zingiber officinale Rosc. modulates gamma radiation-induced conditioned taste aversion. Pharmacol Biochem Behav 81.4 (2005): 864-70.
Sharma JN et al. Suppressive effects of eugenol and ginger oil on arthritic rats. Pharmacology 49.5 (1994): 314-18.
Shoji N, Iwasa A, Takemoto T. Cardiotonic principles of ginger (Zingiber officinale Roscoe). J Pharm Sci 71.10 (1982): 1174-5.
Smith C et al. A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. Obstet Gynecol 103.4 (2004): 639-45.
Sontakke S, Thawani V, Naik MS. Ginger as an antiemetic in nausea and vomiting induced by chemotherapy: A randomized, cross-over, double blind study. Indian J Pharmacol 35.1 (2003): 32-6.
Sripramote M, Lekhyananda N. A randomized comparison of ginger and vitamin B6 in the treatment of nausea and vomiting of pregnancy. J Med Assoc Thailand 86.9 (2003): 846-53.
Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses 39.4 (1992): 342-8.
Stenton SB, Bungard TJ, Ackman ML. Interactions between warfarin and herbal products, minerals, and vitamins: A pharmacist's guide. Can J Hospital Pharm 54.3 (2001): 184-90.
Stewart JJ et al. Effects of ginger on motion sickness susceptibility and gastric function. Pharmacology 42.2 (1991): 111-20.
Thomson M et al. The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins Leukot Essent Fatty Acids 67.6 (2002): 475-8.
Tjendraputra E et al. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorgan Chem 29.3 (2001): 156-63.
Vaes LPJ, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: Nature of the evidence. Ann Pharmacother 34.12 (2000): 1478-82.
Verma SK, Bordia A. Ginger, fat and fibrinolysis. Indian J Med Sci 55.2 (2001): 83-6.
Visalyaputra S et al. The efficacy of ginger root in the prevention of postoperative nausea and vomiting after outpatient gynaecological laparoscopy. Anaesthesia 53.5 (1998): 506-10.
Vishwakarma SL et al. Anxiolytic and antiemetic activity of Zingiber officinale. Phytother Res 16.7 (2002): 621-6.
Vutyavanich T et al. Ginger for nausea and vomiting in pregnancy: Randomized, double-masked, placebo-controlled trial. Obstet Gynecol 97.4 (2001): 577-82.
Weidner MS, Sigwart K. The safety of a ginger extract in the rat. J Ethnopharmacol 73.3 (2000): 513-20.
Wigler I et al. The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis. Osteoarthritis Cartilage 11.11 (2003): 783-9.
Wilasrusmee C, Bruch D, Kittur DS. Zingiber officinale (ginger) extract prolongs cardiac allograft surviaval. Pediatr Transplant Suppl 7.4 (2003): 131.
Willetts KE et al. Effect of a ginger extract on pregnancy-induced nausea: A randomised controlled trial. Aust NZ J Obstet Gynaecol 43.2 (2003): 139-44.
World Health Organization. Rhizoma Zingiberis. Geneva: WHO. Available at: www.who.int/medicines/library/trm/medicinalplants (accessed 15-12-03).
Yamada Y, Kikuzaki H, Nakatani N. Identification of antimicrobial gingerols from ginger (Zingiber officinale Roscoe). J Antibact Antifungal Agents Jpn 20.6 (1992): 309-11.
Yamahara J et al. Cholagocic effect of ginger and its active constituents. J Ethnopharmacol 13.2 (1985): 217-25.
Yamahara J et al. The anti-ulcer effect in rats of ginger constituents. J Ethnopharmacol 23.2-3 (1988): 299-304.
Yamahara J et al. Gastrointestinal motility enhancing effect of ginger and its active constituents. Chem Pharm Bull 38.2 (1990): 430-1.
Yamahara J et al. Stomachic principles in ginger. II: Pungent and anti-ulcer effects of low polar constituents isolated from ginger, the dried rhizoma of Zingiber officinale Roscoe cultivated in Taiwan: The absolute stereostructure of a new diarylheptanoid. Yakugaku Zasshi 112.9 (1992): 645-55 [in Japanese].

Yamahara J et al. Pharmacological study on ginger processing. I: Antiallergic activity and cardiotonic action of gingerols and shogaols. Nat Med 49.1 (1995): 76-83 [in Japanese].
Yoshikawa M et al. 6-Gingesulfonic acid, a new anti-ulcer principle, and gingerglycolipids A, B and C, three new monoacyldigalactosylglycerols from Zingiberis rhizoma originating in Taiwan. Chem Pharm Bull 40.8 (1992): 2239-41.
Yoshikawa M et al. Crude drug processing by far-infrared treatment. II: Chemical fluctuation of the constituents during the drying of Zingiberis Rhizoma. Yakugaku Zasshi 113.10 (1993): 712-17.
Yoshikawa M et al. Stomachic principles in ginger. III: An anti-ulcer principle, 6- gingesulfonic acid, and three monoacyldigalactosylglycerols, gingerglycolipids A, B, and C, from Zingiberis Rhizoma originating in Taiwan. Chem Pharm Bull 42.6 (1994): 1226-30.
Zhou H-L et al. The modulatory effects of the volatile oil of ginger on the cellular immune response in vitro and in vivo in mice. J Ethnopharmacol 105.1-2 (2006): 301-5.

Ginkgo biloba



Historical note *Ginkgo biloba* is one of the world's oldest living tree species, earning it the name 'living fossil'. Its existence can be traced back more than 200 million years and it was commonly found in North America and Europe before the Ice Age. Ginkgo was first introduced into Europe in 1690 by the botanist Engelbert Kaempfer, who described it as the 'tree with duck feet'. Ginkgo has been used medicinally for many centuries and is now one of the most popular therapeutic agents prescribed in Europe by medical doctors. It has been estimated that in Germany and France, prescriptions for ginkgo make up 1% and 1.3%, respectively, of total prescription sales (Pizzorno & Murray 2006). Also popular in the United States, it was the top selling herbal medicine in 1999 with sales of US$148 million.

COMMON NAME
Ginkgo

OTHER NAMES
Adiantifolia, *Arbre aux quarante ecus*, bai guo ye, duck foot tree, fossil tree, gin-nan, icho, Japanese silver apricot, kew tree, maidenhair tree, salisburia, silver apricot, tempeltrae, temple balm, yinhsing

BOTANICAL NAME/FAMILY
Ginkgo biloba (family Ginkgoaceae)

PLANT PARTS USED
In modern times the leaf is used, but traditionally the nut was also used.

CHEMICAL COMPONENTS
Important constituents present in the leaves are the terpene trilactones (i.e. ginkgolides A, B, C and J and bilobalide), many flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols (van Beek 2002).

There has been some interest in ginkgo alkylphenols (ginkgolic acids) because of their allergenic properties, so most manufacturers limit the concentration of alkylphenols to 5 ppm.

Clinical note — Ginkgo extract used in practice
The standardised ginkgo extract is made from dried ginkgo leaves extracted in 60% acetone. Only a fraction of the leaf matter is extracted, 98% is not extracted. Of the 2% extracted the flavones account for 25%, the ginkgolides 3% and the bilobalide 3%. The remaining 69% is not specified (Keller 2001). The drug ratio may vary from 35:1 to 67:1 (average ratio 50:1). This means that, on average, it takes 50 kg dried leaf to produce 1 kg of extract. Standardised ginkgo extract (e.g. EGb 761) must be standardised to 22–27% flavone glycosides, 5–7% terpenes lactones (2.8–3.4% ginkgolides A, B and C, and 2.6–3.2% bilobalide). The content of ginkgolic acids must be less than 5 ppm (Blumenthal et al 2000). Although the standardisation is very specific, the compounds are considered to be marker compounds as the active constituents of *Ginkgo biloba* have not been fully identified (unpubl data: Keller K, Chair of the Herbal Medicinal Products Working Group, European Medicines Evaluation Agency. Quality Assurance of Herbal Medicines, March 2001, Australia Technology Park).

MAIN ACTIONS

The many and varied pharmacological actions of ginkgo preparations are related to the presence of several classes of active constituents.

ANTIOXIDANT

Ginkgo biloba extract and several of its individual constituents, such as quercetin and kaempferol, have demonstrated significant antioxidant properties in vitro (Hibatallah et al 1999, Sloley et al 2000).

The antioxidant effects of *G. biloba* have been shown to reduce the effects of UV radiation on skin (Aricioglu et al 2001, Hibatallah et al 1999, Kim 2001, Lin & Chang 1997). When applied topically, ginkgo increases the activity of superoxide dismutase within skin, thereby enhancing the skin's natural defences.

VASOREGULATION

Vasodilation Ginkgo promotes vasodilation and improves blood flow through arteries, veins and capillaries. Increases in microcirculatory blood flow occur rapidly and have been confirmed under randomised crossover test conditions 1 hour after administration (Jung et al 1990).

Several mechanisms of action are responsible. Currently, these are considered to be: inhibition of NO release, activation of Ca^{2+}-activated K^+ (K_{Ca}) channels, and increased prostacyclin release (Nishida & Satoh 2003).

Reduces oedema Various flavonoids including anthocyanosides and *G. biloba* extracts have been shown to be effective against experimentally induced capillary hyperfiltration (Cohen-Boulakia et al 2000).

ANTIPLATELET AND ANTICOAGULANT

There have been several case reports of *G. biloba* causing haemorrhage during or after surgery (Hauser et al 2002, Schneider et al 2002) and there is evidence that one of its components, ginkgolide B, is a platelet-activating factor antagonist (Smith et al 1996). However, three placebo-controlled studies have failed to detect a significant effect for *G. biloba* on platelet function or coagulation (Bal Dit et al 2003, Jiang et al 2003, Kohler 2004). One was an escalating dose study that found that 120 mg, 240 mg or 480 mg given daily for 14 days did not alter platelet function or coagulation (Bal Dit et al 2003).

ALTERS NEUROTRANSMITTERS

Monoamine oxidase (MAO) inhibition In vitro tests in rat brains suggest that EGb 761 may exert MAO-A and MAO-B inhibitor activity (Wu & Zhu 1999). Tests with isolated constituents kaempferol, apigenin and chrysin have demonstrated these to be potent MAO inhibitors, with greater effect on MAO-A than MAO-B (Sloley et al 2000). It is unclear whether MAO inhibition occurs in vivo.

Serotonin Another in vitro study found that oral EGb 761 significantly increases the uptake of serotonin, but not dopamine, in cerebral cortex samples from mice (Ramassamy et al 1992) and another in vivo study identified an anti-aggressive effect mediated by 5-HT_{2A} receptors (Shih et al 2000).

Cholinergic effects Considering that *G. biloba* appears to be as effective as anticholinesterase drugs, several researchers have investigated whether it exerts cholinergic effects. Evidence from behavioural, in vitro and ex vivo tests with *G. biloba* has shown both direct and indirect cholinergic activity (Das et al 2002, Nathan 2000). The extract appears to increase the rate of acetylcholine turnover and stimulate the binding activity of ligands to muscarinic receptors in the hippocampus (Muller 1989).

GABA receptors Bilobalide in *G. biloba* is a competitive antagonist for GABA-A receptors according to in vitro tests (Huang et al 2003). The effect is almost as potent as bicuculline and pictrotoxinin.

Corticosterone In vivo tests have found EGb 761 has stress-alleviating properties mediated through its moderation of corticosterone levels (Puebla-Perez et al 2003).

NEUROPROTECTION

Ginkgo biloba leaf extract (EGb 761) has demonstrated neuroprotective effects in a variety of studies ranging from molecular and cellular, to animal and human;

however, the cellular and molecular mechanisms remain unclear (Smith et al 2002). Of the constituents studied, it appears that the bilobalide constituent is chiefly responsible for this activity, although others are also involved (DeFeudis & Drieu 2000).

Up until recently, it was believed that the antioxidant, membrane stabilising and platelet-activating factor antagonist effects were chiefly responsible for neuroprotection, but new evidence suggests MAO inhibitor activity and effects at the mitochondria may also be important contributing mechanisms.

Beta-amyloid *Ginkgo biloba* extract EGb 761 protects cells against toxicity induced by beta-amyloid in a concentration-dependent manner, according to in vitro tests (Bastianetto & Quirion 2002a, b, Bastianetto et al 2000). More recently in vivo studies have confirmed that ginkgo extract has an anti-amyloid aggregation effect (Luo 2006). It appears that ginkgo increases transthyretin RNA levels in mouse hippocampus, which is noteworthy because transthyretin is involved in the transport of beta-amyloid and may provide a mechanism to reduce amyloid deposition in brain (Watanabe et al 2001). There is also evidence that *G. biloba* modulates alpha-secretase, the enzyme that cuts the amyloid precursor protein and prevents amyloidogenic fragments from being produced (Colciaghi et al 2004).

Cerebral ischaemia There is evidence from experimental and clinical studies that *G. biloba* extract protects tissues from ischaemia/reperfusion damage (Janssens et al 2000). According to investigation with an experimental model, EGb 761 could prevent and treat acute cerebral ischaemia, but the effect was most pronounced when administered prophylactically (Peng et al 2003).

Stabilisation and protection of mitochondrial function Several in vitro tests have demonstrated that EGb 761 stabilises and protects mitochondrial function (Eckert et al 2005, Janssens et al 2000). These observations are gaining the attention of researchers interested in neurodegenerative diseases as it is suspected that the mitochondria and the phenomenon of mitochondrial permeability transition play a key role in neuronal cell death and the development such diseases (Beal 2003, Shevtsova et al 2005).

IMMUNOSTIMULANT

Immunostimulatory activity has been demonstrated in several experimental models (Puebla-Perez et al 2003, Tian et al 2003, Villasenor-Garcia et al 2004). The beneficial effects of EGb 761 on immune function are based on its antioxidant properties, as well as the cell proliferation-stimulating effect.

ANTI-INFLAMMATORY

The anti-inflammatory activity of ginkgo has been investigated for the whole extract and an isolated biflavonoid component known as ginkgetin, with both forms demonstrating significant anti-inflammatory activity.

Ginkgo extract Intravenously administered ginkgo extract produced an anti-inflammatory effect that was as strong as the same dose of prednisolone (i.e. 1 mg GBE = 1 mg prednisolone) in an experimental model. Ginkgo extract was also found to significantly reduce the concentration of PGE_2, TNF-alpha and NO production in vitro (Ilieva et al 2004). Studies with subcutaneously administered *G. biloba* extract in experimental models have also identified significant anti-inflammatory activity, with the addition of antinociceptive effects (Abdel-Salam et al 2004).

Ginkgetin Ginkgetin showed a stronger anti-inflammatory activity than prednisolone when administered by intraperitoneal injection in an animal model of arthritis. Histological examination of the knee joints confirmed the effect (Kim et al 1999). When used topically in an animal model of chronic skin inflammation and pro-inflammatory gene expression, it was found to inhibit ear oedema by approximately 26% and PGE_2 production by 30% (Lim et al 2006). Histological comparisons revealed that ginkgetin reduced epidermal hyperplasia, inhibited phospholipase A2, and suppressed COX-2 and iNOS expression (Lim et al 2006).

ANTICANCER

Studies conducted with various molecular, cellular and whole animal models have revealed that leaf extracts of *G. biloba* may have anticancer (chemopreventive) properties that are related to its antioxidant, anti-angiogenic and gene-regulatory actions (DeFeudis et al 2003). Both the flavonoid and terpenoid constituents are thought to be responsible for many of these mechanisms, meaning that the whole extract is required for activity. Studies in humans have found that ginkgo extracts inhibit the formation of radiation-induced (chromosome-damaging) clastogenic factors and UV-induced oxidative stress, both effects that may contribute to the overall chemopreventive activity. As a result of these observations, there has been a call by some academics for ginkgo to be more widely investigated and used in the prevention and treatment of cancer (Eli & Fasciano 2006).

OTHER ACTIONS

Inhibition of CYP3A4 has been demonstrated in vitro (Budzinski et al 2000); however, two clinical studies have produced contradictory results (Chavez et al 2006).

Evidence from a recent in vitro study that investigated the effect of individual constituents in ginkgo suggests that several constituents found within ginkgo have

significant inhibitory activity; however, the principal components (terpene trilactones and flavonol glycosides) do not (von Moltke et al 2004). Ultimately, the clinical importance of these potential inhibitors will depend on their concentration within a commercial product and the extent of their bioavailability.

CLINICAL USE

Ginkgo biloba is a complex herb that contains many different active constituents and works by means of multiple mechanisms. In practice, its therapeutic effect is a result of interactions between constituents and mechanisms, giving it applications in many varied conditions. To date, most of the research conducted in Europe has used a standardised preparation known as EGb 761, available commercially as Rokan, Tanakan or Tebonin.

DEMENTIA, MEMORY IMPAIRMENT

Ginkgo biloba has been used and studied as a cognitive activator in a variety of populations, such as cognitively intact people, those with cerebral insufficiency, age-related memory impairment, Alzheimer's dementia or multi-infarct dementia (Itil et al 1998, Le Bars et al 2000, 2002, Oken et al 1998, Wettstein 1999).

A 2002 Cochrane review of the scientific literature concluded that *G. biloba* produces benefits superior to placebo within 12 weeks' treatment in people with acquired cognitive impairment, including dementia, of any degree of severity (Birks et al 2002). Cognition, activities of daily living and measures of mood and emotional function show significant benefit for ginkgo compared with placebo.

Some clinical studies have also found that EGb 761 improves the capacity of geriatric patients to cope with the stressful demands of daily life (Clostre 1999).

Clinical note — What is cerebral insufficiency?
Cerebral insufficiency is a syndrome characterised by a collection of symptoms, although it is not associated with any clear pathological changes. The 12 symptoms associated with this condition are: difficulties of memory and concentration; being absent-minded; confusion; lacking energy; tiredness; decreased physical performance; depressive mood; anxiety; dizziness; tinnitus; and headaches (Kleijnen & Knipschild 1992). Some of these symptoms are also described as early symptoms of dementia and appear to be associated with decreased cerebral blood flow, although frequently no explanation is found.

Use in healthy subjects A number of double-blind studies have investigated the effects of *G. biloba* (150–600 mg/day) in healthy subjects; however, it remains unclear whether benefits can be expected in this population (Cieza et al 2003, Mix &

Crews 2000, 2002, Rigney et al 1999, Solomon et al 2002, Subhan & Hindmarch 1984).

A 6-week, double-blind placebo-controlled trial using a dose of 180 mg/day EGb 761 extract in healthy elderly subjects found that active treatment produced significantly better improvements on a task assessing speed of processing abilities compared with placebo (Mix & Crews 2000). Subjectively, more people rated their ability to remember as improved by the end of treatment with ginkgo compared with placebo, but no significant differences were found between the groups on any of the four objective memory measures. Another randomised, double-blind placebo-controlled study involving 31 subjects (aged 30–59 years) compared the effects of four different doses of ginkgo extract with placebo over 2 days (Rigney et al 1999). Once again, treatment improved various aspects of cognition with the strongest effects seen on memory. A dose of 120 mg ginkgo extract daily produced the best effects, and cognitive-enhancing effects were most apparent in the group aged 50–59 years.

Two more clinical studies to investigate ginkgo in cognitively intact older adults have produced conflicting results (Mix & Crews 2002, Solomon et al 2002). Solomon et al used a dose of 120 mg/day over 6 weeks under double-blind conditions and found no significant differences between treatment and control groups on any outcome measure that included standard neuropsychological tests for memory and concentration. There have been several points of controversy regarding this particular trial, chiefly in regard to the non-identical placebo that was used (a soft gelatin capsule for placebo whereas the ginkgo product was a film-coated tablet). Mix and Crews used a higher dose of 180 mg/day over 6 weeks under the same test conditions and found that people receiving EGb 761 exhibited significantly more improvement on several neuropsychological tests, indicating improved aspects of memory. Additionally, the results of self-rated surveys found that memory improvements were of sufficient magnitude as to be detected by participants in the ginkgo treatment group.

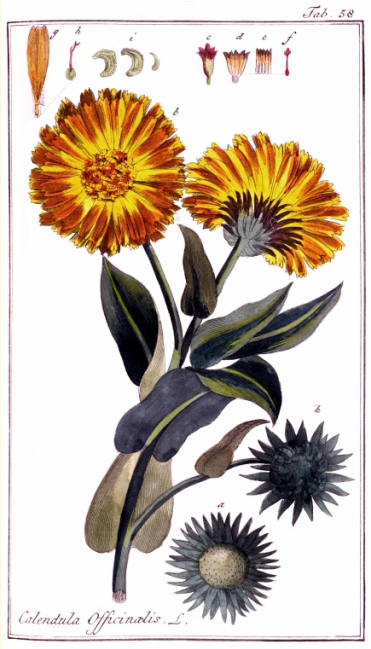
Comparisons with anticholinesterase drugs The type of CNS effects produced by EGb 761 in elderly dementia patients is similar to those induced in tacrine responders and those seen after the administration of other 'cognitive activators', according to a small randomised study involving 18 elderly people diagnosed with mild to moderate dementia (possible or probable Alzheimer's disease) (Itil et al 1998). The results also demonstrated that 240 mg EGb produced typical cognitive activator ECG profiles (responders) in more subjects (8 of 18) than 40 mg tacrine (3 of 18 subjects). A later review concluded that ginkgo extract and second-generation

cholinesterase inhibitors (donepezil, rivastigmine, metrifonate) should be considered equally effective in the treatment of mild to moderate Alzheimer's dementia (Wettstein 2000).

Commission E approves the use of standardised ginkgo extract in dementia syndromes, including vascular, primary degenerative and mixed types (Blumenthal et al 2000).

Dementia prevention The many mechanisms attributed to ginkgo make it an ideal candidate for the long-term prevention of many age-related diseases such as dementia. Currently, a large study involving more than 3000 volunteers is underway in the United States. The Ginkgo Evaluation of Memory (GEM) study will evaluate whether long-term ginkgo use will reduce the incidence of all-cause dementia and Alzheimer's dementia (Colciaghi et al 2004). Secondary outcomes of the trial include measuring effects on the rate of cognitive and functional decline, incidence of cardiovascular and cerebrovascular events, and mortality.

Acute ischaemic stroke *Ginkgo biloba* extract is widely used in the treatment of acute ischaemic stroke in China. A Cochrane systematic review identified 14 trials of which 10 (792 patients) were included (Zeng et al 2005). In those 10 trials, follow-up was performed at 14–35 days after stroke and in all studies neurological outcome was assessed, but none of them reported on disability (activities of daily living function) or QOL and only three trials reported adverse events. Nine of the trials were considered to be of inferior quality. Overall results from the 10 studies found that *G. biloba* extract was associated with a significant increase in the number of improved patients. Of note, one placebo-controlled trial, assessed to be of good quality, failed to show an improvement of neurological deficit at the end of treatment. In view of the short-comings of many trials and limited evidence, high-quality and large-scale randomised controlled trials are still required to determine its efficacy.



DEPRESSION

Although studies investigating the effects of *G. biloba* in cerebral insufficiency, a syndrome that is often characterised by depression, have shown positive results, no clinical studies are available that have investigated its use in clinical depression.

One randomised, double-blind placebo-controlled study has investigated its effects in seasonal affective disorder (SAD). *Ginkgo biloba* extract PN246, in tablet form (Bio-Biloba), was tested in 27 patients with SAD over 10 weeks or until they developed symptoms, starting in a symptom-free phase about 1 month before symptoms were expected. In this trial, *G. biloba* failed to prevent the development of SAD (Lingaerde et al 1999).

More recently, Cieza et al (2003) tested EGb 761 (240 mg/day) on the subjective emotional well-being of healthy older subjects (50–65 years) in a randomised, double-blind study. Ginkgo treatment produced a statistically significant difference for the VAS mental health and for QOL, as well as for the Subjective Intensity Score Mood in week 2 compared with placebo. At the end of the study, statistically significant improvement in the EGb 761 group was observed for the variables: depression, fatigue and anger.

GENERALISED ANXIETY DISORDER

EGb 761 has demonstrated stress-alleviating and anxiolytic-like activity in preclinical studies, and most recently in a randomised study of 107 patients with GAD ($n = 82$) or adjustment disorder with anxious mood ($n = 25$) (Woelk et al 2006). Ginkgo biloba was tested in two different doses (480 mg and 240 mg/day) against placebo over 4 weeks and found to be significantly superior with a dose-response trend being identified. Beneficial effects were observed after 4 days of treatment.

PERIPHERAL VASCULAR DISEASES

Ginkgo has been used in the treatment of intermittent claudication, Raynaud's syndrome and chilblains (Pittler & Ernst 2000, Mouren et al 1994).

Intermittent claudication In 2000, a meta-analysis of eight clinical trials found a significant difference in the increase in pain-free walking distance in favour of *G. biloba* over placebo in intermittent claudication (Pittler & Ernst 2000). An earlier randomised study measuring transcutaneous partial pressure of oxygen during exercise showed that a dose of 320 mg/day EGb 761 taken for 4 weeks significantly decreased the amount of ischaemic area by 38% compared with no change with placebo (Mouren et al 1994).

A more recent 2004 meta-analysis confirmed that ginkgo is more effective than placebo in intermittent claudication (Horsch & Walther 2004). Nine double-blind studies of EGb 761 for intermittent claudication were assessed in a total of 619 patients. A sensitivity analysis of a homogeneous sample in terms of design, treatment duration, inclusion and exclusion criteria and methods of measurement confirms these findings. Most studies have used a dose of 120 mg/day taken in divided doses, although one trial found 240 mg/day gave better results. It should be recommended as long-term therapy and as an adjunct to exercise for the best results.

Commission E approved the use of standardised ginkgo extract for intermittent claudication (Blumenthal et al 2000).

Clinical note — Peripheral arterial disease
Peripheral arterial disease (PAD) is the chronic obstruction of the arteries supplying the lower extremities. The most frequent symptom is intermittent claudication, which results from poor oxygenation of the muscles of the lower extremities and is experienced typically as an aching pain, cramping, or numbness in the calf, buttock, hip, thigh, or arch of the foot. Symptoms are induced by walking or exercise and are relieved by rest. Presently, medical treatment revolves around lifestyle changes, such as increased exercise, and surgery as a final option.

Raynaud's syndrome A standardised *G. biloba* extract (Seredrin) taken over a 10-week period significantly reduced the number of attacks per week (from 13.2 to 5.8) compared with placebo, according to a randomised study (Muir et al 2002).

VERTIGO, TINNITUS AND SUDDEN DEAFNESS

Ginkgo is used to treat these and other symptoms of vestibule-cochlear disorders.

In 1999, a systematic review of five RCTs testing standardised *G. biloba* extracts in people whose primary complaint was tinnitus concluded that treatment with *G. biloba* may result in significant improvements in tinnitus (Ernst & Stevinson 1999). Three years later, a review of eight controlled trials in tinnitus confirmed these findings, stating that ginkgo is significantly superior to placebo or reference drugs when used for periods of 1–3 months (Holstein 2001).

However, results of two double-blind studies conducted more recently have shifted the evidence against the use of *G. biloba* in tinnitus. The first was a large, double-blind, placebo-controlled study involving 1121 people aged between 18 and 70 years with tinnitus and 978 matched controls, which found that 12 weeks of treatment with ginkgo extract, LI 1370 (Lichtwer Pharma, Berlin, Germany), 50 mg, three times daily resulted in no significant differences when subjects assessed their tinnitus in terms of loudness and how troublesome it was (Drew & Davies 2001). A more recent double-blind, placebo-controlled, randomised study of 66 subjects with tinnitus failed to show benefits with active treatment using a dose of 120 mg extract daily over 12 weeks (Rejali et al 2004). The primary outcome measures used were the Tinnitus Handicap Inventory, The Glasgow Health Status Inventory and the average hearing threshold at 0.5, 1, 2 and 4 kHz. In 2004, Rejai et al conducted a meta-analysis of clinical trials and found that 21.6% of patients with tinnitus reported benefit from *G. biloba* versus 18.4% of patients who reported benefit from a placebo.

A 2004 Cochrane systematic review came to a similar conclusion, reporting that the limited evidence currently available does not support the use of ginkgo in tinnitus; however, the authors also pointed out that if a greater level of understanding and

diagnostic accuracy could be reached about the different aetiologies of tinnitus, this may naturally highlight subgroups of patients in whom further controlled trials of *G. biloba* are worth considering (Hilton & Stuart 2004).

Salicylate-induced tinnitus One in vivo study investigating the effects of ginkgo in salicylate-induced tinnitus found a statistically significant decrease in the behavioural manifestation of tinnitus for ginkgo in doses of 25, 50 and 100 mg/kg/day (Jastreboff et al 1997).

Sudden deafness Ginkgo extract was as effective as pentoxifylline in the treatment of sudden deafness, according to one randomised double-blind study (Reisser & Weidauer 2001). Both treatments equally reduced associated symptoms of tinnitus and produced the same effects on the return to normal of speech discrimination. Subjective assessment suggested that *G. biloba* extract was more beneficial than pentoxifylline. EGb 761 (240 mg/day) has also been shown to accelerate and secure recovery of acute idiopathic sudden sensorineural hearing loss, observable within 1 week of treatment under randomised double-blind test conditions (Burschka et al 2001).

Commission E approves the use of standardised ginkgo extract in these conditions when of vascular origin (Blumenthal et al 2000).

MACULAR DEGENERATION, GLAUCOMA AND RETINOPATHY

In regard to these opthalmological conditions, ginkgo has numerous properties that should theoretically make it a useful treatment, such as increasing ocular blood flow, antioxidant and platelet-activating factor inhibitor activity, NO inhibition and neuroprotective abilities.

Macular degeneration Although some positive evidence exists, a 2000 Cochrane review has suggested overall there is insufficient evidence currently available to conclude that *Ginkgo biloba* treatment is effective in macular degeneration, with further testing required (Evans 2000).

Glaucoma In regard to glaucoma, the little research conducted so far appears promising.

Researchers using colour Doppler imaging have observed significantly increased end-diastolic velocity in the ophthalmic artery after treatment with EGb (120 mg/day) in a placebo-controlled, randomised crossover study (Chung et al 1999). A randomised, double-blind crossover study found that EGb 761 (120 mg/day) taken for 4 weeks produces positive effects in normal tension glaucoma (Quaranta et al 2003). Furthermore, ginkgo treatment did not significantly alter intraocular pressure, blood pressure or heart rate and was well tolerated.

Chloroquine retinopathy In vivo tests using electroretinography have identified protective effects against the development of chloroquine-induced retinopathy using *Ginkgo biloba* (Droy-Lefaix et al 1992). This has been observed in both acute and chronic chloroquine toxicity of the retina (Droy-Lefaix et al 1995).

PREVENTION OF ALTITUDE SICKNESS

Four randomised studies have investigated *G. biloba* as prophylactic treatment against altitude sickness, producing mixed results (Chow et al 2005, Gertsch et al 2002, 2004, Roncin et al 1996). One study involving 44 subjects found that a dose of 160 mg/day taken for 5 days as prophylactic treatment resulted in no subject developing the cerebral symptoms of acute mountain sickness versus 41% of subjects in the placebo group. Whereas only three subjects (13.6%) in the EGb 761 group developed respiratory symptoms of acute mountain sickness, 18 (81.8%) in the placebo group developed these symptoms. Besides effectively preventing mountain sickness for moderate altitude (5400 m), treatment also decreased vasomotor disorders of the extremities (Roncin et al 1996). A second study showed that *G. biloba* 180 mg/day started 24 hours before rapid ascent from sea level to 4205 m significantly reduced altitude sickness under double-blind test conditions (Gertsch et al 2002). The two more recent studies compared ginkgo to placebo and acetazolamide and found no significant effects for ginkgo (Chow et al 2005, Gertsch et al 2004). The largest study was conducted by Gertsch et al and involved 487 healthy Western hikers. It compared the effects of ginkgo, acetazolamide (250 mg), combined acetazolamide and ginkgo, and placebo. Participants took at least 3–4 doses before ascent above 4000 m in the Nepal Himalayas. The incidence of acute mountain sickness was 34% for placebo, 12% for acetazolamide, 35% for ginkgo and 14% for combined ginkgo and acetazolamide. Chow et al conducted a smaller study of 57 healthy unacclimatised subjects using a randomised, placebo-controlled design. Subjects were taken to an elevation of 3800 m within 24 hours, with acetazolamide producing significantly better effects than ginkgo or placebo using the Lake Louise Acute Mountain Sickness Scoring System. Subjects receiving ginkgo were as likely as placebo to experience acute mountain sickness whereas acetazolamide was protective.

PREMENSTRUAL SYNDROME

A randomised double-blind study evaluating the effects of EGb 761 in treating congestive symptoms of PMS in a group of 165 women found that treatment over two menstrual cycles (from day 16 until day 5 of the next cycle) was successful.

Treatment was particularly effective in reducing breast symptoms, although neuropsychological symptoms were also alleviated (Tamborini & Taurelle 1993).

VITILIGO

A dose of 120 mg/day ginkgo extract significantly stopped active progression of depigmentation in slow-spreading vitiligo and induced repigmentation in some treated patients under double-blind, placebo-controlled study conditions (Parsad et al 2003). Although the mechanism of action responsible is unknown, antioxidant activity is thought to be important.

ASTHMA

Ginkgo significantly reduced airway hyperreactivity, improved clinical symptoms and pulmonary function in asthmatic patients in one placebo-controlled study (Li et al 1997). Platelet-activating factor inhibitor, antioxidant and anti-inflammatory activities are likely to be involved.

SEXUAL DYSFUNCTION

Due to its vasodilatory effects, ginkgo has been used in the management of sexual dysfunction in cases where compromised circulation is suspected. One open study has been conducted with subjects experiencing sexual dysfunction associated with antidepressant use (Cohen & Bartlik 1998).

Ginkgo extract (average dose 209 mg/day) was found to be 84% effective in treating antidepressant-induced sexual dysfunction, predominantly caused by SSRI, in a study of 63 subjects (Cohen & Bartlik 1998). A relative success rate of 91% was observed for women compared with 76% for men and a positive effect was reported on all four phases of the sexual response cycle: desire, excitement (erection and lubrication), orgasm and resolution. Although this was an open trial, the results are encouraging when one considers the placebo effect is about 25% from past randomised trials of FDA-approved medications for erectile dysfunction (Moyad 2002).

More recently, a small triple-blind (investigator, patient, statistician), randomised, placebo-controlled, trial of *G. biloba* (240 mg/daily for 12 weeks) was undertaken with 24 subjects experiencing sexual impairment caused by antidepressant drugs (Wheatley 2004). The authors report some spectacular individual responses in both groups, but no statistically significant differences, and no differences in side-effects.

PARKINSON'S DISEASE

There is great interest in the application of safe substances, such as *G. biloba*, in neurodegenerative diseases such as Parkinson's disease because of their

neuroprotective and mitochondrial protective effects. Currently, investigation with ginkgo is limited to animal studies of experimentally induced Parkinson's disease, which have shown it to afford some protection against neuronal loss (Ahmad et al 2005, Kim et al 2004).

OTHER USES

Ginkgo biloba is used for many other indications, including improving connective tissue conditions such as haemorrhoids, common allergies, reducing the effects of exposure to radiation and to prevent some of the complications associated with diabetes. In the UK and other European countries, the cardioprotective effects of EGb 761 in myocardial ischaemia and reperfusion are currently being investigated in preclinical studies.

ADJUNCT IN CANCER TREATMENT

As a herb with significant antioxidant activity, ginkgo has been used to reduce the toxic side-effects of some chemotherapeutic drugs. Evidence from in vivo studies demonstrate protective effects against nephrotoxicity induced by cisplatin and cardiotoxicity induced by doxorubicin (Naidu et al 2002, Ozturk et al 2004). Clinical trials are not yet available to determine its effectiveness in practice.

CANCER PREVENTION

A 2006 review puts forward the case that *G. biloba* should be more widely used as a safe, preventative agent for reducing cancer incidence. This recommendation is based on results from numerous in vitro and experimental studies showing that ginkgo affects many factors associated with the incidence and mortality of cancer (Eli & Fasciano 2006).

DOSAGE RANGE

The recommended dose varies depending on indication and condition treated.

GENERAL GUIDE

- Dried herb: 9–10 g/day.
- 120–240 mg of a 50:1 standardised extract daily in divided doses (40 mg extract is equivalent to 1.4–2.7 g leaves).
- Fluid extract (1:1): 0.5 mL three times daily.

ACCORDING TO CLINICAL STUDIES

- Asthma: 40 mg three times daily.
- Dementia and memory impairment: 120–240 mg standardised extract daily in divided doses.

- Intermittent claudication, vertigo: 120–320 mg standardised extract daily in divided doses.
- Normal tension glaucoma: 120 mg standardised extract daily.
- Prevention of altitude sickness: 160 mg standardised extract daily starting 5 days prior to ascent.
- Sexual dysfunction associated with antidepressant drugs: 200 mg standardised extract daily.
- Vitiligo: 120 mg standardised extract daily.

Although some studies report positive effects after 4–6 weeks' continual use, a trial of at least 12 weeks is recommended in chronic conditions.

ADVERSE REACTIONS

Tolerability in 98% of the clinical studies is good or very good (Bilia 2002). In a few cases (less than 0.001%), gastrointestinal upset, headaches and dizziness were reported. It does not appear to alter heart rate and blood pressure, change cholesterol and triglyceride levels or increase intraocular pressure in clinical studies (Chung et al 1999).

Rare case reports of subarachnoid haemorrhage, subdural haematoma, intracerebral haemorrhage, subphrenic haematoma, vitreous haemorrhage and postoperative bleeding have been documented.

SIGNIFICANT INTERACTIONS

PLATELET INHIBITOR DRUGS

Due to its platelet-activating factor antagonist activity, *Ginkgo biloba* may theoretically enhance the effects of these drugs and increase risk of bruising or bleeding; however, three clinical trials have cast doubt on the clinical significance of this activity — observe patients taking this combination.

WARFARIN

Theoretically, ginkgo may increase bleeding risk when used together with warfarin; however, two randomised double-blind studies have found that *Ginkgo biloba* does not affect the pharmacokinetics, pharmacodynamics, INR or clinical effects of warfarin (Engelson et al 2003, Jiang et al 2003), and two clinical trials have not found evidence of significant effects on bleeding (Bal Dit et al 2003, Kohler et al 2004). Due to the potential seriousness of such an interaction, caution is still advised.

CHOLINERGIC DRUGS
Cholinergic activity has been identified for ginkgo; therefore, combined use may theoretically increase drug activity — observe patients using this combination, although the effects may be beneficial when used under supervision.

DOXORUBICIN
In vivo research suggests that ginkgo can prevent doxorubicin-induced cardiotoxicity suggesting a potentially beneficial interaction, although no human studies are available to confirm clinical significance (Naidu et al 2002).

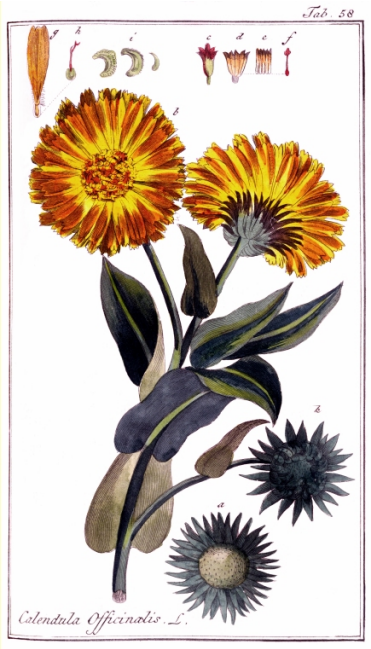
ANTIDEPRESSANT DRUGS
Ginkgo biloba may reduce the sexual dysfunction side-effects of these drugs and improve sleep continuity; however, results from clinical studies are mixed — possible beneficial interaction.

VALPROATE, DILANTIN, DEPAKOTE
There is a report of two patients using valproate who experienced seizures with ginkgo use (Chavez et al 2006). There is also a report of a patient taking Dilantin and Depakote and ginkgo, together with other herbal medicines, who suffered a fatal breakthrough seizure, with no evidence of non-compliance with anticonvulsant medications (Kupiec & Raj 2005). The autopsy report revealed subtherapeutic serum levels for both anticonvulsants Depakote and Dilantin; however, it is uncertain whether effects can be attributed to ginkgo — observe patient taking ginkgo with these medicines.

HALOPERIDOL
In three clinical trials, the effectiveness of haloperidol was enhanced when co-administered with 360 mg daily of ginkgo (Chavez et al 2006) — beneficial interaction.

CISPLATIN
As a herb with significant antioxidant activity, it has also been employed as a means of reducing the nephrotoxic effects of cisplatin, a use supported by one in vivo study (Ozturk et al 2004) — possible beneficial interaction; however, use only under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS
If unusual bleeding or bruising occurs, stop use immediately. Although new clinical evidence suggests that *G. biloba* does not affect clotting times, it may be prudent to suspend use for 1 week prior to major surgery.



CEREBRAL HAEMORRHAGE AND EPILEPSY

Recent, rare case reports have suggested that ginkgo should be used with caution in people with known risk factors for cerebral haemorrhage and epilepsy until further investigation can clarify its safety (Benjamin et al 2001, Granger 2001, Vale 1998).

PREGNANCY USE

Not recommended in pregnancy as insufficient reliable evidence is available to determine safety.

PRACTICE POINTS/PATIENT COUNSELLING

- *Ginkgo biloba* is a complex herb that contains many different active constituents and works by means of multiple mechanisms. Therefore, it has applications in many varied conditions.
- It is an effective treatment in conditions of acquired cognitive impairment, including dementia of any degree of severity and intermittent claudication, according to evidence from meta-analyses.
- Positive evidence also exists for premenstrual syndrome, sudden deafness, Raynaud's syndrome and depression when associated with cognitive decline.
- Largely based on the herb's physiological actions, ginkgo is also used to treat chilblains, haemorrhoids, prevent macular degeneration, glaucoma, sexual dysfunction, impotence, allergies and asthma and improve wellbeing.
- The form of ginkgo most often tested and used is a preparation known as EGb 761, which is standardised to 24% ginkgo flavonol glycosides and 6% terpene lactones.
- Overall, *Ginkgo biloba* is a very safe herb and is extremely well tolerated.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Ginkgo is a very popular herbal treatment that increases peripheral circulation, beneficially influences brain chemicals, protects nerve cells from damage, and may stimulate immune function and reduce inflammation. Scientific evidence has shown it can improve brain function in both healthy and memory-impaired people. It has also been found to improve symptoms of intermittent claudication and may be useful in chilblains, PMS, vitiligo and seasonal affective disorder and possibly sexual dysfunction such as impotence.

When will it start to work?

This will depend on the condition treated and the dose used. Generally, *Ginkgo biloba* is a slow-acting herb that can take anywhere from 4 weeks to 3 months to exert maximal effects.

Are there any safety issues?

Ginkgo has been extensively studied and appears to be extremely safe with virtually no side-effects in healthy people. Some contraindications and interactions are possible, so it is recommended it be taken under professional supervision.

REFERENCES

Abdel-Salam OM et al. Evaluation of the anti-inflammatory, anti-nociceptive and gastric effects of Ginkgo biloba in the rat. Pharmacol Res 49.2 (2004): 133-42.

Ahmad M et al. Ginkgo biloba affords dose-dependent protection against 6-hydroxydopamine-induced parkinsonism in rats: neurobehavioural, neurochemical and immunohistochemical evidences. J Neurochem 93.1 (2005): 94-104.

Aricioglu A et al. Changes in zinc levels and superoxide dismutase activities in the skin of acute, ultraviolet-B-irradiated mice after treatment with Ginkgo biloba extract. Biol Trace Elem Res 80.2 (2001): 175-9.

Bal Dit SC et al. No alteration in platelet function or coagulation induced by EGb761 in a controlled study. Clin Lab Haematol 25.4 (2003): 251-3.

Bastianetto S, Quirion R. EGb 761 is a neuroprotective agent against beta-amyloid toxicity. Cell Mol Biol (Noisy-le-grand) 48.6 (2002a): 693-7.

Bastianetto S, Quirion R. Natural extracts as possible protective agents of brain aging. Neurobiol Aging 23.5 (2002b): 891-7.

Bastianetto S et al. The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. Eur J Neurosci 12.6 (2000): 1882-90.

Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. Ann Neurol 53 (Suppl 3) (2003): S39-47.

Benjamin J et al. A case of cerebral haemorrhage: can Ginkgo biloba be implicated? Postgrad Med J 77.904 (2001): 112-13.

Bilia AR. Workshop report: Ginkgo biloba. Fitoterapia 73.3 (2002): 276-9.

Birks J, Grimley EV, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 4 (2002): CD003120.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Budzinski JW et al. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7.4 (2000): 273-82.

Burschka MA et al. Effect of treatment with Ginkgo biloba extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients. Eur Arch Otorhinolaryngol 258.5 (2001): 213-19.

Chavez ML, Jordan MA, Chavez PI. Evidence-based drug: herbal interactions. Life Sci 78.18 (2006): 2146-57.

Chow T et al. Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: a randomized, placebo-controlled trial. Arch Intern Med 165.3 (2005): 296-301.

Chung HS et al. Ginkgo biloba extract increases ocular blood flow velocity. J Ocul Pharmacol Ther 15.3 (1999): 233-40.

Cieza A, Maier P, Poppel E. [The effect of ginkgo biloba on healthy elderly subjects]. Fortschr Med Orig 121.1 (2003): 5-10.

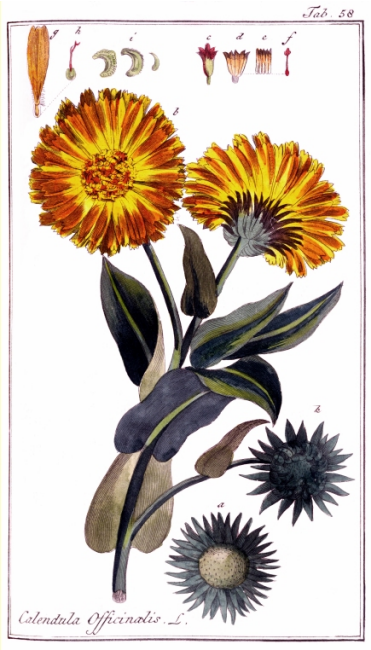
Clostre F. Ginkgo biloba extract (EGb 761): State of knowledge in the dawn of the year 2000. Ann Pharm Fr 57 (Suppl 1) (1999): 1S8-88.

Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. J Sex Marital Ther 24.2 (1998): 139-43.

Cohen-Boulakia F et al. In vivo sequential study of skeletal muscle capillary permeability in diabetic rats: effect of anthocyanosides. Metabolism 49.7 (2000): 880-5.

Colciaghi F et al. Amyloid precursor protein metabolism is regulated toward alpha-secretase pathway by Ginkgo biloba extracts. Neurobiol Dis 16.2 (2004): 454-60.
Das A et al. A comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba: Anticholinesterase and cognitive enhancing activities. Pharmacol Biochem Behav 73.4 (2002): 893.
DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets 1.1 (2000): 25-58.
DeFeudis FV, Papadopoulos V, Drieu K. Ginkgo biloba extracts and cancer: A research area in its infancy. Fundam Clin Pharmacol 17.4 (2003): 405-17.
Droy-Lefaix MT et al. Effect of Gingko biloba extract (EGb 761) on chloroquine induced retinal alterations. Lens Eye Toxic Res 9.3-4 (1992): 521-8.
Droy-Lefaix MT et al. Antioxidant effect of a Ginkgo biloba extract (EGb 761) on the retina. Int J Tissue React 17.3 (1995): 93-100.
Eckert A et al. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by Ginkgo biloba extract EGb 761. Ann NY Acad Sci 1056 (2005): 474-85.
Eli R, Fasciano JA. An adjunctive preventive treatment for cancer: Ultraviolet light and ginkgo biloba, together with other antioxidants, are a safe and powerful, but largely ignored, treatment option for the prevention of cancer. Med Hypotheses 66.6 (2006): 1152-6.
Engelsen J, Nielsen JD, Hansen KF. Effect of coenzyme Q10 and Ginkgo biloba on warfarin dosage in patients on long-term warfarin treatment: A randomized, double-blind, placebo-controlled cross-over trial. Ugeskr Laeger 165.18 (2003): 1868-71.
Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. Clin Otolaryngol 24.3 (1999): 164-7.
Evans JR. Ginkgo biloba extract for age-related macular degeneration. Cochrane Database Syst Rev 2 (2000): CD001775.
Gertsch JH et al. Ginkgo biloba for the prevention of severe acute mountain sickness (AMS) starting one day before rapid ascent. High Alt Med Biol 3.1 (2002): 29-37.
Gertsch JH et al. Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ 328.7443 (2004): 797.
Granger AS. Ginkgo biloba precipitating epileptic seizures. Age Ageing 30.6 (2001): 523-5.
Hauser D, Gayowski T, Singh N. Bleeding complications precipitated by unrecognized Gingko biloba use after liver transplantation. Transplant Int 15.7 (2002): 377-9.
Hibatallah J, Carduner C, Poelman MC. In-vivo and in-vitro assessment of the free-radical-scavenger activity of Ginkgo flavone glycosides at high concentration. J Pharm Pharmacol 51.12 (1999): 1435-40.
Hilton M, Stuart E. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev 2 (2004): CD003852.
Holstein N. Ginkgo special extract EGb 761 in tinnitus therapy: An overview of results of completed clinical trials. Fortschr Med Orig 118.4 (2001): 157-64.
Horsch S, Walther C. Ginkgo biloba special extract EGb 761 in the treatment of peripheral arterial occlusive disease (PAOD): a review based on randomized, controlled studies. Int J Clin Pharmacol Ther 42.2 (2004): 63-72.
Huang SH et al. Bilobalide, a sesquiterpene trilactone from Ginkgo biloba, is an antagonist at recombinant alpha1beta2gamma2L GABA(A) receptors. Eur J Pharmacol 464.1 (2003): 1-8.
Ilieva I et al. The effects of Ginkgo biloba extract on lipopolysaccharide-induced inflammation in vitro and in vivo. Exp Eye Res 79.2 (2004): 181-7.
Itil TM et al. The pharmacological effects of ginkgo biloba, a plant extract, on the brain of dementia patients in comparison with tacrine. Psychopharmacol Bull 34.3 (1998): 391-7.
Janssens D et al. Protection by bilobalide of the ischaemia-induced alterations of the mitochondrial respiratory activity. Fundam Clin Pharmacol 14.3 (2000): 193-201.
Jastreboff PJ et al. Attenuation of salicylate-induced tinnitus by Ginkgo biloba extract in rats. Audiol Neurootol 2.4 (1997): 197-212.

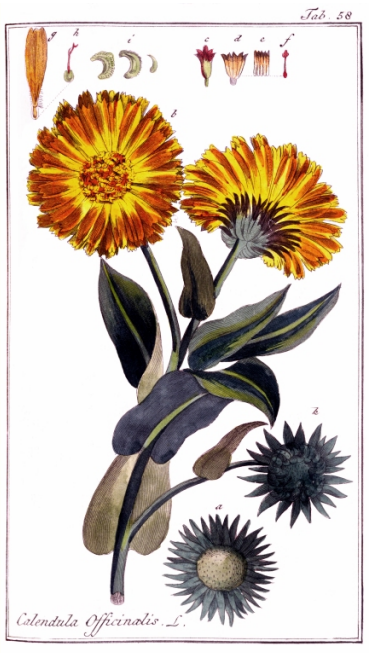
Jiang X et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 59 (2005): 425-32.
Jung F et al. Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. Arzneimittelforschung 40.5 (1990): 589-93.
Kim HK et al. Inhibition of rat adjuvant-induced arthritis by ginkgetin, a biflavone from ginkgo biloba leaves. Planta Med 65.5 (1999): 465-7.
Kim SJ. Effect of biflavones of Ginkgo biloba against UVB-induced cytotoxicity in vitro. J Dermatol 28.4 (2001): 193-9.
Kim MS et al. Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease. Phytother Res 18.8 (2004): 663-6.
Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. Br J Clin Pharmacol 34.4 (1992): 352-8.
Kohler S, Funk P, Kieser M. Influence of a 7-day treatment with Ginkgo biloba special extract EGb 761 on bleeding time and coagulation: a randomized, placebo-controlled, double-blind study in healthy volunteers. Blood Coagul Fibrinolysis 15.4 (2004): 303-9.
Kudolo GB, Orsey S, Blodgett J. Effect of the ingestion of Ginkgo biloba extract on platelet aggregation and urinary prostanoid excretion in healthy and type 2 diabetic subjects. Thromb Res 108.2-3 (2002): 151-60.
Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with Ginkgo biloba. J Anal Toxicol 29.7 (2005): 755-8.
Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 in dementia. Dement Geriatr Cogn Disord 11.4 (2000): 230-7.
Le Bars PL et al. Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer's disease. Neuropsychobiology 45.1 (2002): 19-26.
Li MH, Zhang HL, Yang BY. Effects of ginkgo leave concentrated oral liquor in treating asthma. Zhongguo Zhong Xi Yi Jie He Za Zhi 17.4 (1997): 216-18.
Lim H et al. Effects of anti-inflammatory biflavonoid, ginkgetin, on chronic skin inflammation. Biol Pharm Bull 29.5 (2006): 1046-9.
Lin SY, Chang HP. Induction of superoxide dismutase and catalase activity in different rat tissues and protection from UVB irradiation after topical application of Ginkgo biloba extracts. Methods Find Exp Clin Pharmacol 19.6 (1997): 367-71.
Lingaerde O, Foreland AR, Magnusson A. Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial. Acta Psychiatr Scand 100.1 (1999): 62-6.
Luo Y. Alzheimer's disease, the nematode Caenorhabditis elegans, and Ginkgo biloba leaf extract. Life Sci 78.18 (2006): 2066-72.
Mahmoud F et al. In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A. Jpn J Pharmacol 83.3 (2000): 241-5.
Mix JA, Crews WD Jr. An examination of the efficacy of Ginkgo biloba extract EGb761 on the neuropsychologic functioning of cognitively intact older adults. J Altern Complement Med 6.3 (2000): 219-29.
Mix JA, Crews WD Jr. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings. Hum Psychopharmacol 17.6 (2002): 267-77.
Mouren X, Caillard P, Schwartz F. Study of the antiischemic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. Angiology 45.6 (1994): 413-17.
Moyad MA. Dietary supplements and other alternative medicines for erectile dysfunction. What do I tell my patients? Urol Clin North Am 29.1 (2002): 11-22, vii.
Muir AH et al. The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial. Vasc Med 7.4 (2002): 265-7.
Muller WE. Nootropics, the therapy of dementia between aspiration and reality. Drug News Perspect 2 (1989): 295-300.



Naidu MU et al. Protective effect of Gingko biloba extract against doxorubicin-induced cardiotoxicity in mice. Indian J Exp Biol 40.8 (2002): 894-900.
Nathan P. Can the cognitive enhancing effects of ginkgo biloba be explained by its pharmacology? Med Hypotheses 55.6 (2000): 491-3.
Nishida S, Satoh H. Mechanisms for the vasodilations induced by Ginkgo biloba extract and its main constituent, bilobalide, in rat aorta. Life Sci 72.23 (2003): 2659-67.
Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. Arch Neurol 55.11 (1998): 1409-15.
Ozturk G et al. The effect of Ginkgo extract EGb761 in cisplatin-induced peripheral neuropathy in mice. Toxicol Appl Pharmacol 196.1 (2004):169-75.
Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. Clin Exp Dermatol 28.3 (2003): 285-7.
Peng H, Li YF, Sun SG. Effects of Ginkgo biloba extract on acute cerebral ischemia in rats analyzed by magnetic resonance spectroscopy. Acta Pharmacol Sin 24.5 (2003): 467-71.
Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med 108.4 (2000): 276-81.
Pizzorno J, Murray M. Textbook of Natural Medicine. St Louis: Elsevier, 2006.
Puebla-Perez AM, Lozoya X, Villasenor-Garcia MM. Effect of Ginkgo biloba extract, EGb 761, on the cellular immune response in a hypothalamic-pituitary-adrenal axis activation model in the rat. Int Immunopharmacol 3.1 (2003): 75-80.
Quaranta L et al. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmology 110.2 (2003): 359-62.
Ramassamy C et al. The Ginkgo biloba extract, EGb761, increases synaptosomal uptake of 5-hydroxytryptamine: in-vitro and ex-vivo studies. J Pharm Pharmacol 44.11 (1992): 943-5.
Reisser CH, Weidauer H. Ginkgo biloba extract EGb 761 or pentoxifylline for the treatment of sudden deafness: a randomized, reference-controlled, double-blind study. Acta Otolaryngol 121.5 (2001): 579-84.
Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. Clin Otolaryngol Allied Sci 29.3 (2004): 226-31.
Rigney U, Kimber S, Hindmarch I. The effects of acute doses of standardized Ginkgo biloba extract on memory and psychomotor performance in volunteers. Phytother Res 13.5 (1999): 408-15.
Roncin JP, Schwartz F, D'Arbigny P. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. Aviat Space Environ Med 67.5 (1996): 445-52.
Schneider C et al. [Spontaneous hyphema caused by Ginkgo biloba extract]. J Fr Ophtalmol 25.7 (2002): 731-2.
Shevtsova EF, Kireeva EG, Bachurin SO. [Mitochondria as the target for neuroprotectors]. Vestn Ross Akad Med Nauk 9 (2005): 13-17.
Shih JC et al. Ginkgo biloba abolishes aggression in mice lacking MAO A. Antioxid Redox Signal 2.3 (2000): 467-71.
Sloley BD et al. Identification of kaempferol as a monoamine oxidase inhibitor and potential Neuroprotectant in extracts of Ginkgo biloba leaves. J Pharm Pharmacol 52.4 (2000): 451-9.
Smith PF, Maclennan K, Darlington CL. The neuroprotective properties of the Ginkgo biloba leaf: a review of the possible relationship to platelet-activating factor (PAF). J Ethnopharmacol 50.3 (1996): 131-9.
Smith JV et al. Anti-apoptotic properties of Ginkgo biloba extract EGb 761 in differentiated PC12 cells. Cell Mol Biol (Noisy-le-grand) 48.6 (2002): 699-707.
Solomon PR et al. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 288.7 (2002): 835-40.
Subhan Z, Hindmarch I. The psychopharmacological effects of Ginkgo biloba extract in normal healthy volunteers. Int J Clin Pharmacol Res 4.2 (1984): 89-93.

Tamborini A, Taurelle R. Value of standardized Ginkgo biloba extract (EGb 761) in the management of congestive symptoms of premenstrual syndrome. Rev Fr Gynecol Obstet 88.7-9 (1993): 447-57.
Tian YM et al. Effects of Ginkgo biloba extract (EGb 761) on hydroxyl radical-induced thymocyte apoptosis and on age-related thymic atrophy and peripheral immune dysfunctions in mice. Mech Ageing Dev 124.8-9 (2003): 977-83.
Vale S. Subarachnoid haemorrhage associated with Ginkgo biloba. Lancet 352.9121 (1998): 36.
van Beek TA. Chemical analysis of Ginkgo biloba leaves and extracts. J Chromatogr A 967.1 (2002): 21-55.
Watanabe CM et al. The in vivo neuromodulatory effects of the herbal medicine ginkgo biloba. Proc Natl Acad Sci USA 98.12 (2001): 6577-80.
Wettstein A. Cholinesterase inhibitor and ginkgo extracts in therapy of dementia. A comparison of effectiveness based on controlled studies. Fortschr Med 117.5 (1999): 48-9.
Wettstein A. Cholinesterase inhibitors and Gingko extracts: are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. Phytomedicine 6.6 (2000): 393-401.
Wheatley D. Triple-blind, placebo-controlled trial of Ginkgo biloba in sexual dysfunction due to antidepressant drugs. Hum Psychopharmacol 19.8 (2004): 545-8.
Villasenor-Garcia MM et al. Effect of Ginkgo biloba extract EGb 761 on the nonspecific and humoral immune responses in a hypothalamic-pituitary-adrenal axis activation model. Int Immunopharmacol 4.9 (2004): 1217-22.
von Moltke LL et al. Inhibition of human cytochromes P450 by components of Ginkgo biloba. J Pharm Pharmacol 56.8 (2004): 1039-44.
Woelk H et al. Ginkgo biloba special extract EGb 761((R)) in generalized anxiety disorder and adjustment disorder with anxious mood: A randomized, double-blind, placebo-controlled trial. J Psychiatr Res 2006 [E-pub ahead of print].
Wu WR, Zhu XZ. Involvement of monoamine oxidase inhibition in neuroprotective and neurorestorative effects of Ginkgo biloba extract against MPTP-induced nigrostriatal dopaminergic toxicity in C57 mice. Life Sci 65.2 (1999): 157-64.
Zeng X et al. Ginkgo biloba for acute ischaemic stroke. Cochrane Database Syst Rev 4 (2005): CD003691.

Ginseng—Korean



Historical note *Gin* refers to man and *seng* to essence in Chinese, whereas *Panax* is derived from the Greek word *pan* (all) and *akos* (cure), referring to its use as a cure-all. Ginseng is a perennial herb native to Korea and China and has been used as a herbal remedy in eastern Asia for thousands of years. It is considered to be the most potent Qi or energy tonic in TCM. Modern indications include low vitality, poor immunity, cancer, cardiovascular disease and enhancement of physical performance and sexual function. However, a recent systematic review of RCT found that the efficacy of ginseng root extract could not be established beyond doubt for any of these indications (Coon & Ernst 2002).

COMMON NAME
Korean ginseng

OTHER NAMES
Ren shen (Mandarin), red ginseng, white ginseng

BOTANICAL NAME/FAMILY
Panax ginseng C.A. Meyer (family Araliaceae)

It should be differentiated from *P. aquifolium* (American ginseng), *P. notoginseng* (Tien chi, pseudoginseng), *Eleutherococcus senticosis* (Siberian ginseng) and other ginsengs.

PLANT PART USED
Main and lateral roots. The smaller root hairs are considered an inferior source. There are two types of preparations produced from ginseng: white ginseng, which is prepared by drying the raw herb, and red ginseng, prepared by steaming before drying. Cultivated ginseng differs from wild ginseng and plants from different countries or regions may also differ greatly. Processing of the crude herb to produce red ginseng appears to increase its potency. Steaming has been shown to alter the composition of the ginsenosides; for example, steaming produces the active 20(S)-ginsenoside-Rg(3) (Matsuda et al 2003) and makes certain ginsenosides more cytoxotic (Park et al 2002a).

The British Herbal Pharmacopoeia (1983) stipulates that ginseng should contain not less than 20% solids (70% ethanol). The German Pharmacopoeia requires not less than 1.5% total ginsenosides calculated as ginsenoside Rg 1.

Chewing gums containing ginseng saponins have also been developed and demonstrate therapeutic effects in some trials (Ding et al 2004).

CHEMICAL COMPONENTS

The most characteristic compounds in the ginseng roots are the ginsenosides, and most biological effects have been ascribed to these compounds. The ginsenosides are dammarane saponins and can be divided into two classes: the protopanaxatriol class consisting primarily of Rg1, Rg2, Rf and Re, and the protopanaxadiol class consisting primarily of Rc, Rd, Rb1 and Rb2. Ginseng also contains other saponins, polysaccharides, amino acids (in particular glutamine and arginine) (Kuo et al 2003), essential oils and other compounds. Three new sesquiterpene hydrocarbons have also recently been isolated from the essential oil: panaxene, panaginsene and ginsinsene (Richter et al 2005).

Ginsenosides Rh1, Rh2, and Rg3 are obtained from red ginseng as artifacts produced during steaming. It is likely that ginsenoside is actually a prodrug that is converted in the body by intestinal bacterial deglycosylation and fatty acid esterification into an active metabolite (Hasegawa et al 2004) and therefore extrapolation from in vitro studies or studies in which ginseng or isolated constituents were given by injection must be made very cautiously.

Commercial ginseng preparations are variable in quality. An analysis of 50 products sold in 11 countries show that there is a large variation in the concentration of ginsenosides (from 1.9% to 9.0%). Some products were even found to be void of any specific ginsenosides. Some ginseng products have also been discovered to be contaminated with ephedrine. Therefore, it is essential that only quality ginseng products are used (Cui et al 1994). Although the root hairs have a higher level of total ginsenosides than the main root, the main and lateral roots are the preferred medicinal parts. In all probability, it is the ratio of ginsenosides that is important and that other important compounds are also active.

MAIN ACTIONS

ADAPTOGEN

Clinical note — Adaptogens

Adaptogens are innocuous agents, non-specifically increasing resistance against physical, chemical or biological factors (stressors), having a normalising effect independent of the nature of the pathological state (original definition of adaptogen by Brekhman & Dardymov 1969).

Adaptogens are natural bioregulators, which increase the ability of the organism to adapt to environmental factors and to avoid damage from such factor (revised definition by Panossian et al 1999).

(Refer to the Siberian ginseng monograph for more information about adaptogens and allostasis.)

The pharmacological effects of ginseng are many and varied, contributing to its reputation as a potent adaptogen. The adrenal gland and the pituitary gland are both known to have an effect on the body's ability to respond to stress and alter work capacity (Filaretov et al 1988), and ginseng is thought to profoundly influence the hypothalamic–pituitary–adrenal axis (Kim et al 2003d). The active metabolites of protopanaxadiol and protopanaxatriol saponins reduce acetylcholine-induced catecholamine secretion in animal models (Tachikawa & Kudo 2004, Tachikawa et al 2003) and this may help to explain the purported antistress effects of ginseng.

Ginseng has been shown in numerous animal experiments to increase resistance to a wide variety of chemical, physical and biological stressors. Ginseng extract or its isolated constituents have been shown to prevent immunosuppression induced by cold water swim stress (Luo et al 1993), to counter stress-induced changes from heat stress (Yuan et al 1989), food deprivation (Lee et al 1990), electroshock (Banerjee & Izquierdo 1982) and radiation exposure (Takeda et al 1981). As there are more than 1500 studies on ginseng and its constituents, it is outside the scope of this monograph to include all studies, so we have attempted to include those studies most relevant to the oral use of ginseng.

Animal models suggest that ginseng is most useful for chronic rather than acute stress, significantly reducing elevated scores on ulcer index, adrenal gland weight, plasma glucose, triglycerides, creatine kinase activity, and serum corticosterone during chronic stress (Rai et al 2003).

CARDIOVASCULAR EFFECTS

According to in vitro and animal studies ginseng may benefit the cardiovascular system 'through diverse mechanisms, including antioxidant, modifying vasomotor

function, reducing platelet adhesion, influencing ion channels, altering autonomic neurotransmitters release, improving lipid profiles', and glycaemic control (Zhou et al 2004).

Antihypertensive Red ginseng has been used as an antihypertensive agent in Korea, but its clinical effect is unclear despite several in vivo and in vitro experimental studies. Recent preliminary data suggests that the antihypertensive effects may be partly attributed to an angiotensin-converting enzyme (ACE) inhibitory effect demonstrated by *P. ginseng* extract in vitro (Persson et al 2006). These effects were additive to the traditional ACE inhibitor enalapril.

A study of isolated muscle preparations of animal heart and aorta with an alcohol-based extract of ginseng suggest that the hypotensive effect of ginseng is associated with a direct inhibition of myocardial contractility due to a reduction of calcium ion influx into cardiac cells, as well as the inhibition of catecholamine-induced contractility of vascular smooth muscles (Hah et al 1978).

In a prospective, randomised, double-blind placebo-controlled study of 30 healthy adults, 200 mg ginseng extract given for 28 days was found to increase the QTc interval and decrease diastolic blood pressure 2 hours after ingestion on the first day of therapy. These changes, however, were not thought to be clinically significant (Caron et al 2002).

Antiplatelet Although reports from recent in vitro and in vivo assays claim that *P. ginseng* is not one of the herbs that contributes to the antiplatelet effects of a Korean combination formula known as Dae-Jo-Hwan (Chang et al 2005), a number of studies have found that several ginsenosides inhibit platelet aggregation. Panaxynol has been shown to inhibit platelet aggregation induced by adenosine disphosphate (ADP), collagen and arachidonic acid. Panaxydol and ginsenosides Ro, Rg, and Rg2 inhibit rabbit platelets while panaxydol prevented platelet aggregation and thromboxane formation (Kuo et al 1990).

Antihyperlipidaemic Ginsenoside Rb1 has been shown to lower triglyceride and cholesterol levels via cAMP-production in the rat liver (Park et al 2002b). *P. ginseng* extract (6 g/day) for 8 weeks resulted in a reduction in serum total cholesterol, triglyceride, LDL and plasma malondialdehyde levels and an increase in HDL (Kim & Park 2003) in eight males. Ginseng has also been reported to decrease hepatic cholesterol and triglyceride levels in rats, indicating a potential use of ginseng in the treatment of fatty liver (Yamamoto et al 1983).

Other cardiovascular effects Ginsenoside Rb2 has been shown to enhance the fibrinolytic activity of bovine aortic endothelial cells (Liu et al 2003). In animal studies ginseng inhibits cardiomyocyte apoptosis induced by ischaemia and reperfusion

(Zeng et al 2004) and the crude saponins have been shown to reduce body weight, food intake, and fat content in rats fed a high-fat diet (Kim et al 2005a).

GASTROINTESTINAL

Hepatorestorative Oral administration of Korean red ginseng (250 and 500 mg/kg) on liver regeneration has been investigated in 15 dogs with partial hepatectomy. All haematological values except leukocyte counts were within normal ranges for 3 days postoperatively. The levels of AST and ALT in the ginseng groups were significantly decreased compared with those in the control group ($P < 0.05$). The numbers of degenerative cells and area of connective tissue were significantly decreased in the livers of the dogs treated with ginseng ($P < 0.01$) (Kwon et al 2003).

Antiulcerative Ginseng has been shown in several studies to protect against ulceration. Among the hexane, chloroform, butanol and water fractions, the butanol fraction of a ginseng extract has been shown to be the most potent inhibitor of HCl-induced gastric lesions and ulcers induced by aspirin, acetic acid and Shay (ulcer induced by pylorus ligation). The butanol fraction showed significant increase in mucin secretion, and inhibited malondialdehyde and H^+/K^+ATPase activity in the stomach. These results indicate that the effectiveness of ginseng on gastric damage might be related to inhibition of acid secretion, increased mucin secretion and antioxidant properties (Jeong 2002).

Effects on peristalsis Ginseng root extract, and its components, ginsenoside Rb1(4) and ginsenoside Rd(7), have been shown to significantly ameliorate chemically induced acceleration of small intestinal transit in vivo. The test results suggest that the protective mechanism involves both an inhibitory effect on the cholinergic nervous system and a direct suppressive effect on intestinal muscles (Hashimoto et al 2003).

ANTI-INFLAMMATORY

Both a crude and a standardised extract (G115) of ginseng varying in saponin concentrations have been found to protect against muscle fibre injury and inflammation after eccentric muscle contractions in rats on a treadmill. The oral ginseng extracts significantly reduced plasma creatine kinase levels by about 25% and lipid peroxidation by 15%. Certain markers of inflammation were also significantly reduced (Cabral de Oliveira et al 2001). In a later study, pretreatment with ginseng extract (3, 10, 100 or 500 mg/kg) administered orally for 3 months to male Wistar rats resulted in a 74% decrease in lipid peroxidation caused by eccentric exercise (Voces et al 2004).

The many and varied effects of ginseng may be partly associated with the inhibition of transcription factor NF-kappa B, which is pivotal in the regulation of inflammatory genes. Inhibition of NF-kappa B may reduce inflammation and protect cells against damage.

Topical application of several ginsenosides (Rb1, Rc, Re, Rg1, Rg3) significantly attenuated chemically induced ear oedema in mice. The ginsenosides also suppressed expression of COX-2 and activation of NF-kappa B in the skin. Of the ginsenosides tested, Rg3 was found to be most effective (Surh et al 2002).

IMMUNOMODULATION

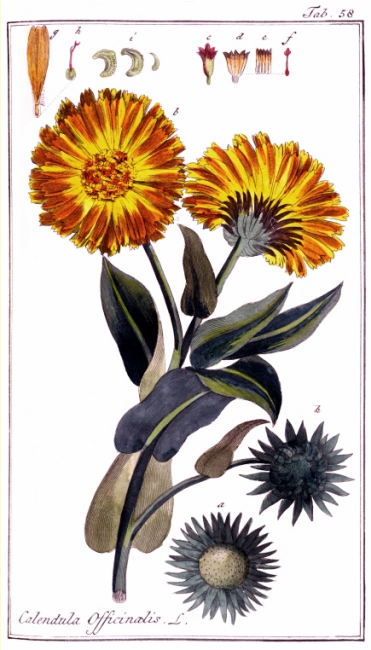
The immunomodulatory effect of ginseng is based on the production of cytokines, activation of macrophages, stimulation of bone marrow cells and stimulation of iNOS, which produces high levels of NO in response to activating signals from Th1-associated cytokines and plays an important role in cytotoxicity and cytostasis (growth inhibition) against many pathogenic microorganisms. In addition to its direct effector function, NO serves as a potent immunoregulatory factor.

Ginseng enhances IL-12 production and may therefore induce a stronger Th1 response, resulting in improved protection against infection from a variety of pathogens (Larsen et al 2004), including *Pseudomonas aeruginosa* lung infection in animal models (Song et al 2005), although other studies suggest that it may also assist in the correction of Th1-dominant pathological disorders (Lee et al 2004a).

Ginseng polysaccharides have been shown to increase the cytotoxic activity of macrophages against melanoma cells, increase phagocytosis and to induce the levels of cytokines, including TNF-alpha, IL-1-beta, IL-6 and IFN-gamma in vitro (Shin et al 2002). Ginseng has been shown to be an immunomodulator and to enhance anti-tumour activity of macrophages in vitro (Song et al 2002). Ginseng has also been shown significantly to enhance NK function in an antibody-dependent cellular cytotoxicity of peripheral blood mononuclear cells in vitro (See et al 1997).

Incubation of macrophages with increasing amounts of an aqueous extract of ginseng showed a dose-dependent stimulation of iNOS. Polysaccharides isolated from ginseng showed strong stimulation of iNOS, whereas a triterpene-enriched fraction from an aqueous extract did not show any stimulation. As NO plays an important role in immune function, ginseng could modulate several aspects of host defence mechanisms due to stimulation of the iNOS (Friedl et al 2001).

Ginseng promotes the production of granulocytes in the bone marrow (granulocytopoiesis). The ginseng saponins have been shown to directly and/or indirectly promote the stromal cells and lymphocytes to produce human granulocyte-macrophage colony-stimulating factor (GM-CSF) and other cytokines and induce



bone marrow haemopoietic cells to express GM-CSF receptors, leading to a proliferation of human colony-forming units for granulocytes and macrophages in vitro (Wang et al 2003).

Ginseng polysaccharides have been shown to have potent antisepticaemic activity by stimulating macrophages and helping modulate the reaction against sepsis induced by *Staphylococcus aureus*. Ginseng polysaccharides have been shown to reduce the intracellular concentration of *S. aureus* in macrophages in infected animals by 50% compared with controls. Combination of the ginseng polysaccharides with vancomycin resulted in 100% survival of the animals whereas only 67% or 50% of the animals survived, respectively, when treated with the ginseng polysaccharides or vancomycin alone (Lim et al 2002a).

According to animal studies long-term oral administration of ginseng extract may potentiate humoural immune response but suppress spleen cell functions (Liou et al 2005).

ANTICANCER

Oral intake of standardised *P. ginseng* extract demonstrates a dose dependant (1, 3 or 10 mg/kg) chemoprotective and antimutagenic effect in animal studies (Panwar et al 2005) and ginsenoside Rg3 has recently been produced as an antiangiogenic anticarcinogenic drug in China (Shibata 2001).

Chemoprotection Oral administration of red ginseng extracts (1% in diet for 40 weeks) significantly ($P < 0.05$) suppressed spontaneous liver tumour formation in male mice. Oral white ginseng was also shown to suppress tumour promotion in vitro and in vivo (Nishino et al 2001).

Dietary administration of red ginseng in combination with 1,2-dimethylhydrazine suppresses colon carcinogenesis in rats (rats were fed 1% ginseng for 5 weeks). It is thought that the inhibition may be partly associated with inhibition of cell proliferation in the colonic mucosa (Fukushima et al 2001).

Oral administration of 50 mg/kg/day for 4 weeks of a ginseng intestinal metabolite has been shown to partially protect against doxorubicin-induced testicular toxicity in mice. The metabolite significantly ($P < 0.01$) prevented decreases in body weight, spermatogenic activities, serum levels of lactate dehydrogenase and creatine phosphokinase induced by doxorubicin. It also significantly attenuated germ cell injuries (Kang et al 2002).

The methanol extract of red ginseng has been shown to attenuate the lipid peroxidation in rat brain and scavenge superoxides in differentiated human promyelocytic leukaemia (HL-60) cells. Topical application of the same extract, as well as purified ginsenoside Rg3, has been demonstrated to suppress skin tumour

promotion in mice. Rg3 also suppresses COX, NF-kappa B and extracellular-regulated protein kinase, which are all involved in tumour promotion (Surh et al 2001).

Pretreatment with oral red ginseng extract significantly reduced the development of cancer from diethylnitrosamine-induced liver cancer nodules in rats (the developmental rate of liver cancer in the experimental group was 14.3% compared with 100% in the control group). When ginseng was given concomitantly with diethylnitrosamine, the hepatoma nodules were smaller than those of the control group, the structure of hepatic tissue was well preserved and the structure of hepatocytes was normal. Ginseng also prolonged the average life span. These findings suggest benefits of ginseng in the prevention and treatment of liver cancer (Wu et al 2001).

Irradiation protection Ginsenosides and specifically panaxadiol have been shown to have radioprotective effects in mice irradiated with high-dose and low-dose gamma radiation. Jejunal crypts were protected by pretreatment with extract of whole ginseng (50 mg/kg body weight intraperitoneally at 12 and 36 hours before irradiation, $P < 0.005$). Extract of whole ginseng ($P < 0.005$), total saponin ($P < 0.01$) or panaxadiol ($P < 0.05$) administration before irradiation (50 mg/kg body weight IP at 12 and 36 hours before irradiation) resulted in an increase in the formation of the endogenous spleen colony. The frequency of radiation-induced apoptosis in the intestinal crypt cells was also reduced by pretreatment with extract of whole ginseng, total saponin and panaxadiol (Kim et al 2003).

These radioprotective effects are partly associated with the immunomodulatory effect of ginseng. Ginsan, a purified polysaccharide isolated from ginseng, has been shown to have a mitogenic activity, induce lymphokine-activated killer cells and increase levels of several cytokines. Ginsan reduced mutagenicity in a dose-dependent manner when applied to rats 30 min before or 15 min after 1.5 Gy of gamma-irradiation. The radioprotective effect of ginsan has been partly attributed to a reduction in radiation-induced genotoxicity (Ivanova et al 2005). Ginsan has also been found to increase the number of bone marrow cells, spleen cells, granulocyte-macrophage colony-forming cells and circulating neutrophils, lymphocytes and platelets significantly in irradiated mice (Song et al 2003).

One of the causes of radiation damage is lipid peroxidation, which alters lysosomal membrane permeability leading to the release of hydrolytic enzymes. Ginseng has been shown to markedly inhibit lipid peroxidation and protect against radiation damage in testes of mice (Kumar et al 2003).

Antitumour, antiproliferative, antimetastatic and apoptosis-inducing Stimulation of the phagocytic activity of macrophages may play a role in

the anticarcinogenic and antimetastasic activities demonstrated for ginseng in vivo (Shin et al 2004b) and research has continually found tumour inhibitory effects, especially in the promotion and progression phases (Helms 2004).

Ginsenosides Rg3, Rg5, Rk1, Rs5 and Rs4 have been shown to be cytotoxic to Hep-1 hepatoma cancer cells in vitro. Their 50% growth inhibition concentration (GI50) values were 41, 11, 13, 37, and 13 micromol/L respectively. Cisplatin had a GI50 of 84 micromol/L in the same assay conditions (Park et al 2002a).

Constituents in ginseng have also been shown to inhibit proliferation of cancer cells. Panaxytriol isolated from red ginseng was shown to have significant dose-dependent cytotoxicity activity and inhibit DNA synthesis in various tumour cells tested (Kim et al 2002a). Ginsenoside Rg3 has displayed inhibitory activity against human prostate cancer cells in vitro (Liu et al 2000).

Ginsenosides, especially 20(R)-ginsenoside Rg3, has been shown to specifically inhibit cancer cell invasion and metastasis (Shibata 2001) and ginsenoside Rh2 has been shown to inhibit human ovarian cancer growth in mice (Nakata et al 1998). It is likely that the anti-tumour promoting activity of Rg3 is mediated through down-regulation of NF-kappa B and other transcription factors (Keum et al 2003).

Oral administration of 20(S)-protopanaxatriol (M4), the main bacterial metabolite of protopanaxatriol-type ginsenosides, has been shown to inhibit melanoma growth in mice and pretreatment was shown to reduce metastases to the lungs. This effect is thought to be due to stimulation of NK-mediated tumour lysis (Hasegawa et al 2002).

The antimetastatic effects of ginseng are related to inhibition of the adhesion and invasion of tumour cells and also to antiangiogenesis activity. Ginsenosides Rg3 and Rb2 have been shown to significantly inhibit adhesion of melanoma cells to fibronectin and laminin, as well as preventing invasion into the basement membrane in vitro. Other experiments have demonstrated that the saponins exert significant antiapoptotic activity, decreasing the number of blood vessels oriented toward the tumour mass (Mochizuki et al 1995, Sato et al 1994).

Ginseng saponins have also been found to promote apoptosis (programmed cell death) in cancer cells in vitro (Hwang et al 2002).

NEUROLOGICAL

Analgesia Intraperitoneal administration of ginsenoside Rf has been shown to potentiate opioid-induced analgesia in mice. Furthermore, ginsenosides prevented tolerance to the opiate that was not associated with opioid or GABA receptors (Nemmani & Ramarao 2003).

Neuroprotection Ginseng saponins have demonstrated dose-dependent neuroprotective activity in vitro and in vivo (Kim et al 2005b). Ginsenosides Rb1 and

Rg1 have a partial neurotrophic and neuroprotective role in dopaminergic cell cultures (Radad et al 2004) and Rg3 has been shown to inhibit chemically induced injuries in hippocampal neurons (Kim et al 2002b). Pretreatment with ginsenosides (50 or 100 mg/kg IP for 7 days) has been shown to be neuroprotective in vivo (Lee et al 2002a). An in vitro survival assay demonstrated that ginsenosides Rb1 and Rg1 protect spinal cord neurons against damage. The ginsenosides protect spinal neurons from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by H_2O_2. The optimal doses are 20–40 micromol/L for ginsenosides Rb1 and Rg1 (Liao et al 2002). The lipophilic fraction of ginseng has been shown to induce differentiation of neurons and promote neuronal survival in the rat cortex. The effect is thought to be mediated via protein-kinase-C-dependent pathways (Mizumaki et al 2002).

It has been suggested that the neuroprotective effects of ginseng against hypoperfusion/reperfusion induced brain injury demonstrated in animal models, suggests a potential for use in CVD (Shah et al 2005).

Cognitive function Following oral consumption, the active metabolites of protopanaxadiol saponins may reactivate neuronal function in Alzheimer's disease according to in vivo evidence (Komatsu et al 2005). Ginseng also enhances the survival of newly generated neurons in the hippocampus which may contribute to the purported benefits of ginseng for improving learning tasks (Qiao et al 2005).

Anticonvulsant Pretreatment (30 minutes) with 100 mg/kg ginseng significantly protected rats against pentylenetetrazole-induced seizures (Gupta et al 2001).

ANTIDIABETIC

Hypoglycaemic/antihyperglycaemic effects Human and animal studies have found American ginseng to lower blood glucose level (Vuksan et al 2000a, b, c, Vuksan et al 2001a, b). Results for Korean ginseng are less consistent (Sievenpiper et al 2003, 2004). Both ginseng root and berry (150 mg/kg) have been shown to significantly decrease fasting blood glucose levels in hyperglycaemic rats (Dey et al 2003). Intraperitoneal administration of glycans (polysaccharides known as panaxan) and other unidentified compounds have demonstrated hypoglycaemic activity in both normal and alloxan-induced hyperglycaemic mice (Waki et al 1982).

Oral administration of *P. ginseng* root (125.0 mg/kg) three times daily for three days reduced hyperglycaemia and improved insulin sensitivity in rats fed a high-fructose chow suggesting a possible role in delaying or preventing insulin resistance (Liu et al 2005). However, these doses are very high and human trials need to be conducted to confirm these results.

Diabetic complications Aqueous extract of ginseng was shown to exert no significant effect on weight in normal rats, while it prevented weight loss in rats with streptozotocin-induced diabetes. Cell proliferation in the dentate gyrus of diabetic rats was increased by ginseng treatment, but it had no effect on cell proliferation in normal rats. These results suggest that ginseng may help reduce the long-term central nervous system complications of diabetes mellitus (Lim et al 2002b).

According to experimental studies ginseng may also inhibit the formation of glycated hemoglobin due to its anti-oxidative activity (Bae & Lee 2004).

STEROID RECEPTOR ACTIVITY

Ginseng has been shown to increase the mounting behaviour of male rats and increase sperm counts in rabbit testes. The effect is not by a direct sex-hormone-like function, but probably via a gonadotropin-like action. Ginsenoside Rb1 has been shown to increase LH secretion by acting directly on the anterior pituitary gland in male rats (Tsai et al 2003). Ginsenoside Rh1 failed to activate the glucocorticoid and androgen receptors, but did demonstrate an interaction with oestrogen receptors in vitro. The effect was much weaker than 17-beta-oestradiol. Ginseng is therefore considered to contain phyto-oestrogens (Lee et al 2003). However, there are conflicting reports about oestrogen binding activity which may in part be explained by the presence or absence of zearalenone, an oestrogenic mycotoxin contaminant (Gray et al 2004).

OTHER ACTIONS

PREVENTION OF DAMAGE FROM TOXINS

Ginseng extract has been shown to be beneficial in the prevention and treatment of testicular damage induced by environmental pollutants. Dioxin is one of the most potent toxic environmental pollutants. Exposure to dioxin either in adulthood or during late fetal and early postnatal development causes a variety of adverse effects on the male reproductive system. The chemical decreases spermatogenesis and the ability to conceive and carry a pregnancy to full term. Pretreatment with 100 or 200 mg/kg ginseng aqueous extract intraperitoneally for 28 days prevented toxic effects of dioxin in guinea pigs. There was no loss in body weight, testicular weight or damage to spermatogenesis (Kim et al 1999). In guinea pigs *P. ginseng* also improves the survival and quality of sperm exposed dioxin (Hwang et al 2004).

PROMOTING HAEMOPOIESIS

Ginseng is traditionally used to treat anaemia. The total saponin fraction, and specifically Rg1 and Rb1, have been shown to promote haemopoiesis by stimulating proliferation of human granulocyte-macrophage progenitors (Niu et al 2001).

ANTIOXIDANT

In vitro studies did not find various extracts of ginseng to be particularly potent antioxidants against several different free radicals (Kim et al 2002c). However, animal models have demonstrated effects in type 2 diabetes (Ryu et al 2005), particularly for the leaf, which may suppress lipid peroxidation in diabetic rats (Jung et al 2005). Ginseng extract has also been shown to protect muscle from exercise-induced oxidative stress in animal studies (Voces et al 2004).

Whether these effects are directly due to the antioxidant activity of ginseng components or secondary to other mechanisms, such as blood glucose regulation, is unclear. Additionally ginseng compounds may require in vivo conversion to active metabolites in order to exert their full effects.

HAIR GROWTH

Red ginseng extract (more so than white ginseng), and especially ginsenoside Rb1 and 20(S)-ginsenoside Rg3, has been shown to promote hair growth in mouse hair follicles in vitro (Matsuda et al 2003).

ANTI-ALLERGIC ACTIVITY

Ginsenosides have been demonstrated to have anti-allergic activity in vitro. One of the metabolites, 20-*O*-beta-D-glucopyranosyl-20(S)-protopanaxadiol, was found to inhibit beta-hexosaminidase release from rat basophil leukaemia cells and potently reduce passive cutaneous anaphylaxis reaction. The inhibitory activity of protopanaxadiol was more potent than that of disodium cromoglycate, an anti-allergic drug. The compound stabilised membranes but had no effect on hyaluronidase and did not scavenge free radicals. These results suggest that the anti-allergic action of protopanaxadiol originates from its cell membrane-stabilising activity and that the ginsenosides are prodrugs with anti-allergic properties (Choo et al 2003).

ANXIOLYTIC EFFECTS

Ginsenosides, and especially ginsenoside Rc, regulate GABA-A receptors in vitro (Choi et al 2003a) and animal models have demonstrated an anxiolytic effect for ginseng saponins (Park et al 2005a).

WOUND HEALING

Ginsenoside Rb2 has been reported to improve wound healing. It is believed that ginsenoside Rb2 enhances epidermal cell proliferation by enhancing the expressions of protein factors related to cell proliferation, such as epidermal growth factor and fibronectin (and their receptors), keratin and collagenase (Choi 2002). Ginsenoside Re may also enhance tissue regeneration by inducing angiogenesis (Huang et al 2005).

IMPROVES ACNE

In an animal model of acne, ginseng extracts reduced the size of comedones by altering keratinisation of the skin and desquamating horny cells in comedones. In a study of experimentally induced hyperkeratosis, ginseng reduced the accumulation of lipids in the epidermis by regulating enzymes associated with epidermal metabolism (Kim et al 1990).

CLINICAL USE

In the scientific arena, ginseng and the various ginsenosides are used in many forms and administered via various routes. This review will focus primarily on those methods commonly used in clinical practice.

CANCER PREVENTION

The various anticancer actions of *P. ginseng*, as demonstrated in animal and in vitro trials, support its use as an agent to prevent the development and progression of cancer. A 5-year prospective study of 4634 patients over 40 years of age found that ginseng reduced the relative risk of cancer by nearly 50% (Yun 1996).

A retrospective study of 905 case-controlled pairs taking ginseng showed that ginseng intake reduced the risk of cancer by 44% (odds ratio equal to 0.56). The powdered and extract forms of ginseng were more effective than fresh sliced ginseng, juice or tea. The preventative effect was highly significant ($P < 0.001$). There was a significant decline in cancer occurrence with increasing ginseng intake ($P < 0.05$) (Yun & Choi 1990).

Epidemiological studies in Korea strongly suggest that cultivated Korean ginseng is a non-organ-specific human cancer preventative agent. In case-control studies, odds ratios of cancer of lip, oral cavity and pharynx, larynx, lung, oesophagus, stomach, liver, pancreas, ovary and colorectum were significantly reduced by ginseng use. The most active compounds are thought to be ginsenosides Rg3, Rg5 and Rh2 (Yun 2003).

Ginseng polysaccharide (18 mg/day) has also been shown to be effective in improving immunological function and quality of life in elderly patients with non-small cell lung cancer (Zhang et al 2004).

Chemotherapy Overexpression of P-glycoprotein or multidrug resistance-associated protein may lead to multidrug resistance of cancer cells. Protopanaxatriol ginsenosides have been shown to sensitise cancer cells to chemotherapeutic agents in vitro by increasing the intracellular accumulation of the drugs through direct interaction with P-glycoprotein (Choi et al 2003b, Kim et al 2003b). The ginsenoside Rh2 possesses strong tumour-inhibiting properties and sensitises multidrug-resistant breast cancer cells to paclitaxel (Jia et al 2004) and animal models demonstrate a

synergistic antitumour effect for ginseng acidic polysaccharides and paclitaxel (Shin et al 2004a).

Panax ginseng polysaccharide (12 mg IV daily) has also been trialled during treatment for ovarian cancer and the authors suggest that it is 'effective, safe and reliable for reducing the toxic effects of chemotherapy' (Fu et al 2005).

DIABETES

The putative effects of Korean ginseng on blood glucose and lipid regulation, oxidative stress, and protein glycation suggests a possible role as an adjunctive therapy in the management of diabetes and diabetic complications.

A double-blind, placebo-controlled study with 36 subjects found that 200 mg ginseng elevated mood, improved psychophysical performance and reduced fasting blood glucose and body weight in patients with newly diagnosed type 2 diabetes (Sotaniemi et al 1995).

CARDIOVASCULAR DISEASE

Although there are reports of ginseng causing hypertension, red ginseng is actually used as an antihypertensive agent in Korea.

Acute administration of an aqueous preparation of Korean ginseng (100 mg/kg body weight) to 12 healthy, non-smoking male volunteers resulted in an increase in NO levels and a concomitant reduction in mean blood pressure and heart rate (Han et al 2005).

Ginseng is often used in practice as an adjuvant to both conventional and CAM treatments. An open clinical study of 44 hypertensive patients found red ginseng, 1.5 g three times daily (4.5 g/day), to be useful as an adjuvant to antihypertensive medication (Han et al 1995). A combination of red ginseng and digoxin was found to be more beneficial than either drug alone in an open study of advanced congestive heart failure. There were no adverse reactions (Ding et al 1995). A combination of ginseng and ginkgo extracts has been found to improve circulation and lower blood pressure in a controlled single-dose study of 10 healthy young volunteers (Kiesewetter et al 1992).

Korean red ginseng has also been shown to improve vascular endothelial function in patients with hypertension. The effect is thought to be mediated through increasing the synthesis of nitric oxide (Sung et al 2000).

HYPERLIPIDAEMIA

In a small trial of eight males receiving 2 g *Panax ginseng* extract three times daily (total PGE 6 g/day) for 8 weeks, serum total cholesterol, LDL, and triglyceride

concentrations were decreased by 12%, 45% and 24%, respectively and a 44% increase in HDL was reported (Kim & Park 2003).

Red ginseng, 1.5 g three times daily before meals for 7 days, reduced liver cholesterol, decreased the atherogenic index and elevated HDL-cholesterol in 11 patients (5 normal subjects and 6 with hyperlipidaemia). Serum cholesterol was not significantly altered, but serum triglycerides were significantly decreased (Yamamoto & Kumagai 1982).

IMMUNOMODULATION

Ginseng has been shown to significantly enhance NK function in healthy subjects and those suffering from chronic fatigue syndrome or AIDS ($P < 0.01$) (See et al 1997).

Ginseng polysaccharide injection has been shown, in a randomised study, to improve immunity in 130 patients with nasopharyngeal carcinoma and to reduce adverse reactions to radiotherapy compared with controls (Xie et al 2001).

Red ginseng powder has been shown to restore immunity after chemotherapy and reduce the recurrence of stage III gastric cancer. The 5-year disease-free survival and overall survival rates were significantly higher in patients taking the red ginseng powder during postoperative chemotherapy versus control (68.2% vs 33.3%, 76.4% vs 38.5%, respectively, $P < 0.05$). Despite the limitation of a small number of patients ($n = 42$), these findings suggest that red ginseng powder may help to improve postoperative survival in these patients. Additionally, red ginseng powder may have some immunomodulatory properties associated with CD3 and CD4 activity in patients with advanced gastric cancer during postoperative chemotherapy (Suh et al 2002).

Vaccine adjuvant activity Ginseng extract (100 mg ginsan G115/day) improved the response to an influenza vaccine in a multicentre, randomised, double-blind, placebo-controlled two-arm study of 227 subjects. Compared with vaccine without the ginseng, the addition of ginseng resulted in fewer cases of influenza and common cold. Ginseng increased NK activity and increased antibody production (Scaglione et al 1996).

The addition of 2 mg ginseng dry extract per vaccine dose has been shown to potentiate the antibody response of commercial vaccines without altering their safety. The enhancing effect of ginseng was demonstrated during the vaccination of pigs against porcine parvovirus and *Erysipelothrix rhusiopathiae* infections using commercially available vaccines (Rivera et al 2003).

COGNITIVE FUNCTION

There is some contention about the benefits of ginseng for improving memory, concentration and learning (Persson et al 2004). Well-controlled clinical trials are lacking and variations in dosage and standardisation may affect study results.

Some studies have demonstrated that ginseng improves the quality of memory and associated secondary memory (Kennedy et al 2001a). In a randomised, placebo-controlled, double-blind, balanced crossover study of healthy, young adult volunteers, 400 mg ginseng was shown to improve secondary memory performance on a Cognitive Drug Research computerised assessment battery and two serial subtraction mental arithmetic tasks. Ginseng also improved attention and the speed of performing the memory tasks (Kennedy et al 2002). In a later double-blind, placebo controlled, balanced, cross-over study of 30 healthy young adults, acute administration of ginseng (400 mg) was again shown to improve speed of attention (Sunram-Lea et al 2005).

In a double-blind, placebo-controlled study of healthy young subjects, ginseng extract (G115) improved accuracy and slowed responses during one of two computerised serial subtraction tests (Serial Sevens), and it was also shown to improve mood during these tasks (Kennedy et al 2001b).

In a double-blind, randomised, placebo-controlled 8–9-week trial standardised ginseng extract 400 mg was found significantly to improve abstract thinking ($P < 0.005$) and reaction time (not significant) in 112 healthy subjects over 40 years of age. Ginseng was found not to affect concentration or memory (Sorensen & Sonne 1996).

In clinical practice Korean ginseng and *Ginkgo biloba* are frequently used in combination for cognitive benefits. Combining ginseng with ginkgo dramatically improves memory, concentration and speed of completing mental tasks (Kennedy et al 2001a, Scholey & Kennedy 2002). In clinical trials ginseng directly modulates cerebroelectrical activity on EEG recordings to a greater extent than *Ginkgo biloba* (Kennedy et al 2003).

In a double-blind, placebo-controlled study, post-menopausal women aged 51–66 years were randomly assigned to 12 weeks' treatment with a combination formula containing 120 mg *Ginkgo biloba* and 200 mg *Panax ginseng* ($n = 30$), or matched placebo ($n = 27$). The combination appeared to have no effect on mood or cognition after 6 and 12 weeks; however, these doses may be too low (Hartley et al 2004). According to other trials it would appear that doses of 400–900 mg of ginseng are required for best results and 200 mg doses have been associated with 'cognitive costs', slowing performance on attention tasks (Kennedy & Scholey 2003).

MENOPAUSAL SYMPTOMS

Korean red ginseng is used to alleviate symptoms associated with menopause; 6 g ginseng for 30 days was shown in a small study of 20 women significantly ($P < 0.001$) to improve menopausal symptoms, in particular fatigue, insomnia and depression. The women treated had a significant decrease in cortisol and cortisol-to-dehydroepiandrosterone ratio ($P < 0.05$). No adverse effects were recorded (Tode et al 1999).

ERECTILE DYSFUNCTION

Korean red ginseng has been shown to alleviate erectile dysfunction and improve the ability to achieve and maintain erections even in patients with severe erectile dysfunction (Price & Gazewood 2003). Ginsenosides can facilitate penile erection by directly inducing the vasodilatation and relaxation of the penile corpus cavernosum. Moreover, the effects of ginseng on the corpus cavernosum appear to be mediated by the release and/or modification of release of NO from endothelial cells and perivascular nerves (Murphy & Lee 2002). In men with type 2 diabetes, oxidative stress has been suggested as a contributing factor to erectile dysfunction and animal studies suggest that ginseng can preserve 'potency' via its antioxidant effect (Ryu et al 2005).

In a double-blind crossover study, 900 mg Korean red ginseng was found to significantly improve the Mean International Index of Erectile Function scores compared with placebo. Significant subjective improvements in penetration and maintenance were reported by participants and penile tip rigidity on the RigiScan showed significant improvement for ginseng versus placebo (Hong et al 2002).

A significant improvement in erectile function, sexual desire, and intercourse satisfaction was demonstrated in 45 subjects following 8 weeks' oral administration of Korean red ginseng (900 mg three times daily) in a double-blind, placebo-controlled, crossover trial. Subjects demonstrated significant improvement in mean International Index of Erectile Function scores compared with placebo (baseline, 28 ± 16.7; Korean red ginseng, 38.1 ± 16.6; placebo, 30.9 ± 15.7) (Hong et al 2003).

QUALITY OF LIFE

An 8-week, randomised, double-blind study found that 200 mg/day ginseng ($n = 15$, placebo: $n = 15$) improved aspects of mental health and social functioning after 4 weeks' therapy but that these differences disappeared with continued use (Ellis & Reddy 2002). A review of eight clinical studies with ginseng found some improvement in QOL scores. However, the findings were equivocal. Despite some positive

results, improvement in overall health-related QOL cannot, given the current research, be attributed to *P. ginseng*. However, the possibility that various facets of QOL may have improved and the potential of early transient effects cannot be discounted (Coleman et al 2003). A double-blind, placebo-controlled, randomised clinical trial of 83 subjects also did not find ginseng to enhance psychological wellbeing in healthy young adults (Cardinal & Engels 2001).

A double-blind, placebo-controlled crossover study found that 1200 mg ginseng was only slightly more effective than placebo and not as effective as a good night's sleep in improving bodily feelings, mood and fatigue in 12 fatigued night nurses. Volunteers slept less and experienced less fatigue but rated sleep quality worse after ginseng administration (Hallstrom et al 1982).

A recent double-blind, placebo-controlled, balanced crossover design of 30 healthy young adults taking *P. ginseng* extract (200 mg or 400 mg) or placebo, demonstrated improvements in performance and subjective feelings of mental fatigue during sustained mental activity. It has been hypothesised that this effect may be due in part to the ability of ginseng to regulate blood glucose levels (Reay et al 2005).

ADAPTOGENIC AND TONIC EFFECTS

A randomised double-blind study involving 232 subjects between the ages of 25 and 60 years found that extract equivalent to about 400 mg ginseng root for 4 weeks significantly improved fatigue. Side-effects were uncommon, with only two subjects withdrawing from the study (Le Gal & Cathebras 1996).

A randomised double-blind study of 83 subjects found that extract equivalent to 1 g ginseng root for 4 months decreased the risk of contracting a common cold or bronchitis, improved appetite, sleep, wellbeing and physical performance (Gianoli & Riebenfeld 1984).

Ginseng is used by many athletes to improve stamina and to facilitate rapid recovery from injuries. To examine the effects of ginseng supplements on hormonal status following acute resistance exercise, eight male college students were randomly given water (control group) or 20 g ginseng root extract treatment immediately after a standardised training exercise. Human growth hormone, testosterone, cortisol, and insulin-like growth factor 1 levels were determined by radioimmunoassay. The responses of plasma hormones following ginseng consumption were not significant between the control and the ginseng groups during the 2-hour recovery period (Youl et al 2002).

Although ginseng is commonly used to improve endurance, a double-blind study of 19 healthy active women found that 400 mg of a ginseng extract (G115) did not

improve supramaximal exercise performance or short-term recovery. Analysis of variance using pre-test to post-test change scores revealed no significant difference between the ginseng and placebo study groups for the following variables measured: peak anaerobic power output, mean anaerobic power output, rate of fatigue, and immediate post-exercise recovery heart rates (Engels et al 2001). A recent study by the same authors also failed to find any benefit from ginseng (400 mg/day G115; equivalent to 2 g *P. ginseng* C.A. Meyer root material for 8 weeks) on improving physical performance and heart rate recovery of individuals undergoing repeated bouts of exhausting exercise (Engels et al 2003).

OTHER USES

GASTROPROTECTION DURING HEART SURGERY

In a trial of 24 children undergoing heart surgery for congenital heart defects, 12 children received 1.35 mg/kg ginsenoside compound or placebo intravenously before and throughout the course of cardiopulmonary bypass surgery. Ginseng administration resulted in attenuation of gastrointestinal injury and inflammation (Xia et al 2005).

RESPIRATORY DISEASE

Ginseng extract (G115) has been shown significantly ($P < 0.05$) to improve pulmonary function test, maximum voluntary ventilation, maximum inspiratory pressure and maximal oxygen consumption (VO_{2max}) in a study of 92 patients suffering moderately severe chronic obstructive pulmonary disease ($n = 49$, G115 100 mg twice daily for 3 months) (Gross et al 2002).

HELICOBACTER PYLORI

Helicobacter pylori can provoke gastric inflammation, ulceration and DNA damage, resulting in an increased risk of carcinogenesis (Park et al 2005b). As preliminary evidence suggests that *P. ginseng* inhibits the growth of *H. pylori* (Kim et al 2003c) and can inhibit adhesion (Lee et al 2004b) it may be useful as a gastroprotective agent against *H. pylori*-associated gastric mucosal cell damage (Park et al 2005b).

HIV INFECTION

Long-term intake of Korean ginseng slows the depletion of $CD4^+$ T cells and may delay disease progression in people with HIV type 1 (Sung et al 2005). Long-term intake (60 ± 15 months) has also been shown to delay the development of resistance mutation to zidovudine (Cho et al 2001).

DOSAGE RANGE

- Extract equivalent to 0.9–3 g crude ginseng root (Bensky & Gamble 1986).

- Standardised extract: 1.5–4.0% total ginsensosides calculated as ginsenoside Rg1.
- Liquid extract (1:2): 1–6 mL/day.
- Cognitive function: doses of 400–900 mg are recommended. Lower doses may be associated with 'cognitive costs' and slowing performance on attention tasks (Kennedy & Scholey 2003).
- Cardiovascular use: 1.5–2 g three times daily.

Many of the clinical studies published in the scientific literature have used a proprietary extract of ginseng standardised to 4% total ginsenosides (G115 or ginsana produced by Pharmaton, Switzerland).

Ginseng is usually given in the earlier part of the day. It should not be given in the evening unless it is used to promote wakefulness. Ginseng is usually not given to children.

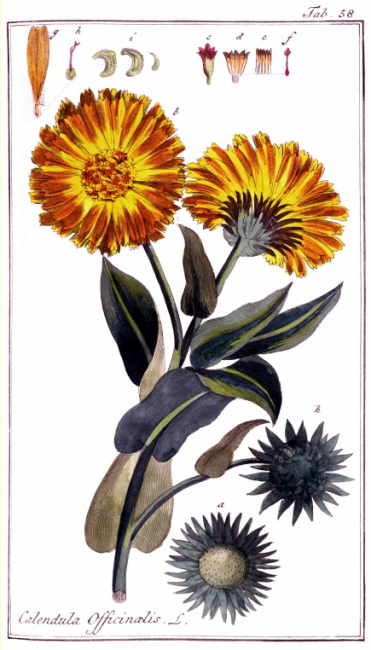
ADVERSE REACTIONS

Ginseng abuse syndrome (hypertension, nervousness, insomnia, morning diarrhoea, inability to concentrate and skin reactions) has been reported and there has been a report of a 28-year-old woman who had a severe headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms showed 'beading' appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis (Ryu & Chien 1995). High doses (15 g/day) have been associated with confusion, depression and depersonalisation in four patients (Coon & Ernst 2002).

However, the majority of the scientific data suggest that ginseng is rarely associated with adverse events or drug interactions. A systematic review found that the most commonly experienced adverse events are headache, sleep and gastrointestinal disorders. Data from clinical trials suggest that the incidence of adverse events with ginseng mono-preparations is similar to that of placebo. Any documented effects are usually mild and transient. Combined preparations are more often associated with adverse events, but causal attribution is usually not possible (Coon & Ernst 2002).

A case of suspected ginseng allergy has recently been reported in the scientific literature. The case involved a 20-year-old male who developed urticaria, dyspnoea and hypotension after ingesting ginseng syrup. The subject recovered fully and was discharged after 24 hours (Wiwanitkit & Taungjararuwinai 2004).

While ginseng use has been associated with the development of hypertension it has actually been shown to reduce blood pressure in several studies (Coon & Ernst 2002).



Ginseng has very low toxicity. Subacute doses of 1.5–15 mg/kg of a 5:1 ginseng extract did not produce negative effect on body weight, food consumption, haematological or biochemical parameters, or histological findings in dogs (Hess et al 1983) and no effects have been observed from the administration of similar doses in two generations of rat offspring (Hess et al 1982).

Traditionally, ginseng is not recommended with other stimulants such as caffeine and nicotine and a case report exists of a 39-year-old female experiencing menometrorrhagia, arrhythmia and tachycardia after using oral and topical ginseng along with coffee and cigarettes (Kabalak et al 2004).

SIGNIFICANT INTERACTIONS

ALBENDAZOLE

Panax ginseng significantly accelerated the intestinal clearance of the anthelmintic, albendazole sulfoxide, when co-administered to rats (Merino et al 2003).

ALCOHOL

Ginseng may increase the clearance of alcohol from the blood according to an open trial of 14 healthy volunteers (Coon & Ernst 2002) — beneficial interaction possible.

CHEMOTHERAPY, RADIOTHERAPY AND GENERAL ANAESTHETICS

Preliminary evidence suggests that *P. ginseng* saponins may reduce nausea and vomiting associated with chemotherapy, radiotherapy and general anaesthetics by antagonising serotonin (5-hydroxytryptamine, 5HT) type 3A receptors (Min et al 2003). Ginseng may also help to sensitise cancer cells to chemotherapeutic agents according to preliminary evidence.

DIGOXIN

Ginseng contains glycosides with structural similarities to digoxin which may modestly interfere with digoxin results (Dasgupta et al 2003). These naturally occurring glycosides may cause false elevation of fluorescence polarisation and falsely low microparticle enzyme results, although Tina-quant results appear unaffected (Dasgupta et al 2005). There are no confirmed case reports of actual interaction (Chow et al 2003, Dasgupta et al 2003).

DRUGS METABOLISED CHIEFLY BY CYP1A AND CYP2D6

Mixed reports exist as to whether ginseng may act as an inhibitor of cytochrome CYP1A (Gurley et al 2005, Lee et al 2002b, Yu et al 2005) or CYP2D6 (Gurley et al 2005) and if so whether the effect is likely to be clinically significant. Observe for increased drug bioavailability and clinical effects.

NIFEDIPINE

Ginseng increased the mean plasma concentration of the calcium channel blocker nifedipine by 53% at 30 minutes in an open trial of 22 healthy subjects. Effects at other time points were not reported (Smith et al 2001). Caution.

VANCOMYCIN

In animal studies the combination of ginseng polysaccharides with vancomycin resulted in a 100% survival rate for animals treated for *Staphylococcus aureus* compared to only 67% or 50% survival in animals treated with ginseng polysaccharides or vancomycin alone (Lim et al 2002b). A beneficial additive effect is possible but clinical use in humans has not yet been established.

WARFARIN

No affects on the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin were revealed in an open-label, crossover randomised trial of 12 healthy male subjects who received a single 25-mg dose of warfarin alone or after 7 days' pretreatment with ginseng (Jiang et al 2004). Whether these effects are consistent in less 'healthy' people likely to be taking warfarin or for prolonged concurrent use is unclear.

There have been two case reports of ginseng reducing the antithrombotic effects of warfarin (Janetzky & Morreale 1997, Rosado 2003). Additionally, it inhibits platelet aggregation according to both in vitro and animal studies. Avoid using this combination unless under medical supervision to monitor antithrombotic effects.

ZIDOVUDINE

Long-term intake (60 ± 15 months) of Korean red ginseng in HIV-1-infected patients has been shown to delay the development of resistance mutation to zidovudine (Cho et al 2001).

CONTRAINDICATIONS AND PRECAUTIONS

Korean ginseng is generally contraindicated in acute infections with fever, and in persons who are very hot, tense and overly stimulated. Overuse may result in headache, insomnia and palpitation (Bensky & Gamble 1986). Ginseng should not be taken concurrently with other stimulants including caffeine and should be discontinued 1 week before major surgery. Use in hypertension should be supervised however it may prove beneficial for this indication.

PREGNANCY USE

Ginseng is traditionally used in Korea as a tonic during pregnancy. The Commission E does not list any restrictions (Blumenthal 2001). However, due to the potential

teratogenicity of some compounds (ginsenoside Rb1) observed under experimental conditions, ginseng should be used cautiously during the first trimester of pregnancy (Chan et al 2003).

In a two-generation rat study, a ginseng extract fed at doses as high as 15 mg/kg/day did not produce adverse effects on reproductive performance, including embryo development and lactation (Hess et al 1982).

PRACTICE POINTS/PATIENT COUNSELLING

TRADITIONAL USE

Ginseng is traditionally used for deficiency of Qi (energy/life force) manifested by shallow respiration, shortness of breath, cold limbs, profuse sweating and a weak pulse (such as may occur from severe blood loss). Ginseng is also used for wheezing, lethargy, lack of appetite, abdominal distention and chronic diarrhoea. Ginseng may also be used for palpitations with anxiety, insomnia, forgetfulness and restlessness associated with low energy and anaemia (Bensky & Gamble 1986).

Scientific evidence There is some scientific evidence for the beneficial effects of ginseng for the following conditions. In practice, it is mostly used as a supportive treatment and combined with other herbs to treat a specific condition.

- Prevention and supportive treatment of cancer.
- Chronic immune deficiency.
- Menopausal symptoms.
- Erectile dysfunction.
- Chronic respiratory disease.
- Enhancement of psychomotor activity, memory and concentration.
- Adaptogenic effects in any chronic condition and for the elderly and infirm.
- Type 1 diabetes.
- Cardiovascular disease (the effects on hypertension remain to be fully investigated).
- Quality of life (equivocal scientific support).

Commission E recommends ginseng as a tonic for invigoration and fortification in times of fatigue, debility and convalescence, or declining capacity for work and concentration. The World Health Organization suggests that ginseng can be used as a prophylactive and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness and loss of concentration and during convalescence (Blumenthal 2001).

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

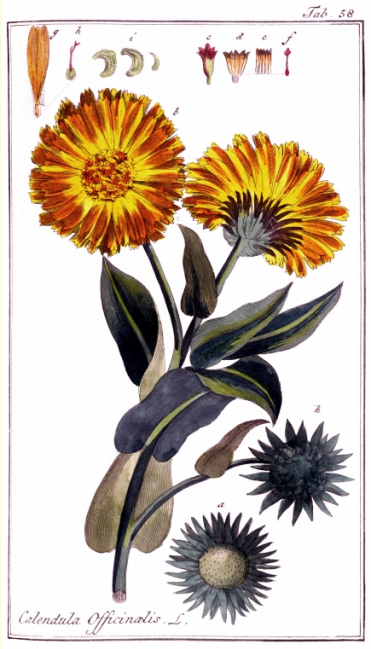
Ginseng is a safe herb used to support the body during times of prolonged stress or chronic disease and to restore mental and physical functioning during the rehabilitative process. Numerous studies have identified a range of pharmacological activites that suggest it may be useful in the treatment of many conditions.

When will it start to work?

In practice, it generally appears that ginseng has a quick onset of action with the condition continuing to improve with long-term use; however, this will vary depending on the individual and the indication.

Are there any safety issues?

Ginseng may interact with warfarin and other blood thinning drugs and should not be used with these medications unless under medical supervision. Avoid use in children or in hypertension unless under supervision. Use with caution in pregnancy.



REFERENCES

Bae J, Lee M. Effect and putative mechanism of action of ginseng on the formation of glycated hemoglobin in vitro. J Ethnopharmacol 91.1 (2004): 137-40.

Banerjee U, Izquierdo JA. Antistress and antifatigue properties of Panax ginseng: comparison with piracetam. Acta Physiol Lat Am 32.4 (1982): 277-85.

Bensky D, Gamble A. Chinese Herbal Medicine: Materia Medica 1843. Seattle, WA: Eastland Press, 1986.

Blumenthal M. Asian ginseng: potential therapeutic uses. Adv Nurse Pract 9.2 (2001): 26-8, 33.

Brekhman II, Dardymov IV. Pharmacological investigation of glycosides from Ginseng and Eleutherococcus. Lloydia 32.1 (1969): 46-51.

British Herbal Medicine Association Scientific Committee. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA, 1983.

Cabral de Oliveira AC, Perez AC, Merino G, Prieto JG, Alvarez AI. Protective effects of Panax ginseng on muscle injury and inflammation after eccentric exercise. Comp Biochem Physiol C Toxicol Pharmacol 130.3 (2001): 369-77.

Cardinal BJ, Engels HJ. Ginseng does not enhance psychological well-being in healthy, young adults: results of a double-blind, placebo-controlled, randomized clinical trial. J Am Diet Assoc 101.6 (2001): 655-60.

Caron MF, Hotsko AL, Robertson S et al. Electrocardiographic and hemodynamic effects of Panax ginseng. Ann Pharmacother 36.5 (2002): 758-63.

Chan L, Chiu P, Lau T. An in-vitro study of ginsenoside Rb1-induced teratogencity using a whole rat embryo culture model. Hum Reprod 18.10 (2003): 2166-8.

Chang G-T, Kang S-K, Kim J-H, Chung K-H, Chang Y-C, Kim C-H. Inhibitory effect of the Korean herbal medicine, Dae-Jo-Whan, on platelet-activating factor-induced platelet aggregation. J Ethnopharmacol 102.3 (2005): 430-9.

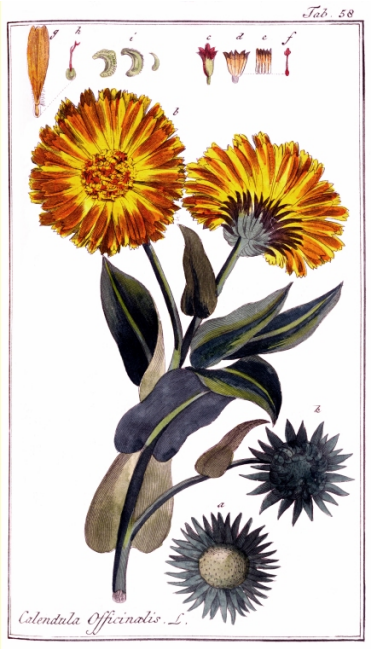
Cho YK, Sung H, Lee HJ, Joo CH, Cho GJ. Long-term intake of Korean red ginseng in HIV-1-infected patients: development of resistance mutation to zidovudine is delayed. Int Immunopharmacol 1.7 (2001): 1295-305.

Choi S. Epidermis proliferative effect of the Panax ginseng ginsenoside Rb2. Arch Pharm Res 25.1 (2002): 71-6.

Choi SE et al. Effects of ginsenosides on GABA(A) receptor channels expressed in Xenopus oocytes. Arch Pharm Res 26.1 (2003a): 28-33.

Choi CH, Kang G, Min YD. Reversal of P-glycoprotein-mediated multidrug resistance by protopanaxatriol ginsenosides from Korean red ginseng. Planta Med 69.3 (2003b): 235-40.

Choo MK, Park EK, Han MJ, Kim DH. Antiallergic activity of ginseng and its ginsenosides. Planta Med 69.6 (2003): 518-22.
Chow L, Johnson M, Wells A, Dasgupta A. Effect of the traditional Chinese medicines Chan Su, Lu-Shen-Wan, Dan Shen, and Asian ginseng on serum digoxin measurement by Tina-quant (Roche) and Synchron LX system (Beckman) digoxin immunoassays. J Clin Lab Anal 17.1 (2003): 22-7.
Coleman CI, Hebert JH, Reddy P. The effects of Panax ginseng on quality of life. J Clin Pharm Ther 28.1 (2003): 5-15.
Coon JT, Ernst E. Panax ginseng: a systematic review of adverse drug reactions and interactions. Drug Safety 25.5 (2002): 323-44.
Cui J, Garle M, Eneroth P, Bjorkhem I. What do commercial ginseng preparations contain? Lancet 344.8915 (1994): 134.
Dasgupta A, Reyes M. Effect of Brazilian, Indian, Siberian, Asian, and North American ginseng on serum digoxin measurement by immunoassays and binding of digoxin-like immunoreactive components of ginseng with Fab fragment of antidigoxin antibody (Digibind). Am J Clin Pathol 124.2 (2005): 229-36.
Dasgupta A et al. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: Significant variation in digoxin-like immunoreactivity among commercial ginsengs. Am J Clin Pathol 119.2 (2003): 298-303.
Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan C-S. Anti-hyperglycemic effects of ginseng: Comparison between root and berry. Phytomedicine 10.6-7 (2003): 600-5.
Ding DZ, Shen TK, Cui YZ. Effects of red ginseng on the congestive heart failure and its mechanism. Zhongguo Zhong Xi Yi Jie He Za Zhi 15.6 (1995): 325-7.
Ding Y, Huo Y, Gu Q, Cheng Y, Chen Y, Chen S. Preparation of ginseng saponin chewing gum and observation of improving intelligence and movement function. Chin J Clin Rehab 8.16 (2004): 3206-7.
Ellis JM, Reddy P. Effects of Panax ginseng on quality of life. Ann Pharmacother 36.3 (2002): 375-9.
Engels HJ, Kolokouri I, Cieslak TJ, Wirth JC. Effects of ginseng supplementation on supramaximal exercise performance and short-term recovery. J Strength Cond Res 15.3 (2001): 290-5.
Engels HJ, Fahlman MM, Wirth JC. Effects of ginseng on secretory IgA, performance, and recovery from interval exercise. Med Sci Sports Exerc 35.4 (2003): 690-6.
Filaretov AA, Bogdanova TS, Podvigina TT, Bodganov AI. Role of pituitary-adrenocortical system in body adaptation abilities. Exp Clin Endocrinol 92.2 (1988): 129-36.
Friedl R, Moeslinger T, Kopp B, Spieckermann PG. Stimulation of nitric oxide synthesis by the aqueous extract of Panax ginseng root in RAW 264.7 cells. Br J Pharmacol 134.8 (2001): 1663-70.
Fu W, Chen L, Huang S, Zou H. The role of Panax ginseng polysaccharide injection in chemotherapy of patients with ovarian cancer. Pharm Care Res 5.2 (2005): 169-71.
Fukushima S, Wanibuchi H, Li W. Inhibition by ginseng of colon carcinogenesis in rats. J Korean Med Sci 16 [Suppl] (2001): S75-80.
Gao Q, Kiyohara H, Cyong J, Yamada H. Chemical properties and anti-complementary activities of polysaccharide fractions from roots and leaves of Panax ginseng. Planta Medica 55.1 (1989): 9-12.
Gianoli A, Riebenfeld D. Doppelblind-Studie zur Beurteilung der Verträglichkeit und Wirkung des standardisierten Ginseng-Extraktes G115®. Cytobiol Rev 8.3 (1984): 177-86.
Gray S, Lackey B, Tate P, Riley M, Camper N. Mycotoxins in root extracts of American and Asian ginseng bind estrogen receptors alpha and beta. Exp Biol Med 229.6 (2004): 560-8.
Gross D et al. Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Monaldi Arch Chest Dis 57.5-6 (2002): 242-6.
Gupta YK, Sharma M, Chaudhary G. Antiepileptic activity of Panax ginseng against pentylenetetrazole induced kindling in rats. Indian J Physiol Pharmacol 45.4 (2001): 502-6.
Gurley B et al. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's Wort, garlic oil, Panax ginseng and Ginkgo biloba. Drugs Aging 22.6 (2005): 525-39.
Hah JS, Kang BS, Kang DH. Effect of Panax ginseng alcohol extract on cardiovascular system. Yonsei Med J 19.2 (1978): 11-18.



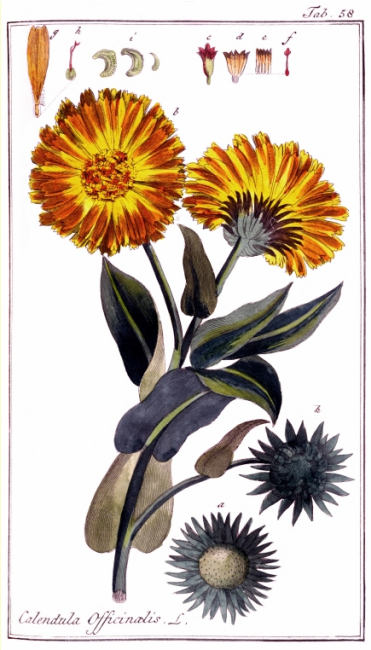
Hallstrom C, Fulder S, Carruthers M. Comp Med East West 6.4 (1982): 277-82.
Han K-H, Choe S-C, Kim H-S et al. Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension assessed by twenty-four-hour ambulatory blood pressure monitoring. J Korean Soc Clin Pharmacol Ther 3.2 (1995): 198-208 [in Korean].
Han K, Shin I, Choi K, Yun Y, Hong J, Oh K. Korea red ginseng water extract increases nitric oxide concentrations in exhaled breath. Nitric Oxide Biol Chem 12.3 (2005): 159-62.
Hartley D, Elsabagh S, File S. Gincosan (a combination of ginkgo biloba and panax ginseng): The effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. Nutr Neurosci 7.5-6 (2004): 325-33.
Hasegawa H. Proof of the mysterious efficacy of ginseng: Basic and clinical trials: Metabolic activation of ginsenoside: Deglycosylation by intestinal bacteria and esterification with fatty acid. J Pharmacol Sci 95.2 (2004): 153-7.
Hasegawa H et al. Prevention of growth and metastasis of murine melanoma through enhanced natural-killer cytotoxicity by fatty acid-conjugate of protopanaxatriol. Biol Pharm Bull 25.7 (2002): 861-6.
Hashimoto K et al. Components of Panax ginseng that improve accelerated small intestinal transit. J Ethnopharmacol 84.1 (2003): 115-19.
Helms S. Cancer prevention and therapeutics: Panax ginseng. Altern Med Rev 9.3 (2004): 259-74.
Hess FG Jr, Parent RA, Cox GE, Stevens KR, Becci PJ. Reproduction study in rats or ginseng extract G115. Food Chem Toxicol 20.2 (1982): 189-92.
Hess FG Jr, Parent RA, Stevens KR, Cox GE, Becci PJ. Effects of subchronic feeding of ginseng extract G115 in beagle dogs. Food Chem Toxicol 21.1 (1983): 95-7.
Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol 168.5 (2002): 2070-3.
Hong B et al. Korean red ginseng effective for treatment of erectile dysfunction. J Fam Pract 52.1 (2003): 20-1.
Huang Y et al. A natural compound, Ginsenoside Re (isolated from Panax ginseng), as a novel angiogenic agent for tissue regeneration. Pharm Res 22.4 (2005): 636-46.
Hwang SJ et al. Diol- and triol-type ginseng saponins potentiate the apoptosis of NIH3T3 cells exposed to methyl methanesulfonate. Toxicol Appl Pharmacol 181.3 (2002): 192-202.
Hwang S, Kim W, Wee J, Choi J, Kim S. Panax ginseng improves survival and sperm quality in guinea pigs exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. BJU Int 94.4 (2004): 663-8.
Ivanova T, Han Y, Son H-J, Yun Y-S, Song J-Y. Antimutagenic effect of polysaccharide ginsan extracted from Panax ginseng. Food Chem Toxicol 2005 [In Press].
Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm 54.6 (1997): 692-3.
Jeong CS. Effect of butanol fraction of Panax ginseng head on gastric lesion and ulcer. Arch Pharm Res 25.1 (2002): 61-6.
Jia W et al. Rh2, a compound extracted from ginseng, hypersensitizes multidrug-resistant tumor cells to chemotherapy. Can J Physiol Pharmacol 82.7 (2004): 431-7.
Jiang X et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 57.5 (2004): 592-9.
Jung C-H, Seog H-M, Choi I-W, Choi H-D, Cho H-Y. Effects of wild ginseng (Panax ginseng C.A. Meyer) leaves on lipid peroxidation levels and antioxidant enzyme activities in streptozotocin diabetic rats. J Ethnopharmacol 98.3 (2005): 245-50.
Kabalak A, Soyal O, Urfalioglu A, Saracoglu F, Gogus N. Menometrorrhagia and tachyarrhythmia after using oral and topical ginseng. J Women's Health 13.7 (2004): 830-3.
Kang J et al. Ginseng intestinal metabolite-I (GIM-I) reduces doxorubicin toxicity in the mouse testis. Reprod Toxicol 16.3 (2002): 291-8.
Kennedy DO, Scholey AB. Ginseng: potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav 75 (2003): 687-700.

Kennedy DO, Scholey AB, Wesnes KA. Differential, dose dependent changes in cognitive performance following acute administration of a Ginkgo biloba/Panax ginseng combination to healthy young volunteers. Nutr Neurosci 4.5 (2001a): 399-412.
Kennedy DO, Scholey AB, Wesnes KA. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. Nutr Neurosci 4.4 (2001b): 295-310.
Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of Ginkgo biloba, ginseng, and a ginkgo/ginseng combination to healthy young adults. Physiol Behav 75.5 (2002): 739-51.
Kennedy DO, Scholey AB, Drewery L, Marsh VR, Moore B, Ashton H. Electroencephalograph effects of single doses of Ginkgo biloba and Panax ginseng in healthy young volunteers. Pharmacol Biochem Behav Plants Central Nervous Syst 75.3 (2003): 701-9.
Keum YS et al. Inhibitory effects of the ginsenoside Rg3 on phorbol ester-induced cyclooxygenase-2 expression, NF-kappaB activation and tumor promotion. Mutat Res 523-524 (2003): 75-85.
Kiesewetter H, Jung F, Mrowietz C, Wenzel E. Hemorrheological and circulatory effects of gincosan. Int J Clin Pharmacol Ther Toxicol 30.3 (1992): 97-102.
Kim S-H, Park K-S. Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol Res 48.5 (2003): 511-13.
Kim H, Jin S, Kim S. Actions of Korean ginseng and benzoyl peroxide on inflammation relevant to acne. Korean J Ginseng Sci 14 (1990): 391-8.
Kim W, Hwang S, Lee H, Song H, Kim S. Panax ginseng protects the testis against 2,3,7, 8-tetrachlorodibenzo-p-dioxin induced testicular damage in guinea pigs. BJU Int 83.7 (1999): 842-9.
Kim JY et al. Inhibitory effect of tumor cell proliferation and induction of G2/M cell cycle arrest by panaxytriol. Planta Med 68.2 (2002a): 119-22.
Kim S, Ahn K, Oh TH, Nah SY, Rhim H. Inhibitory effect of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem Biophys Res Commun 296.2 (2002b): 247-54.
Kim YK, Guo Q, Packer L. Free radical scavenging activity of red ginseng aqueous extracts. Toxicology 172.2 (2002c): 149-56.
Kim SR, Jo SK, Kim SH. Modification of radiation response in mice by ginsenosides, active components of Panax ginseng. In Vivo 17.1 (2003a): 77-81.
Kim S-W et al. Reversal of P-glycoprotein-mediated multidrug resistance by ginsenoside Rg3. Biochem Pharmacol 65.1 (2003b): 75-82.
Kim J, Shin J, Joo-Han M, Baek N, Kim D. Inhibitory effect of ginseng polyacetylenes on infection and vacuolation of Helicobacter pylori. Nat Prod Sci 9.3 (2003c): 158-60.
Kim DH et al. Effects of ginseng saponin administered intraperitoneally on the hypothalamo-pituitary-adrenal axis in mice. Neurosci Lett 343.1 (2003d): 62-6.
Kim J, Hahm D, Yang D, Lee H, Shim I. Effect of crude saponin of Korean red ginseng on high-fat diet-induced obesity in the rat. J Pharmacol Sci 97.1 (2005a): 124-31.
Kim J-H et al. Protective effects of ginseng saponins on 3-nitropropionic acid-induced striatal degeneration in rats. Neuropharmacology 48.5 (2005b): 743-56.
Komatsu K, Tohda C, Zhu S. Ginseng drugs: Molecular and chemical characteristics and possibility as antidementia drugs. Curr Top Nutraceut Res 3.1 (2005): 47-64.
Kumar M, Sharma MK, Saxena PS, Kumar A. Radioprotective effect of Panax ginseng on the phosphatases and lipid peroxidation level in testes of Swiss albino mice. Biol Pharm Bull 26.3 (2003): 308-12.
Kuo SC et al. Antiplatelet components in Panax ginseng. Planta Med 56.2 (1990): 164-7.
Kuo Y-H, Ikegami F, Lambein F. Neuroactive and other free amino acids in seed and young plants of Panax ginseng. Phytochemistry 62.7 (2003): 1087-91.
Kwon YS, Jang KH, Jang IH. The effects of Korean red ginseng (ginseng radix rubra) on liver regeneration after partial hepatectomy in dogs. J Vet Sci 4.1 (2003): 83-92.
Larsen M, Moser C, Hoiby N, Song Z, Kharazmi A. Ginseng modulates the immune response by induction of interleukin-12 production. Apmis 112.6 (2004): 369-73.

Le Gal M, Cathebras K. Pharmaton capsules in the treatment of functional fatigue: A double-blind study versus placebo evaluated by a new methodology. Phytother Res 10 (1996): 49-53.
Lee SP, Honda K, Rhee YH, Inoue S. Chronic intake of panax ginseng extract stabilizes sleep and wakefulness in food-deprived rats. Neurosci Lett 111.1-2 (1990): 217-21.
Lee JH et al. Protective effect of ginsenosides, active ingredients of Panax ginseng, on kainic acid-induced neurotoxicity in rat hippocampus. Neurosci Lett 325.2 (2002a): 129-33.
Lee HC et al. In vivo effects of Panax ginseng extracts on the cytochrome P450-dependent monooxygenase system in the liver of 2,3,7,8-tetrachlorodibenzo-p-dioxin-exposed guinea pig. Life Sci 71.7 (2002b): 759-69.
Lee Y et al. A ginsenoside-Rh1, a component of ginseng saponin, activates estrogen receptor in human breast carcinoma MCF-7 cells. J Steroid Biochem Mol Biol 84.4 (2003): 463-8.
Lee E-J et al. Ginsenoside Rg1 enhances CD4+ T-cell activities and modulates Th1/Th2 differentiation. Int Immunopharmacol 4.2 (2004a): 235-44.
Lee J, Eun K, Uhm C, Chung M, Kyung H. Inhibition of Helicobacter pylori adhesion to human gastric adenocarcinoma epithelial cells by acidic polysaccharides from Artemisia capillaris and Panax ginseng. Planta Med 70.7 (2004b): 615-19.
Liao B, Newmark H, Zhou R. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. Exp Neurol 173.2 (2002): 224-34.
Lim DS et al. Anti-septicaemic effect of polysaccharide from Panax ginseng by macrophage activation. J Infect 45.1 (2002a): 32-8.
Lim BV et al. Ginseng radix increases cell proliferation in dentate gyrus of rats with streptozotocin-induced diabetes. Biol Pharm Bull 25.12 (2002b): 1550-4.
Liou C, Huang W, Tseng J. Long-term oral administration of ginseng extract modulates humoral immune response and spleen cell functions. Am J Chin Med 33.4 (2005): 651-61.
Liu W, Xu S, Che C. Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. Life Sci 67.11 (2000): 1297-306.
Liu JW, Wei DZ, Du CB, Zhong JJ. Enhancement of fibrinolytic activity of bovine aortic endothelial cells by ginsenoside Rb2. Acta Pharmacol Sin 24.2 (2003): 102-8.
Liu T, Liu I, Cheng J. Improvement of insulin resistance by Panax ginseng in fructose-rich chow-fed rats. Horm Metab Res 37.3 (2005): 146-51.
Luo YM, Cheng XJ, Yuan WX. Effects of ginseng root saponins and ginsenoside Rb1 on immunity in cold water swim stress mice and rats. Zhongguo Yao Li Xue Bao 14.5 (1993): 401-4.
Matsuda H, Yamazaki M, Asanuma Y, Kubo M. Promotion of hair growth by ginseng radix on cultured mouse vibrissal hair follicles. Phytother Res 17.7 (2003): 797-800.
Merino G, Molina AJ, Garcia JL, Pulido MM, Prieto JG, Alvarez AI. Ginseng increases intestinal elimination of albendazole sulfoxide in the rat. Comp Biochem Physiol C Toxicol Pharmacol 136.1 (2003): 9-15.
Min K, Koo B, Kang J, Bai S, Ko S, Cho Z. Effect of ginseng saponins on the recombinant serotonin type 3A receptor expressed in Xenopus oocytes: Implication of possible application as an antiemetic. J Altern Complement Med 9.4 (2003): 505-10.
Mizumaki Y et al. Lipophilic fraction of Panax ginseng induces neuronal differentiation of PC12 cells and promotes neuronal survival of rat cortical neurons by protein kinase C dependent manner. Brain Res 950.1-2 (2002): 254-60.
Mochizuki M et al. Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(R)- and 20(S)-ginsenoside-Rg3, of red ginseng. Biol Pharm Bull 18.9 (1995): 1197-202.
Murphy LL, Lee TJ. Ginseng, sex behavior, and nitric oxide. Ann N Y Acad Sci 962 (2002): 372-7.
Nakata H et al. Inhibitory effects of ginsenoside Rh2 on tumor growth in nude mice bearing human ovarian cancer cells. Jpn J Cancer Res 89.7 (1998): 733-40.
Nemmani KV, Ramarao P. Ginsenoside Rf potentiates U-50,488H-induced analgesia and inhibits tolerance to its analgesia in mice. Life Sci 72.7 (2003): 759-68.

Nishino H et al. Cancer chemoprevention by ginseng in mouse liver and other organs. J Korean Med Sci 16 [Suppl] (2001): S66-9.
Niu YP, Jin JM, Gao RL, Xie GL, Chen XH. Effects of ginsenosides Rg1 and Rb1 on proliferation of human marrow granulocyte-macrophage progenitor cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi 9.2 (2001): 178-80.
Panossian A, Wikman G, Wagner H. Plant adaptogens. III. Earlier and more recent aspects and concepts on their mode of action. Phytomedicine 6.4 (1999): 287-300.
Panwar M, Kumar M, Samarth R, Kumar A. Evaluation of chemopreventive action and antimutagenic effect of the standardized Panax Ginseng extract, EFLA400 in Swiss albino mice. Phytother Res 19.1 (2005): 65-71.
Park IH et al. Cytotoxic dammarane glycosides from processed ginseng. Chem Pharm Bull (Tokyo) 50.4 (2002a): 538-40.
Park KH et al. Possible role of ginsenoside Rb1 on regulation of rat liver triglycerides. Biol Pharm Bull 25.4 (2002b): 457-60.
Park J, Cha H, Seo J, Hong J, Han K, Oh K. Anxiolytic-like effects of ginseng in the elevated plus-maze model: Comparison of red ginseng and sun ginseng. Prog Neuropsychopharmacol Biol Psychiatry 29.6 (2005a): 895-900.
Park S et al. Rescue of Helicobacter pylori-induced cytotoxicity by red ginseng. Dig Dis Sci 50.7 (2005b): 1218-27.
Persson J, Bringlov E, Nilsson L, Nyberg L. The memory-enhancing effects of Ginseng and Ginkgo biloba in healthy volunteers. Psychopharmacology 172.4 (2004): 430-4.
Persson IA-L, Dong L, Persson K. Effect of Panax ginseng extract (G115) on angiotensin-converting enzyme (ACE) activity and nitric oxide (NO) production. J Ethnopharmacol (2006) [in Press; Available online 4 January 2006].
Price A, Gazewood J. Korean red ginseng effective for treatment of erectile dysfunction. J Fam Pract 52.1 (2003): 20-1.
Qiao C et al. Ginseng enhances contextual fear conditioning and neurogenesis in rats. Neurosci Res 51.1 (2005): 31-8.
Radad K, Gille G, Moldzio R, Saito H, Rausch W-D. Ginsenosides Rb1 and Rg1 effects on mesencephalic dopaminergic cells stressed with glutamate. Brain Res 1021.1 (2004): 41-53.
Rai D, Bhatia G, Sen T, Palit G. Anti-stress effects of Ginkgo biloba and Panax ginseng: A comparative study. J Pharmacol Sci 93.4 (2003): 458-64.
Reay J, Kennedy D, Scholey A. Single doses of Panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J Psychopharmacol 19.4 (2005): 357-65.
Richter R, Basar S, Koch A, Konig WA. Three sesquiterpene hydrocarbons from the roots of Panax ginseng C.A. Meyer (Araliaceae). Phytochem Rep Structure Elucid 66.23 (2005): 2708-13.
Rivera E, Daggfeldt A, Hu S. Ginseng extract in aluminium hydroxide adjuvanted vaccines improves the antibody response of pigs to porcine parvovirus and Erysipelothrix rhusiopathiae. Vet Immunol Immunopathol 91.1 (2003): 19-27.
Rosado MF. Thrombosis of a prosthetic aortic valve disclosing a hazardous interaction between warfarin and a commercial ginseng product. Cardiology 99.2 (2003): 111.
Ryu SJ, Chien YY. Ginseng-associated cerebral arteritis. Neurology 45.4 (1995): 829-30.
Ryu J et al. Free radical-scavenging activity of Korean red ginseng for erectile dysfunction in non-insulin-dependent diabetes mellitus rats. Urology 65.3 (2005): 611-15.
Salam OM, Nada SA, Arbid MS. The effect of ginseng on bile-pancreatic secretion in the rat. Increase in proteins and inhibition of total lipids and cholesterol secretion. Pharmacol Res 45.4 (2002): 349-53.
Sato K et al. Inhibition of tumor angiogenesis and metastasis by a saponin of Panax ginseng, ginsenoside-Rb2. Biol Pharm Bull 17.5 (1994): 635-9.
Scaglione F, Cattaneo G, Alessandria M, Cogo R. Efficacy and safety of the standardised Ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold [corrected]. Drugs Exp Clin Res 22.2 (1996): 65-72.

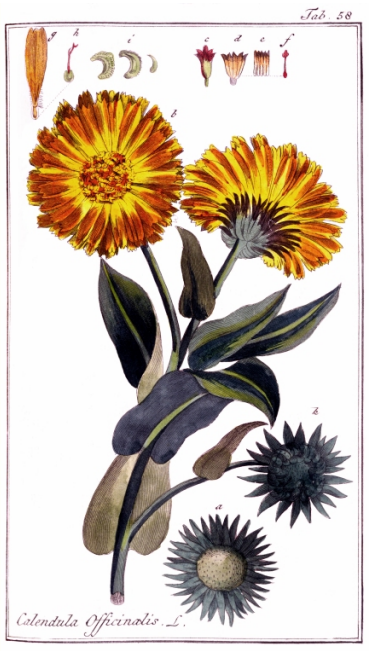
Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand. Hum Psychopharmacol 17.1 (2002): 35-44.
See DM, Broumand N, Sahl L, Tilles JG. In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. Immunopharmacology 35.3 (1997): 229-35.
Shah ZA, Gilani RA, Sharma P, Vohora SB. Cerebroprotective effect of Korean ginseng tea against global and focal models of ischemia in rats. J Ethnopharmacol 101.1-3 (2005): 299-307.
Shibata S. Chemistry and cancer preventing activities of ginseng saponins and some related triterpenoid compounds. J Korean Med Sci 16 [Suppl] (2001): S28-37.
Shin JY et al. Immunostimulating effects of acidic polysaccharides extract of Panax ginseng on macrophage function. Immunopharmacol Immunotoxicol 24.3 (2002): 469-82.
Shin H et al. A further study on the inhibition of tumor growth and metastasis by red ginseng acidic polysaccharide (RGAP). Nat Prod Sci 10.6 (2004a): 284-8.
Shin M, Kim Y, Kwak Y, Song Y, Park J. Enhancement of antitumor effects of paclitaxel (taxol) in combination with red ginseng acidic polysaccharide (RGAP). Planta Med 70.11 (2004b): 1033-8.
Sievenpiper J, Arnason J, Leiter L, Vuksan V. Null and opposing effects of Asian ginseng (Panax ginseng C.A. Meyer) on acute glycemia: results of two acute dose escalation studies. J Am Coll Nutr 22.6 (2003): 524-32.
Sievenpiper J, Arnason J, Leiter L, Vuksan V. Decreasing, null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: The role of ginsenosides. J Am Coll Nutr 23.3 (2004): 248-58.
Smith M, Lin K, Zheng Y. An open trial of nifedipine-herb interactions: nifedipine with St. John's Wort, ginseng, or Ginkgo biloba. Clin Pharmacol Ther 69.2 (2001): 86.
Song JY et al. Induction of secretory and tumoricidal activities in peritoneal macrophages by ginsan. Int Immunopharmacol 2.7 (2002): 857-65.
Song JY et al. Radioprotective effects of ginsan, an immunomodulator. Radiat Res 159.6 (2003): 768-74.
Song Z et al. Ginseng modulates the immune response via its effect on cytokine production. Ugeskr Laeg 167.33 (2005): 3054-6.
Sorensen H, Sonne J. A double-masked study of the effects of ginseng on cognitive functions. Curr Ther Res Clin Exp 57.12 (1996): 959-68.
Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients: Effects of psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminalpropeptide concentration, and body weight. Diabetes Care 18.10 (1995): 1373-5.
Suh SO, Kroh M, Kim NR, Joh YG, Cho MY. Effects of red ginseng upon postoperative immunity and survival in patients with stage III gastric cancer. Am J Chin Med 30.4 (2002): 483-94.
Sun J. Morning/evening menopausal formula relieves menopausal symptoms: a pilot study. J Altern Complement Med 9.3 (2003): 403-9.
Sung J et al. Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. Am J Chin Med 28.2 (2000): 205-16.
Sung H, Kang S, Lee M, Kim T, Cho Y. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. Clin Diagn Lab Immunol 12.4 (2005): 497-501.
Sunram-Lea S, Birchall R, Wesnes K, Petrini O. The effect of acute administration of 400 mg of Panax ginseng on cognitive performance and mood in healthy young volunteers. Curr Top Nutraceut Res 3.1 (2005): 65-74.
Surh YJ, Na HK, Lee JY, Keum YS. Molecular mechanisms underlying anti-tumor promoting activities of heat-processed Panax ginseng C.A. Meyer. J Korean Med Sci 16 [Suppl] (2001): S38-41.
Surh YJ, Lee JY, Choi KJ, Ko SR. Effects of selected ginsenosides on phorbol ester-induced expression of cyclooxygenase-2 and activation of NF-kappaB and ERK1/2 in mouse skin. Ann NY Acad Sci 973 (2002): 396-401.



Tachikawa E, Kudo K. Proof of the mysterious efficacy of ginseng: Basic and clinical trials: Suppression of adrenal medullary function in vitro by ginseng. J Pharmacol Sci 95.2 (2004): 140-4.
Tachikawa E et al. In vitro inhibition of adrenal catecholamine secretion by steroidal metabolites of ginseng saponins. Biochem Pharmacol 66.11 (2003): 2213-21.
Takeda A, Yonezawa M, Katoh N. Restoration of radiation injury by ginseng. I. Responses of X-irradiated mice to ginseng extract. J Radiat Res (Tokyo) 22.3 (1981): 323-35.
Tode T et al. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet 67.3 (1999): 169-74.
Tsai SC, Chiao YC, Lu CC, Wang PS. Stimulation of the secretion of luteinizing hormone by ginsenoside-Rb1 in male rats. Chin J Physiol 46.1 (2003): 1-7.
Voces J et al. Ginseng administration protects skeletal msucle from oxidative stress induced by acute exercise in rats. Braz J Med Biol Res 37.12 (2004): 1863-71.
Vuksan V et al. American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. Arch Intern Med 160.7 (2000a): 1009-13.
Vuksan V et al. American ginseng improves glycemia in individuals with normal glucose tolerance: effect of dose and time escalation. J Am Coll Nutr 19.6 (2000b): 738-44.
Vuksan V et al. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care 23.9 (2000c): 1221-6.
Vuksan V et al. American ginseng (Panax quinquefolius L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals. Am J Clin Nutr 73.4 (2001a): 753-8.
Vuksan V et al. Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr 20.5 [Suppl] (2001b): 370-80S.
Waki I, Kyo H, Yasuda M, Kimura M. Effects of a hypoglycemic component of ginseng radix on insulin biosynthesis in normal and diabetic animals. J Pharmacobiodyn 5.8 (1982): 547-54.
Wang SL, Chen D, Wang YP, Liu YG, Jiang R. Modulation of expression of human GM-CSF and GM-CSFRalpha by total saponins of Panax ginseng. Sheng Li Xue Bao 55.4 (2003): 487-92.
Wiwanitkit V, Taungjararuwinai W. A case report of suspected ginseng allergy. Medscape Gen Med 6.3 (2004): 1-2.
Wu XG, Zhu DH, Li X. Anticarcinogenic effect of red ginseng on the development of liver cancer induced by diethylnitrosamine in rats. J Korean Med Sci 16 (2001) [Suppl]: S61-5.
Xia Z-Y, Liu X-Y, Zhan L-Y, He Y-H, Luo T, Xia Z. Ginsenosides compound (Shen-fu) attenuates gastrointestinal injury and inhibits inflammatory response after cardiopulmonary bypass in patients with congenital heart disease. J Thorac Cardiovasc Surg 130.2 (2005): 258-64.
Xie FY, Zeng ZF, Huang HY. Clinical observation on nasopharyngeal carcinoma treated with combined therapy of radiotherapy and ginseng polysaccharide injection. Zhongguo Zhong Xi Yi Jie He Za Zhi 21.5 (2001): 332-4.
Yamamoto M, Kumagai M. Anti-atherogenic action of Panax Ginseng in rats and in patients with hyperlipidemia. Planta Med 45 (1982): 149-66.
Yamamoto M, Uemura T, Nakama S, Uemiya M, Kumagai A. Serum HDL-cholesterol-increasing and fatty liver-improving actions of Panax ginseng in high cholesterol diet-fed rats with clinical effect on hyperlipidemia in man. Am J Chin Med 11.1-4 (1983): 96-101.
Youl KH, Hwan KS, Jun LW, Byrne HK. Effects of ginseng ingestion on growth hormone, testosterone, cortisol, and insulin-like growth factor 1 responses to acute resistance exercise. J Strength Cond Res 16.2 (2002): 179-83.
Yu C, Chen J, Teng X, Tong V, Chang T. Lack of evidence for induction of CYP2B1, CYP3A23, and CYP1A2 gene expression by Panax ginseng and Panax quinquefolius extracts in adult rats and primary cultures of rat hepatocytes. Drug Metab Dispos 33.1 (2005): 19-22.
Yuan WX, Wu XJ, Yang FX, Shang XH, Zhang LL. Effects of ginseng root saponins on brain monoamines and serum corticosterone in heat-stressed mice. Zhongguo Yao Li Xue Bao 10.6 (1989): 492-6.

Yun TK. Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. Mutat Res 523-524 (2003): 63-74.
Yun T-K, Choi SY. A case-control study of ginseng intake and cancer. Int J Epidemiol 19.4 (1990): 871-6.
Yun TK. Experimental and epidemiological evidence of the cancer-preventive effects of Panax ginseng C.A. Meyer. Nutr Rev 54.11 [Pt 2] (1996): S71-81.
Zeng H, Liu Z, Liu X. Inhibitory effects of Radix ginseng rubra on cardiomyocyte apoptosis induce by ischemia and reperfusion in rats. Chin J Clin Rehab 8.9 (2004): 1784-6.
Zhang L, Liu X, Chen J, He P. Effect of ginseng polysaccharide compound on immunological function and quality of life in elder patients with advanced non-small cell lung cancer. Chin J Clin Rehab 8.5 (2004): 916-17.
Zhou W, Chai H, Lin P, Lumsden A, Yao Q, Chen C. Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. Med Sci Monit 10.8 (2004): RA187-92.

Ginseng—Siberian



Historical note Siberian ginseng has been used for over 2000 years, according to Chinese medical records, where it is referred to as Ci Wu Jia. It was used to prevent colds and flu and to increase vitality and energy. In modern times, it has been used by Russian cosmonauts for improving alertness and energy, and to aid in adaptation to the stresses of life in space. It has also been used as an ergogenic aid by Soviet athletes before international competitions and was used after the Chernobyl accident to counteract the effects of radiation.

OTHER NAMES

Ci Wu Jia, devil's bush, devil's shrub, eleuthero, eleutherococcus, eleuthero root, gokahi, ogap'I, russisk rod, taigawurzel, touch-me-not, Wu Jia Pi

BOTANICAL NAME/FAMILY

Eleutherococcus senticosus (synonym: *Acanthopanax senticosus*) (family Araliaceae)

PLANT PART USED

Root

CHEMICAL COMPONENTS

Glycosides (eleutherosides A–M, includes saponins, coumarins, lignans, phenylpropanoids, oleanolic acids, triterpenes, betulinic acid and vitamins); steroid glycoside (eleutheroside A); lignan (eleutheroside D, sesamine); glycans (eleutherans A–G); triterpenoid saponins; saponin (protoprimulagenin A); hydroxycoumarin (isofraxidin); phenolics; polysaccharides; lignans; coumarins; resin.

Nutrients include magnesium 723 μg/g, aluminium 188 μg/g and manganese 37 μg/g, vitamins A and E (Meacham 2002, Nissen 2003, Skidmore-Roth 2001).

MAIN ACTIONS

ADAPTOGENIC (MODULATES STRESS RESPONSE)

Siberian ginseng appears to alter the levels of different neurotransmitters and hormones involved in the stress response, chiefly at the HPA axis. It degrades the enzyme (catechol-O-methyl transferase), and increases levels of noradrenaline and serotonin in the brain and adrenaline in the adrenal glands, according to animal studies (Abramova et al 1972). Eleutherosides have also been reported to bind to receptor sites for progestin, oestrogen, mineralocorticoids and glucocorticoids in vitro

and therefore may theoretically exert numerous pharmacological actions important for the body's stress response (Pearce et al 1982).

Owing to such actions, herbalists and naturopaths describe the herb's overall action as 'adaptogenic', whereby the body is better able to adapt to change and homeostasis is more efficiently restored. More recently, the term 'allostasis' is being adopted in the medical arena to describe 'the ability to achieve stability through change'.

Clinical note — Allostasis

Allostasis is the body's adaptation to stress. Allostatic (adaptive) systems are critical to survival and enable us to respond to changes in our physical state (such as asleep, awake, standing, sitting, eating, exercising, infection) and psychological states (such as anticipation, fear, isolation, worry and lack of control). The consumption of tobacco, alcohol and our dietary choices also induce allostatic responses (McEwan 1998). These systems are complex and have broad boundaries, in contrast to the body's homeostatic systems (e.g. blood pH and body temperature), which are maintained within a narrow range.

Most commonly, allostatic responses involve the sympathetic nervous system and the HPA axis. Upon activation (e.g. a challenge is perceived), catecholamines are released from nerves and the adrenal medulla, corticotrophin is secreted from the pituitary and cortisol is released from the adrenal cortex. Once the threat has passed (e.g. environment is more comfortable or infection is controlled), the system is inactivated and levels of cortisol and catecholamine secretion return to baseline.

Chronic exposure to stress can lead to allostatic load, a situation resulting from chronic overactivity or underactivity of allostatic systems. The situation is characterised by maladaptive responses whereby systems become inefficient or do not turn off appropriately. Currently, there is much interest in understanding the association between numerous diseases such as cardiovascular disease and overwhelming allostatic load.

One measure that is used to gauge an individual's allostatic response is the cortisol response to a variety of stressors. As such, cortisol is seen as the classical 'stress' hormone.

Although the mechanism of action responsible is still unclear, several theories have been proposed to explain the effect of Siberian ginseng on allostatic systems, largely based on the pharmacological actions observed in test-tube and animal studies.

Siberian ginseng increases levels of noradrenaline, serotonin, adrenaline and cortisol that are able to induce both positive and negative feedback responses

(Abramova et al 1972, Gaffney et al 2001a). Therefore, for example, if allostatic load is such that responses have become inadequate, then the resulting increase in hormone levels would theoretically induce a more efficient response. Alternatively, situations of chronic overactivity, also due to allostatic load, would respond to Siberian ginseng in a different way, with negative feedback systems being triggered to inactivate the stress response (Gaffney et al 2001a). As a result, Siberian ginseng could theoretically induce quite different effects, largely dependent on whether allostatic responses were underactive or overwhelmed.

IMMUNOMODULATION

Siberian ginseng appears to exert an immunomodulatory rather than just an immunosuppressive or stimulating action; however, evidence for the immune enhancing effects of Siberian ginseng is contradictory. Clinical studies in vitro and in vivo have revealed stimulation of general non-specific resistance and an influence on T-lymphocytes, NK cells and cytokines (Bohn et al 1987, Schmolz et al 2001), although other studies suggest that Siberian ginseng does not significantly stimulate the innate macrophage immune functions that influence cellular immune responses (Wang et al 2003). Alternatively, another in vitro study has demonstrated that activation of macrophages and NK cells does occur and may be responsible for inhibiting tumor metastasis both prophylactically and therapeutically (Yoon et al 2004).

The main constituents responsible appear to be lignans (seamin, syringin) and polysaccharides such as glycans, which demonstrate immunostimulant effects in vitro (Davydov & Krikorian 2000, Wagner et al 1984). Additionally, effects on the HPA axis will influence immune responses.

It has been suggested that eleutheroside E may be responsible for the improved recovery from reduced NK activity and the inhibition of corticosterone elevation induced by forced swimming in mice (Kimura & Sumiyoshi 2004) and may contribute to the antifatigue action.

ANTIVIRAL

In vitro studies show a strong antiviral action, inhibiting the replication of RNA type viruses such as human rhinovirus, respiratory syncytial virus and influenza A virus (Glatthaar-Saalmuller et al 2001).

ANABOLIC ACTIVITY

Siberian ginseng extracts have been reported to provide better usage of glycogen and high energy phosphorus compounds and improve the metabolism of lactic and pyruvic acids (Farnsworth et al 1985). Additionally, preliminary evidence of possible

anabolic effects makes this herb a popular treatment among athletes in the belief that endurance, performance and power may improve with its use.

While initial animal studies showed promise for improving weight gain and increasing organ and muscle weight (Farnsworth et al 1995, Kaemmerer & Fink 1980), clinical studies confirming whether anabolic effects occur also in humans could not be located.

OTHER ACTIONS

ANTICOAGULANT AND ANTIPLATELET EFFECTS

A controlled trial using Siberian ginseng tincture for 20 days in 20 athletes detected a decrease in the blood coagulation potential and activity of the blood coagulation factors that are normally induced by intensive training of the athletes (Azizov 1997). Whether the effects also occur in non-athletes is unknown. The 3, 4-dihydroxybenzoic acid constituent of Siberian ginseng has demonstrated antiplatelet activity in vivo (Yun-Choi et al 1987).

VASCULAR RELAXANT

In vitro studies have demonstrated vasorelaxant effects for Siberian ginseng. The effect is thought to be endothelium-dependent and mediated by NO and/or endothelium-derived hyperpolarising factor, depending on the size of the blood vessel. Other vasorelaxation pathways may also be involved (Kwan et al 2004).

ANTI-ALLERGIC

In vitro studies demonstrate that Siberian ginseng has anti-allergic properties in mast-cell-mediated allergic reactions (Jeong et al 2001).

RADIOPROTECTIVE

Animal studies have found that administration of Siberian ginseng prior to a lethal dose of radiation produced an 80% survival rate in mice (Miyanomae & Frindel 1988). This result suggests that Siberian ginseng may protect against radiation toxicity.

NEUROPROTECTIVE

Preliminary animal studies have suggested possible neuroprotective effects in transient middle cerebral artery occlusion in Sprague-Dawley rats. Infarct volume was reduced by 36.6% by inhibiting inflammation and microglial activation in brain ischaemia after intraperitoneal injection of a water extract of Siberian ginseng (Bu et al 2005). Similarly, intraperitoneal injection of Siberian ginseng was found to relieve damage to neurons following hippocampal ischaemia hypoxia and improve the learning and memory of rats with experimentally induced vascular dementia (Ge et al 2004). The saponins present in Siberian ginseng have also been shown to protect

against cortical neuron injury induced by anoxia/ reoxygenation by inhibiting the release of NO and neuron apoptosis in vitro (Chen et al 2004).

HEPATOPROTECTIVE

Animal studies have demonstrated that an intravenous extract of Siberian ginseng decreased thioacetamide-induced liver toxicity when given before and after thioacetamide administration (Shen et al 1991). More recently oral administration of aqueous extract and polysaccharide was found to attenuate fulminant hepatic failure induced by D-galactosamine/lipopolysaccharide in mice, reducing serum AST, ALT and TNF-alpha levels (Park et al 2004). The protective effect is thought to be due to the water-soluble polysaccharides.

REDUCES OBESITY

Animal studies have demonstrated that the inclusion of Siberian ginseng attenuated the 'weight gain, serum LDL-cholesterol concentration and liver triglycerides accumulation in mice with obesity induced by high-fat diets' (Cha et al 2004).

GLYCAEMIC CONTROL AND INSULIN-SENSITISING EFFECT

Animal studies have indicated a potential for hypoglycaemic effects when used intravenously. Eleutherens A–G exert marked hypoglycaemic effects in normal and alloxan-induced hyperglycaemic mice (Hikino et al 1986) and eleutherosides show an insulin-like action in diabetic rats (Dardymov et al 1978). However, these effects have not been borne out in human studies (Farnsworth et al 1985) and may not relate to oral dosages of Siberian ginseng.

A small, double-blind, randomised, multiple-crossover study using 12 healthy participants actually showed an increase in postprandial plasma glucose at 90 and 120 minutes when 3 g Siberian ginseng was given orally 40 minutes before a 75-g oral glucose tolerance test (Sievenpiper et al 2004). More recently, oral administration of an aqueous extract of Siberian ginseng was shown to improve insulin sensitivity and delay the development of insulin resistance in rats (Liu et al 2005). As a result further trials in people with impaired glucose tolerance and/or insulin resistance are warranted.

CLINICAL USE

STRESS

Siberian ginseng is widely used to treat individuals with nervous exhaustion or anxiety due to chronic exposure to stress, or what is now termed 'allostatic load situations'. The biochemical effects on stress responses observed in experimental and human

studies provide a theoretical basis for this indication (Abramova et al 1972, Gaffney et al 2001a).

One placebo-controlled study conducted over 6 weeks investigated the effects of an ethanolic extract of Siberian ginseng (8 mL/day, equivalent to 4 g/day dried root). In the study, active treatment resulted in increased cortisol levels, which may be consistent with animal research suggesting a threshold of stress below which Siberian ginseng increases the stress response and above which it decreases the stress response (Gaffney et al 2001b).

FATIGUE

Siberian ginseng is used to improve physical and mental responses during convalescence or fatigue states. Its ability to increase levels of noradrenaline, serotonin, adrenaline and cortisol provide a theoretical basis for its use in situations of fatigue. However, controlled studies are limited.

A randomised, double-blind, placebo-controlled trial of 300 mg/day (*E. senticosus* dry extract) for 8 weeks assessed health-related QOL scores in 20 elderly people. Improvements were observed in social functioning after 4 weeks of therapy but did not persist to the 8-week time point. It would appear that improvements diminish with continued use (Cicero et al 2004), which may help to explain the practice of giving Siberian ginseng for 6 weeks with a 2-week break before repeating.

A recent randomised placebo-controlled trial evaluated the effectiveness of Siberian ginseng in chronic fatigue syndrome (CFS). No significant improvements were demonstrated overall; however, sub-group analysis showed improvements in fatigue in CFS sufferers with less severe fatigue (Hartz et al 2004). Further studies are required to determine whether Siberian ginseng may be a useful therapeutic option in cases of mild to moderate fatigue.

Commission E approves the use of Siberian ginseng as a tonic in times of fatigue and debility, for declining capacity for work or concentration, and during convalescence (Blumenthal et al 2000). In practice, it is often used in low doses in cases of fatigue due to chronic stress (Gaffney et al 2001a).

ERGOGENIC AID

Siberian ginseng extracts have been reported to provide better usage of glycogen and high-energy phosphorus compounds and improve the metabolism of lactic and pyruvic acids (Farnsworth et al 1985). Additionally, preliminary evidence of possible anabolic effects makes this herb a popular treatment among athletes in the belief that endurance, performance and power may improve with its use.

While initial animal studies showed promise, recent randomised, controlled clinical trials have produced inconsistent results in healthy individuals and athletes (Eschbach et al 2000, Dowling et al 1996, Mahady et al 2000) and a recent review concluded that only poorer quality trials have demonstrated benefit while well-designed trials have not shown significant improvement in endurance performance, cardiorespiratory fitness, or fat metabolism during exercise ranging in duration from 6 to 120 minutes (Goulet & Dionne 2005).

In the mid 1980s, a Japanese controlled study conducted over 8 days showed that Siberian ginseng extract (2 mL twice daily) improved work capacity compared with placebo (23.3% vs 7.5%) in male athletes, owing to increased oxygen metabolism (Asano et al 1986). Increased stamina was also seen.

More recently, a randomised, double-blind crossover trial using a lower dose of 1200 mg/day Siberian ginseng for 7 days reported that treatment did not alter steady-state substrate use or 10 km cycling performance time (Eschbach et al 2000). Additionally, an 8-week, double-blind placebo-controlled study involving 20 experienced distance runners failed to detect significant changes to heart rate, oxygen consumption, expired minute volume, respiratory exchange ratio, perceived exertion or serum lactate levels compared with placebo. Overall, both submaximal and maximal exercise performance was unchanged (Dowling et al 1996).

Clinical studies investigating whether anabolic effects observed in experimental studies occur in humans are lacking.

PREVENTION OF INFECTION

Due to the herb's ability to directly and indirectly modulate immune responses, it is also used to increase resistance to infection. One double-blind study of 1000 Siberian factory workers supports this, reporting a 50% reduction in general illness and a 40% reduction in absenteeism over a 12-month period, following 30 days' administration of Siberian ginseng (Farnsworth et al 1985).

More recently, a 6-month controlled trial in males and females with recurrent herpes infection found that Siberian ginseng (2 g/day) successfully reduced the frequency of infection by 50% (Williams 1995).

In practice, Siberian ginseng is generally used as a preventative medicine, as administration during acute infections is widely thought to increase the severity of the illness, although this has not been borne out in controlled studies using Siberian ginseng in combination with other herbs. A small RCT demonstrated a significant reduction in the severity of familial Mediterranean fever in children using a combination of Siberian ginseng with licorice, andrographis and schisandra (Amaryan et al 2003) and a combination of Siberian ginseng with schisandra and rhodiola was

found to expedite the recovery of patients with acute non-specific pneumonia (Narimanian et al 2005).

OTHER USES

Given the herb's ability to increase levels of serotonin and noradrenaline in animal studies (Abramova 1972), a theoretical basis exists for the use of Siberian ginseng in depression.

In TCM, Siberian ginseng is used to encourage the smooth flow of Qi and blood when obstructed, particularly in the elderly, and is viewed as a general tonic. It is therefore used for a myriad of indications, usually in combination with other herbal medicines.

DOSAGE RANGE

- 1–4 g/day dried root or equivalent preparations.
- Fluid extract (1:2): 2–8 mL/day (15–55 mL/week).
- Tincture (1:5): 10–15 mL/day.
- Extracts with standardised levels of eleutheroside E (>0.5 mg/mL) are recommended.

In practice, all ginsengs tend to be prescribed for no more than 1–3 months at a time with a break of at least several weeks before resuming treatment.

ADVERSE REACTIONS

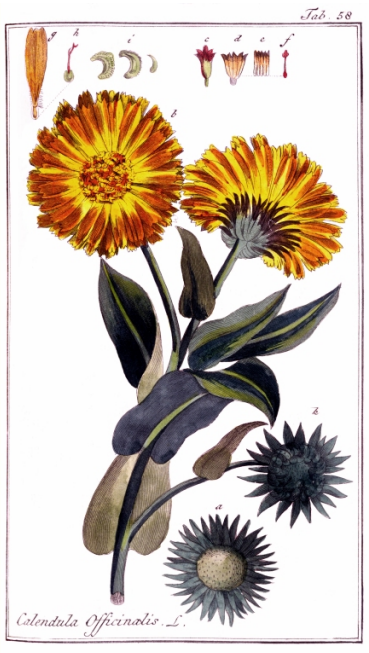
Clinical trials of 6 months' duration have shown no side-effects from treatment (Bohn et al 1987). High doses may cause slight drowsiness, irritability, anxiety, mastalgia, palpitations or tachycardia although these side effects may be more relevant to *Panax ginseng*.

Clinical note — Case reports of Siberian ginseng need careful consideration

Some adverse reactions attributed to Siberian ginseng have subsequently been found to be due to poor product quality, herbal substitution and/or interference with test results. For example, initial reports linking maternal ginseng use to neonatal androgenisation are now suspected to be due to substitution with another herb, *Periploca sepium* (silk vine), as American herb companies importing Siberian ginseng from China have been known to be supplied with two or three species of *Periploca* (Awang 1991). Additionally, rat studies have failed to detect significant androgenic action (Awang 1991, Waller et al 1992) for Siberian ginseng.

Another example is the purported interaction between digoxin and Siberian ginseng, which was based on a single case report of a 74-year-old man found to

have elevated digoxin levels for many years (McRae 1996). It was subsequently purported that the herbal product may have been adulterated with digitalis. Additionally, Siberian ginseng contains glycosides with structural similarities to digoxin that may modestly interfere with digoxin (Dasgupta & Reyes 2005, Dasgupta et al 2003). Considering that clinical symptoms of digoxin toxicity were not observed, it appears likely that an interference with the test methods used is responsible.



SIGNIFICANT INTERACTIONS

As controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity and case reports. Studies have reported that normal doses of Siberian ginseng are unlikely to affect drugs metabolised by CYP2D6 or CYP3A4 (Donovan et al 2003).

ANTICOAGULANTS

An in vivo study demonstrated that an isolated constituent in Siberian ginseng has anticoagulant activity (Yun-Choi et al 1987) and a clinical trial found a reduction in blood coagulation induced by intensive training in athletes (Azizov 1997). Whether these effects also occur in non-athletes is unknown. Observe.

CHEMOTHERAPY

An increased tolerance for chemotherapy and improved immune function has been demonstrated in women with breast cancer undergoing chemotherapy treatment (Kupin 1984, Kupin et al 1986). Caution, as co-administration may theoretically reduce drug effects. However, beneficial interaction may be possible under medical supervision.

DIABETIC MEDICATIONS

Claims that Siberian ginseng has hypoglycaemic effects are based on intravenous use in animal studies and not observed in humans for whom oral intake may actually increase postprandial glycaemia (Sievenpiper et al 2004). Observe diabetic patients taking ginseng.

INFLUENZA VIRUS VACCINE

Ginseng may reduce the risk of post-vaccine reactions (Zykov & Protasova 1984), a possible beneficial interaction.

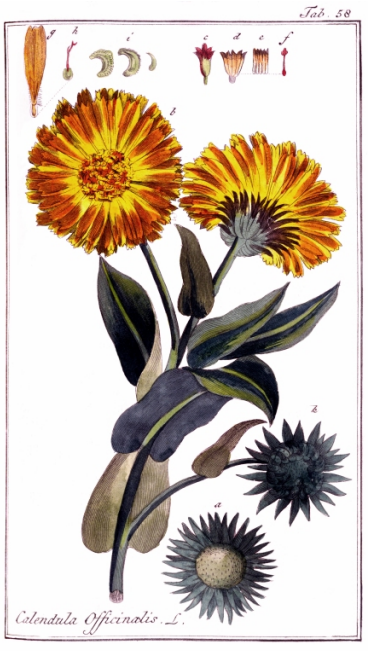
CONTRAINDICATIONS AND PRECAUTIONS

Some authors suggest that high-dose Siberian ginseng should be avoided by those with cardiovascular disease or hypertension (BP >80/90 mmHg) (Mahady et al 2000). Others merely suggest a caution, as reports are largely unsubstantiated (Holford &

Cass 2001). As such, it is recommended that people with hypertension should be monitored if using high doses. A study in elderly people with hypertension over 8 weeks did not affect blood pressure control (Cicero et al 2004).

Due to possible effects on glycaemic control (Sievenpiper et al 2004), care should be taken in people with diabetes until safety is established. Suspend use 1 week before major surgery.

Traditional contraindications include hormonal changes, excess energy states, fever, acute infection, concurrent use of other stimulants and prolonged use.



PREGNANCY USE

Insufficient reliable information is available, but the herb is not traditionally used in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Siberian ginseng appears to alter the levels of different neurotransmitters and hormones involved in the stress response, chiefly at the HPA axis.
- It is widely used to treat individuals with nervous exhaustion or anxiety due to chronic exposure to stress, or what are now termed 'allostatic load situations'. It is also recommended during convalescence or fatigue to improve mental and physical responses.
- Siberian ginseng may increase resistance to infection and has been shown to reduce frequency of genital herpes outbreaks with long-term use.
- The herb is popular among athletes in the belief that endurance, performance and power may improve with its use, but clinical studies have produced inconsistent results.
- It is not recommended for use in pregnancy and people with hypertension should be monitored if using high doses.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Siberian ginseng affects many chemicals involved in switching on and off the body's stress responses. As such, it is used to improve wellbeing during times of chronic stress; however, scientific research has yet to fully investigate its use in this regard. It may also boost immune function and reduce the frequency of genital herpes outbreaks. Evidence for improved performance in athletes in unconvincing.

When will it start to work?

Effects on stress levels should develop within 6 weeks, whereas immune responses develop within 30 days.

Are there any safety issues?

It should not be used in pregnancy and high doses should be used with care by those with hypertension.

REFERENCES

Abramova ZI et al. Lek Sredstva Dal'nego Vostoka 11 (1972): 106-8. In: Mills S, Bone K. Principles and Practices of Phytotherapy. London: Churchill Livingstone, 2000.

Amaryan G et al. Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard(R): a standardized fixed combination of Andrographis paniculata Nees, with Eleutherococcus senticosus Maxim, Schizandra chinensis Bail. and Glycyrrhiza glabra L. extracts in patients with Familial Mediterranean Fever. Phytomedicine 10.4 (2003): 271-85.

Asano K et al. Planta Med 3 (1986): 175-7. In: Mills S, Bone K. Principles and Practices of Phytotherapy. London: Churchill Livingstone, 2000 and Micromedex.

Awang DVC. Maternal use of ginseng and neonatal androgenization (so-called Siberian ginseng is probably Periploca sepium, or silk vine) [Letter.] JAMA 266.3 (1991): 363.

Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. Can Med Assoc J 155.9 (1996): 1237.

Azizov AP. Effects of eleutherococcus, elton, leuzea, and leveton on the blood coagulation system during training in athletes, Eksp Klin Farmakol 60.5 (1997): 58-60 [in Russian].

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bohn B, Nebe CT, Birr C. Flow-cytometric studies with Eleutherococcus senticosus extract as an immunomodulatory agent. Arzneimittelforschung 37.10 (1987): 1193-6.

Bu Y et al. Siberian ginseng reduces infarct volume in transient focal cerebral ischaemia in Sprague-Dawley rats. Phytother Res 19.2 (2005): 167-9.

Cha Y, Rhee S, Heo Y. Acanthopanax senticosus extract prepared from cultured cells decreases adiposity and obesity indices in C57BL/6J mice fed a high fat diet. J Med Food 7.4 (2004): 422-9.

Chen Y, Gu Y, Wu X. Protective effect of acanthopanax senticosus saponins on anoxia/reoxygenation injury of neuron. Chin J Clin Rehab 8.31 (2004): 6964-5.

Cicero A et al. Effects of Siberian ginseng (Eleutherococcus senticosus maxim.) on elderly quality of life: a randomized clinical trial. Arch Gerontol Geriatr 38 (Suppl 1) (2004): 69-73.

Dardymov IV, Khasina EI, Bezdetko GN. Rastit Resur 14.1 (1978): 86-89. In: Mills S, Bone K. Principles and Practices of Phytotherapy. London: Churchill Livingstone, 2000.

Dasgupta A et al. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: Significant variation in digoxin-like immunoreactivity among commercial ginsengs. Am J Clin Pathol 119.2 (2003): 298-303.

Dasgupta A, Reyes MA. Effect of Brazilian, Indian, Siberian, Asian, and North American ginseng on serum digoxin measurement by immunoassays and binding of digoxin-like immunoreactive components of ginseng with Fab fragment of antidigoxin antibody (Digibind). Am J Clin Pathol 124.2 (2005): 229-36.

Davydov M, Krikorian AD. Eleutherococcus senticosus Maxim as an adaptogen: a closer look. J Ethnopharmacol 72.3 (2000): 345-93.

Donovan JL et al. Siberian ginseng (Eleutheroccus senticosus) effects on CYP2D6 and CYP3A4 activity in normal volunteers. Drug Metab Dispos 31.5 (2003): 519-22.

Dowling EA et al. Effect of Eleutherococcus senticosus on submaximal and maximal exercise performance. Med Sci Sports Exerc 28.4 (1996): 482-9.

Eschbach LF et al. The effect of Siberian ginseng (Eleutherococcus senticosus) on substrate utilization and performance. Int J Sport Nutr Exerc Metab 10.4 (2000): 444-51.

Farnsworth NR et al. Siberian ginseng (Eleutherococcus senticosus): current status as an adaptogen. In: Farnsworth NR et al (eds). Economic and Medicinal Plant Research. Vol. 1. London: Academic Press, 1985; 178.

Gaffney BT et al. Panax ginseng and Eleutherococcus senticosus may exaggerate an already existing biphasic response to stress via inhibition of enzymes which limit the binding of stress hormones to their receptors. Med Hypotheses 56.5 (2001a): 567-72.
Gaffney BT et al. The effects of Eleutherococcus senticosus and Panax ginseng on steroidal hormone indices of stress and lymphocyte subset numbers in endurance athletes. Life Sci 70.4 (2001b): 431.
Ge X et al. Effects of acanthopanax senticosus saponins against vascular dementia in rats. Chin J Clin Rehab 8.34 (2004): 7734-5.
Glatthaar-Saalmuller B, Sacher F, Esperester A. Antiviral activity of an extract derived from roots of Eleutherococcus senticosus. Antiviral Res 50 (2001): 223-8.
Goulet ED, Dionne IJ. Assessment of the effects of Eleutherococcus senticosus on endurance performance. Int J Sport Nutr Exerc Metab 15.1 (2005): 75-83.
Hartz AJ et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. Psychol Med 34.1 (2004): 51-61.
Hikino H et al. Isolation and hypoglycemic activity of eleutherans A, B, C, D, E, F, and G: glycans of Eleutherococcus senticosus roots. J Nat Prod 49.2 (1986): 293-7.
Holford P, Cass H. Natural highs. Piatkus (2001): 90.
Jeong HJ et al. Inhibitory effects of mast cell-mediated allergic reactions by cell cultured Siberian Ginseng. Immunopharmacol Immunotoxicol 23.1 (2001): 107-17.
Kaemmerer K, Fink J. Prakt Tierarzt 61.9 (1980): 748, 750-2, 754, 759-60. In: Mills S, Bone K. Principles and Practices of Phytotherapy. London: Churchill Livingstone, 2000; 538.
Kimura Y, Sumiyoshi M. Effects of various Eleutherococcus senticosus cortex on swimming time, NK activity and corticosterone level in forced swimming stressed mice. J Ethnopharmacol 95.2-3 (2004): 447-53.
Kupin VI, Polevaia EB. Stimulation of the immunological reactivity of cancer patients by Eleutherococcus extract. Vopr Onkol 32.7 (1986): 21-6 [in Russian].
Kupin VJ. Eleutherococcus and other biologically active modifiers in oncology. Medexport, Moscow, 1984: 21. In: Lininger SW et al (eds). A-Z Guide to Drug-Herb-Vitamin Interactions. Healthnotes 1999.
Kwan CY et al. Vascular effects of Siberian ginseng (Eleutherococcus senticosus): endothelium-dependent NO- and EDHF-mediated relaxation depending on vessel size. Naunyn Schmiedebergs Arch Pharmacol 369.5 (2004): 473-80.
Liu T et al. Improvement of insulin resistance by Acanthopanax senticosus root in fructose-rich chow-fed rats. Clin Exp Pharmacol Physiol 32.8 (2005): 649-54.
Mahady GB et al. Ginsengs: a review of safety and efficacy. Nutr Clin Care 3.2 (2000): 90.
McEwan BS. Seminars in medicine of the Beth Israel Deaconess Medical Center: Protective and Damaging Effects of Stress Mediators [Review Article]. N Engl J Med 338.3 (1998): 171-9.
McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. Can Med Assoc J 155.3 (1996): 293-5.
Meacham S et al. Nutritional assessments for cancer patients can be improved when mineral concentrations in dietary supplements are considered during medical nutrition therapy consultations. J Nutr Nov 132.11 (2002): 3547S.
Micromedex. Siberian ginseng. Thomson 2003. www.micromedex.com.
Miyanomae T, Frindel E. Radioprotection of hemopoiesis conferred by Acanthopanax senticosus Harms (Shigoka) administered before or after irradiation. Exp Hematol 16.9 (1988): 801-6.
Narimanian M et al. Impact of Chisan(R) (ADAPT-232) on the quality-of-life and its efficacy as an adjuvant in the treatment of acute non-specific pneumonia. Phytomedicine 12.10 (2005): 723-9.
Nissen D (ed). Mosby's Drug Consult. St Louis: Mosby, 2003; 17.
Park EJ et al. Water-soluble polysaccharide from Eleutherococcus senticosus stems attenuates fulminant hepatic failure induced by D-galactosamine and lipopolysaccharide in mice. Basic Clin Pharmacol Toxicol 94.6 (2004): 298-304.
Pearce PT et al. Panax ginseng and Eleutherococcus senticosus extracts: in vitro studies on binding to steroid receptors. Endocrinol Jpn 29.5 (1982): 567-73.

Schmolz MW, Sacher F, Aicher B. The synthesis of Rantes, G-CSF, IL-4, IL-5, IL-6, IL-12 and IL-13 in human whole-blood cultures is modulated by an extract from Eleutherococcus senticosus L. roots. Phytother Res 15.3 (2001): 268-70.
Shen ML et al. Immunopharmacological effects of polysaccharides from Acanthopanax senticosus on experimental animals. Int J Immunopharmacol 13.5 (1991): 549-54.
Sievenpiper JL et al. Decreasing, null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: the role of ginsenosides. J Am Coll Nutr 23.3 (2004): 248-58.
Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. St Louis: Mosby, 2001.
Wagner H et al. Immunostimulant action of polysaccharides (heteroglycans) from higher plants: Preliminary communication. Arzneimittelforschung 34.6 (1984): 659-61 [in German].
Waller DP et al. Lack of androgenicity of Siberian ginseng (Siberian ginseng fails to cause sex differentiation disorder in rats) [Letter]. JAMA 267.17 (1992): 232.
Wang H et al. Asian and Siberian ginseng as a potential modulator of immune function: an in vitro cytokine study using mouse macrophages. Clin Chim Acta 327.1-2 (2003): 123-8.
Williams M. Immunoprotection against herpes simplex type II infection by eleutherococcus root extract. Int J Alt Complement Med 13 (1995): 9-12.
Yoon T et al. Anti-metastatic activity of Acanthopanax senticosus extract and its possible immunological mechanism of action. J Ethnopharmacol 93.2-3 (2004): 247-53.
Yun-Choi HS et al. Potential inhibitors of platelet aggregation from plant sources, III (Part 3). J Nat Prod 50.6 (1987): 1059-64.
Zykov MP, Protasova SF. Prospects of immunostimulationg vaccination against influenza including the use of Eleutherococcus and other preparations of plants. In: New Data on Eleutherococcus: Proceedings of the Second International Symposium on Eleutherococcus. Moscow, 1984: 164-9.

Globe artichoke

Historical note Artichoke has a long history of use as a vegetable delicacy and medicinal agent, and its cultivation in Europe dates back to ancient Greece and Rome. Traditional use of artichoke has always pertained to the liver where it is considered to increase bile flow and act as a protective agent against various toxins. As such, it has been used for jaundice, dyspepsia, nausea, gout, pruritis and urinary stones. It is still a popular medicine in Europe today.

COMMON NAME
Artichoke

OTHER NAMES
Alcachofa, artichaut, alcaucil, carciofo, cynara

BOTANICAL NAME/FAMILY
Cynara scolymus L. (family [Compositae] Asteraceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Key constituents of the leaf include phenolic acids, mainly caffeic acid derivatives (e.g. chlorogenic acid), sesquiterpenes, lactones (e.g. cynaropicrin) and flavonoids (e.g. cynaroside, luteolin derivatives), phytosterols, inulin and free luteolin.

MAIN ACTIONS
The main pharmacologically active constituents are thought to be the phenolic acids and flavonoids.

ANTIOXIDANT
Artichoke leaf extract exerts antioxidant effects, according to in vitro tests (Speroni et al 2003).

HEPATOPROTECTIVE
Improved hepatic regeneration, improved hepatic blood flow, increased hepatocyte counts, increased hepatic RNA concentrations and a stimulation of hepatic cytogenesis have been associated with artichoke extract in animal studies (Ursapharm Arzneimittel 1998).

Tests with primary hepatocyte cultures suggest that artichoke extracts have marked antioxidative and hepatoprotective potential (Gebhardt 1997).

CHOLERETIC AND CHOLAGOGUE

A significant increase in bile flow has been demonstrated in studies using isolated perfused rat liver in vivo after acute treatment, as well as after repeated administration (Saenz et al 2002). Choleretic activity has also been reported in a double-blind placebo controlled study, with maximal effects on mean bile secretion observed 60 minutes after a single dose (Kirchhoff et al 1994).

A study that evaluated the effects of four extracts and phenolic content on bile flow and liver protection demonstrated that the extract with the highest concentration of phenolic derivatives exerted the strongest effect (Speroni et al 2003).

One study determined that treatment does not produce changes to the liver enzymes gamma-GT, AST, ALT or glutamic dehydrogenase (Pittler et al 2002).

DIURETIC

Artichoke administration stimulated urine excretion in animal studies (Ursapharm Arzneimittel 1998).

LIPID-LOWERING

Artichoke leaf extract inhibited cholesterol biosynthesis in primary cultured rat hepatocytes (Gebhardt 1998) and indirect modulation of hydroxymethylglutaryl-CoA-reductase activity is the most likely inhibitory mechanism. When several known constituents were screened for activity, cynaroside, and particularly its aglycone luteolin, were mainly responsible for the effect. These results have been confirmed recently (Gebhardt 2002).

OTHER ACTIONS

Artichoke administration had beneficial effects on lowering blood glucose levels in alloxan-treated rabbits (Ursapharm Arzneimittel 1998). One study using artichoke leaf juice showed it improved endothelial reactivity, most likely by its antioxidant constituents (Lupattelli et al 2004). According to German commission E, human studies have confirmed carminative, spasmolytic and anti-emetic actions (Blumenthal et al 2000).

Clinical note — Inulin: a natural prebiotic

Inulin is a plant-derived carbohydrate that is not digested or absorbed in the small intestine, but is fermented in the colon by beneficial bacteria. It functions as a prebiotic, stimulating growth of bifidobacteria in the intestine and has been associated with enhanced function of the gastrointestinal system and immune

system (Lopez-Molina et al 2005). Increasing levels of beneficial bacteria, such as bifidobacteria, allows them to 'out compete' potentially detrimental organisms and improve the health of the host. Inulin also increases calcium and magnesium absorption, influences blood glucose levels and reduces the levels of cholesterol and serum lipids. Globe artichoke contains 3% of fresh-weight inulin and smaller amounts are found in the leaves.

CLINICAL USE

HYPERLIPIDAEMIA

Data are available from both controlled and uncontrolled studies that have investigated the effects of artichoke leaf extract in hyperlipidemia. Most studies use Hepar SL forte® or Valverde Artischoke bei Verdauungsbeschwerden (artichoke dry extract) containing 450 g of herbal extract as a coated tablet.

Data from five uncontrolled studies and case series suggests that artichoke leaf extract and cynarin have lipid-lowering effects and a possible role as adjunctive therapy in hyperlipidaemia (Ulbricht & Basch 2005).

A Cochrane systematic review that analysed the results of two controlled studies concluded that artichoke leaf extract appears to have a modest positive effect on the levels of total cholesterol and LDL; however, there is insufficient evidence to recommend it as a treatment option for hypercholesterolaemia and trials with larger samples sizes are still required (Pittler et al 2002).

One of the studies was a randomised, placebo-controlled, double-blind, multicentre trial involving 143 subjects with total cholesterol levels >7.3 mmol/L (>280 g/dL) (Englisch et al 2000). A dose of 1800 mg artichoke leaf extract was administered daily for 6 weeks. Active treatment resulted in 18.5% decrease in serum cholesterol compared with 8.6% for placebo, a result that was significant. No differences were observed between the groups for blood levels of either HDL or triglycerides. Although dietary habits were recorded, the food intake was not strictly controlled in the entire patient sample. The second randomised, placebo-controlled, double-blind study involved 44 healthy volunteers and compared 1920 mg artichoke extract daily to placebo over a 12-week treatment period. No significant effects on serum cholesterol levels were observed in this study; however, subgroup analyses suggested that patients with higher initial total cholesterol levels experienced a significant reduction in total cholesterol levels compared to placebo.

ESCOP approves the use of artichoke leaf as an adjunct to a low-fat diet in the treatment of mild to moderate hyperlipidaemia (ESCOP 2003).

DYSPEPSIA

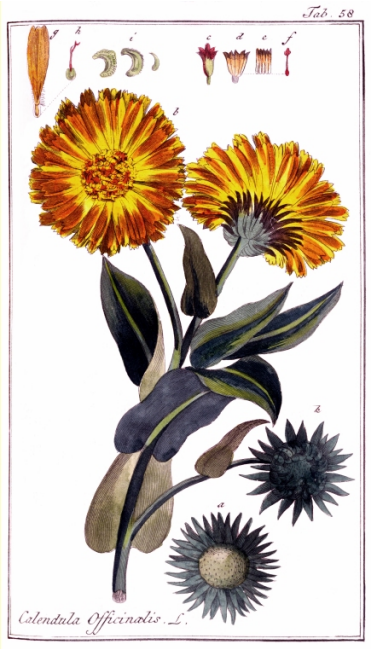
Artichoke leaf extract has been studied as a bile secretion stimulant and primarily recommended in this way for non-ulcer dyspepsia.

A double-blind, randomised, placebo controlled trial of 247 patients with functional dyspepsia (persistent or recurrent pain or discomfort in the upper abdomen with one or more of the following symptoms: early satiety, postprandial fullness, bloating, and nausea) found that treatment with two capsules of 320 mg artichoke leaf extract LI 220 (HeparSL(R) forte) taken three times daily significantly improved overall symptoms over the 6 weeks compared with the placebo (Holtmann et al 2003). Additionally, active treatment significantly improved global QOL scores compared with the placebo.

A randomised, open study of 454 subjects investigated the efficacy of a low-dose artichoke leaf extract (320 mg or 640 mg daily) on amelioration of dyspeptic symptoms and improvement of QOL (Marakis et al 2002). Both doses achieved a significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. Although no differences in primary outcome measures were reported between the two treatment groups, the higher dosage resulted in greater improvements in anxiety.

An uncontrolled study of 553 patients with non-specific digestive disorders (dyspeptic discomforts, functional biliary colic, and severe constipation) experienced a significant reduction of symptoms after 6 weeks of treatment with artichoke extract. Symptoms improved by an average of 70.5%, with strongest effects on vomiting (88.3%), nausea (82.4%), abdominal pain (76.2%), loss of appetite (72.3%), constipation (71.0%), flatulence (68.2%), and fat intolerance (58.8%). In 85% of patients the global therapeutic efficacy of artichoke extract was judged by the physicians as excellent or good. (Fintelmann 1996).

The German Commission E approves artichoke leaf and preparations made from artichoke leaf as a choleretic agent for dyspeptic problems (Blumenthal et al 2000).



IRRITABLE BOWEL SYNDROME

Artichoke leaf extract appears to have substantial benefits in IBS, according to the available evidence; however, large controlled studies are required to confirm these observations.

A subgroup of patients with IBS symptoms was identified from a sample of subjects with dyspeptic syndrome who were being monitored for 6 weeks (Walker et al 2001). Analysis of the data revealed 96% of patients rated artichoke leaf extract as better than or at least equal to previous therapies administered for their symptoms. Physicians also provided favourable reports on its effects in these patients.

More recently, a study of 208 adults with IBS observed before and after a 2-month intervention period of changes in symptoms (Budy et al 2004). A significant reduction in the incidence of IBS by 26.4% and a significant shift in self-reported usual bowel pattern toward 'normal' were also reported after treatment. The Nepean Dyspepsia Index (NDI) total symptom score significantly decreased by 41% after treatment and a significant 20% improvement in the NDI total QOL score.

REDUCING ALCOHOL-INDUCED HANGOVER

Artichoke extract does not prevent the signs and symptoms of alcohol-induced hangover in healthy adults according to a small randomised, double-blind, crossover trial (Pittler et al 2003). The dose used in the study was 960 mg taken immediately before and after consuming alcohol for 2 days.

OTHER USES

Traditional uses include treatment for jaundice, dyspepsia, nausea, gout, pruritis and urinary stones. Due to its choleretic effect, it has also been used to improve digestion of fats.

DOSAGE RANGE

- 1:2 liquid extract: 3–8 mL/day in divided doses.
- 6 g daily of dried cut leaves, pressed juice of the fresh plant or equivalent.

ACCORDING TO CLINICAL STUDIES

- Hyperlipidaemia: 4–9 g/day of dried leaves or 1800 mg/day artichoke leaf extract.
- Dyspepsia: artichoke leaf extract 640 mg/day.
- IBS: artichoke leaf extract 640 mg/day.

ADVERSE REACTIONS

Studies with hyperlipidaemic subjects indicate that globe artichoke leaf extract is generally well tolerated. Mild symptoms of flatulence, hunger and weakness were reported in approximately 1% of subjects when the fresh plant was used (Fintelmann 1996). Contact dermatitis is possible with the fresh plant and urticaria–angio-oedema has been reported in one case of ingestion of raw and boiled herb (Mills & Bone 2005).

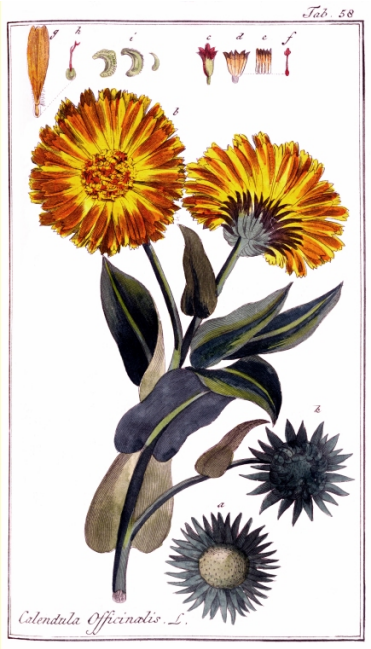
SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Not to be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants.

Herbs with choleretic and cholagogue activity should be used with caution by people with bile duct obstruction (Blumenthal et al 2000), acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis, intestinal spasm or ileus, liver cancer or with unconjugated hyperbilirubinaemia (Mills & Bone 2005).



PREGNANCY USE

Safety has not been scientifically established for the leaf extract.

PRACTICE POINTS/PATIENT COUNSELLING

- Artichoke leaf extract has antioxidant, choleretic, diuretic and lipid-lowering activity and possibly hepatoprotective, anti-emetic and spasmolytic effects.
- According to a Cochrane review of two controlled studies, the effect on lipids is modest and further large scale trials are required. ESCOP recommends that a low-fat diet should also be undertaken when artichoke leaf extract is used for mild to moderate hyperlipidaemia.
- Artichoke leaf extract is an effective symptomatic treatment for non-ulcer dyspepsia and shows promise for IBS.
- The extract is well tolerated with few side-effects, but should not be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants and used with caution in bile duct obstruction, acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis, intestinal spasm or ileus, liver cancer or people with unconjugated hyperbilirubinaemia.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Artichoke leaf extract effectively reduces symptoms in non-ulcer dyspepsia and possibly IBS. It may also modestly reduce cholesterol levels and improve digestion, flatulence and nausea.

When will it start to work?

Symptomatic relief in dyspepsia and IBS appear after 2–3 weeks of treatment; however, further improvements are possible with longer term use. A reduction in cholesterol may take 4–6 weeks and is best achieved when combined with a low-fat diet.

Are there any safety issues?

The extract is well tolerated with few side-effects, but should not be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants and used with caution in bile duct obstruction, acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis,

intestinal spasm or ileus, liver cancer or people with unconjugated hyperbilirubinaemia.

REFERENCES

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000; 10-13.

Bundy R et al. Artichoke leaf extract reduces symptoms of irritable bowel syndrome and improves quality of life in otherwise healthy volunteers suffering from concomitant dyspepsia: a subset analysis. J Altern Complement Med 10 (2004): 667-9.

Englisch W et al. Efficacy of Artichoke dry extract in patients with hyperlipoproteinemia. Arzneimittelforschung 50 (2000): 260-5.

European Scientific Co-operative On Phytomedicine (ESCOP). Cynarae Folium. In: ESCOP Monographs, 2nd edn. Stuttgart: Thieme, 2003: 118-26.

Fintelmann V. Antidyspeptic and lipid-lowering effects of artichoke leaf extract: results of clinical studies into the efficacy and tolerance of Hepar-SL(R) forte involving 553 patients. J Gen Med 1996; 2: 3-19; as cited on Micromedex 27(Healthcare Series). Artichoke. Thomson 2006. Available at: www.micromedex.com (accessed 15-02-06).

Gebhardt R. Antioxidative and protective properties of extracts from leaves of the artichoke (Cynara scolymus L.) against hydroperoxide-induced oxidative stress in cultured rat hepatocytes. Toxicol Appl Pharmacol 144 (1997): 279-86.

Gebhardt R. Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke (Cynara scolymus L.) extracts. J Pharmacol Exp Ther 286 (1998): 1122-8.

Gebhardt R. Inhibition of cholesterol biosynthesis in HepG2 cells by artichoke extracts is reinforced by glucosidase pretreatment. Phytother Res 16 (2002): 368-72.

Holtmann G et al. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. Aliment Pharmacol Ther 18 (2003): 1099-105.

Kirchhoff R et al. Increase in cholesteresis by means of artichoke extract. Phytomedicine 1994; 1: 107-15; as cited on Micromedex 27 (Healthcare Series). Artichoke. Thomson 2006. Available at: www.micromedex.com (accessed 15-02-06).

Lopez-Molina D et al. Molecular properties and prebiotic effect of inulin obtained from artichoke (Cynara scolymus L.). Phytochemistry 66 (2005): 1476-84.

Lupattelli G et al. Artichoke juice improves endothelial function in hyperlipemia. Life Sci 76 (2004): 775-82.

Marakis G et al. Artichoke leaf extract reduces mild dyspepsia in an open study. Phytomedicine 9 (2002): 694-9.

Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis, MO: Churchill Livingstone, 2005; 437-9.

Pittler MH et al. Effectiveness of artichoke extract in preventing alcohol-induced hangovers: a randomized controlled trial. Can Med Assoc J 169 (2003): 1269-73.

Pittler MH, Thompson CO, Ernst E. Artichoke leaf extract for treating hypercholesterolaemia. Cochrane Database Syst Rev 3 (2002): CD003335.

Saenz RT et al. Choleretic activity and biliary elimination of lipids and bile acids induced by an artichoke leaf extract in rats. Phytomedicine 9 (2002): 687-93.

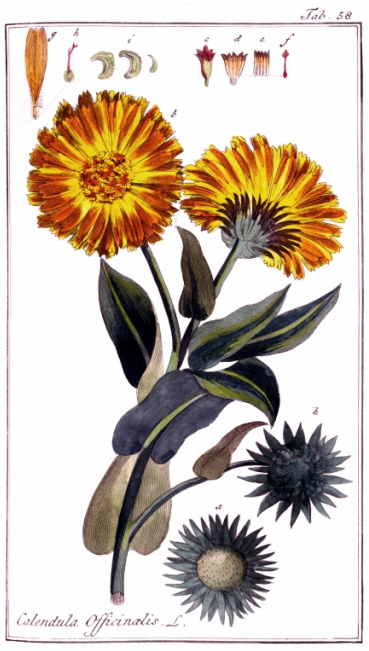
Speroni E et al. Efficacy of different Cynara scolymus preparations on liver complaints. J Ethnopharmacol 86 (2003): 203-11.

Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005; 29-33.

Ursapharm Arzneimittel. Fachinformation: Hepar-POS(R), Artichoke extract. Saarbrucken, Germany: Ursapharm Arzneimittel GmbH, 1998; as cited on Micromedex 27 (Healthcare Series). Artichoke. Thomson 2006. Available at: www.micromedex.com (accessed 15-02-06).

Walker AF et al. Artichoke leaf extract reduces symptoms of irritable bowel syndrome in a post-marketing surveillance study. Phytother Res 15 (2001): 58-61.

Glucosamine



OTHER NAMES

D-Glucosamine, amino monosaccharide, glucosamine sulfate, glucosamine hydrochloride, glucosamine hydroiodide, N-acetyl D-glucosamine, 2-amino-2-deoxy-beta-D-glucopyranose

BACKGROUND AND RELEVANT PHARMACOKINETICS

Glucosamine is a naturally occurring substance that is required for the production of proteoglycans, mucopolysaccharides and hyaluronic acid, substances that make up joint tissue, such as articular cartilage, tendons and synovial fluid. It is also a component of blood vessels, heart valves and mucus secretions (Kelly 1998).

Glucosamine sulfate is 90% absorbed after oral administration. The bioavailability is approximately 20% after first-pass metabolism (Aghazadeh-Habashi et al 2002). Unbound glucosamine is concentrated in the articular cartilage and the elimination half-life is 70 hours, with excretion as CO_2 in expired air, as well as by the kidneys and in faeces (Setnikar 1993). A study of the pharmacokinetics of glucosamine sulfate in humans found that it is rapidly absorbed after oral administration and its elimination half-life was tentatively estimated to average 15 hours, therefore supporting once-daily dosing (Persiani et al 2005). Twice daily dosing with 500 mg of a time-release formula has also been shown to provide comparable serum levels after 24 hours as three divided doses of 500 mg (Basak et al 2004).

Another study of the pharmacokinetics of glucosamine hydrochloride in horses found that the levels attained in serum and synovial fluid were 500-fold lower than those reported to modify chondrocyte anabolic and catabolic activities in tissue and cell culture experiments, leading to the suggestion that the therapeutic benefit of dietary glucosamine may be secondary to its effects on non-articular tissues, such as the intestinal lining, liver, or kidney because these tissues are exposed to much higher levels (Laverty et al 2005).

CHEMICAL COMPONENTS

2-amino-2-deoxy-D-glucose

FOOD SOURCES

Glucosamine is present in chitin from the shells of prawns and other crustaceans. As a supplement, glucosamine is derived from marine exoskeletons or produced synthetically and is available in salt forms, including glucosamine sulfate, glucosamine

hydrochloride, glucosamine hydroiodide and N-acetyl glucosamine. Glucosamine salts are likely to be completely ionised in the stomach, although clinical equivalence of the different salts has not been established. The purity and content of products has been questioned in the USA, where glucosamine is regarded as a food supplement and its quality is unregulated (Consumer-labs).

MAIN ACTIONS

CHONDROPROTECTIVE EFFECT

Glucosamine is a primary substrate and stimulant of proteoglycan biosynthesis and inhibits the degradation of proteoglycans. Glucosamine may also stimulate synovial production of hyaluronic acid, a compound responsible for the lubricating and shock-absorbing properties of synovial fluid (McCarty 1998, McCarty et al 2000). Glucosamine has been found to cause a statistically significant stimulation of proteoglycan production by chondrocytes from human osteoarthritic cartilage culture (Bassleer et al 1998). Glucosamine sulfate has been also found to modify cultured osteoarthritis chondrocyte metabolism by acting on protein kinase C, cellular phospholipase A_2, protein synthesis and possibly collagenase activation (Piperno et al 2000). N-acetyl glucosamine also has been found to produce proliferation of matured cartilaginous tissues and matured cartilage substrate in experimentally produced cartilaginous injuries in rabbits (Tamai et al 2003), and oral administration of glucosamine has been shown to have limited site-specific, partial disease-modifying effect in an animal model of OA (Tiraloche et al 2005). The results of one in-vitro study suggest that the experimental effects of glucosamine are sensitive to the experimental model, the doses and length of treatment and that in the model using bovine chondrocytes pharmacological doses of glucosamine induced a broad impairment in the metabolic activity of the chondrocytes, leading to cell death (de Mattei et al 2002).

Glucosamine was found to have no effect on type 2 collagen fragment levels in serum or urine in a 6-month RCT of 137 subjects with OA of the knee (Cibere et al 2005) and exogenous glucosamine was found not to stimulate chondroitin sulfate synthesis by human chondrocytes in vitro. Furthermore these cells were found to have the capacity to form amounts of glucosamine from glucose far in excess of that provided by levels achievable through oral administration (Mroz & Silbert 2004).

ANTI-INFLAMMATORY

It has been suggested that glucosamine may also have an anti-inflammatory action (Hua et al 2002). Glucosamine, but not N-acetyl glucosamine, inhibited human neutrophil functions such as superoxide generation, phagocytosis, granule enzyme

release and chemotaxis in vitro (Hua et al 2002), and it has been shown that glucosamine and N-acetyl glucosamine both inhibit IL-1-beta- and TNF-alpha-induced NO production in normal human articular chondrocytes (Shikhman et al 2001). Glucosamine has been also found to restore proteoglycan synthesis and prevent the production of inflammatory mediators induced by the cytokine IL-1-beta in rat-articular chondrocytes in vitro (Gouze et al 2001). Furthermore, glucosamine has been found to suppress PGE_2 production and partly suppress NO production in chondrocytes in vitro (Mello et al 2004, Nakamura et al 2004), as well as suppressing the production of matrix metalloproteases in normal chondrocytes and synoviocytes (Nakamura et al 2004).

GLUCOSE METABOLISM

Preliminary evidence from rats suggests that glucosamine may cause changes in glucose metabolism and insulin secretion similar to those seen in type 2 diabetes in both rats (Balkan & Dunning 1994, Giaccari et al 1995, Lippiello et al 2000, Shankar et al 1998) and humans (Monauni et al 2000); however, these findings have been disputed (Echard et al 2001) and to date clinical studies in humans have not demonstrated an effect on glucose metabolism (Anderson et al 2005, Tannis et al 2004).

GASTROINTESTINAL PROTECTION

Glycoproteins are important in protecting the bowel mucosa from damage, and the breakdown of glycosaminoglycans is an important consequence of inflammation of mucosal surfaces (Salvatore et al 2000). Abnormalities in colonic glycoprotein synthesis have been implicated in the pathogenesis of ulcerative colitis and Crohn's disease (Burton & Anderson 1983, Winslet et al 1994).

OTHER ACTIONS

Glucosamine might have some activity against HIV. Preliminary evidence suggests that it inhibits intracellular viral movement and blocks viral replication (Bagasra et al 1991). Recent studies have shown that glucosamine has immunosuppressive properties and can prolong graft survival in mice (Ma et al 2002). Oral, intraperitoneal and intravenous glucosamine has been shown to also significantly reduce CNS inflammation and demyelination in an animal model of multiple sclerosis (Zhang et al 2005).

CLINICAL USE

OSTEOARTHRITIS

There is strong evidence to suggest that glucosamine is effective in treating the symptoms of OA, as well as being effective in slowing the disease progression. A Cochrane review of 16 RCTs has concluded that 'there is good evidence that glucosamine is both effective and safe in treating osteoarthritis' and that 'glucosamine therapy may indeed represent a significant breakthrough in the pharmacological management of osteoarthritis' (Towheed et al 2003). Although most studies have been of OA of the knee, there is some clinical evidence that it is also active against OA of the spine (Giacovelli 1993) and temporomandibular joint (Shankland 1998).

The first placebo-controlled clinical trials investigating glucosamine in OA were published in the early 1980s. Drovanti et al showed that a dose of 1500 mg glucosamine sulfate significantly reduced symptoms of OA, almost twice as effectively and twice as fast as placebo (Drovanti et al 1980). Perhaps the most exciting results were found when electron microscopy analysis of cartilage showed that those taking glucosamine sulfate had cartilage more similar to healthy joints than the placebo group. Based on this finding, researchers suggested that glucosamine sulfate had not only provided symptom relief but also had the potential to induce rebuilding of the damaged cartilage.

Since that time, multiple human clinical trials lasting from a few weeks (Crolle & D'Este 1980, Drovanti et al 1980, Lopes Vaz 1982, McAlindon 2001, Pujalte et al 1980, Qiu et al 1998) to 3 years (Pavelka et al 2002, Reginster et al 2001), as well as systematic reviews (Poolsup et al 2005, Towheed et al 2003, 2006) and meta-analyses (McAlindon et al 2000, Richy et al 2003) have shown that glucosamine sulfate (1500 mg/day) can significantly improve symptoms of pain and functionality measures in patients with OA of the knee, with side-effects comparable to those of placebo. There is also evidence from two long-term (3-year) studies (Pavelka et al 2002, Reginster et al 2000) and one year-long study of glucosamine and chondroitin (Rai et al 2004) that in addition to providing symptomatic relief, glucosamine also slows disease progression, as evidenced by a reduction in joint space narrowing.

Reginster et al (2000) compared the effects of 1500 mg glucosamine sulfate with placebo daily over 3 years in 212 patients aged over 50 years with primary knee OA. This was heralded as a landmark study at the time because it not only detected modest symptom-relieving effects, but was the first to identify significant joint-preserving activity with long-term use. Two years later, Pavelka et al confirmed these results in another randomised double-blind study that involved 202 patients with

knee OA (Pavelka et al 2002) and once again observed that long-term treatment with glucosamine sulfate retarded disease progression. A post hoc analysis of these studies found that the disease-modifying effect was evident in 319 post menopausal women (Bruyere et al 2004) and another subanalysis found that patients with less severe radiographic knee OA, who are likely to experience the most dramatic disease progression, may be particularly responsive to treatment with glucosamine (Bruyere et al 2003).

Not all clinical trials of glucosamine for OA have produced positive results. A 12-week, double-blind, randomised placebo-controlled trial of glucosamine performed over the internet involving 205 subjects with symptomatic knee OA found no difference in pain, stiffness, analgesic use or physical function between the glucosamine and placebo groups (McAlindon et al 2004). In another 6-month randomised, double-blind, placebo-controlled study of glucosamine sulfate in knee OA there was no significant difference in the time to disease flare, symptoms or analgesic medication use between the glucosamine and placebo groups (Cibere et al 2004). A further controlled trial of 80 OA patients using glucosamine sulfate over 6 months found no difference between the glucosamine group and placebo for symptoms, except for a small but significant difference in knee flexion, which was suggested to be caused by measurement error (Hughes & Carr 2002).

Most clinical trials have used a specific patented oral formulation of glucosamine sulfate from Rottapharm, Italy, which is available as a prescription medicine in Europe. Although other forms of glucosamine are used in practice, there is significantly more evidence supporting the use of glucosamine sulfate than others (Reginster et al 2005). An updated Cochrane review that looked at 20 studies involving a total of 2570 patients found that studies using a non-Rottapharm preparation failed to show benefit in pain and function, whereas studies of the Rottapharm preparation found glucosamine to be superior to placebo in the treatment of pain and functional impairment (Towheed et al 2006).

In a multicentre, randomised, parallel-controlled clinical trial of 142 patients comparing glucosamine sulfate and glucosamine hydrochloride, both agents were found to be equally effective in producing improvement in symptoms of OA of the knee after 4 weeks, with a remnant therapeutic effect also occurring in both groups 2 weeks after discontinuing treatment. The glucosamine sulfate group experienced significantly more adverse events, mainly mild stomach discomfort and constipation (Qiu et al 2005).

Combination therapy Chondroitin sulfate and glucosamine are frequently marketed together in combination products and some studies suggest that this

combination is effective in treating symptoms (Das & Hammad 2000, Leffler et al 1999, McAlindon et al 2000, Nguyen et al 2001) and reducing joint space narrowing (Rai et al 2004). This is supported by an in vitro study of horse cartilage that found that a combination of glucosamine and chondroitin was more effective than either product alone in preventing articular cartilage glycosaminoglycan degradation (Dechant et al 2005). Further support for combination therapy comes from an in vivo study of rats, which found that combined treatment with chondroitin and glucosamine prevented the development of cartilage damage and was associated with a reduction in IL-1-beta and matrix metalloprotease-9 synthesis (Chou et al 2005).

The National Institutes of Health (NIH) recently spent US$14 million on a Glucosamine Chondroitin Arthritis Intervention Trial (GAIT), a 24-week, placebo-controlled, parallel, double-blind, five-arm trial involving 1583 patients that aimed to answer the question as to the efficacy of glucosamine hydrochloride and chondroitin by comparing glucosamine alone, glucosamine plus chondroitin, chondroitin alone, placebo and the COX-2 inhibitor celecoxib (Clegg et al 2006, NIH 2002). The results of this study provide good evidence that glucosamine and chondroitin are more effective when given in combination than when either substance is given alone and that combined treatment with glucosamine and chondroitin is more effective than celecoxib for treating moderate to severe, but not mild, arthritis. The design of the GAIT trial can be criticised, however, for the fact that it included a large number of people with very mild disease who were more likely to be susceptible to placebo (as evidenced by the very high (60%) placebo response). Furthermore, the criteria for effectiveness as the primary outcome measure was set very high (20% reduction in WOMAC pain score) and that when the internationally accepted OMERACT-OARSI response criteria for judging clinical trials of OA was used, the combined treatment was significantly better than placebo for patients with either mild or moderate to severe disease (Clegg et al 2006).

Although glucosamine has not been shown to have direct analgesic activity, certain combinations with non-opioid analgesics have demonstrated synergistic (e.g. ibuprofen and ketoprofen), additive (e.g. diclofenac, indomethacin, naproxen and piroxicam), or subadditive (e.g. aspirin and acetaminophen) antinociceptive interactions in the mouse abdominal irritant test, suggesting that combinations of certain ratios of glucosamine and specific NSAIDs might enhance pain relief or provide adequate pain relief with lower doses of NSAIDs (Tallarida et al 2003).

In a 12-week, randomised, placebo-controlled trial of glucosamine and methylsulfonylmethane involving 118 patients, combined therapy was found to

produce a greater and more rapid reduction in pain, swelling and loss of function than either agent alone (Usha & Naidu 2004).

In an in-vivo study of arthritic rats the combination of glucosamine and essence of chicken was more effective in reducing the histopathological severity of arthritis than glucosamine alone (Tsi et al 2003).

A topical preparation containing glucosamine with chondroitin and camphor has been shown to reduce pain from OA of the knee in one RCT (Cohen et al 2003).

Comparisons with NSAIDs There are many studies suggesting that glucosamine is at least as effective as NSAIDs (e.g. 1200 mg ibuprofen) in treating the symptoms of OA (Muller-Fassbender et al 1994, Reichelt et al 1994, Rovati 1992, Ruane & Griffiths 2002), although glucosamine has a slower onset of action, taking 2–3 weeks to establish an effect. The recent GAIT trial (see earlier) found that the combination of glucosamine and chondroitin was more effective than celecoxib in treating moderate to severe OA, whereas glucosamine alone was not (Clegg et al 2006).

OTHER USES

INFLAMMATORY BOWEL DISEASE

It is suggested that glucosamine has an anti-inflammatory action that may include an increased production of heparan sulfate proteoglycans by the vascular endothelium, thereby improving the endothelium's barrier function (McCarty 1998b). It is further suggested that the step in glycoprotein synthesis involving the amino sugar is relatively deficient in patients with inflammatory bowel disease and this could reduce the synthesis of the glycoprotein cover that protects the mucosa from damage by bowel contents (Burton & Anderson 1983, Winslet et al 1994). In a pilot study, N-acetyl glucosamine proved beneficial in children with chronic inflammatory bowel disease (Salvatore et al 2000).

DOSAGE RANGE

- 1500 mg glucosamine/day (500 mg three times daily).
- A 2–3 month trial is generally used to determine whether it is effective for an individual patient.
- Intramuscular glucosamine sulfate: 400 or 800 mg three times/week (Reichelt et al 1994) for 4–6 weeks or longer if required.
- Glucosamine sulfate, hydrochloride, hydroiodide and N-acetyl forms are available. Most research has been done on the sulfate forms and it is unclear as to the difference between these formulations. Topical, intravenous, intramuscular and intra-articular forms are also available in some countries.

ADVERSE REACTIONS

Glucosamine has been used safely in multiple clinical trials lasting from 4 weeks to 3 years with minimal or no adverse effects (Pavelka et al 2002, Pujalte et al 1980, Lopes Vaz 1982, Reginster et al 2001) and a recent Cochrane systematic review suggests that glucosamine is as safe as placebo (Towheed et al 2006). Short-term adverse effects may include mild gastrointestinal problems, drowsiness, skin reactions and headache (Barclay et al 1998). A critical review of clinical trial data for 3063 human subjects suggests that glucosamine does not affect glucose metabolism, that there are no adverse effects of oral glucosamine administration on blood, urine or faecal parameters and that side-effects were significantly less common with glucosamine than with placebo or NSAIDs (Anderson et al 2005).

In a placebo-controlled, double-blinded, randomised clinical trial of 39 patients, glucosamine supplementation was found to have no clinically significant effect on glycaemic control in patients with type 2 diabetes over 12 weeks, and another 12-week randomised double-blind study found that glucosamine sulfate supplementation did not cause glucose intolerance, with no alterations in serum insulin or plasma glucose levels in 19 healthy subjects (Tannis et al 2004).

There is one case report of asthma being exacerbated by glucosamine–chondroitin supplementation (Tallia & Cardone 2002).

SIGNIFICANT INTERACTIONS

Controlled studies are not available. Therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Glucosamine may theoretically enhance the anti-inflammatory activity of NSAIDs — drug dosage may require modification after several weeks' glucosamine use as this is potentially a beneficial combination.

CONTRAINDICATIONS AND PRECAUTIONS

Although there is a theoretical link between glucosamine and insulin resistance, this has not been clearly demonstrated in human trials. Nevertheless, diabetics using glucosamine should have their blood sugar levels checked regularly.

Glucosamine is made from shellfish and, although it is not extracted from the protein component, it should be used with caution in patients with shellfish allergy.

PREGNANCY USE

Insufficient reliable information is available to advise on safety in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Glucosamine is a naturally occurring building block of joint tissue and cartilage.
- Glucosamine is considered effective in treating the pain and disability of OA and it may act to slow the progression of the disease, although several weeks are required before a clinical effect is evident.
- It is considered extremely safe and may reduce the need for NSAIDs (which can have serious side-effects).
- Although chondroitin is sometimes used in conjunction with glucosamine, there is no conclusive evidence that the combination has greater benefit than either substance alone.
- People with severe shellfish allergy should be advised to use a form that is not derived from shellfish.
- Patients with diabetes should monitor their blood glucose levels while taking glucosamine.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Multiple scientific studies have shown that glucosamine sulfate reduces symptoms of OA and may also reduce further progression of the condition. Some people find that they do not require NSAIDs as often when taking it.

When will it start to work?

Symptom relief generally takes 2–3 weeks to establish, but joint protection effects occur only with long-term use of several years.

Are there any safety issues?

Although considered very safe for the general population, it should be used with caution in people with severe shellfish allergies, and diabetics are advised to monitor their blood glucose levels during use.

REFERENCES

Aghazadeh-Habashi A et al. Single dose pharmacokinetics and bioavailability of glucosamine in the rat. J Pharmacy Pharm Sci 5(2) (2002): 181-4.

Anderson JW et al. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. Food Chem Toxicol 43(2) (2005): 187-201.

Bagasra O et al. Anti-human immunodeficiency virus type 1 activity of sulfated monosaccharides: comparison with sulfated polysaccharides and other polyions. J Infect Dis 164(6) (1991): 1082-90.

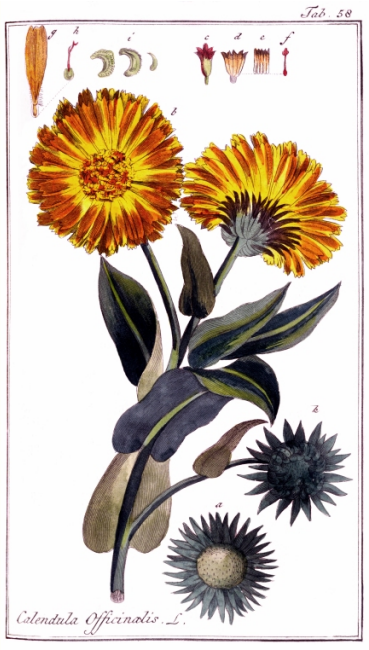
Balkan B, Dunning BE. Glucosamine inhibits glucokinase in vitro and produces a glucose-specific impairment of in vivo insulin secretion in rats. Diabetes 43(10) (1994): 1173-9.

Barclay TS et al. Glucosamine [Comment]. Ann Pharmacother 32(5) (1998): 574-9.

Basak M et al. Comparative bioavailability of a novel timed release and powder-filled glucosamine sulfate formulation: A multi-dose, randomized, crossover study. Int J Clin Pharmacol Ther 42(11) (2004): 597-601.

Bassleer C et al. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. Osteoarthritis Cartilage 6(6) (1998): 427-34.
Bruyere O et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression: Results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. Osteoarthritis Cartilage 11(1) (2003): 1-5.
Bruyere O et al. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: Evidence from two 3-year studies. Menopause (2004) 11(2) : 138-43.
Burton AF, Anderson FH. Decreased incorporation of 14C-glucosamine relative to 3H-N-acetyl glucosamine in the intestinal mucosa of patients with inflammatory bowel disease. Am J Gastroenterol 78(1) (1983): 19-22.
Chou MM et al. Effects of chondroitin and glucosamine sulfate in a dietary bar formulation on inflammation, interleukin-1-beta, matrix metalloprotease-9, and cartilage damage in arthritis. Exp Biol Med 230(4) (2005): 255-62.
Cibere J et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Rheum 51(5) (2004): 738-45.
Cibere J et al. Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers. J Rheumatol 32(5) (2005): 896-902.
Clegg DO et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 354(8) (2006): 795-808.
Cohen M et al. A randomized double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol 30 (2003): 523-8.
Consumer-labs 2; Product Review: Glucosamine and chondroitin.
Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: a controlled clinical investigation. Curr Med Res Opin 7(2) (1980): 104-9.
D'Ambrosio E et al. Glucosamine sulphate: a controlled clinical investigation in arthrosis. Pharmaco Therapeutica 2(8) (1981): 504-8.
Das A Jr, Hammad TA. Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis Cartilage 8(5) (2000): 343-50.
de Mattei M et al. High doses of glucosamine-HCl have detrimental effects on bovine articular cartilage explants cultured in vitro. Osteoarthritis Cartilage 10(10) (2002): 816-25.
Dechant JE et al. Effects of glucosamine hydrochloride and chondroitin sulphate, alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explant metabolism. Equine Vet J 37(3) (2005): 227-31.
Drovanti A, Bignamini AA, Rovati AL. Therapeutic activity of oral glucosamine sulfate in osteoarthrosis: a placebo-controlled double-blind investigation. Clin Ther 3(4) (1980): 260-72.
Echard BW et al. Effects of oral glucosamine and chondroitin sulfate alone and in combination on the metabolism of SHR and SD rats. Mol Cell Biochem 225 (2001): 85-91.
Giaccari A et al. In vivo effects of glucosamine on insulin secretion and insulin sensitivity in the rat: possible relevance to the maladaptive responses to chronic hyperglycaemia. Diabetologia 38(5) (1995): 518-24.
Giacovelli G, Rovati LC. Clinical efficacy of glucosamine sulfate in osteoarthritis of the spine. Rev Esp Rheumatol 20(Suppl 1) (1993): 325.
Gouze JN et al. Interleukin-1beta down-regulates the expression of glucuronosyltransferase I, a key enzyme priming glycosaminoglycan biosynthesis: influence of glucosamine on interleukin-1beta-mediated effects in rat chondrocytes. Arthritis Rheum 44(2) (2001): 351-60.
Hua J et al. Inhibitory actions of glucosamine, a therapeutic agent for osteoarthritis, on the functions of neutrophils. J Leukocyte Biol 71(4) (2002): 632-40.
Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. Rheumatology 41(3) (2002): 279-84.

Kelly GS. The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. Altern Med Rev 3(1) (1998): 27-39.
Laverty S et al. Synovial fluid levels and serum pharmacokinetics in a large animal model following treatment with oral glucosamine at clinically relevant doses. Arthritis Rheum 52(1) (2005): 181-91.
Leffler CT et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. Military Med 164(2) (1999): 85-91.
Lippiello L et al. In vivo chondroprotection and metabolic synergy of glucosamine and chondroitin sulfate. Clin Orthopaed Rel Res (381) (2000): 229-40.
Lopes Vaz A. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthrosis of the knee in out-patients. Curr Med Res Opinion 8(3) (1982): 145-9.
Ma L et al. Immunosuppressive effects of glucosamine. J Biol Chem 277(42) (2002): 39343-9.
McAlindon T. Glucosamine and chondroitin for osteoarthritis? Bull Rheum Dis 50(7) (2001): 1-4.
McAlindon TE et al. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis [Comment]. JAMA 283(11) (2000): 1469-75.
McAlindon T et al. Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial. Am J Med 117(9) (2004): 643-9.
McCarty MF. Enhanced synovial production of hyaluronic acid may explain rapid clinical response to high-dose glucosamine in osteoarthritis. Med Hypotheses 50(6) (1998a): 507-10.
McCarty MF. Vascular heparan sulfates may limit the ability of leukocytes to penetrate the endothelial barrier: implications for use of glucosamine in inflammatory disorders. Med Hypotheses 51(1) (1998b): 11-15.
McCarty MF et al. Sulfated glycosaminoglycans and glucosamine may synergize in promoting synovial hyaluronic acid synthesis. Med Hypotheses 54(5) (2000): 798-802.
Mello DM et al. Comparison of inhibitory effects of glucosamine and mannosamine on bovine articular cartilage degradation in vitro. Am J Vet Res 65(10) (2004): 1440-5.
Monauni T et al. Effects of glucosamine infusion on insulin secretion and insulin action in humans. Diabetes 49(6) (2000): 926-35.
Mroz PJ, Silbert JE. Use of 3H-glucosamine and 35S-sulfate with cultured human chondrocytes to determine the effect of glucosamine concentration on formation of chondroitin sulfate. Arthritis Rheum 50(11) (2004): 3574-9.
Muller-Fassbender H et al. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. Osteoarth Cartil 2(1) (1994): 61-9.
Nakamura H et al. Effects of glucosamine hydrochloride on the production of prostaglandin E2, nitric oxide and metalloproteases by chondrocytes and synoviocytes in osteoarthritis. Clin Exp Rheumatol 22(3) (2004): 293-9.
National Institutes of Health NIH; National Centre for Complementary and Alternative Medicine GAIT Study, 2002. Available at: www.nih.com.
Nguyen P et al. A randomized double-blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorders: a pilot study. Cranio 19(2) (2001): 130-9.
Pavelka K et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 162(18) (2002): 2113-23.
Persiani S et al. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. Osteoarthritis Cartilage 13(12) (2005): 1041-9.
Piperno M et al. Glucosamine sulfate modulates dysregulated activities of human osteoarthritic chondrocytes in vitro. Osteoarth Cartil 8(3) (2000): 207-12.
Poolsup N et al. Glucosamine long-term treatment and the progression of knee osteoarthritis: Systematic review of randomized controlled trials. Ann Pharmacother 39(6) (2005): 1080-7.
Pujalte JM et al. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthrosis. Curr Med Res Opinion 7(2) (1980): 110-14.



Qiu GX et al. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Arzneimittelforschung 48(5) (1998): 469-74.
Qiu GX et al. A multi-central, randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis. Zhonghua Yi Xue Za Zhi 85(43) (2005): 3067-70.
Rai J et al. Efficacy of chondroitin sulfate and glucosamine sulfate in the progression of symptomatic knee osteoarthritis: A randomized, placebo-controlled, double blind study. Bull Postgrad Inst Med Ed Res Chandigarh 38(1) (2004): 18-22.
Reginster JY et al. Evidence of nutriceutical effectiveness in the treatment of osteoarthritis. Curr Rheumatol Reports 2(6) (2000): 472-7.
Reginster JY et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial [Comment]. Lancet 357(9252) (2001): 251-6.
Reginster JY et al. Glucosamine sulphate in osteoarthritis: From symptoms to structure modification. Curr Med Chem Anti-Inflamm Anti-Allergy Agents 4(3) (2005) : 217-20.
Reichelt A et al. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee: A randomised, placebo-controlled, double-blind study. Arzneimittelforschung 44(1) (1994): 75-80.
Richy F et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: A comprehensive meta-analysis. Arch Intern Med 163(13) (2003): 1514-22.
Rovati LC. Clinical research in osteoarthritis: design and results of short-term and long-term trials with disease-modifying drugs. Int J Tissue Reactions 14(5) (1992): 243-51.
Ruane R, Griffiths P. Glucosamine therapy compared to ibuprofen for joint pain. Br J Community Nurs 7(3) (2002): 148-52.
Salvatore S et al. A pilot study of N-acetyl glucosamine, a nutritional substrate for glycosaminoglycan synthesis, in paediatric chronic inflammatory bowel disease. Aliment Pharmacol Ther 14(12) (2000): 1567-79.
Setnikar IP, Canali S. Pharmacokinetics of glucosamine in man. Arzneimittelforschung 43(10) (1993): 1109-13.
Shankar RR et al. Glucosamine infusion in rats mimics the beta-cell dysfunction of non-insulin-dependent diabetes mellitus. Metabolism Clin Exp 47(5) (1998): 573-7.
Shankland WE 2nd. The effects of glucosamine and chondroitin sulfate on osteoarthritis of the TMJ: a preliminary report of 50 patients. Cranio 16(4) (1998): 230-5.
Shikhman AR et al. N-acetylglucosamine prevents IL-1 beta-mediated activation of human chondrocytes. J Immunol 166(8) (2001): 5155-60.
Tallarida RJ et al. Antinociceptive synergy, additivity, and subadditivity with combinations of oral glucosamine plus nonopioid analgesics in mice. J Pharmacol Exp Ther 307(2) (2003): 699-704.
Tallia AF, Cardone DA. Asthma exacerbation associated with glucosamine-chondroitin supplement. J Am Board Fam Pract 15(6) (2002): 481-4.
Tamai Y et al. Enhanced healing of cartilaginous injuries by N-acetyl-glucosamine and glucuronic acid. Carbohydrate Polymers 54(2) (2003): 251-62.
Tannis AJ et al. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. Osteoarth Cartil 2(6) (2004): 506-11.
Tiraloche G et al. Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. Arthritis Rheum 52(4) (2005): 1118-28.
Towheed TE et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev, 2006: 2.
Towheed TE et al. Glucosamine therapy for treating osteoarthritis Cochrane Database Syst Rev, 2003: 1.
Tsi D et al. Effect of Brand's glucosamine with essence of chicken on collagen-induced arthritis in rats. Life Sci 73(23) (2003): 2953-62.
Usha PR, Naidu MUR. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. Clin Drug Invest 24(6) (2004): 353-63.
Winslet MC et al. Mucosal glucosamine synthetase activity in inflammatory bowel disease. Dig Dis Sci 39(3) (1994): 540-4.

Zhang GX et al. Glucosamine abrogates the acute phase of experimental autoimmune encephalomyelitis by induction of th2 response. J Immunol 175(11) (2005): 7202-8.

L-Glutamine

Historical note Glutamine and glutamate were originally described in the mid 19th century and their functions began to be examined in the early 20th century. The role of glutamine in the immune system and gastrointestinal tract has been investigated since the 1980s.

BACKGROUND AND RELEVANT PHARMACOKINETICS

L-glutamine (L-Gln) is a conditionally essential amino acid found in all life forms and the most abundant amino acid in the human body. During conditions of metabolic stress characterised by catabolism and negative nitrogen balance such as trauma (including surgical trauma), prolonged stress, glucocorticoid use, excessive exercise, starvation, infection, sepsis, cancer and severe burns the body is unable to synthesis L-Gln in sufficient quantities to meet biological needs and it becomes essential to have an exogenous intake (Miller 1999, PDRHealth 2006a).

L-glutamine is absorbed from the lumen of the small intestine by active transport (Meng et al 2003) and is then transported to the liver via the portal circulation and enters systemic circulation where it is distributed to various tissues and transported into cells via an active process. Elimination occurs via glomerular filtration and it is almost completely reabsorbed by the renal tubules. Some metabolism of L-Gln takes place in the enterocytes and hepatocytes and it is involved in various metabolic activities, including the synthesis of L-glutamate (catalysed by glutaminase), proteins, glutathione, pyrimidine and purine nucleotides and amino sugars. L-glutamate is converted to L-glutamine by glutamine synthase in the presence of ammonia, ATP and magnesium or manganese.

L-glutamine is predominantly synthesised and stored in skeletal muscles where it comprises around 60% of the free amino acids and makes up 4–5% of muscle protein. In times of metabolic stress, glutamine is released into circulation and transported to tissues in need (Kohlmeier 2003, Miller 1999, PDRHealth 2006a).

Unfortunately L-Gln is not very soluble or stable in solution, especially upon heating for sterilisation, and as a result, until recently, was not included in TPN. The more soluble and stable glutamine dipeptides are now commonly used as the delivery forms in TPN solutions and some nutritional supplements (Kohlmeier 2003, PDRHealth 2000b).

COMMON FORMS AVAILABLE

The terms L-glutamine and glutamine are often used interchangeably. L-glutamine is the amide form of L-glutamic acid and contains 15.7% nitrogen (Kohlmeier 2003). It is also known as 2-aminoglutaramic acid, levoglutamide, (S)-2,5-diamino-5-oxopentaenoic acid and glutamic acid 5-amide.

Two synthetic glutamine dipeptides that may be used in TPN are L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln). D-glutamine, the stereoisomer of L-glutamine, has no known biological activity (Kohlmeier 2003, PDRHealth 2006b).

Since the late 1960s L-Gln has been manufactured for pharmaceutical use using a fermentation broth. The manufacture of high-quality, low-cost L-Gln requires a strain of microorganism with good production efficiency and minimum by-products. Impurities can then be removed from the broth using a nanofiltration membrane to obtain a fine crystalline powder (Kusumoto 2001, Li et al 2003).

FOOD SOURCES

Typical dietary intake of L-Gln is 5–10 g/day (Miller 1999). Sources include animal and plant proteins, vegetable juices (especially cabbage), eggs, wheat, soybeans and fermented foods, such as miso and yoghurt (Kohlmeier 2003, PDRHealth 2006a).

DEFICIENCY SIGNS AND SYMPTOMS

Although traditionally considered a nonessential amino acid, L-Gln is now considered 'conditionally essential' during periods of metabolic stress characterised by catabolism and negative nitrogen balance. Critical illness, stress, and injury can lead to a significant decrease in plasma levels of L-Gln, which if severe can increase the risk of mortality (Boelens et al 2001, Wischmeyer 2003).

Prolonged protein malnutrition may cause growth inhibition, muscle wasting and organ damage (Kohlmeier 2003). In the absence of sufficient plasma glutamine the body will break down skeletal muscle stores, and gut integrity (gut mucosal barrier function) and immunity will be compromised. Because L-Gln is utilised during exercise a more recent phenomenon of deficiency has been explored and glutamine depletion has been linked with 'overtraining syndrome'.

MAIN ACTIONS

L-glutamine has many important biological functions within the human body. It is an important fuel for the intestinal mucosal cells, hepatocytes and rapidly proliferating cells of the immune system, assists in the regulation of acid balance thus preventing acidosis, acts as a nitrogen shuttle protecting the body from high levels of ammonia, and is involved in the synthesis of amino acids (including L-glutamate), GABA, glutathione (an important antioxidant), purine and pyramidine

nucleotides, amino acid sugars in glycoproteins and glycans, and nicotinamide adenine dinucleotide (NAD). It is also involved in protein synthesis and energy production (Boelens et al 2001, Kohlmeier 2003, Miller 1999, Niihara et al 2005, Patel et al 2001, PDRHealth 2006a).

GASTROINTESTINAL PROTECTION/REPAIR

According to in vitro and in vivo research, L-Gln aids in the proliferation and repair of intestinal cells (Chun et al 1997, Rhoads et al 1997, Scheppach et al 1996) and is the preferred respiratory fuel for enterocytes (and also utilised by colonocytes) (Miller 1999). It is thus vital for maintaining the integrity of the intestinal lining and preventing the translocation of microbes and endotoxins into the body. In addition, L-Gln helps to maintain secretory IgA, which functions primarily by preventing the attachment of bacteria to mucosal cells (PDRHealth 2006a, Yu et al 1996).

According to evidence from animal studies it may also assist in preventing atrophy following colostomy (Paulo 2002) and irradiation (Diestel et al 2005), and intestinal injury by inhibiting intestinal cytokine release (Akisu et al 2003). L-glutamine depletion induces apoptosis by triggering intercellular events that lead to cell death (Paquette et al 2005), resulting in altered epithelial barrier competence (increased intestinal permeability), bacterial translocation, and increased mortality. Under experimental conditions, L-Gln may assist in maintaining intestinal barrier function by increasing epithelial resistance to apoptotic injury, reducing oxidative damage, attenuating programmed cell death and promoting re-epithelialisation (Masuko 2002, Ropeleski et al 2005, Scheppach et al 1996) and may thus reduce bacterial and endotoxin translocation (Chun et al 1997).

IMMUNOMODULATION

L-glutamine has demonstrated immunomodulatory activity in animal models of infection and trauma, as well as trauma in humans. L-glutamine acts as the preferred respiratory fuel for lymphocytes, is essential for cell proliferation, and can enhance the function of stimulated immune cells.

Extracellular glutamine concentration affects lymphocyte, IL-2 and IFN-gamma proliferation, cytokine production, phagocytic and secretory macrophage activities and neutrophil bacterial killing (Miller 1999, Newsholme 2001, PDRHealth 2006a). In humans, L-Gln may enhance both phagocytosis and reactive oxygen intermediate production by neutrophils (Furukawa et al 2000) and support the restoration of type-1 T-lymphocyte responsiveness following trauma (Boelens et al 2004). In a randomised trial there was a reduced frequency of pneumonia, sepsis and bacteraemia in

patients with multiple trauma who received glutamine-supplemented enteral nutrition (Houdijk et al 1998).

In addition, effects on the gastrointestinal tract may contribute significantly to immune defence by maintaining gut-associated lymphoid tissue and secretory IgA (preventing the attachment of bacteria to the gut mucosa) and maintaining gut integrity (thus preventing the translocation of microbes and their toxins, especially Gram-negative bacteria from the large intestine) (Miller 1999, Yu et al 1996).

ANTIOXIDANT

As a precursor to glutathione (together with cysteine and glycine), L-Gln can assist in ameliorating the oxidation that occurs during metabolic stress. Glutathione protects epithelial cell membranes from damage, and its depletion can negatively affect gut barrier function and result in severe degeneration of colonic and jejunal epithelial cells (Iantomasi 1994, Ziegler et al 1999). In animal studies it has also been shown to inhibit fatty acid oxidation, resulting in a reduction in body weight and alleviation of hyperglycaemia and hyperinsulinaemia in mice fed a high-fat diet (Opara et al 1996).

ANABOLIC/ANTICATABOLIC

As L-Gln is stored primarily in skeletal muscles and becomes conditionally essential under conditions of metabolic stress, the anticatabolic/anabolic properties of supplemented L-Gln are likely due to a sparing effect on skeletal muscle stores.

Following strenuous exercise, glutamine levels are depleted by approximately 20%, resulting in immunodepression (Castell 2003, Castell & Newsholme 1997, Rogero et al 2002). As a result supplemental L-Gln may be of benefit in athletes to prevent the deleterious effects of glutamine depletion associated with 'over-training syndrome'. Evidence supporting a direct ergogenic effect is currently lacking.

CARDIOPROTECTIVE

In vitro, L-Gln has been shown to assist in the maintenance of myocardial glutamate, ATP and phosphocreatine, and prevention of lactate accumulation (Khogali et al 1998). In addition to its antioxidant properties and effects on hyperglycaemia and hyperinsulinaemia (Opara et al 1996), this may suggest a possible role as a cardioprotective agent.

CLINICAL USE

DEFICIENCY: PREVENTION AND TREATMENT

During periods of increased need, L-Gln is considered conditionally essential. Glutamine depletion can result in increased intestinal permeability, microbial translocation across the gut barrier, impaired wound healing, sepsis and multiple organ

failure (Miller 1999). Experimental studies have proposed a number of benefits for patients with conditions that increase glutamine requirements. The suggested mechanisms include effects on pro-inflammatory cytokine expression, gut integrity, enhanced ability to mount a stress response and improved immune cell function, and studies have shown potential benefit with regard to mortality, length of hospital stay, and infection.

To date the results of studies using glutamine dipeptides in TPN have proven to be very promising in treating patients for whom enteral feeding is impossible. Benefits from studies of enteral glutamine supplementation have tended to be less pronounced but preliminary trials have demonstrated benefits in some conditions, especially at high doses (e.g. 30 g/day enterally) (Wischmeyer 2003).

SURGERY

In a double-blind RCT 37 patients received a TPN solution with or without synthetic alanyl-glutamine dipeptide (0.5 g/kg) for 5 days following major abdominal surgery. The results indicated improved nitrogen economy and a reduction in the length of hospital stay with a resulting reduction in costs (Mertes et al 2000). Reduced oral pain and inflammation has been observed in patients receiving radiation and chemotherapy during bone marrow transplantation who are taking 1 g glutamine four times daily (Miller 1999).

TRAUMA

In a randomised trial using glutamine-enriched enteral nutrition in patients with multiple trauma there was a reduction in the incidence of pneumonia, sepsis, and bacteraemia (Houdijk et al 1998).

BURNS

According to animal studies, oral glutamine supplementation may reduce bacterial and endotoxin translocation after burns by maintaining secretory IgA in the intestinal mucosa (Yu et al 1996).

INFANTS

Very-low-birth-weight infants may be susceptible to glutamine depletion due to limited nutrition in the first weeks of life. In a double-blind randomised, placebo-controlled trial of 102 VLBW infants (gestational age <32 weeks or birth weight <1500 g) receiving enteral glutamine supplementation (0.3 g/kg/day) added to breast milk or to preterm formula between days 3 and 30 of life, glutamine supplementation resulted in a significantly lower rate of infectious morbidity (Berg et al 2005).

Experimental data has suggested that by stimulating the rate of recovery of the villi and lipid synthesising enzymes, L-Gln treatments could improve the efficacy of enteral feeding in infants recovering from bowel damage (Ahdieh et al 1998), although this was not confirmed in that study.

STRENUOUS EXERCISE

Following strenuous exercise glutamine levels are depleted approximately 20% resulting in immunodepression (Castell 2003, Castell & Newsholme 1997, Rogero et al 2002). The provision of glutamine after exercise has been shown to improve immune status (Castell & Newsholme 1997). In a study of 200 elite runners and rowers given a glutamine or placebo drink immediately after and again 2 hours after strenuous exercise, 151 participants returned questionnaires reporting the incidence of infection over the subsequent 7 days. The percentage of athletes reporting no infections was considerably higher in the glutamine group (81%, $n = 72$) compared to the placebo group (49%, $n = 79$, $P < 0.001$) (Castell et al 1996).

A trial assessing the possible ergogenic effects of glutamine supplementation (0.03 g/kg) to improve high-intensity exercise performance in trained males was unable to determine a beneficial effect (Haub et al 1998).

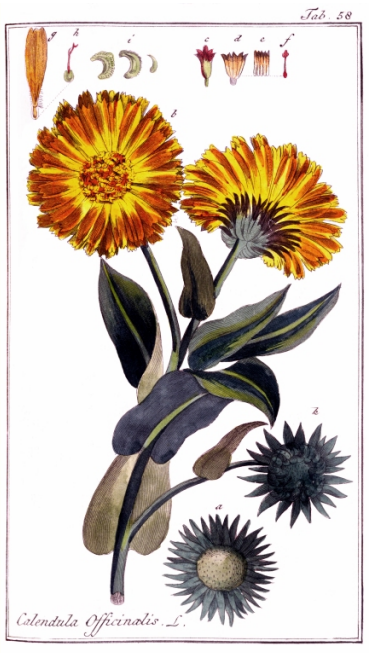
Clinical note — Total parenteral nutrition

L-glutamine is not very soluble or stable in solution, especially upon heating for sterilisation. As a result, until recently it was not included in TPN, resulting in compromised glutamine status in patients for whom reduced immune status and increased intestinal permeability could potentially increase the risk of morbid infection and mortality. The more soluble and stable synthetic glutamine dipeptides (L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln)) have now been developed as delivery forms of L-Gln for use in TPN. The dipeptide forms can also be used orally and have demonstrated a potential for greater bioavailability than glutamine alone (Macedo Rogero et al 2004).

Numerous studies have now been conducted using glutamine dipeptides in TPN and have shown benefit in preventing deterioration of gut permeability and preserving mucosal structure (Hall et al 1996, Jiang et al 1999, PDRHealth 2006a, van der Hulst et al 1993). In addition, animal studies suggest that glutamine-enriched TPN may attenuate the suppression of CYP3A and CYP2C usually associated with TPN (Shaw et al 2002).

In a meta-analysis of European and Asian RCTs in elective surgery patients, 13 studies (pooled $n = 355$) met inclusion criteria and demonstrated a significant

reduction in infectious complication and length of hospital stay (weighted mean difference of 3.86 days) (Jiang et al 2004).



GUT REPAIR

Preliminary research on enteral (as well as parenteral) glutamine supplementation suggests promise for the use of glutamine in gut repair by: (i) protecting the intestinal mucosa from damage and promoting repair, thus improving intestinal permeability and reducing subsequent microbial and endotoxin translocation, promoting glutathione and S-IgA, and (ii) improving gut immunity. However, while there is considerable evidence for the use of glutamine in TPN (Hall et al 1996), clinical evidence using oral supplementation is less convincing. As in vitro data suggests that the colonic mucosa receives its nutrients preferentially from the luminal (not vascular) side (Roediger 1986) it has been suggested that glutamine may be more effective when delivered by the enteral route (Kouznetsova et al 1999). This has yet to be determined in clinical trials.

In a 1998 randomised, double-blind, placebo-controlled, 4-week trial of 24 HIV patients with abnormal intestinal permeability using 0, 4 or 8 g/day of glutamine, the authors reported a dose-dependent trend towards improved intestinal permeability and enhanced intestinal absorption with glutamine supplementation and recommended further studies to be carried out with higher doses (e.g. 20 g/day) over a longer study period (Noyer et al 1998). It is difficult to extrapolate the findings of this study to the wider community for the purpose of gut repair as there are factors involved in HIV/AIDS that may increase the biological demand for glutamine.

L-glutamine enemas, twice daily for 7 days, have been shown to reduce mucosal damage and inflammation in experimental models of colitis in rats (Kaya et al 1999); however, preliminary trials in humans have not confirmed benefit. A 4-week study on 18 children with active Crohn's disease fed a glutamine-enriched polymeric diet (Akobeng et al 2000) and another 4-week study on 14 patients taking 7 g glutamine three times daily (Hond et al 1999a) showed similarly negative results. Longer term studies may provide more convincing results; however, it is possible that glutamine only stabilises gut barrier function under certain conditions and more research is required to elucidate these.

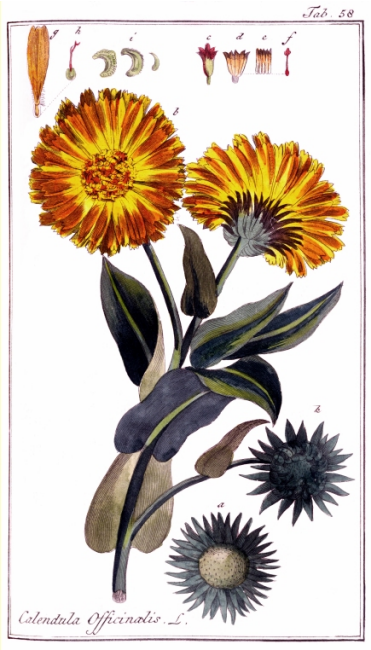
HIV

L-glutamine has been shown to improve glutathione levels and significantly increase lean body mass in HIV patients (Patrick 2000); however, not all studies confirm this latter effect (Huffman & Walgren 2003). Combined therapy with arginine and the

leucine metabolite beta-hydroxy-beta-methylbutyrate has been shown to reverse lean tissue loss in HIV and cancer patients (Rathmacher et al 2004).

During initial HIV infection, the rapid turnover and proliferation of immune cells increases glutamine requirements and later the repeated episodes of infection, fever and diarrhoea may lead to further depletion. As a result the doses used in the trial mentioned above (4 g and 8 g) may have been insufficient to meet the increased requirement in such patients (Noyer et al 1998).

Highly active antiretroviral therapy may be associated with diarrhoea and other gastrointestinal side-effects. In a prospective, randomised, double-blind, crossover study, HIV-infected patients with nelfinavir-associated diarrhoea (for >1 month) received L-Gln (30 g/day) or placebo for 10 days. Glutamine supplementation resulted in a significant reduction in the severity of nelfinavir-associated diarrhoea (Huffman & Walgren 2003). A prospective 12-week trial of 35 HIV-positive men experiencing diarrhoea as a result of nelfinavir or lopinavir/ritonavir therapy was also conducted using probiotics and soluble fibre. When glutamine (30 g/day) was added to the regimen of non-responders at week 4, the response rate improved (Heiser et al 2004).



CANCER PREVENTION

In addition to being the major fuel source for rapidly proliferating intestinal and immune cells, L-Gln is also the main fuel source for many rapidly growing tumours and as a result tumour growth is associated with a depletion in glutamine and glutathione stores and a depression of NK cell activity (Fahr et al 1994, Miller 1999). The increased intestinal permeability, immune suppression and oxidative damage that may result may further compromise the body's ability to deal with the tumour. While concerns exist, and are supported by in vitro evidence, that glutamine supplementation may feed the tumour, animal studies suggest that glutamine supplementation may assist in decreasing tumour growth by enhancing NK cell activity (Fahr et al 1994, Miller 1999). Animal studies have demonstrated that glutamine supplementation prevents the promotion of tumour cells in an implantable breast cancer model (Kaufmann et al 2003). The exact effects in different human tumour cell lines require further elucidation.

Clinical note — Cancer therapy

Side-effects of chemotherapy and radiation therapy can significantly affect the QOL of patients undergoing treatment for cancer. A number of trials have demonstrated the benefits of glutamine supplementation for improving side-effects such as oral pain and inflammation, increased gut permeability and reduced lymphocyte count.

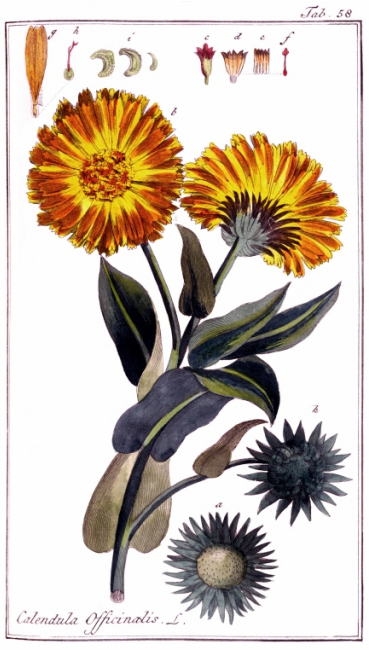
Reduced oral pain and inflammation has been observed in patients receiving radiation and chemotherapy during bone marrow transplantation taking 1 g glutamine four times daily (Miller 1999). In another study, L-Gln (4 g twice daily, swish and swallow) was given to 12 patients receiving doxorubicin, 1 receiving etoposide, and 1 receiving ifosfamide, etoposide, and carboplatinum from day 1 of chemotherapy for 28 days or for 4 days past the resolution of any post-chemotherapy mucositis. Oral supplementation with glutamine significantly decreased the severity of chemotherapy-induced stomatitis (Skubitz & Anderson 1996).

In one report, L-Gln (10 g three times daily), given 24 hours after receiving paclitaxel, appeared to prevent the development of myalgia and arthralgia associated with treatment (PDRHealth 2006a).

In a double-blind, placebo-controlled, randomised trial, oral glutamine (18 g/day) or placebo was given to 70 chemotherapy naive patients with colorectal cancer 5 days prior to their first cycle of 5-fluorouracil (5-FU) (450 mg/m^2) in association with folinic acid (FA) (100 mg/m^2), which was administered intravenously for 5 days. Glutamine treatment was continued for 15 days and was shown to reduce the negative effects on intestinal absorption and permeability induced by the chemotherapy and to potentially reduce diarrhoea (Daniele et al 2001). L-glutamine may also reverse the decrease in goblet cells induced by 5-FU (Tanaka & Takeuchi 2002).

Yoshida et al (1998, 2001) have also shown that 30 g/day L-Gln for 28 days attenuates the increased gut permeability and reduced lymphocyte count observed in patients undergoing cisplatin and 5-FU therapy for oesophageal cancer.

Glutamine may also increase tumour methotrexate concentration and tumoricidal activity and reduce side-effects and mortality rates (Miller 1999, PDRHealth 2006a).



OTHER USES

ALCOHOLISM

Preliminary studies suggested a potential for glutamine to reduce alcohol cravings; however, these effects have not yet been studied in controlled trials on humans (PDRHealth 2006a). More recently, in vitro research has suggested that glutamine supplementation may inhibit the deleterious effects of alcohol on the tight junctions of the gut mucosa and in turn reduce the increased risk for gastrointestinal cancers in alcoholics (Basuroy et al 2005, Seth et al 2004).

ACUTE PANCREATITIS

The enteral administration of L-Gln (15 mg/kg/day) to rats with acute pancreatitis resulted in a reduction in necrosis and infectious complications by decreasing the bacterial translocation rate (Avsar et al 2001).

SICKLE CELL DISEASE

Orally administered L-Gln improves the nicotinamide adenosine dinucleotide (NAD) redox potential of sickle red blood cells (RBC). Investigations of blood samples taken from five adult patients with sickle cell anaemia who had been on L-Gln (30 g/day) therapy for at least 4 weeks consistently resulted in improvement of sickle RBC adhesion to human umbilical vein endothelial cells compared to the control group. The authors conclude that these results suggest positive physiological effects for L-Gln in sickle cell disease (Niihara et al 2005).

OTHER CONDITIONS

Glutamine is a popular supplement in naturopathic practice and sometimes used for conditions that may be associated with compromised intestinal permeability such as food allergies, leaky gut syndrome and malabsorption syndromes, including diarrhoea. It may also be used for conditions such as dermatitis and general fatigue based on the theory that compromised intestinal permeability provides the opportunity for undigested food particles (especially proteins) to enter the systemic circulation and gives rise to an unwanted immune response that manifests as a skin reaction or lethargy.

DOSAGE RANGE

Naturally occurring food proteins contain 4–8% of their amino acid residues as glutamine and so the daily consumption is usually less than 10 g/day (Hall et al 1996).

Supplemental L-Gln is available for oral and enteral use (in capsules, tablets and powder form) and in a dipeptide form for parenteral use.

While solubility and stability are primarily factors for TPN solutions, several factors should also be considered when using oral supplements, as powder forms are often mixed into a solution to enable easy administration of higher doses: 1 g of L-Gln dissolves in 20.8 mL of water at 30°C (PDRHealth 2006a) and is stable for up to 22 days if stored at 4°C (Hornsby-Lewis et al 1994). Ideally, powdered formulas should be consumed immediately after mixing.

- Gut repair: 7–21 g taken orally as a single dose or in divided doses.
- Cancer therapy: 2–4 g twice daily swished in the mouth and swallowed (up to 30 g have been used in trials and given orally in divided doses).
- Critical illness: 5 g/500 mL of enteral feeding solution.

- HIV: 30 g/day taken orally as a single dose or in divided doses.
- Infection: 12–30.5 g in an enteral feeding solution.
- Infants: 0.3 g/kg/day added to breast milk or to preterm formula.

ADVERSE REACTIONS

Toxicity studies in rats fed up to 5% of their diet in LGln showed no toxic events (Tsubuku et al 2004) and glutamine dose–response studies have demonstrated 'good tolerance without untoward clinical or biochemical effects' (Ziegler et al 1999).

Most adverse reactions are mild and uncommon; they include gastrointestinal complaints such as constipation and bloating (PDRHealth 2006a). No evidence of harm has been observed in the studies conducted to date (Wischmeyer 2003).

A report exists of mania in two hypomanic patients after self-medication with up to 4 g/day glutamine (Membane 1984). As glutamine is a pre-cursor of GABA this may provide a possible explanation.

Two cases of a transient increase in liver enzyme levels have also been reported (Hornsby-Lewis et al 1994).

SIGNIFICANT INTERACTIONS

RADIATION AND CHEMOTHERAPY

Benefits have been observed for the use of L-Gln during radiation and chemotherapy (see 'Clinical note – Cancer therapy').

INDOMETHACIN/NSAIDS

Concomitant use of L-Gln (7 g three times daily) and indomethacin may ameliorate the increased intestinal permeability caused by indomethacin. The inclusion of misoprostol may also have a synergistic effect with this combination (Hond et al 1999b, PDRHealth 2006a, Tanaka & Takeuchi 2002) — beneficial interaction possible.

HUMAN GROWTH HORMONE

In patients with severe short bowel syndrome concomitant use of L-Gln and human growth hormone may enhance nutrient absorption (PDRHealth 2006a).

CONTRAINDICATIONS AND PRECAUTIONS

It is contraindicated in patients with hypersensitivity to glutamine or hepatic disease or any condition where there is a risk of accumulation of nitrogenous wastes in the blood, thus increasing the risk of ammonia-induced encephalopathy and coma.

It should only be used in people with chronic renal failure under professional supervision.

PREGNANCY USE

Safety in pregnancy has not been established; however, doses in line with normal dietary intake (approximately 10 g/day) are unlikely to be cause for concern.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

L-glutamine is an amino acid that is used by the immune systems and intestinal cells as a fuel source. People with critical illnesses, stress, burns, injury or having undergone surgery or undertaking strenuous physical exercise require an increased intake to restore glutamine levels to normal and avoid loss of muscle mass and compromised immune function. It also promotes gastrointestinal repair and may improve tolerance to some anticancer treatments.

When will it start to work?

This will depend on the indication for which it is being used.

Are there any safety issues?

Glutamine appears to be a safe supplement; however, it should not be used by people who are hypersensitive to this compound, those with liver disease or any condition where there is a risk of accumulation of nitrogenous wastes in the blood (e.g. Reyes syndrome).

It should only be used by people with chronic renal failure under professional supervision.

REFERENCES

Ahdieh N et al. 1998. L-glutamine and transforming growth factor-alpha enhance recovery of monoacylglycerol acyltransferase and diacylglycerol acyltransferase activity in porcine postischemic ileum. Pediatr Res 43(2) (X): 227-33.

Akisu M et al. The role of dietary supplementation with L-glutamine in inflammatory mediator release and intestinal injury in hypoxia/reoxygenation-induced experimental necrotizing enterocolitis. Ann Nutr Metab 47(6) (2003): 262-6.

Akobeng A et al. Double-blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of active Crohn's disease. J Pediatr Gastroenterol Nutr 30(1) (2000): 78-84.

Avsar F et al. Effects of oral L-glutamine, insulin and laxative on bacterial translocation in acute pancreatitis. Turk J Med Sci 31(4) (2001): 297-301.

Basuroy S et al. Acetaldehyde disrupts tight junctions and adherens junctions in human colonic mucosa: protection by EGF and L-glutamine. Am J Physiol Gastrointest Liver Physiol 289(2) (2005): G367-75.

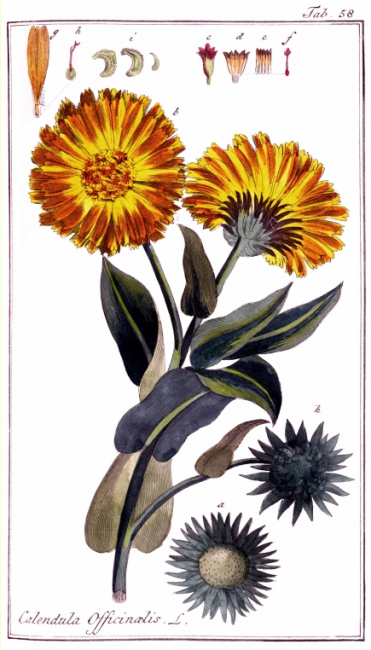
Berg AVD et al. Glutamine-enriched enteral nutrition in very-low-birth-weight infants and effects on feeding tolerance and infectious morbidity: a randomized controlled trial. Am J Clin Nutr 81 (2005): 1397-404.

Boelens PG et al. Glutamine alimentation in catabolic state. J Nutr 131(9 Suppl) (2001): 2569-77S; discussion 2590S.

Boelens PG et al. Glutamine-enriched enteral nutrition increases in vitro interferon-gamma production but does not influence the in vivo specific antibody response to KLH after severe trauma: A prospective, double blind, randomized clinical study. Clin Nutr 23(3) (2004): 391-400.

Castell L. Glutamine supplementation in vitro and in vivo, in exercise and in immunodepression. Sports Med 33(5) (2003): 323-45.

Castell LM, Newsholme EA. The effects of oral glutamine supplementation on athletes after prolonged, exhaustive exercise. Nutrition 13(7-8) (1997): 738-42.
Castell LM et al. Does glutamine have a role in reducing infections in athletes? Eur J Appl Physiol Occup Physiol 73(5) (1996): 488-90.
Chun H et al. Effect of enteral glutamine on intestinal permeability and bacterial translocation after abdominal radiation injury in rats. J Gastroenterol 32 (1997): 189-95.
Daniele B et al. Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomised trial. Gut 48(1) (2001): 28-33.
Diestel CF et al. [Effect of oral supplement of L-glutamine in colonic wall of rats subjected to abdominal irradiation.] Acta Cir Bras 20 (Suppl 1) (2005): 94-100.
Fahr MJ et al. Harry M. Vars Research Award. Glutamine enhances immunoregulation of tumor growth. J Parenter Enteral Nutr 18(6) (1994): 471-6.
Furukawa S et al. Supplemental glutamine augments phagocytosis and reactive oxygen intermediate production by neutrophils and monocytes from postoperative patients in vitro. Nutrition 16(5) (2000): 323-9.
Hall J et al. Glutamine. Br J Surg 83 (1996): 305-12.
Haub MD et al. Acute L-glutamine ingestion does not improve maximal effort exercise. J Sports Med Phys Fitness 38(3) (1998): 240-4.
Heiser CR et al. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. J Int Assoc Physicians AIDS Care 3(4) (2004): 121-9.
Hond E et al. Effect of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease. J Parenter Enteral Nutr 23(1) (1999a): 7-11.
Hond E et al. Effect of glutamine on the intestinal permeability changes induced by indomethacin in humans. Aliment Pharmacol Ther 13(5) (1999b): 679-85.
Hornsby-Lewis L et al. L-glutamine supplementation in home total parenteral nutrition patients: stability, safety and affects on intestinal absorption. J Parenter Enteral Nutr 18 (1994): 268-73.
Houdijk AP et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 352(9130) (1998): 772-6.
Huffman FG, Walgren ME. L-glutamine supplementation improves nelfinavir-associated diarrhea in HIV-infected individuals. HIV Clin Trials 4(5) (2003): 324-9.
Iantomasi T. Glutathione metabolism in Crohn's Disease. Biochem Med Metab Biol 53 (1994): 87-91.
Jiang Z et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomised, double blind, controlled study of 120 patients. J Parenter Enteral Nutr 23 (1999): S62-6.
Jiang ZM et al. The impact of glutamine dipeptides on outcome of surgical patients: systematic review of randomized controlled trials from Europe and Asia. Clin Nutr Suppl 1(1) (2004): 17-23.
Kaufmann Y et al. Effect of glutamine on the initiation and promotion phases of DMBA-induced mammary tumor development. J Parenter Enteral Nutr 27(6) (2003): 411-18.
Kaya E et al. L-glutamine enemas attenuate mucosal injury in experimental colitis. Dis Colon Rectum 42(9) (1999): 1209-15.
Khogali SE et al. Effects of L-glutamine on post-ischaemic cardiac function: protection and rescue. J Mol Cell Cardiol 30(4) (1998): 819-27.
Kohlmeier M. 2003. Glutamine. In: Nutrient Metabolism. St Louis: Elsevier, 2003 280-8.
Kouznetsova L et al. Glutamine reduces phorbol-12,13-dibutyrate-induced macromolecular hyperpermeability in HT-29Cl.19A intestinal cells. J Parenter Enteral Nutr 23(3) (1999): 136-9.
Kusumoto I. Industrial production of L-glutamine. J Nutr 131(9 Suppl) (2001): 2552-5S.
Li S et al. Separation of L-glutamine from fermentation broth by nanofiltration. J Membr Sci 222(1-2) (2003): 191-201.
Macedo Rogero M et al. Plasma and tissue glutamine response to acute and chronic supplementation with L-glutamine and L-alanyl-L-glutamine in rats. Nutr Res 24(4) (2004): 261-70.



Masuko Y. Impact of stress response genes induced by L-glutamine on warm ischemia and reperfusion injury in the rat small intestine. Hokkaido Igaku Zasshi 77(2) (2002): 169-83.
Membane A. L-Glutamine and mania [Letter]. Am J Psychiatry 141 (1984): 1302-3.
Meng Q et al. Regulation of intestinal glutamine absorption by transforming growth factor-beta. J Surg Res 114(2) (2003): 257-8.
Mertes N et al. Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr 19(6) (2000): 395-401.
Miller AL. Therapeutic considerations of L-glutamine: A review of the literature. Altern Med Rev 4(4) (1999): 239-47.
Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? J Nutr 131(9 Suppl) (2001): 2515-22S; discussion 2523-4S.
Niihara Y et al. L-Glutamine therapy reduces endothelial adhesion of sickle red blood cells to human umbilical vein endothelial cells. BMC Blood Disord 5(4) (2005): [Epub ahead of print].
Noyer CM et al. A double-blind placebo-controlled pilot study of glutamine therapy for abnormal intestinal permeability in patients with AIDS. Am J Gastroenterol 93(6) (1998): 972-5.
Opara EC et al. L-glutamine supplementation of a high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice. J Nutr 126(1) (1996): 273-9.
Paquette JC et al. Rapid induction of the intrinsic apoptotic pathway by L-glutamine starvation. J Cell Physiol 202(3) (2005): 912-21.
Patel AB et al. Glutamine is the major precursor for GABA synthesis in rat neocortex in vivo following acute GABA-transaminase inhibition. Brain Res 919(2) (2001): 207-20.
Patrick L. Nutrients and HIV. Part three: N-acetylcysteine, alpha-lipoic acid, L-glutamine, and L-carnitine. Altern Med Rev 5(4) (2000): 290-305.
Paulo FL. Effects of oral supplement of L-glutamine on diverted colon wall. J Cell Mol Med 6(3) (2002): 377-82.
PDRHealth. L-Glutamine. PDRHealth [online]. Thomson Healthcare. Available at: www.pdrhealth (accessed 03-06) 2006a.
PDRHealth. Glutamine peptides. PDRHealth [online]. Thomson Healthcare. Available at: www.pdrhealth (accessed 03-06) 2006b.
Rathmacher JA et al. Supplementation with a combination of beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters. J Parenter Enteral Nutr 28(2) (2004): 65-75.
Rhoads JM et al. L-glutamine stimulates intestinal cell proliferation and activates mitogen-activated protein kinases. Am J Physiol 272(5 Pt 1) (1997): G943-53.
Roediger W. Metabolic basis of starvation diarrhoea: implications for treatment. Lancet 1(8489) (1986): 1082-4.
Rogero M et al. Effect of L-glutamine and L-alanyl-L-glutamine supplementation on the response to delayed-type hypersensitivity test (DTH) in rats submitted to intense training. Rev Bras Cienc Farm 38(4) (2002): 487-97.
Ropeleski MJ et al. Anti-apoptotic effects of L-glutamine-mediated transcriptional modulation of the heat shock protein 72 during heat shock. Gastroenterology 129(1) (2005): 170-84.
Scheppach W et al. Effect of L-glutamine and n-butyrate on the restitution of rat colonic mucosa after acid induced injury. Gut 38(6) (1996): 878-85.
Seth A et al. L-Glutamine ameliorates acetaldehyde-induced increase in paracellular permeability in Caco-2 cell monolayer. Am J Physiol Gastrointest Liver Physiol 287(3) (2004): G510-17.
Shaw AA et al. The influence of L-glutamine on the depression of hepatic cytochrome P450 activity in male rats caused by total parenteral nutrition. Drug Metab Dispos 30(2) (2002): 177-82.
Skubitz KM, Anderson PM. Oral glutamine to prevent chemotherapy induced stomatitis: A pilot study. J Lab Clin Med 127(2) (1996): 223-8.

Tanaka A, Takeuchi K. Prophylactic effect of L-glutamine against intestinal derangement induced 5-fluorouracil or indomethacin in rats. Jpn Pharmacol Ther 30(6) (2002): 455-62.
Tsubuku S et al. Thirteen-week oral toxicity study of L-glutamine in rats. Int J Toxicol 23(2) (2004): 107-12.
van der Hulst RRWJ et al. Glutamine and the preservation of gut integrity. Lancet 341(8857) (1993): 1363-5.
Wischmeyer PE. Clinical applications of L-glutamine: past, present, and future. Nutr Clin Pract 18(5) (2003): 377-85.
Yoshida S et al. Effects of glutamine supplements and radiochemotherapy on systemic immune and gut barrier function in patients with advanced esophageal cancer. Ann Surg 227(4) (1998): 485-91.
Yoshida S et al. Glutamine supplementation in cancer patients. Nutrition 17(9) (2001): 766-8.
Yu B et al. Enhancement of gut immune function by early enteral feeding enriched with L-glutamine in severe burned miniswine. Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi 12(2) (1996): 98-100.
Ziegler T et al. Interactions between nutrients and peptide growth factors in intestinal growth, repair and function. J Parenter Enteral Nutr 23 (1999): S174-83.

Goldenrod

Historical note Goldenrod has been used therapeutically for centuries for bladder conditions and wound healing. The name, *Solidago*, is from the Latin verb 'to make whole'. In 1934, reports from the US Department of Agriculture suggested that goldenrod was considered as a potential future source of commercially prepared rubber, although it was noted that domestication of the plant would be difficult as it is vulnerable to fungal infection and insect attack.

COMMON NAME
Goldenrod

OTHER NAMES
Aaron's rod, blue mountain tea, sweet goldenrod, woundwort

BOTANICAL NAME/FAMILY
Solidago canadensis (Canadian goldenrod), *Solidago virgaurea* (European goldenrod) (family Asteraceae [Compositae]). There are numerous species of goldenrod.

PLANT PARTS USED
Dried aerial parts — flowers and leaves

CHEMICAL COMPONENTS
Flavonoids, including rutin, catechol tannins, triterpene saponins, phenol glycosides, phenolic acids, one essential oil, diterpene lactones, and polysaccharides.

MAIN ACTIONS
The pharmacology of goldenrod has not been significantly investigated; therefore, evidence of activity derives from traditional, in vitro and animal studies.

DIURETIC
Goldenrod is considered an aquaretic medicine, as it promotes fluid loss without an associated disruption to electrolytes. Two animal studies have confirmed diuretic activity (Chodera et al 1991, Leuschner 1995). According to one study, excretion of calcium increases whereas excretion of potassium and sodium decreases (Chodera et al 1991). A review of herbal medicines for the urinary tract concluded that goldenrod is a major diuretic herb (Yarnell 2002).

ANTISPASMODIC AND ANTI-INFLAMMATORY

High doses of a commercial preparation of *S. gigantea* extract (Urol mono) has demonstrated anti-inflammatory activity in an animal model, comparable to those of the pharmaceutical anti-inflammatory medicine diclofenac (Leuschner 1995). Other tests with an extract of *S. virgaurea* have also produced similar results (el Ghazaly et al 1992).

The herbal combination consisting of *Populus tremula*, *Solidago virgaurea* and *Fraxinus excelsior* has demonstrated dose-dependent anti-inflammatory, analgesic and antipyretic effects comparable to those of NSAIDs in several animal models (Okpanyi et al 1989). Although encouraging, the role of *Solidago* in this study is uncertain.

OTHER ACTIONS

Traditionally believed to have an effect on the micro-architecture of the kidney.

ANTIFUNGAL

Inhibitory effects on human pathogenic yeasts such as *Candida* and *Cryptococcus* spp. have been demonstrated for triterpenoid glycosides isolated from *S. virgaurea* (Bader et al 1990).

ANTIBACTERIAL

A moderate antibacterial activity in vitro against certain strains of bacteria, including species of *Bacillus, Proteus* and *Staphylococcus* has been demonstrated from an extract of *S. virgaurea* (Thiem & Goslinska 2002).

ANTICANCER EFFECTS

An extract of *S. virgaurea* has demonstrated antineoplastic activity in vitro using a variety of cell lines, including prostate, breast, small cell lung carcinoma and melanoma, and in vivo in a mouse model of prostate cancer (Gross et al 2002).

CLINICAL USE

Goldenrod has not been significantly investigated under controlled study conditions, so most evidence is derived from traditional use, in vitro and animal studies.

CYSTITIS

The most common use of goldenrod is in the treatment of bladder infections. Both the Commission E (Blumenthal et al 1998) and ESCOP (2003) have approved its use for irrigation of the urinary tract, with ESCOP also indicating usefulness as adjunctive treatment for bacterial UTIs.

ARTHRITIS

The product Phytodolor contains alcoholic extracts of *Populus tremula*, *Fraximus excelsior* and *Solidago virgaurea* and is standardised to 0.14 mg/mL of isofraxidine, 1 mg/mL salicine, and 0.07 mg/mL of total flavonoids. As part of this combination, goldenrod has been investigated in patients with RA, osteoarthritis and back pain. Pain was significantly reduced by treatment with Phytodolor in a placebo-controlled study of 47 patients (Weiner & Ernst 2004). Symptom relief was equally effective amongst patients receiving half strength, normal (60 drops three times daily) or double-strength treatment. A shorter placebo-controlled study of 2 weeks duration found that Phytodolor reduced the need for conventional drug doses in subjects with 'at least one rheumatological diagnosis' (Weiner & Ernst 2004). Similarly, Phytodolor reduced requirements of diclofenac compared to placebo in a smaller study of 30 patients (Weiner & Ernst 2004). A 2-week placebo-controlled study of 30 subjects with osteoarthritis demonstrated that treatment with Phytodolor significantly reduced pain and improved grip strength (Weiner & Ernst 2004). The role of goldenrod in achieving these results is unclear.

INFLAMMATION OF THE NASOPHARYNX WITH CATARRH

Goldenrod is also used to relieve symptoms in this condition. The astringent activity of the tannin components provides a theoretical basis for its use.

OTHER USES

In many countries goldenrod is used to prevent urolithiasis and eliminate renal calculi (Skidmore-Roth 2001). It is also used in children with otitis media and nasal catarrh.

TRADITIONAL USES

Goldenrod is used both internally and externally for a variety of conditions. Internally it is used to treat upper respiratory tract catarrh, arthritis, menorrhagia and urological complaints, vomiting and dyspepsia, and externally it is used to support wound healing and as a mouth rinse for inflammatory conditions of the mouth and gums.

DOSAGE RANGE

- Infusion of dried herb: 0.5–2 g in 150 mL of boiled water for at least 10 minutes.
- Fluid extract (1:1) (g/mL): 0.5–2 mL taken 2–4 times daily between meals.

ADVERSE REACTIONS

Handling the plant has been associated with allergic reactions ranging from allergic rhinoconjunctivitis and asthma to urticaria. There is one study of a cohort predominantly comprising florists who had presented with complaints relating to the handling of plants found that extensive cross-sensitisation to pollen of several

members of the Compositae family (e.g. *Matricaria*, *Chrysanthemum* and *Solidago*) and to pollen of the Amaryllidaceae family (*Alstroemeria* and *Narcissus*) (de Jong et al 1998).

SIGNIFICANT INTERACTIONS

None known

CONTRAINDICATIONS AND PRECAUTIONS

Commission E cautions against use as irrigation therapy when heart or kidney disease is also present (Blumenthal et al 1998).

People with known allergy to goldenrod or who are allergic to the Compositae (Asteraceae) family of plants should avoid this herb.

PREGNANCY USE

From limited use in pregnant women, it appears that no increase in frequency of malformation or other harmful effects have been reported although animal studies are lacking (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Goldenrod has a long history of use but has not been tested in humans to any significant extent.
- Traditionally it has been used internally to reduce upper respiratory catarrh, arthritis, menorrhagia, urological complaints and dyspepsia, and externally to promote wound healing and as a mouth rinse for inflammatory conditions of the mouth and gums.
- In Europe, goldenrod is a popular herb for treating lower UTIs and preventing kidney stones.
- When used as part of the commercial preparation, Phytodolor, it provides effective symptom relief in RA and osteoarthritis according to several clinical studies.
- It is considered an aquaretic herb, which induce diuresis but not potassium and sodium loss.
- Preliminary studies in animal models suggest anti-inflammatory activity comparable to that of NSAIDs, but human studies are not available to confirm the clinical significance of these findings.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Goldenrod has diuretic and anti-inflammatory activity, which may be useful in cases of bladder inflammation, although clinical testing has not yet been conducted to confirm this.

When will it start to work?

This is unknown.

Are there any safety issues?

People who are allergic to goldenrod or the Compositae or Asteraceae families of plants should avoid taking this herb.

REFERENCES

Bader G, Kulhanek Y, Ziegler-Bohme H. The antifungal action of polygalacic acid glycosides. Pharmazie 45.8 (1990): 618-20.

Blumenthal M et al. The Complete German Commission E monographs: Therapeutic Guide to Herbal Medicines. Austin, TX: The American Botanical Council, 1998.

Chodera A et al. Effect of flavonoid fractions of Solidago virgaurea L. on diuresis and levels of electrolytes. Acta Pol Pharm 48.5-6 (1991): 35-7.

de Jong NW et al. Occupational allergy caused by flowers. Allergy 53.2 (1998): 204-9.

European Scientific Co-operative On Phytomedicine (ESCOP), 2nd edn. Stuttgart: Thieme, 2003.

el Ghazaly M et al. Study of the anti-inflammatory activity of Populus tremula, Solidago virgaurea and Fraxinus excelsior. Arzneimittelforschung 42.3 (1992): 333-6.

Gross SC, Goodarzi G, Watabe M, Bandyopadhyay S, Pai SK, Watabe K. Antineoplastic activity of Solidago virgaurea on prostatic tumor cells in an SCID mouse model. Nutr Cancer 43.1 (2002): 76-81.

Leuschner J. Anti-inflammatory, spasmolytic and diuretic effects of a commercially available Solidago gigantea herb extract. Arzneimittelforschung 45.2 (1995): 165-8.

Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis, MO: Churchill Livingstone, 2005.

Okpanyi SN, Schirpke-von Paczensky R, Dickson D. Anti-inflammatory, analgesic and antipyretic effect of various plant extracts and their combinations in an animal model. Arzneimittelforschung 39.6 (1989): 698-703.

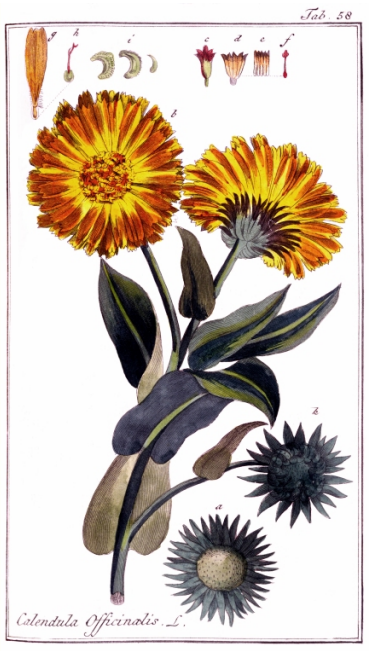
Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. St Louis, MO: Mosby, 2001.

Thiem B, Goslinska O. Antimicrobial activity of Solidago virgaurea L. from in vitro cultures. Fitoterapia 73.6 (2002): 514-16.

Weiner DK, Ernst E. Complementary and alternative approaches to the treatment of persistent musculoskeletal pain. Clin J Pain 20 (2004): 244-55.

Yarnell E. Botanical medicines for the urinary tract. World J Urol 20.5 (2002): 285-93.

Goldenseal



Historical note Goldenseal is indigenous to North America and was traditionally used by the Cherokees and then by early American pioneers. Preparations of the root and rhizome were used for gastritis, diarrhoea, vaginitis, dropsy, menstrual abnormalities, eye and mouth inflammation, and general ulceration. In addition to this, the plant was used for dyeing fabric and weapons. Practitioners of the eclectic school created a high demand for goldenseal around 1847. This ensured the herb's ongoing popularity in Western herbal medicine, but unfortunately led to it being named a threatened species in 1997. Today, most high-quality goldenseal is from cultivated sources.

COMMON NAME
Goldenseal

OTHER NAMES
Eye root, jaundice root, orange root, yellow root

BOTANICAL NAME/FAMILY
Hydrastis canadensis (family Ranunculaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
Isoquinoline alkaloids, including hydrastine (1.5–5%), berberine (0.5–6%) and canadine (tetrahydroberberine, 0.5–1.0%). Other related alkaloids include canadaline, hydrastidine, corypalmine and isohydrastidine.

Clinical note — Isoquinoline alkaloids
Isoquinoline alkaloids are derived from phenylalanine or tyrosine and are most frequently found in the Ranunculaceae, Berberidaceae and Papaveraceae families (Pengelly 2004). This is a very large class of medicinally active compounds that include the morphinane alkaloids (morphine, thebaine and codeine), the ipecac alkaloids (emetine and cephaeline), the atropine alkaloid (boldine), and the protoberberines (berberine and hydrastine). Many other plants contain berberine, including *Berberis vulgaris* (barberry), *Mahonia aquifolium*/*Berberis aquifolium*

(Oregon mountain grape), *Berberis aristata* (Indian barberry), *Coptis chinensis* (Chinese goldthread), *Coptis japonica* (Japanese goldthread) and *Thalictrum minus*.

MAIN ACTIONS

A wealth of empirical data exists for the medicinal use of goldenseal; however, much of the research has been conducted using the chief constituent berberine. It is recommended that goldenseal products be standardised to contain at least 8 mg/mL of berberine and 8 mg/mL of hydrastine (Bone 2003).

ANTIMICROBIAL

In vitro testing has demonstrated antibacterial activity of both the whole extract of goldenseal and the major isolated alkaloids (berberine, beta-hydrastine, canadine and canadaline) against *Staphylococcus aureus*, *Streptococcus sanguis*, *Escherichia coli* and *Pseudomonas aeruginosa* (Scazzocchio et al 2001). In one recent study, two flavonoids isolated from goldenseal were shown to exhibit antibacterial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum* (Hwang et al 2003). An added antimicrobial effect against *S. mutans* was noted with the addition of berberine.

The methanolic extract of the rhizome inhibited the growth of 15 strains of *Helicobacter pylori* in vitro (Mahady et al 2003). The authors identified berberine and beta-hydrastine as the main active constituents.

Berberine alone, and in combination with both ampicillin and oxacillin, has demonstrated strong antibacterial activity against all strains of MRSA in vitro (Yu et al 2005); 90% inhibition was demonstrated with 64 μg/mL or less of berberine. Berberine was also found to enhance the effectivness of ampicillin and oxacillin against MRSA in vitro.

Many of the *Berberis* spp. contain the flavonolignan 5′-methoxyhydnocarpin, which inhibits the expression of the multidrug resistant efflux pumps (Musumeci et al 2003, Stermitz et al 2000a, b); however, it is unknown whether goldenseal contains this compound.

Berberine inhibits the adherence of streptococci to host cells by aiding the release of an adhesin lipoteichoic acid (an acid that is responsible for the adhesion of the bacteria to the host tissue) from the streptococcal cell surface (Sun 1998). Berberine is also able to dissolve lipoteichoic acid–fibronectin complexes once they have been formed. Berberine displays well-defined antimicrobial properties against certain bacteria and such data suggests that it may also be able to prevent adherence and destroy already formed complexes.

Berberine destroys cell wall and sterol biosynthesis in *Candida* spp. in vitro (Park et al 1999).

ANTIDIARRHOEAL

Berberine decreases intestinal activity by activating alpha-2-adrenoceptors and reducing cyclic adenosine monophosphate (cAMP) (Hui et al 1991). Berberine also inhibits intestinal ion secretion and inhibits toxin formation from microbes (Birdsall & Kelly 1997).

Berberine has demonstrated efficacy in vitro for many bacteria that cause infective diarrhoea, including *E. coli*, *Shigella dysenteriae*, *Salmonella paratyphi*, *Clostridium perfringens* and *Bacillus subtilus* (Mahady & Chadwick 2001). It has also demonstrated activity in vitro against parasites that cause diarrhoea, including *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*.

The effects of berberine on cholera toxin-induced water and electrolyte secretion were investigated in an experimental in vivo model (Swabb 1981). Secretions of water, sodium and chlorine were reduced 60–80 minutes after exposure to berberine.

Berberine did not alter ileal water or electrolyte transport in the control model. It produced a significant reduction in fluid accumulation caused by infection with *E. coli* in vivo (Khin-Maung & Nwe Nwe 1992). Oral doses of berberine before the toxin was introduced and intragastric injection after infection were both effective. Berberine was shown to inhibit by approximately 70% the secretory effects of *Vibrio cholerae* and *E. coli* in a rabbit ligated intestinal loop model (Sack & Froehlich 1982). As in the other study, the drug was effective when given either before or after enterotoxin binding. In an investigation using pig jejunum, berberine demonstrated a reduction in water and electrolyte secretion after intraluminal perfusion with *E. coli* (Zhu & Ahrens 1982).

Berberine significantly slowed small intestine transit time in an experimental in vivo model (Eaker & Sninsky 1989). Berberine inhibited myoelectric activity, which appears to be partially mediated by opioid and alpha-adrenergic receptors. The antidiarrhoeal properties of berberine may be partially due to the constituents' ability to delay small intestinal transit time.

CARDIOVASCULAR ACTIONS

Berberine may be effective for congestive heart failure and arrhythmia as it has demonstrated positive inotropic, negative chronotropic, antiarrhythmic and vasodilator properties (Lau et al 2001).

After 8 weeks of treatment oral doses of berberine (10 mg/kg) improved cardiac function and prevented development of left ventricular hypertrophy induced by

pressure overload in rats (Hong et al 2002, 2003). Berberine was found to reduce left ventricular end-diastolic pressure, improve contraction and relaxation and decrease the amount of the atrophied heart muscle.

Berberine has also been found to increase cardiac output in dogs with left ventricular failure due to ischaemia (Huang et al 1992). Over 10 days, intravenous administration of berberine (1 mg/kg, within 3 minutes) followed by a constant infusion (0.2 mg/kg/min, 30 minutes) increased the cardiac output and decreased left ventricular end-diastolic pressure, DBP and systemic vascular resistance, but did not affect heart rate. This study shows that berberine may be able to improve impaired left ventricular function by exerting positive inotropic effects and mild systemic vasodilatation. These results, although interesting, should be evaluated cautiously as the method of administration was intravenous. The hypotensive effects of the berberine derivative, 6-protoberberine (PTB-6) were studied in spontaneously hypertensive rats (Liu et al 1999). PTB-6 lowered SBP in a dose-dependent manner (5 mg/kg:–31.1 ± 1.6 mmHg; 10 mg/kg:–42.4 ± 3.1 mmHg). The berberine derivative also reduced cardiac output and heart rate. The authors conclude that the antihypertensive effect of PTB-6 is probably caused by a central sympatholytic effect.

HYPOCHOLESTEROLAEMIC/ANTI-ATHEROGENIC

Berberine upregulates the LDL receptor (LDLR) by stabilising the LDLR mRNA (Abidi et al 2005, Kong et al 2004). Hamsters fed a high-fat diet for 2 weeks, followed by treatment with oral doses of berberine (100 mg/kg) for 10 days demonstrated a 40% reduction of cholesterol, including a 42% reduction in LDL-cholesterol (Kong et al 2004). No effect on HDL-cholesterol was noted.

Berberine may have potential as an anti-atherosclerotic agent because of a demonstrated inhibition of lysophosphatidylcholine (lysoPC)-induced DNA synthesis and cell proliferation in vascular smooth muscle cells (VSMCs) in vivo (Cho et al 2005). Berberine also inhibited the migration of lysoPC-stimulated VSMCs and the activity of extracellular signal-regulated kinases, reduced transcription factor AP-1 and intracellular reactive oxygen species. This suggests that berberine may be useful for the prevention of atherosclerosis.

ANTIDIABETIC

A glucose-lowering effect similar to metformin was observed in vitro for berberine; however, no effect was seen on insulin secretion (Yin et al 2002).

Similarly, fasting blood glucose, total cholesterol and triglyceride levels significantly decreased after 8 weeks of treatment with 187.5 or 562.5 mg/kg of berberine in an experimental model of glucose intolerance (Leng et al 2004). In an additional in

vitro study using insulin secreted from pancreatic cells, incubated with berberine for 12 hours, the authors concluded that berberine increased insulin production. The relationship of these trials to oral doses in humans is unknown.

Blood glucose, blood lipids, muscle triglycerides and insulin sensitivity were measured before and after the ingestion of berberine or metformin in rats fed a high-fat diet (Gao et al 1997). In this trial berberine and metformin improved insulin resistance and liver glycogen levels, but had no effect on blood glucose, insulin, lipid and muscle triglyceride levels. The study was able to demonstrate that berberine was as effective as metformin for improving insulin sensitivity in the rats.

Berberine inhibits alpha-glucosidase and therefore reduces the transport of glucose through the intestinal epithelium (Pan et al 2003).

ANTI-INFLAMMATORY

Berberine inhibits COX-2 transcriptional activity (Fukuda et al 1999, Kuo et al 2005) and reduces PG synthesis in vitro and in vivo (Kuo et al 2004). Berberine has been found to reduce proliferation of human lymphocytes in vitro by inhibiting DNA synthesis in activated cells (Ckless et al 1995).

IMMUNE ACTIVITY

Intragastric administration of the crude extract of goldenseal for 6 weeks increased the production of IgM in vivo (Rehman et al 1999). Berberine has also been found to induce IL-12 p40, a large subunit of IL-12, through the activation of p38 mitogen-activated protein kinase in mouse macrophages (Kang et al 2002). Interleukin-12 is crucial for the development of the Th1 immune response and thus may also have a therapeutic effect in reducing Th2 allergic disorders. A follow-up study demonstrated that pretreatment with berberine induced IL-12 production in stimulated macrophages and dendritic cells (Kim et al 2003). Macrophages pretreated with berberine had an increased ability to induce IFN-gamma and a reduced ability to induce IL-4 in antigen-primed $CD4^+$ T-cells. Increased levels of IL-12 appear to deviate $CD4^+$ T-cells from the Th2 to the Th1 pathway. This inhibition of type 2 cytokine responses indicate that berberine may be an effective anti-allergic compound.

The immunosuppressive effects of berberine were investigated in an induced autoimmune model in vivo (Marinova et al 2000). Berberine was administered daily (10 mg/kg) for 3 days before intravenous induction of tubulo-interstitial nephritis (TIN).

Significantly less damage and an increase in renal function was demonstrated in the animals pretreated with berberine as compared to controls after 2 months. Berberine decreased CD3, CD4 and CD8 lymphocytes in comparison with non-treated

animals. These results suggest that berberine may exert an immunosuppressive effect in a TIN model. Clinical trials in human kidney autoimmune diseases are warranted.

ANTICANCER

Berberine has demonstrated cytotoxic activity in vitro against many strains of human cancer cells (Hwang et al 2006, Kettmann et al 2004, Kuo et al 2005). This is due in part to the reduction of COX-2 enzymes (Kuo et al 2005, Tai & Luo 2003), damage to the cytoplasmic membrane and DNA fragmentation (Letasiova et al 2005).

The antitumour effects of berberine were investigated on malignant brain tumours in an in vitro and in vivo model (Zhang et al 1990). Berberine (150 mg/mL) demonstrated an ability to kill 91% of cells in six human malignant brain tumour cell lines and 10 mg/kg exhibited an 80.9% cell kill rate against solid brain tumours in vivo. The addition of berberine to 1,3-bis(2-chloroethyl)-1-nitrosourea increased cytotoxicity.

OTHER ACTIONS

Anticatarrhal, astringent, bitter, choleretic, depurative, mucus membrane tonic, vulnerary and oxytocic.

CLINICAL USE

Goldenseal has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies. Many of these have been conducted on the primary alkaloids. All results are for the isolated compound berberine, and although this compound appears to have various demonstrable therapeutic effects, extrapolation of these results to crude extracts of goldenseal is premature. It should also be noted that equivalent doses of the whole extract of goldenseal are exceptionally high.

DIARRHOEA

A double-blind, placebo-controlled, randomised trial examined the effect of berberine alone (100 mg four times daily) and in combination with tetracycline for acute watery diarrhoea in 400 patients (Khin-Maung et al 1985). Patients were divided into four groups and given tetracycline, tetracycline plus berberine, berberine or placebo; 185 patients tested positive for cholera and those in the tetracycline and tetracycline plus berberine groups achieved a significant reduction in diarrhoea after 16 hours and up to 24 hours. The group given berberine alone showed a significant reduction in diarrhoea volume (1 L) and a 77% reduction in cAMP in stools. Noticeably fewer patients in the tetracycline and tetracycline plus berberine groups excreted vibrios in their stool after 24 hours and interestingly no statistically significant improvements for patients with non-cholera diarrhoea in the tetracycline or berberine group were

shown. A later randomised, double-blind clinical trial compared 200 mg of berberine four times daily plus tetracycline, with tetracycline alone in 74 patients with diarrhoea resulting from *V. cholerae* (Khin-Maung et al 1987). There were no statistically significant differences between the two groups.

An RCT evaluated the effect of berberine sulfate in 165 men with *E. coli* or *V. cholerae*-induced diarrhoea as compared to tetracycline (Rabbani et al 1987). Patients with *E. coli* were given a single 400 mg dose and those with *V. cholerae* were given either a single 400 mg dose or 1200 mg (400 mg every 8 hours), combined with tetracycline. Berberine reduced mean stool volumes by 48% in the *E. coli* group as compared to control over 24 hours. Patients in the *V. cholerae* group who received 400 mg of berberine as a single dose also had a reduction in stool volume after 16 hours as compared to placebo. The combination of berberine and tetracycline did not show any statistical improvement over tetracycline alone in the *V. cholerae* group.

A follow-up randomised, placebo-controlled trial was designed to evaluate the antisecretory and antimicrobial potential of various antidiarrhoeal agents including berberine, in patients with active diarrhoea due to *vibrio cholerae* or enterotoxic *E. coli* (Rabbani 1996). Berberine at a lower dose of 200 mg resulted in a reduction in stool volume of between 30% and 50% without significant side-effects. Berberine was again shown to be more effective in the treatment of diarrhoea resulting from *E. coli* than in cholera.

Berberine may also be effective in the treatment of giardiasis. A comparison controlled study of 359 children aged between 4 months and 14 years compared berberine (10 mg/kg/day) with metronidazole (20 mg/kg/day) for up to 10 days (Gupte 1975). Negative stool samples were evident in 90% of children receiving berberine after 10 days with 83% remaining negative after 1 month's duration. The results were comparative with the metronidazole (Flagyl) group (95% after 10 days and 90% after 1 month), without side-effects. In a similar study, 40 children aged 1–10 years with giardiasis were given berberine (5 mg/kg/day), metronidazole (10 mg/kg/day) or placebo (vitamin B syrup) for 6 days (Choudry et al 1972). In the berberine group 48% of children were symptom-free after 6 days and 68% had no giardia cysts on stool analysis as compared to the metronidazole group who experienced a 33% reduction in symptoms and a 100% clearance rate for cysts. These results show that berberine may be more effective than Flagyl for symptom relief, but not as effective for clearing the organism from the gastrointestinal tract. The aforementioned study (Gupte 1975) used a higher dose of berberine (10 mg/kg/day), which produced better results; however, the equivalent amount of goldenseal for

either dose would be exceedingly high based on an average berberine content of 5%, which would be inappropriate.

Small intestinal transit time was evaluated in 30 healthy subjects in a controlled study (Yuan et al 1994). Transit time was significantly delayed from 71.10 ± 22.04 minutes to 98.25 ± 29.03 minutes after oral administration of 1.2 g of berberine. These results suggest that the antidiarrhoeal effect of berberine might be partially due to its ability to delay small intestinal transit time.

HYPERCHOLESTEROLAEMIA

In a RCT, oral doses of 0.5 g of berberine, given twice daily for 3 months in 32 hypercholesterolaemic patients, resulted in a 29% reduction in serum cholesterol, a 35% reduction in triglycerides and a 25% reduction in LDL-cholesterol (Kong et al 2004). HDL-cholesterol levels remained unchanged. Berberine also significantly improved liver function as noted by liver enzyme levels.

CHRONIC CONGESTIVE HEART FAILURE

The efficacy and safety of berberine in chronic congestive heart failure was studied in a randomised, double-blind, controlled study in 156 patients with chronic heart failure (Zeng et al 2003). All patients received conventional treatment and 79 patients in the treatment group also received 1.2–2.0 g/day of berberine for 8 weeks. Quality of life was greatly improved in the berberine group in comparison to controls, as measured by a significant increase in left ventricular ejection fraction, less fatigue and a greater capacity to exercise. A significant reduction in mortality was also noted during the 24-month follow-up (7 in the treatment group as compared to 13).

The acute cardiovascular effects of intravenous berberine (0.02 and 0.2 mg/kg/min for 30 minutes) were studied in 12 patients with refractory congestive heart failure (Marin-Neto et al 1988). At the lower dose, a 14% reduction in heart rate was noted, whereas 0.2 mg/kg resulted in a 48% decrease in systemic vascular resistance and a 41% decrease in pulmonary vascular resistance. Right atrium and left ventricular end-diastolic pressures were reduced by 28% and 32%, respectively. Cardiac index, stroke index, and left ventricular ejection fraction were also significantly enhanced.

EYE INFECTION

A controlled clinical trial of 51 patients with ocular trachoma infections investigated the effectiveness of berberine over 3 weeks with a 1-year follow-up (Babbar et al 1982). Subjects who used the 0.2% berberine either by itself or combined with sulfacetamide demonstrated significant symptom improvement and tested negative for *Chlamydia trachomatis*, with no relapse after 1 year.

A later comparison controlled clinical study also evaluated the effectiveness of the topical treatment of berberine for trachoma in 32 microbiologically confirmed patients (Khosla et al 1992). A 0.2% berberine solution (2 drops in each eye, three times daily) was found to be more effective than sulfacetamide (20%) in reducing both the course of the trachoma and the serum antibody titres against *C. trachomatis*. Berberine eyedrops were compared to berberine plus neomycin ointment, sulfacetamide and placebo in a double-blind, controlled clinical trial in 96 primary school children (Mohan et al 1982). Patients in the berberine group were asked to use 2 drops (0.2% berberine) of the solution in each eye, three times daily and to additionally apply a berberine ointment (0.2%) at night for 3 months. Children treated with only the berberine had an 87% clinical response rate, compared to 58% in the berberine and neomycin group; however, only 50% tested negative in follow-up microbiological tests.

OTHER USES

Menorrhagia, dysmenorrhoea, peptic ulcer, gastritis, dyspepsia, skin disorders, sinusitis, chronic inflammation of mucous membranes and topically for ulceration and infection.

Traditionally, it is used as a bitter digestive stimulant that improves bile flow and liver function.

DOSAGE RANGE

INTERNAL

- Tincture (1:3): 2.0–4.5 mL/day or 15–30 mL/week (Bone 2003)
- Tincture (1:10): 6–12 mL/day (Mills & Bone 2005)
- Dried rhizome and root: 1.5–3 g/day by decoction (Mills & Bone 2005)

EXTERNAL

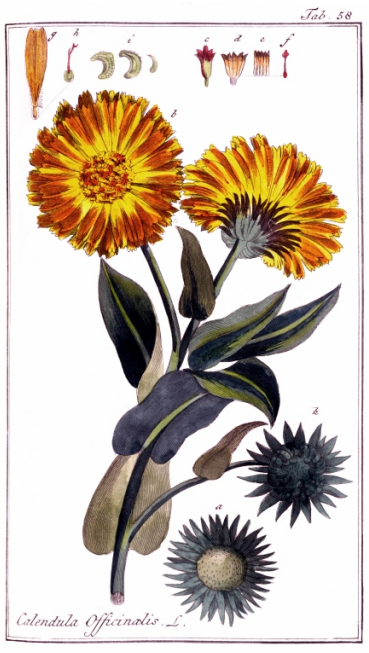
- Eyewash: 0.2% berberine solution, 2 drops in each eye, three times daily (Khosla et al 1992)

Clinical note — Berberine absorption

Berberine is poorly absorbed, with up to 5% bioavailability (Pan et al 2002). In vitro data has clearly demonstrated that berberine is a potent antibacterial; however, in vivo data has established low bioavailability. Berberine has been shown to upregulate the expression and function of the drug transporter P-glycoprotein (Pgp) (Lin et al 1999). Pgp belongs to the super family of ATP-binding cassette transporters that are responsible for the removal of unwanted toxins and metabolites from the cell (Glastonbury 2003). It appears that Pgp in normal

intestinal epithelia greatly reduces the absorption of berberine in the gut. In vivo and in vitro methods have been used to determine the role of Pgp in berberine absorption by using the known Pgp inhibitor cyclosporin A (Pan et al 2002). Co-administration increased berberine absorption six-fold and clearly demonstrated the role of Pgp in absorption.

Increased expression of Pgp can lead to cells displaying multi-drug resistance (Glastonbury 2003). As previously reported a certain flavonolignan in many *Berberis* spp. has the ability to inhibit the expression of multi-drug resistant efflux pumps (Stermitz et al 2000a, b) allowing berberine and certain antibiotics to be more effective.



ADVERSE REACTIONS

Goldenseal is generally regarded as safe in recommended doses (Blumenthal 2003). Higher doses than 0.5 g of pure berberine may cause lethargy, dizziness, dyspnoea, skin and eye irritation, gastrointestinal irritation, nausea, vomiting, diarrhoea, nephritis and kidney irritation (Blumenthal et al 1998).

SIGNIFICANT INTERACTIONS

Because controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity. No drug interactions have been reported; however, an extract of goldenseal has demonstrated inhibition of cytochrome P450 in vitro (Budzinski et al 2000). Theoretically these findings suggests that any drugs metabolised using this pathway may be affected. The clinical relevance of this possible interaction is unknown.

CYCLOSPORIN A

Berberine increased the blood concentration of cyclosporin A in renal transplant patients in a RCT (Wu et al 2005): 52 patients received 0.2 g of berberine orally three times daily for 3 months. The final blood concentration in the berberine/cyclosporin A group was 29.3% higher than the group given cyclosporin A only. The relevance of this to oral ingestion of goldenseal is unknown — caution advised.

CONTRAINDICATIONS AND PRECAUTIONS

Goldenseal is contraindicated in kidney disease because of inadequate excretion of the alkaloids (Blumenthal et al 2003). Berberine has been found to be a potent displacer of bilirubin (Chen 1993). A review published in 1996 stated that berberine can cause severe acute haemolysis and jaundice in babies with glucose-6-phosphate dehydrogenase deficiency (Ho 1996). Goldenseal is therefore not recommended in pregnancy, lactation or cases of neonatal jaundice. Goldenseal is also contraindicated

in hypertension (BHMA 1983) as large amounts of hydrastine have been reported to restrict peripheral blood vessels and cause hypertension (Genest & Hughs 1969). The dose required to induce this effect is unknown and the ability to reach this threshold using the whole extract is unlikely; however, until this is clarified goldenseal is best avoided in hypertension.

PREGNANCY USE

Contraindicated in pregnancy and lactation.

In addition to the preceding concerns about bilirubin, berberine has caused uterine contractions in pregnant and non-pregnant experimental models (Mills & Bone 2005). A recent in vivo study using 65-fold the average human oral dose of goldenseal investigated effects on gestation and birth and found no increase in implantation loss or malformation (Yao 2005). The authors conclude that the low bioavailability of goldenseal from the gastrointestinal tract was likely to explain the differences between in vitro and in vivo effects in pregnancy. Hydrastine (0.5 g) has also been found to induce labour in pregnant women (Mills & Bone 2005). Until more pharmacokinetic studies are done, goldenseal is best avoided in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Goldenseal has been used traditionally as an antidiarrhoeal agent and digestive stimulant.
- It has been used topically as a wash for sore or infected eyes and as a mouth rinse.
- Goldenseal is a bitter digestive stimulant that improves bile flow and improves liver function.
- Most clinical evidence has been conducted using the chemical constituent berberine. This data has shown effectiveness against diarrhoea, congestive heart failure, infection and cholesterol.
- Goldenseal is not to be used in pregnancy or during breastfeeding.
- Use with caution in patients who have hypertension or taking cyclosporin.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Goldenseal may be used in the treatment of diarrhoea, dyspepsia, infection, diabetes and cholesterol. Most of the available research has been done on the alkaloid berberine. More clinical trials of the whole extract are needed to determine if the same effect will be seen.

When will it start to work?

Antibacterial and antidiarrhoeal activity should be apparent quite quickly. The lipid-lowering effects of goldenseal have been reported within 12 weeks.

Are there any safety issues?

The herb should not be taken during pregnancy or lactation and may interact with some medications.

REFERENCES

Abidi P et al. Extracellular signal-regulated kinase-dependent stabilization of hepatic low-density lipoprotein receptor mRNA by herbal medicine berberine. Arterioscler Thromb Vasc Biol 25.10 (2005): 2170-6.

Babbar OP et al. Effect of berberine chloride eye drops on clinically positive trachoma patients. Indian J Med Res 76 (Suppl) (1982): 83-8.

Birdsall T, Kelly G. Therapeutic potential of an alkaloid found in several medicinal plants. Altern Med Rev 2 (1997): 94-103.

Blumenthal M. The ABC Clinical Guide To Herbs. New York: Thieme 2003.

Blumenthal M et al. The Complete German Commission E monographs: Therapeutic Guide to Herbal Medicines. Austin, TX: The American Botanical Council 1998.

Bone K. A Clinical Guide to Blending Liquid Herbs. St Louis: Churchill Livingstone 2003.

British Herbal Medicine Association Scientific Committee. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA 1983.

Budzinski JW et al. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7.4 (2000): 273-82.

Cho BJ et al. Berberine inhibits the production of lysophosphatidylcholine-induced reactive oxygen species and the ERK1/2 pathway in vascular smooth muscle cells. Mol Cells 20.3 (2005): 429-34.

Choudhry VP et al. Berberine in giardiasis. Indian Pediatr 9.3 (1972): 143-6.

Ckless K et al. Inhibition of in-vitro lymphocyte transformation by the isoquinoline alkaloid berberine. J Pharm Pharmacol 47.12A (1995): 1029-31.

Eaker EY, Sninsky CA. Effect of berberine on myoelectric activity and transit of the small intestine in rats. Gastroenterology 96.6 (1989): 1506-13.

Fukuda K et al. Inhibition by berberine of cyclooxygenase-2 transcriptional activity in human colon cancer cells. J Ethnopharmacol 66.2 (1999): 227-33.

Gao CR et al. Experimental study on berberine raised insulin sensitivity in insulin resistance rat models. Zhongguo Zhong Xi Yi Jie He Za Zhi 17.3 (1997): 162-4.

Genest K, Hughs DW. Natural products in Canadian pharmaceuticals. II: Hydrastis canadensis. Can J Pharm Sci 4: 41; as cited in Mahady GB, Chadwick LR. 2001 Golden Seal (Hydrastis canadensis): Is there enough scientific evidence to support safety and efficacy? Nutr Clin Care 4.5 (1969): 243-9.

Glastonbury S. Scientific evaluation of the use of traditional herbal depuratives via modulation of ABC transporters. Aust J Med Herbalism 15.2 (2003): 34-8.

Gupte S. Use of berberine in treatment of giardiasis. Am J Dis Child 129.7 (1975): 866.

Ho NK. Traditional Chinese medicine and treatment of neonatal jaundice. Singapore Med J 37.6 (1996): 645-51.

Hong Y et al. Effect of berberine on regression of pressure-overload induced cardiac hypertrophy in rats. Am J Chin Med 30.4 (2002): 589-99.

Hong Y et al. Effect of berberine on catecholamine levels in rats with experimental cardiac hypertrophy. Life Sci 72.22 (2003): 2499-507.

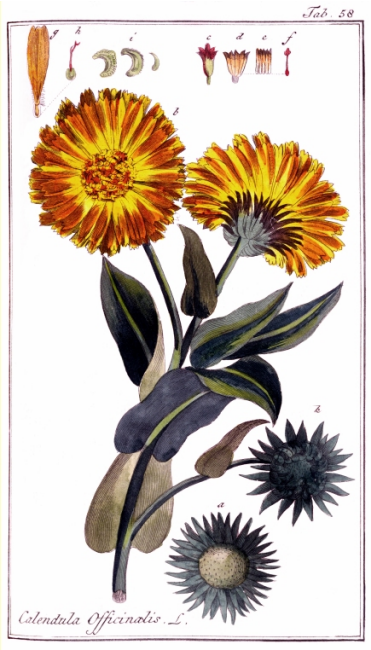
Huang WM et al. Beneficial effects of berberine on hemodynamics during acute ischemic left ventricular failure in dogs. Chin Med J (Engl) 105.12 (1992): 1014-19.

Hui KK et al. Interaction of berberine with human platelet alpha 2 adrenoceptors. Life Sci 49.4 (1991): 315-24.

Hwang BY et al. Antimicrobial constituents from goldenseal (the rhizomes of Hydrastis canadensis) against selected oral pathogens. Planta Med 69.7 (2003): 623-7.

Hwang JM et al. Berberine induces apoptosis through a mitochondria/caspases pathway in human hepatoma cells. Arch Toxicol 80.2 (2006): 62-73.

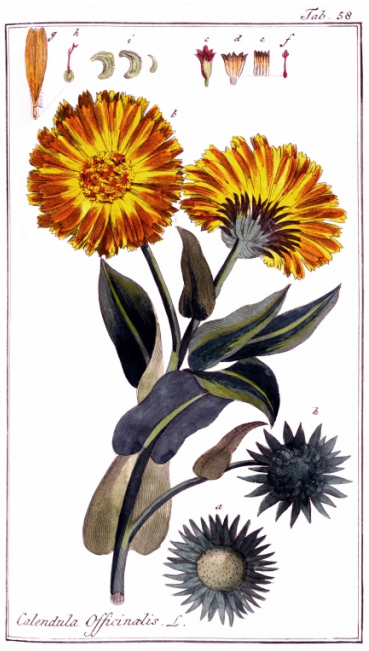
Kang BY et al. Involvement of p38 mitogen-activated protein kinase in the induction of interleukin-12 p40 production in mouse macrophages by berberine, a benzodioxoloquinolizine alkaloid. Biochem Pharmacol 63.10 (2002): 1901-10.
Kettmann V et al. In vitro cytotoxicity of berberine against HeLa and L1210 cancer cell lines. Pharmazie 59.7 (2004): 548-51.
Khin-Maung U, Nwe Nwe W. Effect of berberine on enterotoxin-induced intestinal fluid accumulation in rats. J Diarrhoeal Dis Res 10.4 (1992): 201-4.
Khin-Maung U et al. Clinical trial of berberine in acute watery diarrhoea. BMJ (Clin Res Ed) 291.6509 (1985): 1601-5.
Khin-Maung U et al. Clinical trial of high-dose berberine and tetracycline in cholera. J Diarrhoeal Dis Res 5.3 (1987): 184-7.
Khosla PK et al. Berberine, a potential drug for trachoma. Rev Int Trach Pathol Ocul Trop Subtrop Sante Publique 69 (1992): 147-65.
Kim TS et al. Induction of interleukin-12 production in mouse macrophages by berberine, a benzodioxoloquinolizine alkaloid, deviates CD4+ T cells from a Th2 to a Th1 response. Immunology 109.3 (2003): 407-14.
Kong W et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med 10.12 (2004): 1344-51.
Kuo CL et al. The anti-inflammatory potential of berberine in vitro and in vivo. Cancer Lett 203.2 (2004): 127-37.
Kuo CL et al. Modulation of apoptosis by berberine through inhibition of cyclooxygenase-2 and Mcl-1 expression in oral cancer cells. In Vivo 19.1 (2005): 247-52.
Lau CW et al. Cardiovascular actions of berberine. Cardiovasc Drug Rev 19.3 (2001): 234-44.
Leng SH et al. Therapeutic effects of berberine in impaired glucose tolerance rats and its influence on insulin secretion. Acta Pharmacol Sin 25.4 (2004): 496-502.
Letasiova S et al. Berberine-antiproliferative activity in vitro and induction of apoptosis/necrosis of the U937 and B16 cells. Cancer Lett 239 (2006): 254-62.
Lin HL et al. Up-regulation of multidrug resistance transporter expression by berberine in human and murine hepatoma cells. Cancer 85.9 (1999): 1937-42.
Liu JC et al. The antihypertensive effect of the berberine derivative 6-protoberberine in spontaneously hypertensive rats. Pharmacology 59.6 (1999): 283-9.
Mahady GB, Chadwick LR. Golden Seal (Hydrastis canadensis): Is there enough scientific evidence to support safety and efficacy? Nutr Clin Care 4.5 (2001): 243-9.
Mahady GB et al. In vitro susceptibility of Helicobacter pylori to isoquinoline alkaloids from Sanguinaria canadensis and Hydrastis Canadensis. Phytother Res 17.3 (2003): 217-21.
Marinova EK et al. Suppression of experimental autoimmune tubulointerstitial nephritis in BALB/c mice by berberine. Immunopharmacology 48.1 (2000): 9-16.
Marin-Neto JA et al. Cardiovascular effects of berberine in patients with severe congestive heart failure. 11.4 (1988): 253-60.
Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis: Churchill Livingstone 2005.
Mohan M et al. Berberine in trachoma: A clinical trial. Indian J Ophthalmol 30.2: 69-75; as cited in Mahady GB, Chadwick LR. 2001, Golden Seal (Hydrastis canadensis): Is there enough scientific evidence to support safety and efficacy? Nutr Clin Care 4.5 (1982): 243-9.
Musumeci R et al. Berberis aetnensis C. Presl. extracts: antimicrobial properties and interaction with ciprofloxacin. Int J Antimicrob Agents 22.1 (2003): 48-53.
Pan GY et al. The involvement of P-glycoprotein in berberine absorption. Pharmacol Toxicol 91.4 (2002): 193-7.
Pan GY et al. The antihyperglycaemic activity of berberine arises from a decrease of glucose absorption. Planta Med 69.7 (2003): 632-6.



Park KS et al. Differential inhibitory effects of protoberberines on sterol and chitin biosyntheses in Candida albicans. J Antimicrob Chemother 43.5 (1999): 667-74.
Pengelly A. The Constituents of Medicinal Plants. Sydney: Allen & Unwin 2004.
Piscitelli SC et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 34.2 (2002): 234-8.
Rabbani GH. Mechanism and treatment of diarrhoea due to Vibrio cholerae and Escherichia coli: roles of drugs and prostaglandins. Dan Med Bull 43.2 (1996): 173-85.
Rabbani GH et al. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. J Infect Dis 155.5 (1987): 979-84.
Rehman J et al. Increased production of antigen-specific immunoglobulins G and M following in vivo treatment with the medicinal plants Echinacea angustifolia and Hydrastis Canadensis. Immunol Lett 68.2-3 (1999): 391-5.
Sack RB, Froehlich JL. Berberine inhibits intestinal secretory response of Vibrio cholerae and Escherichia coli enterotoxins. Infect Immun 35.2 (1982): 471-5.
Scazzocchio F et al. Antibacterial activity of Hydrastis canadensis extract and its major isolated alkaloids. Planta Med 67.6 (2001): 561-4.
Stermitz FR et al. Synergy in a medicinal plant: antimicrobial action of berberine potentiated by 5'-methoxyhydnocarpin, a multidrug pump inhibitor. Proc Natl Acad Sci USA 97.4 (2000a): 1433-7.
Stermitz FR et al. 5'-Methoxyhydnocarpin-D and pheophorbide A: Berberis species components that potentiate berberine growth inhibition of resistant Staphylococcus aureus. J Nat Prod 63.8 (2000b): 1146-9.
Sun D et al. Berberine sulfate blocks adherence of streptococcus pyogenes to epithelial cells, fibronectin, and hexadecane. Antimicrob Agents Chemother 32 (9) (1998): 1370-4.
Swabb EA et al. Reversal of cholera toxin-induced secretion in rat ileum by luminal berberine. Am J Physiol 241.3 (1981): G248-52.
Tai WP, Luo HS. [The inhibit effect of berberine on human colon cell line cyclooxygenase-2]. Zhonghua Nei Ke Za Zhi 42.8 (2003): 558-60.
Wu X et al. Effects of berberine on the blood concentration of cyclosporin A in renal transplanted recipients: clinical and pharmacokinetic study. Eur J Clin Pharmacol 61.8 (2005): 567-72.
Yao M et al. A reproductive screening test of goldenseal. Birth Defects Res B Dev Reprod Toxicol 74.5 (2005): 399-404.
Yin J et al. Effects of berberine on glucose metabolism in vitro. Metabolism 51.11 (2002): 1439-43.
Yu HH et al. Antimicrobial activity of berberine alone and in combination with ampicillin or oxacillin against methicillin-resistant Staphylococcus aureus. J Med Food 8.4 (2005): 454-61.
Yuan J et al. Effect of berberine on transit time of human small intestine. Zhongguo Zhong Xi Yi Jie He Za Zhi 14.12 (1994): 718-20.
Zeng XH et al. Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 92.2 (2003): 173-6.
Zhang RX et al. Laboratory studies of berberine used alone and in combination with 1,3-bis(2-chloroethyl)-1-nitrosourea to treat malignant brain tumors. Chin Med J (Engl) 103.8 (1990): 658-65.
Zhu B, Ahrens FA. Effect of berberine on intestinal secretion mediated by Escherichia coli heat-stable enterotoxin in jejunum of pigs. Am. J Vet Res 43.9 (1982): 1594-8.

Grapeseed extract

Historical note In the 1500s a French expedition in North America found itself trapped in ice and forced to survive on salted meat and stale biscuits. After a time, the crew began to show signs of what we now recognise as scurvy. It is believed that the men survived because a Native American Indian showed them how to make a tea from the bark and needles of pine trees. The French explorer wrote of this encounter in a book that was subsequently read by researcher Jacques Masquelier, also a Frenchman, in the 20th century. Intrigued by the story, he began to investigate the chemistry and properties of pine bark and identified oligomeric proanthocyanidin complexes (OPCs). Several years later, he extracted OPCs from grapeseed extract (GSE), which is now considered the superior source of OPCs (Murray & Pizzorno 1999).



COMMON NAME
grapeseed extract

BOTANICAL NAME/FAMILY
Vitis vinifera/Vitaceae

PLANT PARTS USED
Seeds, grape skins

CHEMICAL COMPONENTS
The skin of the grapeseed is a rich source of proanthocyanidins (also referred to as procyanidins). Mixtures of procyanidins are referred to as OPCs. Grapeseed extract contains OPCs made up of dimers or trimers of (+)-catechin and (–)-epicatechin (Fine 2000) and also trimers and polymers of proanthocyanidins. *Vitis vinifera* also contains stilbenes (resveratrol and viniferins) (Bavaresco et al 1999); however, it is unclear whether significant amounts are present in the seeds.

Clinical note — Proanthocyanidins
Proanthocyanidins (PCs) are a group of naturally occurring polyphenolic bioflavonoids that are present in many fruits (e.g. apples, pears, grapes and peaches), vegetables, nuts, beans (e.g. cocoa), seeds, flowers and bark (e.g. pine) (Bavaresco et al 1999). Grapeseeds are a particularly rich source of PCs, containing more than any other grape products, such as red, white or rose wine or grape juice,

and more than most commonly available foods (Rasmussen et al 2005a). Proanthocyanidins are also found in many medicinal herbs such as *Ginkgo biloba, Camellia sinensis, Hypericum perforatum* and *Crataegus monogyna*; however, GSE is considered the superior source. Proanthocyanidins demonstrate a wide range of biological actions according to various in vitro, in vivo and clinical studies. However, in recent years, bioavailability studies have demonstrated that not all orally ingested PCs are absorbed. In particular, PC polymers have negligible absorption from the gastrointestinal tract whereas low-molecular-weight PCs (monomers, dimers and trimers) are absorbed (Rasmussen et al 2005b). In addition, some PCs are degraded by microflora in the caecum and large intestine into low-molecular-weight phenolic acids, chiefly hydroxyphenylpropionic acid and 4-O-methylgallic acid (Ward et al 2004), which are likely to contribute to the biological effects. These findings have implications when interpreting in vitro data because this method of testing does not take into account variations in bioavailability and metabolism in the body.

MAIN ACTIONS

Most evidence of activity derives from in vitro and animal studies for OPCs or GSE; however, some clinical studies are also available. The stilbene resveratrol (3, 4', 5 trihydroxystilbene) has also been the focus of much investigation and exhibits anti-inflammatory, antithrombotic, anticarcinogenic and antibacterial activities, but it is uncertain whether significant amounts are present in the seeds and GSE (Fremont 2000).

ANTIOXIDANT

Grapeseed PC extract has demonstrated excellent free radical scavenging abilities, in both test tube and animal models, and provided significantly greater effects than vitamins C, E and beta-carotene (Bagchi et al 1997, 1998, 2000a, 2001, Castillo et al 2000, Facino et al 1999, Fauconneau et al 1997, Maffei et al 1994, 1996). In vitro tests have further identified a vitamin E sparing effect, in which PCs prevent vitamin E loss and cause alpha-tocopherol radicals to revert to their antioxidant form (Maffei et al 1998).

INHIBITS PLATELET AGGREGATION

Grapeseed extract has been shown to inhibit platelet aggregation, and combining extracts of grapeseed and grape skin produces a far greater antiplatelet effect in test tube and ex vivo tests (Shanmuganayagam et al 2002). Inhibition of platelet function was confirmed more recently by Vitseva et al (2005).

STABILISES CAPILLARY WALLS AND ENHANCES DERMAL WOUND HEALING

In vivo studies have found that PCs stabilise the capillary wall and prevent increases in capillary permeability when chemically induced in tests such as carrageenan-induced hindpaw oedema (Zafirov et al 1990) and dextran-induced oedema (Robert et al 1990). Components in GSE have the ability to cross-link collagen fibres, thereby strengthening the collagen matrix (Tixier et al 1984). Clinical studies confirm that grapeseed extract improves capillary resistance when used at a dose of 150 mg daily (Lagrue et al 1981). Not unexpectedly, research has also identified wound healing properties.

A 2002 study in mice found that topical application of grapeseed PCs considerably accelerated wound contraction and closure and provided additional support during the wound healing process (Khanna et al 2002). It has been shown that a GSE preparation containing 5000 ppm resveratrol facilitates oxidant-induced vascular endothelial growth factor expression in keratinocytes in vitro, which may account for its beneficial effects in promoting dermal wound healing and resolution of related skin disorders (Khanna et al 2001).

ANTICARCINOGENIC, ANTIMUTAGENIC

Several in vitro studies have demonstrated that PCs from *Vitis vinifera* strongly suppress tumour growth and have cytotoxic activity against a range of cancer cells, including breast, lung, prostate and gastric adenoma cells (Bagchi et al 2000b, Joshi et al 2001, Tyagi et al 2003, Ye et al 1999a). More specifically, PCs from grapeseeds exerted antitumour properties in several animal models (Kim et al 2004, Nomoto et al 2004, Ray et al 2005, Zhang et al 2005). One study also found that grapeseed PCs enhanced the growth and viability of human gastric mucosal cells at the same time (Ye et al 1999b).

ANTI-INFLAMMATORY

In vitro evidence suggests GSE has anti-inflammatory activity (Sen & Bagchi 2001). Two compounds isolated from *Vitis vinifera* exhibit non-specific inhibitory activity against COX-1 and -2 (Waffo-Teguo et al 2001).

CARDIOPROTECTIVE EFFECTS

Considering that GSE demonstrates antioxidant, antiplatelet and anti-inflammatory actions, it may have a role in the prevention of cardiovascular disease. A number of researchers have investigated this issue further, mainly using animal models. One series of studies was conducted by Bagchi et al (2003) using a natural, standardised, water-ethanol extract made from California red grapeseeds, which contained approximately 75–80% oligomeric PCs and 3–5% monomeric PCs. According to in

vivo research, treatment with GSE provided resistance to myocardial ischaemia-reperfusion injury, better post-ischaemic ventricular recovery and reduced incidence of reperfusion-induced ventricular fibrillation and ventricular tachycardia, as compared with corresponding control animals. Another study using a hamster atherosclerosis model found that 50 and 100 mg GSE/kg body weight led to a 49% and 63% reduction in foam cells respectively. Additionally, cholesterol and triglyceride lowering activity has been reported (Yu et al 2002).

OTHER ACTIONS

Protection against chemically induced multi-organ toxicity has also been reported (Bagchi et al 2001). Results from a clinical study suggest that GSE increases the rhodopsin content of the retina or accelerates its regeneration after exposure to bright light (Boissin et al 1988).

CLINICAL USE

Free radical damage has been strongly associated with virtually every chronic degenerative disease, including cardiovascular disease, arthritis and cancer. Clearly, due to the potent antioxidant activity of grapeseed, its therapeutic potential is quite broad. Most clinical studies have been conducted in Europe using a commercial product known as Endotelon®. Due to the poor bioavailability of high-molecular-weight PCs, it is advised that products containing chiefly low-molecular-weight PCs be used in practice.

FLUID RETENTION, PERIPHERAL VENOUS INSUFFICIENCY AND CAPILLARY RESISTANCE

Several clinical studies have investigated the use of GSE in fluid retention, capillary resistance or venous insufficiency, producing positive results (Amsellem et al 1987, Delacroix 1981, Constantini et al 1999, Henriet 1993, Lagrue et al 1981).

Hormone replacement therapy and fluctuations in hormone levels can produce symptoms of venous insufficiency in some women. One large study involving 4729 subjects with peripheral venous insufficiency due to HRT showed that GSE decreased the sensation of heaviness in the legs in just over half the subjects by day 45 whereas 89.4% of subjects experienced an improvement by day 90 (Henriet 1993). According to an open multicentre study of women aged 18–50 years with oedema due to premenstrual syndrome, GSE (Endotelon®) administered from day 14 to 28 improved various symptoms of fluid retention such as abdominal swelling, weight gain and pelvic pain and also venous insufficiency (Amsellem et al 1987). The treatment was taken for four cycles, with most women (60.8%) responding after two cycles and 78.8% responding after four cycles.

An open study involving 24 patients with non-complicated chronic venous insufficiency found that over 80% of subjects receiving OPCs (100 mg/day) reported lessened or absent symptoms after 10 days. Symptoms of itching and pain responded best, completely disappearing during the course of treatment in 80% and 53% of the patients respectively (Costantini et al 1999). A double-blind study of 50 patients with symptoms of venous insufficiency found that GSE (Endotelon® 150 mg daily) improved both subjective and objective markers of peripheral venous insufficiency such as pain (Delacroix 1981).

In some pathological conditions, such as inflammation or diabetes, vascular permeability can be abnormally increased (Robert et al 1990). Two studies investigated the effects of GSE on capillary resistance in hypertensive and diabetic patients under both open and double-blind, placebo controlled conditions with treatment producing significant improvements in both groups (Lagrue et al 1981). The studies used a daily dose of 150 mg (Endotelon®).

DIABETIC RETINOPATHY

Grapeseed extract (Endotelon® 150 mg) was found to stabilise diabetic retinopathy in 80% of subjects compared to 47% with placebo, under double-blind test conditions (Arne 1982). These results were obtained by measuring objective markers such as visual acuity, muscular tone, and ocular tone.

EYE STRAIN

A double-blind study involving 75 patients with eye strain caused by viewing a computer screen found that GSE 300 mg daily significantly improved objective and subjective measures (Bombardelli & Morazzoni 1995). Grapeseed extract (Endotelon®) has also been shown significantly to improve visual adaptation to and from bright light in a dual centre study involving 100 volunteers (Boissin et al 1998, Corbe et al 1988). A dose of 200 mg daily over 5 weeks was used. It has been proposed that GSE increases rhodopsin content of the retina or accelerates its regeneration after exposure to bright light.

HYPERLIPIDAEMIA

A randomised, double-blind study of 40 hypercholesterolaemic subjects compared the effects of placebo, chromium polynicotinate (400 μg/day), GSE (200 mg/day) or a combination of both. Over 2 months, the combination treatment decreased total cholesterol and LDL levels significantly but did not significantly alter homocysteine, HDL or blood pressure among the four groups (Preuss et al 2000).

ENHANCES DERMAL WOUND HEALING

A 2002 study in mice found that topical application of grapeseed PCs considerably accelerate wound contraction and closure and provided additional support during the wound healing process (Khanna et al 2002).

Chloasma Chloasma is a condition characterised by hyperpigmentation and is generally considered recalcitrant to treatment. Proathocyanidin-rich GSE successfully reduced hyperpigmentation in women with chloasma after 6 months of oral treatment according to an open study involving 12 subjects (Yamakoshi et al 2004). The study continued for another 6 months but failed to find an additional improvement with further use. The researchers suggested that a preventative effect may be possible with long-term oral GSE when used in the months prior to summer.

PANCREATITIS

It is believed that oxygen-derived free radicals mediate tissue damage in acute and chronic pancreatitis. Therefore, antioxidant treatment is being investigated. A small, open study of three patients with difficult-to-treat chronic pancreatitis found that a commercially available IH636 GSE produced a reduction in the frequency and intensity of abdominal pain, as well as resolution of vomiting in one patient (Bannerjee & Bagchi 2001).

PREVENTING REPERFUSION INJURY

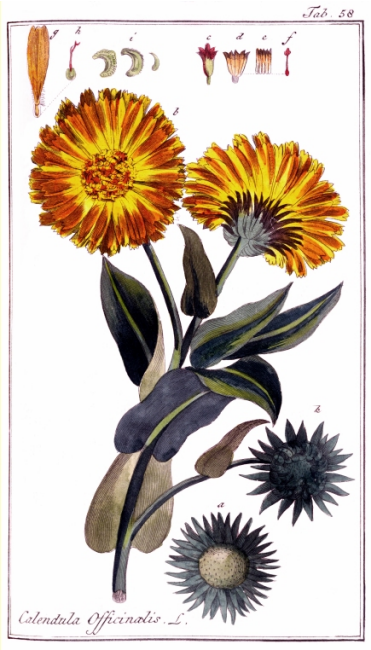
Procyanidin administration reduced the adverse effects of myocardial ischaemia-reperfusion injury during cardiac surgery in several in vivo studies (Facino et al 1999, Maffei et al 1996). This appears to be positively associated with an increase in plasma antioxidant activity.

REDUCES SUN BURN

Topical application of GSE has been shown to enhance sun protection factor in human volunteers (Bagchi et al 2000).

PROTECTION AGAINST MULTI-ORGAN DRUG AND CHEMICAL TOXICITY

The results from a number of in vivo studies have suggested pre-exposure to grapeseed extract can provide multi-organ protection against damage caused by various drugs such as paracetamol, amiodarone, doxorubicin, cadmium chloride and dimethylnitrosamine treatment (Bagchi et al 2000, Bagchi et al 2001).



DOSAGE RANGE

- Fluid extract 1:1 (g/mL): 20–40 mL per week
- Solid dose forms: 12,000 mg of GSE standardised to OPCs* taken 2–3 times daily in order to provide 150–300 mg of OPCs daily.

*Due to the poor bioavailability of high-molecular-weight PCs, it is advised that products containing chiefly low-molecular-weight PCs be used in practice.

TOXICITY
Tests in animal models have found GSE to be extremely safe (Bentivegna & Whitney 2002).

ADVERSE REACTIONS
Studies using doses of 150 mg/day have found it to be well tolerated.

SIGNIFICANT INTERACTIONS
Controlled studies are not available, therefore interactions are theoretical and based on evidence of pharmacological activity.

ANTIPLATELET DRUGS
Additive effect theoretically possible — observe patient.

ANTICOAGULANT DRUGS
Increased risk of bleeding theoretically possible — caution.

IRON AND IRON-CONTAINING PREPARATIONS
Decreased iron absorption. Tannins can bind to iron, forming insoluble complexes — separate doses by 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS
None known.

PREGNANCY USE
Safety has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING
- Grapeseed extract has considerable antioxidant activity and appears to regenerate alpha-tocopherol radicals to their antioxidant form.
- Grapeseed extract also has anti-inflammatory actions, reduces capillary permeability, enhances dermal wound healing and reduces photo-damage, inhibits platelet aggregation and may enhance rhodopsin regeneration or content in the retina.
- It is popular in Europe as a treatment for venous insufficiency and capillary fragility, both of which are supported by clinical evidence. It is also used to relieve eye strain, stabilise diabetic retinopathy and connective tissue disorders.
- Preliminary research has identified cardioprotective effects due to a variety of mechanisms. Possible benefits in pancreatitis and multi-organ protection against

damage caused by several pharmaceutical drugs. Anticarcinogenic activity has also been reported.

- Most clinical research has been conducted in Europe with a commercial grapeseed product known as Endotelon®.
- Due to concerns with bioavailability, it is recommended that only preparations containing low-molecular-weight PCs be used.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

There is evidence that GSE is a useful treatment for venous insufficiency and capillary fragility and has considerable antioxidant activity. It is also used to treat eye strain, diabetic retinopathy, and enhance wound healing when applied locally.

When will it start to work?

It appears to relieve symptoms of venous insufficiency within 10 days and eye strain within 5 weeks.

Are there any safety issues?

Research suggests it is well tolerated and generally safe; however, people taking anticoagulant medicines should refer to their healthcare professional before taking this substance.

References

Amsellem M et al. Endotelon in the treatment of venolymphatic problems in premenstrual syndrome: multicenter study on 165 patients. Tempo Med 282 (1987): 46-57.

Arne JL. Contribution to the study of procyanidolic oligomers: Endotelon in diabetic retinopathy. Gaz Med France 89 (1982): 3610-14.

Bagchi D et al. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. Res Commun Mol Pathol Pharmacol 95 (1997): 179-89.

Bagchi D et al. Protective effects of grape seed proanthocyanidins and selected antioxidants against TPA-induced hepatic and brain lipid peroxidation and DNA fragmentation, and peritoneal macrophage activation in mice. Gen Pharmacol 30 (1998): 771-6.

Bagchi D et al. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. Toxicology 148 (2000): 187-97.

Bagchi D et al. Protection against drug- and chemical-induced multiorgan toxicity by a novel IH636 grape seed proanthocyanidin extract. Drugs Exp Clin Res 27 (2001): 3-15.

Bagchi D et al. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. Mutat Res 523-4 (2003): 87-97.

Banerjee B, Bagchi D. Beneficial effects of a novel IH636 grape seed proanthocyanidin extract in the treatment of chronic pancreatitis. Digestion 63 (2001): 203-6.

Bavaresco L et al. Stilbene compounds: from the grapevine to wine. Drugs Exp Clin Res 25 (1999): 57-63.

Bentivegna SS, Whitney KM. Subchronic 3-month oral toxicity study of grape seed and grape skin extracts. Food Chem Toxicol 40 (2002): 1731-43.

Boissin JP, Corbe C, Siou A. [Chorioretinal circulation and dazzling: use of procyanidol oligomers (Endotelon):]. Bull Soc Ophtalmol Fr 88 (1988): 173-9.

Castillo J et al. Antioxidant activity and radioprotective effects against chromosomal damage induced in vivo by X-rays of flavan-3-ols (procyanidins): from grape seeds (Vitis vinifera): comparative study versus other phenolic and organic compounds. J Agric Food Chem 48 (2000): 1738-45.
Corbe C, Boissin JP, Siou A. [Light vision and chorioretinal circulation: Study of the effect of procyanidolic oligomers (Endotelon):]. J Fr Ophtalmol 11 (1988): 453-60.
Costantini A, De Bernardi T, Gotti A. [Clinical and capillaroscopic evaluation of chronic uncomplicated venous insufficiency with procyanidins extracted from Vitis vinifera]. Minerva Cardioangiol 47 (1999): 39-46.
Delacroix P. Double-blind trial of endotelon in chronic venous insufficiency. Rev Med 27-8 (1981): 1793-802.
Facino RM et al. Diet enriched with procyanidins enhances antioxidant activity and reduces myocardial post-ischaemic damage in rats. Life Sci 64 (1999): 627-42.
Fauconneau B et al. Comparative study of radical scavenger and antioxidant properties of phenolic compounds from Vitis vinifera cell cultures using in vitro tests. Life Sci 61 (1997): 2103-10.
Fine AM. Oligomeric proanthocyanidin complexes: history, structure, and phytopharmaceutical applications. Altern Med Rev 5 (2000): 144-51.
Fremont L. Biological effects of resveratrol. Life Sci 66 (2000): 663-73.
Henriet JP. [Veno-lymphatic insufficiency: 4,729 patients undergoing hormonal and procyanidol oligomer therapy]. Phlebologie 46 (1993): 313-25.
Joshi SS, Kuszynski CA, Bagchi D. The cellular and molecular basis of health benefits of grape seed proanthocyanidin extract. Curr Pharm Biotechnol 2 (2001): 187-200.
Khanna S et al. Upregulation of oxidant-induced VEGF expression in cultured keratinocytes by a grape seed proanthocyanidin extract. Free Radic Biol Med 31 (2001): 38-42.
Khanna S et al. Dermal wound healing properties of redox-active grape seed proanthocyanidins. Free Radic Biol Med 33 (2002): 1089-96.
Kim H et al. Chemoprevention by grape seed extract and genistein in carcinogen-induced mammary cancer in rats is diet dependent. J Nutr 134 (2004): 3445-52S.
Lagrue G, Olivier-Martin F, Grillot A. [A study of the effects of procyanidol oligomers on capillary resistance in hypertension and in certain nephropathies (author's transl):]. Semin Hop 57 (1981): 1399-401.
Maffei FR et al. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera: A mechanism for their capillary protective action. Arzneimittelforschung 44 (1994): 592-601.
Maffei FR et al. Procyanidines from Vitis vinifera seeds protect rabbit heart from ischemia/reperfusion injury: antioxidant intervention and/or iron and copper sequestering ability. Planta Med 62 (1996): 495-502.
Maffei FR et al. Sparing effect of procyanidins from Vitis vinifera on vitamin E in vitro studies. Planta Med 64 (1998): 343-7.
Murray M, Pizzorno J. Procyanidolic oligomers. In: Textbook of Natural Medicine, 2nd edn. London: Churchill-Livingstone, 1999; 899-202.
Nomoto H et al. Chemoprevention of colorectal cancer by grape seed proanthocyanidin is accompanied by a decrease in proliferation and increase in apoptosis. Nutr Cancer 49 (2004): 81-8.
Preuss HG et al. Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. J Med 31 (2000): 227-46.
Rasmussen SE et al. Dietary proanthocyanidins: occurrence, dietary intake, bioavailability, and protection against cardiovascular disease. Mol Nutr Food Res 49 (2005): 159-74.
Ray SD, Parikh H, Bagchi D. Proanthocyanidin exposure to B6C3F1 mice significantly attenuates dimethylnitrosamine-induced liver tumor induction and mortality by differentially modulating programmed and unprogrammed cell deaths. Mutat Res 579 (2005): 81-106.
Robert L et al. [The effect of procyanidolic oligomers on vascular permeability. A study using quantitative morphology]. Pathol Biol (Paris) 38 (1990): 608-16.
Sen CK, Bagchi D. Regulation of inducible adhesion molecule expression in human endothelial cells by grape seed proanthocyanidin extract. Mol Cell Biochem 216 (2001): 1-7.
Shanmuganayagam D et al. Grape seed and grape skin extracts elicit a greater antiplatelet effect when used in combination than when used individually in dogs and humans. J Nutr 132 (2002): 3592-8.

Tixier JM et al. Evidence by in vivo and in vitro studies that binding of pycnogenols to elastin affects its rate of degradation by elastases. Biol Chem Pharmacol 33 (1984): 3933-9.
Tyagi A, Agarwal R, Agarwal C. Grape seed extract inhibits EGF-induced and constitutively active mitogenic signaling but activates JNK in human prostate carcinoma DU145 cells: possible role in antiproliferation and apoptosis. Oncogene 22 (2003): 1302-16.
Vitseva O et al. Grape seed and skin extracts inhibit platelet function and release of reactive oxygen intermediates. J Cardiovasc Pharmacol 46 (2005): 445-51.
Waffo-Teguo P et al. Two new stilbene dimer glucosides from grape (Vitis vinifera) cell cultures. J Nat Prod 64 (2001): 136-8.
Ward NC et al. Supplementation with grape seed polyphenols results in increased urinary excretion of 3-hydroxyphenylpropionic acid, an important metabolite of proanthocyanidins in humans. J Agric Food Chem 52 (2004): 5545-9.
Yamakoshi J et al. Oral intake of proanthocyanidin-rich extract from grape seeds improves chloasma. Phytother Res 18 (2004): 895-9.
Ye X et al. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. Mol Cell Biochem 196 (1999): 99-108.
Yu H et al. [Effect of grape seed extracts on blood lipids in rabbits model with hyperlipidemia]. Wei Sheng Yan Jiu 31 (2002): 114-16.
Zafirov D et al. Antiexudative and capillaritonic effects of procyanidines isolated from grape seeds (V. vinifera). Acta Physiol Pharmacol Bulg 16 (1990): 50-4.
Zhang XY et al. Proanthocyanidin from grape seeds potentiates anti-tumor activity of doxorubicin via immunomodulatory mechanism. Int Immunopharmacol 5 (2005): 1247-57.

Green tea

Historical note Tea has been a popular beverage for thousands of years and was originally grown in China, dating back 5000 years, where it has been used as part of various ceremonies and to maintain alertness. Green tea and the partially fermented oolong tea have remained popular beverages in Asia since that time, whereas black tea is the preferred beverage in many English-speaking countries. Tea was introduced to the Western culture in the 6th century by Turkish traders (Ulbricht & Basch 2005). Second to water, tea is now considered to be the world's most popular beverage.

COMMON NAME
Green tea

OTHER NAMES
Chinese tea, camellia tea, gruner tea, Matsu-cha

BOTANICAL NAME/FAMILY
Camellia sinensis (family Theaceae)

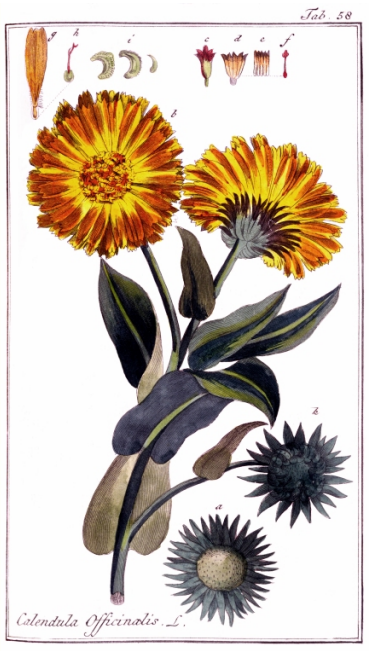
PLANT PART USED
Leaf

CHEMICAL COMPONENTS
The composition of green tea varies according to the growing and harvesting methods, but the most abundant components are polyphenols, which are predominantly flavonoids (e.g. catechin, epicatechin, epicatechin gallate, epigallocatechin gallate, proanthocyanidins). Caffeine content in green tea varies but is estimated at about 3%, along with very small amounts of the other common methylxanthines, theobromine and theophylline (Graham 1992). It also contains many other constituents, such as tannin, diphenylamine, oxalic acid, trace elements and vitamins.

Epigallocatechin gallate is one of the most abundant polyphenols in tea and is regarded as the most significant pharmacologically active component.

Clinical note — The difference between teas
Black, green and oolong tea are produced from the same plant (*Camellia sinensis*) but differ in polyphenol content according to the way the leaves are processed. Black tea is made from oxidised leaves whereas oolong tea is made from partially

oxidised leaves and green tea leaves are not oxidised at all. Because the oxidising process converts many polyphenolic compounds into others with less activity, green tea is considered to have the strongest therapeutic effects and the highest polyphenol content (Lin et al 2003). Caffeine concentrations also vary between the different teas: black tea > oolong tea > green tea > fresh tea leaf (Lin et al 2003). Variation in caffeine content is further influenced by growing conditions, manufacturing processes and size of the tea leaves (Astill et al 2001). The highest quality leaves are the first spring leaf buds, called the 'first flush'. The next set of leaf buds produced is called the 'second flush' and considered to be of poorer quality. Tea varieties also reflect the area they are grown in (e.g. Darjeeling in India), the form produced (e.g. pekoe is cut, gunpowder is rolled) and processing method (black, oolong or green) (Ulbricht & Basch 2005).



MAIN ACTIONS

It is suspected that the polyphenol content is chiefly responsible for the chemoprotective, antiproliferative, antimicrobial and antioxidant activity of green tea. The caffeine content is predominantly responsible for central nervous system activity and an interaction between both appears necessary for increasing thermogenesis.

ANTIOXIDANT

Green tea has consistently demonstrated strong antioxidant activity. In a recent controlled human trial, 24 healthy women consumed 2 cups of green tea (250 mg catechins/day) for 42 days (Erba et al 2005). The results showed a significant increase in plasma antioxidant status, reduced plasma peroxides and reduced LDL-cholesterol when compared with controls. Several other in vitro animal and human studies have also demonstrated that green tea inhibits lipid peroxidation and scavenges hydroxyl and superoxide radicals (Leenen et al 2000, MCS et al 2002, Rietveld & Wiseman 2003, Sung et al 2000).

ANTIBACTERIAL ACTIVITY

Green tea extract has moderate and wide-spectrum inhibitory effects on the growth of many types of pathogenic bacteria, according to in vitro tests, including seven strains of *Staphylococcus* spp., seven strains of *Streptococcus* spp., one strain of *Corynebacterium suis*, 19 strains of *Escherichia coli* and 26 strains of *Salmonella* spp. (Ishihara et al 2001). Green tea has also been found to inhibit *Helicobacter pylori* in an animal model (Matsubara et al 2003). According to one study, which compared the antibacterial activity of black, green and oolong tea, it seems that fermentation adversely affects antibacterial activity, as green tea exhibited the strongest effects, and black tea the weakest (Chou et al 1999). An in vitro study has demonstrated that

green tea can significantly lower bacterial endotoxin-induced cytokine release and therefore may reduce mortality from sepsis (Chen et al 2005).

Oral pathogens Both in vitro and in vivo tests have identified strong antibacterial activity against a range of oral pathogens, such as *Streptococcus mutans, S. salivarius* and *E. coli* (Otake et al 1991, Rasheed & Haider 1998). The mechanism of action appears to involve anti-adhesion effects, with the strongest activity associated with epigallocatechin gallate and epicatechin gallate. Green tea catechins have also showed an antibacterial effect against *Porphyromonas gingivalis* and *Prevotella* spp. in vitro (Hirasawa et al 2002). Furthermore, green tea polyphenols, especially epigallocatechin gallate, have been found to completely inhibit the growth and adherence of *P. gingivalis* on buccal epithelial cells (Sakanaka et al 1996).

ANTIVIRAL ACTIVITY

Three in vitro studies have shown that epigallocatechin gallate strongly inhibits HIV replication (Fassina et al 2002, Chang et al 1994, Tao 1992). The theaflavins from black tea have shown even stronger anti-HIV activity in vitro by inhibiting viral entry into target cells (Liu et al 2005). Antiviral activity has also been identified against Epstein-Barr virus, HSV-1, influenza A and B, rotavirus and enterovirus (Chang et al 2003, Imanishi et al 2002, Mukoyama et al 1991, Tao 1992, Weber et al 2003). Antiviral activity seems to be attributable to interference with virus adsorption (Mukoyama et al 1991).

ANTICARCINOGENIC

Several in vitro studies have shown a dose-dependent decreased proliferation and/or increased apoptosis in a variety of cancer cell lines (lung, prostate, colon, stomach, oral, leukaemia and breast) (Berger et al 2001, Gupta et al 2003, Kavanagh et al 2001, Kinjo et al 2002, Pianetti et al 2002, Valcic et al 1996, Wang & Bachrach 2002, Yoo et al 2002, Zhang et al 2002). Additionally, photochemopreventative effects for green tea and epigallocatechin gallate have been demonstrated in vitro, in vivo and on human skin (Afaq et al 2003).

The mechanism of action by which tea polyphenols exert antimutagenic and antitumorigenic effects is still largely speculative. However, the following has been observed: inhibition of the large multicatalytic protease and metalloproteinases, which are involved in tumour survival and metastasis, respectively, and inhibition of many tumour-associated protein kinases, while not affecting kinase activity in normal cells (Kazi et al 2002, Wang & Bachrach 2002). Tea polyphenols have also been found to inhibit some cancer-related proteins that regulate DNA replication and transform-

ation. More recently, there is increasing evidence that catechins possess anti-angiogenic properties (Sachinidis & Hescheler 2002).

THERMOGENIC ACTIVITY

Although the thermogenic activity of green tea is often attributed to its caffeine content, an in vivo study has shown that stimulation of brown adipose tissue thermogenesis occurs to a greater extent than would be expected from the caffeine content alone (Dulloo et al 2000). The interaction between catechin polyphenols and caffeine on stimulating noradrenaline release and reducing noradrenaline catabolism may be responsible. Clinical investigation has produced similar results, with green tea consumption significantly increasing 24-hour energy expenditure and urinary noradrenaline excretion, whereas an equivalent concentration of caffeine had no effect on these measures (Dulloo et al 2000).

OTHER ACTIONS

Green tea exhibits a variety of other pharmacological actions, such as anti-inflammatory activity, CNS stimulation, inhibition of platelet aggregation, stimulation of gastric acid secretion and diuresis, increased mental alertness, relaxation of extracerebral vascular and bronchial smooth muscle, and reduced cholesterol, triglyceride and leptin levels (Fassina et al 2002, Sayama et al 2000).

CLINICAL USE

Evidence is largely based on epidemiological studies with few clinical studies available.

CANCER PREVENTION

Epidemiological studies have generally shown a decreased occurrence of cancer in those individuals who drink green tea regularly, although this has not been observed in all studies. A 2003 prospective cohort study using 13-year follow-up data found increased green tea consumption was associated with an apparent delay of cancer onset and death, and all cause deaths (Nakachi et al 2003). A phase 2 RCT evaluated the effects of green tea on oxidative DNA damage in 143 heavy smokers over 4 months and found a significant reduction in damage as evaluated from urine and plasma (Hakim et al 2003). A small, controlled, pilot study concluded with similar results when cells from the oral mucosa of smokers showed much less oxidative damage when compared with controls (Schwartz et al 2005). These trials indicate that green tea may be effective in reducing cancer in smokers, but much larger trials are needed. In contrast, a 2001 prospective study in Japan found no association between green tea consumption and cancer incidence (Nagano et al 2001).

CANCER TREATMENT

Overall, the current evidence does not support the use of green tea as a cancer treatment; however, there are some exceptions, which suggest an adjunctive role. Green tea increased the survival rate of patients with epithelial ovarian cancer in a cohort of 309 Chinese women (Zhang et al 2004). Most (77.9%) of the women in the treatment group were alive at the 3-year follow-up as compared with 47.9% of the control group.

In a RCT, 90 patients with cervical lesions infected with human papilloma virus were given either a capsule containing 200 mg of (-)-epigallocatechin-3-gallate (EGCG) and/or an ointment containing 200 mg of polyphenon E to be applied daily (Ahn et al 2003). There was a 69% responder rate when compared with placebo, with the ointment showing the best effects.

CARDIOVASCULAR PROTECTION

Epidemiological studies suggest that green tea consumption is associated with a reduced risk of cardiovascular disease (Maeda et al 2003). A 2000 prospective cohort study of 8552 people in Japan found that those consuming more than 10 cups per day, compared with those consuming fewer than 3 cups, had a decreased relative risk of death from cardiovascular disease (Nakachi et al 2000). One cross-sectional study involving 1371 men aged over 40 years found that increased green tea consumption was associated with decreased serum concentrations of total cholesterol and triglyceride and an increase in HDL, together with a decrease in LDL- and VLDL-cholesterols (Imai & Nakachi 1995).

DENTAL CARIES AND GINGIVITIS

Green tea extract tablets and chewable oral preparations have been investigated for effects on dental plaque formation and gingival health under RCT conditions, overall producing favourable results (Liu & Chi 2000).

A double-blind study investigated the effects of green tea catechins and polyphenols on the gingiva when used in the form of chewable oral sweets (Krahwinkel & Willershausen 2000). Compared with placebo, the green tea product chewed eight times a day significantly decreased gingival inflammation and improved periodontal structures before the 21-day test period was complete.

Another study investigated Chinese green tea polyphenol tablets for effects on plaque formation in 150 volunteers (Liu & Chi 2000). The randomised, controlled crossover study showed that green tea polyphenol tablets used for 2 weeks were able to reduce the plaque index compared with placebo treatment.

SUNBURN PROTECTION

More than 150 in vitro and in vivo studies have reported the benefits of green tea for the skin (Hsu 2005). Many mechanisms appear to be responsible; green tea protects against UV and PUVA-induced carcinogenesis and DNA damage and is a potent antioxidant, antiinflammatory, anticarcinogenic and vulnerary (Hsu 2005). Research with human volunteers has found that topical application of green tea to skin half an hour before UV exposure protects against the development of sunburn and epidermal damage (Elmets et al 2001). The effect is dose dependent and strongest for the epigallocatechin gallate and epicatechin gallate polyphenols.

WEIGHT LOSS

Animal studies have found that green tea consumption reduces food intake, decreases leptin levels and body weight and increases thermogenesis. However, little clinical evidence is available to determine whether similar effects are seen in humans (Sayama et al 2000). One open study did find that a green tea extract AR25 (80% ethanolic dry extract standardised at 25% catechins) taken by moderately obese patients resulted in a 4.6% decrease in body weight and 4.5% decrease in waist circumference after 3 months' treatment (Chantre & Lairon 2002). However, a recent double-blind, placebo-controlled parallel trial, with 46 women attempting a weight-loss program over 87 days, showed no difference between the green tea group and the placebo group (Diepvens et al 2005). Both groups lost the same amount of weight and displayed similar metabolic parameters at the end of the study period.

OTHER USES

Green tea has many other uses, based on results of animal or in vitro tests or on the known pharmacological activity of constituents such as tannin and caffeine. Some of these other uses are treatment of diarrhoea, Crohn's disease, dyspepsia and other digestive symptoms, promoting alertness and cognitive performance, reducing symptoms of headache and promoting diuresis.

COLITIS

Animal studies have shown anti-inflammatory activity in colitis (Varilek et al 2001).

RENAL FAILURE

Green tea extract blocks the development of cardiac hypertrophy in experimental renal failure and reduces oxidative stress, according to the results of investigation with animal models (Priyadarshi et al 2003, Yokozawa et al 1996).

DIABETES
Animal studies have identified that green tea polyphenols reduce serum glucose levels and improve kidney function in diabetes (Sabu et al 2002, Rhee et al 2002).

DOSAGE RANGE
In general, it appears that 8–10 cups of green tea/day are required.

ADVERSE REACTIONS
Due to the caffeine content of the herb, CNS stimulation and diuresis is possible when consumed in large amounts.

One clinical study found an absence of any severe adverse effects when 15 green tea tablets were taken daily (2.25 g green tea extracts, 337.5 mg EGCG and 135 mg caffeine) for 6 months (Fujiki et al 1999).

SIGNIFICANT INTERACTIONS
Controlled studies are not available for green tea, so interactions are speculative and based on evidence of pharmacological activity. Therefore, clinical significance is unknown.

ANTICOAGULANTS
Antagonistic interaction — a case of excessive consumption (2.25–4.5 L of green tea/day) was reported to inhibit warfarin activity and decrease the INR (Taylor & Wilt 1999). Intake of large quantities of green tea should be done with caution.

HYPOGLYCAEMIC AGENTS
Caffeine-containing beverages can increase blood sugar levels when used in sufficient quantity (200 mg of caffeine); however, hypoglycaemic activity has been reported for green tea, which could theoretically negate this effect (Ulbricht & Basch 2005) — the outcome of this combination is uncertain, therefore observe patient.

IRON
Tannins found in herbs such as *Camellia sinensis* can bind to iron and reduce its absorption — separate doses by at least 2 hours. Protein and iron have also been found to interact with tea polyphenols and decrease their antioxidant effects in vitro (Alexandropoulou et al 2006). The clinical significance of this is as yet unknown.

CNS STIMULANTS
Based on the caffeine content of the herb, high intakes of green tea can theoretically increase the CNS stimulation effects of drugs such as nicotine and beta-adrenergic agonists (e.g. salbutamol); however, the clinical significance of this is unknown — observe patient.

CNS DEPRESSANTS

Based on the caffeine content of the herb, high intakes of green tea can theoretically decrease the CNS depressant effects of drugs such as benzodiazepines; however, the clinical significance of this is unknown — observe patient.

DIURETICS

Based on the caffeine content of the herb, high intakes of green tea can theoretically increase the diuretic effects of drugs such as frusemide; however, the clinical significance of this is unknown — observe patient.

DRUGS METABOLISED BY CYP1A2

The inhibitory effect of caffeine on CYP1A2 may cause other interactions, but this is speculative for green tea.

CONTRAINDICATIONS AND PRECAUTIONS

Excessive intake will increase the likelihood of adverse effects due to the caffeine content and therefore is not recommended for people with hypertension, cardiac arrhythmias, severe liver disease, anxiety disorders or insomnia.

PREGNANCY USE

Usual dietary intakes appear safe; however, excessive use is not recommended due to the caffeine content of green tea.

PRACTICE POINTS/PATIENT COUNSELLING

- Green tea is made from the same plant as black tea, but it contains greater amounts of polyphenols and generally less caffeine.
- Green tea has been found to have significant antioxidant activity and protect against sunburn when applied topically.
- It has antibacterial activity and is used in oral preparations to reduce plaque and improve gingival health.
- Several in vitro and animal studies have shown anticarcinogenic activity for a range of cancers and some epidemiological evidence further suggests cancer protective effects may occur; however, further research is required.
- Epidemiological evidence suggests green tea may reduce cardiovascular disease.
- Preliminary evidence from animal studies has shown that it increases thermogenesis, decreases appetite, reduces inflammation in colitis, reduces glucose levels in diabetes and may be useful in renal failure.
- It is not known whether use will promote weight loss in humans as research results are inconsistent.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Green tea has strong antioxidant effects and some population studies suggest that regular consumption may reduce the risk of cancer and cardiovascular disease. Early research has found it may be useful for sunburn protection, reducing dental plaque formation, colitis, diabetes, renal disease and as an antiseptic. However, further research is required.

When will it start to work?

This will depend on the reason it is being used. Preventative health benefits are likely to take several years of regular daily tea consumption. Effects on oral health care appear to develop more quickly, within 2 weeks.

Are there any safety issues?

Research suggests that green tea is a safe substance when used in usual dietary doses, but excessive consumption may produce side-effects, chiefly because of the caffeine content.

REFERENCES

Afaq F et al. Inhibition of ultraviolet B-mediated activation of nuclear factor kappaB in normal human epidermal keratinocytes by green tea constituent (-)-epigallocatechin-3-gallate. Oncogene 22.7 (2003): 1035-44.

Ahn et al. Protective effects of green tea extracts (polyphenon E and EGCG) on human cervical lesions. Eur J Cancer Prev 12.5 (2003): 383-90.

Alexandropoulou I, Komaitis M, Kapsokefalou M. Effects of iron, ascorbate, meat and casein on the antioxidant capacity of green tea under conditions of in vitro digestion. Food Chem 94 (2006): 359-65.

Astill C et al. Factors affecting the caffeine and polyphenol contents of black and green tea infusions. J Agric Food Chem 49.11 (2001): 5340-7.

Berger SJ et al. Green tea constituent (-)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells. Biochem Biophys Res Commun 288.1 (2001): 101-5.

Chang CW, Hsu FL, Lin JY. Inhibitory effects of polyphenolic catechins from Chinese green tea on HIV reverse transcriptase activity. J Biomed Sci 1.3 (1994): 163-6.

Chang et al. Inhibition of Epstein-Barr virus lytic cycle by (-)-epigallocatechin gallate. Biochem Biophys Res Commun 301.4, (2003): 1062-8.

Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. Phytomedicine 9.1 (2002): 3-8.

Chen X, Li W, Wang H. More tea for septic patients? Green tea may reduce endotoxin-induced release of high mobility group box 1 and other pro-inflammatory cytokines. Med Hypotheses 66.3 (2006): 660-3.

Chou CC, Lin LL, Chung KT. Antimicrobial activity of tea as affected by the degree of fermentation and manufacturing season. Int J Food Microbiol 48.2 (1999): 125-30.

Diepvens et al. Metabolic effects of green tea and of phases of weight loss. Physiol Behav 87.1 (2006): 185-91.

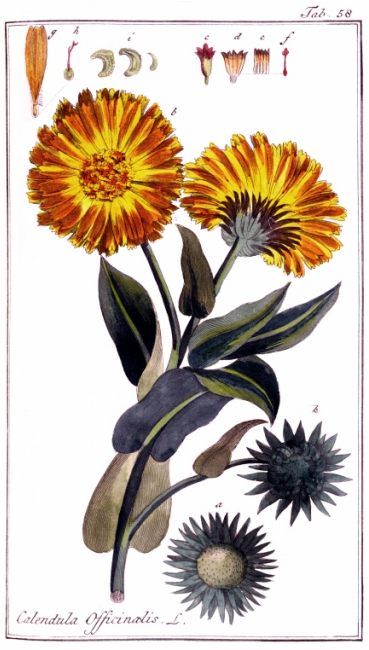
Dulloo AG et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. Am J Clin Nutr 70.6 (1999): 1040-5.

Dulloo AG et al. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. Int J Obes Relat Metab Disord 24.2 (2000): 252-8.

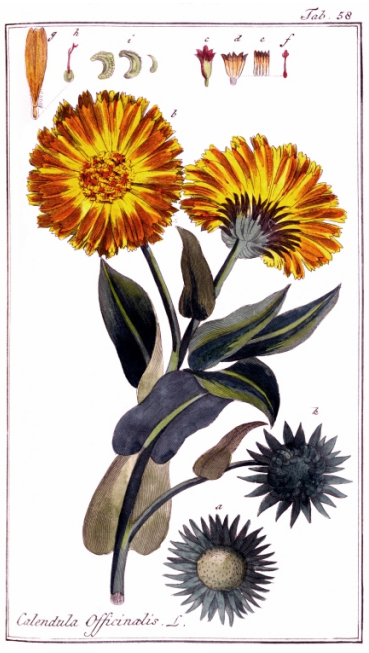
Elmets CA et al. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. J Am Acad Dermatol 44.3 (2001): 425-32.

Erba D et al. Effectiveness of moderate green tea consumption on antioxidative status and plasma lipid profile in humans. J Nutr Biochem 16.3 (2005): 144-9.
Fassina G et al. Polyphenolic antioxidant (-)-epigallocatechin-3-gallate from green tea as a candidate anti-HIV agent. AIDS 16.6 (2002): 939-41.
Fujiki H et al. Mechanistic findings of green tea as cancer preventive for humans. Proc Soc Exp Biol Med 220.4 (1999): 225-8.
Graham HN. Green tea composition, consumption, and polyphenol chemistry. Prev Med 21.3 (1992): 334-50.
Gupta S, Hussain T, Mukhtar H. Molecular pathway for (-)-epigallocatechin-3-gallate-induced cell cycle arrest and apoptosis of human prostate carcinoma cells. Arch Biochem Biophys 410.1 (2003): 177-85.
Hakim et al. Effect of increased tea consumption on oxidative DNA damage among smokers: A randomized controlled study. J Nutr 133.10 (2003): 3303-9s.
Hirasawa M et al. Improvement of periodontal status by green tea catechin using a local delivery system: a clinical pilot study. J Periodontal Res 37.6 (2002): 433-8.
Hsu S. Green tea and the skin. J Am Acad Dermatol 52.6 (2005): 1049-59.
Imai K, Nakachi K. Cross sectional study of effects of drinking green tea on cardiovascular and liver diseases. BMJ 310.6981 (1995): 693-6.
Imanishi N et al. Additional inhibitory effect of tea extract on the growth of influenza A and B viruses in MDCK cells. Microbiol Immunol 46.7 (2002): 491-4.
Ishihara N et al. Improvement of intestinal microflora balance and prevention of digestive and respiratory organ diseases in calves by green tea extracts. 68.2-3 (2001): 217-29.
Kavanagh KT et al. Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture. J Cell Biochem 82.3 (2001): 387-98.
Kazi A et al. Potential molecular targets of tea polyphenols in human tumor cells: significance in cancer prevention. In Vivo 16.6 (2002): 397-403.
Kinjo J et al. Activity-guided fractionation of green tea extract with antiproliferative activity against human stomach cancer cells. Biol Pharm Bull 25.9 (2002): 1238-40.
Krahwinkel T, Willershausen B. The effect of sugar-free green tea chew candies on the degree of inflammation of the gingiva. Eur J Med Res 5.11 (2000): 463-7.
Leenen R et al. A single dose of tea with or without milk increases plasma antioxidant activity in humans. Eur J Clin Nutr 54.1 (2000): 87-92.
Lin YS et al. Factors affecting the levels of tea polyphenols and caffeine in tea leaves. J Agric Food Chem 51.7 (2003): 1864-73.
Liu S et al. Theaflavin derivatives in black tea and catechin derivatives in green tea inhibit HIV-1 entry by targeting gp41. Biochim Biophys Acta 1723.1-3 (2005): 270-81.
Liu T, Chi Y. Experimental study on polyphenol anti-plaque effect in humans. Zhonghua Kou Qiang Yi Xue Za Zhi 35.5 (2000): 383-4.
Maeda K et al. Green tea catechins inhibit the cultured smooth muscle cell invasion through the basement barrier. Atherosclerosis 166.1 (2003): 23-30.
Matsubara S et al. Suppression of Helicobacter pylori-induced gastritis by green tea extract in Mongolian gerbils. Biochem Biophys Res Commun 310.3 (2003): 715-19.
Mukoyama A et al. Inhibition of rotavirus and enterovirus infections by tea extracts. Jpn J Med Sci Biol 44.4 (1991): 181-6.
Nagano J et al. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control 12.6 (2001): 501-8.
Nakachi K et al. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. Biofactors 13.1-4 (2000): 49-54.
Nakachi K, Eguchi H, Imai K. Can teatime increase one's lifetime? Ageing Res Rev 2.1 (2003): 1-10.
Otake S et al. Anticaries effects of polyphenolic compounds from Japanese green tea. Caries Res 25.6 (1991): 438-43.

Pianetti S et al. Green tea polyphenol epigallocatechin-3 gallate inhibits Her-2/neu signaling, proliferation, and transformed phenotype of breast cancer cells. Cancer Res 62.3 (2002): 652-5.
Priyadarshi S et al. Effect of green tea extract on cardiac hypertrophy following 5/6 nephrectomy in the rat. Kidney Int 63.5 (2003): 1785-90.
Rasheed A, Haider M. Antibacterial activity of Camellia sinensis extracts against dental caries. Arch Pharm Res 21.3 (1998): 348-52.
Rhee SJ, Kim MJ, Kwag OG. Effects of green tea catechin on prostaglandin synthesis of renal glomerular and renal dysfunction in streptozotocin-induced diabetic rats. Asia Pac J Clin Nutr 11.3 (2002): 232-6.
Rietveld A, Wiseman S. Antioxidant effects of tea: evidence from human clinical trials. J Nutr 133.10 (2003): 3285-92S.
Sabu MC et al. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. J Ethnopharmacol 83.1-2 (2002): 109-16.
Sachinidis A, Hescheler J. Are catechins natural tyrosine kinase inhibitors? Drug News Perspect 15.7 (2002): 432-8.
Sakanaka S et al. Inhibitory effects of green tea polyphenols on growth and cellular adherence of an oral bacterium, Porphyromonas gingivalis. Biosci Biotechnol Biochem 60.5 (1996): 745-9.
Sayama K et al. Effects of green tea on growth, food utilization and lipid metabolism in mice. In Vivo 14.4 (2000): 481-4.
Schwartz JL et al. Molecular and cellular effects of green tea on oral cells of smokers: a pilot study. Mol Nutr Food Res 49.1 (2005): 43-51.
Sung H et al. In vivo antioxidant effect of green tea. Eur J Clin Nutr 54.7 (2000): 527-9.
Tao P. The inhibitory effects of catechin derivatives on the activities of human immunodeficiency virus reverse transcriptase and DNA polymerases. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 14.5 (1992): 334-8.
Taylor JR, Wilt VM. Probable antagonism of warfarin by green tea. Ann Pharmacother 33.4 (1999): 426-8.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Valcic S et al. Inhibitory effect of six green tea catechins and caffeine on the growth of four selected human tumor cell lines. Anticancer Drugs 7.4 (1996): 461-8.
Varilek GW et al. Green tea polyphenol extract attenuates inflammation in interleukin-2-deficient mice, a model of autoimmunity. J Nutr 131.7 (2001): 2034-9.
Wang YC, Bachrach U. The specific anti-cancer activity of green tea (-)-epigallocatechin-3-gallate (EGCG). Amino Acids 22.2 (2002): 131-43.
Weber JM et al. Inhibition of adenovirus infection and adenain by green tea catechins. Antiviral Res 58.2 (2003): 167-73.
Yokozawa T et al. Effectiveness of green tea tannin on rats with chronic renal failure. Biosci Biotechnol Biochem 60.6 (1996): 1000-5.
Yoo HG et al. Induction of apoptosis by the green tea flavonol (-)-epigallocatechin-3-gallate in human endothelial ECV 304 cells. Anticancer Res 22.6A (2002): 3373-8.
Zhang H et al. Modification of lung cancer susceptibility by green tea extract as measured by the comet assay. Cancer Detect Prev 26.6 (2002): 411-18.
Zhang M et al. Green tea consumption enhances survival of epithelial ovarian cancer. Int J Cancer 112.3 (2004): 465-9.



Guarana



Historical note Guarana has been used by the Amazonian Indians of South America for centuries to enhance energy levels, suppress appetite, increase libido and protect them from malaria. More recently, hot guarana beverages have been adopted by the greater population as a tonic to enhance wellbeing, in much the same way coffee is drunk in Australia.

COMMON NAME
Guarana

OTHER NAMES
Brazilian cocoa, guarana gum, guarana paste, quarana, quarane, uabano, uaranzeiro, zoom

BOTANICAL NAME/FAMILY
Paullinia cupana (family Sapindaceae)

PLANT PART USED
Seeds

CHEMICAL COMPONENTS
Guarana seeds are a rich source of caffeine, containing 3–6% on a dry weight basis (Saldana et al 2002). Other major compounds include theobromine, theophylline, tannins, resins, protein, fat and saponins (Duke 2003).

MAIN ACTIONS
A review of the scientific literature reveals that guarana itself has only recently been the subject of clinical studies. As such, studies pertaining to caffeine are sometimes used to explain the herb's action, an approach that presupposes the other constituents are either inactive or of such weak effect they need not be recognised. Although this approach is convenient and provides us with some understanding of the herb's pharmacological effects, the results of three recent clinical studies suggest that guarana's effects on cognitive function are due to more than its caffeine content.

CNS STIMULANT
Although guarana has not been clinically investigated for its effects on the CNS there is a great deal of evidence to show that caffeine is an antagonist of the adenosine receptor, which produces a net increase in CNS activity because the inhibitory action

of adenosine is blocked (Smith 2002). This results in the release of a variety of neurotransmitters (e.g. noradrenaline, acetylcholine, dopamine, and the GABA/benzodiazepine system).

OTHER ACTIONS

INHIBITS PLATELET AGGREGATION

Guarana inhibits platelet aggregation both in vitro and in vivo (Bydlowski et al 1988, 1991). Decreased thromboxane synthesis may in part explain this activity.

MAY INCREASE GASTRIC ACID SECRETION AND DELAY GASTRIC EMPTYING

This has been demonstrated in a clinical study using a herbal combination known as 'YGD', which contains yerbe mate (leaves of *Ilex paraguayenis*), guarana (seeds of *Paullinia cupana*) and damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) (Andersen & Fogh 2001). Whether stand-alone treatment with guarana will produce similar effects is unknown.

CHEMOPROTECTIVE

Guarana has been shown to be chemoprotective in a mouse hepatocarcinogenesis model (Fukumasu et al 2005). The herb was found to reduce the cellular proliferation of preneoplastic cells.

ANTIBACTERIAL

In vitro data has demonstrated the antibacterial and antioxidant effects of the ethanolic extract of guarana, thought to be due to the phenolic compounds (Basile et al 2005). Guarana was shown to be effective against many pathogens of the digestive tract including *Escherichia coli*, *Salmonella typhimurium* and *Staphylococcus aureus*. This adds weight to the traditional use of guarana for diarrhoea.

OTHER ACTIONS RELATING TO CAFFEINE CONTENT

Although these have not been tested for guarana directly, the caffeine content, which is well absorbed from the herb, may cause mild dilation of the blood vessels; an increase in blood pressure, renin and catecholamine release, urine output, metabolic rate, lipolysis, respiration, intestinal peristalsis; and inhibition of CYP1A2. Caffeine also possesses thermogenic properties (Astrup 2000).

CLINICAL USE

ALERTNESS

Although clinical studies using guarana are not available, anecdotal evidence has suggested that it may produce similar effects to caffeine on subjective feelings of wellbeing, energy, motivation and self-confidence (Mumford et al 1994). Guarana

may exert a mild antidepressant effect as demonstrated in forced-swimming and open field tests in mice (Campos et al 2005)

ENHANCED COGNITIVE FUNCTION AND ALERTNESS

Two recent double-blind studies have confirmed that guarana has significant effects on cognitive function and provide evidence that these effects are not just mediated by the herb's caffeine content (Haskell et al 2005, Kennedy et al 2004).

One double-blind, placebo-controlled study assessed the effects of four different doses of guarana (37.5, 75, 150 and 300 mg) in 22 subjects (Haskell et al 2005). Cognitive performance and mood were assessed at baseline and again 1, 3 and 6 hours after each dose using the Cognitive Drug Research computerised assessment battery, serial subtraction tasks, a sentence verification task and visual analogue mood scales. All doses improved picture and word recognition, results on the Bond–Lader visual analogue scales and caffeine research visual analogue scales showing improvements in alertness and reduced ratings of headache. The two lower doses produced better results than the two higher doses, which were associated with impaired accuracy of choice reaction and on one of the subtraction tests. Several observations suggest that these effects were not due to caffeine alone. Firstly, effects were still apparent 6 hours after administration and secondly, better results were obtained with a dose of 37.5 mg than 300 mg with a caffeine content of less than 5 mg in the lowest dose.

Another double-blind, placebo controlled study investigated the effects of a single dose of guarana (75 mg) on cognition, in combination with and in comparison to ginseng (*Panax ginseng* 200 mg) in 28 healthy volunteers (Kennedy et al 2004). Guarana was shown to produce comparable effects to ginseng in improved task performance with all three treatments better than placebo. However, guarana was superior to ginseng in improving the speed of performed tasks. Once again, given the low caffeine content (9 mg) of the guarana extract used in that study, the effects are unlikely to be attributable to its caffeine content alone, particularly as the dose was shown to be as effective as a 16-fold dose of pure caffeine.

Two previous randomised, double-blind studies have investigated the effects of guarana on cognitive function and produced negative results (Galduroz & Carlini 1994, 1996). One study involving 45 healthy elderly volunteers found that guarana treatment was ineffective (Galduroz & Carlini 1996), which confirmed the findings of a previous study conducted by the same authors (Galduroz & Carlini 1994). Studies in some animal models have produced positive results for both single-dose and long-term administration of guarana, observing a positive effect on memory acquisition and memory maintenance (Espinola et al 1997).

ERGOGENIC AID

Guarana is also used as an ergogenic aid by some athletes, most likely because caffeine and theophylline have been used in this way, to improve performance in training and competition (Graham 2001). No human studies testing guarana for effects on physical performance could be located. Referring to caffeine studies, it appears that ergogenic effects are observed under some conditions but not others (Doherty et al 2002, Hunter et al 2002, Ryu et al 2001). Testing guarana in several animal models has also produced contradictory results. Significant increases in physical capacity have been observed with a dose of 0.3 mg/mL of a guarana suspension after 100 and 200 days' treatment. However, the same effect was not seen with a concentration of 3.0 mg/mL nor of a solution of caffeine 0.1 mg/mL (Espinola et al 1997).

APPETITE SUPPRESSANT AND WEIGHT-LOSS AID

Weight-loss products often contain guarana, in the belief that it suppresses appetite and may have thermogenic and diuretic activities. An animal study designed to evaluate the effects of guarana and decaffeinated guarana found that only the caffeinated herb was effective for weight loss (Lima et al 2005). To date, most clinical studies have investigated the effects of guarana in combination with other herbs. A double-blind, RCT testing a combination of yerbe mate (leaves of *Ilex paraguayenis*), guarana (seeds of *Paullinia cupana*) and damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) found that the preparation significantly delayed gastric emptying, reduced the time to perceived gastric fullness and induced significant weight loss over 45 days in overweight patients (Andersen & Fogh 2001). Another randomised double-blind placebo-controlled trial evaluated the effects of guarana in combination with Ma Huang (*Ephedra* spp.) and concluded that the formula was effective for weight-loss in overweight men after 8 weeks of treatment (Boozer et al 2001). Although encouraging, the effects of guarana as a stand-alone treatment need to be confirmed.

OTHER USES

Traditionally, guarana has been used as an aphrodisiac, treatment for diarrhoea, and as a beverage in some cultures.

DOSAGE RANGE

ACCORDING TO CLINICAL TRIALS

- Cognition, alertness and mood: doses between 37.5 and 75 mg are sufficient to provide effects for at least 6 hours.

For other indications, guarana has not been significantly researched. Based on caffeine content, it is advised that doses should not exceed that amount that will provide approximately 250 mg of caffeine daily. This is equivalent to 2.5–4 g guarana/day, depending on the caffeine content of the preparation.

TOXICITY

Animal tests have shown that high doses of 1000–2000 mg/kg (intraperitoneal and oral) do not induce significant alterations in parameters for toxicological screening, suggesting an absence of toxicity (Mattei et al 1998).

ADVERSE REACTIONS

Due to a lack of clinical studies testing guarana as a stand-alone treatment, it is difficult to determine what adverse reactions may exist.

Based on caffeine content, the following adverse effects may theoretically occur at high doses: agitation, tremor, anxiety, restlessness, headache, seizures, tachycardia and premature ventricular contractions, diarrhoea, gastrointestinal cramping, nausea and vomiting and diuresis.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

CNS STIMULANTS

Additive stimulant activity is theoretically possible — use with caution.

CNS SEDATIVES

Antagonistic effects are theoretically possible due to the herb's CNS stimulant activity. However, one in vivo study found no interaction with pentobarbital. Observe patients taking this combination.

DIURETICS

Additive diuresis effects are theoretically possible — use this combination with caution.

ANTICOAGULANTS

Increased bleeding is theoretically possible as in vitro and in vivo research has identified antiplatelet activity for guarana — use this combination with caution.

ANTIHYPOTENSIVE DRUGS

Antagonist effects theoretically possible — use caution.

ANTIPLATELET DRUGS

Additive effects are theoretically possible as in vitro and in vivo research has identified antiplatelet activity for guarana — observe patients taking this combination.

DIGOXIN

Long-term use of high-dose supplements can result in reduced potassium levels, which lowers the threshold for drug toxicity. Avoid long-term use of high-dose guarana preparations.

DRUGS METABOLISED BY CYP1A2

The inhibitory effect of caffeine on CYP1A2 may cause other interactions, but this is highly speculative for guarana.

CONTRAINDICATIONS AND PRECAUTIONS

Caffeine is no longer a prohibited substance under the Olympic Games antidoping code.

Refer to the following website for further information — www.multimedia.olympic.org.

Contraindicated in hypertension and cardiac arrhythmias.

Use with caution in anxiety states, hypertension, diabetes, gastric ulcers and chronic headache.

Suspend use of concentrated extracts 1 week before major surgery.

PREGNANCY USE

The use of caffeine-containing preparations should be limited during pregnancy; therefore, the caffeine content of guarana products should be checked before use.

PRACTICE POINTS/PATIENT COUNSELLING

- Guarana has mild CNS stimulant properties and may increase alertness, cognitive function and possibly mood.
- Current evidence is inconclusive as to whether guarana also enhances physical stamina.
- It has been used in combination with other herbs as a weight-loss aid with some degree of success. However, it is unknown what role guarana played in achieving these results.
- In some sensitive individuals, guarana may produce CNS stimulant-related side-effects, such as elevated heart rate and blood pressure, tremor, restlessness and excitability.
- Guarana also shows antimicrobial and chemoprotective activities in preliminary studies.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Guarana is a herbal stimulant that increases alertness, cognitive function and possibly mood.

When will it start to work?

Effects are expected 1–2 hours after ingestion, although this will vary depending on the individual and the current level of wakefulness.

Are there any safety issues?

Used in small amounts, it is likely to have a degree of stimulant activity and decrease fatigue; however, as with all stimulants, excessive use or long-term use can be detrimental to health. Guarana should be used with caution in people with hypertension, anxiety states, gastric ulcers, diabetes and some types of cardiovascular disease. It may also interact with a variety of medicines and therefore it is recommended to consult your healthcare professional if you are currently taking pharmaceutical medication.

REFERENCES

Andersen T, Fogh J. Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. J Hum Nutr Diet 14.3 (2001): 243-50.

Astrup A. Thermogenic drugs as a strategy for treatment of obesity. Endocrine 13.2 (2000): 207-12.

Basile A et al. Antibacterial and antioxidant activities of ethanol extract from Paullinia cupana Mart. J Ethnopharmacol 130 (2005): 32-6.

Boozer CN et al. An herbal supplement containing Ma Huang–Guarana for weight loss: a randomized, double-blind trial. Int J Obes.Relat Metab Disord 25.3 (2001): 316-24.

Brice CF, Smith AP. Effects of caffeine on mood and performance: a study of realistic consumption. Psychopharmacology (Berl) 164.2 (2002): 188-92.

Bydlowski SP, D'Amico EA, Chamone DA. An aqueous extract of guarana (Paullinia cupana) decreases platelet thromboxane synthesis. Braz J Med Biol Res 24.4 (1991): 421-4.

Bydlowski SP, Yunker RL, Subbiah MT. A novel property of an aqueous guarana extract (Paullinia cupana): inhibition of platelet aggregation in vitro and in vivo. Braz J Med Biol Res 21.3 (1988): 535-8.

Campos AR et al. Acute effects of guarana (Paullinia cupana Mart.) on mouse behaviour in forced swimming and open field tests. Phytother Res 19.5 (2005): 441-3.

Doherty M et al. Caffeine is ergogenic after supplementation of oral creatine monohydrate. Med Sci Sports Exerc 34.11 (2002): 1785-92.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture-Agricultural Research Service-National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, March 2003. www.ars-grin.gov/duke.

Espinola EB et al. Pharmacological activity of Guarana (Paullinia cupana Mart.) in laboratory animals. J Ethnopharmacol 55.3 (1997): 223-9.

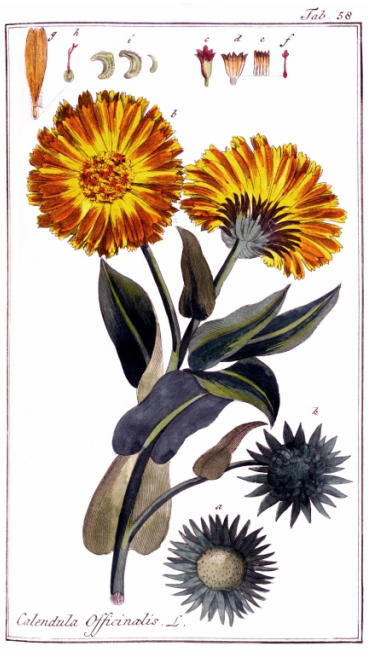
Fukumasu H et al. Chemopreventive effects of Paullinia cupana Mart var. sorbilis, the guarana, on mouse hepatocarcinogenesis. Cancer Lett 233.1 (2006): 158-64.

Galduroz JC, Carlini EA. Acute effects of the Paullinia cupana, Guarana on the cognition of normal volunteers. Rev Paul Med 112.3 (1994): 607-11.

Galduroz JC, Carlini EA. The effects of long-term administration of guarana on the cognition of normal, elderly volunteers. Rev Paul Med 114.1 (1996): 1073-8.

Graham TE. Caffeine and exercise: metabolism, endurance and performance. Sports Med 31.11 (2001): 785-807.
Haskell CF et al. A 10 dose ranging study of the cognitive and mood effects of guarana. Behav Pharmacol 16 (Suppl 1) (2005): S26.
Hunter AM et al. Caffeine ingestion does not alter performance during a 100-km cycling time-trial performance. Int J Sport Nutr Exerc Metab 12.4 (2002): 438-52.
Kennedy DO et al. Improved cognitive performance in human volunteers following administration of guarana (Paullinia cupana) extract: comparison and interaction with Panax ginseng. Pharmacol Biochem Behav 79.3 (2004): 401-11.
Lima WP et al. Lipid metabolism in trained rats: Effect of guarana (Paullina cupana Mart.) supplementation. Clin Nutr 24 (2005): 1019-28.
Mattei R et al. Guarana (Paullinia cupana): toxic behavioral effects in laboratory animals and antioxidants activity in vitro. J Ethnopharmacol 60.2 (1998): 111-16.
Mumford GK et al. Discriminative stimulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology (Berl) 115.1-2 (1994): 1-8.
Ryu S et al. Caffeine as a lipolytic food component increases endurance performance in rats and athletes. J Nutr Sci Vitaminol (Tokyo) 47.2 (2001): 139-46.
Saldana MD et al. Extraction of methylxanthines from guarana seeds, mate leaves, and cocoa beans using supercritical carbon dioxide and ethanol. J Agric Food Chem 50.17 (2002): 4820-6.
Smith A. Effects of caffeine on human behavior. Food Chem Toxicol 40.9 (2002): 1243-55.

Gymnema sylvestre



Historical note Gymnema has been called the sugar destroyer because the leaf suppresses the ability to taste sweet on the tongue. It has been used to treat diabetes, as well as to aid metabolic control when combined with other herbal medicines.

COMMON NAME
Gymnema

OTHER NAMES
Asclepias geminate, gur-mar (sugar destroyer), gemnema melicida, gokhru, gulrmaro, gurmar, gurmara, gurmarbooti, kar-e-khask, kharak, merasingi, meshasringi, masabedda, *Periploca sylvestris*, sirukurinjan

BOTANICAL NAME/FAMILY
Gymnema sylvestre (family Asclepiadaceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Gymnema contains gymnemasaponins, gymnemasides, gymnemic acids and gypenosides (Duke 2003), as well as a range of nutrients including ascorbic acid, beta-carotene, chromium, iron, magnesium and potassium. The main active chemical components appear to be the gymnemic acids, gymnemasaponins and the polypeptide gurmarin.

MAIN ACTIONS

SWEET TASTE SUPPRESSION
The constituent, gymnemic acid, inhibits the ability to taste sweetness in animal models (Fushiki et al 1992, Harada & Kasahara 2000, Kurihara 1969, 1992) and humans (Frank et al 1992). In humans, the administration of 5 mmol/L gurmarin to the tongue raised the threshold ability to taste sucrose from 0.01 mol/L to 1 mol/L for several hours. It is suggested that gurmarin acts on the apical side of the taste cell, possibly by binding to the sweet taste receptor protein (Miyasaka & Imoto 1995).

ANTIDIABETIC

Gymnema's antidiabetic activity appears to be due to a combination of mechanisms, including reduction of intestinal absorption of glucose (Shimizu et al 2001), inhibition of active glucose transport in the small intestine (Yoshioka 1986), suppression of glucose-mediated release of gastric inhibitory peptide (Fushiki et al 1992), increased activity of the enzymes responsible for glucose uptake and use (Shanmugasundaram et al 1983), stimulation of insulin secretion (Persaud et al 1999, Sugihara et al 2000) and increasing the number of islets of Langerhans and number of pancreatic beta cells (Prakash et al 1986, Shanmugasundaram et al 1990). *Gymnema montanum* (a related species) has also been shown to have antidiabetic, antiperoxidative and antioxidant effects in diabetic rats (Ananthan et al 2003) and antioxidant activity evident in the liver, kidney (Ananthan et al 2004) and brain tissue (Ramkumar et al 2004).

Animal studies suggest that gymnema will reduce blood sugar levels in response to a glucose load in streptozotocin-induced mildly diabetic rats (Okabayashi et al 1990) and alloxan-induced diabetic rats (Shanmugasundaram et al 1983, Srivastava et al 1985), but will not affect blood sugar levels in normal or spontaneously hypertensive rats (Preuss et al 1998). Gymnema extract has been found to return blood sugar and insulin levels to normal in streptozotocin-induced diabetic rats after 20–60 days and to double the number of pancreatic islet and beta cells (Shanmugasundaram et al 1990), as well as maintaining stable blood glucose levels in rats given beryllium nitrate (Prakash et al 1986).

There are currently two negative studies. One study using a dose of 120 mg/kg/day oral gymnema did not find improvements in insulin resistance in insulin-resistant, streptozotocin-induced diabetic rats (Tominaga et al 1995) and the other study, from Brazil using dried powdered leaves of gymnema, found no effect on blood glucose, body weight or food or water consumption in non-diabetic and alloxan-diabetic rats (Galletto et al 2004).

Gymnemic acids have demonstrated hypoglycaemic activity in dexamethasone-induced hyperglycaemic mice (Gholap & Kar 2005) and gymnema, together with other ayurvedic herbs, has been shown to have hypoglycaemic activity in streptozotocin-induced diabetic mice (Mutalik et al 2005) and rats (Babu & Prince 2004). Gymnema has also been shown to protect the lens against sugar-induced cataract by multiple mechanisms (Moghaddam et al 2005) and protect against the adverse effects of lipid peroxidation on brain and retinal cholinesterases, suggesting a use in preventing the cholinergic neural and retinal complications of hyperglycaemia in diabetes (Ramkumar et al 2005).

REDUCES CHOLESTEROL LEVELS

Gymnema extract reduces fat digestibility and increases faecal excretion of cholesterol, neutral sterols and acid steroids, as well as reducing serum cholesterol and triglyceride levels, according to two animal studies (Nakamura et al 1999, Shigematsu et al 2001). Nakamura et al also found that oral administration of gymnema decreased body weight and food intake.

ANTIMICROBIAL ACTIVITY

The ethanolic extract of *Gymnema sylvestre* leaves demonstrated antimicrobial activity against *Bacillus pumilis, B. subtilis, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Satdive et al 2003). Antiviral activity has also been reported (Porchezhian & Dobriyal 2003).

OTHER ACTIONS

Gymnema has been found to contain an ATPase inhibitor, which has been shown to block the effect of ATPase from snake venom (Manjunatha & Veerabasappa 1982). According to one animal study, oral administration of gymnema reduces body weight and food intake (Nakamura et al 1999).

CLINICAL USE

SWEET TASTE SUPPRESSION AND WEIGHT LOSS

A controlled trial of normal volunteers found that an aqueous gymnema extract with concentrated gymnemic acid reduced sweetness perception by 50%, resulting in reduced caloric consumption 1.5 hours after the sweetness-numbing effect stopped (Brala & Hagen 1983). This result supports the findings of animal studies. In a 6-week randomised, double-blind, placebo-controlled study, a multi-herbal formula that included gymnema was found to significantly reduce body weight and fat loss in obese adults after 6 weeks (Woodgate & Conquer 2003); however, the role of gymnema in achieving these results is unknown.

DIABETES TYPE 1 AND TYPE 2

Orally, gymnema leaf is used to treat both type 1 and type 2 diabetes and hyperglycaemia. There are two clinical trials that suggest that gymnema may be useful in reducing blood glucose levels in both type 1 and type 2 diabetes. In one study the ability of the GS4 extract (400 mg/day) to supplement the use of conventional oral hypoglycaemic agents (glibenclamide or tolbutamide) was studied in 22 patients with type 2 diabetes over 18–20 months. Treatment resulted in a significant reduction in fasting blood glucose (174 ± 7 vs 124 ± 5 mg/dL), HbA_{1c} (11.91 ± 0.3 vs 8.48 ± 0.13%) and glycosylated plasma protein levels (3.74 ± 0.07

vs 2.46 ± 0.05 μg hexose/mg protein) and raised insulin levels, whereas no changes were observed in the control group. This allowed for a decrease in conventional drug dosage and in five cases, blood glucose homeostasis was maintained with GS4 alone, suggesting that beta-cell function may have been restored (Baskaran et al 1990). In a second study, 27 type 2 diabetes patients were treated with 400 mg of an aqueous extract of gymnema in addition to insulin. Insulin requirements were reduced, as were fasting blood sugar levels, HbA_{1c}, glycosylated plasma protein levels and serum lipids (Shanmugasundaram et al 1990).

A small, double-blind, randomised, placebo-controlled trial of a multi-herbal Ayurvedic formula containing gymnema showed significantly improved glucose control and reduced HbA_{1c} levels in patients with type 2 diabetes within the 3-month test period (Hsia et al 2004).

Clinical note — Herbs and diabetes

Diabetes has been recognised since ancient times and as early as 700–200 BC two types of diabetes were recorded in India, one of which was diet related and the other was described as genetic. Diabetes has also been recognised in China for thousands of years, where it is attributed to yin deficiency and treated with an integrated approach that involves more than lowering blood glucose. At least 30 different herbal medicines are used in the management of diabetes and its complications, with several of these having outstanding beneficial potential.

HYPERCHOLESTEROLAEMIA AND HYPERTRIGLYCERIDAEMIA

Short-term animal studies have shown that gymnema extracts are able to reduce serum cholesterol and triglyceride levels in experimentally induced hyperlipidaemic rats (Bishayee & Chatterjee 1994) and in spontaneously hypertensive rats (Preuss et al 1998), as well as in humans with type 2 diabetes (Shanmugasundaram et al 1990). These results have not yet been established by long-term studies.

OTHER USES

Gymnema has been used as a snake bite cure because it inhibits venom ATPase (Manjunatha & Veerabasappa 1982), and has also been used as a leaf paste to treat toe mycosis.

In Ayurvedic medicine, gymnema is used as an antimalarial, digestive stimulant, laxative and diuretic and as a treatment for cough, fever, urinary conditions and diabetes.

DOSAGE RANGE

The typical therapeutic dose of an extract, standardised to contain 24% gymnemic acids, is 400–600 mg/day. When used to regulate blood sugar, gymnema may best be administered in divided doses with meals.

DIABETES

- Liquid extract (1:1): 25–75 mL/week or 3.6–11.0 mL/day.
- 6–60 g/day of dried leaf infusion

SWEET CRAVING AND REDUCING SWEET PERCEPTION

- Liquid extract (1:1): 1–2 mL dropped onto the tongue and rinsed off — repeat every 2–3 hours as required.

ADVERSE REACTIONS

Theoretically, gastric irritation can occur, because of the saponin content. There are two case reports of hepatotoxicity resulting from the consumption of a weight-loss formula containing gymnema and other herbs, including *Garcinia cambogia*, willow bark, glucomannan, green tea and guarana (Stevens et al 2005). In one study, gymnema was found to have a toxic effect in mice, producing increased lipid peroxidation at doses of 26.8 mg/kg, but was safe and antiperoxidative at doses of 13.4 mg/kg (Gholap & Kar 2005). In another study it was concluded that there was no toxic effect in rats treated with gymnema at doses of more than 500 mg/kg for 52 weeks (Ogawa et al 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

HYPOGLYCAEMIC AGENTS AND INSULIN

Gymnema may enhance the blood-glucose-lowering effects of insulin and hypoglycaemic agents, so should be used with caution. In practice the interaction may be useful, as a reduction in the drug dose could theoretically be achieved under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Blood glucose levels should be monitored closely when used in conjunction with insulin and hypoglycaemic agents.

PREGNANCY USE

There is insufficient reliable information available about the safety of gymnema in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Gymnema suppresses the ability to taste sweet on the tongue.
- It may be useful as a weight-loss aid.
- Clinical studies have shown that gymnema can be used to help control blood sugar levels in diabetes.
- When used with hypoglycaemic medications, blood sugar levels need to be monitored to prevent hypoglycaemia.
- Preliminary research suggests that it may also have a role in elevated cholesterol and triglyceride levels.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Gymnema has the uncanny ability to reduce the tongue's perception of sweetness. It can also stabilise blood sugar levels and may be useful as a weight-loss aid.

When will it start to work?

It reduces the taste of sweetness rapidly, lasting for several hours, but effects on blood sugar develop with long-term use.

Are there any safety issues?

Diabetic patients on medication should carefully monitor their blood sugar levels when taking this herb, because it may further reduce levels.

REFERENCES

Ananthan R et al. Antidiabetic effect of Gymnema montanum leaves: effect on lipid peroxidation induced oxidative stress in experimental diabetes. Pharmacol Res 48.6 (2003): 551-6.

Ananthan R et al. Modulatory effects of Gymnema montanum leaf extract on alloxan-induced oxidative stress in Wistar rats. Nutrition 20.3 (2004): 280-5.

Babu PS, Prince PSM. Antihyperglycaemic and antioxidant effect of hyponidd, an ayurvedic herbomineral formulation in streptozotocin-induced diabetic rats. J Pharm Pharmacol 56.11 (2004): 1435-42.

Baskaran K et al. Antidiabetic effect of leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. J Ethnopharmacol 30(3) (1990): 295-300.

Bishayee A, Chatterjee M. Hypolipidaemic and antiatherosclerotic effects of oral Gymnema sylvestre R. Br leaf extract in albino rats fed on a high fat diet. Phytother Res 8 (1994): 118-20.

Brala PM, Hagen RL. Effects of sweetness perception and calorie value of a preload on short term intake. Physiol Behav 30(1) (1983): 1-9.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003. www.ars-grin.gov/duke.

Frank RA et al. The effect of Gymnema sylvestre extracts on the sweetness of eight sweeteners. Chem Senses 17.5 (1992): 461-79.

Fushiki T et al. An extract of Gymnema sylvestre leaves and purified gymnemic acid inhibits glucose-stimulated gastric inhibitory peptide secretion in rats. J Nutr 122.12 (1992): 2367-73.

Galletto R et al. Absence of antidiabetic and hypolipidemic effect of Gymnema sylvestre in non-diabetic and alloxan-diabetic rats. Braz Arch Biol Technol 47.4 (2004): 545-51.

Gholap S, Kar A. Gymnemic acids from Gymnema sylvestre potentially regulates dexamethasone-induced hyperglycemia in mice. Pharm Biol 43.2 (2005): 192-5.
Harada S, Kasahara Y. Inhibitory effect of gurmarin on palatal taste responses to amino acids in the rat. Am J Physiol Reg Integr Comp Physiol 278.6 (2000): R1513-17.
Hsia SH et al. Effect of Pancreas Tonic (an Ayurvedic herbal supplement) in type 2 diabetes mellitus. Metab Clin Exp 53.9 (2004): 1166-73.
Kurihara T. Antisweet activity of gymnemic acid A1 and its derivatives. Life Sci 8(9) (1969): 537-43.
Kurihara Y. Characteristics of antisweet substances, sweet proteins, and sweetness-inducing proteins. Crit Rev Food Sci Nutr 32.3 (1992): 231-52.
Manjunatha Kini R, Veerabasappa Gowda T. Studies on snake venom enzymes. Part II: Partial characterization of ATPases from Russell's viper (Vipera russelli) venom and their interaction with potassium gymnemate. Indian J Biochem Biophys 19.5 (1982): 342-6.
Miyasaka A, Imoto T. Electrophysiological characterization of the inhibitory effect of a novel peptide gurmarin on the sweet taste response in rats. Brain Res 676.1 (1995): 63-8.
Moghaddam MS et al. Effect of Diabecon on sugar-induced lens opacity in organ culture: mechanism of action. J Ethnopharmacol 97.2 (2005): 397-403.
Mutalik S et al. Effect of Dianex, a herbal formulation on experimentally induced diabetes mellitus. Phytother Res 19.5 (2005): 409-15.
Nakamura Y et al. Fecal steroid excretion is increased in rats by oral administration of gymnemic acids contained in Gymnema sylvestre leaves. J Nutr 129.6 (1999): 1214-22.
Ogawa Y et al. Gymnema sylvestre leaf extract: a 52-week dietary toxicity study in Wistar rats. J Food Hyg Soc Jpn 45.1 (2004): 8-18.
Okabayashi Y et al. Effect of Gymnema sylvestre, R.Br. on glucose homeostasis in rats. Diabetes Res Clin Pract 9(2) (1990): 143-8.
Persaud SJ et al. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J Endocrinol 163.2 (1999): 207-12.
Porchezhian E, Dobriyal RM. An overview on the advances of Gymnema sylvestre: Chemistry, pharmacology and patents. Pharmazie 58.1 (2003): 5-12.
Prakash AO et al. Effect of feeding Gymnema sylvestre leaves on blood glucose in beryllium nitrate treated rats. J Ethnopharmacol 18.2 (1986): 143-6.
Preuss HG et al. Comparative effects of chromium, vanadium and Gymnema sylvestre on sugar-induced blood pressure elevations in SHR. J Am Coll Nutr 17(2) (1998): 116-23.
Ramkumar KM et al. Modulatory effect of Gymnema montanum leaf extract on brain antioxidant status and lipid peroxidation in diabetic rats. J Med Food 7.3 (2004): 366-71.
Ramkumar KM et al. Modulation of impaired cholinesterase activity in experimental diabetes: effect of Gymnema montanum leaf extract. J Basic Clin Physiol Pharmacol 16.1 (2005): 17-35.
Satdive RK, Abhilash P, Fulzele DP. Antimicrobial activity of Gymnema sylvestre leaf extract. Fitoterapia 74.7 (2003): 699-701.
Shanmugasundaram KR et al. Enzyme changes and glucose utilisation in diabetic rabbits: The effect of Gymnema sylvestre, R.Br. J Ethnopharmacol 7.2 (1983): 205-34.
Shanmugasundaram KR et al. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Ethnopharmacol 30.3 (1990): 265-79.
Shigematsu N et al. Effect of administration with the extract of Gymnema sylvestre R. Br leaves on lipid metabolism in rats. Biol Pharm Bull 24.6 (2001): 713-17.
Shimizu K et al. Structure-activity relationships of triterpenoid derivatives extracted from Gymnema inodorum leaves on glucose absorption. Jpn J Pharmacol 86.2 (2001): 223-9.
Srivastava Y et al. Hypoglycemic and life-prolonging properties of Gymnema sylvestre leaf extract in diabetic rats. Isr J Med Sci 21(6) (1985): 540-2.
Stevens T et al. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut [7]. Ann Intern Med 142.6 (2005): 477-8.

Sugihara Y et al. Antihyperglycemic effects of gymnemic acid IV, a compound derived from Gymnema sylvestre leaves in streptozotocin-diabetic mice. J Asian Natural Prod Res 2.4 (2000): 321-7.
Tominaga M et al. Effects of seishin-renshi-in and Gymnema sylvestre on insulin resistance in streptozotocin-induced diabetic rats. Diabetes Res Clin Pract 29(1) (1995): 11-17.
Woodgate DE, Conquer JA. Effects of a stimulant-free dietary supplement on body weight and fat loss in obese adults: a six-week exploratory study. Curr Ther Res 64.4 (2003): 248-62.
Yoshioka S. Inhibitory effects of gymnemic acid and an extract from the leaves of Zizyphus jujuba on glucose absorption in the rat small intestine. J Yonago Med Assoc 37 (1986): 142-54.

Hawthorn

Historical note The name 'hawthorn' comes from 'hedgethorn', after its use as a living fence in much of Europe. Dioscorides and Paracelsus praised hawthorn for its heart-strengthening properties and it is also known in TCM. It has since been shown to have many different positive effects on the heart and is a popular prescription medicine in Germany for heart failure (Rigelsky & Sweet 2002).

COMMON NAME
Hawthorn

OTHER NAMES
Aubepine, bianco spino, crataegi (azarolus, flos, folium, folium cum flore [flowering top], fructus [berry], nigra, pentagyna, sinaica boiss), English hawthorn, Chinese hawthorn, fructus oxyacanthae, fructus spinae albae, hagedorn, hedgethorn, maybush, maythorn, meidorn, oneseed hawthorn, shanzha, weissdorn, whitehorn

BOTANICAL NAME/FAMILY
Crataegus laevigata, *C. cuneata*, *C. oxyacantha*, *C. monogyna*, *C. pinnatifida* (family Rosaceae [Rose])

PLANT PARTS USED
Extracts of the leaf and flower are most commonly used, although the fruit (berries) may also be used.

CHEMICAL COMPONENTS
Leaves and flowers contain about 1% flavonoids, such as rutin, quercitin, vitexin, hyperisise, 1–3% oligomeric procyanidins including catechin and epicatechin, triterpenes, sterols, polyphenols, coumarins, tannins (Blumenthal et al 2000). Although the therapeutic actions cannot be attributed to single compounds, the herb has been standardised to flavonoid content (hyperoside as marker) and procyanidins (epicatechin as marker). RP WS 1442 is a hydro-alcoholic extract of hawthorn prepared from leaves and blossoms and standardised to 18.75% oligomeric procyanidins. It has been found that bioequivalent extracts as determined by noradrenaline-induced contraction of isolated guinea pig aorta rings can be obtained using 40–70% ethanol or methanol as the extraction solvent, whereas aqueous

extracts had markedly different constituents and pharmacological effects (Vierling et al 2003).

MAIN ACTIONS

CARDIOVASCULAR EFFECTS

Hawthorn has been extensively studied, and there is good research evidence to support cardiovascular actions that include increasing the force of myocardial contraction (positive inotropic action), increasing coronary blood flow, reducing myocardial oxygen demand, protecting against myocardial damage, improving heart rate variability, as well as hypotensive and antiarrhythmic effects (Mills & Bone 2000). Hawthorn therefore differs from other inotropic agents, which reduce the refractory period and increase the risk of arrhythmias (Joseph et al 1995).

In vitro studies using isolated frog and guinea pig heart preparations, as well as in vivo studies on dogs and cats, report increased myocardial contractility and stroke volume. In vitro and in vivo studies on rats report an antiarrhythmic action and a significant cardioprotective effect during cardiac ischaemia (al Makdessi et al 1996, 1999, Jayalakshmi & Devaraj 2004, Min et al 2005, Veveris et al 2004).

Hawthorn flavonoids have also been shown to decrease the cytotoxicity of hypoxia to human umbilical vein endothelial cells in vitro (Lan et al 2005), as well as protect against delayed cell death caused by ischaemia/reperfusion brain injury in gerbils (Zhang et al 2004). These effects have been attributed to improving energy metabolism, scavenging oxygen free radicals and inhibiting production of free radicals in ischaemic myocardium (Min et al 2005, Zhang et al 2004).

Dose-dependent increases in coronary blood flow have been shown in isolated human coronary arteries and it has been suggested that this is caused by membrane hyperpolarisation of vascular smooth-muscle cells due to potassium channel activation (Siegel et al 1996). Other in vitro evidence suggests that phosphodiesterase inhibition may underlie the myocardial action of hawthorn (Schussler et al 1995).

Much of hawthorn's cardiovascular activity is attributed to its flavonoid constituents (Nemecz 1999) and hawthorn extract is classified as a flavonoid drug in Germany. Studies using isolated guinea pig hearts suggest that the oligomeric procyanidins contribute to the vasodilating and positive inotropic effects of hawthorn (Schussler et al 1995), and ischaemia–reperfusion studies in rats suggest that these compounds are also responsible for cardioprotective effects (Chatterjee et al 1997).

Several procyanidins have shown ACE inhibition in vitro, in a reversible and non-competitive manner (Uchida et al 1987). Although the original study identifying this

activity tested isolated procyanidins from another herb, they are found in relatively high concentration in hawthorn extracts (Murray 1995).

ANTIOXIDANT

It has been suggested that the part of the mechanism for hawthorn's cardiovascular protective effects may be due to protection against human LDL from oxidation or indirect protection via maintenance of alpha-tocopherol (Zhang et al 2001), as hawthorn extract has been found to possess antioxidant activity in vitro (Periera et al 2000, Rajalakshmi et al 2000) with effective inhibition of oxidative processes, efficient scavenging of O_2-and possible enhancement of glutathione biosynthesis (Ljubuncic et al 2005).

Hawthorn's free radical scavenging capacity is considered to relate to its total phenolic proanthocyanidin and flavonoid content (Bahorun et al 1996, Rakotoarison et al 1997). This is supported by a study that demonstrated that the capacity of hawthorn extracts to inhibit Cu^{2+}-induced LDL oxidation is linked to their content in total polyphenols, proanthocyanidins (global and oligomeric forms), as well as to their content of two individual phenolics: a flavonol, the dimeric procyanidin B2, and a flavonol glycoside, hyperoside (Quettier-Deleu et al 2003). The highest antioxidant activity appears to be found in the flower buds, which are high in proanthocyanidin content, and the leaves, which are high in flavonoid content (Bahorun et al 1994).

LIPID-LOWERING

The monomeric catechins and oligomeric procyanidins are thought to contribute to a hypocholesterolaemic effect. This may occur through a variety of mechanisms including an upregulation of hepatic LDL receptors, enhanced degradation of cholesterol to bile acids and suppression of cholesterol biosynthesis (Rajendran et al 1996), as well as inhibition of cholesterol absorption mediated by downregulation of intestinal acyl CoA:cholesterol acyltransferase activity (Zhang et al 2002).

A traditional multi-herbal Chinese formula containing hawthorn has been found to prevent experimental hypercholesterolaemia in rats, probably due to its choleretic function (Cheng et al 2004). A different multi-herbal Chinese formula was also found to protect vascular endothelial cells from excess cholesterol in vivo (Tu et al 2003).

ANTIVIRAL

The *O*-glycosidic flavonoids and the oligomeric proanthocyanidins exhibited significant inhibitory activity against herpes simplex virus type 1 in vitro (Shahat et al 2002).

ANTI-INFLAMMATORY

Flavonoids from hawthorn have demonstrated anti-inflammatory and hepatoprotective activity in vitro and in vivo. It is thought that this is achieved by reducing the release of PGE_2 and NO in vitro, as well as decreasing the serum levels of the hepatic enzyme markers, reducing the incidence of liver lesions, such as neutrophil infiltration and necrosis, and decreasing the hepatic expression of iNOS and COX-2 in vivo (Kao et al 2005).

A hydro-alcoholic extract from the flower heads of *C. oxyacantha* has also been found to inhibit thromboxane A2 biosynthesis in vitro (Nemecz 1999).

Hawthorn fruit has been shown to be protective in experimental models of inflammatory bowel disease in mice with restoration of body weight and colon length, increased haemoglobin count, reduced signs of inflammation, such as infiltration by polymorphonuclear leukocytes and multiple erosive lesions, along with improved survival (Fujisawa et al 2005).

OTHER ACTIONS

Hawthorn may decrease uterine tone and motility and exert antispasmodic and analgesic effects. The high procyanidin content in the herb provides a theoretical basis for other actions such as antimicrobial, anti-allergic and collagen-stabilising effects.

An aqueous extract of hawthorn leaves exhibited hypoglycaemic activity in streptozotocin-diabetic rats, but not in normal rats, without affecting basal plasma insulin concentrations (Jouad et al 2003). Hawthorn has also been found to have hepatoprotective effects in rats with myocardial infarction, with protection against alterations in tissue marker enzymes of experimentally induced liver injury and a reversal of histological changes (Thirupurasundari et al 2005). A multi-herbal Chinese medicine formula containing hawthorn reversed alcohol-induced fatty liver and liver damage in rats (Kwon et al 2005).

CLINICAL USE

CONGESTIVE HEART FAILURE

There is considerable experimental and clinical evidence supporting the use of hawthorn as an effective treatment for congestive cardiac failure in patients with slight, mild limitation of activity who are comfortable at rest or with mild exertion (i.e. NYHA class II).

A meta-analysis of rigorous clinical trials of the use of hawthorn extract to treat patients with chronic heart failure (NYHA classes I–III) included eight trials involving 632 subjects. The results of the meta-analysis showed that treatment with standard-

ised hawthorn extracts produced significant improvement in maximal workload, pressure–heart rate product, as well as symptoms such as dyspnoea and fatigue as compared with placebo (Pittler et al 2003). The hawthorn extract most commonly used in these trials was WS 1442, which is standardised to 18.8% oligomeric procyanidins. In some cases, hawthorn extract was used as an adjunct to standard therapy (such as diuretics) and the daily dose ranged from 160 mg to 1800 mg.

A review of the results of 13 clinical trials published from 1981 to 1996, involving over 839 patients, suggests that a daily dose of 900 mg hawthorn extract improves exercise tolerance, anaerobic threshold and ejection fraction, as well as subjective symptoms (Kraft 2000). Studies comparing hawthorn extract LI 132 (Crataegutt novo 450, 1 tablet twice daily) to the ACE inhibitor captopril suggests that the LI 132 extract is comparable in effectiveness to a dose of 37.5 mg captopril, but may be better tolerated (Tauchert 1994).

These findings are supported by the results of more recent studies. A recent prospective, cohort study involving 952 patients with NYHA stage II heart failure compared the use of the WS 1442 extract of hawthorn either alone or in conjunction with conventional therapy to conventional medication. After 2 years, the hawthorn cohort was found to have similar or more pronounced improvements than the conventional medication group with reduced fatigue, stress dyspnoea, and palpitations along with marked reduction in the use of drugs such as ACE inhibitors, cardiac glycosides, diuretics and beta-blockers (Habs 2004).

In two further double-blind studies of NYHA class II patients, one using the WS 1442 extract in 40 patients (Zapfe 2001) and another using the Rob 10 standardised extract of fresh hawthorn berries in 88 patients (Rietbrock et al 2001), 3 months' treatment with hawthorn led to significantly improved exercise tolerance, reduced subjective symptoms, and was found to be safe and well tolerated. In 2003, another placebo-controlled, randomised, parallel-group, multicentre trial confirmed the efficacy and safety of a standardised extract of fresh berries of *Crataegus oxyacantha* L. and *C. monogyna* Jacq. (crataegisan) in patients with cardiac failure NYHA class II (Degenring et al 2003). This study of 143 patients (mean age 64.8 years) used a dose of 30 drops of the extract taken three times daily for 8 weeks and found a significant increase in exercise tolerance, but no difference in symptoms or blood pressure–heart rate product. Researchers suggested that dyspnoea and fatigue do not occur until a significantly higher wattage had been reached in the bicycle exercise testing and that further improvements were likely to occur if treatment time was extended.

In another RCT of patients with marked limitation of activity, who were comfortable only at rest (NYHA class III), 209 patients received standardised extract

WS 1442 at doses of either 900 mg or 1800 mg or placebo in addition to pre-existing diuretic treatment. After 16 weeks, significant dose-dependent improvements in exercise capacity and clinical signs and symptoms were seen with the herbal extract, with patients on the higher dosage experiencing less adverse events such as dizziness and vertigo (Tauchert et al 2002). A large, international, multicentre double-blind study is investigating the influence of the WS 1442 extract on mortality of up to 2300 cardiac patients over 24 months (Holubarsch et al 2000).

In an observational cohort study of 212 patients, a homeopathic hawthorn preparation was found to be non-inferior to standard treatment (ACE inhibitor/diuretics) for mild cardiac insufficiency in all parameters except blood pressure reduction (Schroder et al 2003).

As well as being shown to be effective when used alone, hawthorn is effective in reducing symptoms of congestive heart failure when used in combination with other herbs such as camphor. This was demonstrated in an open study of 319 patients (Harder & Rietbrock 1990), as well as in a double-blind study of 190 patients (Schmidt et al 2000).

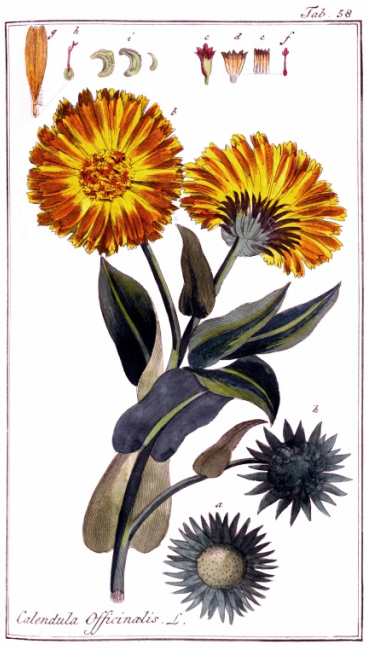
Commission E supports the use of hawthorn leaf and flower to treat decreased cardiac output (NYHA class II) (Blumenthal et al 2000).

ARRHYTHMIAS, HYPERTENSION AND ATHEROSCLEROSIS

In addition to treating congestive cardiac failure, hawthorn has traditionally been used to treat arrhythmias, hypertension and atherosclerosis, with some evidence to support these uses, although large controlled clinical studies are required (Petkov 1979).

In one double-blind RCT of 92 subjects aged 40–60 years, a hydro-alcoholic extract of Iranian hawthorn (*C. curvisepala* Lind) given three times daily was found to produce a significant decrease in both systolic and diastolic blood pressure after 3 months. Antihypertensive activity was also observed in one uncontrolled study that used hawthorn berry tincture (equivalent to 4.3 g/day of berry) (Mills & Bone 2000), whereas three randomised, double-blind, placebo-controlled, clinical trials have shown that a combination of natural D-camphor and an extract from fresh hawthorn berries was effective in treating orthostatic hypotension (Georg Belz & Loew 2003, Hempel et al 2005, Kroll et al 2005).

One study that focused primarily on mild hypertension compared the hypotensive effect of low dose hawthorn extract (500 mg) and magnesium supplements, individually and in combination, to placebo. Walker et al found hawthorn treatment significantly reduced resting diastolic blood pressure at week 10 compared with the other groups. In addition, a trend towards a reduction in anxiety was also observed



with hawthorn treatment, which is an interesting observation as sedative effects have been observed in animal models.

HYPERLIPIDAEMIA

Hawthorn fruit extract has been reported to reduce serum lipid levels, as well as to reduce lipid deposits in the liver and aortas of rats (Shanthi et al 1994) and rabbits (Zhang et al 2002) fed a hyperlipidaemic diet. In combination with other traditionally used Chinese herbs, hawthorn has been shown to also reduce serum lipid levels in both animals (He et al 1990, la Cour et al 1995) and humans (Chen et al 1995, Guan et al 1995).

ADJUSTMENT DISORDER

The results of a double-blind trial of 182 people suggest that hawthorn in combination with other herbs such as passiflora and valeriana may be beneficial for people with adjustment disorder with anxious mood (Bourin et al 1997). Another double-blind trial of 264 people found that a combination containing *Crataegus oxyacantha* and *Eschscholtzia californica* along with magnesium was effective in treating mild-to-moderate anxiety disorder (Hanus et al 2004).

OTHER USES

As it has a high flavonoid content, hawthorn is also used to strengthen connective tissue, decrease capillary fragility, and prevent collagen destruction of joints and therefore may be beneficial in the treatment of certain connective tissue disorders (Mills & Bone 2000). Hawthorn has been traditionally used as a diuretic and to treat kidney and bladder stones. In practice, it is also used at the first signs of a herpes simplex infection, to prevent lesion formation and halt infection.

DOSAGE RANGE

- Infusion of dried herb: 0.2–2 g three times daily.
- Tincture of leaf (1:5): 3.5–17.5 mL/day.
- Fluid extract (1:2): 3–6 mL/day.
- Herpes simplex outbreak: 4 mL three times daily at the first sign of infection for a maximum of 2 days.

TOXICITY

No target toxicity to 100-fold the human dose of the WS 1442 extract is defined (Schlegelmilch & Heywood 1994). This is in contrast to inotropic drugs, such as digoxin, which generally have a low therapeutic index.

ADVERSE REACTIONS

Sweating, nausea, fatigue and a rash on the hands have been reported in one clinical trial using a commercial preparation containing 30 mg hawthorn extract standardised to 1 mg procyanidins (Iwamoto et al 1981). Headache, sweating, dizziness, palpitations, sleepiness, agitation, and gastrointestinal symptoms have also been reported (Rigelsky & Sweet 2002).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

CARDIAC GLYCOSIDES

Hawthorn may theoretically potentiate the effects of cardiac glycosides, as both in vitro and in vivo studies indicate that it has positive inotropic activity. Furthermore, the flavonoid components of hawthorn may also affect P-glycoprotein function and cause interactions with drugs that are P-glycoprotein substrates, such as digoxin. In practice, however, a randomised crossover trial with eight healthy volunteers evaluating digoxin 0.25 mg alone for 10 days and digoxin 0.25 mg with *Crataegus* special extract WS 1442 (hawthorn leaves with flowers) 450 mg twice daily for 21 days found no significant difference to any measured pharmacokinetic parameters, suggesting that hawthorn and digoxin in these doses may be co-administered safely (Tankanow et al 2003). Caution — use under professional supervision and monitor drug requirements.

ANTIHYPERTENSIVE DRUGS

Theoretically, hawthorn may potentiate blood pressure-lowering effects, thereby requiring modified drug doses. Observe patients taking this combination and monitor drug requirements — interaction may be beneficial under professional supervision.

PREGNANCY USE

In vivo and in vitro evidence of uterine activity has been reported, therefore this herb should not be used in pregnancy (Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Hawthorn has positive inotropic action, increases coronary blood flow, reduces myocardial oxygen demand, protects against myocardial damage, improves heart rate variability, as well as having hypotensive and antiarrhythmic effects.
- Although considered relatively effective, heart disease can be a very serious medical condition with a rapidly changing course and should not be treated without close

medical supervision. In particular, chest pain and shortness of breath are extremely serious symptoms that require immediate medical attention.
- It may take 2–6 weeks' treatment to notice a benefit of treatment with hawthorn, and heart rate and blood pressure should be monitored.
- Hawthorn also exhibits antioxidant, anti-inflammatory, antiviral and lipid-lowering activity.
- Great care should be exercised if hawthorn is to be combined with other drugs that affect the heart.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

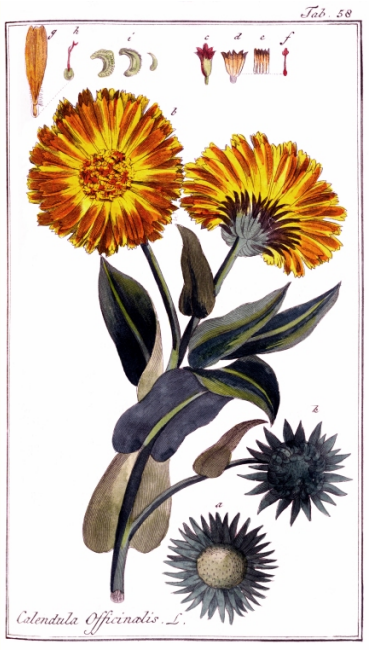
Hawthorn appears to be useful in treating a variety of heart conditions such as high blood pressure, hyperlipidaemia and heart failure.

When will it start to work?

Studies suggest it will start to have effects in 2–6 weeks.

Are there any safety issues?

Heart conditions are potentially serious, therefore professional supervision is required.



REFERENCES

al Makdessi S, Sweidan H, Mullner S, Jacob R. Myocardial protection by pretreatment with Crataegus oxyacantha: an assessment by means of the release of lactate dehydrogenase by the ischemic and reperfused Langendorff heart. Arzneimittelforschung 1996; 46(1): 25-7.

al Makdessi S, Sweidan H, Dietz K, Jacob R. Protective effect of Crataegus oxyacantha against reperfusion arrhythmias after global no-flow ischemia in the rat heart. Basic Res Cardiol 1999; 94(2): 71-7.

Bahorun T, Trotin F, Pommery J, Vasseur J, Pinkas M. Antioxidant activities of Crataegus monogyna extracts. Planta Med 1994; 60(4): 323-8.

Bahorun T et al. Oxygen species scavenging activity of phenolic extracts from hawthorn fresh plant organs and pharmaceutical preparations. Arzneimittelforschung 1996; 46(11): 1086-9.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bourin M, Bougerol T, Guitton B, Broutin E. A combination of plant extracts in the treatment of outpatients with adjustment disorder with anxious mood: controlled study versus placebo. Fundam Clin Pharmacol 1997; 11(2): 127-32.

Chatterjee SS, Koch E, Jaggy H, Krzeminski T. In vitro and in vivo studies on the cardioprotective action of oligomeric procyanidins in a Crataegus extract of leaves and blooms. Arzneimittelforschung 1997; 47(7): 821-5.

Chen JD, Wu YZ, Tao ZL, Chen ZM, Liu XP. Hawthorn (shan zha) drink and its lowering effect on blood lipid levels in humans and rats. World Rev Nutr Diet 1995; 77: 147-54.

Cheng BJ et al. Preventive effect of traditional herbal formulae against experimental hypercholesterolemia in rats with special reference to blood lipoprotein cholesterol levels. J Ethnopharmacol 2004; 94(2-3): 275-8.

Degenring FH, Suter A, Weber M, Saller R. A randomised double blind placebo controlled clinical trial of a standardised extract of fresh Crataegus berries (Crataegisan) in the treatment of patients with congestive heart failure NYHA II. Phytomedicine 2003; 10(5): 363-9.

Fujisawa M et al. Protective effect of hawthorn fruit on murine experimental colitis. Am J Chin Med 2005; 33(2): 167-80.

Georg Belz G, Loew D. Dose-response related efficacy in orthostatic hypotension of a fixed combination of D-camphor and an extract from fresh Crataegus berries and the contribution of the single components. Phytomedicine 2003; 10(Suppl 4): 61-7.
Guan Y, Zhao S. Yishou jiangzhi (de-blood-lipid) tablets in the treatment of hyperlipemia. J Trad Chin Med 1995; 15(3): 178-9.
Habs M. Prospective, comparative cohort studies and their contribution to the benefit assessments of therapeutic options: heart failure treatment with and without Hawthorn special extract WS 1442. Forsch Komplement Klass Naturheilk [Res Complement Nat Class Med] 2004; 11(Suppl 1): 36-9.
Hanus M et al. Double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium in mild-to-moderate anxiety disorders. Curr Med Res Opin 2004; 20(1): 63-71.
Harder S, Rietbrock N. Moeglicher Weg zur Einschraenkung von Benzodiazepin-Verordnungen. Therapiewoche 1990; 40(14): 971-6.
He G. Effect of the prevention and treatment of atherosclerosis of a mixture of Hawthorn and Motherworn. Zhong Xi Yi Jie He Za Zhi 1990; 10(6): 326, 361.
Hempel B et al. Efficacy and safety of a herbal drug containing hawthorn berries and D-camphor in hypotension and orthostatic circulatory disorders/results of a retrospective epidemiologic cohort study. Arzneimittelforschung 2005; 55(8): 443-50.
Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M. Survival and prognosis: investigation of Crataegus extract WS 1442 in congestive heart failure (SPICE): rationale, study design and study protocol. Eur J Heart Fail 2000; 2(4): 431-7.
Iwamoto M, Sato T, Ishizaki T. The clinical effect of Crataegutt in heart disease of ischemic or hypertensive origin: A multicenter double-blind study. Planta Med 1981; 42(1): 1-16.
Jayalakshmi R, Devaraj SN. Cardioprotective effect of tincture of Crataegus on isoproterenol-induced myocardial infarction in rats. J Pharm Pharmacol 2004; 56(7): 921-6.
Joseph G, Zhao Y, Klaus W. Pharmacologic action profile of crataegus extract in comparison to epinephrine, amirinone, milrinone and digoxin in the isolated perfused guinea pig heart. Arzneimittelforschung 1995; 45(12): 1261-5.
Jouad H et al. Hawthorn evokes a potent anti-hyperglycemic capacity in streptozotocin-induced diabetic rats. J Herb Pharmacother 2003; 3(2): 19-29.
Kao E-S et al. Anti-inflammatory potential of flavonoid contents from dried fruit of Crataegus pinnatifida in vitro and in vivo. J Agric Food Chem 2005; 53(2): 430-6.
Kraft K. Crataegus (common hawthorn) extracts in cardiac failure: are there new promising results and outlooks? Perfusion 2000; 13(1): 495-8.
Kroll M et al. A randomized trial of Korodin(R) Herz-Kreislauf-Tropfen as add-on treatment in older patients with orthostatic hypotension. Phytomedicine 2005; 12(6-7): 395-402.
Kwon H-J et al. Amelioration effects of traditional Chinese medicine on alcohol-induced fatty liver. World J Gastroenterol 2005; 11(35): 5512-16.
la Cour B, Molgaard P, Yi Z. Traditional Chinese medicine in treatment of hyperlipidaemia. J Ethnopharmacol 1995; 46(2): 125-9.
Lan W-J et al. Regulative effects of hawthorn leaves flavonoids on cytotoxicity, NO and Ca2+ in hypoxia-treated human umbilical vein endothelial cells. Hang Tian Yi Xue Yu Yi Xue Gong Cheng [Space Med Med Eng] 2005; 18(3): 157-60.
Ljubuncic P et al. Antioxidant activity of Crataegus aronia aqueous extract used in traditional Arab medicine in Israel. J Ethnopharmacol 2005; 101(1-3): 153-61.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Min Q et al. Protective effects of hawthorn leaves flavonoids on cardiac function in rats suffered from myocardial ischemia reperfusion injury. Chin Pharm J 2005; 40(7): 515-17.
Murray M. The Healing Power of Herbs. Rocklin, CA: Prima Health, 1995.
Nemecz G. Hawthorn. US Pharm 1999; 24(2): www.uspharmacist.com.

Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.
Periera DS, Rocha R, Silva CM, Mira L, Duarte MF, Florencio MH. Antioxidants in medicinal plant extracts. A research study of the antioxidant capacity of Crataegus, Hamamelis and Hydrastis. Phytother Res 2000; 14(8): 612-16.
Petkov V. Plants and hypotensive, antiatheromatous and coronarodilatating action. Am J Chin Med 1979; 7(3): 197-236.
Pittler MH et al. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. Am J Med 2003; 114(8): 665-74.
Quettier-Deleu C et al. Hawthorn extracts inhibit LDL oxidation. Pharmazie 2003; 58(8): 577-81.
Rajalakshmi K, Gurumurthi P, Devaraj SN. Effect of eugenol and tincture of crataegus (TCR) on in vitro oxidation of LDL + VLDL isolated from plasma of non-insulin dependent diabetic patients. Indian J Exp Biol 2000; 38(5): 509-11.
Rajendran S, Deepalakshmi PD, Parasakthy K, Devaraj H, Devaraj SN. Effect of tincture of Crataegus on the LDL-receptor activity of hepatic plasma membrane of rats fed an atherogenic diet. Atherosclerosis 1996; 123(1-2): 235-41.
Rakotoarison DA et al. Antioxidant activities of polyphenolic extracts from flowers, in vitro callus and cell suspension cultures of Crataegus monogyna. Pharmazie 1997; 52(1): 60-4.
Rietbrock N, Hamel M, Hempel B, Mitrovic V, Schmidt T, Wolf GK. Actions of standardized extracts of Crataegus berries on exercise tolerance and quality of life in patients with congestive heart failure. Arzneimittelforschung 2001; 51(10): 793-8.
Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. Am J Health Syst Pharm 2002; 59(5): 417-22.
Schlegelmilch R, Heywood R. Toxicity of Crataegus (hawthorn) extract (WS 1442). J Am Coll Toxicol 1994; 13(2): 103-11.
Schmidt U, Albrecht M, Schmidt S. Effects of an herbal crataegus-camphor combination on the symptoms of cardiovascular diseases. Arzneimittelforschung 2000; 50(7): 613-19.
Schroder D et al. Efficacy of a homeopathic Crataegus preparation compared with usual therapy for mild (NYHA II) cardiac insufficiency: results of an observational cohort study. Eur J Heart Fail 2003; 5(3): 319-26.
Schussler M, Holzl J, Fricke U. Myocardial effects of flavonoids from Crataegus species. Arzneimittelforschung 1995; 45(8): 842-5.
Shahat AA et al. Antiviral and antioxidant activity of flavonoids and proanthocyanidins from Crataegus sinaica. Planta Med 2002; 68(6): 539-41.
Shanthi S, Parasakthy K, Deepalakshmi PD, Devaraj SN. Hypolipidemic activity of tincture of Crataegus in rats. Indian J Biochem Biophys 1994; 31(2): 143-6.
Siegel G et al: Molecular physiological effector mechanisms of hawthorn extract in cardiac papillary muscle and coronary vascular smooth muscle. Phytother Res 1996; 10 [Suppl.]: S195-8.
Tankanow R et al. Interaction study between digoxin and a preparation of hawthorn (Crataegus oxyacantha). J Clin Pharmacol 2003; 43(6): 637-42.
Tauchert M. Efficacy and safety of crataegus extract WS 1442 in comparison with placebo in patients with chronic stable New York Heart Association class-III heart failure. Am Heart J 2002; 143(5): 910-15.
Tauchert M, Gildor A, Lipinski J. High-dose Crataegus extract WS 1442 in the treatment of NYHA stage II heart failure. Herz 1994; 24(6): 465-74.
Thirupurasundari CJ et al. Liver architecture maintenance by tincture of Crataegus against isoproterenol-induced myocardially infarcted rats. J Med Food 2005; 8(3): 400-4.
Tu Z et al. Protective effects of CVPM on vascular endothelium in rats fed cholesterol diet. Clin Chim Acta 2003; 333(1-2): 85-90.
Uchida S et al. Inhibitory effects of condensed tannins on angiotensin converting enzyme. Jpn J Pharmacol 1987; 43(2): 242-6.

Veveris M et al. Crataegus special extract WS(R) 1442 improves cardiac function and reduces infarct size in a rat model of prolonged coronary ischemia and reperfusion. Life Sci 2004; 74(15): 1945-55.
Vierling W et al. Investigation of the pharmaceutical and pharmacological equivalence of different Hawthorn extracts. Phytomedicine 2003; 10(1): 8-16.
Walker AF et al. Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension. Phytotherapy Res 2002; 16(1): 48-54.
Zapfe JG. Clinical efficacy of crataegus extract WS 1442 in congestive heart failure NYHA class II. Phytomedicine 2001; 8(4): 262-6.
Zhang Z, Chang Q, Zhu M, Huang Y, Ho WK, Chen Z. Characterization of antioxidants present in hawthorn fruits. J Nutr Biochem 2001; 12(3): 144-52.
Zhang Z, Ho WK, Huang Y, James AE, Lam LW, Chen ZY. Hawthorn fruit is hypolipidemic in rabbits fed a high cholesterol diet. J Nutr 2002; 132(1): 5-10.
Zhang D-L et al. Oral administration of Crataegus flavonoids protects against ischemia/reperfusion brain damage in gerbils. J Neurochem 2004; 90(1): 211-19.

Honey

Historical note Honey has been used since ancient times as a healing agent for wounds and a treatment for gastric complaints. In ancient Greece, Hippocrates recommended honey and vinegar for pain and honey combinations for fever. It is also recommended by the Bible and Koran as a medicinal agent. Over the past few decades, scientific research has confirmed its role as a successful wound treatment. It is also known as *honig* and *miel blanc*.

CHEMICAL COMPONENTS

Caffeic acids, benzoic acid and its esters, phenolic acid and its esters, flavanoids, beeswax, inhibin, glucose oxidase and catalase, although other as yet unidentified constituents also exist (Aysan et al 2002).

The composition of a particular honey greatly depends on the composition of the nectar it originated from, and therefore the plant species involved in its production.

MAIN ACTIONS

ANTIBACTERIAL

The type of plant species involved in honey production is significant, as some confer greater antibacterial properties than others. Currently, evidence suggests honey produced from the tea trees *Leptospermum scoparium* (New Zealand manuka) and *Lipolygalifolium* (Australian jelly bush) are the most effective, but batch testing is still required to verify the antibacterial activity of commercially produced preparations. However, other honeys, not specifically promoted for their anti-bacterial qualities, may still have antibacterial activity (Lusby et al 2005).

Several mechanisms of action account for the antibacterial effect of honey.

Hydrogen peroxide content Hydrogen peroxide has antiseptic properties and is naturally produced in honey. The relative levels of two enzymes, glucose oxidase and catalase, within honey influence the amount of hydrogen peroxide produced. Additionally, diluting full-density honey encourages greater hydrogen peroxide and gluconic acid production from glucose (Aysan et al 2002). Differences in antimicrobial activity among honeys from various floral sources may, in part, be a reflection of these natural variations.

High osmolarity Honey has a high sugar and low water content, with sugar concentration reaching up to 80% in some seasons. Its high osmolarity is considered

important because sugar molecules bind existing water molecules, thereby reducing the amount of water available to bacteria.

Low pH Honey is an acidic substance and therefore unfavourable to the growth of certain bacteria. In vitro testing shows that *Leptospermum* honey can inhibit the growth of several important bacterial pathogens, including *Escherichia coli*, *Salmonella typhimurium*, *Shigella sonnei*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Streptococcus mutans* (Steinberg et al 1996, Taormina et al 2001).

Honey has also been tested for efficacy against a range of drug-resistant bacteria, with positive results (Cooper et al 2002). Eighteen strains of methicillin-resistant *Staphylococcus aureus* and 27 strains of vancomycin-sensitive and resistant enterococci isolated from infected wounds and hospital surfaces were sensitive to concentrations below 10% w/v of manuka honey and pasture honey. Artificial honey was also effective, but concentrations three times greater were required to produce similar results.

Phenolic compounds The antioxidant activity of honey has been associated with the levels of phenolic compounds found in a range of floral honeys, with antioxidant activity varying between 43.0% and 95.7%. The responsible compounds suggested include p-coumaric acid, kaempferol, chrysin and apigenin (Baltrusaityte et al 2006). The variation in the concentration of the phenolic compounds between different floral honeys is further confirmed through another study, which found millefiori honey highest in polyphenols, flavonoids, and a corresponding high antioxidant activity, when compared with *Acacia* honey (Blasa et al 2006).

DEODORISES WOUNDS

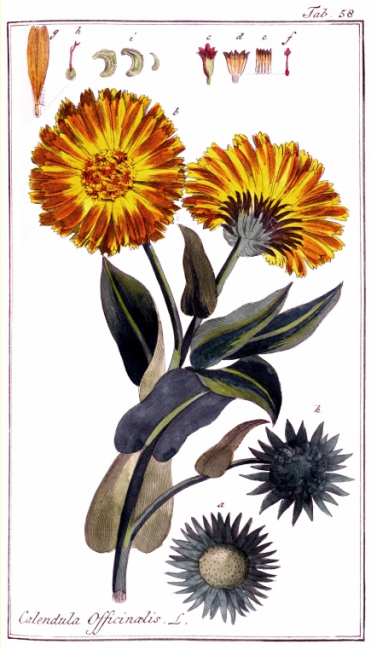
Bacteria use the glucose found in honey in preference to amino acids, thereby producing lactic acid instead of malodorous products (Molan 2001).

DEBRIDING

The topical application of honey to a wound tends to lift debris to the surface, allowing for easier cleaning, which may be related to its high osmolarity. Honey does not adhere to the surface, allowing for easier and less painful wound dressing changes (Subrahmanyam 1998).

ENHANCES WOUND HEALING

Clinical evidence suggests that the application of honey hastens granulation and epithelialisation of necrotic tissue by various mechanisms. It appears to stimulate the growth of new blood capillaries and cytokine production, thereby stimulating tissue regeneration. The high viscosity of honey and its hygroscopic character allows it to



form a physical barrier, creating a moist environment and a reduction in local oedema (Aysan et al 2002). Clinically, it appears that epithelialisation is accelerated between day 6 and 9 (Subrahmanyam 1998), and that honey is more beneficial than EUSOL as a wound dressing agent (Okeniyi et al 2005).

ANTIOXIDANT

The phenolic compounds found in honey, namely the flavonoids, render it a good source of antioxidants (Al-Mamary et al 2002, Schramm et al 2003). In vitro tests have confirmed a significant link between absorbance and antioxidant power, with darker, more opaque honeys having stronger antioxidant power than lighter, clearer honeys (Taormina et al 2001). More specifically, manuka honey has been identified to be a specific scavenger of superoxide anions (Inoue et al 2005).

IMMUNOMODULATION

An animal study has shown that both immunocompetent and immunodeficient mice had increased humoral immunity following administration with honey (Karmakar et al 2004).

OTHER ACTIONS

An in vitro study showed that honey prevented binding of *Salmonella interiditis* to intestinal epithelial cells (Alnaqdy et al 2005) at dilutions of up to 1:8.

Preliminary studies suggest honey may have an impact on reducing the intoxicating effects of alcohol; however, that research was of questionable quality, and a better standard of research is required to validate this effect (Onyesom 2004, 2005).

Honey may also have an antimutagenic activity against a common food carcinogen and mutagen Trp-p-1 (Wang et al 2002).

CLINICAL USE

BURNS

Honey-dressed wounds had a more rapid reduction in local inflammation, better infection control and more rapid healing than for standard treatment with silver sulfadiazine (SSD) in a randomised clinical trial (Subrahmanyam 1998). Of the 25 patients with wounds, 84% treated with honey achieved satisfactory epithelialisation by day 7 and 100% by day 21 compared with 72% and 84% respectively with SSD. Histological evidence confirmed honey's superiority, with 80% of wounds showing significant reparative activity and decreased inflammation by day 7 compared with 52% with SSD.

WOUND HEALING

Honey applications have been used to treat various types of wounds, such as leg ulcers and bed sores. Honey has also been used to enhance postoperative wound healing and partial-thickness wounds such as split-thickness skin graft donor sites.

One study involving 59 patients with wounds or ulcers not responding to conventional treatment were treated with topical unprocessed honey. Of these, 58 cases were reported as showing remarkable recovery, with all sterile wounds remaining sterile until healed and infected wounds becoming sterile within 1 week. The one case that did not respond involved a malignant ulcer. Clinically, honey promoted rapid debridement of wounds, epithelialisation and reduced oedema surrounding the ulcers (Efem 1988). Vardi et al (1998) found that 5–10 mL of unprocessed honey applied twice daily to infants not responding to at least 2 weeks of conventional treatment was able to produce a marked clinical improvement within 5 days and complete wound closure after 21 days.

A non-randomised, prospective open study compared the effects of honey-impregnated gauze, paraffin gauze, hydrocolloid dressings and saline-soaked gauzes in 88 patients who underwent skin grafting (Misirlioglu et al 2003). Honey gauzes produced a faster epithelialisation and reduced the sensation of pain compared with paraffin and saline-soaked gauzes. This effect was the same as that observed for hydrocolloid dressings.

A honey-medicated dressing was tested for ease of use and efficacy in a study involving 60 patients with chronic, complicated surgical or acute traumatic wounds (Ahmed et al 2003). In 59 patients, the preparation was considered easy to use and helpful in cleaning wounds.

A RCT of 101 haemodialysis patients compared thrice-weekly application of Medihoney with mupirocin for the healing of catheter exit sites. This study found the honey to be safe, effective and more affordable than mupirocin for this group (Johnson et al 2005).

FOURNIER'S GANGRENE

In 1996, the effects of topical unprocessed honey, together with traditional treatment in a rare condition known as Fournier's gangrene (FG) were investigated (Hejase et al 1996). FG is an extensive fulminant infection of the genitals, perineum or the abdominal wall and is generally regarded as a difficult-to-manage infectious disease. The major gross pathological findings are oedema and necrosis of the subcutaneous tissues when the male genitalia are involved, necessitating aggressive treatment.

In this study, 38 patients admitted with the diagnosis of FG were treated with broad-spectrum triple antimicrobial therapy, broad debridement, exhaustive cleaning

and application of unprocessed honey dressings daily for 2 weeks. Rapid changes to wound healing rate occurred after 10 days' honey use — advancing necrosis ceased, wounds became sterile, odour was reduced and fluid was absorbed from wounds. Honey also enhanced the growth and multiplication of epithelial cells from the wound edges and reduced the need for scrotal plastic surgery. As a result of the impressive results obtained, these researchers highly recommend honey dressings in gangrenous wounds, suggesting that it significantly improved patient outcomes.

OTHER USES

ALLERGIC RHINOCONJUNCTIVITIS

Honey does not reduce symptoms of allergic rhinoconjunctivitis, according to results from a randomised study of 36 volunteers (Rajan et al 2002). The study compared the effects of unpasteurised unfiltered honey with filtered and pasteurised honey and corn syrup with synthetic honey flavouring and found that an oral dose of 1 tablespoon daily of either honey produced the same results as placebo.

HELICOBACTER PYLORI INFECTION

Honey inhibits *H. pylori* in test tube studies (Ali et al 1991, Osato et al 1999), although no controlled studies are available to clarify its effectiveness in humans.

PERIODONTAL DISEASE

In vitro tests show that honey can inhibit the growth of oral bacteria (Steinberg et al 1996). As a follow-up investigation, 10 volunteers were asked to swish 5 mL of honey around their mouths for 4 minutes then swallow. At 10 minutes after honey use, oral bacterial counts were significantly decreased.

ECZEMA

Topically applied honey is sometimes used to enhance skin healing and prevent infection in eczema. Although controlled trials are not available, the clinical evidence generally supporting efficacy in wound healing provides a theoretical basis for its use in this condition.

COLON CANCER

Preliminary animal studies on experimentally induced colon cancer show the potential for reduced disease development (Duleva & Bajkova 2005), but further study is necessary to validate this for clinical use.

DYSBIOSIS

Honey may assist in inhibiting the growth of the pathogenic bacteria *Clostridium perfringens* and *Eubacterium aerofaciens*, while not affecting, or possibly promoting,

the growth of beneficial *Bifidobacterium* spp. (*B. longum*, *B. adolescentis*, *B. breve*, *B. bifidum* and *B. infantis*) (Shin & Ustunol 2005).

DOSAGE RANGE

Honey is applied topically (see 'Tips on how best to use honey in practice' below).

TOXICITY

Not applicable — used externally.

ADVERSE REACTIONS

A mild transient stinging may occur when applied to open wounds. If this is too uncomfortable, honey can be washed away with warm water.

Allergic reactions have also been reported, but these are considered rare.

SIGNIFICANT INTERACTIONS

None known

CONTRAINDICATIONS AND PRECAUTIONS

DIABETICS

Honey contains a large concentration of glucose. If applied to large open wounds, it may theoretically elevate blood sugar levels — monitor blood sugar levels.

PREGNANCY USE

Safety has not been scientifically established, but historical use suggests that it is safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Topical application of honey has been used to enhance wound healing and infection control.
- Honey has a deodorising and debriding effect on wounds, accelerates epithelialisation and reduces inflammation and pain.
- Effects are generally seen within 7 days of use.
- Not all honeys have significant antibacterial properties; however, research has identified the New Zealand *Leptospermum* (manuka honey) and Australian jelly bush honey as having potent activity.
- The honey to be used as a topical wound-healing agent or dermatological treatment should ideally be sterile and tested for clinical activity.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will honey do for me?

If you apply a honey preparation that has tested positive for antibacterial activity, it will enhance wound healing, reduce pain and inflammation, and reduce the risk of wound infection.

When will it start to work?
Studies have found that by the 7th day of use, most wounds show considerable improvement and healing.

Are there any safety issues?
Using sterile honey preparations is recommended.

Tips on how best to use honey in practice*

- Ensure that there is an even coverage of the wound surface.
- Cavities may be filled by pouring in slightly warmed honey.
- Spreading honey on a dressing pad or gauze rather than on the wound directly will be more comfortable for the patient.
- The amount of honey needed depends on the amount of fluid leaking from the wound — if honey becomes diluted, it will be less effective; typically, 20 mL of honey is used on a 10 cm × 10 cm dressing.
- Cover with absorbent secondary dressings to prevent honey oozing out from the dressing. Change the dressings more frequently if the honey is being diluted — otherwise change every day or two.

*Adapted from www.worldwidewounds.com and www.manukahoney.co.uk.

REFERENCES

Ahmed AK et al. Honey-medicated dressing: transformation of an ancient remedy into modern therapy. Ann Plast Surg 50.2 (2003): 143-8.

Alanqdy A et al. Inhibition effect of honey on the adherence of Salmonella to intestinal epithelial cells in vitro. Int J Food Microbiol 103.3 (2005): 347-51.

Ali AT, Chowdhury MN, al Humayyd MS. Inhibitory effect of natural honey on Helicobacter pylori. Trop Gastroenterol 12.3 (1991): 139-43.

Al-Mamary M et al. Antioxidant activities and total phenolics of different types of honey; Nutr Res 22.9 (2002): 1041-7.

Aysan E et al. The role of intra-peritoneal honey administration in preventing post-operative peritoneal adhesions. Eur J Obstet Gynecol Reprod Biol 104.2 (2002): 152.

Baltrusaityte V, Venskutonis PR, Ceksteryte V. Radical scavenging activity of different floral origin honey and beebread phenolic extracts. Food Chem 2006 [in press].

Blasa M et al. Raw Millefiori is packed full of antioxidants. Food Chem 97.2 (2006): 217-22.

Cooper RA, Molan PC, Harding KG. The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. J Appl Microbiol 93.5 (2002): 857-63.

Duleva V, Bajkova D. Preventive action of honey on experimental colon tumorogenesis. Arch Balk Med Union 40.1 (2005): 49-51

Efem SE. Clinical observations on the wound healing properties of honey. Br J Surg 75.7 (1988): 679-81.

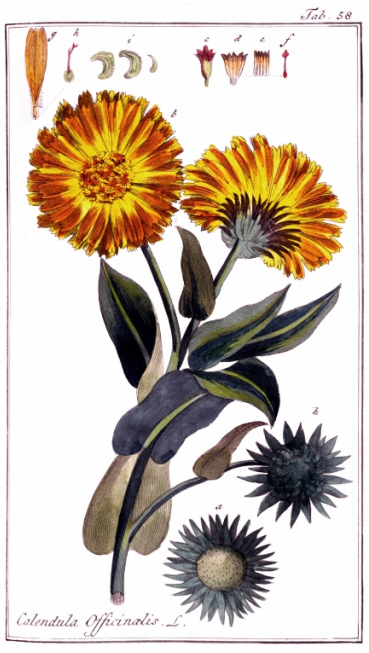
Hejase MJ et al. Genital Fournier's gangrene: experience with 38 patients. Urology 47.5 (1996): 734-9.

Inoue K et al. Identification of phenolic compound in manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection. J Sci Food Agric 85.5 (2005): 872-8.

Karmakar S et al. Haematinic and immunomodulatory effects of honey on immunocompetent, immunodeficient and splenectomised experimental rodents. Phytomedica 5 (2004): 107-10.

Lusby PE, Coombes AL, Wilkinson JM. Bactericidal activity of different honeys against pathogenic bacteria. Arch Med Res 36.5 (2005): 464-7.
Misirlioglu A et al. Use of honey as an adjunct in the healing of split-thickness skin graft donor site. Dermatol Surg 29.2 (2003): 168-72.
Molan PC. Potential of honey in the treatment of wounds and burns. Am J Clin Dermatol 2.1 (2001): 13-19.
Okeniyi JAO et al. Comparison of healing of incised abscess wounds with honey and EUSOL dressing. J Alt Comp Med 11.3 (2005): 511-13.
Onyesom I. Effect of Nigerian citrus (Citrus sinensis Osbeck) honey on ethanol metabolism. S African Med J 94.12 (2004): 984-6.
Onyesom I. Honey-induced stimulation of blood ethanol elimination and its influence on serum triacylglycerols and blood pressure in man. Ann Nutr Metab 49.5 (2005): 319-24.
Osato MS, Reddy SG, Graham DY. Osmotic effect of honey on growth and viability of Helicobacter pylori. Dig Dis Sci 44.3 (1999): 462-4.
Rajan TV et al. Effect of ingestion of honey on symptoms of rhinoconjunctivitis. Ann Allergy Asthma Immunol 88.2 (2002): 198-203.
Schramm DD et al. Honey with high levels of antioxidants can provide protection to healthy human subjects. J Agric Food Chem 51.6 (2003): 1732-5.
Shin H-S, Ustunol Z. Carbohydrate composition of honey with different floral sources and their influence on growth of selected intestinal bacteria: An in vitro comparison. Food Res Int 38.6 (2005): 721-8.
Steinberg D, Kaine G, Gedalia I. Antibacterial effect of propolis and honey on oral bacteria. Am J Dent 9.6 (1996): 236-9.
Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns 24.2 (1998): 157-61.
Taormina PJ, Niemira BA, Beuchat LR. Inhibitory activity of honey against foodborne pathogens as influenced by the presence of hydrogen peroxide and level of antioxidant power. Int J Food Microbiol 69.3 (2001): 217-25.
Vardi A et al. Local application of honey for treatment of neonatal postoperative wound infection. Acta Paediatr 87.4 (1998): 429-32.
Wang X-H, Andrae L, Engesteth NJ. Antimutagenic effect of various honeys and sugars against Trp-p-1. J Agric Food Chem 50.23 (2002): 6923-8.

Hops



Historical note Although hops are most famous for producing the bitter flavour in beer, this plant has been used since ancient times to treat digestive complaints and for its slight narcotic and sedative actions. The climbing nature of the herb influenced its common name, as this is derived from the Anglo-Saxon *hoppan*, which means 'to climb'.

COMMON NAME
Hops

OTHER NAMES
Common hops, European hops, hop strobile, hopfen, houblon, humulus, lupulus, lupulin

BOTANICAL NAME/FAMILY
Humulus lupulus (family Cannabinaceae)

PLANT PART USED
Dried strobiles

CHEMICAL COMPONENTS
Resinous bitter principles (mostly alpha-bitter and beta-bitter acids) and their oxidative degradation products, polyphenolic condensed tannins, volatile oil, polysaccharides, mainly monoterpenes and sesquiterpenes, flavonoids (xanthohumol, isoxantholumol, kaempferol, quercetin and rutin), phenolic acids, and amino acids (Blumenthal et al 2000).

MAIN ACTIONS
Traditionally, hops are viewed as a bitter tonic with antispasmodic, relaxant and sedative actions.

SEDATIVE
A long history of use within well-established systems of traditional medicine, together with scientific testing, have suggested that hops have significant sedative activity (Blumenthal et al 2000). A recent in vivo study found that both the extract of hops and a fraction containing alpha-bitter acids had significant sedative properties in mice (Zanoli et al 2005). Both extracts were also found to have an antidepressant action.

ANTIMICROBIAL

Hops extract and hops oil have activity against the Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and the fungus *Trichophyton mentagrophytes* var. *interdigitale*, but almost no activity against the Gram-negative bacterium *Escherichia coli* and the yeast *Candida albicans* (Langezaal et al 1992). A review of the antimicrobial properties concluded that hops were also effective against the parasite *Plasmodium falciparum* and a range of viruses including HSV types 1 and 2, cytomegalovirus and HIV (Gerhauser 2005a). The mechanism of anti-HIV activity is not fully understood, but it is thought that the flavonoid xanthohumol may inhibit transcription (Wang et al 2004).

OESTROGENIC EFFECTS

Hops showed significant competitive binding to alpha and beta oestrogen receptors and upregulation of progesterone receptors in vitro (Liu et al 2001). The oestrogenic activity is thought to be due to the constituent 8-prenylnaringenin (Milligan et al 1999, 2000), which is converted by intestinal microflora from isoxanthohumol (Possemiers et al 2005).

POSSIBLE CHEMOPREVENTATIVE EFFECTS

A chalcone flavonoid, xanthohumol and a flavone isomer of xanthohumol found in hops act as antiproliferative agents in vitro (Miranda et al 1999, Stevens & Page 2004). In vitro data has demonstrated that hops induces detoxification enzymes, in particular quinone reductase, which may contribute to its chemoprotective effects (Dietz et al 2005). A review concluded that this compound has the ability to protect in the initiation, promotion and progression stages of cancer (Gerhauser 2005b).

OTHER ACTIONS

CYTOCHROME P450 INDUCTION

Colupulone, a beta-bitter acid, was reported to induce the cytochrome P450 system and increase mRNA levels of cytochrome 2B and 3A in rats (Shipp et al 1994). Another study found that the flavonoids from hops inhibit the cytochrome P450 system in humans, in particular cytochromes 1A1, 1b1, 1A2, but not 2E1 or 3A4 (Henderson et al 2000). A recent review concluded that hops inhibits phase 1 detoxification and enhances phase two by inducing quinone reductase (Gerhauser et al 2002, Stevens & Page 2004). The clinical significance of these findings is unknown.

ANTI-INFLAMMATORY

Hops may demonstrate an anti-inflammatory action. The chalones, including xanthohumol, from hops significantly reduced NO by suppressing iNOS in mouse

macrophage cells (Zhao et al 2003, 2005). Xanthohumol has also been reported to inhibit COX-1 and COX-2 activity (Gerhauser 2005b).

CLINICAL USE

In practice, the herb is prescribed in combination with other herbal medicines, such as valerian and passionflower. As is representative of clinical practice, most studies have investigated the effects of hops in combination with other herbs.

RESTLESSNESS AND ANXIETY

Based on the herb's sedative activity, it is likely to have some effect in the treatment of restlessness and anxiety, but careful dosing would be required to avoid sedation. This indication has been approved by Commission E and ESCOP (Blumenthal et al 1998).

SLEEP DISTURBANCES

Although there have been no clinical studies to support hops as a stand-alone sedative agent, several studies have demonstrated formulas combining hops with other sedative herbs are effective for insomnia.

Two randomised double-blind studies have investigated the effects of an oral preparation of hops and valerian in sleep disorders (Gerhard et al 1996, Schmitz & Jackel 1998). One study observed equivalent efficacy and tolerability of a hops–valerian preparation comparable to benzodiazepine treatment, with withdrawal symptoms only reported for benzodiazepine use (Schmitz & Jackel 1998). Improvement in subjective perceptions of sleep quality was confirmed in another study, which also reported that a hops–valerian combination was well tolerated compared with flunitrazepam (Gerhard et al 1996).

A pilot study (Fussel et al 2000) tested a preparation containing a fixed combination of valerian extract (500 mg) and hops extract (120 mg) known as Ze 91019 in 30 subjects with mild-to-moderate, non-organic insomnia. The treatment was used at bedtime and found to reduce sleep latency and wake time as diagnosed by polysomnographic examination.

Hops has also been used as a bath additive for sleep disturbances. A randomised double-blind study involving 40 patients found that taking three hops baths (4 g hops in a concentrated extract) on successive days significantly improved both objective and subjective sleep quality (Bone 1996).

Commission E and ESCOP support the use of hops for sleep disturbances, such as difficulty falling asleep and insomnia (Blumenthal et al 2000).

Based on the available evidence, further investigation is required to determine whether hops acts as a mild sedative independently, as a synergist, or does not have sedative action.

MENOPAUSE

A randomised, double-blind, placebo-controlled trial of a standardised extract of hops (100 μg and 250 μg 8-prenylnaringenin) demonstrated a significant reduction in menopausal discomfort, in particular hot flushes, after 12 weeks of treatment in 67 women (Heyerick et al 2005). Interestingly, no dose–response relationship could be made, as the lower standardised dose was shown to be more effective.

INDIGESTION

Due to the herb's bitter nature, it is used to stimulate digestion and in the treatment of common digestive complaints such as dyspepsia and indigestion.

OTHER USES

Traditionally, hops are also used to treat neuralgia, depression and pain, and to wean patients off pharmaceutical sedative medicines. Topically it is used to treat leg ulcers and oedema.

DOSAGE RANGE

- Infusion or decoction: 0.5 g in 150 mL water.
- Fluid extract (1:1) (g/mL): 0.5 mL/day; 0.5–1 mL three times daily.
- Tincture (1:5) (g/mL): 1–2.5 mL/day.
- Also used as a bath additive (4 g hops in a concentrated extract) and in pillows.

TOXICITY

Not known

ADVERSE REACTIONS

Drowsiness is theoretically possible at excessive doses. Contact with the herb or oil has resulted in reports of systemic urticaria, allergic dermatitis, respiratory allergy and anaphylaxis (Pradalier et al 2002).

SIGNIFICANT INTERACTIONS

Interactions reported here are theoretical and have yet to be tested clinically for significance.

PHARMACEUTICAL SEDATIVES

Additive effects are theoretically possible — observe the patient (this interaction may be beneficial).

DRUGS METABOLISED CHIEFLY WITH CYP2B OR CYP3A

Altered drug effect — CYP induction and inhibition has been demonstrated. However, it is unknown if these effects are clinically significant — observe the patient for signs of altered drug effectiveness.

ANTI-OESTROGENIC DRUGS
Hops may alter the efficacy of these medicines; use with caution in patients taking anti-oestrogenic drugs.

CONTRAINDICATIONS AND PRECAUTIONS
According to one source, hops should be used with caution in depression (Ernst et al 2001). Due to the herb's oestrogenic activity, disruption to the menstrual cycle is considered possible. Use is contraindicated in patients with oestrogen-dependent tumours.

PREGNANCY USE
Caution in pregnancy because of possible hormonal effects.

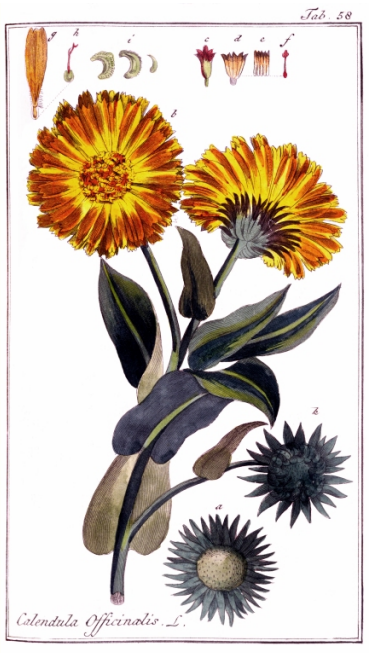
PRACTICE POINTS/PATIENT COUNSELLING
- Hops is often used as a mild sedative in combination with other herbs such as valerian and passionflower.
- Several randomised trials have found that the combination of hops and valerian improve sleep quality, without next-day drowsiness; however, further investigation is required to determine the role of hops in achieving this effect.
- Although generally taken orally, it has also been successfully used as a bath additive and in aromatherapy pillows to induce sleep.
- It is traditionally used to treat anxiety, restlessness, pain, neuralgia and indigestion.
- It should not be used in patients with oestrogen-dependent tumours, and should be used with caution in pregnancy.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Hops may be a useful treatment for anxiety and restlessness, and when combined with other sedative herbs, such as valerian or passionflower, improves sleep quality without inducing next-day hangover effects.
When will it start to work?
Several doses may be required; however, effects are generally seen within 2 weeks.
Are there any safety issues?
Constituents in the herb appear to have some oestrogenic activity, therefore people with oestrogen-dependent tumours should avoid its use.

REFERENCES
Blumenthal M et al. The Complete German Commission E monographs: Therapeutic Guide to Herbal Medicines. Austin, TX: The American Botanical Council, 1998.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Bone K. Hops. Prof Monitor 1996; 16: 2.

Dietz BM et al. Xanthohumol isolated from Humulus lupulus inhibits menadione-induced DNA damage through induction of quinone reductase. Chem Res Toxicol 2005; 18: 1296-305.
Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.
Fussel A, Wolf A, Brattstrom A: Effect of a fixed valerian-Hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study. Eur J Med Res 2000; 5: 385-90.
Gerhard U et al. Vigilance-decreasing effects of 2 plant-derived sedatives. Schweiz Rundsch Med Prax 1996; 85.15: 473-81.
Gerhauser C. Broad spectrum antiinfective potential of xanthohumol from hop (Humulus lupulus L.) in comparison with activities of other hop constituents and xanthohumol metabolites. Mol Nutr Food Res 2005a; 49: 827-31.
Gerhauser C. Beer constituents as potential cancer chemopreventative agents. Eur J Cancer 2005b; 41: 1941-54.
Gerhauser C et al. Cancer chemopreventive activity of Xanthohumol, a natural product derived from hop. Mol Cancer Ther 2002; 1: 959-69.
Henderson MC et al. In vitro inhibition of human P450 enzymes by prenylated flavonoids from hops, Humulus lupulus. Xenobiotica 2000; 30: 235-51.
Heyerick A et al. A first prospective randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. Maturitas 2005; 54.2: 164-75.
Langezaal CR, Chandra A, Scheffer JJ. Antimicrobial screening of essential oils and extracts of some Humulus lupulus L. cultivars. Pharm Week Sci 1992; 14.6: 353-6.
Liu J et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 2001; 49.5: 2472-9.
Milligan SR et al. Identification of a potent phytoestrogen in hops (Humulus lupulus L.) and beer. J Clin Endocrinol Metab 1999; 84.6: 2249-52.
Milligan SR et al. The endocrine activities of 8-prenylnaringenin and related hop (Humulus lupulus L.) flavonoids. J Clin Endocrinol Metab 2000; 85.12: 4912-15.
Miranda CL et al. Antiproliferative and cytotoxic effects of prenylated flavonoids from hops (Humulus lupulus) in human cancer cell lines. Food Chem Toxicol 1999; 37.4: 271-85.
Possemiers S et al. Activation of proestrogens from hops (Humulus lupulus L.) by intestinal microbiota; conversion of isoxanthohumol into 8-prenylnaringenin. J Agric Food Chem 2005; 53: 6281-8.
Pradalier A, Campinos C, Trinh C. Systemic urticaria induced by hops. Allerg Immunol (Paris) 2002; 34.9: 330-2.
Schmitz M, Jackel M. Comparative study for assessing quality of life of patients with exogenous sleep disorders (temporary sleep onset and sleep interruption disorders) treated with a hops-valarian preparation and a benzodiazepine drug. Wien Med Wochenschr 1998; 148.13: 291-8.
Shipp EB, Mehigh CS, Helferich WG. The effect of colupulone (a HOPS beta-acid) on hepatic cytochrome P-450 enzymatic activity in the rat. Food Chem Toxicol 1994; 32.11: 1007-14.
Stevens JF, Page JE. Xanthohumol and related prenylflavonoids from hops and beer: to your good health! Phytochemistry 2004; 65: 1317-30.
Wang Q et al. Xanthohumol, a novel anti-HIV-1 agent purified from Hops Humulus lupulus. Antiviral Res 2004; 64: 189-94.
Zanoli P et al. New insight in the neuropharmacological activity of Humulus lupulus L. J Ethnopharmacol 2005; 102.1: 102-6
Zhao F et al. Inhibitors of nitric oxide production from hops (Humulus lupulus L.). Biol Pharm Bull 2003; 26: 61-5.
Zhao F et al. Phenylflavonoids and phloroglucinol derivatives from hops (Humulus lupulus). J Nat Prod 2005; 68: 43-9.

Horse chestnut



Historical note The horse chestnut tree is commonly found in ornamental gardens throughout Europe, growing up to 35 metres in height. The seeds are not edible due to the presence of alkaloid saponins, but both the dried seeds and bark of the horse chestnut tree have been used medicinally since the 16th century. The seeds are also used for the children's game 'conkers' and were used to produce acetone during World Wars I and II. In modern times, a dry extract referred to as horse chestnut seed extract (HCSE) is standardised to contain 16–21% triterpene glycosides (anhydrous escin). HCSE has been extensively researched for its beneficial effects and is commonly used by general practitioners in Germany for the treatment of chronic venous insufficiency. Homoeopathic preparations of both the leaf and seed are also used for treating haemorrhoids, lower back pain, and varicose veins and the buds and flower are used to make the Bach flower remedies chestnut bud and white chestnut. The active component escin is also used intravenously and topically in cosmetics (Bombardelli et al 1996, Herbalgram 2000, PDRHealth 2006).

OTHER NAMES

Aescule, buckeye, chestnut, Castaño de Indias, graine de marronier d'inde, escine, eschilo, hestekastanje, hippocastani semen, marron europeen, marronnier, roßkastaniensamen, Spanish chestnut

BOTANICAL NAME/FAMILY

Aesculus hippocastanum (family [Sapindaceae] Hippocastanaceae).

It should be differentiated from *A. chinensis*, *A. turbinate*, *A. indica*, *A. californica* and *A. glabra*.

PLANT PARTS USED

Seed. Less commonly bark, flower, and leaf.

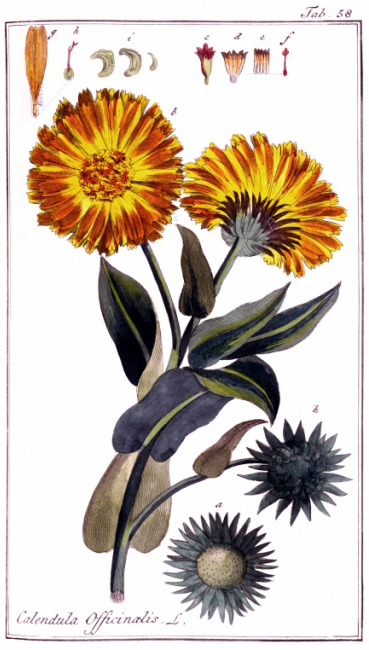
CHEMICAL COMPONENTS

Horse chestnut seed contains 3–6% escin (aescin), a complex mixture of triterpene saponins (including the triterpene oligoglycosides escins Ia, Ib, IIa, IIb, and IIIa) (Yoshikawa et al 1996), the acylated polyhydroxyoleanene triterpene oligoglycosides escins IIIb, IV, V, and VI and isoescins Ia, Ib, and V (Yoshikawa et al 1998), and the sapogenols hippocaesculin and barringtogenol-C (Konoshima & Lee 1986), flavonoids

(including flavonol oligosides of quercetin and kaempferol) (Hubner et al 1999), condensed tannins, quinines, sterols (including stigmasterol, alpha-spinasterol, and beta-sitosterol) (Senatore et al 1989), sugars (including glucose, xylose, and rhamnose) (Hubner et al 1999), and fatty acids (including linolenic, palmitic, and stearic acids) (Herbalgram 2000). It also contains the toxic glycoside esculin (aesculin), a hydroxycoumarin that may increase bleeding time due to antithrombin activity (NMCD 2006).

Horse chestnut bark and flowers also contain the sterols stigmasterol, alpha-spinasterol and beta-sitosterol (NMCD 2006).

Although the majority of trials in the scientific literature have focused on the benefits of the HCSE extract, some authors suggest that the flavonoids contained in *A. hippocastanum* may provide additional benefits (Mills & Bone 2000).



MAIN ACTIONS

The major benefits of *A. hippocastanum* are related to its ability to prevent the degradation of vascular walls, maintaining vascular integrity and in turn preventing vascular hyperpermeability and the resulting oedema.

VASOPROTECTIVE/NORMALISES VASCULAR PERMEABILITY

Horse chestnut appears to prevent the activation of leucocytes and therefore inhibit the activity of lysosomal enzymes (hyaluronidase and possibly elastase) involved in the degradation of proteoglycan (the main component of the extravascular matrix), thus reducing the breakdown of mucopolysaccharides in vascular walls (Pittler & Ernst 2004). Escin is the major constituent thought to be responsible for the inhibitory effects on hyaluronidase. Interestingly, ruscogenins found in *Ruscus aculeatus* L. (butcher's broom) while ineffective on hyaluronidase activity exhibits significant anti-elastase activity (Facino et al 1995), which may explain the practice by many herbalists of combining the two herbs.

By reducing degradation, the synthesis of proteoglycans is able to occur, which reduces capillary hyperpermeability, preventing the leakage of fluid into intercellular spaces that results in oedema. The anti-exudative activity appears to be mediated by PGF_{2alpha} (Berti et al 1977). In animal studies the escins Ia, Ib, IIa, and IIb have been shown to reduce capillary hypermermeability induced by histamine, ascetic acid, carrageenan and serotonin (Guillaume & Padioleau 1994, Matsuda et al 1997).

Aesculus hippocastanum promotes the proliferation behaviour of human endothelial cells in vitro in a dose-dependent manner (Fallier-Becker et al 2002) and may therefore also play a role in maintaining as well as protecting vascular walls.

By improving vascular tone, horse chestnut standardised extract (HCSE) may improve the flow of blood back to the heart, as demonstrated in animal studies in which it significantly increased, within normal arterial parameters, femoral venous pressure and flow, as well as thoracic lymphatic flow (Guillaume & Padioleau 1994).

ANTI-OEDEMA

By inhibiting the degradation of vascular walls, horse chestnut prevents the excessive exudation of fluid through the walls of the capillaries that would result in oedema. In animal experiments HCSE reduces oedema of both inflammatory and lymphatic origin (Guillaume & Padioleau 1994). Escin also appears to possess a weak diuretic activity (Mills & Bone 2000, NMCD 2006), which may support its anti-oedematous action.

ANTI-INFLAMMATORY

In animal studies the escins Ia, Ib, IIa, and IIb have been shown to reduce capillary hyperpermeability induced by histamine, ascetic acid, carrageenan and serotonin (Guillaume & Padioleau 1994, Matsuda et al 1997). A sterol extract of horse chestnut bark was shown to have anti-inflammatory effects comparable to calcium phenylbutazone in a study of rats with carrageenan-induced paw oedema (Senatore et al 1989).

ANTIOXIDANT

HCSE dose-dependently inhibits both enzymatic and non-enzymatic lipid peroxidation in vitro (Guillaume & Padioleau 1994).

OTHER ACTIONS

Animal studies have demonstrated that isolated escins Ia, Ib, IIa, and IIb inhibit gastric emptying time and ethanol absorption, and exert a hypoglycaemic activity in the oral glucose tolerance test in rats (Matsuda et al 1999, Yoshikawa et al 1996).

CLINICAL USE

HCSE is chiefly used in chronic pathological conditions of the veins where there is increased activity of lysosomal enzymes resulting in damage to and hyperpermeability of vascular walls (Herbalgram 2000). Numerous pharmacological and clinical trials have confirmed the efficacy of HCSE in stabilising the walls of the venous system and improving conditions such as chronic venous insufficiency (Blekic 1996).

CHRONIC VENOUS INSUFFICIENCY

There is strong evidence that HCSE is an effective treatment for chronic venous insufficiency (CVI). A recent Cochrane review that assessed 17 RCT of HCSE capsules (standardised to escin) concluded that signs and symptoms of CVI improve with HCSE as compared with placebo (Pittler & Ernst 2006). Six of seven placebo-controlled trials

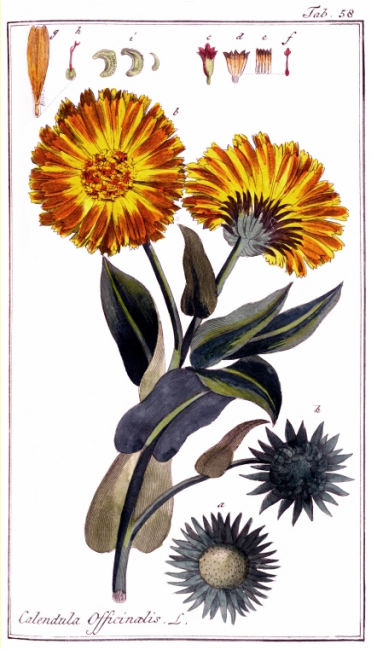
reported a significant reduction in leg pain for HCSE compared with placebo, another study reported a statistically significant improvement compared with baseline and one study reported that HCSE may be as effective as treatment with compression stockings. Pruritus was assessed in eight placebo-controlled trials. Four trials ($n = 407$) showed a statistically significant reduction compared with placebo and two trials showed a statistically significant difference in favour of HCSE compared with baseline, whereas one trial found no significant differences for a score including the symptom pruritus compared with compression. Meta-analysis of six trials ($n = 502$) suggested a reduction in leg volume compared with placebo, as did the studies in which the circumference at calf and ankle was assessed overall. Adverse events were usually mild and infrequent.

An earlier meta-analysis of 13 RCT ($n = 051$) and 3 observational studies ($n = 10{,}725$) found that HCSE reduced leg volume by 46.4 mL (95% CI, 11.3–81.4 mL) and increased the likelihood of improvement in leg pain 4.1-fold (95% CI, 0.98–16.8), oedema 1.5-fold (95% CI, 1.2–1.9) and pruritis 1.7-fold (95% CI, 0.01–3.0). Observational studies reported significant improvements in pain, oedema, and leg fatigue/heaviness (Siebert et al 2002).

A case observational study involving more than 800 general practitioners and more than 5,000 patients with CVI taking HCSE reported that symptoms of pain, tiredness, tension and swelling in the leg, as well as pruritis and tendency to oedema, all improved markedly or disappeared completely, with the additional advantage of better compliance than compression therapy (Greeske & Pohlmann 1996). In an open study carried out to assess the safety and tolerability of *A. hippocastanum*, 91 subjects received a tablet (equiv. 50 mg escin) twice daily for 8 consecutive weeks. At the end of the study the majority of patients rated horse chestnut to be good or very good for Widmer stage I and II CVI (Dickson et al 2004).

In patients suffering from CVI, oedema can give rise to trophic skin changes, inflammatory lesions, and an increase in blood coagulability with the associated risk of thrombosis development. Therapy should therefore be aimed at providing protection against oedema at the earliest possible stage of venous disease (Widmer CVI stages I or II) to prevent complications (Pohlmann et al 2000). As HCSE therapy appears to provide more significant benefits in the earlier stages (less so with the advancement of the condition) (Ottillinger & Greeske 2001) it would appear prudent to initiate HCSE therapy early in order to prevent or delay the need for compression therapy, which is associated with discomfort and poor patient compliance. In the later stages combined treatment with compression stockings and HCSE may provide added benefit (Blaschek 2004, Pittler & Ernst 2004).

Although the standard dose used in clinical trials appears to be equivalent to 50 mg escin twice daily, one study observed that reducing the dose to 50 mg escin once daily at 8 weeks appeared to maintain similar benefits to the twice daily routine at the end of the 16-week observation period (Pohlmann et al 2000).



VENOUS LEG ULCERATION

Chronic venous leg ulceration (VLU) is a common recurrent problem in the elderly population and may result in immobility, with 45% of patients being housebound (Baker & Stacey 1994). As a result, individuals with VLU frequently experience depression, anxiety, social isolation, sleeplessness and reduced working capacity (Leach 2004). CVI, which is characterised by an increase in capillary permeability, inflammatory reactions, decreased lymphatic reabsorption, oedema and malnutrition of tissues, is a precursor to VLU. As HCSE increases venous tone while reducing venous fragility and capillary permeability and possesses anti-oedematous and anti-inflammatory properties, it has been speculated that by improving microcirculation, ulceration may be delayed or prevented (Blaschek 2004).

A preliminary 12-week triple-blind, randomised, placebo-controlled trial of 42 participants with active VLU suggested a potential role for HCSE; however, further large scale trials are required to fully elucidate the potential use in practice (Leach 2004). The second stage of this trial was a descriptive survey exploring current opinion and usage of such therapies. The author concluded that positive results from clinical trials may facilitate the incorporation of the extract into clinical practice, although the integration into mainstream medicine may be 'constrained by medical and organizational gate keeping' (Leach 2004).

HAEMORRHOIDS

Horse chestnut is also used both orally and topically for the treatment of haemorrhoids. Although it has not been investigated for this indication, escin has been shown to significantly improve signs and symptoms according to a placebo-controlled double-blind study of 72 volunteers with haemorrhoids. Symptom relief was experienced by 82% of subjects compared with 32% for placebo, and swelling improved in 87% compared with 38% for placebo (Sirtori 2001). Symptom improvement required at least 6 days of treatment to become established and the dose used was 40 mg escin three times daily.

OTHER USES

Traditionally the seeds are used to treat conditions affecting the veins, including haemorrhoids, phlebitis and varicose veins; bruising, diarrhoea, fever, enlarged prostate, eczema, menstrual pain, painful injuries, sprains, swelling, and spinal

problems. The leaf is used for soft tissue swelling from bone fracture and sprains, complaints after concussion, cough, arthritis, and rheumatism, and the bark for malaria and dysentery, and topically for SLE and skin ulcers (NMCD 2006, PDRHealth 2006).

There is some evidence to support its use for preventing post-operative oedema (Sirtori 2001) and the antioxidant, vascular toning and anti-inflammatory effects of *A. hippocastanum*, as well as the presence of flavonoids and other active constituents, may support some of the other traditional uses (Wilkinson & Brown 1999).

DOSAGE RANGE

- CVI: HCSE standardised to 50–100 mg escin twice daily. The dose may be reduced to a maintenance dose of 50 mg escin once daily after 8 weeks (Pohlmann et al 2000).
- Australian manufacturers recommend 2–5 mL/day of 1:2 liquid extract.
- 1–2 g dried seed daily (Mills & Bone 2005).

ADVERSE REACTIONS

According to clinical trials *A. hippocastanum* and HCSE appear to be well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritus. Post marketing surveillance reports adverse effects of 0.7% (Micromedex 2003, NMCD 2006, PDRHealth 2006, Pittler & Ernst 2004, Siebert et al 2002).

Horse chestnut contains a toxic glycoside esculin (aesculin), a hydroxycoumarin that may increase bleeding time because of its antithrombin activity and may be lethal when the raw seeds, bark, flower or leaves are used orally. Poisoning has been reported from children drinking tea made with twigs and leaves (NMCD 2006).

Symptoms of overdose include diarrhoea, vomiting, reddening of the face, severe thirst, muscle twitching, weakness, loss of coordination, visual disturbances, enlarged pupils, depression, paralysis, stupor and loss of consciousness (NMCD 2006, PDRHealth 2006).

Horse chestnut can also cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex (Diaz-Perales et al 1999).

Isolated cases of kidney and liver toxicity have occurred after intravenous and intramuscular administration (Micromedex 2003, Mills & Bone 2005, NMCD 2006).

SIGNIFICANT INTERACTIONS

ANTIPLATELET/ ANTICOAGULANT MEDICATIONS

Properly prepared HCSE should not contain esculin and should not carry the risk of antithrombin activity — observe. Clinical significance unclear.

HYPOGLYCAEMIC AGENTS

Due to possible hypoglycaemic activity, blood glucose levels should be monitored when horse chestnut or HCSE and hypoglycaemic agents are used concurrently (Yoshikawa et al 1996) — observe. Clinical significance unclear.

CONTRAINDICATIONS AND PRECAUTIONS

As saponins may cause irritation to the gastric mucosa and skin, *A. hippocastanum* should be taken with food, should not be applied topically to broken or ulcerated skin and should be avoided by people with infectious or inflammatory conditions of the gastrointestinal tract, including coeliac disease and malabsorption disorders.

Horse chestnut flower, raw seed, branch bark, or leaf may be toxic and are not recommended (Tiffany et al 2002).

Avoid use in the presence of hepatic or renal impairment (Micromedex 2003, NMCD 2006, PDRHealth 2006).

PREGNANCY USE

Safety in pregnancy and lactation has not been well established.

PRACTICE POINTS/PATIENT COUNSELLING

- Horse chestnut extract has been extensively researched for its beneficial effects and is commonly used by general practitioners in Germany for the treatment of CVI. There is strong evidence to support its use for this indication.
- In practice, a dry extract is used (HCSE standardised to contain 16–21% triterpene glycosides (anhydrous escin)).
- HSCE is also used for venous leg ulceration because it increases venous tone while reducing venous fragility and capillary permeability, and possesses anti-oedematous and anti-inflammatory properties.
- HSCE is also used in the treatment of haemorrhoids. Although it has not been investigated for this indication, escin has been shown to significantly improve signs and symptoms under double-blind study conditions.
- HSCE is well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritis.
- Horse chestnut can cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Horse chestnut standardised extract (HSCE) will relieve signs and symptoms of chronic venous insufficiency such as pain, pruritis and oedema. It may also be of benefit in

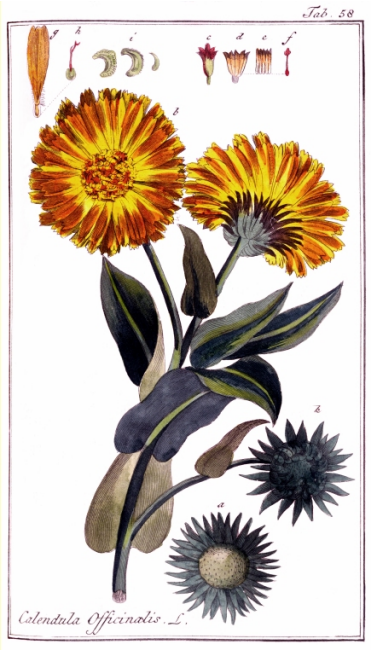
alleviating signs and symptoms in people with haemorrhoids and has been used in venous leg ulceration.

When will it start to work?

Beneficial effects in chronic venous insufficiency have been reported within 3–6 weeks; however, 12 weeks may be required in some cases. Escin provided symptom relief in haemorrhoids after 6 days of treatment.

Are there any safety issues?

HSCE is well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritis. It can cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex.



REFERENCES

Baker SR, Stacey MC. Epidemiology of chronic leg ulcers in Australia. Aust NZ J Surg 64(4) (1994): 258-61.

Berti F, Omini C, Longiave D. The mode of action of aescin and the release of prostaglandins. Prostaglandins 14(2) (1977): 241-9.

Blaschek W. Aesculus hippocastanum: Horse chestnut seed extract in the treatment of chronic venous insufficiency. Z Phytother 25(1) (2004): 21-30.

Blekic J. Horse chestnut seeds (Aesculus hippocastanum L.) in the treatment of phlebopathological disorders. Farm Glas 52(6) (1996): 145-55.

Bombardelli E, Morazzoni P, Griffini A. 1996. Aesculus hippocastanum L. Fitoterapia 67(6) (1996): 483-511.

Diaz-Perales A et al. Cross-reactions in the latex-fruit syndrome: A relevant role of chitinases but not of complex asparagine-linked glycans. J Allergy Clin Immunol 104(3) (1999): 681-7.

Dickson S et al. An open study to assess the safety and efficacy of Aesculus hippocastanum tablets (Aesculaforce 50 mg) in the treatment of chronic venous insufficiency. J Herb Pharmacother 4(2) (2004): 19-32.

Facino RM et al. Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from Hedera helix, Aesculus hippocastanum, and Ruscus aculeatus: factors contributing to their efficacy in the treatment of venous insufficiency. Arch Pharm (Weinheim) 328(10) (1995): 720-4.

Fallier-Becker P, Borner M, Weiser M. Proliferation modulating effect of Aesculus hippocastanum, Coenzyme Q10 and Heparsuis on endothelial cells. Biol Med 31(1) (2002): 10-14.

Greeske K, Pohlmann BK. (Horse chestnut seed extract: an effective therapy principle in general practice: Drug therapy of chronic venous insufficiency.) Fortschr Med 114(15) (1996): 196-200.

Guillaume M, Padioleau F. Veinotonic effect, vascular protection, antiinflammatory and free radical scavenging properties of horse chestnut extract. Arzneimittelforschung 44(1) (1994): 25-35.

Herbalgram. Horse chestnut seed extract. In: Council AB, editor. Excerpt from: Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Hubner G, Wray V, Nahrstedt A. Flavonol oligosaccharides from the seeds of Aesculus hippocastanum. Planta Med 65(7) (1999): 636-42.

Konoshima T, Lee KH. Antitumor agents, 82: Cytotoxic sapogenols from Aesculus hippocastanum. J Nat Prod 49(4) (1986): 650-6.

Leach MJ. The clinical feasibility of natural medicine, venotonic therapy and horsechestnut seed extract in the treatment of venous leg ulceration: a descriptive survey. Complement Ther Nursing Midwif 10(2) (2004): 97-109.

Matsuda H et al. Effects of escins Ia, Ib, IIa, and IIb from horse chestnut, the seeds of Aesculus hippocastanum L., on acute inflammation in animals. Biol Pharm Bull 20(10) (1997): 1092-5.

Matsuda H et al. Effects of escins Ia, Ib, IIa, and IIb from horse chestnuts on gastric emptying in mice. Eur J Pharmacol 368(2-3) (1999): 237-43.
Micromedex. (Horse chestnut: Alternative Medicine Summary). Thomson, 2003. Available at: www.micromedex.com (accessed 10-01-06).
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone; 448-55, 2000.
Mills S, Bone K. The Essential Guide to Herbal Safety. St Louis: Elsevier, 2005.
Natural Medicines Comprehensive Database (NMCD online) Horse chestnut: Monograph, 2006. Available at www.naturaldatabase.com (accessed 10-01-06)
Ottillinger B, Greeske K. Rational therapy of chronic venous insufficiency chances and limits of the therapeutic use of horse-chestnut seeds extract. BMC Cardiovasc Disord 1 (2001): 5.
PDRHealth (online). Horse chestnut, 2006. Available at: www.pdrhealth (accessed 10-01-06)
Pittler M, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. Cochrane Database Syst Rev 4: (2006) CD003230.
Pohlmann G, Bar H, Figulla H. Studies on dose dependency of the edema protective effect of extracts from horse chestnut in female patients suffering from chronic venous insufficiency. Vasomed 12(2) (2000): 69-75.
Senatore F et al. Steroidal constituents and anti-inflammatory activity of the horse chestnut (Aesculus hippocastanum L.) bark. Boll Soc Ital Biol Sper 65(2) (1989): 137-41.
Siebert U et al. Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency: A meta-analysis of randomized controlled trials and large observational studies. Int Angiol 21(4) (2002): 305-15.
Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. Pharmacol Res 44(3) (2001): 183-93.
Tiffany N et al. Horse chestnut: a multidisciplinary clinical review. J Herb Pharmacother 2(1) (2002): 71-85.
Wilkinson J, Brown A. Horse chestnut: Aesculus hippocastanum: Potential applications in cosmetic skin-care products. Int J Cosmet Sci 21(6) (1999): 437-47.
Yoshikawa M et al. Bioactive saponins and glycosides. III. Horse chestnut. (1): The structures, inhibitory effects on ethanol absorption, and hypoglycemic activity of escins Ia, Ib, IIa, IIb, and IIIa from the seeds of Aesculus hippocastanum L. Chem Pharm Bull (Tokyo) 44(8) (1996): 1454-64.
Yoshikawa M et al. Bioactive saponins and glycosides. XII. Horse chestnut. (2): Structures of escins IIIb, IV, V, and VI and isoescins Ia, Ib, and V, acylated polyhydroxyoleanene triterpene oligoglycosides, from the seeds of horse chestnut tree (Aesculus hippocastanum L., Hippocastanaceae). Chem Pharm Bull (Tokyo) 46(11) (1998): 1764-9.

Horseradish

Historical note Horseradish is a commonly used spice with a long history of use in traditional medicine. The leaves are used in cooking and as a salad green. Horseradish is one of the 'five bitter herbs' of the biblical Passover.

COMMON NAME
Horseradish

OTHER NAMES
Amoraciae rusticanae radix, great mountain root, great raifort, mountain radish, pepperrot, red cole

BOTANICAL NAME/FAMILY
Armoracia rusticana, synonym *Armoracia lopathifolia*; *Cochlearia armoracia*, *Nasturtium armoracia*, *Roripa armoracia* (family Brassicaceae [Cruciferae])

PLANT PARTS USED
Fresh or dried roots and leaves

CHEMICAL COMPONENTS
Horseradish root contains volatile oils: glucosinolates (mustard oil glycosides); gluconasturtiin and sinigrin (S-glucosides); coumarins (aesculetin, scopoletin); phenolic acids, including caffeic acid derivatives and hydroxycinnamic acid derivatives, ascorbic acid; asparagin; resin; and peroxidase enzymes. Horseradish is one of the richest plant sources of peroxidase enzymes, which are commonly used as oxidising agents in commercial chemical tests.

MAIN ACTIONS
Horseradish is widely known for its pungent burning flavour. The pungency of horseradish is due to the release of allyl isothiocyanate and butylthiocyanate upon crushing (Yu et al 2001). These mustard oil constituents may irritate the mucous membranes upon contact or inhalation and may act as circulatory and digestive stimulants; however, the mechanism of action has not been fully elucidated (Blumenthal et al 2000, Jordt et al 2004). It has been found that topical application of allyl isothiocyanate to the skin activates sensory nerve endings producing pain, inflammation and hypersensitivity to thermal and mechanical stimuli due to

depolarising the same sensory neurons that are activated by capsaicin and tetrahydrocannabinol (THC) (Jordt et al 2004).

CIRCULATORY STIMULANT

The mustard oils released when horseradish is crushed may be responsible for this activity.

DIGESTIVE STIMULANT

Again, it is suspected that the mustard oils may be responsible.

OTHER ACTIONS

Isothiocyanates may inhibit thyroxine formation and be goitrogenic (Langer 1965) although this has not been demonstrated clinically.

The peroxidase enzymes assist in wound healing, whereas the sulphur-containing compounds may decrease the thickness of mucus by altering the structure of its mucopolysaccharide constituents (Mills & Bone 2000). Antispasmodic and antimicrobial effects have also been reported (Blumenthal et al 2000, Newell et al 1996).

Horseradish has been found to lower plasma cholesterol and faecal bile acid excretion in mice fed a cholesterol enriched diet possibly due to interference with exogenous cholesterol absorption (Balasinska et al 2005).

Horseradish has also been found to contain compounds that inhibit tumour cell growth and COX-1 enzymes (Weil et al 2005).

CLINICAL USE

The therapeutic effectiveness of horseradish has not been significantly investigated.

NASAL CONGESTION AND SINUSITIS

Horseradish is widely used in combination with other ingredients such as garlic in herbal decongestant formulations. Although clinical research is not available to confirm efficacy, anecdotal evidence suggests that a mild, transient decongestant effect occurs.

OTHER USES

It has been used traditionally to treat both bronchial and urinary infections, joint and tissue inflammation, as well as treating gall bladder disorders, reducing oedema and as an abortifacient (Skidmore-Roth 2001).

DOSAGE RANGE

- The typical dose of horseradish is 2–20 g/day of the root or equivalent preparations.

- Topical preparations with a maximum of 2% mustard oil content are commonly used (Blumenthal et al 2000).

ADVERSE REACTIONS

Despite the potential for severe irritation, horseradish is generally recognised as safe for human consumption in quantities used as food. Consuming large amounts of horseradish can cause gastrointestinal upset, vomiting and diarrhoea, and irritation of mucous membranes. Skin contact with fresh horseradish can cause irritation and blistering or allergic reactions.

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Internal use should be avoided in people with stomach and intestinal ulcers and kidney disorders, as well as in children under the age of 4 years (Blumenthal et al 2000).

Traditionally, horseradish is considered a warming herb that will exacerbate any 'hot' condition and is specifically indicated for 'cold' conditions.

PREGNANCY USE

The mustard oils released upon crushing are potentially toxic, therefore doses exceeding dietary intakes are contraindicated (Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Horseradish has been used as a vegetable, condiment, diuretic and treatment for bronchial and urinary infections, joint and tissue inflammation, and swelling.
- It is widely used together with other herbal ingredients such as garlic, as a decongestant in the treatment of colds and sinusitis.
- No scientific investigation has been undertaken to support its use, although anecdotal evidence suggests it may be useful.
- Horseradish is generally safe when the root is ingested in usual dietary amounts, although excessive intake may cause irritation to the stomach, respiratory tract and kidneys.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Anecdotal evidence suggests it may have decongestant effects and is a very popular treatment when combined with other herbs such as garlic, to relieve the symptoms of colds and sinusitis.

When will it start to work?

It may relieve symptoms within the first few doses, but scientific tests are not available to confirm this.

Are there any safety issues?

Horseradish can be quite irritating for some people due to its bitter and pungent characteristics.

REFERENCES

Balasinska B et al. Dietary horseradish reduces plasma cholesterol in mice. Nutr Res 25.10 (2005): 937-45.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Jordt S-E et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 427 (2004): 260-5.

Langer PSV. Goitrogenic activity of allylisothiocyanate: a widespread natural mustard oil. Endocrinology 76 (1965): 151-5.

Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.

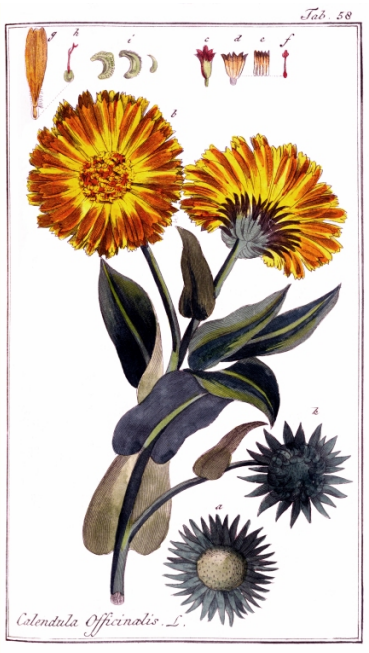
Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.

Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. St Louis: Mosby, 2001.

Weil MJ et al. Tumor cell proliferation and cyclooxygenase inhibitory constituents in horseradish (Armoracia rusticana) and Wasabi (Wasabia japonica). J Agric Food Chem 53.5 (2005): 1440-4.

Yu EY et al. In situ observation of the generation of isothiocyanates from sinigrin in horseradish and wasabi. Biochim Biophys Acta 1527.3 (2001): 156-60.

Iodine



BACKGROUND AND RELEVANT PHARMACOKINETICS

Iodine is an essential trace element required for the proper functioning of the thyroid gland. It is mainly consumed as iodide salts obtained from sea salt, shellfish and seawater fish and vegetables, which are more bioavailable than the organic form of iodine. The iodine content of soil is considered to be one of the most variable of all mineral levels, influenced by local geography and the type and quantity of fertiliser used in agriculture (Gropper et al 2005). The amount of iodine present in local drinking water (0.1–100 μg/L) is reported to be a good indication of soil levels (Geissler & Powers 2005). In iodine-deficient areas, the iodide concentration in drinking water is <2 μg/L (<15.8 nmol/L), whereas in areas close to the sea, the drinking water contains 4 to 10 μg/L (31.5–78.8 nmol/L) (Beers 2005).

Iodide is rapidly absorbed from the small intestine and distributed via the blood to a range of tissues, most notably the thyroid, which traps absorbed iodide through an ATP-dependent iodide pump. The thyroid contains 80% of the body's iodine pool, which is approximately 15 mg in adults. Some is also found in the salivary, gastric and mammary glands (exclusively during pregnancy and lactation in the latter), as well as in the ovaries. As is the case with the thyroid, uptake into these tissues is regulated by thyroid-stimulating hormone (TSH) (Gropper et al 2005, Kohlmeier 2003).

Iodine is excreted via the kidneys and excretion occurs when the needs of the thyroid have been met and an excess remains (Kohlmeier 2003). The amount of iodine excreted in the urine reflects plasma levels and has been used since the middle of the 20th century to assess iodine status. Interestingly there is no renal conservation mechanism for this mineral and the only evidence of iodine preservation comes from the scavenging and recycling of thyroid hormones by the selenium-dependent deiodinase DII (Kohlmeier 2003). Of the total amount excreted, 20% occurs via faeces and additional losses can occur through sweat, which, although a minor eliminatory pathway under normal circumstances, can be a significant contributor for people living in hot climates with low dietary consumption (Gropper et al 2005).

Kohlmeier (2003) notes the Wolff-Chaikoff effect, which is the reduction in thyroid hormone production in response to acute large doses of iodine and was first described over 50 years ago. It is reported to occur through the downregulation of the active-transport mechanism present in the thyroid in response to high blood

levels. Other evidence points to temporary inhibition of thyroid peroxidase and therefore reduced thyroglobulin iodination reactions (Markou et al 2001).

FOOD SOURCES

Iodine can occur in foods as either an inorganic or organic salt, or as thyroxine in animal sources. Unlike many other essential nutrients, the organic form of iodine found in animal products has poor bioavailability, whereas the iodide salts found in the sea are almost completely absorbed (Jones 2002).

However, irrespective of whether it is animal or plant derived, food from the land has enormous variability in terms of iodine content, from 1 to 10 μg/kg, (Geissler & Powers 2005) due to iodine's high solubility, which results in it leaching from the soil with heavy rain and weathering (Wahlqvist 2002).

Additionally, chemicals known as goitrogens are naturally found in some foods (e.g. brassica [cabbage] family) and these interfere with iodine utilisation and thyroid hormone production.

BEST SOURCES

Due to the high levels in the ocean of bioavailable iodide, all sea-dwelling creatures, animal or plant, are considered superior dietary sources.

- Seawater fish
- Shellfish
- Sea vegetables such as seaweeds
- Sea salt
- Iodised salt (fortified form of table salt)
- Commercially manufactured breads due to the iodate dough oxidisers
- Dairy milk (variable)

In Australia milk no longer supplies a significant amount of iodine, whereas in the United Kingdom it is still an important dietary source because of the use of both supplemented feeds and iodine-based antiseptics in the dairy industry (Geissler & Powers 2005).

DEFICIENCY SIGNS AND SYMPTOMS

PRIMARY DEFICIENCY

Iodine deficiency results when iodide intake is <20 μg/day (Kasper et al 2005). In situations of moderate deficiency, TSH induces thyroid hypertrophy in order to concentrate iodide, resulting in a goitre. Most of these cases remain euthyroid, but in cases of severe iodine deficiency, myxoedema may result in adults and cretinism in infants, both of which are serious conditions.

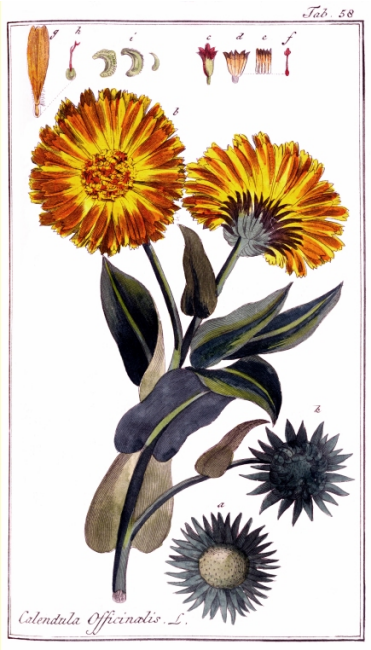
Myxoedema is characterised by swelling of the hands, face, feet and peri-orbital tissues and can lead to coma and death if sufficiently severe and left untreated. Endemic cretinism is divided into two forms, neurologic or myxoedematous, depending on the interplay of genetics and iodine deficiency. Usually children with neurologic cretinism are mentally deficient and often deaf mute but of normal height and strength and may have goitre. Myxoedematous cretinism is characterised by dwarfism, mental deficiency, dry skin, large tongue, umbilical hernia, muscular incoordination and puffy facial features. Concomitant selenium deficiency may be a contributing factor in myxoedematous cretinism. Early treatment with thyroid hormone supplementation can promote normal physical growth; however, intellectual disability may not be prevented and in very severe cases death may ensue.

The term 'iodine deficiency disorders' (IDD) has been coined to refer to the collection of health problems that result from iodine deficiency, ranging from the mild and common (e.g. goitre) to severe and life threatening (e.g. cretinism and myxoedema) (Gropper et al 2005).

Although severe iodine deficiency is rare in Australia and New Zealand, many parts of the world are well known for their low iodine levels. Countries where iodine deficiency is a primary concern include China, Latin America, South-East Asia and the eastern Mediterranean (Wahlqvist 2002). A report conducted by the World Health Organization in 2005 found that while many countries had succeeded in reaching optimal iodine nutrition through enhanced monitoring and fortification programs over the past decade, an estimated 285 million school-age children and close to 2 million adults worldwide still suffer from iodine deficiency (Andersson et al 2005).

Fetal deficiency The fetus depends solely on maternal thyroid hormones during the first trimester of pregnancy (Soldin et al 2002). From week 11 of gestation, thyroid hormone synthesis usually begins but remains dependent on the maternal provision of iodine. Consequently adequate functioning of both the maternal and the fetal thyroid glands plays a critical role in fetal neuropsycho-intellectual development. A range of studies has confirmed that 'mild but measurable' psychomotor deficits in early childhood are the potential sequelae of subclinical hypothyroidism and hypothyroxaemia caused by mild to moderate iodine deficiency in pregnancy (Soldin et al 2002).

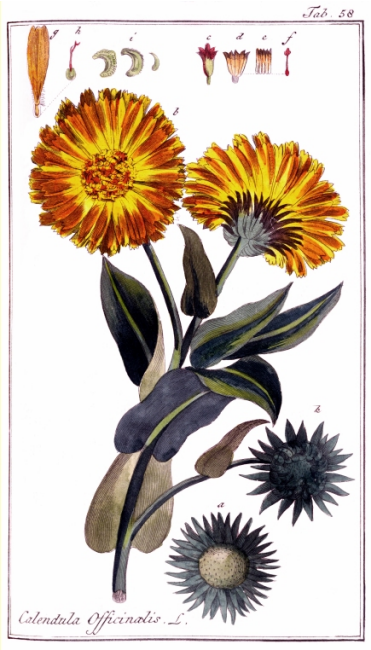
Because of the severe neurological consequences of untreated congenital hypothyroidism, neonatal screening programs have been established in some developed countries.



SECONDARY DEFICIENCY

High consumption of goitrogens can induce a secondary deficiency state. Goitrogens are substances that inhibit iodine metabolism and include thiocyanates found in the cabbage family (e.g. cabbage, kale, cauliflower, broccoli, turnips and Brussels sprouts) and in linseed, cassava, millet, soybean and competing entities, such as other members of the halogen family (e.g. bromine, fluorine and lithium, as well as arsenic) (Gropper et al 2005). Most researchers agree, however, that moderate intake of goitrogens in the diet is not an issue, except when accompanied by low iodine consumption (Gropper 2005, Kohlmeier 2003). A very rare cause of secondary iodine deficiency and hypothyroidism is TSH deficiency.

Low selenium intake Low dietary intake of selenium is a factor that exacerbates the effects of iodine deficiency. Selenium is found in the thyroid gland in high concentrations, and while iodine is required for thyroid hormone synthesis, selenium-dependent enzymes are required for the peripheral conversion of thyroxine (T_4) to its biologically active form triiodothyronine (T_3) (Higdon 2003), as well as the general recycling of iodine. Selenium deficiency results in decreased T_4 catabolism, which leads to increased production of peroxide and thyroid cell destruction, fibrosis and functional failure.



SIGNS AND SYMPTOMS

MILD HYPOTHYROIDISM

This refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism.

CONGENITAL HYPOTHYROIDISM

According to Isselbacher (2005), the majority of infants appear normal at birth and <10% are diagnosed based on clinical features:

- prolonged jaundice
- feeding problems
- hypotonia
- enlarged tongue
- delayed bone maturation
- umbilical hernia.

Importantly, permanent neurologic damage results if treatment is delayed.

ADULT HYPOTHYROIDISM

According to Beers (2005), the clinical signs of hypothyroidism in adults are:

- weakness, tiredness and sleepiness
- dry skin

- cold intolerance
- hair loss and diffuse alopecia
- poor memory and difficulty concentrating
- constipation
- reduced appetite and weight gain
- dyspnoea
- hoarse voice
- increased susceptibility to infectious diseases
- increased susceptibility to cardiovascular diseases
- paraesthesia
- puffy hands, feet and face and peripheral oedema
- impaired hearing
- menorrhagia (later amenorrhoea)
- carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain
- reduced myocardial contractility and pulse rate, leading to a reduced stroke volume and bradycardia.

MAIN ACTIONS

THYROID HORMONE PRODUCTION

Iodine is essential for the manufacture of T_4 and T_3, which are hormones that influence growth, maturation, thermogenesis, oxidation, myelination of the CNS and the metabolism of all tissues (Jones 2002). The thyroid hormones, especially T_3, exert their effects by binding to nuclear receptors on cell surfaces, which in turn triggers binding of the zinc fingers of the receptor protein to the DNA (Gropper 2005).

OTHER ACTIONS

Due to the concentration of appreciable iodine levels in a range of other tissues, including salivary, gastric and lactating mammary glands, as well as the ovaries, questions remain about the potential for additional actions of iodine. One currently proposed model suggests iodine is an indirect antioxidant, via its capacity to reduce elevated TSH, a trigger of increased peroxide levels in the body (Smyth 2003).

CLINICAL USE

Increased iodine intake can be achieved through dietary modification and supplementation with tablets. Dietary modification usually refers to increased intake of iodised salt, but may also refer to use of iodised water, iodised vegetable oil or seafood.

TREATMENT AND PREVENTION OF DEFICIENCY

Iodine deficiency is accepted as the most common cause of brain damage worldwide, with IDD affecting 740 million people (Higdon 2003). Although it is well accepted that severe deficiency is responsible, evidence is now emerging that mild deficiency during pregnancy is also important and can have subtle effects on brain development, lowering intellectual functioning and inducing psychomotor deficits in early childhood. Preliminary data are also emerging to suggest an association between iodine deficiency hypothyroidism of pregnancy and the incidence of ADHD in the offspring; however, this still requires confirmation in larger studies (Soldin et al 2002, Vermiglio et al 2004).

PREGNANCY

Severe iodine deficiency is uncommon in Western countries, such as Australia and New Zealand, but several local surveys have identified that mild to moderate deficiency is more prevalent than once thought. A research group at Monash Medical Centre in Melbourne screened 802 pregnant women and found that 48.4% of Caucasian women had urinary iodine excretion (UIE) concentrations below 50 μg/L compared to 38.4% of Vietnamese women and 40.8% of Indian/Sri Lankan women (Hamrosi et al 2005). These figures are disturbing when the WHO defines healthy UIE levels as greater than 100 μg/L, mild deficiency is diagnosed at 51–100 μg/L and moderate to severe deficiency at $<$50 μg/L (Gunton et al 1999). A study conducted at a Sydney hospital involving 81 women attending a 'high' risk clinic found moderate to severe iodine deficiency in 18.8% of subjects and mild iodine deficiency in another 29.6% (Gunton et al 1999), the former clearly too close to the WHO maximum acceptable level of 20%. This study also revealed that almost 5% of the sample had UIE $<$25 μg/L.

Based on such results it may well be expected that endemic cretinism could emerge, and that it has not yet occurred in Australia may be due to a low to moderate intake of goitrogens and adequate selenium levels.

INFANTS

Results of a study investigating TSH levels in a group of infants within 72 hours of birth at the Royal North Shore Hospital in Sydney suggest that endemic IDD may be emerging (McEldruff 2002). Currently, the WHO recommends that less than 3% of newborns should have TSH levels greater than 5 mIU/L and of the 1773 infants enrolled in the study, 5–10% had a TSH reading $>$5 mIU/L, which is clearly outside WHO recommendations and provides evidence of insufficient iodine levels during pregnancy.

CHILDREN AND ADOLESCENTS

Evidence of iodine deficiency is not limited to pregnant women and newborns and has also been demonstrated in Australian schoolchildren (Li et al 2006). Iodine status in schoolchildren is based on median UIE values and is categorised as normal (UIE ≥100 μg/L) or as mild (UIE 50–99 μg/L), moderate (UIE 20–49 μg/L) and severe deficiency (UIE <20 μg/L). The UIE is considered in combination with the child's sex, year of school and presence of goitre.

A study of Melbourne schoolchildren aged 11–18 years found that 76% (439/577) had abnormal UIE values, with 27% (156/577) having values consistent with moderate–severe iodine deficiency (McDonnell et al 2003). The median UIE value in girls was lower than that in boys (64 μg/L vs 82 μg/L), and girls had significantly lower UIE values overall ($P < 0.002$). A study of 324 schoolchildren aged 5–13 years from the Central Coast of New South Wales produced similar results and there was a median UIE concentration of 82 μg/L, with 14% of children having levels below 50 μg/L (Guttikonda et al 2003).

More recently, these findings were confirmed in the Australian National Iodine Nutrition Study, which identified inadequate iodine intake in the Australian population and called for the urgent implementation of mandatory iodisation of all edible salt in Australia (Li et al 2006). The study consisted of a survey of 1709 schoolchildren aged 8–10 years in the five mainland Australian States and was conducted between July 2003 and December 2004. It found that, overall, children in mainland Australia are borderline iodine deficient, with a national median UIE of 104 μg/L. On a State basis, children in Victoria and New South Wales are mildly iodine deficient, with median UIE levels of 89 μg/L and 73.5 μg/L, respectively, South Australian children are borderline iodine deficient, with a median UIE of 101 μg/L, whereas both Queensland and Western Australian children are iodine sufficient, with median UIE levels of 136.5 μg/L and 142.5 μg/L, respectively. Researchers attributed the decline in iodine intake to changes within the dairy industry, with chlorine-containing sanitisers now replacing iodine-containing sanitisers and decreased intake of iodised salt.

In 2001 an iodine supplementation program was initiated in Tasmania because it was identified as an area of endemic goitre by the Department of Health Services. The programme involves the use of iodised salt in 80% of Tasmania's bread production and aims to reduce the incidence of iodine deficiency. Despite encouraging preliminary data (Doyle & Seal 2003), iodine levels are still inadequate according to the WHO standards. There have been conflicting opinions about the success of this programme, with the largest study demonstrating evidence of ongoing iodine deficiency (Seal et al 2003, Guttikonda et al 2002).

Iodine deficiency in children and adolescents is associated with poorer school performance, reduced achievement motivation and a higher incidence of learning disabilities (Tiwari et al 1996). A meta-analysis of 18 studies from 8 countries of people aged between 2 and 30 years showed that iodine deficiency alone reduced mean IQ scores by 13.5 points in children (Bleichrodt et al 1996). From both a public health and a socioeconomic perspective, these findings have significant repercussions.

ADULTS

A study of non-pregnant adults in 1999 demonstrated iodine deficiency in 26.3% of 'healthy' subjects and 34.1% of diabetic subjects (Gunton et al 1999).

Clinical note — Why is iodine deficiency on the rise?

The emergence or re-emergence of iodine deficiency is not limited to Australia. One study found that the median UIE had declined by more than 50% in between 1971 and 1994 in the United States (Gunton et al 1999).

Three reasons have been proposed to explain the emergence of iodine deficiency in developed countries. First, milk has traditionally been viewed as a good dietary source of iodine; however, since the 1990s its iodine content has reduced significantly because iodine-containing sanitisers have been gradually replaced with chlorine-containing sanitisers. The significance of this change within the dairy industry was recently shown by Li et al (2006) who compared the iodine content of Australian milk products from 1975 and 2004. They identified mean iodine concentrations of 593.5 μg/L and 583 μg/L from samples taken from Victoria and NSW respectively in 1975 compared to a median concentration of 195 μg/L in 2004 (250 mL providing 50–60 μg iodine). Interestingly, the same researchers demonstrated that dairy products and water in northern and central Queensland contain higher iodine levels, which may explain the lower incidence of iodine deficiency in these areas (Li et al 2006). In spite of this, a survey of dietary habits of Tasmanian schoolchildren has revealed that consumption of dairy products is associated with improved iodine status (Hynes et al 2004), a case of some being better than none.

A second reason may relate to public health campaigns that have resulted in increased awareness of the potential adverse effects of salt and reduced its consumption, but failed to highlight the potential benefits of a moderate intake of iodised salt. In addition, few food manufacturers use iodised salt in their products, further reducing exposure to iodine (Gunton et al 1999).

Lastly, the mineral depletion of soils is another possible contributing factor, in particular the depletion of selenium. Considering its role in iodine utilisation,

selenium deficiency would potentiate the effects of iodine deficiency. Other theoretical considerations include increased environmental exposure to halogens, such as fluorine and chlorine, and increased consumption of goitrogens, such as soy, in the diet.

Although identifying the key factors responsible for the growth of iodine deficiency is important (Thomson 2004), many authors argue that implementation of national iodine monitoring and surveillance of the iodine content in foods is the most immediate concern (Laurberg & Nohr 2006, Li et al 2006, McDonnell et al 2001). Lessons learnt from Tasmania's iodine supplementation program, where state-wide bread fortification failed to reduce the prevalence of iodine deficiency in children, indicate that greater efforts are required to create significant improvements in iodine status.

NON-TOXIC GOITRE THYROIDECTOMY

One 12 month study involving 139 patients who had undergone thyroidectomy for non-toxic goitre identified that supplementing L-thyroxine therapy with iodised salt produced significant improvements in thyroid function compared with stand alone L-thyroxine therapy (Carella 2002).

OTHER USES

PREVENTION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER?

Emerging data from research conducted over the past 15 years suggest a possible link between low maternal iodine status and increased risk of ADHD in the offspring. According to a report published in 2004, 11 of 16 children born to women living in a moderately iodine-deficient region in Italy developed ADHD compared to no offspring from the 11 control mothers living in a marginally iodine-deficient region (Vermiglio et al 2004).

On the other hand, another group of researchers investigated whether T_4 levels at birth could represent a biomarker for later development of ADHD and found that all newborns in the sample had T_4 within the normal range and no correlation between values and risk could be demonstrated (Soldin 2002, Soldin et al 2003). This evidence invalidated TSH levels as a biomarker of risk, but does not disprove a link between iodine and ADHD, as earlier studies found that those newborns who later developed ADHD were all euthyroid at birth (Vermiglio et al 2004).

Although further investigation is required to clarify these observations, they have provided a new avenue for ADHD research.

FIBROCYSTIC BREAST DISEASE AND CYCLIC MASTALGIA

A 1993 review that focused on three clinical studies suggests that iodine supplementation may improve objective and subjective outcomes, including pain and fibrosis, for women with fibrocystic breast disease and cyclic mastalgia (Ghent et al 1993). Together the trials involved 1000 women and used a variety of different forms, the most successful being molecular iodine at a dose of 0.08 mg/kg (approximately equivalent to 500 μg/day in a 60 kg woman) (Ghent et al 1993).

Recently a placebo-controlled trial conducted with 11 euthyroid women with cyclic mastalgia tested different doses of molecular iodine ranging from 1.5 to 6 mg/day and showed that after 3 months of treatment, 50% of patients consuming 3 or 6 mg/day experienced a significant decrease in pain (Kessler 2004). Although no dose-related adverse events were detected, further investigation is required to confirm both efficacy and safety.

BREAST CANCER

There is suggestive evidence of a preventive role for iodine in breast cancer. As far back as 1896 research has suggested a link between iodine deficiency, thyroid disease and breast cancer (Smyth 2003). More recently, epidemiological data have demonstrated a correlation between increased incidence of breast cancer and a range of thyroid conditions, most notably hypothyroidism (Smyth 2003). In addition, the observed low rates of breast cancer in Japan are speculated to be partly due to a high dietary iodine intake, further suggesting a protective effect.

It is noteworthy that both the thyroid and the breast share the capacity to concentrate iodide, which exerts an antioxidant effect and protects cells from peroxidative damage (Venturi 2001). Whereas the thyroid retains this capacity throughout life, the breast can only concentrate iodide during pregnancy and lactation, states associated with a reduced risk of breast cancer. It has been theorised that with iodine insufficiency during pregnancy and lactation, the protective effect of iodide may be compromised, concomitant with diminished antioxidant activity. Researchers speculate that this scenario may be compounded by coexisting selenium deficiency (Turken et al 2003).

Besides the diminished antioxidant effect, studies with animal models show that iodine deficiency results in changes in the mammary gland that makes it more sensitive to the effects of oestradiol (Strum 1979). Oestradiol stimulates cell division, which eventually results in cyst formation, and dietary supplementation with iodine can improve these alterations.

At present the only interventional evidence comes from studies of rats, which found that administration of Lugol's iodine or iodine-rich Wakame seaweed

suppressed the development of induced mammary tumours (Funahashi et al 2001) and rigorous human studies are required.

WATER PURIFICATION

Iodine-releasing tablets and iodine tincture have been used for many years to decontaminate water and have been used by the United States Army since WWII. A weak aqueous solution of 3–5 ppm of elemental iodine can destroy a wide range of enteroviruses, ameobae and their cysts, bacteria and their spores, as well as algae. Under temperate conditions of 25°C the disinfection process takes 15 minutes, longer in colder conditions. Adding to the versatility of iodine as a water decontamination agent is its ability to act over a wide range of pH and still be effective in the presence of ammonia and amino ions from nitrogenous wastes that may be also present in the water (Kahn & Visscher 1975).

ANTISEPTIC

Iodine solution is widely used as a topical antiseptic in the treatment of superficial wounds. It is a highly effective method of decontaminating intact skin and minor wounds and has a low toxicity profile. Povidone-iodine preparations have replaced older iodine solutions and are now the most widely used form.

Although the treatment is considered safe, a number of recent reports of iodine toxicity in newborns receiving ongoing treatment with topical iodine-based solutions suggests that it should be used with caution as an ongoing treatment in this group and TSH monitoring considered where appropriate (Khashua 2005).

DOSAGE RANGE

AUSTRALIAN RDI

- Infants
  - 0–6 months: 90 μg/day
  - 7–12 months: 110 μg/day
- Children
  - 1–3 years: 90 μg/day
  - 4–8 years: 90 μg/day
  - 9–14 years: 120 μg/day
  - >14 years: 150 μg/day
- Adults: 150 μg/day
- Pregnancy: 220 μg/day
- Lactation: 270 μg/day
- Upper level of intake
  - 1–3 years: 200 μg/day

4–8 years: 300 μg/day
9–13 years: 600 μg/day
14–18 years
(including pregnancy, lactation): 900 μg/day
Adults >18 years
(including pregnancy, lactation): 1100 μg/day

These are the newly revised Australian RDIs, which are more closely aligned with the WHO recommendations than previously.

ACCORDING TO CLINICAL STUDIES

- ADHD prevention: adequate intake to prevent maternal deficiency (approximately 250 μg/day).
- Fibrocystic breast disease and cyclic mastalgia: 500 μg to 6 mg molecular iodine/day.
- Breast cancer prevention: dose is unknown; however, it is suggested that women meet RDI to prevent deficiency.
- Water disinfectant: 3–5 ppm in water or 8 drops of 2% tincture to approximately 1 L of water.

TOXICITY

Chronic iodine toxicity results when iodide intake is approximately 2 mg daily or greater (Beers 2005). Overconsumption of iodine can induce both hypo- and hyperthyroidism, depending on the patient's pre-existing susceptibility (Wahlqvist 2002). Excess iodine during pregnancy has also been associated with increased risk of postpartum thyroiditis (Guan et al 2005). Alternatively, there are many cases in which excesses have been tolerated without any overt consequences (Geissler & Powers 2005, Gropper et al 2005). Intake of very high doses can lead to a brassy taste in the mouth, increased salivation, gastric irritation and acneiform skin lesions.

SIGNIFICANT INTERACTIONS

GOITROGENS

These are substances that interfere with iodine utilisation or thyroid hormone production and include thiocyanates found in the cabbage family (e.g. cabbage, kale, cauliflower, broccoli, turnips and Brussels sprouts) and in linseed, cassava, millet and soybean — separate intake of iodine and goitrogens where possible.

SOY

The actions of this particular goitrogen are two-fold: ingestion of soy appears to inhibit iodine absorption to some extent (particularly when presented in its thyroxine

form in the gut) and also high levels of the isoflavones genistein and daidzein can inhibit T_3 and T_4 production — separate intake of iodine and goitrogens where possible. Particular attention should be paid to minimising soy consumption in individuals taking thyroid hormone supplementation, as it has been shown that soy consumption can increase dosage requirements.

SELENIUM

Selenium is intrinsic to the metabolism and activity of the thyroid hormones, facilitating the conversion of T_4 to T_3 and is also responsible for the only iodine recycling pathway of the body through the action of the deiodinases on excess or unnecessary thyroid hormones to release the iodine — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

THYROID CONDITIONS

Due to the complex and diverse causes of thyroid conditions, it is advised that iodine supplementation should be avoided unless under the supervision of a medical practitioner.

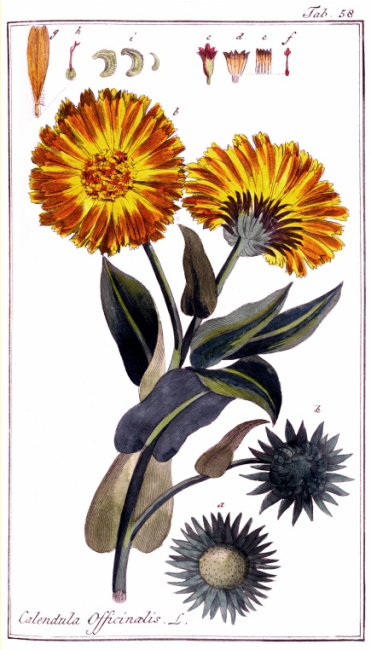
PREGNANCY USE

Up until 2006, the Australian recommended daily intake of iodine was 150 μg for pregnant women and 170 μg for lactating women; however, as a reflection of new research, the Australian RDI levels for pregnancy have been revised. Care should be taken to avoid ingestion of excessive amounts during pregnancy due to suspected links with increased rates of postpartum thyroiditis and other disorders of thyroid function (Guan et al 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Iodine is an essential trace element required for healthy functioning of the thyroid gland and for normal growth and development.
- It is mainly consumed as iodide salts from sea salt, shellfish, seawater fish and vegetables.
- Iodine is essential for the manufacture of thyroxine (T_4) and triiodothyronine (T_3), which are hormones that influence growth, maturation, thermogenesis, oxidation, myelination of the CNS and the metabolism of all tissues (Jones 2002).
- Iodine supplementation is commonly used to prevent and treat deficiency. There is also some evidence that it may reduce pain in fibrocystic breast disease and cyclic mastalgia and suggestive evidence of a protective role against breast cancer; however, rigorous research is required to confirm these observations.

- Current evidence points to widespread mild to moderate iodine deficiency in Australia, suggesting that dietary intake is inadequate and supplementation or fortification of foods with additional iodine may be required.



ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Adequate intake of iodine is critical for healthy thyroid function and normal growth and development. Ensuring adequate intake becomes critical during pregnancy and breastfeeding when the infant is solely dependent on the mother's intake for normal growth and brain development. Currently there is some suggestive evidence that adequate iodine particularly during the female reproductive years may be protective against breast cancer and supplementation may relieve symptoms of breast pain in fibrocystic breast disease and cyclic mastalgia.

When will it start to work?

The time frames depend on the indication it is being used to treat and the level of deficiency. In the case of breast pain, studies suggest 3 months of treatment are required to attain significant symptom relief.

Are there any safety issues?

People with pre-existing thyroid conditions should only increase iodine intake under professional supervision. Doses in excess of the RDI should be avoided unless under the supervision of a medical practitioner.

REFERENCES

Andersson M et al. Current global iodine status and progress over the last decade towards elimination of iodine deficiency. Bull World Health Organ 83.7 (2005): 518-25.

Beers MH. Merck Manual Home Edition. Whitehouse, NJ: Merck & Co., 2005. Available at: www.merck.com (accessed 04-04-2006).

Bleichrodt N et al. The benefits of adequate iodine intake. Nutr Rev 54.4 (1996): S72-8.

Carella C et al. Iodized salt improves the effectiveness of L-thyroxine therapy after surgery for nontoxic goitre: a prospective and randomized study. Clin Endocrinol (Oxf) 57.4 (2002): 507-13.

Doyle Z, Seal J. The Tasmanian iodine monitoring program in schools. Asia Pacific J Clin Nutr 12 (Suppl) (2003): S14.

Funahashi H et al. Seaweed prevents breast cancer? Jpn J Cancer Res 92.5 (2001): 483-7.

Geissler C, Powers H (eds). Human Nutrition, 11th edn. Elsevier, 2005.

Ghent WR et al. Iodine replacement in fibrocystic disease of the breast. Can J Surg 36.5 (1993): 453-60.

Gropper S et al. Advanced Nutrition and Human Metabolism, 4th edn. Belmont, CA: Wadsworth Thomson Learning, 2005.

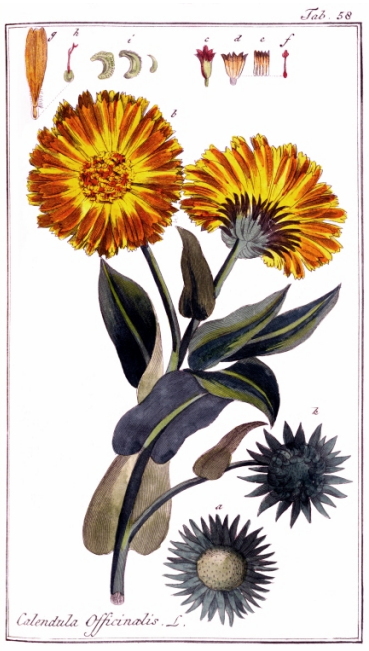
Guan H et al. High iodine intake is a risk factor of post-partum thyroiditis: result of a survey from Shenyang, China. J Endocrinol Invest 28.10 (2005): 876-81.

Gunton JE et al. Iodine deficiency in ambulatory participants at a Sydney teaching hospital: is Australia truly iodine replete? Med J Aust 171.9 (1999): 467-70.

Guttikonda K et al. Recurrent iodine deficiency in Tasmania, Australia: a salutary lesson in sustainable iodine prophylaxis and its monitoring. J Clin Endocrinol Metab 87.6 (2002): 2809-15.

Guttikonda K et al. Iodine deficiency in urban primary school children: a cross-sectional analysis. Med J Aust 179.7 (2003): 346-8.
Hamrosi MA et al. Iodine status in pregnant women living in Melbourne differs by ethnic group. Asia Pacific J Clin Nutr 14.1 (2005): 27-31.
Higdon J. An evidence-based approach to vitamins and minerals. In: Iodine. New York: Thieme, 2003; 130-7.
Jones GP. Minerals. In: Wahlqvist M (ed). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002; 275-6.
Hynes KL et al. Persistent iodine deficiency in a cohort of Tasmanian school children: associations with socio-economic status, geographical location and dietary factors. Aust NZ J Public Health 28.5 (2004): 476-81.
Kahn FH, Visscher BR. Water disinfection in the wilderness: a simple, effective method of iodination. West J Med 122.5 (1975): 450-3.
Kasper DL et al. Harrison's Principles of Internal Medicine, 16th edn. New York: McGraw Hill, 2005. Available at: www.accessmedicine.com (accessed 04-04-2006).
Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. Breast J 10.4 (2004): 328-36.
Kohlmeier M. Nutrient Metabolism. London: Elsevier, 2003.
Li M et al. Are Australian children iodine deficient? Results of the Australian National Iodine Nutrition Study. Med J Aust 184.4 (2006): 165-9.
Markou K et al. Iodine-induced hypothyroidism. Thyroid 11.5 (2001): 501-10.
McDonnell CM et al. Iodine deficiency and goitre in schoolchildren in Melbourne, 2001. Med J Aust 178.4 (2003): 159-62.
Seal JA et al. Tasmania: doing its wee bit for iodine nutrition [Letter]. Med J Aust 179.8 (2003): 451-2.
Smyth PP. The thyroid, iodine and breast cancer. Breast Cancer Res 5.5 (2003): 235-8 [Epub ahead of print].
Soldin OP et al. Newborn thyroxine levels and childhood ADHD. Clin Biochem 35.2 (2002): 131-6.
Soldin OP et al. Lack of a relation between human neonatal thyroxine and pediatric neurobehavioral disorders. Thyroid 13.2 (2003): 193-8.
Strum JM. Effect of iodide-deficiency on rat mammary gland. Virchows Arch B Cell Pathol Incl Mol Pathol 30.2 (1979): 209-20.
Thomson CD. Selenium and iodine intakes and status in New Zealand and Australia. Br J Nutr 91.5 (2004): 661-72.
Tiwari BD et al. Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. Am J Clin Nutr 63.5 (1996): 782-6.
Turken O et al. Breast cancer in association with thyroid disorders. Breast Cancer Res 5.5 (2003): R110-13.
Venturi S. Is there a role for iodine in breast diseases? Breast 10.5 (2001): 379-82.
Vermiglio F et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 89.12 (2004): 6054-60.
Wahlqvist M (ed.). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.

Iron



BACKGROUND AND RELEVANT PHARMACOKINETICS

Iron is an essential mineral found in the body in haem or non-haem form. The average human body contains 2–4 g of iron. Although the metal exists in several oxidation states in nature, only the ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms are stable in the aqueous environment of the body (Groff & Gropper 2000).

Iron is found in the body in: haemoglobin (65%); myoglobin (10%); enzymes (1–5%); the transport form, transferrin (0.05%); and the storage forms ferritin (4–9%) and haemosiderin (1–4%).

The haem form of iron is more soluble than the non-haem form and is absorbed 2–3 times more readily. It is absorbed via mucosal cells in the small intestine. Non-haem iron is bound to other substances in food, and must first be liberated by gastric secretions such as hydrochloric acid and pepsin. As such, absorption is best in the acidic environment of the stomach (Groff & Gropper 2000).

Clinical note — Factors affecting the absorption of iron

If the dietary intake of iron is adequate, it is often assumed that a patient's iron levels will be within the normal range. In practice, this is not always the case as absorption is significantly affected by a number of factors, thereby increasing or decreasing the amount of ingested dietary iron that reaches the systemic circulation.

Here is a brief summary of the main influences on absorption.

SOLUBILITY ENHANCERS OF NON-HAEM IRON

- Acids (including ascorbic acid) aid solubility of non-haem iron, thus improving absorption; the addition of 20 mg ascorbic acid has been shown to increase non-haem iron absorption by 39% (Hallberg et al 2003).
- Sugars (e.g. fructose) aid absorption.
- Meat stimulates digestive secretions, and breakdown products such as cysteine-containing peptides aid absorption (Hurrell et al 1988). The addition of red meat increases non-haem iron absorption by 85% (Hallberg et al 2003). This appears to be dose-dependent, as a recent study found that the addition of 60 g Danish pork meat three times daily improved the absorption of non-haem iron from 5.3% to 7.9% (Bach-Kristensen et al 2005) although addition of smaller amounts were not as effective (Baech et al 2003).

- Alcohol appears to improve iron uptake. The consumption of up to two alcoholic drinks per day is associated with reduced risk of iron deficiency and more than two can increase the risk of iron overload (Ioannou et al 2004).

SOLUBILITY INHIBITORS OF NON-HAEM IRON

- Polyphenols, including tannin derivatives of gallic acid (tea has been reported to reduce iron absorption by 60%, coffee by 40%) (Kaltwasser et al 1998, Morck et al 1983). A number of studies have shown that tea catechins can inhibit intestinal non-haem iron absorption (Ullmann et al 2005); however, polyphenols do not have chelating effects on cooked haem iron (Breet et al 2005). Recent studies suggest that impaired absorption is unlikely to be significant in people with normal iron stores (Breet et al 2005, Ullmann et al 2005). The addition of milk to tea may reduce the chelating effects.
- Phytic acid (whole grains).
- Oxalic acid (spinach, chard, chocolate, berries).
- Calcium — single-meal studies have established that calcium (including calcium phosphate and foods such as milk) reduces iron absorption by up to 70% (Hallberg et al 1991); however, the effect may not be as pronounced when calcium is served as part of a whole diet. For instance, the consumption of a glass of milk or the equivalent amount of calcium from fortified food does not appear to decrease non-haem iron absorption (Grinder-Pedersen et al 2004). Although it remains to be shown in iron-deficient persons, long-term iron status does not seem to be compromised by high calcium intake (Molgaard et al 2005).
- Zinc competes with iron for absorption (Solomons 1983) — inorganic zinc supplements may reduce iron absorption by 66–80% (Crofton et al 1989), and supplements containing both iron and zinc may not be as efficacious as the same doses given in isolation (Fischer Walker et al 2005, Lind et al 2003), but nutrients consumed in a meal may not be as affected (Whittaker 1998).
- Manganese may reduce absorption by 22–40% (Rossander-Hulten 1991).
- Rapid intestinal transit time.
- Malabsorption syndromes.
- *Helicobacter pylori* infection (Ciacci et al 2004).
- Gastrointestinal blood loss (Higgins & Rockey 2003).
- Insufficient digestive secretions (including achlorhydria).
- Antacids and PPI.

CHEMICAL COMPONENTS

Ferrous sulfate is the most widely studied form. Other ferrous forms include ascorbate, carbonate, citrate, fumarate, gluconate, lactate, succinate and tartarate (non-haem iron). Iron from ferrous sulfate has a significantly greater bioavailability than ferrous glycine chelate or ferric EDTA (Ferreira da Silva et al 2004). Other ferric forms include ammonium citrate, chloride, citrate, pyrophosphate and sulfate. Amino acid chelates, such as iron glycine, are also available. Dietary ferritin is equally well absorbed as ferrous sulfate and therefore food sources are likely to be effective (Davila-Hicks et al 2004). Cooking in iron pots may also improve iron status (Geerligs et al 2003).

FOOD SOURCES

The average Western diet is estimated to contain 5–7 mg iron/1000 kcal.

HAEM IRON

About 50–60% of the iron in animal sources is in the haem form. Sources include liver, lean red meat, poultry, fish, oysters, clams, shellfish, kidney and heart.

NON-HAEM IRON

This is found in plant and dairy products in the form of iron salts and makes up about 85% of the average intake. Sources include nuts, legumes, fruit, dried fruit, vegetables including beetroot, grains and tofu. Dairy is a relatively poor source of iron.

A number of iron-fortified foods are also available and include egg yolks, dried fruit, dark molasses, wholegrain and enriched bread, pasta, cereal, soy sauce, Thai fish sauce, milk, orange juice and wines.

Considering that minerals such as calcium may reduce iron absorption, fortification of some foods may be relatively ineffectual unless absorption enhancers such as vitamin C are also included (Davidsson et al 1998).

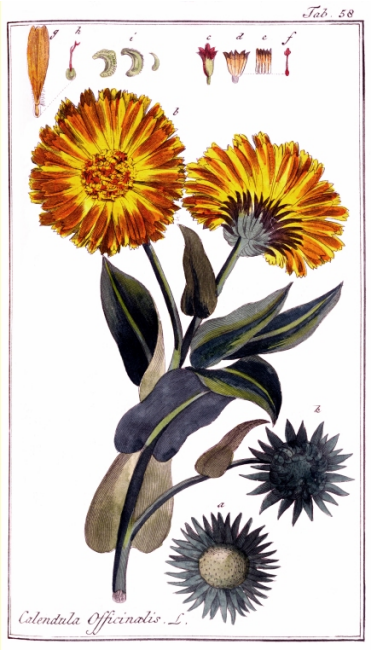
DEFICIENCY SIGNS AND SYMPTOMS

Iron deficiency is the most common nutritional deficiency in the world (Gillespie et al 1991) and may occur with or without anaemia.

Iron deficiency anaemia, also known as hypochromic microcytic anaemia, results in reduced work capacity in adults and a reduced ability to learn in children. Signs and symptoms include:

- fatigue and lethargy
- decreased resistance to infection
- cardiovascular and respiratory changes, which can progress to cardiac failure if left untreated

- increased lead absorption, which in turn inhibits haem synthesis
- decreased selenium and glutathione peroxidase levels
- pale inside lower eyelid or mouth
- pale-coloured nail bed
- pale lines on stretched palm (palmar creases)
- ridged, spoon-shaped, thin flat nails
- brittle hair
- impaired cognitive and motor function
- adverse pregnancy outcomes and increased perinatal maternal mortality (NMCD 2006)
- reduced thyroid function and ability to make thyroid hormones (Beard et al 1990)
- difficulty maintaining body temperature in a cold environment.



PRIMARY DEFICIENCY

Primary deficiency is most common in vegetarians, the elderly, those with protein-calorie malnutrition, and during periods of increased iron requirement due to expanded blood volume in infancy, adolescence and pregnancy.

SECONDARY DEFICIENCY

Underlying causes of iron-deficiency anaemia include blood loss, inefficient absorption due to gastrointestinal disturbances and increased destruction of red blood cells.

- Blood loss (menstruation, menorrhagia, bleeding haemorrhoids, parasites, bleeding peptic ulcer, malignancy, *H. pylori* infection, gastrointestinal bleeding due to medication such as NSAIDs).
- Inefficient absorption (chronic gastrointestinal disturbances, malabsorption syndromes, coeliac disease) (Annibale et al 2001).
- Increased destruction of red blood cells (malaria, high-intensity exercise).

MAIN ACTIONS

Iron plays a central role in many biochemical processes in the body.

OXYGEN TRANSPORT AND STORAGE

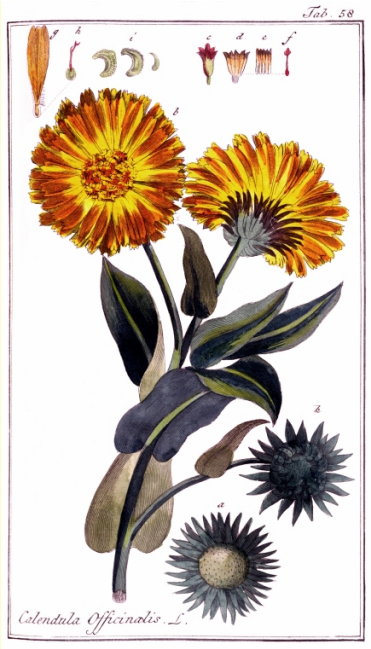
The key function of iron is to facilitate oxygen transport by haemoglobin, the oxygen-carrying pigment of erythrocytes. It is also involved in oxygen storage by myoglobin, an iron-containing protein that transports and stores oxygen within muscle and releases it to meet increased metabolic demands during muscle contraction.

IMMUNITY

Iron is vital for the proliferation of all cells including those of the immune system. Iron deficiency causes several defects in both humoral and cellular immunity (Bowlus

2003), including a reduction in peripheral T cells secondary to atrophy of the thymus and inhibition of thymocyte proliferation (Bowlus 2003) and a reduction in IL-2 production (Bergman et al 2004). Reduced IL-2 production may partly explain the increased susceptibility to infections and cancer in patients with iron deficiency anaemia (Bergman et al 2004). Supplementation of ferrous sulfate (60 mg Fe) once daily for 8 weeks has been shown to reduce the incidence and duration of upper-respiratory tract infections in children (de-Silva et al 2003).

However, there is also preliminary evidence that iron may be implicated in the pathogenesis of auto-immune disorders, including SLE, scleroderma, type 1 diabetes, Goodpasture syndrome, multiple sclerosis and RA (Bowlus 2003). Current evidence suggests that moderately elevated iron stores may be associated with an overall increased risk for cancer, especially colorectal cancer (McCarty 2003). Additionally, it has been proposed that iron may increase HIV replication and the rate of progression of HIV infection, although doses of 60 mg of elemental iron twice weekly for 4 months did not appear to affect HIV-1 viral load in clinical studies (Olsen et al 2004). Although maintaining adequate iron status may be important for immunity, the benefits of routine supplementation in the absence of deficiency cannot be justified.



ENZYME SYSTEMS

Both haem and non-haem iron are a part of many enzymes that are involved in:

- cellular respiration
- amino acid metabolism (e.g. carnitine)
- detoxification (as part of cytochrome P450 enzymes in the liver)
- protection against free radical damage
- synthesis of nutrients such as vitamin A
- synthesis of hormones and neurotransmitters (serotonin and noradrenaline)
- synthesis of collagen and elastin.

CLINICAL USE

Iron supplementation is administered using various routes (e.g. by injection or orally). This review will only focus on oral supplementation as this is the form generally used by the public and available OTC.

IRON DEFICIENCY

Iron supplementation is used to rectify deficiency states resulting from inadequate intake, increased requirements such as pregnancy, increased losses such as menstruation and where absorption is affected due to gastric bypass or chronic gastrointestinal disturbances. Currently, researchers are attempting to clarify the best forms,

administration routes and dosage regimens to use in different iron deficiency situations.

Clinical note — Testing for iron deficiency
As isolated haemoglobin has both low specificity and low sensitivity for determining iron status, the optimal diagnostic approach is to also measure the serum ferritin as an index of iron stores and the serum transferrin receptor as an index of tissue iron deficiency (Cook 2005, Flesland et al 2004, Mei et al 2005).

Iron deficiency anaemia Current evidence suggests that weekly administration of iron is an effective strategy for the treatment and prevention of iron deficiency and iron deficiency anaemia in most population groups including pregnant women and children (Agarwal et al 2003, Mukhopadhyay et al 2004, Siddiqui et al 2004, Sungthong et al 2004, Yang et al 2004) and is associated with lower cost, fewer side-effects and improved compliance (Haidar et al 2003).

Sixty children (age 5–10 years) with iron deficiency anemia were given ferrous sulfate (200 mg) daily or weekly for 2 months with similar efficacy and fewer side-effects in the once weekly group (Siddiqui et al 2004). In another study children receiving weekly doses of ferrous sulfate (300 mg) had similar improvements in haemoglobin, but a significantly higher increase in IQ than those taking the same dose of iron 5 days per week (Sungthong et al 2004). The doses used in these trials may be higher than those actually required to correct deficiency.

Patients, such as the elderly, who are particularly vulnerable to the dose-dependent adverse effects of iron supplementation should be given the lowest effective dose. A randomised trial of 90 hospitalised elderly patients demonstrated that 15 mg of liquid ferrous gluconate produced similar improvements in haemoglobin and ferritin over 60 days to 150 mg of ferrous calcium citrate tablets without the negative side-effects (Rimon et al 2005).

In all cases the lowest safe and effective dose at the lowest frequency of dosing should be used to correct iron deficiency with or without anaemia.

Pregnancy A supplement of 40 mg ferrous iron/day from 18 weeks of gestation appears adequate to prevent iron deficiency in 90% of the women and iron deficiency anaemia in at least 95% of the women during pregnancy and postpartum (Milman et al 2005). A single weekly dose of 200 mg elemental iron, however, may be sufficient as this has been shown to be comparable with 100 mg elemental iron daily on erythrocyte indices (Mukhopadhyay et al 2004). Although iron supplementation is often used as stand-alone treatment in pregnant iron-deficient women, one RCT indicated that a combination of iron and folate therapy (80 mg iron protein

succinylate, with 0.370 mg folinic acid daily) for 60 days produces a better therapeutic response than iron-only supplementation (Juarez-Vazquez et al 2002).

Due to the possibility of uncontrolled lipid peroxidation, predictive of adverse effects for mother and foetus, iron supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone (Lachili et al 2001).

Postpartum anaemia Postpartum anaemia is associated with breathlessness, tiredness, palpitations, maternal infections and impaired mood and cognition. A 2004 Cochrane review suggested that further high-quality trials were required before the benefits of iron supplementation or iron-rich diets in the treatment of postpartum anaemia could be established (Dodd et al 2004). Since then a randomised placebo-controlled study of iron sulfate (80 mg daily) for 12 weeks starting 24–48 hours after delivery demonstrated an improvement in haemoglobin levels and iron stores (Krafft et al 2005) and supplementation of ferrous sulfate (125 mg) with folate (10 μg) and vitamin C (25 mg) demonstrated improvements in cognitive function, as well as depression and stress compared with folate and vitamin C alone (Beard et al 2005). However, further studies are still warranted.

Unexplained fatigue without anaemia Iron supplementation is sometimes used in women who are not anaemic (haemoglobin >117 g/L) yet complain of fatigue. A recent, double-blind, randomised placebo-controlled trial designed to determine the subjective response to iron therapy in non-anaemic women (haemoglobin >117 g/L) with unexplained fatigue found that supplementation with oral ferrous sulfate (80 mg/day elemental iron) for 4 weeks reduced the level of fatigue in the iron group by 29% compared with 13% in the placebo group. Subgroup analysis showed that only women with ferritin concentrations <50 μg/L improved with oral supplementation. This was common in 85% of subjects and 51% of subjects had ferretin concentrations <20 μg/L (Verdon et al 2003). This study suggests that iron deficiency anaemia may be present despite haemoglobin and ferritin levels being within the 'normal' range and that the lower reference levels for women may need to be revised.

Improving athletic performance in marginally deficient people Sports anaemia is a common finding among professional and non-professional athletes engaging in strenuous physical activity. Possible mechanisms include: dilutional pseudoanaemia, which is caused by plasma volume expansion greater than that of the red blood cell mass, but does not reflect actual blood loss and will generally normalise within 3–5 days of ceasing training; intravascular haemolysis due to mechanical trauma such as 'foot strike haemolysis', which can result in urinary loss of iron; or transient ischaemia resulting from vasoconstriction of the splanchnic and

renal vessels, which can also result in blood loss from the gastrointestinal and urinary tracts (Merkel et al 2005).

In a placebo-controlled trial, iron supplementation (50 mg ferrous sulphate twice daily) for 6 weeks significantly improved iron status and maximal oxygen uptake ($Vo2_{max}$) after 4 weeks' concurrent aerobic training in previously marginally deficient and untrained women (Brownlie et al 2002). In a later randomised double-blind placebo-controlled study of 41 untrained iron-deficient women without anaemia, ferrous sulfate (100 mg) for 6 weeks improved endurance capacity after aerobic training (Brownlie et al 2004).

Due to the potential side-effects of inappropriate iron supplementation and the possibility of masking more serious underlying complaints, athletes should only be supplemented if iron deficiency is established on the basis of biological criteria (Zoller & Vogel 2004). Supplementing antioxidants (vitamin E 500 mg/day, vitamin C 1 g/day, beta-carotene 30 mg/day) may assist in preventing exercise-induced decreases in iron status and antioxidant defences (Aguilo et al 2004) and may be a safer option in iron-replete athletes.

Perioperative care Iron is sometimes given before surgery to reduce postoperative decreases in haemoglobin (Andrews et al 1997). However, this use is contentious and numerous studies have failed to report benefits for preoperative autologous blood collection (Cid et al 2005) or for correcting anaemia associated with cardiac surgery (Madi-Jebara et al 2004) or orthopaedic surgery, such as hip or knee arthroplasty (Mundy et al 2005, Weatherall & Maling 2004).

Cognitive function Iron supplementation has been shown to improve cognitive function and depression in postpartum anaemic women (Beard et al 2005); however, the majority of trials in this area focus on childhood development. An association between iron-deficiency anaemia and poor cognitive and motor development with behavioural problems has been observed, and attention deficit may be substantially improved with iron supplementation (elemental iron 5 mg/kg/day) for up to 3 months (Otero et al 2004). Two-month supplementation of 15 mg iron (and multivitamin) versus multivitamin alone in iron-deficient anaemic preschoolers resulted in improvements in discrimination (specifically selective attention), accuracy and efficiency (Metallinos-Katsaras et al 2004).

Recently however, a systematic review reported no effects on motor development scores and only modest improvements in mental development scores, although these were more prevalent in those who were initially anaemic or iron-deficient (Sachdev et al 2005). Preventing iron deficiency appears to be a rapid and effective means of

improving infant lead levels, even in non-anaemic infants (Wolf et al 2003) and this may also contribute to benefits in some children.

Improving cognition in children and postpartum women appears to be the result of correcting iron deficiency and it cannot be inferred that iron supplementation will benefit cognitive function in iron-replete individuals.

OTHER USES

Iron has also been suggested for use in attention-deficit disorder and aphthous stomatitis, although positive clinical trials to support these uses are lacking.

Breath-holding spells Iron supplementation may significantly reduce the incidence of breath holding spells, especially in iron-deficient children as shown in a RCT (Daoud et al 1997).

Haemodialysis Intravenous iron is frequently, but contentiously, prescribed for the aggressive management of anaemia associated with dialysis (Agarwal et al 2004, Gillespie & Wolf 2004, Ruiz-Jaramillo et al 2004).

DOSAGE RANGE

- Therapeutic dose: 2–5 mg/kg/day; however, in many cases the equivalent of this dose may be given weekly.
- In cases of deficiency, initial effects on haemoglobin and erythrocyte concentrations take about 2 weeks but it may take 6–12 months to build iron stores (Groff & Gropper 2000).
- The Australian Iron Status Advisory Panel advocates dietary intervention as the first treatment option for mild iron deficiency (serum ferritin 10–15 μg/L) (Patterson et al 2001). Trials have shown a significant increase in serum ferritin levels (26%) using dietary intervention alone (Heath et al 2001).

Australian RDI	Dosage (mg/day)
Infants (0–6 months; breastfed)	0.2
Infants (7–12 months)	11
Children (1–13 years)	8–9
Girls (14–18 years)	15
Boys (14–18 years)	11
Men (>19 years)	8
Women (19 to menopause)	18
After menopause	8
Pregnancy/lactation	9–27

Iron is expressed as a range to allow for differences in bioavailability of iron from different Australian foods.

Studies have shown that there can be a significant sex difference in haemoglobin and other indicators of iron status during infancy. Some of these may be genetically determined, whereas others seem to reflect an increased incidence of true iron deficiency in boys (Domellof et al 2002).

TOXICITY

Iron toxicity causes severe organ damage and death. The most pronounced effects are haemorrhagic necrosis of the gastrointestinal tract, which manifests as vomiting, bloody diarrhoea and hepatotoxicity.

Conditions that increase risk of toxicity include:

- Haemochromatosis (iron overload) — excess storage of iron in the body, which can cause organ and tissue damage (especially liver and heart) and an increased risk for hepatic carcinoma. It may be caused by an excessive oral intake, a genetic defect that causes the body to absorb more iron than normal, or repeated blood transfusions.
- Haemosiderosis — iron overload without tissue damage.
- Iron-loading anaemias — thalassaemia and sideroblastic anaemia.

ADVERSE REACTIONS

Oral supplements may cause gastrointestinal disturbances such as nausea, diarrhoea, constipation, heartburn and upper gastric discomfort.

Taking supplements with food appears to reduce the possibility of gastrointestinal side-effects.

Iron toxicity and subsequent organ damage can develop from long-term excessive intake. Liquid iron preparations can discolour teeth — brush teeth after use.

SIGNIFICANT INTERACTIONS

Iron interacts with a variety of foods, herbs and drugs through several different mechanisms. Most commonly, the formation of insoluble complexes occurs whereby both iron and drug absorption is hindered. Separation of doses by several hours will often reduce the severity of this type of interaction. Additionally, substances that alter gastric pH have the theoretical ability to reduce iron absorption. A summary of interactions has been presented in table form for easy reference.

Drug/therapeutic substance	Mechanism	Possible outcome	Action required
ACE inhibitors	Reduced absorption of ACE inhibitors. A small clinical trial found that concomitant iron administration reduced area-under-the-curve plasma levels of unconjugated captopril by 37% (Lee et al 2001, Schaefer et al 1998)	Reduced drug effect	Separate doses by at least 2 hours
Antacids and products containing aluminium, calcium or magnesium	Reduces iron absorption (O'Neil-Cutting & Crosby 1986)	Reduced effect of iron	Separate doses by at least 2 hours
Ascorbic acid	Increases iron absorption	Increased effects of iron	Beneficial interaction possible — caution in haemochromatosis
Cholestyramine and colestipol	In vitro investigations have shown that cholestyramine and colestipol both bind iron citrate (Leonard et al 1979)	Reduced effect of iron	Monitor for iron efficacy if cholestyramine is being used concurrently Separate doses by 4 hours. Increased iron intake may be required with long-term therapy
Cimetidine	Iron can bind cimetidine in the gastrointestinal tract and reduce its absorption (Campbell et al 1993)	Reduced effect of iron and drug	Separate doses by at least 2 hours
Dairy products and eggs	May reduce iron absorption	Reduced effect of iron	Monitor for iron efficacy
Erythropoietin	Pharmacodynamic interaction (Carnielli et al 1998)	Additive pharmaco-logical effect possible	Beneficial interaction possible

Drug/therapeutic substance	Mechanism	Possible outcome	Action required
H_2-receptor antagonists (antiulcer drugs)	Iron absorption is dependent upon gastric pH; therefore, medications that affect gastric pH may interfere with absorption of iron (Aymard et al 1988)	Reduced effect of iron	Monitor for iron efficacy if these drugs are being used concurrently
Haloperidol	May cause decreased blood levels of iron (Leenders et al 1994, Threlkeld 1998)	Reduced effect of iron	Monitor for iron efficacy if these drugs are being used concurrently Increased iron intake may be required with long-term therapy
L-dopa and carbidopa	May reduce bioavailability of carbidopa and L-dopa (van Woert 1977)	Reduced drug effect	Separate doses by 2 hours
Omeprazole and other proton-pump inhibitors	Reduced iron absorption due to changes in gastric pH	Reduced effect of iron	Monitor for iron efficacy if omeprazole is being used concurrently
Penicillamine	Reduced drug and iron absorption	Reduced drug and iron effect	Separate doses by at least 2 hours Sudden withdrawal of iron during penicillamine use has been associated with penacillamine toxicity and kidney damage (Harkness & Blake 1982) — caution
Quinolone antibiotics (e.g. norfloxacin)	Reduced drug absorption (Brouwers 1992)	Reduced drug effect	Take drug 2 hours before or 4–6 hours after iron dosing Monitor patient for continued antibiotic efficacy
Sulfasalazine	May bind together, decreasing the absorption of both (Dukes & Duncan 1995)	Reduced drug and iron effect	Separate doses by at least 2 hours

Drug/therapeutic substance	Mechanism	Possible outcome	Action required
Tannins — herbs with significant tannin content (e.g. green tea, bilberry, raspberry leaf)	Tannin can bind to iron and reduce its absorption	Reduced effect of iron	Monitor for iron efficacy if these herbs are being used concurrently Separate doses by 2 hours
Tetracycline antibiotics (e.g. minocycline, doxycycline)	Reduced drug and iron absorption (Neuvonen 1976)	Reduced drug effect	Monitor for iron efficacy if tetracyclines are being used long term Separate doses by 4 hours
L-thyroxine	Decreased drug absorption possible. Iron supplements may decrease absorption of thyroid medication; however, iron deficiency may impair the body's ability to make thyroid hormones	Reduced drug effect	Thyroid function should be monitored and L-thyroxine dose may need alteration during treatment with iron Separate doses by at least 2–4 hours (Shakir et al 1997)
Vitamin A	Iron supplementation may cause a redistribution of retinol inducing vitamin A deficiency in infants with marginal vitamin A status (Wieringa et al 2003)	Redistribution of retinol	Iron supplementation in infants should be accompanied by measures to improve vitamin A status

CONTRAINDICATIONS AND PRECAUTIONS

Iron poisoning can occur due to accidental ingestion of excess iron supplements. As such, iron supplements should be kept in childproof bottles and out of the reach of children.

Caution should be exercised when supplementing iron to infants or children with apparently normal growth when the iron status of the child is unknown. A double-blind placebo-controlled trial showed that while iron therapy produced a significant improvement of mean monthly weight gain and linear growth in iron-deficient children, it significantly decreased the weight gain and linear growth of iron-replete children (Majumdar et al 2003). This study confirms the results of earlier studies (Dewey et al 2002).

- Iron supplements should not be used in haemochromatosis, haemosiderosis, or iron-loading anaemias (thalassaemia, sideroblastic anaemia).
- Daily oral iron supplementation providing 50 mg elemental iron for 8 weeks did not result in increased oxidative damage in the plasma of college-aged women, although this does not rule out oxidative damage in tissues as demonstrated in animal studies (Gropper et al 2003). While the use of iron supplements may potentially result in oxidative damage, this is not likely to be significant in lower doses used to correct deficiency states; however, risk should always be assessed against benefit before prescribing iron supplements.
- Elevated levels of serum ferritin have been implicated in the pathogenesis of vascular (and other) diseases, although this remains controversial (McCarty 2003, Zacharski et al 2004).
- Haem-rich flesh foods may need to be limited in people with insulin resistance due to a possible link with increased cancer risk mediated by iron excess in such populations (McCarty 2003).
- Iron supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone, as unnecessary iron supplementation can result in adverse effects. The lowest safe and effective dose and frequency of dose should be recommended.

PREGNANCY USE

Oral iron preparations are considered safe in pregnancy; however, unnecessary iron supplementation can result in uncontrolled lipid peroxidation, predictive of adverse effects for mother and foetus. Supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone (Lachili et al 2001).

PRACTICE POINTS/PATIENT COUNSELLING

- Iron is an essential mineral that facilitates oxygen transport and storage in the body and is part of many enzyme systems.
- Haem iron, found in animal products, is absorbed 2–3-fold better than non-haem forms found in vegetable sources. However, iron absorption is influenced by many factors, such as other foods ingested, medicines and gastric activity.
- Iron deficiency is the most common nutritional deficiency in the world and may occur with or without anaemia. Excessive blood loss during menstruation is the most common cause.
- Supplements are generally used to treat or prevent deficiency. Excess iron can be dangerous and lead to organ damage and death.
- As inappropriate iron supplementation can inhibit growth in non-deficient children and adversely affect pregnancy outcomes, iron status should be tested before administration.
- Correction of iron deficiency with or without anaemia may be achieved with lower doses than those recommended in some trials. In many case once weekly dosing of iron is as effective as daily dosing and improves compliance while reducing side-effects and cost.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Iron is necessary for health and wellbeing. It facilitates oxygen transport and storage in the body and is part of many enzyme systems. Iron deficiency is the most common deficiency in the world.

When will it start to work?

Iron deficiency responds to supplementation within 2 weeks; however, 6–12 months may be required to build up the body's iron stores.

Are there any safety issues?

Excess iron can be dangerous and ultimately lead to severe organ damage and death.

REFERENCES

Agarwal KN, Gomber S, Bisht H, Som M. Anemia prophylaxis in adolescent school girls by weekly or daily iron-folate supplementation. Indian Pediatr 40(4) (2003): 296-301.

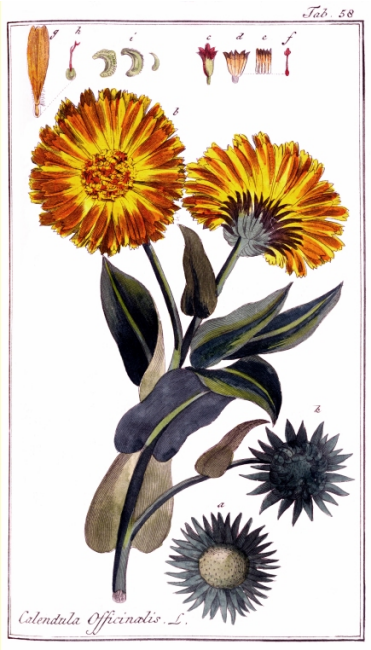
Agarwal R, Vasavada N, Sachs NG, Chase S. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int 65(6) (2004): 2279-89.

Aguilo A et al. Antioxidant diet supplementation influences blood iron status in endurance athletes. Int J Sport Nutr Exerc Metab 14(2) (2004): 147-60.

Andrews CM, Lane DW, Bradley JG. Iron pre-load for major joint replacement. Transfus Med 7(4) (1997): 281-6.

Annibale B et al. Efficacy of gluten-free diet alone on recovery from iron deficiency anemia in adult celiac patients. Am J Gastroenterol 96(1) (2001): 132-7.

Aymard JP et al. Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol Adverse Drug Exp 3 (1988): 430-48.
Bach-Kristensen M, Hels O, Morberg C, Marving J, Bugel S, Tetens I. Pork meat increases iron absorption from a 5-day fully controlled diet when compared to a vegetarian diet with similar vitamin C and phytic acid content. Br J Nutr 94(1) (2005): 78-83.
Baech SB et al. Nonheme-iron absorption from a phytate-rich meal is increased by the addition of small amounts of pork meat. Am J Clin Nutr 77(1) (2003): 173-9.
Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anaemia. Am J Clin Nutr 52 (1990): 813-19.
Beard JL et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr 135(2) (2005): 267-72.
Bergman M, Bessler H, Salman H, Siomin D, Straussberg R, Djaldetti M. In vitro cytokine production in patients with iron deficiency anemia. Clin Immunol 113(3) (2004): 340-4.
Bowlus CL. The role of iron in T cell development and autoimmunity. Autoimmun Rev 2(2) (2003): 73-8.
Breet P, Kruger HS, Jerling JC, Oosthuizen W. Actions of black tea and Rooibos on iron status of primary school children. Nutr Res 25(11) (2005): 983-94.
Brouwers J. Drug interactions with quinolone antibacterials. Drug Safety 7(4) (1992): 268-81.
Brownlie T, Utermohlen V, Hinton PS, Giordano C, Haas JD. Marginal iron deficiency without anemia impairs aerobic adaptation among previously untrained women. Am J Clin Nutr 75(4) (2002): 734-42.
Brownlie T, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am J Clin Nutr 79(3) (2004): 437-43.
Campbell NR, Hasinoff BB, Meddings JB, Anderson WD, Robertson S, Granberg K. Ferrous sulfate reduces cimetidine absorption. Dig Dis Sci 38(5) (1993): 950-4.
Carnielli VP, Da Riol R, Montini G. Iron supplementation enhances responses to high doses of recombinant human erythropoietin in preterm infants. Arch Dis Child Fetal Neonatal Ed 79(1) (1998): F44-8.
Ciacci C et al. Helicobacter pylori impairs iron absorption in infected individuals. Dig Liver Dis 36(7) (2004): 455-60.
Cid J, Ortin X, Contreras E, Elies E. [Oral iron and folic acid supplements in a preoperative autologous blood collection program : a randomized study]. Med Clin (Barc) 124(18) 2005: 690-1.
Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol 18(2) (2005): 319-32.
Crofton R et al. Inorganic zinc and the absorption of ferrous iron. Am J Clin Nutr 50 (1989): 141-4.
Daoud AS, Batieha A, al-Sheyyab M, Abuekteish F, Hijazi S. Effectiveness of iron therapy on breath-holding spells. J Pediatr 130(4) (1997): 547-50.
Davidsson L, Walczyk T, Morris A, Hurrell RF. Influence of ascorbic acid on iron absorption from an iron-fortified, chocolate-flavored milk drink in Jamaican children. Am J Clin Nutr May; 67(5) (1998): 873-7.
Davila-Hicks P, Theil EC, Lonnerdal B. Iron in ferritin or in salts (ferrous sulfate) is equally bioavailable in nonanemic women. Am J Clin Nutr 80(4) (2004): 936-40.
de-Silva A, Atukorala S, Weerasinghe I, Ahluwalia N. Iron supplementation improves iron status and reduces morbidity in children with or without upper respiratory tract infections: a randomized controlled study in Colombo, Sri Lanka. Am J Clin Nutr 77(1) (2003): 234-41.
Dewey KG, et al. Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. J Nutr 132(11) (2002): 3249-55.
Dodd J, Dare MR, Middleton P. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database Syst Rev (4) (2004): CD004222.
Domellof M et al. Sex differences in iron status during infancy. Pediatrics 110(3) (2002): 545-52.
Dukes DE Jr, Duncan BS. Applied Therapeutics: The Clinical Use of Drugs, 6th edn. Philadelphia: Lippincott Williams & Wilkins 24-7, 1995.



Ermis B, Demirel F, Demircan N, Gurel A. Effects of three different iron supplementations in term healthy infants after 5 months of life. J Trop Pediatr 48(5) (2002): 280-4.
Ferreira da Silva L, Dutra-de-Oliveira JE, Marchini JS. Serum iron analysis of adults receiving three different iron compounds. Nutr Res 24(8) (2004): 603-11.
Fischer Walker C, Kordas K, Stoltzfus RJ, Black RE. Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. Am J Clin Nutr 82(1) (2005): 5-12.
Flesland O, Eskelund A-K, Flesland AB, Falch D, Solheim BG, Seghatchian J. Transferring receptor in serum. A new tool in the diagnosis and prevention of iron deficiency in blood donors. Transf Aph Sci 31(1) (2004): 11-16.
Geerligs PP, Brabin B, Mkumbwa A, Broadhead R, Cuevas LE. The effect on haemoglobin of the use of iron cooking pots in rural Malawian households in an area with high malaria prevalence: a randomized trial. Trop Med Int Health 8(4) (2003): 310-15.
Gillespie RS, Wolf FM. Intravenous iron therapy in pediatric hemodialysis patients: a meta-analysis. Pediatr Nephrol 19(6) (2004): 662-6.
Gillespie S, Mason JB, Kevany J, (eds). Controlling Iron Deficiency. Geneva, Switzerland: United Nations Administrative Committee on Coordination/Subcommittee on Nutrition. State-of-the-Art Series: Nutrition Policy, Discussion Paper No. 9, 1991.
Grinder-Pedersen L, Bukhave K, Jensen M, Hojgaard L, Hansen M. Calcium from milk or calcium-fortified foods does not inhibit nonheme-iron absorption from a whole diet consumed over a 4-d period. Am J Clin Nutr 80(2) (2004): 404-9.
Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism. Belmont, CA: Wadsworth 402-19, 2000.
Gropper SS, Kerr S, Barksdale JM. Non-anemic iron deficiency, oral iron supplementation, and oxidative damage in college-aged females. J Nutr Biochem 14(7) (2003): 409-15.
Haidar J, Omwega AM, Muroki NM, Ayana G. Daily versus weekly iron supplementation and prevention of iron deficiency anaemia in lactating women. East Afr Med J 80(1) (2003): 11-16.
Hallberg L et al. Calcium: effect of different amounts of nonhaeme- and haeme-iron absorption in humans. Am J Clin Nutr 53 (1991): 112-19.
Hallberg L, Hoppe M, Andersson M, Hulthen L. The role of meat to improve the critical iron balance during weaning. Pediatrics 111 (4 Pt. 1) (2003): 864-70.
Harkness JAL, Blake DR. Penicillamine nephropathy and iron. Lancet ii (1982): 1368-9.
Heath AL, Skeaff CM, O'Brien SM, Williams SM, Gibson RS. Can dietary treatment of non-anemic iron deficiency improve iron status? J Am Coll Nutr 20(5) (2001): 477-84.
Higgins PDR, Rockey DC. Iron-deficiency anemia. Tech Gastrointest Endosc 5(3) (2003): 134-41.
Hurrell R et al. Iron absorption in humans: bovine serum albumin compared with beef muscle and egg white. Am J Clin Nutr 47 (1988): 102-7.
Ioannou GN, Dominitz JA, Weiss NS, Heagerty PJ, Kowdley KV. The effect of alcohol consumption on the prevalence of iron overload, iron deficiency, and iron deficiency anemia. Gastroenterology 126(5) (2004): 1293-301.
Juarez-Vazquez J, Bonizzoni E, Scotti A. Iron plus folate is more effective than iron alone in the treatment of iron deficiency anaemia in pregnancy: a randomised, double blind clinical trial. Br J Obstet Gynaecol 109(9) (2002): 1009-14.
Kaltwasser JP, Werner E, Schalk K, Hansen C, Gottschalk R, Seidl C. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. Gut 43(5) (1998): 699-704.
Krafft A, Perewusnyk G, Hanseler E, Quack K, Huch R, Breymann C. Effect of postpartum iron supplementation on red cell and iron parameters in non-anaemic iron-deficient women: a randomised placebo-controlled study. Br J Obstet Gynaecol 112(4) (2005): 445-50.
Lachili B et al. Increased lipid peroxidation in pregnant women after iron and vitamin C supplementation. Biol Trace Elem Res 83(2) (2001): 103-10.
Lee SC, Park SW, Kim DK. Iron supplementation inhibits cough associated with ACE Inhibitors. Hypertension 38 (2001): 166-70.

Leenders KL et al. Blood to brain iron uptake in one rhesus monkey using [Fe-52]-citrate and positron emission tomography (PET): influence of haloperidol. J Neural Transm 43[Suppl] (1994): 123-32.
Leonard JP, Desager JP, Beckers C, Harvengt C. In vitro binding of various biological substances by two hypocholesterolaemic resins: Cholestyramine and colestipol. Arzneim Forsch/Drug Res 29 (1979): 979-81.
Lind T et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: interactions between iron and zinc. Am J Clin Nutr 77(4) (2003): 883-90.
Madi-Jebara SN et al. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth 18(1) (2004): 59-63.
Majumdar I, Paul P, Talib VH, Ranga S. The effect of iron therapy on the growth of iron-replete and iron-deplete children. J Trop Pediatr 49(2) (2003): 84-8.
McCarty MF. Hyperinsulinemia may boost both hematocrit and iron absorption by up-regulating activity of hypoxia-inducible factor-1[alpha]. Med Hypoth 61(5-6) (2003): 567-73.
Mei Z et al. Hemoglobin and ferritin are currently the most efficient indicators of population response to iron interventions: an analysis of nine randomized controlled trials. J Nutr 135(8) (2005): 1974-80.
Merkel D et al. Prevalence of iron deficiency and anemia among strenuously trained adolescents. J Adolesc Health 37(3) (2005): 220-3.
Metallinos-Katsaras E, Valassi-Adam E, Dewey KG, Lonnerdal B, Stamoulakatou A, Pollitt E. Effect of iron supplementation on cognition in Greek preschoolers. Eur J Clin Nutr 58(11) (2004): 1532-42.
Milman N et al. Iron prophylaxis during pregnancy: how much iron is needed? A randomized dose-response study of 20-80 mg ferrous iron daily in pregnant women. Acta Obstet Gynecol Scand 84(3) (2004): 238-47.
Molgaard C, Kaestel P, Michaelsen KF. Long-term calcium supplementation does not affect the iron status of 12-14-year-old girls. Am J Clin Nutr 82(1) (2005): 98-102.
Morck T, Lynch S, Cook J. Inhibition of food iron absorption by coffee. Am J Clin Nutr 37 (1983): 416-20.
Mukhopadhyay A, Bhatla N, Kriplani A, Agarwal N, Saxena R. Erythrocyte indices in pregnancy: effect of intermittent iron supplementation. Natl Med J India 17(3) (2004): 135-7.
Mundy GM, Birtwistle SJ, Power RA. The effect of iron supplementation on the level of haemoglobin after lower limb arthroplasty. J Bone Joint Surg Br 87(2) (2005): 213-7.
Natural Medicines Comprehensive Database (NMCD online). Iron. Available from (2006): http://www.naturaldatabase.com (Accessed 10 Nov 2005).
Neuvonen PJ. Interactions with the absorption of tetracyclines. Drugs 11(1) (1976): 45-54.
O'Neil-Cutting MA, Crosby WH. The effect of antacids on the absorption of simultaneously ingested iron. JAMA 255 (1986): 1468-70.
Olsen A, Mwaniki D, Krarup H, Friis H. Low-dose iron supplementation does not increase HIV-1 load. J Acquir Immune Defic Syndr 36(1) (2004): 637-8.
Otero GA, Pliego-Rivero FB, Contreras G, Ricardo J, Fernandez T. Iron supplementation brings up a lacking P300 in iron deficient children. Clin Neurophysiol 115(10) (2004): 2259-66.
Patterson AJ, Brown WJ, Roberts DC, Seldon MR. Dietary treatment of iron deficiency in women of childbearing age. Am J Clin Nutr 74(5) (2001): 650-6.
Rimon E et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med 118(10) (2005): 1142-7.
Rossander-Hulten L et al. Competitive inhibition of iron absorption by manganese and zinc. Am J Clin Nutr 54 (1991): 152-6.
Ruiz-Jaramillo M-L, Guizar-Mendoza JM, Gutierrez-Navarro M-J, Dubey-Ortega LA, Amador-Licona N. Intermittent versus maintenance iron therapy in children on hemodialysis: a randomized study. Pediatr Nephrol 19(1) (2004): 77-81.
Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. Public Health Nutr 8(2) (2005): 117-32.
Schaefer JP et al. Ferrous sulphate interacts with captopril. Br J Clin Pharmacol 46(4) (1998): 377-81.

Shakir KM, Chute JP, Aprill BS, Lazarus AA. Ferrous sulfate-induced increase in requirement for thyroxine in a patient with primary hypothyroidism. South Med J 90(6) (1997): 637-9.
Siddiqui IA, Rahman MA, Jaleel A. Efficacy of daily vs. weekly supplementation of iron in schoolchildren with low iron status. J Trop Pediatr 50(5) (2004): 276-8.
Solomons N. Competetive mineral-mineral interaction in the intestine. In): Inglett G (ed.). Nutritional Bioavailability of Zinc. Oxford (Am Chem Soc Symp) 201 (1983): 247-71.
Sungthong R, Mo-suwan L, Chongsuvivatwong V, Geater AF. Once-weekly and 5-days a week iron supplementation differentially affect cognitive function but not school performance in Thai children. J Nutr 134(9) (2004): 2349-54.
Threlkeld DS (ed.). Central nervous system drugs, antipsychotic agents. In: Facts and Comparisons Drug Information. St Louis, MO: Wolter Kluwer Health, 1998; 266k–266m. Cited in: Lininger SW et al (eds). A-Z Guide to Drug-Herb-Vitamin Interactions. Roseville, CA: Healthnotes, 1999.
Ullmann U, Haller J, Bakker GC, Brink EJ, Weber P. Epigallocatechin gallate (EGCG) (TEAVIGO) does not impair nonhaem-iron absorption in man. Phytomedicine 12(6-7) (2005): 410-15.
van Woert MH et al. Long-term therapy of monoclonus and other neurological disorders with L-5-hydroxytryptophan and carbidopa. N Engl J Med 296 (1977): 70-5.
Verdon F et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial (Primary care). BMJ 326(7399) (2003): 1124.
Weatherall M, Maling TJ. Oral iron therapy for anaemia after orthopaedic surgery: randomized clinical trial. Aust NZ J Surg 74(12) (2004): 1049-51.
Whittaker P. Iron and zinc interactions in humans. Am J Clin Nutr 68 (1998): 442-6S.
Wieringa FT et al. Redistribution of vitamin A after iron supplementation in Indonesian infants. Am J Clin Nutr 77(3) (2003): 651-7.
Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. J Pediatrics 143(6) (2003): 789-95.
Yang Q, Yin S, Zhao X, An J. Effect of daily or once weekly iron supplementation on growth and iron status of preschool children. Wei Sheng Yan Jiu 33(2) (2004): 205-7.
Zacharski LR, Chow BK, Howes PS, Lavori PW, Shamayeva G. Implementation of an iron reduction protocol in patients with peripheral vascular disease: VA cooperative study no. 410: The Iron (FE) and Atherosclerosis Study (FEAST). Am Heart J 148(3) (2004): 386-92.
Zlotkin S, Arthur P, Antwi KY, Yeung G. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. Pediatrics 108(3) (2001): 613.
Zoller H, Vogel W. Iron supplementation in athletes: first do no harm. Nutrition 20(7-8) (2004): 615-19.

Kava kava

Historical note For many centuries, Pacific Islanders have used the kava kava root to prepare a beverage used in welcoming ceremonies for important visitors. Drinking kava is not only done to induce pleasant mental states but also to reduce anxiety and promote socialising. It is believed that the first report about kava came to the West from Captain James Cook during his voyages through the Pacific region.

COMMON NAME
Kava kava

OTHER NAMES
Kawa, awa, intoxicating pepper, rauschpfeffer, sakau, tonga, yagona

BOTANICAL NAME/FAMILY
Piper methysticum (family Piperaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
The most important constituents responsible for the pharmacological activity of kava rhizome are the fat-soluble kava lactones (kavapyrones), mainly methysticin, dihydromethisticin, kavain, dihydrokavain and desmethoxyangonin and flavonoids (flavokavains).

MAIN ACTIONS

CNS EFFECTS
The kava lactones reach a large number of targets that influence CNS activity. They interact with dopaminergic, serotonergic, GABA-ergic and glutamatergic neurotransmission, seem to inhibit monoamine oxidase B and exert multiple effects on ion channels, according to in vitro and in vivo research (Grunze et al 2001). Additionally, animal studies show that kava lactones are chiefly responsible for these effects that give rise to many of the herb's clinical actions (Cairney et al 2002).
Hypnotic Although the exact mechanism of action is not yet understood, it has been observed that sleep promotion may be due to the preferential activity of D,L-

kavain and kava extract on the limbic structures and, in particular, the amygdalar complex (Holm et al 1991) in the brain.

In an EEG brain-mapping study it was demonstrated that D,L-kavain could induce a dose-dependent increase in delta-, theta- and alpha-1 power, as well as a decrease in alpha-2 and beta power. These results indicate a sedative effect at the higher dose range (Frey 1991).

Anxiolytic effects A recent study showed that kava extract produces a statistically significant dose-dependent anxiolytic-like behavioural change in rat models of anxiety (Garrett et al 2003). The effect is not mediated through the benzodiazepine binding site on the GABA-A receptor complex, as flumazenil, a competitive benzodiazepine receptor antagonist, did not block this effect.

ANALGESIC AND LOCAL ANAESTHETIC

Both the aqueous and lipid-soluble extracts of kava exhibit antinociceptive properties in experimental animal models (Jamieson & Duffield 1990). The effect is not mediated by an opiate pathway, as naloxone does not reduce the effects when administered in doses that reverse the effects of morphine. More recently, in vitro research has identified several compounds found in kava that have the ability to inhibit COX-1 and to a lesser extent COX-2 enzyme activities (Wu et al 2002).

The local anaesthetic effect of kava is well known for topical use and has been described as similar to procaine and cocaine (Mills & Bone 2000).

ANTISPASMODIC ACTIVITY

Antispasmodic activity for skeletal muscle has been observed in vitro and in vivo for both kava extract and kava lactones (Mills & Bone 2000). In vivo research suggests that kavain impairs vascular smooth muscle contraction, likely through inhibition of calcium channels (Martin et al 2002).

OTHER ACTIONS

CYTOCHROME IINHIBITION

Although in vitro studies published in 2002 suggested whole kava extract and kavalactones have widespread inhibitory effects on various cytochrome enzymes, such as CYP3A4 (Unger et al 2002), more recent in vivo tests found no effects on CYP3A4/5, CYP1A2 or CYP2D6, but did demonstrate significant inhibition (approximately 40%) of CYP2E1 (Gurley et al 2005).

CLINICAL USE

Kava extracts are popular in Europe and have been investigated in numerous clinical trials, primarily in European countries. As a result, many research papers have been

published in languages other than English. In order to provide a more complete description of the evidence available, secondary sources have been used where necessary.

NERVOUS ANXIETY

A 2000 Cochrane review of the scientific literature assessed the results from seven, double-blind, randomised placebo-controlled trials and concluded that kava extract has significant anxiolytic activity and is superior to placebo for the symptomatic treatment of anxiety (Pittler & Ernst 2000). An update of this review was published in 2003 and analysed results from 12 clinical studies involving 700 subjects (Pittler & Ernst 2003). The results of 7 studies that used the Hamilton Anxiety Scale (HAM-A) score were pooled and a significant reduction in anxiety was observed for kava treatment compared with placebo. The results of the five studies that were not submitted to meta-analysis largely support these findings. The extract most commonly tested was WS 1490 at a dose of up to 300 mg daily. Preliminary evidence suggests it may be equivalent to benzodiazepines for non-psychotic anxiety.

Safety According to the authors of the review, none of the trials reported any hepatotoxic events and seven trials measured liver enzyme levels as safety parameters and reported no clinically significant changes.

MENOPASUAL AND PERIMENOPASUAL ANXIETY

A randomised placebo-controlled study conducted with 40 menopausal women found that using kava extract, together with HRT, led to significant reductions in anxiety, as measured by the HAM-A scale at both 3- and 6-month follow-up (De et al 2000).

A 3-month, randomised, open study of 68 perimenopausal women showed that treatment with kava (100 mg/day) significantly reduced anxiety ($P < 0.001$) at 1 month and 3 months. This was significantly greater than that spontaneously occurring in controls ($P < 0.009$) (Cagnacci et al 2003).

GENERALISED ANXIETY DISORDER

An 8-week randomised, double-blind, multicentre clinical trial involving 129 outpatients with GAD showed that kava kava LI 150 (400 mg/day) was as effective as buspirone in the acute treatment of GAD, with about 75% of patients responding to treatment (Boerner et al 2003).

Comparative studies Comparative studies suggest the absence of significant differences between benzodiazepines and kavain or kava extract as treatments for anxiety. A 1993 double-blind comparative study involving 174 subjects over 6 weeks demonstrated that 300 mg/day of a 70% kava lactone extract produced a similar

improvement in anxiety level, as measured by HAM-A scores, to 15 mg oxazepam or 9 mg bromazepam taken daily (Woelk et al 1993). D,L-kavain produced equivalent anxiolytic effects to oxazepam in 38 outpatients with neurotic or psychosomatic disturbances, under double-blind study conditions (Lindenberg & Pitule-Schodel 1990).

Benzodiazepine withdrawal Kava may have a role in reducing anxiety and improving subjective wellbeing during benzodiazepine withdrawal, according to a 2001 randomised, double-blind, placebo-controlled study (Malsch & Kieser 2001). During the first 2 weeks of that study, kava dose was increased from 50 mg to 300 mg/day while benzodiazepine use was tapered off during the same period. Kava extract was superior to placebo in reducing anxiety as measured by the HAM-A scale and improved subjects' feelings of wellbeing according to a subjective wellbeing scale (Bf-S total scores).

Lack of tolerance The results from a randomised, double-blind trial conducted over 25 weeks have found that physical tolerance does not develop to kava kava extract and it is well tolerated (Volz & Kieser 1997). Evidence from a randomised double-blind study conducted with 84 patients has shown that treatment with kavain (one of the active constituents of kava kava) produces continuous improvements in parameters such as memory function, vigilance, fluency of mental functions and reaction time. Interestingly, these effects were reported over a relatively short period of 3 weeks (Scholing & Clausen 1977). Another randomised double-blind trial conducted with 52 patients over 28 days not only confirmed anxiolytic activity but also found that kavain promoted subjective vitality-related performance (Lehmann et al 1989).

Commission E approves the use of kava in conditions of nervous anxiety and restlessness (Blumenthal et al 2000).

INSOMNIA

The hypnotic activity of kava extract was confirmed in a RCT in which a single dose of 300 mg kava extract was found to improve the quality of sleep significantly (Emser & Bartylla 1991, as reported by Ernst et al 2001). In vivo experiments with D,L-kavain have shown that it reduces active wakefulness and significantly prolongs sleep, compared with placebo (Holm et al 1991).

OTHER USES

Traditionally, the herb has been used to treat urinary tract infections, asthma, conditions associated with pain, gonorrhoea and syphilis, and to assist with weight

reduction, muscle relaxation and sleep. Topically, it has been used as a local anaesthetic and to treat pruritus.

DOSAGE RANGE

- Cut rhizome: 1.7–3.4 g/day.
- Dried rhizome: 1.5–3 g/day in divided doses or equivalent to 60–120 mg kavapyrones daily.
- Fluid extract (1:2): 3–8.5 mL/day in divided doses.
- Ideally, ethanolic extracts should contain > 20 mg/mL kava lactones.

ACCORDING TO CLINICAL STUDIES

- Anxiety: generally doses up to 300 mg daily of kava extract WS 1490 providing 105–210 mg kavalactones. A kava extract LI 150 (400 mg/day) was used successfully in generalised anxiety disorder.
- Insomnia — a single dose of 300 mg kava extract.
- Benzodiazepine withdrawal — 300 mg/day of kava extract.

ADVERSE REACTIONS

In RCT, the incidence of adverse effects to kava kava has been found to be similar to placebo. Two post-marketing surveillance studies involving more than 6000 patients found adverse effects in 2.3% and 1.5% of patients taking 120–240 mg standardised extract (Ernst 2002). The most common side-effects appear to be gastrointestinal upset and headaches.

HEPATOTOXICITY

A systematic review assessing the safety of kava which included a total of 7078 patients taking kava extract equivalent to 10 mg to 240 mg kavalactones per day for 5–7 weeks identified no cases of hepatotoxicity (Stevinson et al 2002). Considering that case reports of hepatotoxicity exist, they should be considered a very rare event based on the evidence.

LONG-TERM USE

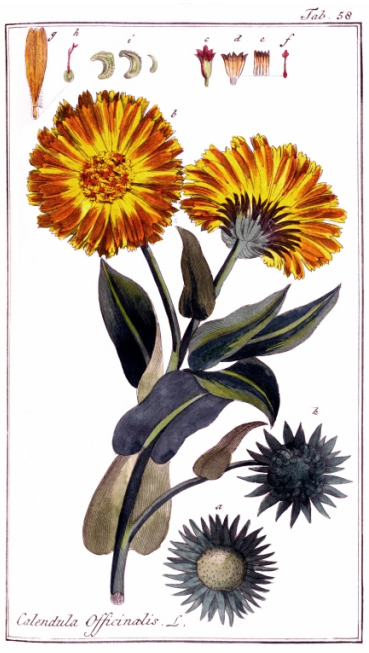
Most adverse effects, such as yellow discolouration of the skin, hair and nails, have been associated with excessive long-term use. This temporary condition is known as 'kava dermopathy' and reverses once kava use is discontinued. A 2003 report found no evidence of brain dysfunction in heavy and long-term kava users (Cairney et al 2003).

Clinical note — Commercial kava products and links to hepatotoxicity
Conflicting reports abound. On 15 August 2002, the TGA initiated a voluntary recall of all products containing kava kava. The response was undertaken due to incoming

details from European countries of case reports of hepatotoxicity apparently associated with the use of commercial kava products. The decision to remove kava from the market has been viewed as controversial and questioned by many people. Toxicological and clinical studies have shown that kava extracts are virtually devoid of toxic effects and when assessed primarily by the British regulatory authority (MCA) and a German research group, a critical analysis of the suspected cases in Germany reveals that a very probable causal relationship could be established in only one patient (Teschke et al 2003). It is suspected that a rare, immunologically mediated, idiosyncratic mechanism may be responsible (Schulze et al 2003) and the extraction process used to produce kava products also had an influence. It now appears that the aqueous method results in extraction of glutathione, in addition to kava lactones, an important factor for protecting the liver from potential damage, whereas the acetone extraction method does not (Whitton et al 2003). As a result, kava products made with the acetone extraction process are more toxic than those produced via aqueous extraction methods. This is an important distinction to make as most European products were made using acetone extraction, whereas Australian products were chiefly made via aqueous extraction. Interestingly, fulminant hepatic failure has not been documented with traditional use in Pacific countries nor in the Northern Territory where Aboriginal kava drinkers consume kava lactones in doses estimated to be 10–50-fold the recommended levels (Currie & Clough 2003). Several reports published in 2003 have found no evidence of aqueous kava extracts inducing irreversible liver toxicity in vivo (Singh & Devkota 2003) or in humans (Clough et al 2003). One study involving long-term users of aqueous kava extracts found that although changes to liver function could occur at moderate levels of consumption, they are reversible and begin to return to baseline after 1–2 weeks' abstinence from kava. Genetic polymorphism of many cytochrome enzymes, leading to inter-individual variation in drug metabolism, may be another important factor in the marked discrepancy in hepatotoxic response to kava (Singh 2005).

Australia was not alone, and other countries also issued health advisory cautions or banned kava-containing products from sale. Although these actions effectively removed kava products from the market, the traditional kava beverage continued to be consumed in the Pacific Islands and the kava-producing countries of the Pacific found the controversy surprising given the long history of apparent safe use in the Pacific. In January 2003 the Kava Evaluation Group was established in Australia to review the accumulating safety data and by August that same year the Complementary Medicine Evaluation Committee recommended to the TGA that certain forms of

kava could be considered safe. The TGA accepted these recommendations and amended the regulations accordingly. Currently, there is a limit of 125 mg kavalactones allowable per tablet or capsule and all products must not provide more than 250 mg kavalactones in the recommended daily dose.



SIGNIFICANT INTERACTIONS

ALCOHOL

Potentiation of CNS sedative effects has been reported in an animal study; however, one double-blind placebo-controlled study found no additive effects on CNS depression or safety related performance (Herberg 1993). Alternatively, a study of 10 subjects found that when alcohol and kava were combined, kava potentiated both the perceived and measured impairment compared to alcohol alone (Foo & Lemon 1997). Caution.

BARBITURATES

Additive effects are theoretically possible. Use with caution and monitor drug dosage. However, interaction may be beneficial under professional supervision.

BENZODIAZEPINES

Additive effects are theoretically possible. Use with caution and monitor drug dosage. However, interaction may be beneficial under professional supervision. The combination has been used successfully to ease symptoms of benzodiazepine withdrawal.

L-DOPA MEDICATION

Antagonistic effects are theoretically possible, thereby reducing the effectiveness of L-dopa. Avoid concurrent use unless under professional supervision.

METHADONE AND MORPHINE

Additive effects with increased CNS depression are theoretically possible, so use with caution, although interactions may be beneficial under professional supervision.

SUBSTRATES FOR CYP3A4

Although in vitro evidence suggests that kava inhibits CYP3A4, in vivo tests found no such effect. Until further research is conducted to determine whether the effect is clinically significant, interactions with drugs chiefly metabolised by CYP3A4 are speculative.

SUBSTRATES FOR CYP2E1

Inhibition of CYP2E1 has been demonstrated in vivo — serum levels of CYP2E1 substrates may become elevated — use caution.

CONTRAINDICATIONS AND PRECAUTIONS

Endogenous depression — according to Commission E (Blumenthal et al 2000).

Although clinical studies indicate no adverse effects on vigilance, the herb's CNS effects may slow some individuals' reaction times, thereby affecting ability to drive a car or operate heavy machinery. Additionally, it should not be used by people with pre-existing liver disease and long-term continuous use should be avoided unless under medical supervision. It should be used with caution in the elderly and in those with Parkinson's disease.

PREGNANCY USE

Not recommended for use in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Kava kava is a scientifically proven treatment for the symptoms of anxiety and stress states. Its anxiety-reducing effects are similar to those of 15 mg oxazepam or 9 mg bromazepam, yet physical tolerance and reduced vigilance have not been observed.
- It also reduces symptoms of anxiety related to menopause when used together with HRT, and reduces withdrawal symptoms associated with benzodiazepine discontinuation.
- It has anxiolytic, sedative, antispasmodic, analgesic and local anaesthetic activity.
- Although the herb is considered to have a low incidence of adverse effects, long-term use should be carefully supervised because of the possibility of developing adverse reactions.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Kava kava is an effective herbal relaxant that reduces symptoms of anxiety and restlessness. It is also used to relieve anxiety in menopause, insomnia and symptoms of benzodiazepine withdrawal.

When will it start to work?

Anxiety-relieving effects are usually seen within the first few weeks of use.

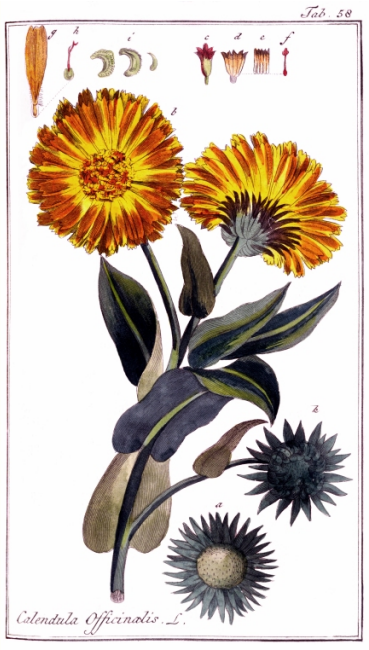
Are there any safety issues?

Taking high doses long term has been associated with a number of side-effects and should be avoided.

REFERENCES

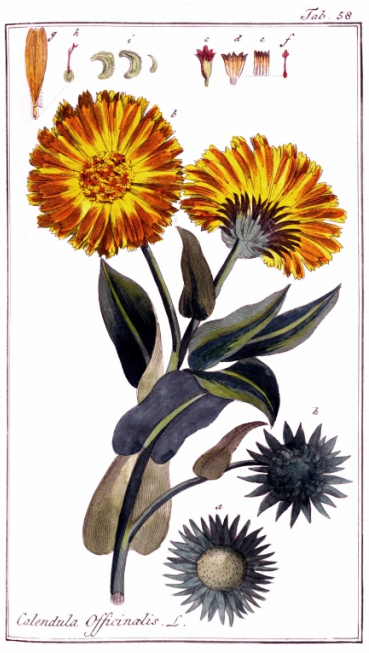
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Boerner RJ et al. Kava-kava extract LI 150 is as effective as opipramol and Buspirone in generalised anxiety disorder: an 8-week randomized, double-blind multi-centre clinical trial in 129 out-patients. Phytomedicine 10 (Suppl 4) (2003): 38-49.
Cagnacci A, Arangino S, Renzi A, Zanni AL, Malmusi S, Volpe A. Kava-kava administration reduces anxiety in perimenopausal women. Maturitas 44.2 (2003): 103-9.
Cairney S, Maruff P, Clough AR. The neurobehavioural effects of kava. Aust NZ J Psychiatry 36.5 (2002): 657-62.
Cairney S et al. Saccade and cognitive function in chronic kava users. Neuropsychopharmacology 28.2 (2003): 389-96.
Clough AR, Bailie RS, Currie B. Liver function test abnormalities in users of aqueous kava extracts. J Toxicol Clin Toxicol 41.6 (2003): 821-9.
Currie BJ, Clough AR. Kava hepatotoxicity with Western herbal products: does it occur with traditional kava use? Med J Aust 178.9 (2003): 421-2.
De L et al. Assessment of the association of Kava-Kava extract and hormone replacement therapy in the treatment of postmenopause anxiety. Minerva Ginecol 52.6 (2000): 263-7.
Emser W, Bartylla K. Verbesserung der Schlafqualitat: Zur Wirkung von Kava-extrakt WS1490 auf das Schlafmuster bei Gesunden. Tw Neurologie Psychiatrie 5 (1991): 636-42 as cited by Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.
Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med 136.1 (2002): 42-53.
Foo H, Lemon J. Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance. Drug Alcohol Rev 16.2 (1997):147-55.
Frey R. Demonstration of the central effects of D,L-kawain with EEG brain mapping. Fortschr Med 109.25 (1991): 505-8.
Garrett KM, Basmadjian G, Khan IA, Schaneberg BT, Seale TW. Extracts of kava (Piper methysticum) induce acute anxiolytic-like behavioral changes in mice. Psychopharmacology (Berl) 170.1 (2003): 33-41.
Grunze H et al. Kava pyrones exert effects on neuronal transmission and transmembraneous cation currents similar to established mood stabilizers: a review. Prog Neuropsychopharmacol Biol Psychiatry 25.8 (2001): 1555-70.
Gurley BJ et al. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 77.5 (2005): 415-26.
Herberg KW. Effect of kava-special extract WS 1490 combined with ethyl alcohol on safety-relevant performance parameters. Blutalkohol 30(2) (1993): 96-105.
Holm E et al. The action profile of D,L-kavain: Cerebral sites and sleep-wakefulness-rhythm in animals. Arzneimittelforschung 41.7 (1991): 673-83.
Jamieson DD, Duffield PH. The antinociceptive actions of kava components in mice. Clin Exp Pharmacol Physiol 17.7 (1990): 495-507.
Lehmann E et al. The efficacy of Cavain in patients suffering from anxiety. Pharmacopsychiatry 22.6 (1989): 258-62.
Lindenberg D, Pitule-Schodel H. D,L-kavain in comparison with oxazepam in anxiety disorders. A double-blind study of clinical effectiveness. Fortschr Med 108.2 (1990): 49-54.
Malsch U, Kieser M. Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. Psychopharmacology (Berl) 157.3 (2001): 277-83.
Martin HB et al. Kavain attenuates vascular contractility through inhibition of calcium channels. Planta Med 68.9 (2002): 784-9.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. J Clin Psychopharmacol 20.1 (2000): 84-9.
Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev no. 1 (2003): CD003383.



Scholing WE, Clausen HD. On the effect of d,l-kavain: experience with neuronika (author's transl). Med Klin 72.32-33 (1977): 1301-6.
Schulze J, Raasch W, CP Siegers. Toxicity of kava pyrones, drug safety and precautions: a case study. Phytomedicine 10 (Suppl 4) (2003): 68-73.
Singh YN, Devkota AK. Aqueous kava extracts do not affect liver function tests in rats. Planta Med 69.6 (2003): 496-9.
Singh YN. Potential for interaction of kava and St. John's wort with drugs. J Ethnopharmacol 100.1-2 (2005): 108-13.
Stevinson C, Huntley A, Ernst E. A systematic review of the safety of kava extract in the treatment of anxiety. Drug Saf 25.4 (2002): 251-61.
Teschke R, Gaus W, Loew D. Kava extracts: safety and risks including rare hepatotoxicity. Phytomedicine 10.5 (2003): 440-6.
Unger M et al. Inhibition of cytochrome P450 3A4 by extracts and kavalactones of Piper methysticum (Kava-Kava). Planta Med 68.12 (2002): 1055-8.
Volz HP, Kieser M. Kava-kava extract WS 1490 versus placebo in anxiety disorders: a randomized placebo-controlled 25-week outpatient trial. Pharmacopsychiatry 30.1 (1997): 1-5.
Whitton PA, Lau A, Salisbury A, Whitehouse J, Evans CS. Kava lactones and the kava-kava controversy Phytochemistry 64.3 (2003): 673-9.
Woelk H et al. The treatment of patients with anxiety: A double-blind study – kava extract WS1490 vs benzodiazepine Z. Allgemeinmed 69 (1993): 271-7; as cited in Nissen D (ed). Mosby's Drug Consult. St Louis: Mosby, 2003.
Wu D, Nair MG, DeWitt DL. Novel compounds from Piper methysticum Forst (kava kava) roots and their effect on cyclooxygenase enzyme. J Agric Food Chem 50.4 (2002): 701-5.

Lavender



Historical note Lavender was used as an antiseptic in ancient Arabian, Greek and Roman medicines. Its generic name comes from the Latin *lavare*, to wash, and it was used as a bath additive as well as an antiseptic in the hospitals and sick rooms of ancient Persia, Greece and Rome (Blumenthal et al 2000). In the 17th century, Culpeper described lavender as having 'use for pains in the head following cold, cramps, convulsions, palsies and faintings' (Battaglia 1995). Lavender was also used traditionally to scent bed linen and to protect stored clothes from moths. This was such a well-accepted practice that the phrase 'laying up in lavender' was used metaphorically to mean 'putting away in storage' (Kirk-Smith 2003). Lavender is now widely used to scent perfumes, pot-pourri, toiletries and cosmetics, as well as to flavour food. Lavender is commonly adulterated with related species that can vary in their constituents. Spike lavender yields more oil but is of lower quality. Lavandin is a hybrid of spike lavender and true lavender.

COMMON NAME
Lavender

OTHER NAMES
Common lavender, English lavender, French lavender, garden lavender, Spanish lavender, spike lavender, true lavender

BOTANICAL NAME/FAMILY
Lavandula angustifolia (synonyms: *L. officinalis*, *L. vera*, *L. spica*); *L. dentata*; *L. latifolia*; *L. pubescens*; *L. stoechas* (family Labiatae)

PLANT PARTS USED
Flower

CHEMICAL COMPONENTS
Lavender flowers contain between 1% and 3% essential oil. The oil is a complex mixture of many different compounds, the amounts of which can vary between species. The most abundant compounds include linalyl acetate (30–55%), linalool (20–35%), cineole, camphor, coumarins and tannins (5–10%) (Schulz et al 1998), together with 1,8-cineole, thymol and carvacrol (Aburjai et al 2005). Perillyl alcohol and D-limonene have been shown to exert anticancer effects (see clinical note).

Clinical note — Perillyl alcohol and anticancer effects?

Perillyl alcohol and D-limonene are monoterpenes found in lavender (also cherries, mint and celery seeds) and have shown chemotherapeutic and chemoprotective effects in a wide variety of in vitro and animal models (Shi & Gould 2002) and are currently being examined in human clinical trials (Gould 1997, Kelloff et al 1999). Perillyl alcohol treatment has resulted in 70–99% inhibition of 'aberrant hyperproliferation', a late-occurring event preceding mammary tumourigenesis in vivo (Katdare et al 1997) and, together with limonene, perillyl alcohol has been shown to induce the complete regression of rat mammary carcinomas by what appears to be a cytostatic and differentiation process (Shi & Gould 1995). Perillyl alcohol has also been shown to inhibit human breast cancer cell growth in vitro and in vivo (Yuri et al 2004) and inhibit the expression and function of the androgen receptor in human prostate cancer cells (Chung et al 2006).

A variety of mechanisms has been proposed to explain these effects. The compounds may act via interfering with RAS signal transduction pathways that regulate malignant cell proliferation (Hohl 1996) and have been found to promote apoptosis in pancreatic adenocarcinoma cells (Stayrook et al 1997) and liver tumours in vivo (Mills et al 1995). Perillyl alcohol, together with D-limonene, has been found to preferentially inhibit HMG-CoA reductase in tumour cells (Elson et al 1999), as well as inhibit ubiquinone synthesis and block the conversion of lathosterol to cholesterol, which may add to its antitumour activity (Ren & Gould 1994). Limonene is oxidised by the CYP2C9 and CYP2C19 enzymes in human liver microsomes (Miyazawa et al 2002a) and there are reported sex-related differences in the oxidative metabolism of limonene by liver microsomes in rats (Miyazawa et al 2002b).

Although in vitro and animal studies have demonstrated the ability of perillyl alcohol to inhibit tumourigenesis in the mammary gland, liver, and pancreas, the results are not yet conclusive and one animal study testing perillyl alcohol detected a weakly promoting effect early in nitrosamine-induced oesophageal tumourigenesis in rats (Liston et al 2003). In initial phase II clinical trials, perillyl alcohol administered orally, four times daily, at a dose of 1200 mg/m^2 had no clinical antitumour activity on advanced ovarian cancer (Bailey et al 2002), metastatic androgen-independent prostate cancer (Liu G et al 2003), or metastatic colorectal cancer (Meadows et al 2002).

MAIN ACTIONS

Lavender and several of its constituents have been tested for pharmacological activity.

SEDATIVE/ANXIOLYTIC

The sedative properties of the essential oil and its main constituents (linalool and linalyl acetate) were shown to have a dose-dependent effect in mice and to reverse caffeine-induced hyperactivity in mice (Buchbauer et al 1991, Lim et al 2005), as well as reduce stress, as indicated by modulation of ACTH, catecholamine and gonadotropin levels in experimental menopausal rats (Yamada et al 2005), and reduce cortisol responses in infant Japanese macaques (Kawakami et al 2002). Inhalation of lavender has also been shown to produce a dose-dependent anticonvulsant effect in both rats and mice (Yamada et al 1994).

In human trials, inhalation of lavender has been shown to induce relaxation and sedation (Schulz et al 1998) and to alter EEG responses (Diego et al 1998, Dimpfel et al 2004, Lee et al 1994, Sanders et al 2002, Yagyu 1994), as well as significantly decreasing heart rate and increasing high-frequency spectral components to produce calm and vigorous mood states in healthy volunteers (Kuroda et al 2005). Transdermal absorption of linalool without inhalation produced a decrease in systolic blood pressure and a smaller decrease of skin temperature with no effects on subjective evaluation of wellbeing in healthy human subjects (Heuberger et al 2004), and another study found that lavender scent was associated with lower fatigue following an anxiety-provoking task (Burnett et al 2004).

These positive studies are contrasted by studies with negative findings. Lavender aromatherapy did not significantly improve scores on the Hospital Anxiety and Depression Scale or the Somatic and Psychological Health Report (SPHERE) in a RCT of 313 patients undergoing radiotherapy (Graham et al 2003) and a study of 169 subjects, including both depressed and non-depressed subjects, showed lavender increased fatigue, tension, confusion, and total mood disturbance, and decreased vigour (Goel & Grasso 2004).

ANTIMICROBIAL

Various in vitro data suggest that lavender oil has antibacterial (Dadalioglu & Evrendilek 2004, Larrondo & Calvo-Torras 1995), antifungal (Inouye et al 2001) and mitocidal activities (Perrucci et al 1996, Refaat et al 2002), with both lavender and linalool having fungistatic and fungicidal activity against *Candida albicans* strains at high concentrations and inhibiting germ tube formation and hyphal elongation at low concentrations, suggesting it may be useful for reducing fungal progression and the spread of infection in host tissues (D'Auria et al 2005). Lavender has been shown to be active alone and to work synergistically with tea tree oil against the fungi responsible for tinea and onychomycosis (Cassella et al 2002).

The fungistatic properties of linalool have led to the suggestion that it could be used to complement environmental measures in preventing fungal contamination in storage areas of libraries (Rakotonirainy & Lavedrine 2005).

CARMINATIVE

Linalool, one of lavender's major components, demonstrated spasmolytic activity when tested on an in vitro preparation of guinea-pig ileum smooth muscle (Lis-Balchin & Hart 1999).

ANTINEOPLASTIC EFFECTS

In vitro and animal studies suggest that perillyl alcohol and D-limonene (see Clinical note) may have useful chemotherapeutic and chemoprotective effects in a range of cancers, including cancer of the colon, liver, lung, breast, pancreas and prostate, as well as in melanoma (Micromedex database 2003). These results have not yet been confirmed in human studies.

OTHER ACTIONS

When applied topically, lavender oil has rubefacient properties (Fisher & Painter 1996) and is thought to have analgesic, antihistaminic and anti-inflammatory activities. A small study comparing the effects of a bath containing lavender oil, synthetic lavender oil, and distilled water in reducing perineal discomfort after childbirth found lower mean discomfort scores in the lavender group; however, the differences between groups were not significant (Cornwell & Dale 1995).

Traditionally, lavender oil is considered to have a balancing effect on the CNS, acting as an aromatic stimulant or calming agent.

Extracts of *L. multifida* have been found to have topical anti-inflammatory activity in mice, with some extracted compounds having activity comparable to that of indomethacin (Sosa et al 2005). At high concentrations (0.1%) lavender oil has also been found to suppress TNF-alpha-induced neutrophil adherence (Abe et al 2003). Lavender has also demonstrated powerful anti-oxidant activity (Gulcin et al 2004), as well as antimutagenic activity (Evandri et al 2005) and antiplatelet and antithrombotic properties demonstrated both in vitro and in vivo (Ballabeni et al 2004).

CLINICAL USE

Although few scientific or clinical studies have been conducted with lavender oil, much of the evidence supporting its use is based on the known pharmacological actions of the constituents and a long history of traditional use.

ANXIETY, INSOMNIA AND MOOD ENHANCEMENT

A number of controlled trials and observational studies suggest that inhalation of ambient lavender oil has a relaxing effect and is able to reduce anxiety and improve mood, concentration and sleep.

In a study of 31 healthy volunteers intermittent exposure to ambient lavender oil over a 30-minute period was found to increase the percentage of deep or slow-wave sleep in men and women with corresponding reports of higher vigour the morning after lavender exposure (Goel et al 2005). That study also reported gender-specific effects with increased stage 2 (light) sleep, as well as decreased rapid-eye movement sleep and the amount of time needed to reach wakefulness after first falling asleep in women, and opposite effects in men. In a 4-week randomised double-blind, pilot study lavender tincture (1:5 in 50% alcohol) 60 drops/day was not as effective as imipramine for treating depression; however, a combination of lavender tincture and imipramine was found to be more effective than imipramine alone with better and earlier improvement (Akhondzadeh et al 2003). In another randomised, placebo controlled, pilot study, using a crossover design, lavender aromatherapy produced a non-significant improvement in insomnia compared with exposure to almond oil (Lewith et al 2005). A case study of four geriatric patients with impaired sleep also found that lavender aromatherapy increased sleep time and was comparable in effectiveness to hypnotics or tranquillisers (Hardy & Stretch 1995). A double-blind study of 140 patients found that an essential oil spray or gargle containing lavender with 14 other essential oils significantly reduced snoring as reported by bed partners (Prichard 2004).

In hospitalised patients, aromatherapy with lavender oil was found to significantly reduce anxiety in a study of 14 female haemodialysis patients (Itai et al 2000). Another controlled trial of 200 subjects found that lavender aromatherapy reduced anxiety and improved mood in patients waiting for dental treatment (Lehrner et al 2005).

A number of studies have examined the use of lavender aromatherapy and massage with lavender oil (see below) for reducing agitation in dementia patients; however, these studies are generally small and results have been mixed. A placebo-controlled study found that lavender aromatherapy effectively reduced agitated behaviour in 15 patients with severe dementia (Holmes et al 2002), but it had no effect on reducing agitation in another controlled trial of 7 severely demented patients (Snow et al 2004), nor was there effect on reducing resistive behaviour in 13 people with dementia in a residential aged care facility (Gray & Clair 2002).

In a RCT involving 80 non-depressed women, adding lavender oil to a bath was found to enhance the general mood-enhancing effects of daily bathing and produce a reduction in pessimism (Morris 2002). It has been suggested that the relaxing effects may be useful in the treatment of chronic pain (Buckle 1999) and this is supported by a study reporting that while lavender did not elicit a direct analgesic effect it did alter affective appraisal of the pain experience with retrospective impression of pain intensity and pain unpleasantness from experimentally-induced heat, pressure, and ischaemic pain being reduced after treatment with lavender aromatherapy (Gedney et al 2004).

When used in combination with massage Overall, the evidence supporting the use of lavender oil in massage is encouraging; however, most studies are relatively small and there are mixed reports of its efficacy.

A controlled trial of 122 patients found massage with lavender oil improved mood and perceived levels of anxiety in 122 intensive care patients (Dunn et al 1995). In a RCT, eight sessions of acupressure using lavender essential oil over 3 weeks was found to be effective in relieving pain, neck stiffness and stress in 32 adults with sub-acute non-specific neck pain (Yip & Tse 2006). In another controlled trial, a 2-week lavender aromatherapy hand massage program produced significant improvements in emotion and aggressive behaviour in elderly people with Alzheimer's type dementia (Lee 2005). Alternatively, one RCT involving 42 subjects found that the addition of lavender essential oil did not appear to increase the beneficial effects of massage for patients with advanced cancer (Soden et al 2004).

Use in animals Lavender aromatherapy has also been found to produce increased resting and reduced movement and vocalisation in dogs housed in a rescue shelter (Graham et al 2005).

Commission E supports the use of oral lavender in mood disturbances such as restlessness and insomnia (Blumenthal et al 2000).

IMPROVED CONCENTRATION

In a RCT, exposure to lavender aromatherapy during breaks resulted in significantly higher concentration levels during the afternoon period when concentration was found to be lowest in a control group (Sakamoto et al 2005). Lavender oil aromatherapy has also been found to reduce mental stress and increase arousal rate (Motomura et al 2001), elicit a subjective sense of 'happiness' (Vernet-Maury et al 1999) and to produce increased relaxation, less depressed mood and faster and more accurate mathematical computations (Field et al 2005). In a RCT, lavender aromatherapy tended to enhance calculating speed and calculating accuracy in female but not male subjects (Liu et al 2004), but results from another study suggest

that lavender reduced working memory and impaired reaction times for both memory and attention-based tasks compared with controls (Moss et al 2003).

A controlled study of dementia patients found that a blend of lavender, sweet marjoram, patchouli and vetiver essential oils in a cream massaged 5 times/day for 4 weeks onto the bodies and limbs of 56 aged care facility residents with moderate to severe dementia produced a small but significant improvement in Mini Mental State Examination associated with increased mental alertness and awareness and resistance to nursing care procedures compared with massage with cream alone (Bowles et al 2002).

DYSPEPSIA AND BLOATING

Although there have been no clinical trials to investigate its use, lavender is commonly recommended for gastrointestinal disorders as a carminative and antiflatulent to soothe indigestion, colic, dyspepsia and bloating (Blumenthal et al 2000). Based on the antispasmodic actions of a key constituent, linalool, lavender may be useful in these conditions. No controlled clinical studies could be located to determine its effectiveness for these indications.

ALOPECIA

A RCT of scalp massage using thyme, rosemary, lavender and cedarwood essential oils in 86 patients with alopecia areata found a significant improvement in hair growth after 7 months (Hay et al 1998). Although the efficacy of lavender as a stand-alone treatment was not clarified with this trial, it is known that the herb has some antibacterial and antifungal activity that may play a role. In a single case study, topical application of lavender, together with other essential oils, was reported to assist in treating scalp eczema (De Valois 2004).

PERINEAL DISCOMFORT FOLLOWING CHILDBIRTH

A RCT in 635 women following childbirth found that using lavender oil in bath water was safe and pleasant to use and that there was a tendency towards lower discomfort scores between the third and fifth day (Dale & Cornwell 1994). In that study, 6 drops of pure lavender oil was added to the bath.

INSECT BITES

In vitro and animal studies suggest that lavender oil inhibits immediate-type allergic reactions by inhibition of mast-cell degranulation (Kim & Cho 1999).

OTHER USES

Lavender has a long history of use as a sedative, antidepressive, antimicrobial, carminative (smooth muscle relaxant), as a topical agent for burns and insect bites

(Cavanagh & Wilkinson 2002) and as an insect repellant. Lavender has also been used to treat migraines and neuralgia, as an astringent to treat minor cuts and bruises, and is used externally for strained muscles, as well as acne, eczema and varicose ulcers (Fisher & Painter 1996). It is also used in a gargle for loss of voice.

In Australia, lavender essential oil is the most popular aromatherapy oil, out-selling the second most popular (orange) oil by more than seven times (F Kheery (In Essence) pers. commun. 2002). It is often combined with bergamot and cedarwood oils for relieving anxiety and stress and combined with marjoram to induce sleep.

DOSAGE RANGE

Probably no other herb is available in as many forms as lavender.

- Infusion (tea): 1.5 g dried flowers in 150 mL water.
- Internal: 1–4 drops (20–80 mg) on a sugar cube.
- Liquid extract (1:2): 2–4.5 mL/day.
- External use: mix 20 drops of oil with 20 mL of carrier oil such as almond oil. May be applied undiluted to insect bites or stings.
- As a bath additive: 20–100 g lavender flowers are commonly steeped in 2 L boiling water, strained, and then added to the bathwater.
- Aromatherapy: use a few drops of lavender oil on a suitable oil diffuser or on a pillow slip to assist sleep.

Lavender oil is quickly absorbed by the skin and constituents linalool and linalyl acetate have been detected in the blood 5 minutes after administration. Blood levels peak after 19 minutes and are negligible by 90 minutes.

TOXICITY

Although there are no specific reports of toxicity, it is suggested that no more than two (2) drops be taken internally. There is the potential for irritant or allergenic skin reactions with the topical use of lavender oil as it has been found to be cytotoxic to human skin cells in vitro (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v), possibly due to membrane damage. The activity of linalool was found to reflect the cytotoxicity of the whole oil, whereas the cytotoxicity of linalyl acetate was found to be higher than that of the oil, suggesting suppression of its activity by an unknown factor in the oil (Prashar et al 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

PHARMACEUTICAL SEDATIVES

Theoretically, lavender can potentiate the effects of sedatives, so observe patients taking this combination closely — beneficial interaction possible under professional supervision.

ANTIDEPRESSANTS

Lavender tincture may have additive effects when used with these medicines — beneficial interaction possible.

PREGNANCY USE

No restrictions known for external use.

Safety of internal use has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING

- The active part of lavender is the volatile oil, which has relaxing, sedative, antispasmodic and antiseptic activity.
- Lavender can be taken as a tincture or tea, or the oil can be applied topically, used in baths or inhaled from a diffuser.
- It is advised that topical preparations be tested on a small area of skin before widespread application.
- Lavender has traditionally been used for sleep disorders, anxiety and nervous stomach, as well as to treat minor cuts, burns, bruises and insect bites and is commonly found in cosmetics and toiletries.
- Lavender contains substances that are currently being studied for cancer prevention.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Lavender oil is used to assist in relaxation, digestive problems and as first aid for minor skin conditions.

When will it start to work?

As a relaxant, effects may be felt on the first day of use, but this will depend on the dose and form used.

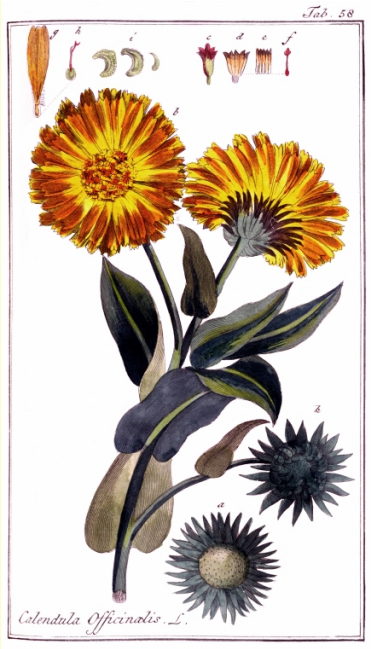
Are there any safety issues?

Although lavender has not been scientifically studied as extensively as some other herbal medicines, historical use suggests it is generally safe.

REFERENCES

Abe SN et al. Suppression of tumor necrosis factor-alpha-induced neutrophil adherence responses by essential oils. Mediat Inflamm 12(6) (2003): 323-8.

Aburjai TM et al. Chemical composition of the essential oil from different aerial parts of lavender (Lavandula coronopofolia Poiert) (Lamiaceae) grown in Jordan. J Essent Oil Res 17(1) (2005): 49-51.
Akhondzadeh SL et al. Comparison of Lavandula angustifolia Mill. tincture and imipramine in the treatment of mild to moderate depression: A double-blind, randomized trial. Prog Neuro-Psychopharmacol Biol Psychiatry 27(1) (2003): 123-7.
Bailey HH et al. A phase II trial of daily perillyl alcohol in patients with advanced ovarian cancer: eastern cooperative oncology group study E2E96. Gynecol Oncol 85(3) (2002): 464-8.
Ballabeni VM et al. Novel antiplatelet and antithrombotic activities of essential oil from Lavandula hybrida Reverchon grosso. Phytomedicine 11(7-8) (2004): 596-601.
Battaglia S. The Complete Guide to Aromatherapy. Brisbane: The Perfect Potion, 1995.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Bowles EJ et al. Effects of essential oils and touch on resistance to nursing care procedures and other dementia-related behaviours in a residential care facility. Int J Aromather 12(1) (2002): 22-9.
Buchbauer G et al. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Z Naturforschung – Section C – Biosci 4611-12 (1991): 1067-72.
Buckle J. Use of aromatherapy as a complementary treatment for chronic pain. Alternative Ther Health Med 5.5 (1999): 42-51.
Burnett KM et al. Scent and mood state following an anxiety-provoking task. Psychol Rep 95(2) (2004): 707-22.
Cassella SJ et al. Synergistic antifungal activity of tea tree (Melaleuca alternifolia) and lavender (Lavandula angustifolia) essential oils against dermatophyte infection. Int J Aromather 12(1(2002).): 2-15.
Cavanagh HM, Wilkinson JM. Biological activities of lavender essential oil. Phytother Res 16.4 (2002): 301-8.
Chung B et al. Perillyl alcohol inhibits the expression and function of the androgen receptor in human prostate cancer cells. Cancer Lett 236(2) (2006): 222-8.
Cornwell S, Dale A. Lavender oil and perineal repair. Mod Midwife. 5(3) (1995): 31-3.
D'Auria F et al. Antifungal activity of Lavandula angustifolia essential oil against Candida albicans yeast and mycelial form. Med Mycol 43(5) (2005): 391-6.
Dadalioglu I, Evrendilek GA. Chemical compositions and antibacterial effects of essential oils of Turkish oregano (Origanum minutiflorum), bay laurel (Laurus nobilis), Spanish lavender (Lavandula stoechas L.), and fennel (Foeniculum vulgare) on common foodborne pathogens. J Agric Food Chem 52(26) (2004): 8255-60.
Dale A, Cornwell S. The role of lavender oil in relieving perineal discomfort following childbirth: a blind randomized clinical trial. J Adv Nurs 19.1 (1994): 89-96.
De Valois B. Using essential oils to treat scalp eczema. Int J Aromather 14(1) (2004): 45-7.
Diego MA et al. Aromatherapy positively affects mood, EEG patterns of alertness and math computations. Int J Neurosci 96.3-4 (1998): 217-24.
Dimpfel WI et al. Effects of lozenge containing lavender oil, extracts from hops, lemon balm and oat on electrical brain activity of volunteers. Eur J Med Res 9(9) (2004): 423-31.
Dunn C et al. Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit. J Adv Nurs 21.1 (1995): 34-40.
Elson CE et al. Isoprenoid-mediated inhibition of mevalonate synthesis: Potential application to cancer. Proc Soc Exp Biol Med 221.4 (1999): 294-311.
Evandri M et al. The antimutagenic activity of Lavandula angustifolia (lavender) essential oil in the bacterial reverse mutation assay. Food Chem Toxicol 43(9) (2005): 1381-7.
Field T et al. Lavender fragrance cleansing gel effects on relaxation. Int J Neurosci 115(2) (2005): 207-22.
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.
Gedney J et al. Sensory and affective pain discrimination after inhalation of essential oils. Psychosom Med 66(4) (2004): 599-606.



Goel N, Grasso DJ. Olfactory discrimination and transient mood change in young men and women: variation by season, mood state, and time of day. Chronobiol Int 21(4-5) (2004): 691-719.
Goel N et al. An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiol Int 22(5) (2005): 889-904.
Gould MN. Cancer chemoprevention and therapy by monoterpenes. Environ Health Perspect 105 (Suppl. 4] (1997): 977-9.
Graham P et al. Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. J Clin Oncol 21(12) (2003): 2372-6.
Graham L et al. The influence of olfactory stimulation on the behaviour of dogs housed in a rescue shelter. Appl Anim Behav Sci 91(1-2) (2005): 143-53.
Gray SG, Clair AA. Influence of aromatherapy on medication administration to residential-care residents with dementia and behavioral challenges. Am J Alzheim Dis Other Dement 17(3) (2002): 169-74.
Gulcin I et al. Comparison of antioxidant activity of clove (Eugenia caryophylata Thunb) buds and lavender (Lavandula stoechas L.). Food Chem 87(3) (2004): 393-400.
Hardy MK-S, Stretch DD. Replacement of drug treatment for insomnia by ambient odour. Lancet 346 (1995): 701.
Hay IC et al. Randomized trial of aromatherapy. Successful treatment for alopecia areata [Comment]. Arch Dermatol 134.11 (1998): 1349-52.
Heuberger E et al. Transdermal absorption of (-)-linalool induces autonomic deactivation but has no impact on ratings of well-being in humans. Neuropsychopharmacology 29(10) (2004): 1925-32.
Hohl RJ. Monoterpenes as regulators of malignant cell proliferation. Adv Exp Med Biol 401 (1996): 137-46.
Holmes C et al. Lavender oil as a treatment for agitated behaviour in severe dementia: A placebo controlled study. Int J Geriatr Psychiatry 17(4) (2002): 305-8.
Inouye S et al. In-vitro and in-vivo anti-Trichophyton activity of essential oils by vapour contact. Mycoses 44.3-4 (2001): 99-107.
Itai T et al. Psychological effects of aromatherapy on chronic hemodialysis patients. Psychiatry Clin Neurosci 54.4 (2000): 393-7.
Katdare M et al. Prevention of mammary preneoplastic transformation by naturally-occurring tumor inhibitors. Cancer Lett 111.1-2 (1997): 141-7.
Kawakami K et al. The calming effect of stimuli presentation on infant Japanese Macaques (Macaca fuscata) under stress situation: a preliminary study. Primates 43(1) (2002): 73-85.
Kelloff GJ et al. Progress in cancer chemoprevention. Ann NY Acad Sci 889 (1999): 1-13.
Kim HM, Cho SH. Lavender oil inhibits immediate-type allergic reaction in mice and rats. J Pharm Pharmacol 51.2 (1999): 221-6.
Kirk-Smith M. The psychological effects of lavender II: scientific and clinical evidence. Int J Aromather 13(2-3) (2003): 82-9.
Kuroda K et al. Sedative effects of the jasmine tea odor and (R)-(-)-linalool, one of its major odor components, on autonomic nerve activity and mood states. Eur J Appl Physiol 95(2-3) (2005): 107-14.
Larrondo JVA, Calvo-Torras MA. Antimicrobial activity of essences from labiates. Microbios 82.332 (1995): 171-2.
Lee CF et al. Responses of electroencephalogram to different odors. Ann Physiol Anthropol 13.5 (1994): 281-91.
Lee SY. The effect of lavender aromatherapy on cognitive function, emotion, and aggressive behavior of elderly with demenita. Taehan Kanho Hakhoe Chi 35(2) (2005): 303-12.
Lehrner J et al. Ambient odors of orange and lavender reduce anxiety and improve mood in a dental office. Physiol Behav 86(1-2) (2005): 92-5.
Lewith GT et al. A single-blinded, randomized pilot study evaluating the aroma of Lavandula augustifolia as a treatment for mild insomnia. J Altern Complement Med 11(4) (2005): 631-7.
Lim WC et al. Stimulative and sedative effects of essential oils upon inhalation in mice. Arch Pharm Res 28(7) (2005): 770-4.

Lis-Balchin M, Hart S. Studies on the mode of action of the essential oil of lavender (Lavandula angustifolia P. Miller). Phytotherapy Res 13.6 (1999): 540-2.
Liston BW et al. Perillyl alcohol as a chemopreventive agent in N-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis. Cancer Res 63(10) (2003): 2399-403.
Liu G et al. Phase II trial of perillyl alcohol (NSC 641066) administered daily in patients with metastatic androgen independent prostate cancer. Invest New Drugs 21(3) (2003): 367-72.
Liu M et al. Influences of lavender fragrance and cut flower arrangements on cognitive performance. Int J Aromather 14(4) (2004): 169-74.
Meadows S et al. Phase II trial of perillyl alcohol in patients with metastatic colorectal cancer. Int J Gastrointest Cancer 32(2-3) (2002): 125-8.
Micromedex. Lavender. Thomson 2003. www.micromedex.com
Mills JJ et al. Induction of apoptosis in liver tumors by the monoterpene perillyl alcohol. Cancer Res 55.5 (1995): 979-83.
Miyazawa M et al. Metabolism of (+)- and (–)-limonenes to respective carveols and perillyl alcohols by CYP2C9 and CYP2C19 in human liver microsomes. Drug Metab Dispos 30(5) (2002a): 602-7.
Miyazawa M et al. Sex differences in the metabolism of (+)- and (-)-limonene enantiomers to carveol and perillyl alcohol derivatives by cytochrome P450 enzymes in rat liver microsomes. Chem Res Toxicol 15(1) (2002b): 15-20.
Morris N. The effects of lavender (Lavendula angustifolium) baths on psychological well-being: two exploratory randomised control trials. Complement Ther Med 10(4) (2002): 223-8.
Moss M et al. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci 113(1) (2003): 15-38.
Motomura N et al. Reduction of mental stress with lavender odorant. Percept Motor Skills 93.3 (2001): 713-18.
Perrucci S et al. The activity of volatile compounds from Lavandula angustifolia against psoroptes cuniculi. Phytother Res 10.1 (1996): 5-8.
Prashar AI et al. Cytotoxicity of lavender oil and its major components to human skin cells. Cell Prolif 37(3) (2004): 221-9.
Prichard AJN. The use of essential oils to treat snoring. Phytother Res 18(9) (2004): 696-9.
Rakotonirainy MS, Lavedrine B. Screening for antifungal activity of essential oils and related compounds to control the biocontamination in libraries and archives storage areas. Int Biodeterior Biodegrad 55(2) (2005): 141-7.
Refaat AM et al. Acaricidal activity of sweet basil and French lavender essential oils against two species of mites of the family tetranychidae (Acari: Tetranychidae). Acta Phytopathol Entomol Hung 37(1-3) (2002): 287-98.
Ren Z, Gould MN. Inhibition of ubiquinone and cholesterol synthesis by the monoterpene perillyl alcohol. Cancer Lett 76.2-3 (1994): 185-90.
Sakamoto R et al. Effectiveness of aroma on work efficiency: Lavender aroma during recesses prevents deterioration of work performance. Chem Senses 30(8) (2005): 683-91.
Sanders C et al. EEG asymmetry responses to lavender and rosemary aromas in adults and infants. Int J Neurosci 112(11) (2002): 1305-20.
Schulz V, Hansel R, Tyler VE. Rational Phytotherapy: A Physician's Guide to Herbal Medicine. Berlin: Springer, 1998.
Shi W, Gould MN. Induction of differentiation in neuro-2A cells by the monoterpene perillyl alcohol. Cancer Lett 95.1-2 (1995): 1-6.
Shi W, Gould MN. Induction of cytostasis in mammary carcinoma cells treated with the anticancer agent perillyl alcohol. Carcinogenesis 23.1 (2002): 131-42.
Snow AL et al. A controlled trial of aromatherapy for agitation in nursing home patients with dementia. J Altern Complement Med 10(3) (2004): 431-7.
Soden K et al. A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 18(2) (2004): 87-92.

Sosa S et al. Extracts and constituents of Lavandula multifida with topical anti-inflammatory activity. Phytomedicine 12(4) (2005): 271-7.
Stayrook KR et al. Induction of the apoptosis-promoting protein Bak by perillyl alcohol in pancreatic ductal adenocarcinoma relative to untransformed ductal epithelial cells. Carcinogenesis 18.8 (1997): 1655-8.
Vernet-Maury E et al. Basic emotions induced by odorants: a new approach based on autonomic pattern results. J Auton Nerv Sys 75.2-3 (1999): 176-83.
Yagyu T. Neurophysiological findings on the effects of fragrance: lavender and jasmine. Integr Psychiatry 10.2 (1994): 62-7.
Yamada K et al. Anticonvulsive effects of inhaling lavender oil vapour. Biol Pharm Bull 17(2) (1994): 359-60.
Yamada K et al. Effects of inhaling the vapor of Lavandula burnatii super-derived essential oil and linalool on plasma adrenocorticotropic hormone (ACTH), catecholamine and gonadotropin levels in experimental menopausal female rats. Biol Pharm Bull 28(2) (2005): 378-9.
Yip YB, Tse SH-M. An experimental study on the effectiveness of acupressure with aromatic lavender essential oil for sub-acute, non-specific neck pain in Hong Kong. Complement Ther Clin Pract 12(1) (2006): 18-26.
Yuri T et al. Perillyl alcohol inhibits human breast cancer cell growth in vitro and in vivo. Breast Cancer Res Treat 84(3) (2004): 251-60.

Lemon balm

Historical note Lemon balm was used in ancient Greece and Rome as a topical treatment for wounds. In the Middle Ages it was used internally as a sedative and by the 17th century, English herbalist Culpeper claimed it could improve mood and stimulate clear thinking. Nowadays, it is still used to induce a sense of calm and help with anxiety, but is also added to cosmetics, insect repellants, furniture polish and food.

COMMON NAME
Lemon balm

OTHER NAMES
Balm mint, bee balm, blue balm, common balm, cure-all, dropsy plant, garden balm, sweet balm

BOTANICAL NAME/FAMILY
Melissa officinalis (family Labiatae)

PLANT PART USED
Aerial parts

CHEMICAL COMPONENTS
Flavonoids, phenolic acids, tannins, triterpenes, essential oil and sesquiterpenes. Of note, the herb contains citronellal, caffeic acid, eugenol, rosmarinic acid and choline (Wake et al 2000). Growing and harvesting methods have a major influence on the amount of volatile oil present in the leaves. It has been found that the oil content in the herb is highest in the top third and lowest in the bottom two-thirds (Mrlianova et al 2002).

MAIN ACTIONS

ANXIOLYTIC AND SEDATIVE
Over the years, a number of studies involving rodents have suggested specific anxiolytic or sedative effects (Kennedy et al 2002, Soulimani et al 1991). More recently, a double-blind placebo-controlled study has confirmed anxiolytic activity is clinically significant for lemon balm essential oil (Ballard et al 2002). In 2005 a double-blind, placebo-controlled, randomised, crossover trial of a whole extract of lemon balm (300 and 600 mg) in 18 healthy adults found a significant reduction in

stress in the volunteers taking 600 mg (Kennedy et al 2004). A number of possible active components of the dried leaf and essential oil of the herb may be responsible for these effects, such as eugenol and citronellol, which bind to GABA-A receptors and increase the affinity of GABA to receptors (Aoshima & Hamamoto 1999).

ANTIVIRAL

A lemon balm extract was found to have significant virucidal effects against HSV-1 within 3 and 6 hours of treatment in vitro and in animal tests (Dimitrova et al 1993). The volatile oils from *M. officinalis* have also been shown to inhibit the replication of HSV-2 in vitro (Allahverdiyer et al 2004).

ANTIBACTERIAL AND ANTIFUNGAL

One in vitro study found that lemon balm extract exhibited activity against bacteria, filamentous fungi and yeasts (Larrondo et al 1995). It is likely that the constituent eugenol is chiefly responsible, as it has well established antibacterial activity against such organisms as *Escherichia coli* and *Staphylococcus aureus* (Walsh et al 2003).

CHOLINERGIC

Lemon balm exhibits CNS acetylcholine receptor activity, with both nicotinic and muscarinic binding properties (Wake et al 2000). In vitro data has demonstrated that lemon balm is a weak inhibitor of acetylcholinesterase and has a moderate affinity to the GABA-A benzodiazepine receptor site (Salah & Jager 2005). This indicates that lemon balm may have a role to play in the treatment of Alzheimer's disease and epilepsy. However, a 2003 randomised, double-blind, placebo-controlled, crossover trial demonstrated that lemon balm did not inhibit cholinesterase. The trial demonstrated improved cognitive function and mood and concluded that for these reasons it was a valuable adjunct to Alzheimer's therapy (Kennedy et al 2003).

Clinical note

Long before the current biologically based theory of cholinergic abnormalities in Alzheimer's dementia emerged, western European medicine systems have traditionally used several herbs that are now known to exert cholinergic activity (such as sage and lemon balm) for their dementia-treating properties.

ANTI-INFLAMMATORY, ANALGESIC AND ANTISPASMODIC

The plant extract exerts analgesic activity at high doses in vivo (Soulimani et al 1991). Two constituents in lemon balm have documented anti-inflammatory activity, achieved through different mechanisms of action. Rosmarinic acid, a naturally occurring constituent found in *M. officinalis*, inhibits several complement-dependent inflammatory processes (Englberger et al 1988, Peake et al 1991). Eugenol, another

important component, inhibits COX-1 and -2 activities in vitro (Huss et al 2002, Kelm et al 2000). Both the whole volatile oil and its main component citral have demonstrated antispasmodic ability on isolated rat ileum (Sadraei et al 2003).

ANTIOXIDANT

Lemon balm has shown antioxidant activity in several studies (Hohmann et al 1999). According to a 2003 study, concentrations of antioxidants within lemon balm are >75 mmol/100 g (Dragland et al 2003).

CARDIOVASCULAR EFFECTS

Aqueous extracts of lemon balm have been shown to slow cardiac rate but not alter the force of contraction in isolated rat hearts (Gazola et al 2004). An extract of lemon balm reduced blood cholesterol and lipid levels in rats fed a high fat and alcohol diet (Bolkent et al 2005). Interestingly, the extract also increased glutathione levels and reduced lipid peroxidation in the liver, demonstrating a hepatoprotective effect.

OTHER ACTIONS

In vitro testing has also identified anti-HIV activity with inhibitory activity against HIV-1 reverse transcriptase (Yamasaki et al 1998), inhibition of TSH binding to thyroid plasma membranes and the extrathyroidal enzymic T4-5'-deiodination to T3 (Auf'mkolk et al 1984a), and antitumour activity (Chlabicz & Galasinski 1986, Galasinski 1996, Galasinski et al 1996).

CLINICAL USE

In clinical practice, lemon balm is often prescribed in combination with other herbal medicines. As a reflection of this, many clinical studies have investigated the effects of lemon balm as an ingredient of a herbal combination, making it difficult to determine the efficacy of this herb individually.

ANXIETY

Although used traditionally as a treatment for anxiety, most modern-day evidence comes from in vivo studies, as the herb has not been clinically tested to a significant degree. However, the essential oil of lemon balm has been investigated under double-blind placebo-controlled conditions and found to be a safe and effective treatment for clinically significant agitation in people with severe dementia (Ballard et al 2002). The trial, which involved 71 subjects, found that after 1 month's treatment, patients were less agitated, less socially withdrawn and spent more time in constructive activities than those in the placebo group.

Commission E approves the use of lemon balm in the treatment of anxiety and restlessness (Blumenthal et al 2000).

COGNITIVE FUNCTION

Lemon balm has been used for centuries to improve cognitive function and encouraging results from a 2002 clinical study confirm that it can influence memory.

The randomised, double-blind crossover study involving 20 healthy young volunteers found that single doses of lemon balm were able to modulate both mood and cognitive performance in a dose- and time-dependent manner (Kennedy et al 2002). In this study, treatment with the lowest dose (300 mg) increased self-rated 'calmness' within 1 hour whereas the 600 mg and 900 mg doses produced significant effects on memory task performance, observable at both 2.5 hours and 4 hours after administration. The highest tested dose (900 mg) was found to significantly reduce alertness within 1 hour, suggesting a dose–response effect.

ALZHEIMER'S DISEASE

A randomised, double-blind, placebo-controlled trial demonstrated the efficacy and safety of *M. officinalis* in 42 patients aged 65–80 with mild to moderate Alzheimer's disease who were given 60 drops/day for 4 months (Akhondzadeh et al 2003). Outcome measures included significantly better cognition and reduced agitation.

INSOMNIA

In clinical practice, lemon balm is often prescribed in combination with other herbs such as valerian in the treatment of insomnia. As a reflection of this, a randomised, double-blind multicentre study investigated the effects of a commercial valerian and lemon balm herbal combination (Songha Night) in 98 healthy subjects (Cerny & Schmid 1999). Treatment was administered over a 30-day period and consisted of 3 tablets taken half an hour before bedtime, providing a total dose of 1–6 g valerian and 1–2 g lemon balm. Herbal treatment was found to significantly improve sleep quality and was well tolerated.

Another randomised, double-blind crossover study found that the same combination of valerian and lemon balm taken over 9 nights was as effective as triazolam in the treatment of insomnia (Dressing et al 1992). The dose used was equivalent to 1.4 g dried valerian and 0.9 g dried lemon balm.

As with all herbal combination studies, it is difficult to determine the contribution each individual herb made to the end result. As such, these studies are encouraging but the role of lemon balm as a stand-alone treatment for insomnia remains unclear.

Commission E approves the use of lemon balm in the treatment of insomnia (Blumenthal et al 2000).

GASTROINTESTINAL CONDITIONS ASSOCIATED WITH SPASM AND NERVOUSNESS

To date, only studies using lemon balm in combination with other herbs are available.

A 15-day open study involving 24 subjects with chronic non-specific colitis investigated whether a combination of lemon balm, St John's wort, dandelion, marigold and fennel could provide symptom relief (Chakurski et al 1981). Excellent results were obtained by the end of the study, with herbal treatment resulting in the disappearance of spontaneous and palpable pains along the large intestine in 95.83% of patients. A double-blind study using a herbal tea prepared from chamomile, lemon balm, vervain, licorice and fennel in infantile colic has also been conducted. A dose of 150 mL offered up to three times daily was found to eliminate symptoms of colic in 57% of infants, whereas placebo was helpful in only 26% after 7 days' treatment (Weizman et al 1993).

Commission E supports the use of lemon balm for functional gastrointestinal conditions (Blumenthal et al 2000).

HERPES SIMPLEX TYPE I — EXTERNAL USE

The topical use of lemon balm preparations for HSV infection is very popular in Europe. Results from a randomised double-blind study in 66 subjects with a history of recurrent herpes labialis (>3 episodes/year) found that standardised lemon balm ointment (700 mg crude herb per gram) applied four times daily for 5 days significantly shortened healing time, prevented infection spread and produced rapid symptom relief (Koytchev et al 1999). Decreased symptoms and increased rate of healing were also observed in another double-blind study of lemon balm cream in 116 subjects (Woelbling & Leonhardt 1994).

OTHER USES

Animal studies have identified a dose-dependent anti-ulcerogenic activity for lemon balm extract, which has been histologically confirmed. This activity is associated with a reduced acid output and an increased mucin secretion, an increase in PGE_2 release and a decrease in leukotrienes (Khayyal et al 2001).

DOSAGE RANGE

- Fresh herb: 1.5–4.5 g two–three times daily.
- Infusion: 1.5–4.5 g in 150 mL water.
- Fluid extract (1:1) (g/mL): 6–12 mL/day.
- Ointment: 700 mg/g ointment applied four times daily for herpes simplex infection.

TOXICITY

Not known

ADVERSE REACTIONS

Lemon balm is well tolerated according to one double-blind, randomised crossover study (Kennedy et al 2002).

SIGNIFICANT INTERACTIONS

Controlled clinical studies are not available, so interactions are speculative and based on evidence of activity.

BARBITURATES

Increased sedative effects: one animal study (Soulimani et al 1991) found that concomitant administration of lemon balm extract with pentobarbital produced an increased sedative effect — observe patients taking this combination.

CHOLINERGIC DRUGS

Additive effects are theoretically possible and may be beneficial — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

Hypothyroidism — one in vitro study found that an extract of *M. officinalis* inhibited both the extrathyroidal enzymic T4-5'-deiodination to T3 and the T4-5'-deiodination (Auf 'mkolk et al 1984b). Whether this has any clinical significance has yet to be determined.

PREGNANCY USE

Safety has not been scientifically established and is unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- Lemon balm has been used traditionally to treat insomnia, irritability, restlessness, anxiety and dementia. It is also used to relieve gastrointestinal symptoms associated with spasms and nervousness.
- Used topically as a cold sore treatment, it significantly reduces symptoms, shortens the healing period and prevents infection spread. It may be suitable both as an active treatment and as a preventative agent in cases of chronic recurrent herpes simplex infections.
- Lemon balm may have some anti-inflammatory and antispasmodic activity.
- The essential oil is used in aromatherapy to relieve anxiety and promote calm and a sense of wellbeing, which has been confirmed in one clinical study.
- One clinical study has found that it can modulate both mood and cognitive performance in a dose- and time-dependent manner.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

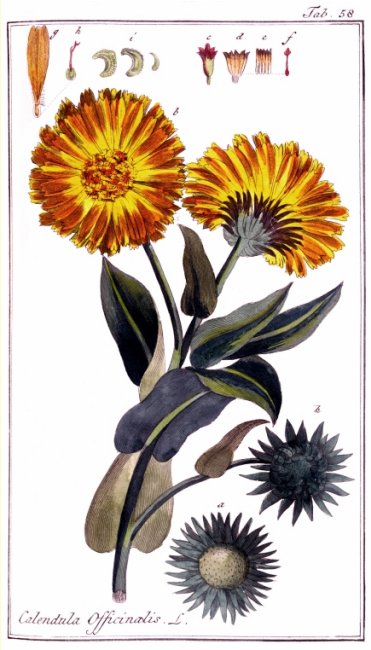
Lemon balm has several different actions and is used for a number of different conditions. Taking the herb internally may help reduce anxiety and improve mood and mental concentration. When taken together with valerian, it can relieve insomnia. It may also relieve stomach spasms associated with nervousness, or in chronic, non-specific colitis when taken as part of a specific herbal combination. Melissa cream applied four times daily to herpes simplex infections can reduce symptoms, accelerate healing and reduce the chance of the infection spreading.

When will it start to work?

Approximately 1 month's treatment with the essential oil is required for calming effects on agitation in dementia to be seen. Taken internally with valerian, effects on sleep may be seen after 9 days' use. Improved memory occurred within 2.5 hours according to one study; however, it is not known if and when effects are seen in dementia. Melissa cream has been shown to significantly reduce symptoms of herpes simplex within 2 days, when applied four times daily.

Are there any safety issues?

One study using lemon balm in tablet form found that it was well tolerated. Drug interactions are theoretically possible and this herb should be used cautiously in people with hypothyroidism.



REFERENCES

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi A, Khani M. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double-blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 74 (2003): 863-6.

Allahverdiyer A, Duran N, Ozguven M, Koltas S. Antioxidant activity of the volatile oils of Melissa officinalis L. against herpes simplex virus type-2. Phytomedicine 11 (2004): 657-61.

Aoshima H, Hamamoto K. Potentiation of GABAA receptors expressed in Xenopus oocytes by perfume and phytoncid. Biosci Biotechnol Biochem 63.4 (1999): 743-8.

Auf 'mkolk M et al. Inhibition by certain plant extracts of the binding and adenylate cyclase stimulatory effect of bovine thyrotropin in human thyroid membranes. Endocrinology 115.2 (1984a): 527-34.

Auf 'mkolk M et al. Antihormonal effects of plant extracts: iodothyronine deiodinase of rat liver is inhibited by extracts and secondary metabolites of plants. Horm Metab Res 16.4 (1984b): 188-92.

Ballard CG et al. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin Psychiatry 63.7 (2002): 553-8.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

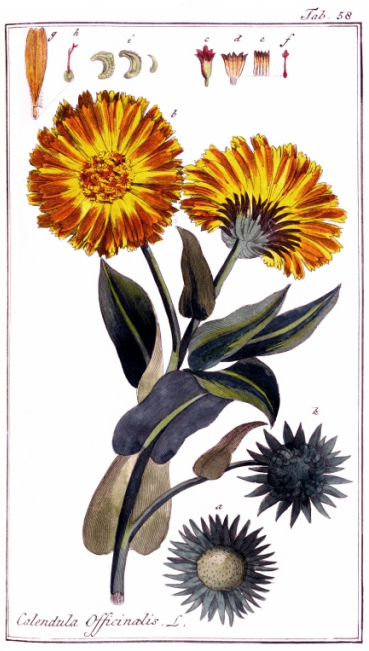
Bolkent S, Yanardag R, Kavabulut-Bulan O, Yesilyaprak B. Protective role of Melissa officinalis L extract on liver of hyperlipidemic rats: A morphological and biochemical study. J Ethnopharmacol 99 (2005): 391-8.

Cerny A, Schmid K. Tolerability and efficacy of valerian/lemon balm in healthy volunteers: a double-blind, placebo-controlled, multicentre study. Fitoterapia 70.3 (1999): 221-8.

Chakurski I et al. Treatment of chronic colitis with an herbal combination of Taraxacum officinale, Hipericum perforatum, Melissa officinalis, Calendula officinalis and Foeniculum vulgare. Vutr Boles 20.6 (1981): 51-4.
Chlabicz J, Galasinski W. The components of Melissa officinalis L. that influence protein biosynthesis in-vitro. J Pharm Pharmacol 38.11 (1986): 791-4.
Dimitrova Z et al. Antiherpes effect of Melissa officinalis L. extracts. Acta Microbiol Bulg 29 (1993): 65-72.
Dragland S et al. Several culinary and medicinal herbs are important sources of dietary antioxidants. J Nutr 133.5 (2003): 1286-90.
Dressing H et al. Insomnia: are valerian/balm combinations of equal value to benzodiazepine? Therapiewoche 42 (1992): 726-36.
Englberger W et al. Rosmarinic acid: a new inhibitor of complement C3-convertase with anti-inflammatory activity. Int J Immunopharmacol 10.6 (1988): 729-37.
Galasinski W. Eukaryotic polypeptide elongation system and its sensitivity to the inhibitory substances of plant origin. Proc Soc Exp Biol Med 212.1 (1996): 24-37.
Galasinski W et al. The substances of plant origin that inhibit protein biosynthesis. Acta Pol Pharm 53.5 (1996): 311-18.
Gazola R, Machado D, Ruggiero C, Singi G, Alexandra MM. Lippa alba, Melissa officinalis, Cymbopogon citratus: effects of the aqueous extracts on the isolated hearts of rats. Pharmacol Res 50 (2004): 477-80.
Hohmann J et al. Protective effects of the aerial parts of Salvia officinalis, Melissa officinalis and Lavandula angustifolia and their constituents against enzyme-dependent and enzyme-independent lipid peroxidation. Planta Med 65.6 (1999): 576-8.
Huss U et al. Screening of ubiquitous plant constituents for COX-2 inhibition with a scintillation proximity based assay. J Nat Prod 65.11 (2002): 1517-21.
Kelm MA et al. Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomedicine 7.1 (2000): 7-13.
Kennedy DO et al. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav 72.4 (2002): 953-64.
Kennedy DO et al. Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. Neuropsychopharmacology 28.10 (2003): 1871-81.
Kennedy DO, Little W, Scholey AB. Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm). Psychosom Med 66.4 (2004): 607-13.
Khayyal MT et al. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung 51.7 (2001): 545-53.
Koytchev R, Alken RG, Dundarov S. Balm mint extract (Lo-701) for topical treatment of recurring herpes labialis. Phytomedicine 6.4 (1999): 225-30.
Larrondo JV, Agut M, Calvo-Torras MA. Antimicrobial activity of essences from labiates. Microbios 82.332 (1995): 171-2.
Mrlianova M et al. The influence of the harvest cut height on the quality of the herbal drugs Melissae folium and Melissae herba. Planta Med 68.2 (2002): 178-80.
Peake PW et al. The inhibitory effect of rosmarinic acid on complement involves the C5 convertase. Int J Immunopharmacol 13.7 (1991): 853-7.
Sadraei H, Ghannadi A, Malekshahi K. Relaxant effect of essential oil of Melissa officinalis and citral on rat ileum contractions. Fitoterapia 74 (2003): 445-52.
Salah S, Jager A. Screening of traditionally used Lebanese herbs for neurological activities. J Ethnopharmacol 97 (2005): 145-9.
Soulimani R et al. Neurotropic action of the hydroalcoholic extract of Melissa officinalis in the mouse. Planta Med 57.2 (1991): 105-9.
Wake G et al. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J Ethnopharmacol 69.2 (2000): 105-14.

Walsh SE et al. Activity and mechanisms of action of selected biocidal agents on Gram-positive and -negative bacteria. J Appl Microbiol 94.2 (2003): 240-7.
Weizman Z et al. Efficacy of herbal tea preparation in infantile colic. J Pediatr 122.4 (1993): 650-2.
Woelbling RH, Leonhardt K. Local therapy of herpes simplex with dried extract from Melissa officinalis. Phyto medicine 1 (1994): 25-31.
Yamasaki K et al. Anti-HIV-1 activity of herbs in Labiatae. Biol Pharm Bull 21.8 (1998): 829-33.

Licorice



Historical note Licorice root has been used in Europe since prehistoric times, and its medicinal use is well documented (Fiore et al 2005). References to licorice date back to approximately 2500 BC on Assyrian clay tablets and Egyptian papyri. It has been used as both a food and a medicine since ancient times. The genus name, meaning 'sweet root', is attributed to the first century Greek physician Dioscorides. The herb is also popular in traditional Chinese and Ayurvedic medicine (Blumenthal et al 2000).

OTHER NAMES

Alcacuz, Chinese licorice, licorice root, liquorice, sweet root, gan cao, kanzo, radix glycyrrhizae, yashimadhu

BOTANICAL NAME/FAMILY

Glycyrrhiza glabra L. (family Leguminosae)

It should be differentiated from: *G. uralensis* (synonyms: Chinese licorice, gan cao, licorice root, sweet root), *G. inflata* (synonyms: gan cao, zhigancao), *G. pralidiflora*, *G. glandifera*, *G. pallida*, *G. tyica* and *G. violocea*, although some studies do not always clearly state which form is used.

PLANT PARTS USED

Root and stolon

CHEMICAL COMPONENTS

Licorice contains several triterpenoid saponins, the most studied of which is glycyrrhizin (GL, also known as glycyrrhizic acid or glycyrrhizinic acid).

Other important constituents include: flavonoids (isoflavonoids, liquiritin, isoliquiritin, liquiritigenin, formononetin, glabridin and the chalcones [isoliquiritigenin, licochalcone A and B]); sterols (beta-sitosterol); polysaccharides (arabinogalactans); coumarins (glycerin); glabrol; amines; glucose, sucrose; resin; and volatile oil (Blumenthal et al 2000).

Among different samples of *G. glabra* there may be significant differences in the content of active constituents and biological activity (Statti et al 2004). The lack of standardisation of herbs such as licorice provides a challenge for demonstrating reproducible efficacy in clinical settings.

Clinical note — Glycyrrhizin (GL), glycyrrhetinic acid (GA) and side-effects
GL is mainly absorbed after presystemic hydrolysis to glycyrrhetinic acid (GA; 18-beta-glycyrrhetinic acid (glycyrrhetic acid; the aglycone of glycyrrhizin)). On excretion via the bile it may be reconjugated to GA by commensal bowel flora and then reabsorbed (Gunnarsdottir & Johannesson 1997, Hattori et al 1983, Ploeger et al 2001). GL and GA are associated with the side-effects encountered with high-dose or long-term licorice use, such as elevated blood pressure and fluid retention. In people with prolonged gastrointestinal transit time, GA can accumulate after repeated intake. As GA is 200–1000-fold more powerful an inhibitor of 11-beta-hydroxysteroid dehydrogenase (11HSD) than GL, this may lead to more significant mineralocorticoid effects (Ploeger et al 2001). In order to minimise the risk of side-effects, practitioners often use a deglycyrrhizinised form of licorice (DGL).

While *G. glabra*, *G. uralensis* and *G. inflata* are often seen as similar remedies, there are some differences in the constituents, such as the phenolic contents (Mills & Bone 2000).

MAIN ACTIONS

MINERALOCORTICOID EFFECT

The GA constituent in licorice (and its metabolite 3-monoglucuronyl-glycyrrhetinic acid) inhibits the enzyme 11HSD (Kato et al 1995), which catalyses the conversion of cortisol into its inactive metabolite, cortisone. This results in delayed excretion and prolonged activity of cortisol. Additionally, GL and GA bind to mineralocorticoid and glucocorticoid receptors and may displace cortisol from its carrier molecule, transcortin (Nissen 2003).

Pseudohyperaldosteronism As cortisol levels rise, they stimulate mineralocorticoid receptors in the distal renal tubule (Walker et al 1992). This creates pseudohyperaldosteronism, which has the same clinical features as primary aldosteronism, including sodium retention, fluid retention and oedema, hypertension, hypokalaemia and metabolic alkalosis (Armanini et al 1996, Heldal & Midtvedt 2002, Kato et al 1995, vanUum et al 1998, Walker & Edwards 1994).

A case report suggests that the symptoms occur despite low plasma levels of aldosterone (Nobata et al 2001). Decreased plasma renin activity (Bernardi et al 1994, Epstein et al 1977) and increased cortisol levels result in vasoconstriction of vascular smooth muscle (Dobbins & Saul 2000, Walker et al 1992), which may further exacerbate the hypertensive effects. This may be of particular significance in patients with prolonged intestinal transit time where GA levels can accumulate (Ploeger et al 2001).

ANTI-INFLAMMATORY

The anti-inflammatory action of GA is largely mediated by cortisol, an endogenous hormone with anti-inflammatory action (Teelucksingh et al 1990). Several studies have found that GA inhibits the activity of 11HSD and hepatic delta-4-5-beta-steroid reductase, preventing the conversion of cortisol to its inactive metabolite, cortisone (Kageyama et al 1997, MacKenzie et al 1990, Soma et al 1994, Whorwood et al 1993). As such, cortisol activity is prolonged and levels may rise, thereby increasing its anti-inflammatory effects.

For this reason licorice has also been investigated for its ability to potentiate the effects of steroid medications (Teelucksingh et al 1990).

This mechanism alone does not fully account for the anti-inflammatory effects of licorice as oral doses of GL also appear to exert an effect in adrenalectomised rats (Gujral et al 2000). The DGL also exerts anti-inflammatory effects. Steroid-like activity has also been attributed to the liquiritin constituent (Bradley 1992) and in vitro studies of *G. inflata* reveal that the licochalcone flavonoids A and B inhibit the formation of leukotrienes B4 and C4, cyto-B-induced lysosomal enzyme, platelet-activating factor, N-formyl-methionyl-leucyl-phenylalanine and calcium ionophore A (Kimura et al 1993a). The anti-inflammatory response may also be enhanced by inhibition of the generation of reactive oxygen by neutrophils (Akamatsu et al 1991).

MUCOPROTECTIVE

Early investigation into the mucoprotective qualities of licorice led to the development of an anti-inflammatory and antiulcer medication, carbenoxolone, an ester derivative of GA, used to treat gastric and oesophageal ulcer disease. Researchers have suggested that it may exert its mucoprotective effects by increasing mucosal blood flow as well as mucus production, and by interfering with gastric prostanoid synthesis (Guslandi 1985). Animal studies indicate that licorice preparations such as DGL improve the environment in the stomach by increasing mucus production, thereby allowing for proliferation of tissue and healing to occur. DGL increases mucus production by increasing the number of fundus glands and the number of mucus-secreting cells on each gland (van Marle et al 1981).

The increase in mucus production seen with carbenoxolone and licorice appears to occur in a number of epithelial tissues other than the digestive tract. It has been reported in the lungs and also bladder, according to in vivo studies (Mooreville et al 1983), and in the trachea, accounting for its expectorant properties (Bradley 1992).

ANTI-ULCER EFFECTS

Licorice demonstrates the ability to promote mucosal repair and reduce symptoms of active ulcer (Larkworthy & Holgate 1975).

The anti-ulcer effects of licorice are due to inhibition of 15-hydroxyprostaglandin dehydrogenase, (which converts PGE_2 and F_{2alpha} to their inactive forms) and delta 13-PG reductase. Licorice-derived compounds therefore increase the local concentration of PGs that promote mucus secretion and cell proliferation in the stomach, leading to healing of ulcers (Baker 1994).

Anti-inflammatory activity (as described above) further contributes to the herb's symptom-relieving action.

ANTIVIRAL

Both oral and injectable dose forms of licorice have been tested and found to have activity against a range of viruses. This effect is mediated by the constituents GL and GA (Jeong & Kim 2002). It should be noted that current studies focus largely on GL, which is converted in the gut to GA and may not produce the same results as those demonstrated for GL in vitro.

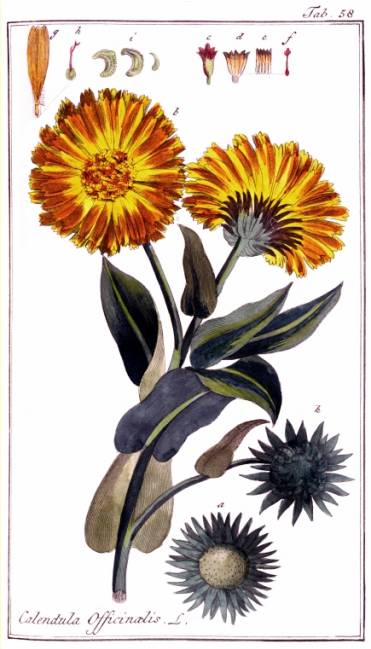
SARS-associated coronavirus In vitro studies have shown GL to inhibit SARS-CV (clinical isolates FFM-1 and FFM-2) replication by inhibiting adsorption and penetration of the virus in the early steps of the replicative cycle. Glycyrrhizin was most effective when given both during and after the adsorption period. High concentrations of GL (4000 mg/L) were found to completely block replication of the virus (Cinatl et al 2003). The ability of GL to reduce platelet accumulation in the lungs (Yu et al 2005) may also support this use and provide a possible therapeutic option for further investigation.

HIV Preliminary evidence indicates that intravenous administration of GL may reduce replication of HIV. High-dose GL (1600 mg/day) was most effective in reducing HIV type 1 p24 antigen and increasing lymphocytes (Hattori et al 1989). In vitro, GL has the potential to inhibit viral replication in cultures of peripheral blood mononuclear cells from HIV-infected patients infected with a non-syncytium-inducing variant of HIV (Sasaki et al 2002–03).

Influenza Animal studies have shown that GL offers protection against influenza virus in mice through stimulation of IFN-gamma production by T cells (Utsunomiya et al 1997).

Epstein–Barr virus In vitro studies suggest that GL may interfere with an early step of the EBV replication cycle (possibly penetration) (Lin 2003a).

Herpes simplex virus 1 In Kaposi sarcoma-associated herpes virus (KSHV), GL reduced the synthesis of a viral latency protein and induced apoptosis of infected cells



(Cohen 2005) terminating KSHV latent infection of B lymphocytes (Bradbury 2005). Early in vitro studies found that GL inactivated HSV irreversibly (Pompei et al 1979). Animal studies show that intraperitoneal administration of GL reduces HSV-1 viral replication and improves survival from herpetic encephalitis in mice (Sekizawa et al 2001). Whether GL may act against other latent herpes viruses or be suitable for clinical use against KSHV requires further elucidation (Bradbury 2005).

ANTIBACTERIAL

A number of constituents in licorice, including phenolic compounds (glicophenone and glicoisoflavanone), licochalcone A and isoflavones, were found to have antibacterial effects on MRSA and MSSA in vitro (Hatano et al 2000).

EXPECTORANT

Expectorant effects may be attributed to the ability of licorice to stimulate tracheal mucus secretion, facilitating the elimination of mucus from the respiratory tract (Bradley 1992).

ANTITUSSIVE

In animal studies licorice produces a persistent antitussive effect, which is mediated by liquiritin apioside in the earlier phase and liquiritin and liquiritigenin (a metabolite of liquiritin apioside) in the later phase (Kamei et al 2005).

ANTIOXIDANT

In vitro research has identified seven antioxidant compounds from an acetone extract of licorice: four isoflavans (hispaglabridin A, hispaglabridin B, glabridin and 4'-*O*-methylglabridin), two chalcones (isoprenylchalcone derivative and isoliquiritigenin) and an isoflavone (formononetin) (Vaya et al 1997). Isoflavones from licorice were also shown to be effective in protecting mitochondrial function against oxidative stresses (Haraguchi 2000).

Reduces lipid peroxidation Macrophage-mediated oxidation of LDL-cholesterol plays a major role in early atherogenesis. In animal models glabridin accumulates in macrophages and inhibits macrophage-mediated oxidation of LDL by up to 80% (Aviram 2004). DGL (100 mg/day for 2 weeks) was found to reduce lipid peroxidation of LDL-cholesterol after 1 week's use according to a placebo-controlled trial (Fuhrman et al 1997).

ANTICANCER EFFECTS

Licorice has demonstrated potent anti-angiogenic and antitumour activity in animal studies (Sheela et al 2005). Animal and in vitro studies have shown licorice components to be effective in reducing the occurrence and number of tumour cells in

several cancer models (Shibata 1994, Wang & Mukhtar 1994, Wang & Nixon 2001), inducing apoptosis and potentiating the effect of paclitaxel and vinblastine chemotherapy (Rafi et al 2000). In vitro research reveals that chalcone and isoliquiritigenin significantly inhibit the proliferation of prostate cancer cell lines in a dose- and time-dependent manner and that beta-hydroxy-DHP inhibits breast and prostate tumour cells (Kanazawa et al 2003, Maggiolini et al 2002, Rafi et al 2002). Isoliquiritigenin has also been shown to significantly inhibit the proliferation of lung and colon cancer cells, restrain cell cycle progression and induce apoptosis (Ii et al 2004, Takahashi et al 2004).

Although the exact mechanism of action is still being determined, a 2001 review indicates that licorice and its derivatives may protect against carcinogen-induced DNA damage and that GA is an inhibitor of lipo-oxygenase and cyclo-oxygenase, inhibits protein kinase C, and down-regulates the epidermal growth factor receptor (Wang & Nixon 2001).

COGNITIVE FUNCTION

Glycyrrhiza glabra has shown promise as a memory-enhancing agent in both exteroceptive and interoceptive behavioural models of memory in mice. The effect is possibly due to facilitation of cholinergic transmission in the mouse brain (Dhingra et al 2004, Parle et al 2004). Effects on humans have yet to be demonstrated; however, a clinical trial of 170 elderly subjects is currently planned (Bielenberg 2005).

HEPATOPROTECTIVE EFFECTS

Animal studies demonstrate that licorice protects hepatocytes by inhibiting experimentally induced lipid peroxidation (Rajesh & Latha 2004). In vitro studies have shown hepatoprotective effects of GL against aflatoxin B1-induced cytotoxicity in human hepatoma cells (Chan et al 2003) and animal studies have shown GA exerts hepatoprotective effects against carbon tetrachloride-induced liver injury (Jeong et al 2002).

Several mechanisms appear to be responsible for the hepatoprotective effect. Glycyrrhizic acid enhances the detoxifying activity of the liver enzyme CYP1A1 and glutathione S-transferase and protects against oxidative stress, when induced by aflatoxin (Chan et al 2003).

Animal studies have found that GA inhibits expression of the liver enzyme CYP2E1. Once again, antioxidant mechanisms appear to be involved, as GA prevented glutathione depletion, an increase in ALT, AST activity, and hepatic lipid peroxidation in a dose-dependent manner when carbon tetrachloride exposure occurred (Jeong et

al 2002). In addition isoliquiritigenin may stimulate the proliferation of human hepatocytes according to in vitro studies (De Bartolo et al 2005).

ANTIPLATELET EFFECT

Isoliquiritigenin purified from licorice has been shown to inhibit platelet aggregation in vitro and in vivo (Francischetti et al 1997, Kimura et al 1993a, Tawata et al 1992). Whether the effect is clinically significant for licorice remains to be determined. New data indicates that GL is an effective thrombin inhibitor in vivo (Mendes–Silva et al 2003).

OTHER ACTIONS

SEX HORMONES

Testosterone Whether licorice consumption affects testosterone levels is still unknown, as conflicting results have been obtained from clinical studies. Armanini et al have conducted a series of trials investigating the effects of licorice on testosterone levels in males with mixed results (Armanini et al 1999, 2003a).

One study showed that licorice (7 g/day equivalent to 0.5 g GA) was able to reversibly reduce testosterone levels within 7 days, by inhibiting 17,20-lyase (involved in the conversion of 17-hydroxyprogesterone to androstenedione) and 17-beta-hydroxysteroid dehydrogenase (involved in the conversion of androstenedione to testosterone) (Armanini et al 1999). Another study twice attempted to replicate these results, but was unable to detect an effect on testosterone levels in either study; the authors suggest that inappropriate use of statistical tests in the first study may explain the varying results (Josephs et al 2001).

More clinically promising are the results from a small trial of nine healthy women (22–26 years) in the luteal phase of their menstrual cycle. The women received 3.5 g licorice (containing 7.6% w/w of GL) daily for two cycles. Total serum testosterone decreased from 27.8 (±8.2) to 19.0 (±9.4) ng/dL in the first month and to 17(±6.4) ng/dL in the second month of therapy (Armanini et al 2004). Further larger scale trials are required to confirm these effects in women with conditions of elevated testosterone such as hirsutism and PCOS.

Oestrogen Licorice contains isoflavones, including licochalcone-A, which are also known as 'phyto-oestrogens' because they act as partial oestrogen agonists in the body (Setchell & Cassidy 1999). Additionally, in vitro studies suggest that stimulation of aromatase activity promotes oestradiol synthesis (Takeuchi et al 1991).

Liquiritigenin and isoliquiritigenin have displayed oestrogenic affinity to sex hormone-binding globulin and oestrogen receptors in vitro (Hillerns et al 2005) and

glabridin and glabrene have both demonstrated oestrogen-like activities similar to oestradiol-17(beta) in animal studies (Somjen et al 2004a).

In vitro studies also suggest the potential for glabridin to enhance osteoblast function (Choi 2005). As a result glabridin has been proposed as a possible therapeutic aid in the prevention of osteoporosis and inflammatory bone diseases (Choi 2005), as well as cardiovascular diseases and bone disorders, in postmenopausal women (Somjen et al 2004a, b).

IMMUNOMODULATION

Although immunostimulating effects have been observed in experimental models (Lin et al 1996), elevated cortisol levels, which are also induced by licorice, may theoretically reduce this effect (Padgett & Glaser 2003).

INHIBITION OF ALDOLASE REDUCTASE

In vitro studies show that licorice may suppress sorbitol accumulation in red blood cells by inhibiting aldolase reductase (Zhou & Zhang 1990). The isoliquiritigenin component appears to be responsible (Aida et al 1990a). This may have positive implications in diabetes.

ANTIDEPRESSANT (SEROTONIN REUPTAKE INHIBITION)

Several flavonoid constituents in licorice (glabridin 60%, 4'-*O*-methylglabridin 53% and glabrene 47%) inhibit serotonin reuptake in a dose-dependent manner, according to in vitro research. An antidepressant activity could theoretically result, although this remains to be tested clinically (Ofir et al 2003).

CLINICAL USE

PEPTIC ULCER AND DYSPEPSIA

The anti-inflammatory, mucoprotective and anti-ulcer activities of licorice make it an attractive treatment for peptic ulcer. While these effects have been attributed to the GL and GA constituents, the DGL, which contains <3% GL, has also been investigated and appears to produce the most promising results when used long term (Bardhan et al 1978, Larkworthy & Holgate 1975). DGL also promotes differentiation of undifferentiated cells to mucous cells and stimulates mucus production and secretion (van Marle et al 1981).

In an uncontrolled trial of 32 patients with chronic duodenal ulcer, 3800 mg/day of DGL (in five divided doses) produced signs of healing in all cases and total restoration of mucosa in a majority of subjects. Although treatment continued for 24 weeks, considerable improvement was seen in 56% of patients by week 12 and in

78% by week 16 (Larkworthy & Holgate 1975). A shorter 4-week trial of 96 patients with gastric ulcer failed to produce the same positive results (Bardhan et al 1978).

DGL plus antacid (Caved-S; 2 tablets chewed three times daily between meals) was as effective as cimetidine (200 mg three times daily plus 400 mg at night) after 6 weeks, according to one randomised single-blind trial of 100 volunteers with peptic ulcer. The two treatments continued to produce similar results after 12 weeks and recurrence rates after both medications were reduced were also similar (Morgan et al 1982).

Commission E approves the use of licorice for the treatment of gastric and duodenal ulcers (Blumenthal et al 2000).

DERMATITIS

The anti-inflammatory effect induced by GA provides a theoretical basis for its use as a topical anti-inflammatory agent (much like hydrocortisone) in the treatment of dermatitis.

In practice, GA has been used to potentiate the effects of weak steroids (such as hydrocortisone) in order to increase pharmacological effects without the need for stronger corticosteroids (Teelucksingh et al 1990). It is assumed that increasing corticosteroid activity in this way will not attract an increase in adverse effects; however, no studies have yet confirmed this.

An early study comparing the effects of hydrocortisone- and GA-containing ointments in dermatitis found that hydrocortisone was usually superior in acute and infantile eczemas, whereas GA was superior for chronic and subacute conditions (Evans 1958).

It should be noted that GA is many times more powerful an inhibitor of 11HSD than GL and therefore should theoretically induce far stronger anti-inflammatory effects. GA is not present in licorice but is produced in the gastrointestinal tract from GL; therefore, it is uncertain whether topical preparations containing pure licorice are likely to produce significant anti-inflammatory effects.

VIRAL INFECTIONS

The antiviral activity demonstrated in animal and in vitro trials provide a theoretical basis for its use in the treatment of SARS-associated CV (Cinatl et al 2003), HIV (Hattori et al 1989, Sasaki et al 2002–03), influenza (Utsunomiya et al 1997), EBV (Lin 2003a) and HSV-1 (Pompei et al 1979, Sekizawa et al 2001). Until controlled studies are available, the clinical effectiveness of this treatment remains unknown.

RESPIRATORY TRACT INFECTIONS

Licorice increases mucous production within the respiratory tract and exerts an expectorant action. When combined with its anti-inflammatory, antiviral and possible immune-enhancing effects, it is a popular treatment for upper and lower respiratory tract infections. In practice, it is often used to treat coughs (especially productive types) and bronchitis (Bradley 1992).

Commission E approves the use of licorice for catarrhs of the upper respiratory tract (Blumenthal et al 2000).

CHRONIC STRESS

Traditionally, licorice is viewed as an 'adrenal tonic', most likely due to its ability to slow cortisol breakdown. It may be of benefit in patients experiencing allostatic load due to chronic stress and who are therefore unable to mount a healthy stress response. This is also known as adrenocorticoid insufficiency. Currently, controlled trials are not available to determine its effectiveness in this situation.

Whether this effect is desirable in patients without adrenocorticoid insufficiency and for whom increased cortisol levels may prove problematic is open to conjecture. Chronically high cortisol levels have been associated with desensitisation of the HPA axis, insulin resistance, depression and immunosuppression (Blackburn-Munroe 2001, Jessop 1999, Mitchell & Mitchell 2003). In the initial stages of stress, increased cortisol levels trigger negative feedback mechanisms to keep stress under control and, therefore, short-term use may be warranted but is unlikely to be beneficial unless some adrenocorticoid insufficiency exists.

(For more information see 'Clinical note — Allostasis and adaptation to stress' in the Siberian ginseng monograph.)

OTHER USES

Licorice has also been used traditionally as a sweetener and aromatic flavouring agent.

Although controlled trials are lacking, licorice is also used for a number of other conditions, largely based on evidence of pharmacological activity.

CHRONIC FATIGUE SYNDROME

The ability of licorice to slow cortisol catabolism may provide a theoretical basis for its use in cases of CFS accompanied by low cortisol levels. A case report exists of a patient experiencing improved physical and mental stamina and recovery from CFS following use of licorice dissolved in milk (2.5 g/500 mL/day) (Baschetti 1995, 1996).

POLYCYSTIC OVARY DISEASE

The possibility that licorice may lower testosterone levels in women provides a theoretical basis for its use in PCOS (Armanini et al 2004). While trials using licorice as a stand-alone treatment are lacking, studies of licorice in combination with other herbal medicines such as peony have produced promising results, showing reductions in LH:FSH ratio, ovarian testosterone production and improvements in ovulation (Takahashi & Kitao 1994, Takahashi et al 1988).

PREVENTING DIABETIC COMPLICATIONS

In diabetic patients with neuropathy, retinopathy or nephropathy, sorbitol:glucose ratios are significantly higher than in those without these complications and ratios increase as complications become more severe (Aida et al 1990b). As licorice and its component isoliquiritigenin have been shown to inhibit aldolase reductase and suppress sorbitol accumulation in red blood cells in vitro (Aida et al 1990b, Zhou & Zhang 1990), a theoretical basis exists for its use in the prevention of diabetic complications.

MENOPAUSE

Inhibition of serotonin reuptake and possible oestrogenic activity provide a theoretical basis for its use in pre- and postmenopausal women with mild to moderate depression (Ofir et al 2003, Takeuchi et al 1991).

Constituents in licorice may bind to oestrogen receptors, enhance osteoblast function and attenuate vascular injury and atherosclerosis (Choi 2005, Somjen et al 2004a, b) suggesting a possible role in the prevention of bone disorders and cardiovascular diseases in postmenopausal women.

WEIGHT LOSS

The action of GA in blocking 11HSD type 1 at the level of fat cells may help to explain preliminary evidence suggesting an ability to reduce body fat mass and the thickness of thigh fat (Armanini et al 2003b, 2005).

ADDISON'S DISEASE

The ability of licorice to reduce cortisol breakdown provides a theoretical basis for its use in Addison's disease, either as a stand-alone treatment, when adrenocortical function is not severely impaired, or as an adjunct to cortisone therapy. While studies in the 1950s confirm this use (Borst et al 1953, Calvert 1954, Pelser et al 1953), recent studies are not available. A case report exists of an 11-year-old boy with hypoparathyroidism and Addison's disease developing hypermineralocorticoidism following excessive intake of licorice (300–400 g/day, equiv. 600–800 mg GL) concurrently with hydrocortisone and 9-alpha-fluorocortisol.

Pseudohyperaldosteronism persisted after treatment with 9-alpha-fluorocortisol was withdrawn and hydrocortisone was reduced; however, symptoms only diminished after the complete withdrawal of licorice. It was suggested that inhibition of 11HSD by licorice was responsible due to increased levels of free cortisol (Doeker & Andler 1999).

DOSAGE RANGE

- Fluid extract (1:1): 2–4 mL three times daily or 15–40 mL/week (Australian manufacturer recommendations).
- Root: 5–15 g/day (equivalent to 200–600 mg of glycyrrhizin).
- Tea: pour 150 mL boiling water over 1 teaspoon (2–4 g) licorice root, simmer for 5 minutes and filter through a tea strainer after cooling.
- Chronic gastritis: 1 cup of licorice tea after each meal.

ACCORDING TO CLINICAL STUDIES

- Chronic duodenal ulcers: 3800 mg/day of DGL (in five divided doses) before meals and at bedtime.
- Ideally, licorice extracts should contain >30 mg/mL GL.

ADVERSE REACTIONS

Many of the adverse effects attributed to licorice are due to GA at doses above 100–400 mg/day. For this reason, the DGL may be safer and more appropriate in cases where GL or GA are not required for efficacy.

Side-effects may be more pronounced in people with essential hypertension who appear to be more sensitive to the inhibition of 11HSD by licorice than normotensive subjects (Sigurjonsdottir et al 2003).

- Hypercortisolism and pseudohyperaldosteronism — associated with sodium retention, potassium loss and suppression of the renin–angiotensin–aldosterone system and presenting as hypertension, fluid retention, breathlessness, hypernatraemia and hypokalaemia (Bernardi et al 1994, Blachley & Knochel 1980, Dellow et al 1999, Kageyama et al 1997, Wash & Bernard 1975).
- Hypokalaemia — may present as hypotonia and flaccid paralysis, peripheral oedema, polyuria, proximal myopathy, lethargy, paraesthesiae, muscle cramps, headaches, tetany, breathlessness and hypertension (deKlerk et al 1997, Eriksson et al 1999). In practice, licorice is often mixed with the potassium-rich herb dandelion leaf, which also has mild diuretic effects.
- Hypokalaemic paralysis — although rare, some cases have been reported as a result of chronic licorice use (Corsi et al 1983, Lin et al 2003b, Shintani et al 1992, vanden-Bosch et al 2005).

- Rhabdomyolysis — a number of cases are reported in the scientific literature (Firenzuoli & Gori 2002, van-den-Bosch et al 2005) as a result of severe hypokalaemia.
- Dropped head syndrome — a case report exists of DHS (isolated weakness of the extensor muscles of the neck) due to licorice-induced hypokalemia (Yoshida & Takayama 2003).
- Hypertension encephalopathy may occur even at low doses in susceptible patients with 11-beta-HSD deficiency (Russo et al 2000).
- Reduced 11-beta-HSD activity may have a role in increased sodium retention in pre-eclampsia, renal disease and liver cirrhosis. Reduced placental levels may explain the link between reduced birth weight and adult hypertension (the Barker hypothesis) (Quinkler & Stewart 2003).
- Juvenile hypertension — inhibition of 11HSD may also contribute to a rare form of juvenile hypertension (Chamberlain & Abolnik 1997, White et al 1997).
- Visual disturbance — ingestion of high doses of licorice (110–900 g) has been reported to elicit symptoms of visual disturbance in a case series of five patients. This may be attributed to the possible ability of licorice to 'stimulate retinal and occipital vasospasm and vasospasm of vessels supplying the optic nerve' (Dobbins & Saul 2000).

SIGNIFICANT INTERACTIONS

Controlled trials exist that have identified drug interactions. However, in most cases, the interactions are based on evidence of pharmacological activity, case reports or theoretical reasoning. The DGL form is considered safer and less likely to result in drug interactions.

ANTICOAGULANTS

Isoliquiritigenin inhibits platelet aggregation and GL inhibits prothrombin according to in vitro and in vivo tests (Francischetti et al 1997, Kimura et al 1993a, Tawata et al 1992). Whether the effect is clinically significant for licorice remains to be determined — use high doses with caution.

ANTIHYPERTENSIVES

High-dose GL taken long term can lead to increased blood pressure, thereby reducing drug efficacy. Caution — monitor blood pressure when high-dose licorice preparations are taken for longer than 2 weeks.

CHEMOTHERAPY (PACLITAXEL AND VINBLASTINE)
A constituent of licorice has demonstrated significant potentiation of paclitaxel and vinblastine chemotherapy in vitro (Rafi et al 2000). Observe — beneficial interaction is theoretically possible under medical supervision.

CORTICOSTEROIDS
Concurrent use of licorice preparations potentiates the effects of topical and oral corticosteroids (e.g. prednisolone). Some practitioners employ licorice to minimise requirements for or aid in withdrawal from corticosteroid medications. Beneficial interaction is possible under professional supervision, but patients should be monitored closely for corticosteroid excess (Chen et al 1991, Homma et al 1994).

DIGOXIN
Hypokalaemia increases sensitivity to cardiac glycoside drugs, therefore increased digoxin toxicity is possible when licorice is used in high doses for more than 2 weeks. A case report exists of congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative (Harada et al 2002). Avoid long-term use of high-dose licorice preparations and digoxin concurrently.

ORAL CONTRACEPTIVE PILL
An increased risk of side-effects such as hypokalaemia, fluid retention and elevated blood pressure due to increased mineralocorticoid effect exists. This has been demonstrated in case reports (Bernardi et al 1994, deKlerk et al 1997) — use this combination with caution when licorice is used in high dose or for more than 2 weeks and observe patients closely.

DIURETICS (INCLUDING LOOP, THIAZIDE AND POTASSIUM-SPARING)
Case reports exist in which patients experience hypokalaemia and hypertension with concomitant use of licorice and diuretics (deKlerk et al 1997, Farese et al 1991, Folkerson et al 1996) due to increased potassium excretion. Avoid long-term use of licorice and diuretics concurrently unless under professional supervision. Monitor potassium levels.

TESTOSTERONE
Licorice may decrease testosterone levels, although clinical tests have produced conflicting results (Armanini et al 1999, 2003a, 2004, Sakamoto & Wakabayashi 1988, Takeuchi et al 1991). Observe and monitor patients for reduced testosterone effects.

DICLOFENAC SODIUM (NSAID)

In vitro studies have shown that the addition of GL enhanced the topical absorption of diclofenac sodium (Nokhodchi et al 2002), which may be a beneficial interaction.

POTASSIUM

Licorice may reduce the effect of potassium supplementation. A case report exists of a 69-year-old female developing hypokalaemia while taking potassium supplements and a mouth freshener containing licorice concurrently. The daily intake of GA was estimated at 6–10 mg/day (Kageyama et al 1997). In many cases potassium supplementation may be beneficial in reducing the hypokalaemic side-effects of licorice.

DRUGS METABOLISED BY LIVER ENZYMES CYP3A4, 2B6, 2C9, 2E1 OR 1A1

Licorice inhibits CYP3A4 in vitro (Budzinski et al 2000), the glabridin constituent inhibits CYP2B6, 2C9 and 3A4 in vitro (Kent et al 2002), GA inhibits expression of CYP2E1 in animal studies (Jeong et al 2002) and GL enhances the detoxifying activity of CYP1A1 (Chan et al 2003). Until testing in humans can establish whether the effects are clinically significant and relevant to licorice in therapeutic doses, caution is advised if licorice is administered with drugs chiefly metabolised by these enzymes. (See chapter on Interactions for more information.)

CONTRAINDICATIONS AND PRECAUTIONS

Licorice should be used with caution in people with hypertension (or a genetic predisposition to hypertension) or fluid retention, and is contraindicated in hypotonia, severe renal insufficiency, hypokalaemia, liver cirrhosis and cholestatic liver disease (Blumenthal et al 2000). The effects are likely to be dose-dependent and more likely in people with essential hypertension with a particular tendency to 11HSD inhibition by licorice (Sigurjonsdottir et al 2001, 2003). It is also contraindicated in people with a deficiency in 11HSD (Russo et al 2000).

Long-term use (>2 weeks) at therapeutic doses should be monitored closely due to the potential side-effects. Additionally, a high-potassium low-sodium diet should be consumed during treatment (Bradley 1992, McGuffin et al 1997).

As licorice may questionably reduce testosterone levels in men, it should be used with caution in men with a history of impotence, infertility or decreased libido (Armanini et al 1999, Zava et al 1998).

PREGNANCY USE

Licorice is contraindicated in pregnancy. A Finnish trial found that high consumption of licorice during pregnancy increased the likelihood of early delivery but did not significantly affect birth weight or maternal blood pressure (Strandberg et al 2001).

PRACTICE POINTS/PATIENT COUNSELLING

- Licorice has been used as a food, flavouring agent and medicine since ancient times.
- It exhibits mineralocorticoid, anti-inflammatory, antioxidant, mucoprotective and ulcer-healing activity in humans. Antiviral, antibacterial, antitumour, expectorant and hepatoprotective effects have also been demonstrated in animal or test tube studies. Significant effects on oestrogen and testosterone levels remain to be established in controlled trials as evidence is inconsistent.
- Licorice is a popular treatment for respiratory tract infections, gastrointestinal ulcers and dyspepsia. It is also used to treat chronic stress and numerous other conditions, largely based on evidence of pharmacological activity.
- Glycyrrhetinic acid has been used topically as an anti-inflammatory agent and also together with cortisone preparations to increase effects.
- High-dose licorice (>100 mg glycyrrhizin) used for more than 2 weeks can induce hypokalaemia and pseudoaldosteronism in susceptible individuals. As such, it should be used with caution and under professional supervision. Additionally, it interacts with numerous medicines. The DGL form is considered safer.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Licorice has many effects in the body, the most well-established ones being reducing inflammation; enhancing healing of peptic ulcers; and treating infections such as bronchitis and cough.

When will it start to work?

Beneficial effects in peptic ulcer occur within 6–12 weeks, although DGL is usually used to avoid side-effects. Symptoms of dyspepsia should respond within the first few doses. Effects in bronchitis will vary between individuals.

Are there any safety issues?

Used in high doses for more than 2 weeks, licorice can induce several side-effects such as raised blood pressure and fluid retention and may interact with a number of drugs. The DGL form is considered safer.

REFERENCES

Aida K et al. Isoliquiritigenin: a new aldose reductase inhibitor from glycyrrhizae radix. Planta Med 56 (1990a): 254-8.

Aida K, Tawata M, Shindo H, Onaya T. Clinical significance of erythrocyte sorbitol-blood glucose ratios in type II diabetes mellitus. Diabetes Care 13(5) (1990b): 461-7.

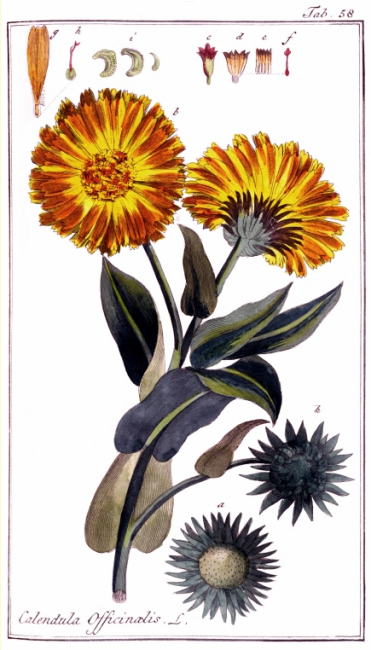
Akamatsu H, Komura J, Aada Y. Mechanism of anti-inflammatory action of glycyrrhizin: effect on neutrophil functions including reactive oxygen species generation. Planta Med 57 (1991): 119-21.

Armanini D et al. Further studies on the mechanism of the mineralocorticoid action of licorice in humans. J Endocrinol Invest 19 (1996): 624-9.

Armanini D, Bonanni G, Palermo M. Reduction of serum testosterone in men by licorice. N Engl J Med 341(15) (1999): 1158.
Armanini D, Bonanni G, Mattarello MJ, Fiore C, Sartorato P, Palermo M. Licorice consumption and serum testosterone in healthy man. Exp Clin Endocrinol Diabetes 111(6) (2003a): 341-3.
Armanini D et al. Effect of licorice on the reduction of body fat mass in healthy subjects. J Endocrinol Invest 26(7) (2003b): 646-50.
Armanini D et al. Licorice reduces serum testosterone in healthy women. Steroids 69(11-12) (2004): 763-6.
Armanini D, Nacamulli D, Francini-Pesenti F, Battagin G, Ragazzi E, Fiore C. Glycyrrhetinic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. Steroids 70(8) (2005): 538-42.
Aviram M. Flavonoids-rich nutrients with potent antioxidant activity prevent atherosclerosis development: the licorice example. Int Congr Ser 1262 (2004): 320-7.
Baker ME. Licorice and enzymes other than 11 beta-hydroxysteroid dehydrogenase: an evolutionary perspective. Steroids 59(2) (1994): 136-41.
Bardhan KD et al. Clinical trial of deglycyrrhizinised licorice in gastric ulcer. Gut 19 (1978): 779-82.
Baschetti R. Chronic fatigue syndrome and licorice (Letter). NZ Med J 108 (1995): 156-7.
Baschetti R. Chronic fatigue syndrome and neurally mediated hypotension (Letter). JAMA 275 (1996): 359.
Bernardi M et al. Effects of prolonged ingestion of graded doses of licorice by healthy volunteers. Life Sci 55(11) (1994): 863-72.
Bielenberg J. Dementias: New perspectives of therapy with constituents of liquorice root. Arzt Naturheilverfahr Regul Med 46(3) (2005): 155-60.
Blachley JD, Knochel JP. Tobacco chewer's hypokalemia: licorice revisited. N Engl J Med 302(14) (1980): 784-5.
Blackburn-Munroe GRE. Chronic pain, chronic stress and depression: Coincidence or consequence? J Neuroendocrinol 13 (2001): 1009-23.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 237, 2000.
Borst JG, Ten Holt SP, De Vries LA, Molhuysen JA. Synergistic action of liquorice and cortisone in Addisons and Simmonds' disease. Lancet 1(14) (1953): 657-63.
Bradbury J. Liquorice compound beats latent herpesvirus. Lancet Inf Dis 5(4) (2005): 201.
Bradley PR (ed.). British Herbal Compendium, Vol 1: A Handbook of Scientific Information on Widely Used Plant Drugs. Bournemouth, Dorset, UK: British Herbal Medicine Association, 1992.
Budzinski JW et al. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7 (2000): 273-82.
Calvert RJ. Liquorice extract in Addison's disease; successful, long-term therapy. Lancet 266(6816) (1954): 805-7.
Chamberlain J, Abolnik I. Pulmonary edema following a licorice binge (Letter). West J Med 167(3) (1997): 184-5.
Chan HT, Chan C, Ho JW. Inhibition of glycyrrhizic acid on aflatoxin B1-induced cytotoxicity in hepatoma cells. Toxicology 188(2-3) (2003): 211-17.
Chen MF et al. Effect of oral administration of glycyrrhizin on the pharmacokinetics of prednisolone. Endocrinol Jpn 38(2) (1991): 167-74.
Choi E-M. The licorice root derived isoflavan glabridin increases the function of osteoblastic MC3T3-E1 cells. Biochem Pharmacol 70(3) (2005): 363-8.
Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of licorice roots, and replication of SARS-associated coronavirus. (Research letters: possible treatment for severe acute respiratory syndrome.) Lancet 361 (2003): 2045-6.
Cohen JI. Licking latency with licorice. J Clin Invest 115(3) (2005): 591-3.
Corsi FM et al. Acute hypokalemic myopathy due to chronic licorice ingestion: report of a case. Ital J Neurol Sci 4(4) (1983): 493-7.

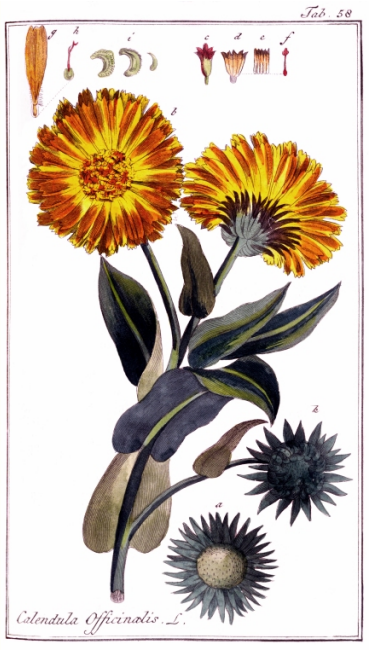
De Bartolo L et al. Effect of isoliquiritigenin on viability and differentiated functions of human hepatocytes maintained on PEEK-WC-polyurethane membranes. Biomaterials 26(33) (2005): 6625-34.
deKlerk G, Neiuwenhuis M, Beutler J. Hypokalemia and hypertension associated with use of liquorice flavoured chewing gum. BMJ 314(7082) (1997): 731-2.
Dellow EL, Unwin RJ, Honour JW. Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. Nephrol Dial Transplant 14 (1999): 218-20.
Dhingra D, Parle M, Kulkarni SK. Memory enhancing activity of Glycyrrhiza glabra in mice. J Ethnopharmacol 91(2-3) (2004): 361-5.
Dobbins KRB, Saul RF. Transient visual loss after licorice ingestion. J Neuroophthalmol 20(1) (2000): 38-41.
Doeker BM, Andler W. Liquorice, growth retardation and Addison's disease. Horm Res 52(5) (1999): 253-5.
Epstein MT, Espiner EA, Donald RA, Hughes H. Effect of eating licorice on the renin-angiotensin aldosterone axis in normal subjects. BMJ 1(6059) (1977): 488-90.
Eriksson JW, Carlberg B, Hillorn V. Life-threatening ventricular tachycardia due to liquorice-induced hypokalemia; J Intern Med 245(3) (1999): 307-10.
Evans FQ. The rational use of glycyrrhetinic acid in dermatology. Br J Clin Pract 12(4) (1958): 269-79.
Farese RV Jr et al. Licorice-induced hypermineralcorticoidism. N Engl J Med 325 (1991): 1223-7.
Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D. A history of the therapeutic use of liquorice in Europe. J Ethnopharmacol 99(3) (2005): 317-24.
Firenzuoli F, Gori L. Rhabdomyolysis due to licorice ingestion. Recent Prog Med 93(9) (2002): 482-3 (in Italian).
Folkerson L, Knudsen NA, Teglbjaerg PS. Licorice. A basis for precautions one more time! Ugeskr Laeger 158(51) (1996): 7420-1.
Francischetti et al. Identification of glycyrrhizin as a thrombin inhibitor. Biochem Biophys Res Commun 235 (1997): 259-63.
Fuhrman B et al. Licorice extract and its major polyphenol glabridin protect low-density lipoprotein against lipid peroxidation: in vitro and ex vivo studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 66 (1997): 267-75.
Gujral ML et al. Ind J Med Sci 1961; 15: 624-9; as cited in: Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Gunnarsdottir S, Johannesson T. Glycyrrhetic acid in human blood after ingestion of glycyrrhizic acid in licorice. Pharmacol Toxicol 81 (1997): 300-2.
Guslandi M. Ulcer-healing drugs and endogenous prostaglandins. Int J Clin Pharmacol Ther Toxicol 23 (1985): 398-402.
Harada T, Ohtaki E, Misu K, Sumiyoshi T, Hosoda S. Congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative. Cardiology 98(4) (2002): 218.
Haraguchi H, Yoshida N, Ishikawa H, Tamura Y, Mizutani K, Kinoshita T. Protection of mitochondrial functions against oxidative stresses by isoflavans from Glycyrrhiza glabra; J Pharm Pharmacol 52(2) (2000): 219-23.
Hatano T et al. Phenolic constituents of licorice. VII: Structures of glicophenone and glicoisoflavone, and effects of licorice phenolics on methicillin-resistant Staphylococcus aureus. Chem Pharm Bull (Tokyo) 48(9) (2000): 1286-92.
Hattori M et al. Metabolism of glycyrrhizin by human intestinal flora; Planta Med 48 (1983): 38-42.
Hattori T et al. Preliminary evidence for inhibitory effect of glycyrrhizin on HIV replication in patients with AIDS. Antiviral Res 11 (1989): 255-62.
Heldal K, Midtvedt K. Licorice: not just candy. Tidsskr Nor Laegeforen 122(8) (2002): 774-6 (in Norwegian).
Hillerns PI, Zu Y, Fu YJ, Wink M. Binding of phytoestrogens to rat uterine estrogen receptors and human sex hormone-binding globulins. Z Naturforsch (C) 60(7-8) (2005): 649-56.
Homma M et al. A novel 11-beta-hydroxysteroid dehydrogenase inhibitor contained in Saiboku-To, a herbal remedy for steroid-dependent bronchial asthma; J Pharm Pharmacol 46(4) (1994): 305-9.

Ii T et al. Induction of cell cycle arrest and p21CIP1/WAF1 expression in human lung cancer cells by isoliquiritigenin. Cancer Lett 207(1) (2004): 27-35.
Jeong HG, Kim JY. Induction of inducible nitric oxide synthase expression by 18b-glycyrrhetinic acid in macrophages. FEBS Lett 513 (2002): 208-12.
Jeong HG et al. Hepatoprotective effects of 18beta-glycyrrhetinic acid on carbon tetrachloride-induced liver injury: inhibition of cytochrome P450 2E1 expression. Pharmacol Res 46(3) (2002): 221-7.
Jessop DS. Stimulatory and inhibitory regulators of the hypothalamo-pituitary-adrenocortical axis. Baillieres Clin Endocrinol Metab 13 (4) (1999): 491-501.
Josephs RA, Guinn JS, Harper ML, Askari F. Licorice consumption and salivary testosterone concentrations. Lancet 358(9293) (2001): 1613-14.
Kageyama K et al. A case of pseudoaldosteronism induced by a mouth refresher containing licorice. Endocr J 44(4) (1997): 631-2.
Kamei J et al. Pharmacokinetic and pharmacodynamic profiles of the antitussive principles of Glycyrrhizae radix (licorice), a main component of the Kampo preparation Bakumondo-to (Mai-men-dong-tang). Eur J Pharmacol 507(1-3) (2005): 163-8.
Kanazawa M et al. Isoliquiritigenin inhibits the growth of prostate cancer. Eur Urol 43(5) (2003): 580-6.
Kato H et al. 3-Monoglucuronyl-glycyrrhetinic acid is a major metabolite that causes licorice-induced pseudoaldosteronism. J Clin Endocrinol Metab 80(6) (1995): 1929-33.
Kent UM, Aviram M, Rosenblat M, Hollenberg PF. The licorice root derived isoflavan glabridin inhibits the activities of human cytochrome P450S 3A4, 2B6, and 2C9. Drug Metab Dispos 30(6) (2002): 709-15.
Kimura Y, Okuda H, Okuda T. Effects of flavonoids isolated from licorice roots (Glycyrrhiza inflata bat) on arachidonic acid metabolism and aggregation in human platelets. Phytother Res 7 (1993a): 341-7.
Larkworthy W, Holgate PF. Deglycyrrizinised licorice in the treatment of chronic duodenal ulcer. Practitioner 215 (1290) (1975): 787-92.
Lin IH et al. Chin Med J (Engl) 109 (2) (1996): 138-42; as cited in: Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Lin JC. Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication in vitro. Antiviral Res 59(1) (2003): 41-7.
Lin SH, Yang SS, Chau T, Halperin ML. An unusual cause of hypokalemic paralysis: chronic licorice ingestion. Am J Med Sci 325(3) (2003): 153-6.
MacKenzie MA, Hoefnagels WH, Jansen RW, Benraad TJ, Kloppenborg PW. The influence of glycyrrhetinic acid on plasma cortisol and cortisone in healthy young volunteers. J Clin Endocrinol Metab 70(6) (1990): 1637-43.
Maggiolini M et al. Estrogenic and antiproliferative activities of isoliquiritigenin in MCF7 breast cancer cells. J Steroid Biochem Mol Biol 82(4-5) (2002): 315-22.
McGuffin M et al (eds). American Herbal Products Association's Botanical Safety Handbook. Boca Raton, FL: CRC Press, 1997; as cited in Micromedex. Thomson 2003. www.micromedex.com
Mendes–Silva W, Assafim M, Ruta B, Monteiro RQ, Guimaraes JA, Zingali RB. Antithrombotic effect of Glycyrrhizin, a plant-derived thrombin inhibitor. Thromb Res. 112(1-2) (2003): 93-8.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone 465-78, 2000.
Mitchell D, Mitchell P. Diabetes. J Complement Med 2(5) (2003): 14-19.
Mooreville M, Fritz RW, Mulholland SG. Enhancement of the bladder defense mechanism by an exogenous agent. J Urol 130(3) (1983): 607-9.
Morgan AG et al. Comparison between cimetidine and Caved-S in the treatment of gastric ulceration, and subsequent maintenance therapy. Gut 23 (1982): 545-51.
Nissen D (ed). Mosby's Drug Consult. St Louis: Mosby IV-35, 2003.
Nobata S, Ohira T, Nagae H, Ushiyama T, Suzuki K, Fujita K. Licorice-induced pseudoaldosteronism in a patient with a non-functioning adrenal tumor. Hinyokika Kiyo 47(9) (2001): 633-5 (in Japanese).

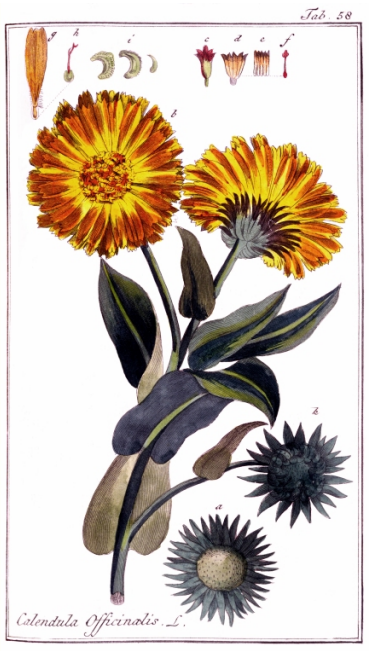


Nokhodchi A, Nazemiyeh H, Ghafourian T, Hassan-Zadeh D, Valizadeh H, Bahary LA. The effect of glycyrrhizin on the release rate and skin penetration of diclofenac sodium from topical formulations. Farmaco 57(11) (2002): 883-8.
Ofir R, Tamir S, Khatib S, Vaya J. Inhibition of serotonin re-uptake by licorice constituents. J Mol Neurosci 20(2) (2003): 135-40.
Padgett DA, Glaser R. How stress influences the immune response. Trends Immunol 24(8) (2003): 444-8.
Parle M, Dhingra D, Kulkarni SK. Memory-strengthening activity of Glycyrrhiza glabra in exteroceptive and interoceptive behavioral models. J Med Food 7(4) (2004): 462-6.
Pelser HE, Willebrands AF, Frenkel M, Van Der Heide RM, Groen J. Comparative study of the use of glycyrrhizinic and glycyrrhetinic acids in Addison's disease. Metabolism 2(4) (1953):322-34.
Ploeger B, Mensinga T, Sips A, Seinen W, Meulenbelt J, DeJongh J. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. Drug Metab Rev 33(2) (2001): 125-47.
Pompei R, Flore O, Marccialis MA, Pani A, Loddo B. Glycyrrhizic acid inhibits virus growth and inactivates virus particles. Nature 281(5733) (1979): 689-90.
Quinkler M, Stewart PM. Hypertension and the cortisol-cortisone shuttle. J Clin Endocrinol Metab 88(6) (2003): 2384-92.
Rafi MM et al. Modulation of bcl-2 and cytotoxicity by licochalcone-A, a novel estrogenic flavonoid. Anticancer Res 20(4) (2000): 2653-8.
Rafi MM et al. Novel polyphenol molecule isolated from licorice root (Glycrrhiza glabra) induces apoptosis, G2/M cell cycle arrest, and Bcl-2 phosphorylation in tumor cell lines. J Agric Food Chem 50(4) (2002): 677-84.
Rajesh M, Latha M. Protective activity of Glycyrrhiza glabra Linn. on carbon tetrachloride-induced peroxidative damage. Indian J Pharmacol 36(5) (2004): 284-7.
Russo S, Mastropasqua M, Mosetti MA, Persegani C, Paggi A. Low doses of licorice can induce hypertension encephalopathy. Am J Nephrol 20(2) (2000): 145-8.
Sakamoto K, Wakabayashi K. Inhibitory effect of glycyrrhetinic acid on testosterone production in rat gonads. Endocrinol Jpn 35 (1988): 333-42.
Sasaki H, Takei M, Kobayashi M, Pollard RB, Suzuki F. Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients. Pathobiology 70(4) (2002-2003): 229-36.
Sekizawa T, Yanagi K, Itoyama Y. Glycyrrhizin increases survival of mice with herpes simplex encephalitis. Acta Virol 45(1) (2001): 51-4.
Setchell, K, Cassidy A. Dietary isoflavones: Biological effects and relevance to human health. J Nutr 129 (1999): 758-67S.
Sheela ML, Ramakrishna MK, Salimath BP. Angiogenic and proliferative effects of the cytokine VEGF in Ehrlich ascites tumor cells is inhibited by Glycyrrhiza glabra. Int Immunopharmacol 6(3) (2006): 494-8.
Shibata S. Antitumor-promoting and anti-inflammatory activities of licorice principles and their modified compounds, in Food Phytochemicals II: Teas, Spices, and Herbs. Int J Pharmacog 32(1) (1994): 75-89.
Shibata S. A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. Yakugaku Zasshi 120(10) (2000): 849-62.
Shintani S et al: Glycyrrhizin (Licorice)-induced hypokalemic myopathy. Eur Neurol 32(1) (1992): 44-51.
Sigurjonsdottir HA et al. Licorice-induced rise in blood pressure: a linear dose-response relationship. J Hum Hypertens 15 (2001): 549-52.
Sigurjonsdottir HA, Manhem K, Axelson M, Wallerstedt S. Subjects with essential hypertension are more sensitive to the inhibition of 11 beta-HSD by licorice. J Hum Hypertens 17(2) (2003): 125-31.
Soma R, Ikeda M, Morise T, Miyamori I, Takeda R. Effect of glycyrrhizin on cortisol metabolism in humans. Endocr Regul 28(1) (1994): 31-4.
Somjen D et al. Estrogenic activity of glabridin and glabrene from licorice roots on human osteoblasts and prepubertal rat skeletal tissues. J Steroid Biochem Mol Biol 91(4-5) (2004a): 241-6.
Somjen D, Knoll E, Vaya J, Stern N, Tamir S. Estrogen-like activity of licorice root constituents: glabridin and glabrene, in vascular tissues in vitro and in vivo. J Steroid Biochem Mol Biol 91(3) (2004b): 147-55.

Statti GA, Tundis R, Sacchetti G, Muzzoli M, Bianchi A, Menichini F. Variability in the content of active constituents and biological activity of Glycyrrhiza glabra. Fitoterapia 75(3-4) (2004): 371-4.
Strandberg TE et al. Birth outcome in relation to licorice consumption during pregnancy. Am J Epidemiol 153 (2001): 1085-8.
Takahashi K, Kitao M. Effect of TJ-68 (Shakuyaku-Kanzo-To) on polycystic ovarian disease. Int J Fertil 39(2) (1994): 69-76.
Takahashi K, Yoshino K, Shirai T, Nishigaki A, Araki Y, Kitao M. Effect of a traditional herbal medicine (Shakuyaku-Kanzo-To) on testosterone secretion in patients with polycystic ovary syndrome detected by ultrasound. Nippon Sanka Fujinka Gakkai Zasshi 40(6) (1988): 789-92.
Takeuchi T et al. Effect of paeoniflorin, glycyrrhizin and glycyrrhetic acid on ovarian androgen production. Am J Chin Med 19(1) (1991): 73-8.
Takahashi T et al. Isoliquiritigenin, a flavonoid from licorice, reduces prostaglandin E_2 and nitric oxide, causes apoptosis, and suppresses aberrant crypt foci development. Cancer Sci 95(5) (2004): 448-53.
Tawata M et al. Anti-platelet action of isoliquiritigenin, an aldose reductase inhibitor in licorice. Eur J Pharmacol 212(1) (1992): 87-92.
Teelucksingh S, Mackie AD, Burt D, McIntyre MA, Brett L, Edwards CR. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. Lancet 335(8697) (1990): 1060-3.
Utsunomiya T et al. Glycyrrhizin, an active component of licorice roots, reduces morbidity and mortality of mice infected with lethal doses of influenza virus. Antimicrob Agents Chemother 41(3) (1997): 551-6.
van Marle J, Aarsen PN, Lind A, van Weeren-Kramer J. Deglycyrrhizinised licorice (DGL) and the renewal of rat stomach epithelium. Eur J Pharmacol 72(2-3) (1981): 219-25.
van-den-Bosch AE, van-der-Klooster JM, Zuidgeest DM, Ouwendijk RJ, Dees A. Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. Neth J Med 63(4) (2005): 146-8.
vanUum SHM et al. The role of 11-beta-hydroxysteroid dehydrogenase in the pathogenesis of hypertension. Cardiovasc Res 38 (1998): 16-24.
Vaya J, Belinky PA, Aviram M. Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. Free Rad Biol Med 23 (1997): 302-13.
Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralcorticoid excess. Endocrinol Metab Clin N Am 23 (1994): 359-77.
Walker BR, Connacher AA, Webb DJ, Edwards CR. Glucocorticoids and blood pressure: a role for the cortisol/cortisone shuttle in the control of vascular tone in man. Clin Sci (Lond) 83(2) (1992): 171-8.
Wang ZY, Mukhtar H. Anticarcinogenesis of licorice and its major triterpenoid constituents, in Food Phytochemicals II: Teas, Spices, and Herbs. Am Chem Soc 329-34, 1994.
Wang ZY, Nixon DW. Licorice and cancer. Nutr Cancer 39(1) (2001): 1-11.
Wash LK, Bernard JD. Licorice-induced pseudoaldosteronism. Am J Hosp Pharm 32(1) (1975): 73-4.
Werbach MR, Murray MT. Botanical Influences on Illness: a Sourcebook of Clinical Research. Tarzana, CA: Third Line Press, 1994.
White PC et al. 11 beta-hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. Endocr Rev 18(1) (1997): 135-56.
Whorwood CB, Sheppard MC, Stewart PM. Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. Endocrinology 132(6) (1993): 2287-92.
Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. Clin Neurol Neurosurg 105(4) (2003): 286-7.
Yu Z et al. Critical roles of platelets in lipopolysaccharide-induced lethality: effects of glycyrrhizin and possible strategy for acute respiratory distress syndrome. Int Immunopharmacol 5(3) (2005): 571-80.
Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217 (1998): 369-78.
Zhou Y, Zhang J. Effects of baicalin and liquid extract of licorice on sorbitol level in red blood cells of diabetic rats. Zhongguo Zhong Yao Za Zhi 15(7) (1990): 433-5, 448 (in Chinese).



Lutein and Zeaxanthin



BACKGROUND AND RELEVANT PHARMACOKINETICS

Lutein and its isomer zeaxanthin are yellow-coloured, xanthophyll carotenoids that are not converted into vitamin A. The bioavailability of lutein and zeaxanthin from food sources is influenced by the food matrix and the type and extent of food processing, but most notably by the presence of fat in the diet (Castenmiller et al 1999), with dietary fat intake being inversely related to serum levels (Nolan et al 2004). Cooking may increase their bioavailability by disrupting the cellular matrix and protein complexes, and supplemental sources may be significantly more bioavailable than food sources (Castenmiller et al 1999). One clinical study found that plasma lutein was higher when lutein was consumed with a high-fat spread (207% increase) than with a low-fat spread (88% increase) (Roodenburg et al 2000). This was supported by a small in vitro study showing that dietary lutein is absorbed more efficiently with 24 g of avocado oil or 150 g of avocado fruit (Unlu et al 2005). For each 10% increase in dietary lutein and zeaxanthin, serum levels are seen to increase by 1% (Gruber et al 2004).

When ingested, lutein and zeaxanthin are transported from the intestine to the liver via chylomicrons. They are then transported via LDL and HDL to various parts of the body (Yeum & Russell 2002). Lutein and zeaxanthin are present in the eye, blood serum, skin, cervix, brain, breast and adipose tissue. In the eye lutein is more prominent at the edges of the retina and in the rods (Bernstein 2001, Bone 1997). Lutein appears to undergo some metabolism in the retina to *meso*-zeaxanthin. Zeaxathin is primarily concentrated in the centre of the retina and the cones, where it is present in concentrations nearly 1000-fold those found in other tissues, thus giving the macula lutea or yellow spot of the retina its characteristic colour (Krinsky et al 2003).

Lower serum concentrations of zeaxanthin have been associated with male gender, smoking, younger age, lower non-HDL cholesterol, greater ethanol consumption and higher BMI (Brady et al 1996). Lutein and zeaxanthin, together with other carotenoids, have also been found to be lower in people with chronic cholestatic liver disease, which can be attributed to malabsorption of fat-soluble vitamins, as well as other mechanisms of hepatic release (Floreani et al 2000). In an epidemiological study involving 7059 participants, lower serum lutein and zeaxanthin levels was significantly associated with smoking, heavy drinking, being white, female, or not being physically

active, having lower dietary lutein and zeaxanthin, a higher percentage of fat mass, a higher waist-hip ratio, lower serum cholesterol, a higher white blood cell count, and high levels of C-reactive protein (Gruber et al 2004).

In a pharmacokinetic study involving 20 healthy volunteers, serum zeaxanthin levels were found to have an effective half-life for accumulation of 5 days and a terminal elimination half-life of around 12 days (Hartmann et al 2004). This was confirmed by another study that also found that lutein did not affect the concentrations of other carotenoids in healthy volunteers (Thurmann et al 2005). Similarly, high doses (50 mg) of beta-carotene over 5 years were not found to influence serum levels of lutein and zeaxanthin (Mayne et al 1998). It has been suggested that the associations between macula pigment density and serum lutein, serum zeaxanthin and adipose lutein concentrations are stronger in men (Broekmans et al 2002, Johnson et al 2000) and that the processes governing accumulation and/or stabilisation of zeaxanthin in fat tissue are different for males and females (Nolan et al 2004). This is supported by the finding that serum lutein and zeaxanthin concentrations vary with the menstrual cycle, with levels being higher in the late follicular than in the luteal phase (Forman et al 1998).

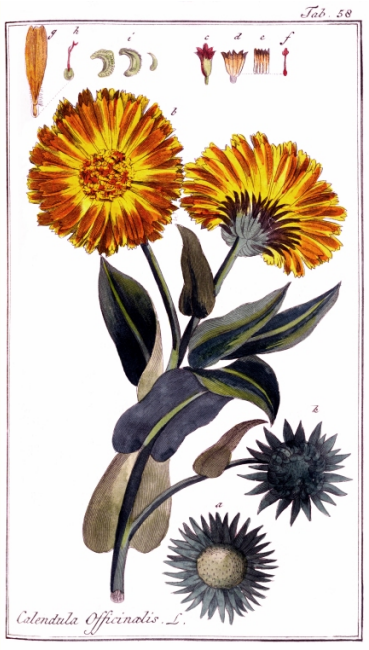
CHEMICAL COMPONENTS

Lutein and zeaxanthin are isomers and have identical chemical formulas, differing only in the location of a double bond in one of the hydroxyl groups. Lutein is known as beta, epsilon-carotene-3,3′diol whereas zeaxanthin is known as all-*trans* beta-carotene-3,3′-diol.

FOOD SOURCES

Foods differ in their relative amounts of lutein and zeaxanthin, with lutein generally being more abundant. Lutein is found in dark green leafy vegetables such as spinach and kale, as well as in sweet corn and egg yolks, whereas zeaxanthin is found in sweet corn, egg yolk, orange peppers (capsicums), persimmons, tangerines, mandarins and oranges.

Lutein and zeaxanthin are primarily extracted from marigold flowers (*Tagetes erecta*) for use in supplements and are available in either free or esterified form. The esters typically contain two fatty acid groups that must be cleaved by pancreatic esterases and their absorption requires higher levels of dietary fat (Roodenburg et al 2000).

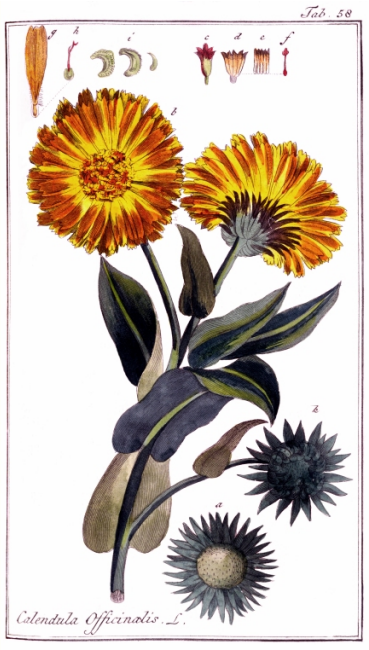


DEFICIENCY SIGNS AND SYMPTOMS

It has been suggested that zeaxanthin and lutein be considered conditionally essential nutrients because low serum levels or low dietary intake are associated with low macular pigment density and increased risk of ARMD (Semba & Dagnelie 2003).

Epidemiological studies have also found an association between low serum carotenoid levels, including lutein and zeaxanthin levels, with all-cause mortality (De Waart et al 2001), the risk of inflammatory polyarthritis (Pattison et al 2005), breast cancer (Tamimi et al 2005), prostate cancer (Jian et al 2005), colon cancer (Nkondjock & Ghadirian 2004), cervical cancer (Garcia-Closas et al 2005, Kim et al 2004), human papilloma virus persistence (Garcia-Closas et al 2005), type 2 diabetes and impaired glucose metabolism (Coyne et al 2005), chronic cholestatic liver diseases (Floreani et al 2000), Alzheimer's disease and vascular dementia (Polidori et al 2004), and low fruit and vegetable consumption (Al-Delaimy et al 2005).

Carotenoids have also emerged as an excellent tissue marker for a diet rich in fruits and vegetables, and measurement of plasma and tissue carotenoids is considered to have an important role in defining optimal diets (Al-Delaimy et al 2005, Brevik et al 2004, Handelman 2001).



MAIN ACTIONS

ANTIOXIDANT

Lutein and zeaxanthin are both powerful antioxidants, with activity having been demonstrated in a number of in vitro tests (Higashi-Okai et al 2001, Iannone et al 1998, Naguib 2000). In vitro studies of human lens epithelial cells also indicate that their antioxidant activity may protect the lens from UVB radiation (Chitchumroonchokchai et al 2004). According to animal studies, lutein increases glutathione levels and reduces retinal apoptosis following ischaemic reperfusion (Dilsiz et al 2005).

BLUE LIGHT FILTER

The yellow colour of lutein and zeaxanthin is due to their ability to absorb blue light, which is believed to contribute to their protective function because blue light is at the high energy, and therefore the most damaging, end of the visible spectrum (Krinsky et al 2003). Lutein and zeaxanthin thus serve as an optical filter for blue light, reducing chromatic aberration and preventing damage to the photoreceptor cell layer (Krinsky et al 2003).

MACULAR PIGMENT DEVELOPMENT

Lutein and zeaxanthin are entirely of dietary origin and are initially absent in newborns but gradually accumulate over time (Nussbaum et al 1981). It has been

generally accepted that macular pigment density decreases with age; however, there are conflicting results. In one prospective, observational study involving 390 patients, macular pigment density was not found to change significantly with age, even when elderly subjects with cataracts and ARMD were considered (Ciulla & Hammond 2004). Other studies, however, have found that macular pigment does indeed decline with age in both normal eyes (Beatty et al 2001, Bernstein et al 2002) and those with ARMD (Bernstein et al 2002) and Stargardt macular dystrophy (Zhao et al 2003), but not in retinitis pigmentosa or choroideremia (Zhao et al 2003).

Although lutein and zeaxanthin levels in the serum, diet, and retina correlate, the nature of the relationships between lutein and zeaxanthin in foodstuffs, blood and the macula are confounded by many variables, including processes that influence digestion, absorption, and transport and accumulation and stabilisation of the carotenoids in the tissues (Beatty et al 2004). It is suggested, however, that lutein and zeaxanthin are transported into an individual's retina in the same proportions found in his or her blood (Bone 1997).

Two clinical studies have demonstrated that increasing lutein intake will increase macular pigment density within 4 weeks (Berendschot et al 2000, Hammond et al 1997). More recently, a clinical study confirmed the association between macular pigmentation, dietary lutein intake and serum lutein levels (Burke et al 2005).

IMMUNOMODULATION

Lutein modulates cellular and humoral-mediated immune responses, according to animal studies (Kim et al 2000a, b). In particular, high levels of C-reactive protein and a high white blood cell count have been identified in individuals with low serum levels of lutein (Gruber et al 2004). In a case-controlled study serum lutein and zeaxanthin, together with other carotenoids, were also found to be lower in children with acute phase infections compared to healthy controls (Cser et al 2004).

PHOTOPROTECTION

According to an animal study, lutein reduces the risk of sunburn, as well as the local UVB-radiation-induced immune suppression and reactive oxygen species generation that are implicated in photocarcinogenesis (Lee et al 2004). A protective effect on skin cancer, however, has not been observed in human cohort studies. One prospective cohort study involving 43,867 men and 85,944 women found no significant inverse association between intake of lutein and squamous cell carcinoma (Fung et al 2003), and an increased risk of squamous cell carcinoma was observed for people with multiple prior non-melanoma skin cancers and high serum levels of lutein and zeaxanthin (Dorgan et al 2004). The clinical significance of these findings is uncertain.

CLINICAL USE

AGE-RELATED MACULAR DEGENERATION

The evidence that lifetime oxidative stress plays an important role in the development of ARMD is now compelling (Hogg & Chakravarthy 2004). ARMD is thought to be the result of free radical damage to photoreceptors within the macula, and therefore it is suspected that inefficient macular antioxidant systems play a role in disease development. Low levels of lutein and zeaxanthin in the diet, serum or retina, as well as excessive exposure to blue light and cigarette smoking, are therefore considered to increase the risk of ARMD (Bone et al 2003). People with cystic fibrosis are theoretically at increased risk of ARMD because they have reduced lutein in the macular pigment (Schupp et al 2004).

Epidemiological and autopsy studies have found an inverse relationship between lutein and zeaxanthin intake and macular pigment density (Bone et al 2001, Curran-Celentano et al 2001). Plasma lutein and macular pigment density have also been demonstrated to increase with lutein supplementation in ARMD patients (Bernstein et al 2002) and healthy controls (Koh et al 2004), suggesting that ARMD is not associated with intestinal malabsorption of carotenoids and that a diseased macula can accumulate and stabilise lutein and/or zeaxanthin (Koh et al 2004). Conclusive evidence as to whether increased intake of lutein or zeaxanthin will reduce the incidence of ARMD is still unavailable (Berendschot et al 2002, Broekmans et al 2002, Hammond et al 1997).

Interestingly, two case-controlled studies have found that lycopene, rather than lutein or zeaxanthin, was reduced in the serum of ARMD patients (Cardinault et al 2005, Mares-Perlman et al 1995). It was suggested that this result could be due to antioxidant protection of lutein and zeaxanthin by lycopene or different dietary habits.

Recent studies have produced encouraging results for people with pre-existing ARMD. Improvements of up to 92% in visual acuity tests were observed when subjects consumed a diet designed to contain approximately 150 g of spinach 4–7 times a week (Richer 1999), and in 30 patients with early ARMD and visual acuity of 6/9 or better daily supplementation with lutein, vitamin E and nicotinamide for 180 days improved macular function (Falsini et al 2003). The results from the Lutein Antioxidant Supplementation Trial provide further support for lutein supplementation in ARMD (Richer et al 2004). This was a double-blind, randomised, placebo-controlled study involving 90 subjects with atrophic ARMD who were given 10 mg lutein, 10 mg lutein plus broad spectrum antioxidants/vitamins/minerals, or placebo for 1 year. At baseline and every 4 months during the study period, subjects were

examined for changes in macular pigment density (MPD), photostress recovery, contrast sensitivity, and visual acuity. Both the lutein and lutein + antioxidant groups achieved an increase of 36% and 43%, respectively, in MPD, whereas the placebo group experienced a slight decrease. Significant improvements in visual acuity, objective visual function parameters, photostress recovery, and contrast sensitivity were also observed with lutein therapy (Richer et al 2004).

Clinical note — ARMD

ARMD is the leading cause of blindness in people over 65 years of age (Pratt 1999). Its exact aetiology is unknown; however, several risk factors have been established such as lighter iris colour, positive family history, lifestyle factors (e.g. cigarette smoking), hypertension, female gender and low serum concentrations of carotenoids (Cardinault et al 2005). The disease causes a loss of central vision and can impair most activities essential for independent living, such as reading, driving and writing. The prevalence of ARMD and its social and economic consequences are increasing in line with the ageing population.

CATARACTS

Lens density has been found to inversely correlate to macular lutein and zeaxanthin levels (Hammond et al 1997) and numerous observational studies have found that increased consumption of foods high in lutein and zeaxanthin is associated with a decreased risk for cataracts (Brown et al 1999, Tavani 1996). In one study involving 77,466 female nurses from the Nurses Health Study, those with the highest quintile for consumption of zeaxanthin and lutein were found to have a 22% reduction in the risk of cataract extraction (Chasan-Taber et al 1999). These results contrast with those from a cohort study of 478 women without previously diagnosed cataracts, which failed to detect a significant inverse relationship between lutein intake and lens opacities over a 13–15-year follow-up period (Jacques et al 2001).

The link between lutein and cataracts is supported by a small randomised placebo-controlled trial of 17 patients with clinically diagnosed age-related cataracts that found that supplementation with lutein 15 mg three times weekly for up to 2 years resulted in improved visual performance (visual acuity and glare sensitivity) compared with placebo (Olmedilla et al 2003).

RETINITIS PIGMENTOSA

Daily supplementation with 40 mg of lutein over 9 weeks followed by 20 mg for a further 16 weeks was found to significantly improve visual acuity in a 26-week trial

involving 16 subjects with retinitis pigmentosa, many of whom were also taking other supplements (Dagnelie et al 2000).

ATHEROSCLEROSIS

Oxidative modification of LDL in the vascular wall seems to be a key factor in atherosclerosis development and thus lipid-soluble antioxidants that can protect LDLs may have a role in atherosclerosis prevention (Cherubini et al 2005); however, the relationship between lutein and zeaxanthin status and atherosclerosis is unclear.

Plasma levels of lutein, beta-cryptoxanthin and zeaxanthin were correlated to carotid intima–media thickness in a 3-year case-controlled study of 231 subjects (Iribarren et al 1997), as well as in an 18-month epidemiological study of 573 subjects, suggesting that these carotenoids may be protective against early atherosclerosis (Dwyer et al 2004). Lutein intake has also been found inversely associated with the risk of ischaemic stroke in an observational study involving 43,738 males (Ascherio et al 1999), as well as being inversely associated with the risk of subarachnoid haemorrhage in a cohort study of 26,593 male smokers (Hirvonen et al 2000). Serum levels of lutein and zeaxanthin, however, were not associated with atherosclerosis risk in a case-control study involving 108 cases of aortic atherosclerosis in an elderly population (Klipstein-Grobusch et al 2000).

The foregoing findings contrast with those from two case-controlled studies that found a positive correlation between lutein and zeaxanthin levels and cardiovascular risk. A nested, case-control study of 499 cases of cardiovascular disease with matched controls taken from the Physicians' Health Study found that concentrations of plasma lutein, zeaxanthin and retinol corresponded to a moderate increase in cardiovascular disease (Sesso et al 2005). Similarly, myocardial infarction risk was positively associated with lutein and zeaxanthin levels in adipose tissue and the diet in a case-controlled study of 1456 cases of first acute myocardial infarction and matched controls (Kabagambe et al 2005). The clinical significance of these findings is unclear and requires further investigation.

ALZHEIMER'S DEMENTIA

Dementia has been found to be associated with increased protein oxidative modification and the depletion of a large spectrum of antioxidant micronutrients, including lutein and zeaxanthin (Polidori et al 2004). A clinical study of 25 subjects with mild cognitive impairment, 63 subjects with AD and 56 healthy individuals found that serum lutein levels were lowest in the first two groups, particularly those with AD (Rinaldi et al 2003).

CANCER PREVENTION

High dietary intake of lutein has been associated with reduced risk of some cancers, most notably endometrial and ovarian cancer, but not all cancers, according to epidemiological evidence (Freudenheim et al 1996, Fung et al 2003, Gann et al 1999, Giovannucci et al 1995, Huang et al 2003, Ito et al 2003, Lu et al 2001, McCann et al 2000, Michaud et al 2000, Nomura et al 1997, Schuurman et al 2002, Terry et al 2002).

Lung cancer The link between carotenoid intake and lung cancer has undergone extensive scrutiny and extensive epidemiological evidence suggests a reduction in lung cancer risk with high dietary intake of carotenoids (Cooper et al 1999). Initial research used food composition tables and therefore focused on beta-carotene, for which data was available; however, the dietary intake of beta-carotene and other carotenoids such as lutein and zeaxanthin are highly correlated (Ascherio et al 1992) and as food composition data for these nutrients has become available studies have suggested a link between dietary lutein intake and reduced lung cancer risk (Cooper et al 1999).

Three large population studies of diet and lung cancer have revealed a non-significant association between high lutein intake and lower risk of lung cancer (Ito et al 2003, Michaud et al 2000, Ziegler et al 1996), and a significant trend was observed in another population-based case-control study (Le Marchand et al 1993). A nested case control study also found that serum lutein and zeaxanthin were lower in those with lung cancer than in controls (Comstock et al 1997). These results are contrasted with those from a case-control study of 108 cases of lung cancer in a Chinese occupational cohort that found that higher serum carotenoid levels, including lutein and zeaxanthin, were significantly associated with increased lung cancer risk among alcohol drinkers, while having a possible protective association among non-drinkers (Ratnasinghe et al 2000).

Cervical cancer A recent systematic review suggests that lutein/zeaxanthin is likely to have a protective effect for cervical neoplasia and possibly for human papilloma virus persistence (Garcia-Closas et al 2005).

Endometrial cancer An epidemiological study involving 232 patients with endometrial cancer and 639 controls found that an intake of more than 7.3 mg/day of lutein was associated with a 70% reduced risk of endometrial cancer (McCann et al 2000).

Ovarian cancer A case-control study found that weekly intake of lutein of more than 24 mg was associated with a 40% reduction in the risk for developing ovarian cancer compared with weekly consumption of less than 3.8 μg (Bertone et al 2001).

Breast cancer High lutein and zeaxanthin intake has been related to reduced risk of breast cancer (Dorgan et al 1998, Toniolo et al 2001). High lutein intake (>7 mg/day) was associated with a 53% reduction in the risk of developing breast cancer compared with low consumption (<3.7 mg/day) in a population-based case-control study of 608 premenopausal women over age 40 (Freudenheim et al 1996). Similar risk reductions were found in a nested case-control study of 540 New York women (Toniolo et al 2001) and another nested case-control study of 969 cases of breast cancer and matched controls from the Nurses' Health Study found that the risk of breast cancer was 25–35% less for women with the highest quintile compared with that for women with the lowest quintile of lutein/zeaxanthin and total carotenoid intake (Tamimi et al 2005). Although this association is encouraging, another study of 4697 women followed over 25 years found no significant relationships between lutein intake and breast cancer risk (Jarvinen et al 1997).

Gastric cancer High serum lutein levels have been associated with a higher incidence of gastric carcinoma, according to a cohort study of 29,584 patients with oesophageal and stomach cancer (Abnet et al 2003); however, this association requires further investigation.

Bowel cancer The relationship between lutein and zeaxanthin intake and colon cancer is uncertain. A case-control study involving 1993 cases of colon cancer and 2410 controls found that lutein intake, as measured by a food frequency score, was inversely associated with colon cancer and another case-control study of 223 subjects with histologically confirmed colon or rectal cancer identified a non-significant inverse association with lutein (Levi et al 2000). A cohort analysis of 5629 women, however, found no such association (Terry et al 2002). More recently, a case-controlled study found that women with high intakes of long-chain polyunsaturated fatty acids had an inverse association between lutein and zeaxanthin intake and the risk of colon cancer risk (Nkondjock & Ghadirian 2004). Further investigation is required to clarify these findings because animal studies suggest low doses of lutein inhibit aberrant crypt foci formation, whereas high doses may increase the risk by 9–59% (Raju et al 2005).

Prostate cancer Overall, epidemiological evidence suggests that lutein and zeaxanthin intake has no influence over the risk of prostate cancer (Bosetti et al 2004, Gann et al 1999, Giovannucci et al 1995, Huang et al 2003, Lu et al 2001, Nomura et al 1997, Schuurman et al 2002). However, when lutein was included as part of a mixed carotenoid and tocopherol extract, the combination was effective in an in vitro study of prostate cancer cell lines (Lu et al 2005) and a case-controlled study of 130 patients with adenocarcinoma of the prostate found that prostate cancer risk was seen to decline with increasing consumption of carotenoids, including lycopene,

alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin (Jian et al 2005).

Laryngeal cancer A case-control study involving 537 subjects identified an inverse relationship between dietary lutein and zeaxanthin intake, together with the intake of other carotenoids, and the risk of laryngeal cancer (Bidoli et al 2003).

OTHER USES

Lutein and zeaxanthin may be used as part of a general antioxidant supplement, often taken in conjunction with other carotenoids in cases where there is known or suspected increased oxidative load.

DOSAGE RANGE

ACCORDING TO CLINICAL STUDIES

- Macular protection: lutein 6–20 mg/day; zeaxanthin 2–5 mg/day.
- Cataracts — improving visual performance: lutein 15 mg three times weekly.

TOXICITY

Lutein and zeaxanthin are generally recognised as safe in doses up to 2 mg/kg.

ADVERSE REACTIONS

Insufficient reliable information available.

SIGNIFICANT INTERACTIONS

VITAMIN C

Lutein showed increased antioxidant efficacy with vitamin C in an animal study (Blakeley et al 2003). Further to this, a small in vivo study showed 2000 mg of vitamin C enhanced the absorption of lutein (Tanumihardjo et al 2005).

VITAMIN E

Vitamin E showed increased antioxidant efficacy with lutein according to an animal study (Blakeley et al 2003).

PHYTOSTEROLS

High dietary intake of phytosterol esters (6.6 g/day) reduced plasma levels of lutein by 14% in a small clinical trial; however, this was reversed by increasing fruit and vegetable intake (Clifton et al 2004).

ORLISTAT

Theoretically, long-term use of orlistat leads to reduced plasma levels of lutein due to reduced gastric absorption (Australian Medicines Handbook) — increased dietary intake of lutein should be considered.

OLESTRA

Lutein and zeaxathin levels have been found to decrease with long-term use of olestra (Tulley et al 2005) — increased dietary intake of lutein should be considered.

CONTRAINDICATIONS AND PRECAUTIONS

Lutein and zeaxathin is contraindicated in people with a hypersensitivity to these carotenoids or their food sources.

PREGNANCY USE

Eating dietary amounts of foods rich in lutein and zeaxathin is likely to be safe. Women at risk of premature rupture of the membranes are cautioned against very high intake because one study observed a fourfold greater risk of membrane rupture with high serum lutein levels (Matthews & Neil 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Lutein and zeaxanthin are antioxidant carotenoids found in spinach, corn, egg yolk, squash and greens.
- Lutein and zeaxanthin are essential for the development of macular pigment, which protects photoreceptor cells in the retina from free radical damage.
- Epidemiological studies have generally found an inverse relationship between lutein and zeaxanthin intake and macular degeneration; however, conclusive evidence as to whether increased intakes will reduce the incidence of ARMD is still unavailable.
- One controlled study has found that long-term use of lutein supplements may increase visual performance in people with pre-existing cataracts.
- High dietary intake of lutein has been associated with reduced risk of some cancers, most notably endometrial and ovarian cancer, but not all cancers, according to epidemiological evidence.
- Supplements containing lutein and zeaxanthin should be taken with food as dietary fat improves their absorption.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Lutein and zeaxathin is important for eye health and may also reduce the risk of developing endometrial and ovarian cancer over time.

When will it start to work?

Increased intake of lutein can improve macular health within 4 weeks; however, clinical effects develop slowly and may not be detected for 6 months. In regard to improving visual performance in people with pre-existing cataracts, effects take even longer (≈2 years).

Are there any safety issues?

Lutein and zeaxanthin are generally considered safe.

REFERENCES

Abnet CC et al. Prospective study of serum retinol, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin and esophageal and gastric cancers in China. Cancer Causes Control 14.7 (2003): 645-55.

Al-Delaimy et al. Plasma carotenoids as biomarkers of intake of fruits and vegetables: ecological-level correlations in the European Prospective Investigation into Cancer and Nutrition (EPIC). Eur J Clin Nutr 59.12 (2005): 1397-408.

Ascherio A et al. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. J Nutr 122.9 (1992): 1792-801.

Ascherio A et al. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. Ann Intern Med 130.12 (1999): 963-70.

Australian Medicines Handbook. Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists. Available at: www.amh.hcn.net.au (accessed 06-12-05).

Beatty S et al. Macular pigment and risk for age-related macular degeneration in subjects from a northern European population. Invest Ophthalmol Vis Sci 42.2 (2001): 439-46.

Beatty S et al. Macular pigment optical density and its relationship with serum and dietary levels of lutein and zeaxanthin. Arch Biochem Biophys 430.1 (2004): 70-6.

Berendschot TT et al. Influence of lutein supplementation on macular pigment, assessed with two objective techniques. Invest Ophthalmol Vis Sci 41.11 (2000): 3322-6.

Berendschot TT et al. Lens aging in relation to nutritional determinants and possible risk factors for age-related cataract. Arch Ophthalmol 120.12 (2002): 1732-7.

Bernstein PS et al. Identification and quantification of carotenoids and their metabolites in the tissues of the human eye. Exp Eye Res 72.3 (2001): 215-23.

Bernstein PS et al. Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients. Ophthalmology 109.10 (2002): 1780-7.

Bertone ER et al. A population-based case-control study of carotenoid and vitamin A intake and ovarian cancer (United States). Cancer Causes Control 12.1 (2001): 83-90.

Bidoli E et al. Micronutrients and laryngeal cancer risk in Italy and Switzerland: a case control study. Cancer Causes Control 14.5 (2003): 477-84.

Blakely S et al. Lutein interacts with ascorbic acid more frequently than with (alpha)-tocopherol to alter biomarkers of oxidative stress in female Zucker obese rats. J Nutr 133.9 (2003): 2838-44.

Bone R et al. Distribution of lutein and zeaxanthin stereoisomers in the human retina. Exp Eye Res 64.2 (1997): 211-18.

Bone R et al. Macular pigment in donor eyes with and without AMD: A case-control study. Invest Ophthalmol Vis Sci 42.1 (2001): 235-40.

Bone R et al. Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. J Nutr 133.4 (2003): 992-8.

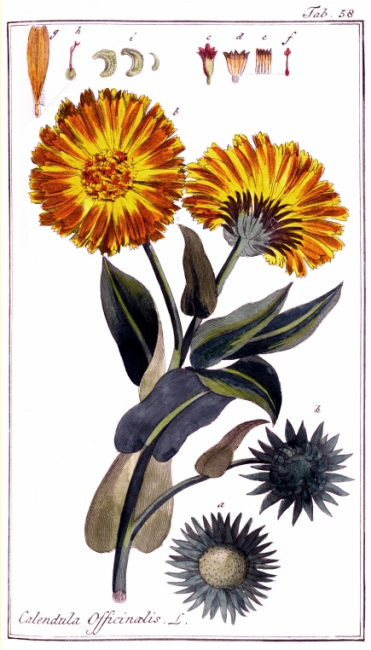
Bosetti C et al. Retinol, carotenoids and the risk of prostate cancer: A case-control study from Italy. Int J Cancer 112.4 (2004): 689-92.

Brady WE et al. Human serum carotenoid concentrations are related to physiologic and lifestyle factors. J Nutr 126.1 (1996): 129-37.

Brevik A et al. Six carotenoids in plasma used to assess recommended intake of fruits and vegetables in a controlled feeding study. Eur J Clin Nutr 58.8 (2004): 1166-73.

Broekmans WM et al. Macular pigment density in relation to serum and adipose tissue concentrations of lutein and serum concentrations of zeaxanthin. Am J Clin Nutr 76.3 (2002): 595-603.

Brown L et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. Am J Clin Nutr 70.4 (1999): 517-24.
Burke JD, Curran-Celentano J, Wenzel AJ. Diet and serum carotenoid concentrations affect macular pigment optical density in adults 45 years and older. J Nutr 135.5 (2005): 1208-15.
Cardinault N et al. Lycopene but not lutein nor zeaxanthin decreases in serum and lipoproteins in age-related macular degeneration patients. Clin Chim Acta 357 (2005): 34-42.
Castenmiller JJ et al. The food matrix of spinach is a limiting factor in determining the bioavailability of beta-carotene and to a lesser extent of lutein in humans. J Nutr 129.2 (1999): 349-55.
Chasan-Taber L et al. A prospective study of vitamin supplement intake and cataract extraction among U.S. women. Epidemiology 10.6 (1999): 679-84.
Cherubini A et al. Role of antioxidants in atherosclerosis: Epidemiological and clinical update. Current Pharm Design 11.16 (2005): 2017-32.
Chitchumroonchokchai C et al. Xanthophylls and [alpha]-tocopherol decrease UVB-induced lipid peroxidation and stress signaling in human lens epithelial cells. J Nutr 134.12 (2004): 3225.
Ciulla TA, Hammond BR Jr. Macular pigment density and aging, assessed in the normal elderly and those with cataracts and age-related macular degeneration. Am J Ophthalmol 138.4 (2004): 582-7.
Clifton PM et al. High dietary intake of phytosterol esters decreases carotenoids and increases plasma plant sterol levels with no additional cholesterol lowering. J Lipid Res 45.8 (2004): 1493-9.
Comstock GW et al. The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity. Cancer Epidemiol Biomarkers Prev 6.11 (1997): 907-16.
Cooper DA et al. Dietary carotenoids and lung cancer: a review of recent research. Nutr Rev 57.5 (1999): 133-45.
Coyne T et al. Diabetes mellitus and serum carotenoids: findings of a population-based study in Queensland, Australia. Am J Clin Nutr 82.3 (2005): 685-93.
Cser MA et al. Serum carotenoid and retinol levels during childhood infections. Ann Nutr Metab 48.3 (2004): 156.
Curran-Celentano J et al. Relation between dietary intake, serum concentrations, and retinal concentrations of lutein and zeaxanthin in adults in a Midwest population. Am J Clin Nutr 74.6 (2001): 796-802.
Dagnelie G, Zorge IS, McDonald TM. Lutein improves visual function in some patients with retinal degeneration: a pilot study via the Internet. Optometry 71 (2000): 147-64.
De Waart FG et al. Serum carotenoids, [alpha]-tocopherol and mortality risk in a prospective study among Dutch elderly. Int J Epidemiol 30.1 (2001): 136-43.
Dilsiz N et al. Protective effects of various antioxidants during ischemia-reperfusion in the rat retina. Graefe's Arch Clin Exp Ophthalmol (2005): 1-7.
Dorgan JF et al. Relationships of serum carotenoids, retinol, [alpha]-tocopherol, and selenium with breast cancer risk: Results from a prospective study in Columbia, Missouri (United States). Cancer Causes Control 9.1 (1998): 89-97.
Dorgan JF et al. Serum carotenoids and (alpha)-tocopherol and risk of nonmelanoma skin cancer. Cancer Epidemiol Biomarkers Prev 13.8 (2004): 1276-82.
Dwyer JH et al. Progression of carotid intima-media thickness and plasma antioxidants: The Los Angeles Atherosclerosis Study. Arterioscler Thromb Vasc Biol 24.2 (2004): 313-19.
Falsini B et al. Influence of short-term antioxidant supplementation on macular function in age-related maculopathy: a pilot study including electrophysiologic assessment. Ophthalmology 110.1 (2003): 51-60.
Floreani A et al. Plasma antioxidant levels in chronic cholestatic liver diseases. Aliment Pharmacol Ther 14.3 (2000): 353-8.
Forman MR et al. Effect of menstrual cycle phase on the concentration of individual carotenoids in lipoproteins of premenopausal women: a controlled dietary study. Am J Clin Nutr 67.1 (1998): 81-7.
Freudenheim JL et al. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. J Natl Cancer Inst 88.6 (1996): 340-8.

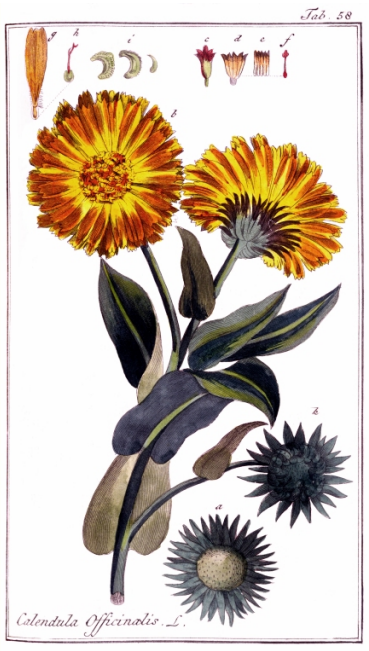


Fung TT et al. Vitamin and carotenoid intake and risk of squamous cell carcinoma of the skin. Int J Cancer 103.1 (2003): 110-15.
Gann PH et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res 59.6 (1999): 1225-30.
Garcia-Closas R et al. The role of diet and nutrition in cervical carcinogenesis: A review of recent evidence. Int J Cancer 117.4 (2005): 629-37.
Giovannucci E et al. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 87.23 (1995): 1767-76.
Gruber M et al. Correlates of serum lutein + zeaxanthin: Findings from the Third National Health and Nutr Examination Survey. J Nutr 134.9 (2004): 2387-94.
Hammond BR Jr et al. Dietary modification of human macular pigment density. Invest Ophthalmol Vis Sci 38.9 (1997): 1795-801.
Handelman GJ. The evolving role of carotenoids in human biochemistry. Nutrition 17.10 (2001): 818-22.
Hartmann D et al. Plasma kinetics of zeaxanthin and 3′-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. Am J Clin Nutr 79.3 (2004): 410-17.
Higashi-Okai K et al. Identification and antioxidant activity of several pigments from the residual green tea (Camellia sinensis) after hot water extraction. J Univ Occupat Environ Health 23.4 (2001): 335-44.
Hirvonen T et al. Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. Stroke 31.10 (2000): 2301-6.
Hogg R, Chakravarthy U. AMD and micronutrient antioxidants. Current Eye Res 29.6 (2004): 387-401.
Huang HY et al. Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. Am J Epidemiol 157.4 (2003): 335-44.
Iannone A et al. Antioxidant activity of carotenoids: an electron-spin resonance study on beta-carotene and lutein interaction with free radicals generated in a chemical system. J Biochem Mol Toxicol 12.5 (1998): 299-304.
Iribarren C et al. Association of serum vitamin levels, LDL susceptibility to oxidation, and autoantibodies against MDA-LDL with carotid atherosclerosis: A case-control study: The ARIC Study Investigators (Atherosclerosis Risk in Communities). Arterioscler Thromb Vasc Biol 17.6 (1997): 1171-7.
Ito Y et al. Serum carotenoids and mortality from lung cancer: a case-control study nested in the Japan Collaborative Cohort (JACC) study. Cancer Sci 94.1 (2003): 57-63.
Jacques PF et al. Long-term nutrient intake and early age-related nuclear lens opacities. Arch Ophthalmol 119.7 (2001): 1009-19.
Jarvinen R et al. Diet and breast cancer risk in a cohort of Finnish women. Cancer Lett 114.1-2 (1997): 251-3.
Jian L et al. Do dietary lycopene and other carotenoids protect against prostate cancer? Int J Cancer 113.6 (2005): 1010-14.
Johnson E et al. Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density. Am J Clin Nutr 71.6 (2000): 1555-62.
Kabagambe EK et al. Some dietary and adipose tissue carotenoids are associated with the risk of nonfatal acute myocardial infarction in Costa Rica. J Nutr 135.7 (2005): 1763-9.
Kim HW et al. Dietary lutein stimulates immune response in the canine. Vet Immunol Immunopathol 74.3-4 (2000a): 315-27.
Kim HW et al. Modulation of humoral and cell-mediated immune responses by dietary lutein in cats. Vet Immunol Immunopathol 73.3-4 (2000b): 331-41.
Kim YT et al. Relation between deranged antioxidant system and cervical neoplasia. Int J Gynecol Cancer 14.5 (2004): 889-95.
Klipstein-Grobusch K et al. Serum carotenoids and atherosclerosis: The Rotterdam Study. Atherosclerosis 148.1 (2000): 49-56.
Koh H-H et al. Plasma and macular responses to lutein supplement in subjects with and without age-related maculopathy: A pilot study. Exp Eye Res 79.1 (2004): 21-7.

Krinsky NI, Landrum JT, Bone RA. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 23 (2003): 171-201.
Le Marchand L et al. Intake of specific carotenoids and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2.3 (1993): 183-7.
Lee EH et al. Dietary lutein reduces ultraviolet radiation-induced inflammation and immunosuppression. J Invest Dermatol 122.2 (2004): 510-17.
Levi F et al. Selected micronutrients and colorectal cancer. a case-control study from the canton of Vaud, Switzerland. Eur J Cancer 36.16 (2000): 2115-19.
Lu QY et al. Inverse associations between plasma lycopene and other carotenoids and prostate cancer. Cancer Epidemiol Biomarkers Prev 10.7 (2001): 749-56.
Lu QY et al. Inhibition of prostate cancer cell growth by an avocado extract: role of lipid-soluble bioactive substances. J Nutr Biochem 16.1 (2005): 23-30.
Mares-Perlman JA et al. Serum antioxidants and age-related macular degeneration in a population-based case-control study. Arch Ophthalmol 113.12 (1995): 1518-23.
Mathews F, Neil A. Antioxidants and preterm prelabour rupture of the membranes. Br J Obstet Gynaecol 112.5 (2005): 588-94.
Mayne ST et al. Effect of supplemental [beta]-carotene on plasma concentrations of carotenoids, retinol, and [alpha]-tocopherol in humans. Am J Clin Nutr 68.3 (1998): 642-7.
McCann SE et al. Diet in the epidemiology of endometrial cancer in western New York (United States). Cancer Causes Control 11.10 (2000): 965-74.
Michaud DS et al. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. Am J Clin Nutr 72.4 (2000): 990-7.
Naguib YM. Antioxidant activities of astaxanthin and related carotenoids. J Agric Food Chem 48.4 (2000): 1150-4.
Nkondjock A, Ghadirian P. Dietary carotenoids and risk of colon cancer: Case-control study. Int J Cancer 110.1 (2004): 110-16.
Nolan J et al. Macular pigment and percentage of body fat. Invest Ophthalmol Vis Sci 45.11 (2004): 3940-50.
Nomura AM et al. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. Cancer Epidemiol Biomarkers Prev 6.7 (1997): 487-91.
Nussbaum JJ, Pruett RC, Delori FC. Historic perspectives: Macular yellow pigment: The first 200 years. Retina 1.4 (1981): 296-310.
Olmedilla B et al. Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. Nutr 19.1 (2003): 21-4.
Pattison DJ et al. Dietary beta-cryptoxanthin and inflammatory polyarthritis: results from a population-based prospective study. Am J Clin Nutr 82.2 (2005): 451-5.
Polidori MC et al. Plasma antioxidant status, immunoglobulin G oxidation and lipid peroxidation in demented patients: Relevance to Alzheimer disease and vascular dementia. Dementia Geriatr Cognitive Disord 18.3-4 (2004): 265-70.
Pratt S. Dietary prevention of age-related macular degeneration. J Am Optom Assoc 70.1 (1999): 39-47.
Ratnasinghe DM et al. Serum carotenoids are associated with increased lung cancer risk among alcohol drinkers, but not among non-drinkers in a cohort of tin miners. Alcohol Alcoholism 35.4 (2000): 355-60.
Richer S. ARMD-pilot (case series) environemental intervention data. J Am Optom Assoc 70 (1999): 24-36.
Richer S et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry 75 (2004): 216-30.
Rinaldi P et al. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol Aging 24.7 (2003): 915-19.
Roodenburg AJ et al. Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. Am J Clin Nutr 71.5 (2000): 1187-93.

Schupp C et al. Lutein, zeaxanthin, macular pigment, and visual function in adult cystic fibrosis patients. Am J Clin Nutr 79.6 (2004): 1045-52.
Schuurman AG et al. A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands). Cancer Causes Control 13.6 (2002): 573-82.
Semba RD, Dagnelie G. Are lutein and zeaxanthin conditionally essential nutrients for eye health? Med Hypotheses 61.4 (2003): 465-72.
Sesso HD et al. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in men. Am J Clin Nutr 81.5 (2005): 990-7.
Tamimi RM et al. Plasma carotenoids, retinol, and tocopherols and risk of breast cancer. Am J Epidemiol 161.2 (2005): 153.
Tanumihardjo SA, Li J, Dosti MP. Lutein absorption is facilitated with cosupplementation of ascorbic acid in young adults. J Am Dietetic Assoc 105.1 (2005): 114-18.
Tavani A, Negri E, La Vecchia C. Food and nutrient intake and risk of cataract. Ann Epidemiol 6 (1996): 41-6.
Terry P et al. Dietary carotenoid intake and colorectal cancer risk. Nutr Cancer 42.2 (2002): 167-72.
Thurmann PA et al. Plasma kinetics of lutein, zeaxanthin, and 3-dehydro-lutein after multiple oral doses of a lutein supplement. Am J Clin Nutr 82.1 (2005): 88-97.
Toniolo P et al. Serum carotenoids and breast cancer. Am J Epidemiol 153.12 (2001): 1142-7.
Tulley RT et al. Daily intake of multivitamins during long-term intake of olestra in men prevents declines in serum vitamins A and E but not carotenoids. J Nutr 135.6 (2005): 1456-61.
Unlu NZ et al. Carotenoid absorption from salad and salsa by humans is enhanced by the addition of avocado or avocado oil. J Nutr 135.3 (2005): 431.
Yeum KJ, Russell RM. Carotenoid bioavailability and bioconversion. Ann Rev Nutr 22 (2002): 483-504.
Zhao D-Y et al. Resonance Raman measurement of macular carotenoids in retinal, choroidal, and macular dystrophies. Arch Ophthalmol 121.7 (2003): 967-72.
Ziegler RG et al. Importance of alpha-carotene, beta-carotene, and other phytochemicals in the etiology of lung cancer. J Natl Cancer Inst 88.9 (1996): 612-15.

Lycopene



BACKGROUND AND RELEVANT PHARMACOKINETICS

Lycopene is a fat-soluble, non-provitamin A carotenoid that imparts the red colour to tomatoes, guava, rosehip, watermelon and pink grapefruit. Animals and humans do not synthesise lycopene, so they must depend on dietary sources. Research shows that bioavailability of lycopene varies depending on factors such as food source, other foods in the diet, the presence of other carotenoids and dietary fat, cooking temperatures and processing.

Processing, and heating in particular, has been found to significantly increase lycopene bioavailability, as it induces the isomerisation of lycopene from the *trans*- to *cis*-configuration (Shi & Le Maguer 2000). In other words, lycopene is best absorbed from tomato products such as pastes and sauces, rather than from unprocessed fresh tomatoes.

Lycopene is widely distributed in the human body and is one of the major carotenoids found in human serum (between 21% and 43% of total carotenoids). High concentrations are found in the adrenal gland and testes, although significant amounts are also found in the liver, adipose tissue, prostate, kidney and ovaries (El Sohemy et al 2002, Gerster 1997, Johnson 1998, Stahl et al 1992). Lycopene has also been detected in high concentrations in ciliary body and retinal pigment epithelium (Khachik et al 2002).

CHEMICAL COMPONENTS

Lycopene is a 40-carbon acyclic carotene with 11 conjugated and 2 unconjugated double bonds, normally in the all-*trans*-configuration, but the double bonds are subject to isomerisation, and various *cis*-isomers (mainly 5, 9, 13 or 15) are found in plasma and plants (Holloway et al 2000). The *cis*-isomer has better bioavailability from foods.

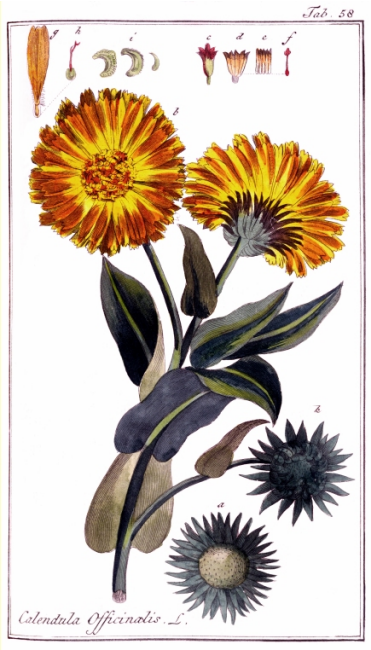
FOOD SOURCES

The richest sources of lycopene are red tomatoes and processed tomato products. Other sources include watermelon, pink grapefruit and papaya. The lycopene content of food depends on the cultivars grown and the growing conditions.

It is currently estimated that daily intake from all dietary sources ranges between 0.5 and 27 mg/person/day or 0.08 and 0.45 mg/kg/day (Jonker et al 2003).

DEFICIENCY SIGNS AND SYMPTOMS

Although lycopene is not considered an essential nutrient, it is important for wellbeing and optimal health. As such, deficiency signs and symptoms are unknown.



MAIN ACTIONS

ANTIOXIDANT

The many conjugated double bonds of lycopene make it a powerful antioxidant and its activity in vitro is nearly twice as great as beta-carotene (Cantrell et al 2003, Shi & Le Maguer 2000).

REDUCES LDL-CHOLESTEROL LEVELS AND LIPID OXIDATION

A significant 14% reduction in plasma LDL-cholesterol concentrations has been shown for a dose of 60 mg/day lycopene taken over 3 months by healthy volunteers. While the mechanism of action is unclear, in vitro testing suggests HMG-CoA reductase inhibition and enhancement of LDL receptor activity in macrophages (Fuhrman et al 1997). Lycopene also prevents oxidation of lipids and LDL cholesterol, according to a clinical study by Agarwal & Rao (1998).

CHEMOPREVENTATIVE ACTIVITY

Anticancer activity of lycopene has been demonstrated in cell and tissue culture studies and animal tumour models. Lycopene appears to inhibit human cancer cell growth by interfering with growth factor receptor signalling and cell cycle progression without producing toxicity or apoptosis (Heber & Lu 2002, Stahl et al 2000). In vitro and in vivo evidence supports the theory that antiproliferative activity is achieved by upregulation of a gene, connexin 43, which restores direct intercellular gap junctional communication, usually deficient in many human tumours. This restoration of normal intercellular gap junctional communication is associated with decreased proliferation. Investigation using animal models also suggests that lycopene may exert its chemopreventative effects by modulating lipid peroxidation and enhancing the activities of phase 2 enzymes, specifically those in the glutathione redox cycle (Bhuvaneswari et al 2001, Bhuvaneswari & Nagini 2005, Velmurugan et al 2002). A cell culture study using endometrial, mammary and lung human cancer cells has identified that lycopene has stronger antiproliferative activity than alpha- and beta-carotenes (Levy et al 1995).

Of special significance in prostate cancer prevention is the finding that lycopene interferes with local testosterone activation by reducing the expression of 5-alpha-reductase I in prostate tumours in a rat model (Siler et al 2004). As a consequence, several androgen target genes in the tumours were drastically downregulated.

OTHER ACTIONS

The Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) study showed that low plasma levels of lycopene were associated with an 18% increase in intima–media thickness (IMT) of the common carotid artery wall in men as compared with men in whom plasma levels were higher than median (Rissanen et al 2002). Lycopene also shows anti-inflammatory activity (Bhuvaneswari & Nagini 2005).

CLINICAL USE

The clinical effects of lycopene are studied in relation to dietary intake and oral supplementation. It should be noted that the assessment of dietary lycopene intake varies with the method used to collect dietary information and the food composition databases used to estimate nutritional content (Shils 2006).

CANCER PREVENTION

Lycopene is often included as an ingredient in antioxidant combination supplements and is thought to contribute to risk reduction for cancer. Some studies have investigated the effects of lycopene on risk of disease, although many consider it as part of the carotenoid group and study its effects in this way.

Total cancer risk A 2002 Japanese study involving 2444 people who were followed for 9 years found that high serum levels of lycopene, total carotenes and carotenoids were significantly and inversely associated with subsequent mortality from all causes and cancers of all sites after adjusting for gender, age and serum levels of total cholesterol, alpha-tocopherol and retinol (Ito et al 2002).

In particular, there is some evidence that lycopene levels are inversely proportional to cancers of the prostate, stomach and cervix.

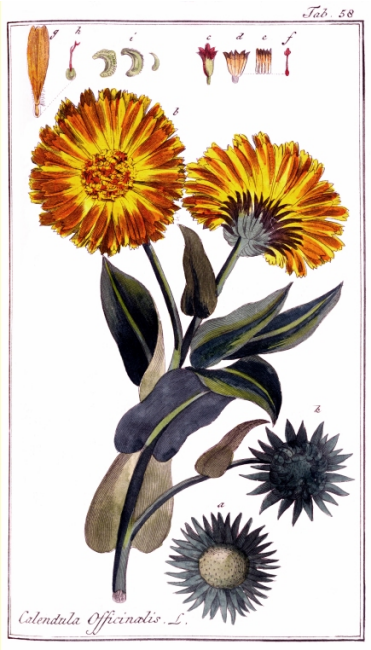
Prostate cancer A review of 15 epidemiological studies concluded that although results are not yet definitive, overall the data suggest that increased consumption of lycopene from tomatoes and tomato-based products may be prudent in order to reduce the risk of prostate cancer (Giovannucci 2002). More specifically, five studies found a 30–40% reduction in prostate cancer risk associated with high tomato or lycopene consumption, three found a non-significant 30% reduction in risk, and seven were not supportive of an association. The largest epidemiological study was conducted by the Harvard Medical School, which assessed the diets of 47,894 volunteers and identified several foods as significantly associated with lower prostate cancer risk (Giovannucci et al 1995). They were tomato sauce, tomatoes and pizza, which are primary sources of lycopene. Additionally, consumption of more than 10 servings per week was required for protective effects to be observed.

Besides the epidemiological data on primary prevention, there are some reports of short- to medium-term clinical intervention trials with lycopene supplement or

tomatoes. A small study of men with high-grade prostate intraepithelial neoplasia (HGPIN), a precursor of prostate cancer, showed that supplementation with 4 mg lycopene twice daily for 1 year had a chemopreventative effect, preventing progression of HGPIN to prostate cancer (Mohanty et al 2005). Three of four studies found that either lycopene or tomatoes significantly reduces serum levels of prostate-specific antigen (PSA) (Ansari & Gupta 2004, Bowen et al 2002, Clark et al 2006, Kucuk et al 2002). Kucuk et al conducted a randomised study involving 26 men, which found that taking a tomato oleoresin extract containing 30 mg lycopene for 3 weeks resulted in smaller prostate tumours, less involvement of surgical margins and/or extra-prostatic tissues with the cancer and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia compared with controls (Kucuk et al 2001). Additionally, plasma PSA levels were reduced. Another study, by Bowen et al (2002), involving 32 patients with localised prostate cancer found that consuming tomato sauce-based pasta dishes for 3 weeks (providing 30 mg lycopene/day) reduced serum PSA levels by 17.5% and, overall, significantly reduced DNA damage in both leukocyte and prostate tissue. A lycopene supplement (Lycored softules) for 3 months in 20 patients with metastatic hormone refractive prostate cancer (HRPC) significantly reduced PSA levels and provided relief in bone pain and lower urinary tract symptoms (Ansari & Gupta 2004). HRPC was defined as an increase in PSA levels of more than twice the normal value (0–4 ng/mL) confirmed in two consecutive determinations at 2-week intervals in the presence of castrate levels of testosterone. In contrast, no effect on PSA levels was observed in a dose-escalating study of 36 men, which tested high doses of lycopene in biochemically relapsed prostate cancer (Clark et al 2006). The doses studied were 15, 30, 45, 60, 90, and 120 mg/day taken for 1 year and significant elevations of plasma lycopene were noted at 3 months and then appeared to plateau for all six dose levels.

Stomach Although mixed results were previously obtained from case–control studies, recent evidence is supportive of lycopene as a protective agent in stomach cancer (De Stefani et al 2000, Garcia-Closas et al 1999, Tsugane et al 1992, Yuan et al 2004).

The relationship between pre-diagnostic serum levels of carotenoids and risk of gastric cancer was determined in a study involving 761 middle-aged or older men in Shanghai, China, with a follow-up of 12 years (Yuan et al 2004). High serum levels of alpha- and beta-carotenes and lycopene were significantly associated with reduced risk of developing gastric cancer (all P values for trend ≤ 0.05) whereas no statistically significant relationships among the serum levels of beta-cryptoxanthin,



lutein/zeaxanthin, retinol, alpha-tocopherol and gamma-tocopherol were identified with gastric cancer risk.

Cervix Results from two case–control studies have found an association between low serum lycopene levels and existing cervical cancer, but it is uncertain whether this can be interpreted as a risk factor because depleted levels may be a result of tumour usage, the increased burden of oxidative stress or both (Nagata et al 1999, Palan et al 1996).

PREVENTION OF CARDIOVASCULAR DISEASE

Recent epidemiological studies have shown an inverse relationship between tissue and serum levels of lycopene and risk of acute coronary event or stroke and degree of IMT of the common carotid artery (Kohlmeier et al 1997, Rissanen et al 2002, 2003, Sesso et al 2004).

Strong population-based evidence comes from the large Women's Health Study ($n = 39{,}876$), the European Community Multicenter Study on Antioxidants, Myocardial Infarction and Breast Cancer (EURAMIC) study and the Kuopio Ischaemic Heart Disease Risk Factor study (Kohlmeier et al 1997, Rissanen et al 2003, Sesso et al 2004).

In the Women's Health Study, higher plasma lycopene concentrations were associated with a lower risk of cardiovascular disease (Sesso et al 2004). Specifically, for cardiovascular disease, exclusive of angina, women in the upper three quartiles had a significant multivariate risk reduction of 50% compared with those in the lowest quartile. For the EURAMIC study, 1379 individuals (662 patients, 717 controls) from 10 European countries were recruited (Kohlmeier et al 1997). Needle aspiration biopsy samples of adipose tissue were taken shortly after myocardial infarction, and levels of alpha- and beta-carotenes, lycopene, and alpha-tocopherol were measured. After adjusting for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal history of heart disease, only lycopene levels were found to be protective. The effect also appeared to be dose-dependent.

In the Kuopio Ischaemic Heart Disease Risk Factor study, 1028 middle-aged men (aged 46–64 years) from Finland were examined and classified into quartiles according to their serum lycopene concentration (Rissanen et al 2003). The men in the lowest quartile had a significantly higher mean IMT of the common carotid artery (CCA-IMT) and maximal CCA-IMT than the others. Once again, a dose-dependent effect was observed as the mean and maximal CCA-IMT increased linearly across the quarters of serum lycopene concentration. This particular finding is important because increased IMT of the CCA has been shown to predict coronary events.

REDUCING RISK OF MACULAR DEGENERATION

Lycopene supplements are sometimes used to reduce the risk of developing macular degeneration and generally support eye health. In general, it is taken in combination with other carotenoids, such as zeaxanthin and lutein, for this indication for which there is supportive evidence (Cardinault et al 2005). Few studies are available to determine whether lycopene as a sole agent exerts clinically significant protective effects. One cohort study of 159 older people found no inverse association between lycopene intake and 5-year incidence of early age-related macular degeneration (ARMD) (Flood et al 2002). Alternatively, a recent study comparing 34 patients with ARMD to 21 control subjects found that of the serum carotenoid concentrations measured, only lycopene was decreased significantly in the serum LDL and HDL fractions ($P < 0.05$).

CATARACT PREVENTION

Studies have identified protective effects for lycopene against oxidative changes in human lens epithelial cells in vitro and reduced incidence and grading of cataract in test animals (Gupta et al 2003, Mohanty et al 2002, Pollack et al 1996). A cross-sectional survey of 372 older volunteers also produced positive results, finding the risk of cortical cataract was lowest in people with the highest plasma concentrations of lycopene (Gale et al 2001).

PROTECTION AGAINST UV-INDUCED PHOTODAMAGE

Oral ingestion Increasing lycopene intake to 16 mg/day (using tomato paste) over a 10-week period has been shown to provide significant protection against erythema formation following UV irradiation, compared with placebo (Stahl & Sies 2002). The protective effects appear to develop slowly, as tests conducted at 4 weeks found no significant changes. Protective effects were also seen in another study that compared the synthetic lycopene with concentrated tomato extract (Lyc-o-mato) (Aust et al 2005). The daily dose of lycopene was approximately 10 mg/day, which was lower in than the previous study. Again, 12 weeks were required to detect significant protective effects against UV-induced erythema and the effect was more pronounced in the group using a natural lycopene source.

Topical use Results from an experimental model show that topical lycopene also has protective effects against acute UV-induced photodamage (Andreassi et al 2004, Fazekas et al 2003). Furthermore, it may act as a preventative agent via inhibition of epidermal ornithine decarboxylase activity, reducing inflammatory responses, maintaining normal cell proliferation, and possibly preventing DNA damage, as indicated by blocking the necessitating step of apoptosis following UVB injury.

OTHER USES
General antioxidant nutrient.

DOSAGE RANGE
BASED ON AVAILABLE EVIDENCE
- Hypercholesterolaemia: 60 mg/day.
- One large study on lycopene and prostate cancer suggested that a daily intake of approximately 6.5 mg was protective (Giovannucci et al 1995).
- Sunburn protection: 10–16 mg/day.

TOXICITY
Animal studies have shown that 600 mg lycopene/kg/day is not toxic (Jonker et al 2003).

ADVERSE REACTIONS
Animal studies have demonstrated that 600 mg lycopene/kg/day does not produce adverse effects, and is well tolerated (Jonker et al 2003). This level is far in excess of usual dietary intake in humans.

SIGNIFICANT INTERACTIONS
DRUGS REDUCING FAT ABSORPTION (E.G. CHOLESTYRAMINE, ORLISTAT)
Drugs that reduce fat absorption, such as cholestyramine, colestipol and orlistat, may also reduce the absorption of lycopene — separate doses by at least 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS
Hypersensitivity to lycopene or its food sources.

PREGNANCY USE
Eating dietary amounts of foods rich in lycopene is likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING
- Lycopene is a fat-soluble, non-provitamin A carotenoid that imparts the red colour to tomatoes and is most bioavailable from processed food sources such as tomato paste.
- Lycopene has antioxidant and cholesterol-lowering activity and may reduce the risk of developing cardiovascular disease, according to epidemiological evidence.
- Epidemiological evidence generally suggests that higher intakes of tomato-based products reduce the risk of prostate cancer and possibly stomach cancer and cataracts.

- Preliminary evidence suggests that intervention with tomato-enriched products or lycopene may decrease tumour size in localised prostate cancer and reduce prostate specific antigen levels.
- Increased intake of lycopene has also been associated with reduced risk of cortical cataract and sunburn. Preliminary evidence also suggests topical application of lycopene protects against UV-induced erythema (sunburn).

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Lycopene is an antioxidant vitamin that may reduce the risk of developing prostate and stomach cancer, cardiovascular disease and cataracts. It also protects the skin from sunburn and may reduce cholesterol levels when ingested in high doses.

When will it start to work?

Risk reduction is likely to be a result of many years of consistently high intakes. Protective effects against sunburn have been reported after 10 weeks.

Are there any safety issues?

Safety studies conducted in animals suggest that lycopene is very safe and well tolerated.

REFERENCES

Agarwal S, Rao AV. Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. Lipids 33.10 (1998): 981-4.

Andreassi M et al. Antioxidant activity of topically applied lycopene. J Eur Acad Dermatol Venereol 18.1 (2004): 52-5.

Ansari MS, Gupta NP. Lycopene: A novel drug therapy in hormone refractory metastatic prostate cancer. Urol Oncol Semin Orig Invest 22.5 (2004): 415-20.

Aust O et al. Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema. Int J Vitam Nutr Res 75.1 (2005): 54-60.

Bhuvaneswari V, Nagini S. Lycopene: a review of its potential as an anticancer agent. Curr Med Chem Anticancer Agents 5.6 (2005): 627-35.

Bhuvaneswari V et al. Chemopreventive efficacy of lycopene on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. Fitoterapia 72.8 (2001): 865-74.

Bowen P et al. Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis. Exp Biol Med (Maywood) 227.10 (2002): 886-93.

Cantrell A et al. Singlet oxygen quenching by dietary carotenoids in a model membrane environment. Arch Biochem Biophys 412.1 (2003): 47-54.

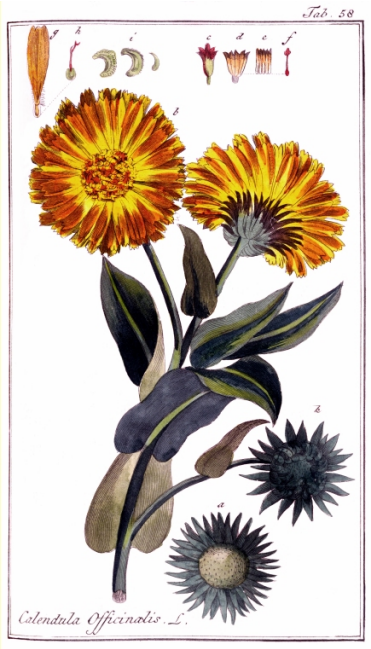
Cardinault N et al. Lycopene but not lutein nor zeaxanthin decreases in serum and lipoproteins in age-related macular degeneration patients. Clin Chim Acta 357.1 (2005): 34-42.

Clark PE et al. Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. Urology 67.6 (2006): 1257-61.

De Stefani E et al. Dietary carotenoids and risk of gastric cancer: a case-control study in Uruguay. Eur J Cancer Prev 9.5 (2000): 329-34.

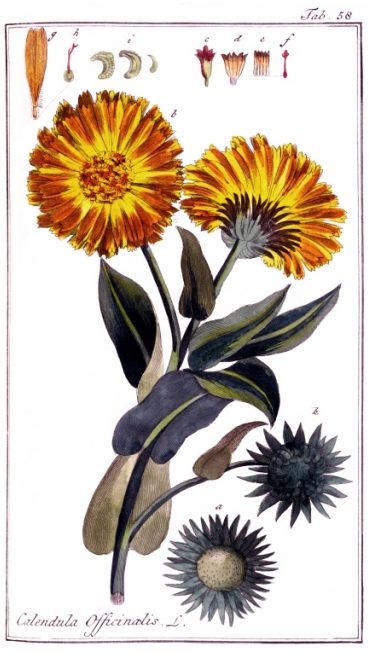
El Sohemy A et al. Individual carotenoid concentrations in adipose tissue and plasma as biomarkers of dietary intake. Am J Clin Nutr 76.1 (2002): 172-9.

Fazekas Z et al. Protective effects of lycopene against ultraviolet B-induced photodamage. Nutr Cancer 47.2 (2003): 181-7.
Flood V et al. Dietary antioxidant intake and incidence of early age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 109.12 (2002): 2272-8.
Fuhrman B, Elis A, Aviram M. Hypocholesterolemic effect of lycopene and beta-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor activity in macrophages. Biochem Biophys Res Commun 233.3 (1997): 658-62.
Gale CR et al. Plasma antioxidant vitamins and carotenoids and age-related cataract. Ophthalmology 108.11 (2001): 1992-8.
Garcia-Closas R et al. Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. Cancer Causes Control 10.1 (1999): 71-5.
Gerster H. The potential role of lycopene for human health. J Am Coll Nutr 16.2 (1997): 109-26.
Giovannucci E et al. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 87.23 (1995): 1767-76.
Giovannucci E. A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Exp Biol Med (Maywood) 227.10 (2002): 852-9.
Gupta SK et al. Lycopene attenuates oxidative stress induced experimental cataract development: an in vitro and in vivo study. Nutrition 19.9 (2003): 794-9.
Heber D, Lu QY. Overview of mechanisms of action of lycopene. Exp Biol Med (Maywood) 227.10 (2002): 920-3.
Holloway DE et al. Isomerization of dietary lycopene during assimilation and transport in plasma. Free Radic Res 32.1 (2000): 93-102.
Ito Y et al. Serum antioxidants and subsequent mortality rates of all causes or cancer among rural Japanese inhabitants. Int J Vitam Nutr Res 72.4 (2002): 237-50.
Johnson EJ. Human studies on bioavailability and plasma response of lycopene. Proc Soc Exp Biol Med 218.2 (1998): 115-20.
Jonker D et al. Ninety-day oral toxicity study of lycopene from Blakeslea trispora in rats. Regul Toxicol Pharmacol 37.3 (2003): 396-406.
Khachik F et al. Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. Exp Biol Med (Maywood) 227.10 (2002): 845-51.
Kohlmeier L et al. Lycopene and myocardial infarction risk in the EURAMIC Study. Am J Epidemiol 146.8 (1997): 618-26.
Kucuk O et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarkers Prev 10.8 (2001): 861-8.
Kucuk O et al. Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood) 227.10 (2002): 881-5.
Levy J et al. Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. Nutr Cancer 24.3 (1995): 257-66.
Mohanty I et al. Lycopene prevents sugar-induced morphological changes and modulates antioxidant status of human lens epithelial cells. Br J Nutr 88.4 (2002): 347-54.
Mohanty NK et al. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. Urol Oncol Semin Orig Invest 23.6 (2005): 383-5.
Nagata C et al. Serum carotenoids and vitamins and risk of cervical dysplasia from a case-control study in Japan. Br J Cancer 81.7 (1999): 1234-7.
Palan PR et al. Plasma levels of beta-carotene, lycopene, canthaxanthin, retinol, and alpha- and tau-tocopherol in cervical intraepithelial neoplasia and cancer. Clin Cancer Res 2.1 (1996): 181-5.
Pollack A et al. Inhibitory effect of lycopene on cataract development in galactosemic rats. Metab Pediatr Syst Ophthalmol 19-20 (1996): 31-6.
Rissanen T et al. Lycopene, atherosclerosis, and coronary heart disease. Exp Biol Med (Maywood) 227.10 (2002): 900-7.



Rissanen TH et al. Serum lycopene concentrations and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. Am J Clin Nutr 77.1 (2003): 133-8.
Sesso HD et al. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. Am J Clin Nutr 79.1 (2004): 47-53.
Shi J, Le Maguer M. Lycopene in tomatoes: chemical and physical properties affected by food processing. Crit Rev Biotechnol (20.4 (2000): 293-334.
Shils M. Modern Nutrition in Health and Disease, 10th edn. Lippincott Williams and Wilkins, 2006. Available at: www.ovid.com (Accessed 13-6-2006).
Siler U et al. Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. FASEB J 18.9 (2004): 1019-21.
Stahl W, Sies H. Carotenoids and protection against solar UV radiation. Skin Pharmacol Appl Skin Physiol 15.5 (2002): 291-6.
Stahl W et al. Cis-trans isomers of lycopene and beta-carotene in human serum and tissues. Arch Biochem Biophys 294.1 (1992): 173-7.
Stahl W et al. Stimulation of gap junctional communication: comparison of acyclo-retinoic acid and lycopene. Arch Biochem Biophys 373.1 (2000): 271-4.
Tsugane S et al. Cross-sectional study with multiple measurements of biological markers for assessing stomach cancer risks at the population level. Environ Health Perspect 98 (1992): 207-10.
Velmurugan B et al. Prevention of N-methyl-N'-nitro-N-nitrosoguanidine and saturated sodium chloride-induced gastric carcinogenesis in Wistar rats by lycopene. Eur J Cancer Prev 11.1 (2002): 19-26.
Yuan JM et al. Prediagnostic levels of serum micronutrients in relation to risk of gastric cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev 13.11 (2004): 1772-80.

L-Lysine



BACKGROUND

L-Lysine is absorbed from the small intestine and is transported to the liver via the portal circulation where it is involved in protein biosynthesis and partly metabolised.

CHEMICAL COMPONENTS

L-Lysine is the biologically active stereoisomer of lysine.

MAIN ACTIONS

ESSENTIAL AMINO ACID

The human body cannot synthesise L-lysine so it must be taken in through the diet. The richest sources of L-lysine are animal proteins such as meat and poultry. It is also found to lesser extents in eggs, beans and dairy products (Bratman & Kroll 2000).

ANTIVIRAL

L-Lysine has an inhibitory effect on the multiplication of HSV in cell cultures (Griffith et al 1981, Milman et al 1980). It appears to act as an antimetabolite and competes with arginine for inclusion into viral replicative processes (Griffith et al 1981). As such, lysine retards the viral growth promoting action of arginine.

CALCIUM REGULATION

L-Lysine may be involved in the cellular absorption, regulation and use of calcium (Civitelli et al 1992). In vitro tests with human osteoblasts indicate that lysine has a positive effect on osteoblast proliferation, activation and differentiation (Torricelli et al 2003).

OTHER ACTIONS

L-Lysine is required for biosynthesis of carnitine, collagen and elastin.

CLINICAL USE

HERPES SIMPLEX — PREVENTION AND TREATMENT

A number of clinical studies have investigated the effects of oral L-lysine supplementation as prophylaxis or treatment of herpes virus infections, overall producing contradictory results (Digiovanna & Blank 1984, Griffith et al 1978, 1987, McCune et al 1984, Milman et al 1978, 1980, Thein & Hurt 1984, Walsh et al 1983, Wright 1994).

One randomised, double-blind crossover study found that supplementation with 1248 mg/day of L-lysine decreased the recurrence rate of HSV attacks in non-

immunocompromised subjects, but did not shorten healing time during an outbreak (McCune et al 1984). Another double-blind trial compared the effects of 1000 mg L-lysine three times daily for 6 months with placebo treatment in 52 subjects. This time, not only was L-lysine found to decrease recurrence rates, but also symptoms were significantly diminished in severity and healing time significantly reduced (Griffith et al 1987). An open study of 45 patients with recurring HSV infection found that L-lysine supplementation accelerated recovery and reduced recurrence. The doses used were between 312 and 1200 mg/day in single or multiple doses (Griffith et al 1978). Thein and Hurt (1984) conducted a 12-month, double-blind crossover trial involving 26 subjects with recurring herpes lesions and found that a dose of 1000 mg/day had protective effects against lesion formation. Furthermore, once supplementation ceased, an increase in lesion frequency occurred. This study went further than others, identifying that serum lysine levels need to exceed 165 nmol/mL in order for clinical effects to become significant.

Two further double-blind studies produced negative results. Doses of 1000 mg or 1200 mg/day were tested, both failing to produce prophylactic or treatment effects for herpes simplex (Digiovanna & Blank 1984, Milman et al 1980).

However, an epidemiological survey of 1543 volunteers asking about the perceived effectiveness of lysine supplements to treat herpes infections over a 6-month trial period indicated positive results (Walsh et al 1983). Of those people with cold sores or fever blisters, 92% claimed lysine supplements were 'very effective' or 'an effective form' of treatment and 81% of those with genital herpes and who had tried other forms of treatment also claimed positive results.

In practice, doses of >3000 mg/day are used as treatment during an acute episode, based on the positive findings of the Griffith study. This is combined with a diet low in arginine-rich foods, such as chocolate, peas, nuts and beer, and high in lysine-rich foods such as baked beans and eggs.

OTHER USES

OSTEOPOROSIS PREVENTION

Two studies have investigated the effects of oral L-lysine supplementation on calcium use to determine whether L-lysine has a role in the prevention of osteoporosis. In these tests, oral L-lysine was shown to significantly increase intestinal absorption of calcium and decrease renal excretion in both healthy women and those with osteoporosis (Civitelli et al 1992).

ANXIETY AND MOOD DISTURBANCES

According to a randomised, double-blind trial, fortification of lysine in a wheat-based (L-lysine deficient) diet significantly reduced anxiety score in males, but not females with high baseline anxiety. It is suspected that L-lysine's action as a 5-HT_4 receptor antagonist and benzodiazepine receptor agonist are responsible for the observed effect (Smriga et al 2004). In contrast, a prospective study of 29 133 men (aged 50–69 years) found no association between L-lysine intake and depressed mood (Hakkareainen et al 2003).

DOSAGE RANGE

HERPES SIMPLEX INFECTIONS

- Prevention: 1000–3000 mg/day.
- Acute treatment: minimum 3000 mg/day in divided doses taken between meals until lesions have healed.

OSTEOPOROSIS PREVENTION

- 400–800 mg L-lysine taken together with calcium supplementation.

TOXICITY

Not known

ADVERSE REACTIONS

Doses greater than 10–15 g/day may cause gastrointestinal discomfort with symptoms of nausea, vomiting and diarrhoea.

SIGNIFICANT INTERACTIONS

CALCIUM

Clinical tests have found L-lysine enhances intestinal absorption and decreases renal excretion of calcium (Civitelli et al 1992) — potentially beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with the rare genetic disorder hyperlysinaemia/hyperlysinuria (Hendler et al 2001). High-dose lysine supplements should be used with caution in hypercalcaemic states, and by people with kidney or liver disease.

PREGNANCY USE

Safety is unknown for high-dose supplements; however, dietary intake levels are safe.

PRACTICE POINTS/PATIENT COUNSELLING

- L-Lysine is an essential amino acid found in foods such as animal proteins, eggs and milk.
- It has been shown to inhibit HSV multiplication in vitro.
- Supplemental L-lysine is popular as a prophylactic and treatment for HSV.
- Studies have yielded inconsistent results suggesting that there may be individual variation in responses.
- Doses used as prophylaxis range from 1000–3000 mg/day with treatment doses generally above 3000 mg/day.
- L-Lysine may also enhance intestinal absorption of calcium and reduces its renal excretion.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

L-Lysine supplements may reduce the frequency and severity of herpes simplex outbreaks. It may also improve the way the body absorbs and retains calcium.

When will it start to work?

Studies suggest that several months' treatment may be required, with a long-term approach recommended.

Are there any safety issues?

L-Lysine appears to be a very safe supplement, although safety has not been established in pregnancy and lactation for high-dose supplements.

REFERENCES

Bratman S, Kroll D. Natural Health Bible. Rocklin, CA: Prima Health, 2000.

Civitelli R et al. Dietary L-lysine and calcium metabolism in humans. Nutrition 8.6 (1992): 400-5.

Digiovanna JJ, Blank H. Failure of lysine in frequently recurrent herpes simplex infection: Treatment and prophylaxis. Arch Dermatol 120.1 (1984): 48-51.

Griffith RS, Norins AL, Kagan C. A multicentered study of lysine therapy in herpes simplex infection. Dermatologica 156.5 (1978): 257-67.

Griffith RS, DeLong DC, Nelson JD. Relation of arginine-lysine antagonism to herpes simplex growth in tissue culture. Chemotherapy 27.3 (1981): 209-13.

Griffith RS et al. Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis. Dermatologica 175.4 (1987): 183-90.

Hakkarainen et al. Association of dietary amino acids with low mood. Depression Anxiety 18.2 (2003): 89-94.

Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.

McCune MA et al. Treatment of recurrent herpes simplex infections with L-lysine monohydrochloride. Cutis 34.4 (1984): 366-73.

Milman N, Scheibel J, Jessen O. Failure of lysine treatment in recurrent herpes simplex labialis. Lancet 2.8096 (1978): 942.

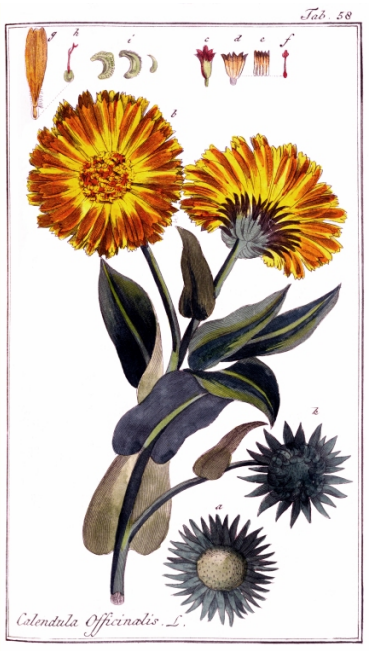
Milman N, Scheibel J, Jessen O. Lysine prophylaxis in recurrent herpes simplex labialis: a double-blind, controlled crossover study. Acta Derm Venereol 60.1 (1980): 85-7.

Smriga M et al. Lysine fortification reduces anxiety and lessens stress in family member in economically weak communities in Northwest Syria. Proc Natl Acad Sci USA 101.22 (2004): 8285-8.

Thein DJ, Hurt WC. Lysine as a prophylactic agent in the treatment of recurrent herpes simplex labialis. Oral Surg Oral Med Oral Pathol 58.6 (1984): 659-66.
Torricelli P et al. Human osteopenic bone-derived osteoblasts: essential amino acids treatment effects. Artif Cells Blood Substit Immobil Biotechnol 31.1 (2003): 35-46.
Walsh DE, Griffith RS, Behforooz A. Subjective response to lysine in the therapy of herpes simplex. J Antimicrob Chemother 12 (1983): 489-96.
Wright EF. Clinical effectiveness of lysine in treating recurrent aphthous ulcers and herpes labialis. Gen Dent 42.1 (1994): 40-2.

Magnesium

Historical note The word magnesium comes from the name of the Greek city Magnesia, where large deposits of magnesium were found. Magnesium, in the form of Epsom salts, has long been used therapeutically as a laxative although it is also used in many other ways, such as a foot soak to soften rough spots and absorb foot odour and as a bath additive to ease muscle aches and pains.



BACKGROUND AND RELEVANT PHARMACOKINETICS

Magnesium (Mg) is the fourth most abundant cation in the body, with 50–60% sequestered in the bone and the remaining being distributed equally between muscle and non-muscular soft tissue. Only about 1% of total body Mg is found in the extracellular fluid.

Dietary intake, renal and intestinal function finely balance and maintain plasma magnesium concentrations.

Absorption of dietary Mg starts within 1 hour of ingestion, with salts of high solubility having the most complete absorption (e.g. magnesium citrate). Magnesium absorption also requires selenium, parathyroid hormone and vitamins B6 and D and is hindered by phytate, fibre, alcohol, excess saturated fat, phosphorus or calcium intake (Johnson 2001, Saris et al 2000). Healthy people absorb 30–40% of ingested Mg; this can increase to 70% in cases of low intake or deficiency (Braunwald et al 2003). Once absorbed, it is transported to the liver, enters the systemic circulation and is transported around the body and ultimately excreted via the kidneys.

Clinical note — Magnesium citrate: the superior supplement

Several forms of Mg are available in OTC supplements; however, not all exhibit the same bioavailability. According to a randomised, double-blind, placebo-controlled study, magnesium amino chelate and magnesium citrate are better absorbed than magnesium oxide in healthy individuals (Walker et al 2003). Of the three, magnesium citrate led to the greatest increase in mean serum Mg concentration, a result evident after acute dosing (24 hours) and chronic dosing (60 days). Furthermore, although mean erythrocyte Mg concentration showed no differences among groups, chronic magnesium citrate supplementation resulted in the greatest mean salivary Mg concentration compared with all other treatments.

FOOD SOURCES

Good dietary sources of Mg include legumes, wholegrain cereals, nuts, dark green leafy vegetables, cocoa, soy flour, seeds, nuts, mineral water and hard water.

DEFICIENCY SIGNS AND SYMPTOMS

When reduced intakes or increased losses of magnesium, potassium or phosphorus occur (the three major intracellular elements), losses of the others generally follow. As such, many deficiency symptoms are also due to alterations in potassium and/or phosphorus status and manifest as neurological or neuromuscular symptoms.

Symptoms of deficiency include:

- muscle spasms
- anorexia
- nausea and vomiting
- muscular weakness and spasms
- lethargy
- insomnia
- depression
- mental confusion and decreased attention span
- personality changes
- hyper-irritability and excitability
- vertigo
- cardiac arrhythmia, tetany and ultimately convulsions can develop if deficiency is prolonged.

Although Mg deficiency is a common clinical problem, serum levels are often overlooked or not measured in patients at risk for the disorder. About 10% of patients admitted to hospitals and up to 65% of patients in intensive care units may be Mg deficient (Braunwald et al 2003).

Low Mg states are associated with several serious diseases such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapse, metabolic syndrome, diabetes mellitus, hyperlipidaemia, pre-eclampsia and eclampsia (Fox et al 2001, Guerrero-Romero & Rodriguez-Moran 2002). Epidemiological evidence suggests that a low dietary intake of Mg is also associated with impaired lung function, bronchial hyperreactivity and wheezing, and risk of stroke (Ascherio et al 1998, Hill et al 1997). Magnesium deficiency may also play a role in the pathophysiology of Tourette's syndrome (Grimaldi 2002).

PRIMARY DEFICIENCY

A primary deficiency is rare in healthy people as the kidneys are extremely efficient at maintaining Mg homeostasis. However, deficiency is possible in protein–calorie

malnutrition (e.g. kwashiorkor). Experiments have shown that people fed low Mg diets develop deficiency symptoms such as anorexia, nausea and vomiting, weakness and lethargy within weeks.

Marginal deficiencies are far more common and very often undiagnosed. There is evidence that daily Mg intake has declined substantially since the beginning of last century, with dietary surveys showing the average intake in Western countries is often below the RDI (Saris et al 2000).

SECONDARY DEFICIENCY

Most Mg deficiencies occur due to a combination of insufficient dietary intake and/or intestinal malabsorption and increased Mg depletion. There are many factors that predispose to deficiency and these are listed in the table below.

Medicines increasing risk of deficiency Many pharmaceutical drugs have the potential to cause hypomagnesaemia (e.g. loop diuretics, cisplatin, corticosteroids, cyclosporin, antibiotics such as tetracyclines and aminoglycosides).

RISK FACTORS FOR MAGNESIUM DEPLETION

Dietary	Excessive intake of ethanol, salt, phosphoric acid (soft drinks), caffeine Protein–energy malnutrition
Endocrine disorders	Hyperaldosteronism Hyperparathyroidism with hypercalcaemia Hyperthyroidism Diabetes mellitus and glycosuria
Lifestyle	Profuse sweating Intense, prolonged stress

Gastrointestinal disorders	Coeliac disease Infections Inflammatory bowel diseases Malabsorption syndromes Pancreatitis Partial bowel obstruction Vomiting/diarrhoea
Pharmaceutical drugs	Aminoglycoside antibiotics Cisplatin Corticosteroids Cyclosporin Loop diuretics Tetracycline antibiotics
Renal	Metabolic disorders Acidosis Nephrotoxic drugs (e.g. cisplatin, cyclosporin)
Other	Hyperthermia Hypercatabolic states such as burns Phosphate depletion Potassium depletion Pregnancy Lactation Excessive menstruation Long-term parenteral nutrition combined with loss of body fluids (e.g. diarrhoea) Parasitic infection (e.g. pinworms)

(Braunwald et al 2003, Johnson 2001, McDermott et al 1991, Sanders et al 1999, Shils et al 1999)

MAIN ACTIONS

Magnesium plays an essential role in a wide range of fundamental biological reactions in the body. It is involved in over 300 essential enzymatic reactions and is necessary for every major biological process. It is especially important for those enzymes that use nucleotides as cofactors or substrates and plays a role in many processes that are of central importance in the biochemistry of each cell, particularly in energy metabolism. It is also required for many other important biological functions such as:

- nerve conduction
- regulation of vascular tone
- muscle activity
- amino acid and protein synthesis
- DNA synthesis and degradation
- immune function.

INTERACTION WITH OTHER NUTRIENTS

Magnesium is extremely important for the metabolism of calcium, potassium, phosphorus, zinc, copper, iron, sodium, lead, cadmium and the intracellular homeostasis and activation of thiamine (Johnson 2001). It acts as a calcium antagonist and interacts with nutrients such as potassium, phosphorus, vitamin B6 and boron.

OTHER ACTIONS

In its macro form, oral Mg salts have a laxative and antacid activity and are practically insoluble in water.

CLINICAL USE

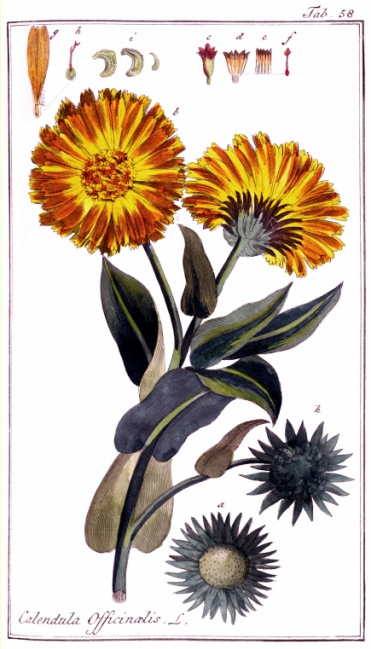
In practice, Mg is administered by various routes such as intramuscular injection and intravenous infusion. This review will focus only on oral Mg, as this is the form most commonly used by the general public, outside the hospital setting.

DEFICIENCY: TREATMENT AND PREVENTION

Magnesium supplementation is traditionally used to correct deficiency states or avoid deficiency in people at increased risk, such as people with malabsorption syndromes and chronic alcoholics (Saris et al 2000). Low serum Mg levels <0.7 mmol/L (1.8 mg/dL, 1.5 meq/L) are indicative of Mg deficiency, although symptoms occur when serum Mg is <0.5 mmol/L (1.2 mg/dL, 1.0 meq/L) (Braunwald et al 2003).

CARDIOVASCULAR DISEASE

Low Mg states are associated with several cardiovascular diseases, such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve



prolapse, stroke, non-occlusive myocardial infarction and hyperlipidaemia (Fox et al 2001, Frishman et al 2005, Guerrero-Romero & Rodriguez-Moran 2002, Rasmussen et al 1988, Saris et al 2000).

Although the pathophysiology of each condition is multifactorial, the multiple biological effects of Mg in the cardiovascular system suggest an important cardioprotective role. In the heart, it acts as a calcium-channel blocker and promotes resting polarisation of the cell membrane, thereby reducing arrhythmias (Shattock et al 1987). It also helps prevent serum coagulation (Frishman et al 2005). Low Mg selectively impairs the release of NO from the coronary endothelium, resulting in vasoconstriction and possibly coronary embolism.

In experimental animals, dietary Mg deficiency exacerbates atherosclerosis and vascular damage because it has a modulatory role in controlling lipid metabolism in the arterial wall.

Mitral valve prolapse It has been suggested that hypomagnesaemia is common in patients with mitral valve prolapse and therefore supplementation to correct this deficiency could exert beneficial clinical effects (Kitlinski et al 2004). In 1997, one study of 141 subjects with symptomatic mitral valve prolapse confirmed this suspicion by identifying hypomagnesaemia in 60% of patients (Lichodziejewska et al 1997). A randomised, double-blind, crossover study followed those Mg-deficient people and found that 5 weeks' Mg supplementation significantly alleviated symptoms of weakness, chest pain, dyspnoea, palpitation and anxiety (Lichodziejewska et al 1997). The dose regimen used was 3 tablets of magnesium carbonate 600 mg (7 mmol elementary Mg) daily for the first week followed by 2 tablets daily until the fifth week.

Symptoms of coronary artery disease (CAD) In 2003, the results from a multicentre, multinational, prospective, randomised, double-blind and placebo-controlled trial showed that 6 months' oral Mg supplementation in patients with CAD results in a significant improvement in exercise tolerance, exercise-induced chest pain, and QOL (Shechter et al 2003). The study used oral magnesium citrate (15 mmol twice daily) as Magnosolv-Granulat (total Mg 365 mg). Previously, randomised placebo-controlled studies have shown that oral Mg supplementation in CAD patients is associated with significant improvement in brachial artery endothelial function and inhibits platelet-dependent thrombosis, providing several potential mechanisms by which Mg could beneficially alter outcomes in these patients (Shechter et al 1999, 2000).

Hypertension Magnesium supplementation produces a modest dose-dependent blood pressure-lowering effect according to a 2002 meta-analysis of 20 randomised trials that involved 1220 subjects (Jee et al 2002). For each 10 mmol/day increase in

Mg intake, a further reduction of 4.3 mmHg in SBP and of 2.3 mmHg in DBP was observed.

Stroke A prospective study of 43,738 men (Health Professional Follow-Up Study) conducted over 8 years showed an inverse association between dietary Mg intake and the risk of total stroke (Ascherio et al 1998). The inverse association was stronger in hypertensive than normotensive men and was not materially altered by adjustments for blood pressure levels. The study also identified an inverse association between low dietary fibre intake and stroke.

Dyslipidaemia Oral Mg supplementation (magnesium oxide 12 mmol/day) taken over 3 months effectively reduced plasma lipids compared with placebo in people with ischaemic heart disease (Rasmussen et al 1989). The double-blind study showed that Mg produced a 13% increase in molar ratio of apolipoprotein A1:apolipoprotein B compared with a 2% increase in the placebo group, which was statistically significant. This was caused by a decrease in apolipoprotein B concentrations, which were reduced by 15% in the Mg group as compared with a slight increase in the placebo group. Additionally, triglyceride levels decreased by 27% after Mg treatment. Overall, these beneficial results are associated with a decrease in cardiovascular mortality.

Arrhythmia prevention in congestive heart failure Although Mg is usually administered intravenously when indicated in this condition, one controlled study using oral Mg showed that it significantly reduced the incidence of arrhythmias in patients with stable congestive heart failure (Bashir et al 1993). The double-blind crossover study used magnesium chloride (3204 mg/day in divided doses).

MIGRAINE HEADACHES: PREVENTION

People who suffer with recurrent migraines appear to have lower intracellular Mg levels (demonstrated in both red blood cells and white blood cells) than those who do not experience migraines. (See 'Feverfew' monograph for more information about migraine aetiology.)

Two randomised, double-blind studies using high-dose oral Mg have found it to be useful in migraine sufferers, reducing frequency and/or number of days with migraine headache (Peikert et al 1996, Taubert 1994). One placebo-controlled study using a lower dose found no benefit in reducing the frequency of migraine headaches (Pfaffenrath et al 1996).

A dose of 24 mmol Mg (600 mg trimagnesium dicitrate) taken daily over 12 weeks produced a 42% reduction in frequency of attack compared with 16% with placebo in one study of 81 patients, with a mean attack frequency of 3.6 migraine headaches each month (Peikert et al 1996). Effects were observed after week 9 and treatment

also significantly decreased the number of days with migraine. Significant decreases in migraine frequency were also observed in a crossover study that used the same dose and form of oral Mg (Taubert 1994).

Menstrual migraine headache Oral Mg supplementation decreases pain, premenstrual symptoms and the number of days with migraine headache, according to one double-blind placebo-controlled study (Facchinetti et al 1991a). Treatment consisted of 360 mg/day of Mg (pyrollidone carboxylic acid) starting on day 15 of the menstrual cycle and continuing until the onset of menses.

Migraine prophylaxis in children Oral magnesium oxide (9 mg/kg/day) given in three divided doses with food may decrease headache frequency and severity according to a multicentre, randomised, double-blind, placebo-controlled trial (Wang et al 2003). The 16-week study involved children aged 3–17 years who reported a 4-week history of at least weekly, moderate-to-severe headache with a throbbing or pulsatile quality, associated anorexia/nausea, vomiting, photophobia, sonophobia, or relief with sleep, but no fever or evidence of infection. Of note, 27% of subjects ($n = 42$ magnesium oxide; $n = 44$ placebo) failed to complete the study, thereby hindering interpretation of the results.

Clinical note — What is the link between magnesium and migraine?
Magnesium seems to play a significant role in the pathogenesis of migraine, with low brain levels and impaired Mg metabolism reported in migraine sufferers (Thomas et al 2000). Magnesium has an effect on serotonin receptors, NO synthesis and release, and a variety of other migraine-related receptors and neurotransmitters. It is also essential for mitochondrial function within the cell. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionised Mg (Mauskop & Altura 1998). Pilot studies of migraine patients have suggested that disordered energy metabolism or Mg deficiencies may be responsible for hyperexcitability of neuronal tissue in migraine patients (Boska et al 2002). As such, factors that decrease neuronal excitability, such as Mg, may alter the threshold for triggering attacks (Boska et al 2002).

KIDNEY STONE PREVENTION

Magnesium deficiency is one of many risk factors for the development of kidney stones (Anderson 2002). Others include nutritional deficiencies of water, calcium, potassium and vitamin B6, excessive intakes of animal protein, fat, sugar, oxalates, colas, alcohol, caffeine, salt and vitamin D, lifestyle factors, and a positive family history.

A prospective double-blind study of 64 patients who were randomly assigned to receive placebo or potassium-magnesium citrate (42 mEq potassium, 21 mEq magnesium and 63 mEq citrate) daily for up to 3 years showed that the combination supplement reduced the risk of developing recurrent calcium oxalate kidney stones by 85% (Ettinger et al 1997).

PREMENSTRUAL SYNDROME

Three double-blind studies using oral Mg supplements in women with PMS have produced positive results for decreasing symptoms such as fluid retention and mood swings (Facchinetti et al 1991b, Rosenstein et al 1994, Walker et al 1998). According to all studies, clinical effects develop slowly, starting during the second menstrual cycle.

Although it is not clear what mechanism of action is responsible, a number of studies have identified decreased Mg concentrations in both red blood cell and mononuclear blood cells of women with PMS (Rosenstein et al 1994).

Dysmenorrhoea A Cochrane review of seven randomised trials investigating the effects of various treatments for dysmenorrhoea included three trials comparing Mg with placebo. Overall, Mg was found to be more effective than placebo for pain relief and resulted in less extra medication being required (Wilson & Murphy 2001).

OSTEOPOROSIS PREVENTION

Magnesium comprises about 1% of bone mineral and is involved in a number of activities supporting bone strength, preservation, and remodelling. As the Mg content of bone mineral decreases, bone calcium crystals become larger and more brittle. Therefore, low Mg states increase the risk of osteoporosis. Several studies have investigated the effects of supplemental Mg on bone density, generally finding it has positive effects.

One long-term study has reported an increase in bone density for magnesium hydroxide supplementation in a group of menopausal women (Sojka & Weaver 1995). After the 2-year test period, fracture incidence was also reduced. Another 2-year study showed that Mg supplementation in postmenopausal women with osteoporosis results in increased bone mass at the wrist after 1 year, with no further increase after 2 years of supplementation (Stendig-Lindberg et al 1993). The regimen used here was oral Mg 750 mg/day for the first 6 months followed by 250 mg/day thereafter.

Clinical note — Peak bone mass
The best opportunity to influence bone mass occurs early in life. It has been estimated that approximately 40% of peak bone mass is accumulated during

adolescence with peak bone mass in the hip achieved by age 16–18 years (Weaver 2000). The spinal vertebrae are still able to increase in mass until the third decade of life, when total peak bone mass reaches 99% by age 26.6 years (±3.7 years). As such, ensuring an adequate intake of calcium and Mg early in life is essential for attaining optimal bone mass.

ASTHMA

Magnesium is sometimes used in the treatment of acute asthma because it can influence bronchial vasomotor tone, pulmonary vascular muscle contractility, mast-cell granulation and neurohumoral mediator release (Mathew & Altura 1988). Although it is most often used as an infusion or in an inhaled form for this indication, results of two randomised, double-blind studies suggest that oral supplements also significantly alleviate asthma symptoms (Bede et al 2003, Hill et al 1997). Hill et al found that treatment improved symptoms, although it failed to change objective measures of airflow or airway reactivity and Bede et al found a significant decrease in bronchodilator use after 8 weeks compared with placebo. This was a 12-week study using oral magnesium citrate in 89 children (4–16 years) with mild or moderate persistent bronchial asthma. The dose used was 200 mg daily for children aged 7 years and 290 mg for those older than 7 years.

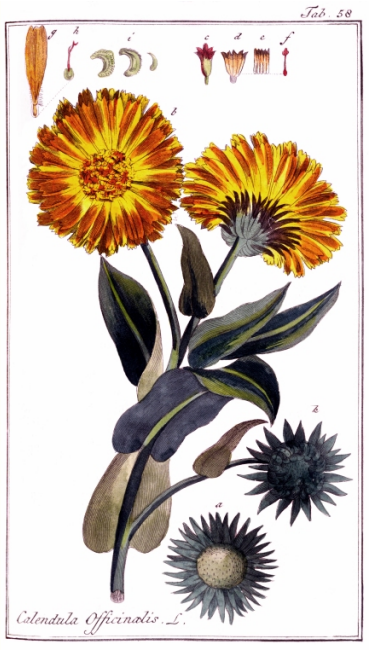
PREGNANCY

A 2001 Cochrane review of seven studies involving 2689 women concluded that although not all trials were positive, oral Mg taken before the 25th week of gestation was associated with a lower frequency of preterm birth, a lower frequency of low birthweight, and fewer small-for-gestational-age infants.

Additionally, fewer hospitalisations during pregnancy and fewer cases of antepartum haemorrhage were associated with Mg use.

Unfortunately, a lack of high-quality evidence currently exists to conclusively state that dietary Mg supplementation during pregnancy is beneficial, according to the authors, with further research still required to confirm these findings (Makrides & Crowther 2001).

Pregnancy-induced leg cramps A 2002 Cochrane review of five randomised trials of treatments for leg cramps in pregnancy concluded that the best evidence is for magnesium lactate or citrate taken as 5 mmol in the morning and 10 mmol in the evening for pregnant women experiencing leg cramps (Young & Jewell 2002).



DIABETES MELLITUS

A strong association between Mg, diabetes and hypertension has been reported in the literature (Ascherio et al 1998). Deficiency aggravates insulin resistance and predisposes diabetics to cardiovascular diseases.

Several randomised studies investigating oral Mg supplementation have shown improvements in diabetic control (Paolisso et al 1992, Rodriguez-Moran & Guerrero-Romero 2003). The most recent double-blind trial that involved 63 patients with type 2 diabetes (treated with glibenclamide) and reduced serum Mg levels demonstrated that the addition of oral Mg over 16 weeks significantly improves insulin sensitivity and metabolic control (Rodriguez-Moran & Guerrero-Romero 2003).

CONSTIPATION

In high doses Mg exerts a laxative effect, which is used in practice for the short-term treatment of constipation and in order to get the bowel ready for surgical or diagnostic procedures. It is often used in the form of magnesium hydroxide (milk of magnesia) or magnesium sulfate (Epsom salts).

DYSPEPSIA

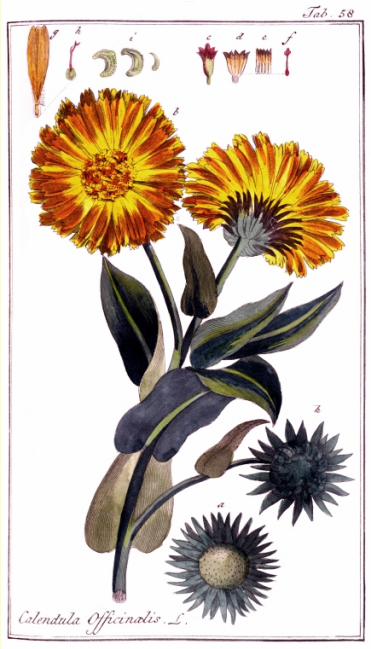
As magnesium hydroxide (milk of magnesia), Mg is used to reduce symptoms of dyspepsia and gastric acidity and acts as an antacid by forming magnesium chloride in the stomach. Magnesium oxide is also used for its antacid properties, which are greater than magnesium carbonate and sodium bicarbonate (Reynolds et al 1982). Magnesium trisilicate is the form used when a prolonged antacid activity is required.

CHRONIC LEG CRAMPS

Two randomised, double-blind studies have investigated the use of oral Mg supplements in people with leg cramps. Frusso et al (1999) conducted a crossover trial involving 45 individuals who had experienced at least six cramps during the previous month. Subjects were given 1 month of oral magnesium citrate (900 mg twice daily) followed by a matching placebo for 1 month, or visa versa. This treatment regimen failed to reduce the severity, duration or number of nocturnal leg cramps. In contrast, Roffe et al (2002) tested magnesium citrate equivalent to 300 mg magnesium in subjects suffering regular leg cramps and identified a trend towards fewer cramps with active treatment ($P = 0.07$). Significantly more subjects thought that the treatment had helped after magnesium than after placebo (36 (78%) and 25 (54%) respectively). Interestingly, in both studies patients improved over time regardless of the treatment they received.

OTHER USES

Oral Mg supplements are used in a variety of different conditions, most notably those involving muscle spasm or tension, pain and/or psychological and physical symptoms of stress and hyperexcitability. This includes IBS, restless legs syndrome, fibromyalgia, chronic fatigue syndrome, anxiety states, tension headaches, ADHD and insomnia. Together with vitamin B6, Mg is a popular treatment in autism. Preliminary evidence also suggests it may be beneficial for women with detrusor muscle instability (incontinence) or sensory urgency.



DOSAGE RANGE

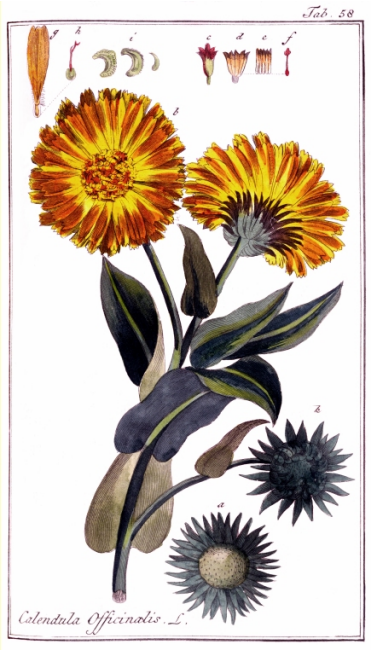
AUSTRALIAN RDI FOR ADULTS

- Men
  - 19–30 years: 400 mg/day.
  - >30 years: 420 mg/day.
- Women
  - 19–30 years: 310 mg/day.
  - >30 years: 320 mg/day.
- Pregnancy
  - ≤18 years: 400 mg/day.
  - >18 years: 350 mg/day.
- Lactation
  - ≤18 years: 360 mg/day.
  - >18 years: 310 mg/day.

ACCORDING TO CLINICAL STUDIES

- Hypertension: 360–600 mg/day.
- Arrhythmia prevention in congestive heart failure: magnesium chloride 3204 mg/day in divided doses.
- Migraine: 600 mg trimagnesium dicitrate daily.
- Migraine prophylaxis in children: magnesium oxide (9 mg/kg/day).
- PMS fluid retention symptoms: 200 mg magnesium (as magnesium oxide) daily.
- PMS mood swings: magnesium pyrrolidone carboxylic acid (360 mg) taken three times daily, from day 15 of the menstrual cycle to the onset of menstrual flow.
- Mitral valve prolapse: 3 tablets magnesium carbonate 600 mg (7 mmol of elementary Mg) daily for the first week followed by 2 tablets daily.
- Coronary artery disease symptoms: oral magnesium citrate (15 mmol twice daily as Magnosolv-Granulat, total magnesium 365 mg).

- Diabetes type 2: 50 mL magnesium dichloride solution (containing 50 g/1000 mL solution) daily.
- Kidney stone prevention: magnesium hydroxide 400–500 mg/day.
- Nocturnal leg cramps: magnesium citrate equivalent to 300 mg magnesium daily.
- Asthma: magnesium citrate 200–290 mg daily.
- Osteoporosis prevention: 250 mg taken at bedtime on an empty stomach, increased to 250 mg three times daily for 6 months, followed by 250 mg/day for 18 months.



ADVERSE REACTIONS

The most common adverse effects of oral supplements are diarrhoea (18.6%) and gastric irritation (4.7%) (Peikert et al 1996). Typically, doses above 350 mg/day (elemental) may be associated with adverse effects.

SIGNIFICANT INTERACTIONS

The interactions included in this section are relevant for oral supplementation and do not refer to other administration routes, although there may be an overlap.

AMINOGLYCOSIDES (E.G. GENTAMYCIN)

Drug may reduce absorption of Mg — monitor for signs and symptoms of Mg deficiency, as increased Mg intake may be required with long-term therapy.

CALCIUM-CHANNEL BLOCKERS

Magnesium may enhance the hypotensive effect of calcium-channel blockers: monitor patients and their drug requirements — possible beneficial interaction.

FLUOROQUINOLONES

Magnesium may decrease absorption of fluoroquinolone antibiotics — separate doses by at least 2 hours before or 4 hours after oral Mg.

LOOP DIURETICS AND THIAZIDE DIURETICS

Increased Mg intake may be required with long-term therapy because these drugs increase Mg loss — monitor Mg efficacy and status with long-term drug use.

TETRACYCLINE ANTIBIOTICS

Tetracyclines form insoluble complexes with Mg, thereby reducing absorption of both — separate doses by at least 2 hours.

ANTIARRHYTHMIC DRUGS

Additive effect theoretically possible because high-dose oral Mg exerts antiarrhythmic activity according to one clinical study — observe patients taking this combination.

POTASSIUM-SPARING DIURETICS
May increase the effects of supplemental Mg — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

- Magnesium supplementation is contraindicated in renal failure and heart block (unless a pacemaker is present).
- Hypermagnesaemia can develop in patients with renal failure and receiving Mg-containing antacids or laxatives and with accidental Epsom salt ingestion.
- Overuse of magnesium hydroxide or magnesium sulfate may cause deficiencies of other minerals or lead to toxicity.

PREGNANCY USE

Pregnant women and nursing mothers are advised to consume sufficient Mg (see Australian RDI in Dosage Range).

PRACTICE POINTS/PATIENT COUNSELLING

- Magnesium is an essential mineral in human nutrition with a wide range of biological functions.
- Low Mg states are associated with several serious diseases such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapse, metabolic syndrome, stroke, diabetes mellitus, hyperlipidaemia, pre-eclampsia and eclampsia.
- Although supplementation is traditionally used to correct or avoid deficiency states, research has also shown a role in the management of numerous disease states, e.g. cardiovascular disease, premenstrual syndrome, dysmenorrhoea, migraine prevention, diabetes, kidney stone prevention, osteoporosis prevention, dyspepsia and constipation. Preliminary research also suggests a possible benefit in asthma, women with detrusor muscle instability (incontinence) and pregnancy-induced leg cramps.
- Oral Mg supplements are also used in a variety of different conditions, most notably, those involving muscle spasm or tension, pain and/or psychological and physical symptoms of stress and hyperexcitability.
- Numerous drug interactions exist, so care should be taken to ensure safe use.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

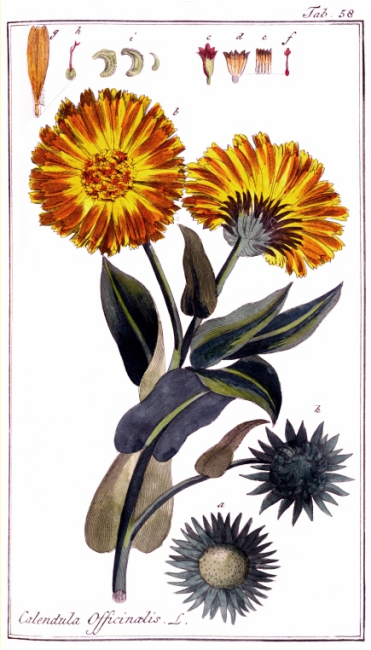
Magnesium is essential for health and wellbeing. Although used to prevent or treat deficiency states, it is also used to alleviate many conditions such as cardiovascular disease and PMS, and prevent migraine and muscular spasms.

When will it start to work?

This will depend on the indication it is being used to treat.

Are there any safety issues?

In high doses, supplements can cause diarrhoea. High-dose supplements should not be used by people with severe kidney disease or heart block.



REFERENCES

Anderson RA. A complementary approach to urolithiasis prevention. World J Urol 20.5 (2002): 294-301.

Ascherio A et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 98.12 (1998): 1198-204.

Bashir Y et al. Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. Am J Cardiol 72.15 (1993): 1156-62.

Bede O et al. Urinary magnesium excretion in asthmatic children receiving magnesium supplementation: a randomized, placebo-controlled, double-blind study. Magnes Res 16.4 (2003): 262-70.

Boska MD et al. Contrasts in cortical magnesium, phospholipid and energy metabolism between migraine syndromes. Neurology 58.8 (2002): 1227-33.

Braunwald E et al. Harrison's Principles of Internal Medicine. New York: McGraw Hill, 2003.

Ettinger B et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol 158.6 (1997): 2069-73.

Facchinetti F et al. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache 31.5 (1991a): 298-301.

Facchinetti F et al. Oral magnesium successfully relieves premenstrual mood changes. Obstet Gynecol 78.2 (1991b): 177-81.

Fox C, Ramsoomair D, Carter C. Magnesium: its proven and potential clinical significance. South Med J 94.12 (2001): 1195-201.

Frishman WH, Grattan JG, Mamtani R. Alternative and complementary medical approaches in the prevention and treatment of cardiovascular disease. Current Prob Cardiol 30.8 (2005): 383-459.

Frusso R et al. Magnesium for the treatment of nocturnal leg cramps: a crossover randomized trial. J Fam Pract 48.11 (1999): 868-71.

Grimaldi BL. The central role of magnesium deficiency in Tourette's syndrome: causal relationships between magnesium deficiency, altered biochemical pathways and symptoms relating to Tourette's syndrome and several reported comorbid conditions. Med Hypotheses 58.1 (2002): 47-60.

Guerrero-Romero F, Rodriguez-Moran M. Low serum magnesium levels and metabolic syndrome. Acta Diabetol 39.4 (2002): 209-13.

Hill J et al. Investigation of the effect of short-term change in dietary magnesium intake in asthma. Eur Respir J 10.10 (1997): 2225-9.

Jee SH et al. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. Am J Hypertens 15.8 (2002): 691-6.

Johnson S. The multifaceted and widespread pathology of magnesium deficiency. Med Hypotheses 56.2 (2001): 163-70.

Kitlinski M et al. Is magnesium deficit in lymphocytes a part of the mitral valve prolapse syndrome? Magnes Res 17.1 (2004): 39-45.

Lichodziejewska B et al. Clinical symptoms of mitral valve prolapse are related to hypomagnesemia and attenuated by magnesium supplementation. Am J Cardiol 79.6 (1997): 768-72.

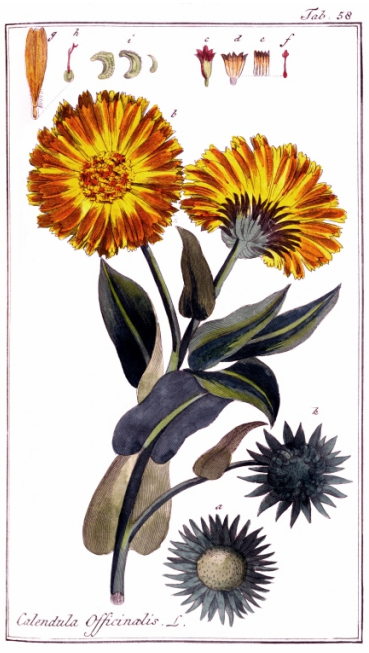
Makrides M, Crowther CA. Magnesium supplementation in pregnancy. Cochrane Database Syst Rev 4 (2001): CD000937.

Mathew R, Altura BM. Magnesium and the lungs. Magnesium 7.4 (1988): 173-87.

Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. Clin Neurosci 5.1 (1998): 24-7.
McDermott KC, Almadrones LA, Bajorunas DR. The diagnosis and management of hypomagnesemia: a unique treatment approach and case report. Oncol Nurs Forum 18.7 (1991): 1145-52.
Paolisso G et al. Daily magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr 55.6 (1992): 1161-7.
Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 16.4 (1996): 257-63.
Pfaffenrath V et al. Magnesium in the prophylaxis of migraine: a double-blind placebo-controlled study. Cephalalgia 16.6 (1996): 436-40.
Rasmussen HS et al. Magnesium deficiency in patients with ischemic heart disease with and without acute myocardial infarction uncovered by an intravenous loading test. Arch Intern Med 148.2 (1988): 329-32.
Rasmussen HS et al. Influence of magnesium substitution therapy on blood lipid composition in patients with ischemic heart disease: A double-blind, placebo controlled study. Arch Intern Med 149.5 (1989): 1050-3.
Reynolds JEF et al. Martindale Extra Pharmacopoeia, 28th edn. London: The Pharmaceutical Press, 1982.
Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: A randomized double-blind controlled trial. Diabetes Care 26.4 (2003): 1147-52.
Roffe C et al. Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. Med Sci Monit 8.5 (2002): CR326-30.
Rosenstein DL et al. Magnesium measures across the menstrual cycle in premenstrual syndrome. Biol Psychiatry 35.8 (1994): 557-61.
Sanders GT, Huijgen HJ, Sanders R. Magnesium in disease: a review with special emphasis on the serum ionized magnesium. Clin Chem Lab Med 37.11-12 (1999): 1011-33.
Saris NE et al. Magnesium: An update on physiological, clinical and analytical aspects. Clin Chim Acta 294.1-2 (2000): 1-26.
Shattock MJ, Hearse DJ, Fry CH. The ionic basis of the anti-ischemic and anti-arrhythmic properties of magnesium in the heart. J Am Coll Nutr 6.1 (1987): 27-33.
Shechter M et al. Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease. Am J Cardiol 84.2 (1999): 152-6.
Shechter M et al. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation 102.19 (2000): 2353-8.
Shechter M et al. Effects of oral magnesium therapy on exercise tolerance, exercise-induced chest pain, and quality of life in patients with coronary artery disease. Am J Cardiol 91.5 (2003): 517-21.
Shils ME et al. Magnesium. In: Modern Nutrition in Health and Disease, 9th edn. Baltimore: Williams and Wilkins, 1999; Ch 9.
Sojka JE, Weaver CM. Magnesium supplementation and osteoporosis. Nutr Rev 53.3 (1995): 71-4.
Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. Magnes Res 6.2 (1993): 155-63.
Taubert K. Magnesium in migraine: Results of a multicenter pilot study. Fortschr Med 112.24 (1994): 328-30.
Thomas J et al. Free and total magnesium in lymphocytes of migraine patients: effect of magnesium-rich mineral water intake. Clin Chim Acta 295.1-2 (2000): 63-75.
Walker AF et al. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. J Womens Health 7.9 (1998): 1157-65.
Walker AF et al. Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. Magnes Res 16.3 (2003): 183-91.
Wang F et al. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache 43.6 (2003): 601-10.

Weaver CM. Calcium and magnesium requirements of children and adolescents and peak bone mass. Nutrition 16.7-8 (2000): 514-16.
Wilson ML, Murphy PA. Herbal and dietary therapies for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 3 (2001): CD002124.
Young GL, Jewell D. Interventions for leg cramps in pregnancy. Cochrane Database Syst Rev 1 (2002): CD000121.

Meadowsweet



Historical note Meadowsweet was one of the most sacred herbs used by ancient Celtic druid priests, hundreds of years ago (Blumenthal et al 2000). Modern-day aspirin owes its origins to the salicin content isolated from meadowsweet in the early 1800s. In fact, the name aspirin relates to this herb's former genus name 'Spiracea'.

COMMON NAME
Meadowsweet

OTHER NAMES
Bridewort, dolloff, dropwort, fleur d'ulmaire, gravel root, lady of the meadow, meadow-wort, queen of the meadow, spireae flos

BOTANICAL NAME/FAMILY
Filipendula ulmaria (family Rosaceae)

PLANT PART USED
Aerial parts

CHEMICAL COMPONENTS
Phenolic glycosides, essential oil, tannins, mucilage, flavonoids (up to 6% in fresh flowers) and ascorbic acid. The herb also contains various salicylate constituents including methyl salicylate, salicin and salicylic acid.

MAIN ACTIONS

GASTROPROTECTIVE EFFECTS
In vivo tests have identified protective effects against stomach ulcers induced by acetylsalicylic acid, but no protection was seen against ulcers produced under high acid environments or due to stimulation by histamine (Barnaulov & Denisenko 1980). Based on these observations, it appears that the effect may involve a PG-mediated mechanism.

ANTI-INFLAMMATORY AND ANALGESIC
The high salicylate content of the herb suggests it may have anti-inflammatory and analgesic activity. Clinical studies using another salicylate-containing herb, willowbark, has shown that doses of 120–240 mg salicin daily has analgesic, antinociceptive and anti-inflammatory activity (Marz & Kemper 2002). Whether the

salicin content found in meadowsweet is of sufficient quantity and bioavailability to produce the same effects is unknown.

OTHER ACTIONS

In vitro tests have identified antioxidant and anticoagulant activity (Calliste et al 2001, Liapina & Koval'chuk 1993). Bacteriostatic activity has also been reported in vitro against *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa* (Rauha et al 2000).

CLINICAL USE

Meadowsweet has not been significantly investigated under clinical trial conditions, so evidence is largely derived from traditional, in vitro and animal studies.

SUPPORTIVE THERAPY FOR COLDS

Commission E approval for this condition is based on historical use in well-established systems of medicine, in vitro tests and animal studies (Blumenthal et al 2000).

GASTROINTESTINAL CONDITIONS

Meadowsweet is often used to treat gastrointestinal conditions associated with hyperacidity, such as gastritis, acidic dyspepsia and peptic ulceration. In vivo testing has found a decoction made from flowers of meadowsweet reduced experimentally induced ulcers caused by acetylsalicylic acid. Additionally, it promoted healing of chronic stomach ulcers induced by ethanol (Barnaulov & Denisenko 1980). Currently there is no evidence available to confirm an antacid activity.

CONDITIONS ASSOCIATED WITH MILD TO MODERATE PAIN

Based on its significant salicylate content, meadowsweet is also prescribed for conditions associated with mild to moderate pain. However, no clinical study is available to confirm efficacy. Positive clinical evidence does exist for the herb willowbark in these conditions, which similarly contains the important salicylate ingredient 'salicin' (see Willowbark monograph).

OTHER USES

Meadowsweet has traditionally been used as a treatment for diarrhoea based on the herb's appreciable tannin content. It has also been used for conditions associated with mild to moderate pain (most likely due to the herb's significant salicylate content), fever and inflammation.

DOSAGE RANGE

As no clinical trials are available to determine effective doses, the following doses are a general guideline.

- Fresh flowers: 2.5–3.5 g/day.
- Fresh herb: 4–5 g/day.
- Infusion: steep 2–3 g in 150 mL boiled water for 10 minutes and drink as hot as tolerable.
- Fluid extract (1:1) (g/mL): 2–3 mL/day.

TOXICITY

Not known

ADVERSE REACTIONS

Although salicylates are present, they appear to cause less gastrointestinal irritation than acetylsalicylic acid. In fact, a meadowsweet preparation protected against acetylsalicylic acid-induced stomach ulcers in vivo (Barnaulov & Denisenko 1980).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are based on evidence of activity and are largely theoretical and speculative.

WARFARIN

As increased bleeding may occur, observe patients taking warfarin concurrently. The herb has been shown to exert anticoagulant activity in vitro and in vivo, but the clinical significance of these results is unknown (Liapina & Koval'chuk 1993).

ASPIRIN AND SIMPLE ANALGESICS

Theoretically, meadowsweet may enhance anti-inflammatory and antiplatelet effects. Observe patients taking this combination — beneficial interaction possible.

CONTRAINDICATIONS AND PRECAUTIONS

Meadowsweet should not be taken by people with salicylate sensitivity. Suspend use of concentrated extracts 1 week before major surgery.

PREGNANCY USE

Not recommended.

PRACTICE POINTS/PATIENT COUNSELLING

- Meadowsweet is traditionally used as a herbal antacid, analgesic and antipyretic, antidiarrhoeal and treatment for urinary tract infections.
- Commission E approves its use as supportive therapy for the common cold.

- It contains several different salicylates that are thought to be responsible for much of its clinical activity.
- Although it contains salicylates, the herb does not appear to cause significant gastrointestinal irritation and may in fact have anti-ulcer activity.
- People who are salicylate sensitive should not take this herbal medicine.
- In practice, it is often combined with herbs such as chamomile and marshmallow in the treatment of gastrointestinal complaints.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Traditionally, the herb has been used to treat gastrointestinal complaints such as dyspepsia and diarrhoea, urinary tract infections and joint aches and pains. It is also used as supportive therapy for the common cold.

When will it start to work?

Symptomatic relief should be experienced within the first few doses.

Are there any safety issues?

People who are salicylate sensitive should not take meadowsweet.

REFERENCES

Barnaulov OD, Denisenko PP. Anti-ulcer action of a decoction of the flowers of the dropwort, Filipendula ulmaria (L.) Maxim. Farmakol Toksikol 43.6 (1980): 700-5.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

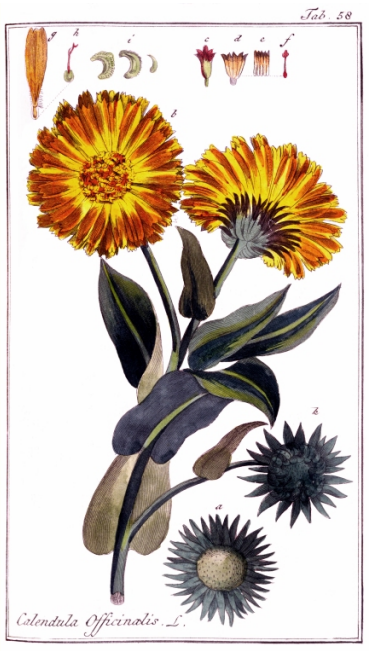
Calliste CA et al. Free radical scavenging activities measured by electron spin resonance spectroscopy and B16 cell antiproliferative behaviors of seven plants. J Agric Food Chem 49.7 (2001): 3321-7.

Liapina LA, Koval'chuk GA. A comparative study of the action on the hemostatic system of extracts from the flowers and seeds of the meadowsweet (Filipendula ulmaria (L.) Maxim.). Izv Akad Nauk Ser Biol4 (1993): 625-8.

Marz RW, Kemper F. Willow bark extract: effects and effectiveness: Status of current knowledge regarding pharmacology, toxicology and clinical aspects. Wien Med Wochenschr 152.15-16 (2002): 354-9.

Rauha JP et al. Antimicrobial effects of Finnish plant extracts containing flavonoids and other phenolic compounds. Int J Food Microbiol 56.1 (2000): 3-12.

Mullein



Historical note Over the centuries, mullein has been used in various ways. Taken internally, it has been used to treat respiratory conditions and tumours; applied topically, its use has been to relieve itch and dress wounds. It was also used to make candlewicks for casting out evil spirits. Due to its robust nature, mullein is now considered a serious weed pest of roadsides and industrial areas in countries such as the USA.

OTHER NAMES

Aaron's rod, Adam's flannel, blanket herb, bunny's ears, candlewick plant, flannel-leaf, great mullein, Jacob's staff

BOTANICAL NAME/FAMILY

Verbascum densiflorum, *Verbascum phlomides*, *Verbascum thapsus* (family Scrophulariaceae)

PLANT PARTS USED

Flower — dried petals, leaves

CHEMICAL COMPONENTS

The flower contains water-soluble mucilage, polysaccharides, flavonoids (including apigenin, luteolin, kaempferol and rutin), caffeic acid derivatives, iridoid monoterpenes, triterpene saponins (verbascosaponin), sterols and invert sugar.

One of the most investigated constituents isolated from plants in the *Verbascum* species is verbascoside, an iridoid glucoside. Whether the pharmacological effects demonstrated for this single constituent can be extrapolated to explain those for mullein is uncertain, as the effects of any herb are due to a number of phyto-constituents and their interaction with each other and the body. As such, information about verbascoside is included here in order to provide a further insight into the herb, but it should be interpreted accordingly.

Verbascoside has also been isolated from other herbs such as *Verbena officinalis*, *Echinacea purpurea* roots, *Euphrasia pectinata*, *Phlomis longifolia*, *Pedicularis plicata*, *Duranta erecta*, *Marrubium alysson*, *Leonurus glaucescens* and *Balotta nigra* (Calis et al 1992a, b, Deepak & Handa 2000, Ersoz et al 2000, 2001, Liao et al 1999, Seidel et al 2000, Sloley et al 2001, Takeda et al 1995).

MAIN ACTIONS

Mullein has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

DEMULCENT AND EMOLLIENT

Traditionally, these actions were thought to occur primarily within the respiratory system, especially the lungs. However, topical preparations of mullein also exert an emollient action on the skin (Blumenthal et al 2000). This is most likely due to the herb's high mucilaginous content.

Clinical note — Natural mucilages found in herbs

Mucilages are large, highly branched polymeric structures made from many different sugar and uronic acid units. They are hydrophilic and are capable of trapping water, causing them to swell in size and develop a gel-like consistency. The gels tend to have soothing properties and can be broken down by bowel flora when taken internally (Mills & Bone 2000). They are known to have beneficial effects on burns, wounds and ulcers when applied externally, and on gastric inflammation and irritation and diarrhoea when taken internally.

ANTIMICROBIAL

Antiviral action Mullein extract exhibits antiviral activity against fowl plague virus, several influenza A strains and influenza B strain, as well as HSV in vitro (McCutcheon et al 1995, Serkedjieva 2000, Slagowska et al 1987, Zanon et al 1999, Zgorniak-Nowosielska et al 1991). Antiviral activity has been demonstrated for both infusions and alcoholic extracts (Serkedjieva 2000).

Antibacterial action In vitro studies have demonstrated antibacterial activity for mullein extracts (aqueous, ethanol and methanol) against *Klebsiella pneumonia*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Escherichia coli* (Turker & Camper 2002). Of the three extracts tested, aqueous extract exhibited the strongest antibacterial action.

ANTITUMOUR

Some plants, such as mullein, were used in folk medicine as sources of antitumour remedies. An in vitro study has identified inhibitors of protein biosynthesis in *Verbascum thapsiforme* flowers. Researchers found that a saponin glycoside and its aglycon, isolated from the flowers, directly inactivates ribosomes (Galasinski et al 1996). The constituent, verbascoside, has been shown to inhibit telomerase activity in human gastric carcinoma cells in test tube studies, resulting in inhibition of tumour growth (Zhang et al 2002). Cytotoxic effects for verbascoside have also been

identified against rat hepatoma and sarcoma cells, and cytostatic activity on human epithelial carcinoma cells (Saracoglu et al 1995).

OTHER ACTIONS

The verbascoside constituent demonstrates antioxidant activity in vitro (Gao et al 1999). The saponins in mullein are thought to exert an expectorant activity; however, further investigation is required to confirm this.

CLINICAL USE

Mullein has not been subjected to significant clinical investigation; therefore, information is generally derived from traditional usage, phytochemical research or evidence of pharmacological activity. In practice, this herbal medicine is often combined with other herbs in order to strengthen clinical effects.

CHRONIC OTITIS MEDIA

To date, no controlled studies are available to determine the clinical effectiveness of mullein as a stand-alone treatment. However, two double-blind studies that tested a herbal combination ear-drop product (containing mullein) in children have produced positive results. The first study involved 103 children aged 6–18 years and found that a naturopathic herbal ear drop known commercially as Otikon (consisting of *Allium sativum*, *Verbascum thapsus*, *Calendula* flowers and *Hypericum perforatum* in olive oil) was as effective as local anaesthetic ear drops (containing ametocaine and phenazone in glycerin) in the management of ear pain associated with acute otitis media. Treatment lasted for 3 days and produced a statistically significant improvement (Sarrell et al 2001). The second was a randomised, double-blind study involving 171 children aged 5–18 years who had otalgia and clinical findings associated with middle-ear infection (Sarrell et al 2003). Children receiving herbal ear drops containing *Allium sativum*, *Verbascum thapsus*, *Calendula* flowers, *Hypericum perfoliatum*, lavender, and vitamin E in olive oil achieved better pain relief than controls; however, the pain appeared to be self-limiting with significant improvements seen in all groups over 3 days. The dose used was 5 drops three times daily.

PRODUCTIVE AND DRY COUGH

Traditionally, mullein is combined with other demulcent or expectorant herbal medicines such as *Glycyrrhiza glabra*, *Tussilago farfara* and *Althea officinalis* in the treatment of productive cough.

Commission E approves the use of mullein flowers for catarrhs of the respiratory tract (Blumenthal et al 2000). This is largely based on traditional use extending back to ancient times, and phytochemical investigation from in vitro and in vivo studies.

TOPICAL USE

Mullein is used topically for wounds, burns, bruises, haemorrhoids, pruritis and to soften the skin. The high mucilage and tannin content of the herb provides a theoretical basis for its use in these situations as an antipruritic and astringent agent. To date, no controlled studies are available to determine its effectiveness.

OTHER USES

Mullein is included in herbal combination treatments for a variety of respiratory conditions such as bronchitis. Traditionally it is also used for diarrhoea, dysentery, haemorrhoids and laryngitis.

DOSAGE RANGE

- Fluid extract (1:1): 1.5–2 mL twice daily.
- Tincture (1:5): 7.5–10 mL twice daily.
- Dried leaf: 12–24 g/day.
- Decoction: 1.5–2 g of herb in 250 mL of cold water, brought to the boil for 10 minutes, taken twice daily.

ADVERSE REACTIONS

A case of contact dermatitis has been reported (Romaguera et al 1985).

SIGNIFICANT INTERACTIONS

Controlled studies are not available.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Insufficient reliable information is available; however, Commission E states that no restrictions are known (Blumenthal et al 2000).

PRACTICE POINTS/PATIENT COUNSELLING

- Mullein flowers have been used since ancient times as an expectorant and anticatarrhal agent in conditions of productive cough and respiratory infections.
- It is most commonly used in combination with other demulcent and expectorant herbal medicines in the treatment of productive and dry cough.
- In vitro studies have identified antiviral and antibacterial activity.
- Mullein has not been subjected to significant clinical investigation; therefore, information is generally derived from traditional usage or evidence of pharmacological activity. As such, Commission E approves its use for catarrhs of the respiratory tract.

- Used in the form of a herbal combination ear drop, significant anaesthetic activity has been demonstrated.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Mullein has been used since ancient times as a treatment for productive coughs and catarrhal states. In modern times, it is also used to treat chronic otitis media, and has antiviral action against influenza virus and HSV. Currently, more scientific investigation is required to confirm efficacy for these indications.

When will it start to work?

Ear drops containing mullein within a herbal combination exerted significant anaesthetic effects within 1–2 days.

Are there any safety issues?

Although safety has not been scientifically established, a long history of use suggests that it is a safe substance when used at the recommended doses.

REFERENCES

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Calis I et al. Phenylpropanoid glycosides from Marrubium alysson. Phytochemistry 31.10 (1992a): 3624-6.

Calis I et al. Two phenylpropanoid glycosides from Leonurus glaucescens. Phytochemistry 31.1 (1992b): 357-9.

Deepak M, SS Handa. Antiinflammatory activity and chemical composition of extracts of Verbena officinalis. Phytother Res 14.6 (2000): 463-5.

Ersoz T et al. An iridoid glucoside from Euphrasia pectinata. J Nat Prod 63.10 (2000): 1449-50.

Ersoz T et al. Iridoid and phenylethanoid glycosides from Phlomis longifolia var. longifolia. Nat Prod Lett 15.5 (2001): 345-51.

Galasinski W et al. The substances of plant origin that inhibit protein biosynthesis. Acta Pol Pharm 53.5 (1996): 311-18.

Gao JJ, Igalashi K, Nukina M. Radical scavenging activity of phenylpropanoid glycosides in Caryopteris incana. Biosci Biotechnol Biochem 63.6 (1999): 983-8.

Liao F et al. Retardation of skeletal muscle fatigue by the two phenylpropanoid glycosides: verbascoside and martynoside from Pedicularis plicata maxim. Phytother Res 13.7 (1999): 621-3.

McCutcheon AR et al. Antiviral screening of British Columbian medicinal plants. J Ethnopharmacol 49.2 (1995): 101-10.

Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.

Romaguera C, Grimalt F, Vilaplana J. Occupational dermatitis from Gordolobo (Mullein). Contact Dermatitis 12.3 (1985): 176.

Saracoglu I et al. Studies on constituents with cytotoxic and cytostatic activity of two Turkish medicinal plants Phlomis armeniaca and Scutellaria salviifolia. Biol Pharm Bull 18.10 (1995): 1396-400.

Sarrell EM, Mandelberg A, Cohen HA. Efficacy of naturopathic extracts in the management of ear pain associated with acute otitis media. Arch Pediatr Adolesc Med 155.7 (2001): 796-9.

Sarrell EM, Cohen HA, Kahan E. Naturopathic treatment for ear pain in children. Pediatrics 111.5 (Pt 1) (2003): e574-9.

Seidel V et al. Phenylpropanoids from Ballota nigra L. inhibit in vitro LDL peroxidation. Phytother Res 14.2 (2000): 93-8.

Serkedjieva J. Combined antiinfluenza virus activity of Flos verbasci infusion and amantadine derivatives. Phytother Res 14.7 (2000): 571-4.
Slagowska A, Zgorniak-Nowosielska I, Grzybek J. Inhibition of herpes simplex virus replication by Flos verbasci infusion. Pol J Pharmacol Pharm 39.1 (1987): 55-61.
Sloley BD et al. Comparison of chemical components and antioxidants capacity of different Echinacea species. J Pharm Pharmacol 53.6 (2001): 849-57.
Takeda Y et al. Iridoid glucosides from the leaves and stems of Duranta erecta. Phytochemistry 39.4 (1995): 829-33.
Turker AU, Camper ND. Biological activity of common mullein, a medicinal plant. J Ethnopharmacol 82.2–3 (2002): 117-25.
Zanon SM et al. Search for antiviral activity of certain medicinal plants from Cordoba, Argentina. Rev Latinoam Microbiol 41.2 (1999): 59-62.
Zgorniak-Nowosielska I et al. Antiviral activity of Flos verbasci infusion against influenza and Herpes simplex viruses. Arch Immunol Ther Exp (Warsz) 39.1-2 (1991): 103-8.
Zhang F et al. In vitro modulation of telomerase activity, telomere length and cell cycle in MKN45 cells by verbascoside. Planta Med 68.2 (2002): 115-18.

Myrrh

Historical note The resin that seeps out of the bark of the *Commiphora* plant has been considered an important medicinal product in the Middle East, China and India since biblical times. Because of its antimicrobial activity, myrrh has historically been used, alone and in combination with other herbs, to treat infections and inflammations of the oral cavity, in purification rituals, to embalm bodies, dress infected wounds and as a treatment for leprosy.

COMMON NAME
Myrrh

OTHER NAMES
Abyssinian myrrh, bal, bol, common myrrh, heerabol, hirabol myrrh, gum myrrh tree, gummi myrrh, Somali myrrh, Yemen myrrh

BOTANICAL NAME/FAMILY
Commiphora molmol (family Burseraceae)

PLANT PARTS USED
Gum resin, stem, leaves

CHEMICAL COMPONENTS
Myrrh contains three main components: gum resin 30–60%; alcohol-soluble resins 20–40%; volatile oils (2–10%).

Guggul is the oleo-gum-resin exudate from *Commiphora mukul*, which is also used therapeutically and has been scientifically investigated. Resins are sticky, water-insoluble substances that are secreted where a plant is damaged by incision or natural causes. The viscous substance hardens shortly after secretion, but may be returned to a liquid state with heating. Resins tend to be soluble in alcohol. Guggulipid is extracted from guggul and contains plant sterols (guggulsterones E and Z) which are thought to be its main pharmacologically active constituents (Ulbricht et al 2005).

MAIN ACTIONS

ANTISEPTIC
Antifungal and antibacterial activity has been observed in vitro against standard pathogenic strains of *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans* (Dolara et al 2000). The oleo-gum-resin of *C. mukul*

was shown to be comparable to kanamycin against both Gram (+) and Gram (–) bacteria in vitro (Saeed & Sabir 2004).

LIPID-LOWERING EFFECTS

Several mechanisms of action are considered responsible for this effect. The guggulsterones act as antagonists of the bile-acid receptor and of the farsenoid X receptor, which are involved in bile acid regulation and cholesterol metabolism. Crude guggul contains ion-exchange resins that may remove bile from the intrahepatic circulation (Urizar et al 2002, Wu et al 2002).

According to one review, eleven clinical studies have generally demonstrated that guggulipid from *C. mukul* significantly reduces triglyceride and total cholesterol levels; however, results from a recent double-blind randomised study were negative (Ulbricht et al 2005).

ANTI-INFLAMMATORY

Myrrhanol A, a triterpene isolated from *C. mukul* gum resin, produces potent anti-inflammatory activity, as observed in an animal model of inflammation. In this study, anti-inflammatory activity was more marked than that of hydrocortisone (Kimura et al 2001). An animal model of RA confirmed significant anti-inflammatory effects with oral administration, also resulting in decreased joint swelling (Sharma & Sharma 1977). A small, uncontrolled trial of *C. mukul* for patients with osteoarthritis ($n = 30$) has shown treatment with 500 mg (3.5% guggulsterones) of the herb, three times daily for 2 months resulted in reduced joint inflammation, swelling and pain (Singh et al 2003). Although this suggests the effects may be clinically significant, further investigation is required.

LOCAL ANAESTHETIC

Several compounds found within myrrh exert local anaesthetic activity, chiefly by blocking the inward sodium current across membranes (Dolara et al 2000).

OTHER ACTIONS

ANTISPASMODIC

One major component, T-cadinol, and several minor components possess smooth muscle-relaxing properties according to ex vivo tests (Andersson et al 1997, Claeson et al 1991).

INCREASES GLUCOSE TOLERANCE

An extract of myrrh effectively increased glucose tolerance in both normal and diabetic rats (Al Awadi & Gumaa 1987).

LOCAL ASTRINGENT AND ENHANCED WOUND HEALING

Myrrh has astringent activity, promotes tissue granulation and enhances wound healing (Blumenthal et al 2000).

CLINICAL USE

TOPICAL TREATMENT OF ORAL OR PHARYNGEAL INFLAMMATION

Often used as a component of gargles, mouthwashes or paints for these indications, there are few controlled clinical trials or in vitro studies on the effects of myrrh on cells derived from the human oral cavity. A 2003 in vitro study investigating the effects of myrrh oil on a number of key cells implicated in gingivitis found that low concentrations of myrrh oil reduced gingival fibroblast production of proinflammatory cytokines and, therefore, the participation of these cells in gingival inflammation associated with gingivitis and periodontitis (Tipton 2003). This is thought to be, at least in part, due to inhibition of PGE_2 (Tipton et al 2005).

Commission E approved myrrh for these indications (Blumenthal et al 2000).

EXTERNAL TREATMENT OF MINOR INFLAMMATORY CONDITIONS AND WOUNDS

Myrrh is incorporated into salves and topical preparations for the treatment of bed sores, minor wounds and haemorrhoids. Although no clinical trials are available, the antimicrobial, anti-inflammatory, astringent and local anaesthetic activities of myrrh provide a theoretical basis for efficacy.

HYPERLIPIDAEMIA, HYPERCHOLESTEROLAEMIA, HYPERTRIGLYCERIDAEMIA

Szapary et al (2005) conducted a double-blind, placebo-controlled, randomised trial with 103 subjects with LDL-cholesterol levels of 3.37–5.19 mmol/L. A standardised dose of 1000 mg of guggulipid (containing 2.5% guggulsterones) was given to one treatment group, while a higher standardised dose of 2000 mg was given to the other, three times daily for 8 weeks. Results showed a decrease of LDL-cholesterol in the placebo group of 5%, an increase of 4% in the 1000 mg group and an increase of 5% in the 2000 mg group. Overall this constituted a 9% and 10% increase in LDL-cholesterol with guggulipid treatment. In comparison, several randomised clinical trials and in vivo tests using various extracts of guggul have reported significant lowering of total cholesterol, triglycerides and LDL-cholesterol levels and increases in HDL-cholesterol (Gopal et al 1986, Malhotra et al 1977, Nityanand et al 1989, Singh et al 1990). In two reports, the duration of the lipid-lowering effect continued for 6–20 weeks after discontinuation of therapy (Gopal et al 1986, Nityanand et al 1989). One clinical study showed the lipid-lowering effects of a preparation of guggul fraction A (1.5 g/day) was similar to clofibrate (2 g/day) (Malhotra et al 1977).

A larger study of 235 volunteers conducted under double-blind randomised conditions showed that patients with hypercholesterolaemia responded better to guggulipid (1.5 g/day) than to clofibrate (1.5 g/day). However, those with hypertriglyceridaemia responded better to clofibrate (Nityanand et al 1989). Many of these trials have been criticised for being small and methodologically flawed or poorly reported (Ulbricht et al 2005). Again, more large-scale clinical trials need to be done to assess the efficacy of guggulipid in hypercholesterolaemia.

OTHER USES

TRADITIONAL INDICATIONS

Myrrh has been used in TCM, Tibetan medicine, Ayurvedic medicine, Middle Eastern medicine and in Europe; therefore, it has numerous traditional indications. Myrrh has been used to treat infections, respiratory conditions, mouth ulcers, gingivitis, pharyngitis, respiratory catarrh, dysmenorrhoea, amenorrhoea, menopausal symptoms, wounds and haemorrhoids. It has also been used to treat arthritis and as an embalming agent.

PARASITIC DISEASES

Schistosomiasis Schistosomiasis is an important trematode infection affecting over 200 million people in the tropics and subtropics (Kumar & Clark 2002). After malaria, it is the next most important parasitic disease with chronic infection causing significant morbidity. Currently, the drug praziquantel is often recommended, but it does not affect the immature stage and may not abort an early infection. Additionally, a drug-resistant strain has developed (Beers & Berkow 2003). Due to these factors, there is great interest in discovering alternative treatments.

One clinical study involving 204 patients with schistosomiasis produced impressive results with a 3 day oral dose regimen producing a cure rate of 92% (Sheir et al 2001). Re-treatment of non-responders increased the overall cure rate to 98%. A field study produced similar results with 97.4% of subjects infected with the *Schistosoma haematobium* strain and 96.2% infected with the *S. mansoni* strain successfully clearing the parasite after ingesting 1200 mg of *Commiphora molmol* daily for 6 days (bo-Madyan et al 2004a). However, two randomised trials, controlled with the drug praziquantel, have both shown little effectiveness of myrrh against the parasite (Barakat et al 2005, Botros et al 2005).

Fascioliasis Human fascioliasis occurs in Europe, Africa, China and South America and is infection with *Fasciola hepatica*, which is acquired by eating contaminated watercress. The flukes mature in the bile ducts and cause biliary tract obstruction and liver damage (Beers & Berkow 2003).

A small study of seven infected patients found that treatment with myrrh over 6 consecutive days produced alleviation of all symptoms and signs, and a dramatic drop in egg count, with eggs no longer detected 3 weeks after treatment (Massoud et al 2001a). Furthermore, high eosinophil counts, elevated liver enzymes and *Fasciola* antibody titres returned to normal. A field study showed that myrrh (1200 mg daily for 6 days) cleared the parasite in 94.1% of infected people at the 3-month follow-up (bo-Madyan et al 2004b).

Mosquitocidal The oil and oleo-resin from the plant extract of *C. molmol* exhibits larvicidal activity against *Culex pipiens* larvae (Massoud et al 2001b).

Historical note — Myrrh and mummification
Chemical treatments were an essential part of the mummification process in ancient Egypt. Several different plant products were used in the process, one of which was oil of myrrh. Interestingly, modern-day research has discovered that the oil has molluscicidal properties against several Egyptian snail species, suggesting it may have been a wise choice for protecting mummified remains against destruction (Allam et al 2001).

ACNE

Three months' treatment with guggulipid (equivalent to 25 mg guggulsterone) was found to be as effective as tetracycline in the treatment of nodulocystic acne in a randomised clinical study of 20 patients (Thappa & Dogra 1994).

DOSAGE RANGE

INTERNAL PREPARATIONS — COMMIPHORA MOLMOL

- Fluid extract (1:1) (g/mL): 2 mL/day.
- Tincture (1:5): 0.5–2 mL three times daily.

INTERNAL PREPARATIONS — GUGGULIPID

- Acne: a dose equivalent to 25 mg guggulsterone taken once to twice daily.
- Hyperlipidaemia — 500–1000 mg of standardised guggulipid administered two to three times daily.

*Guggulipid preparations are often standardised to 2.5–5% of guggulsterones.

EXTERNAL PREPARATIONS

- Tincture (1:5) (g/mL) in 90% ethanol can be used in different concentrations to produce different therapeutic products.
- Mouthwash or gargle: 30–60 drops tincture in a glass of warm water.

- Paint: the undiluted tincture can be applied directly to gums or mucous membranes of the mouth two to three times a day.

TOXICITY

A dose of 10 mg/kg/day was given to subjects in one study with no serious adverse effects (Sheir et al 2001).

ADVERSE REACTIONS

Restlessness, mild abdominal discomfort and gastrointestinal symptoms, such as diarrhoea and nausea, have been reported, mainly with orally administered extracts. Allergic dermatitis has also been reported for topical usage. The standardised guggulsterone (guggulipid) preparations tend to be far better tolerated.

SIGNIFICANT INTERACTIONS

Interactions are theoretical and based on in vitro and in vivo data; therefore, clinical significance is unclear and remains to be confirmed.

DIABETIC MEDICATION

In vivo studies suggest myrrh may have hypoglycaemic effects and therefore would have additive effects with diabetic medications. Monitor for changes in serum glucose in patients taking these medications.

LIPID-LOWERING MEDICATION

Guggul may have cholesterol-lowering activity and therefore have additive effects with other lipid-lowering medications — observe patients taking this combination and monitor drug requirements. Beneficial interaction possible.

ANTICOAGULANT AND ANTIPLATELET MEDICATION

Guggul inhibited platelet aggregation in vitro and in a clinical study, therefore concurrent use may theoretically increase the risk of bruising and bleeding (Bordia & Chuttani 1979). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking these combinations.

DILTIAZEM

Reduced efficacy possible. A clinical study confirmed guggulipid reduces bioavailability of this medicine (Dalvi et al 1994). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking this combination.

PROPRANOLOL

Reduced efficacy possible. A clinical study confirmed guggulipid reduces bioavailability of this medicine (Dalvi et al 1994). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

Do not use in cases of known allergy. Suspend use of guggul preparations 1 week before major surgery.

PREGNANCY USE

Contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Myrrh has been used since ancient times in a variety of forms as an antiseptic, anti-inflammatory and analgesic medicine.
- It has been used as a topical preparation to reduce inflammation and enhance wound healing — in vivo evidence suggests the anti-inflammatory activity of one of the main constituents is stronger than hydrocortisone and local anaesthetic activity is likely.
- Preliminary evidence suggests that it may be a useful treatment in gingivitis and periodontal disease.
- The preparation known as guggulipid, which comes from *Commiphora* species, may have lipid-lowering effects according to clinical studies; however, evidence is contradictory and further research is required to confirm this.
- Myrrh is not to be used in pregnancy and may interact with a number of medications when used orally.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Traditionally, the herb has been used as a mouthwash or topical paint to relieve symptoms of mouth ulcers, sore throats and gum disease. It has also been used as a topical application for inflamed skin conditions and wounds. Scientific research confirms antiseptic, anti-inflammatory and local anaesthetic effects and significant antiparasitic effects. The preparation known as guggulipid, which comes from *Commiphora* species, may lower total cholesterol levels.

When will it start to work?

A mouthwash or paint should provide rapid symptom relief.

Antiparasitic activity has been reported within 3 days' use in some parasitic infestations.

The lipid-lowering effects of guggulipid have been reported within 12 weeks.

Are there any safety issues?

The herb should not be taken during pregnancy and may interact with some medications.

REFERENCES

Al Awadi FM, Gumaa KA. Studies on the activity of individual plants of an antidiabetic plant mixture. Acta Diabetol Lat 24.1 (1987): 37-41.

Allam AF, el Sayad MH, Khalil SS. Laboratory assessment of the molluscicidal activity of Commiphora molmol (Myrrh) on Biomphalaria alexandrina, Bulinus truncatus and Lymnaea cailliaudi. J Egypt Soc Parasitol 31.3 (2001): 683-90.

Andersson M et al. Minor components with smooth muscle relaxing properties from scented myrrh (Commiphora guidotti). Planta Med 63.3 (1997): 251-4.

Barakat R, Elmorshedy H, Fenwick A. Efficacy of myrrh in the treatment of human schistosomiasis mansoni. Am J Trop Med Hyg 73.2 (2005): 365-7.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn; Rahway, NJ: Merck and C, 2003.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

bo-Madyan AA, Morsy TA, Motawea SM. Efficacy of myrrh in the treatment of schistosomiasis (haematobium and mansoni) in Ezbet El-Bakly, Tamyia Center, El-Fayoum Governorate, Egypt. J Egypt Soc Parasit 34.2 (2004a): 423-46.

bo-Madyan AA, Morsy TA, Motawea SM, Morsy AT. Clinical trial of Mirazid in treatment of human fascioliasis, Ezbet El-Bakly (Tamyia Center) Al-Fayoum Governorate. J Egypt Soc Parasit 34.3 (2004b): 807-18.

Bordia A, Chuttani SK. Effect of gum guggulu on fibrinolysis and platelet adhesiveness in coronary heart disease. Indian J Med Res 70 (1979): 992-6.

Botros S et al. Efficacy of mirazid in comparison with praziquantel in Egyptian Schistosoma mansoni-infected school children and households. Am J Trop Med Hyg 72.2 (2005): 119-23.

Claeson P, Andersson R, Samuelsson G. T-cadinol: a pharmacologically active constituent of scented myrrh: introductory pharmacological characterization and high field ^{1}H- and ^{13}C-NMR data. Planta Med 57.4 (1991): 352-6.

Dalvi S S et al. Effect of gugulipid on bioavailability of diltiazem and propranolol. J Assoc Physicians India 42.6 (1994): 454-5.

Dolara P et al. Local anaesthetic, antibacterial and antifungal properties of sesquiterpenes from myrrh. Planta Med 66.4 (2000): 356-8.

Gopal K et al. Clinical trial of ethyl acetate extract of gum gugulu (gugulipid) in primary hyperlipidemia. J Assoc Physicians India 34.4 (1986): 249-51.

Kimura I et al. New triterpenes, myrrhanol A and myrrhanone A, from guggul-gum resins, and their potent anti-inflammatory effect on adjuvant-induced air-pouch granuloma of mice. Bioorg Med Chem Lett 11.8 (2001): 985-9.

Kumar P, Clark M. Clinical Medicine, 5th edn. WB Saunders, 2002.

Malhotra SC, Ahuja MM, Sundaram KR. Long term clinical studies on the hypolipidaemic effect of Commiphora mukul (Guggulu) and clofibrate. Indian J Med Res 65.3 (1977): 390-5.

Massoud A et al. Preliminary study of therapeutic efficacy of a new fasciolicidal drug derived from Commiphora molmol (myrrh). Am J Trop Med Hyg 65.2 (2001a): 96-9.

Massoud AM, Labib IM, Rady M. Biochemical changes of Culex pipiens larvae treated with oil and oleo-resin extracts of Myrrh Commiphora molmol. J Egypt Soc Parasitol 31.2 (2001b): 517-29.

Nityanand S, Srivastava JS, Asthana OP. Clinical trials with gugulipid: A new hypolipidaemic agent. J Assoc Physicians India 37.5 (1989): 323-8.

Saeed MA, Sabir AW. Antibacterial activities of some constituents from oleo-gum-resin of Commiphora mukul. Fitoterapia 75.2 (2004): 204-8.

Sharma JN, Sharma JN. Comparison of the anti-inflammatory activity of Commiphora mukul (an indigenous drug) with those of phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. Arzneimittelforschung 27.7 (1977): 1455-7.

Sheir Z et al. A safe, effective, herbal antischistosomal therapy derived from myrrh. Am J Trop Med Hyg 65.6 (2001): 700-4.
Singh V et al. Stimulation of low density lipoprotein receptor activity in liver membrane of guggulsterone treated rats. Pharmacol Res 22.1 (1990): 37-44.
Singh BB, Mishra LC, Vinjamury SP, Aquilina N, Singh VJ, Shepard N. The effectiveness of Commiphora mukul for osteoarthritis of the knee: An outcomes study. Altern Ther Health Med 9.3 (2003): 74-9.
Szapary P et al. Guggulippid for the treatment of hypercholesterolemia. JAMA 290.6 (2003): 765-72.
Thappa DM, Dogra J. Nodulocystic acne: oral gugulipid versus tetracycline. J Dermatol 21.10 (1994): 729-31.
Tipton DA, Lyle B, Babich H, Dabbous KH. In vitro cytotoxic and anti-inflammatory effects of myrrh oil on human gingival fibroblasts and epithelial cells. Toxicol In Vitro 17.3 (2003): 301-10.
Tipton DA, Hamman NR, Dabbous MK. Effect of myrrh oil on IL-1beta stimulation of NF-kappaB activation and PGE(2) production in human gingival fibroblasts and epithelial cells. Toxicol In Vitro 20.2 (2005): 248-55.
Ulbricht C et al. Guggal for hyperlipidemia: A review by the natural standard research collaboration. Complement Ther Pract 13 (2005): 279-90.
Urizar NL et al. A natural product that lowers cholesterol as an antagonist ligand for FXR. Science 296.5573 (2002): 1703-6.
Wu J et al. The hypolipidemic natural product guggulsterone acts as an antagonist of the bile acid receptor. Mol Endocrinol 16.7 (2002): 1590-7.

New Zealand green-lipped mussel

Historical note The Mytilidae are a family of bivalve molluscs that first appeared approximately 400 million years ago (Scotti et al 2001). In New Zealand, they include the green-lipped mussel, which is also known as *Perna canaliculus* and has the Maori name kuku. Also known as *Perna viridis*, the green-lipped mussel has been used to treat arthritis by the Maoris for many years.

BACKGROUND AND RELEVANT PHARMACOKINETICS

There is insufficient reliable information available.

CHEMICAL COMPONENTS

Green-lipped mussel contains minerals, mucopolysaccharides and numerous other constituents; however, the protein and lipid content is considered the most important for pharmacological activity. Virtually all of the protein content is comprised of pernin, a self-aggregating glycoprotein rich in histidine and aspartic acid (Scotti et al 2001).

A lipid-rich extract, prepared by supercritical fluid (CO_2) extraction of freeze-dried stabilised NZ green-lipped mussel, is commercially available as Lyprinol. The main lipid classes in this preparation are sterol esters, triglycerides, free fatty acids (mainly EPA and DHA), sterols and phospholipids (Sinclair et al 2000).

MAIN ACTIONS

Most investigation has been conducted with one of two commercial preparations: Seatone or Lyprinol.

ANTI-INFLAMMATORY

Significant anti-inflammatory activity has been observed in both humans and animals with NZ green-lipped mussel (Halpern 2000, Miller & Ormrod 1980, Miller et al 1993). The mechanism of action is not well understood, but results from test tube and animal studies suggest inhibition of leukotriene B4 synthesis and PGE_2 production by activated macrophages and prostaglandin inhibitor actions (Miller & Wu 1984, Miller et al 1993).

OTHER ACTIONS

Not known

CLINICAL USE

Few primary sources are available, so secondary sources have been used where necessary in order to provide a more complete description of the evidence available.

RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

Arthritis is a significant problem in both humans and animals. In dogs, the most common form of joint disease is OA, which has been successfully treated by green-lipped mussel powder in one double-blind randomised study (Bierer & Bui 2002). Active treatment was shown significantly to improve total arthritic score, and alleviate joint pain and swelling at the end of week six compared with controls. More specifically, 83% of dogs in the active treatment group experienced a 30% or greater reduction in total arthritic scores and of these, 18% showed a 70% or greater improvement. Only 7% of controls showed a 30% or greater improvement with no dogs showing a 50% or greater improvement. The doses of green-lipped mussel powder ranged from 450 mg to 1000 mg/day, depending on body weight.

Clinical testing in humans has produced inconsistent results. One randomised clinical trial using Seatone in 35 patients with RA found no significant difference in chemical or clinical parameters compared with placebo, after 6 months' use (Larkin et al 1985). However, another study found that both freeze-dried powder and lipid extract of green-lipped mussel were effective in reducing symptoms in OA and RA (Gibson & Gibson 1998). Unfortunately, further details of this second study are not available. A more recent study, also conducted over 6 months, but this time comparing Lyprinol with placebo, found an improvement in mainly subjective measurements for OA; however, the results overall were still inconclusive (Lau et al 2004).

ASTHMA

Forty-six asthmatics received either two capsules Lyprinol or placebo daily over 8 weeks under double-blind randomised test conditions (Emelyanov et al 2002). Active treatment resulted in a significant improvement on several parameters such as daytime wheeze, reduced concentration of exhaled H_2O_2 and an increase in morning PEF, compared with placebo.

OTHER USES

A preliminary animal study has shown Lyprinol to be of potential benefit in inflammatory bowel disease. As this study compared Lyprinol with both olive oil and fish oil, it suggests that another component, beyond the fatty acid content, is providing the therapeutic benefit (Tenikoff et al 2005).

DOSAGE RANGE
The studies of NZ green-lipped mussel have used 210 mg/day of the lipid extract or 1050–1150 mg/day of the freeze-dried powder.

TOXICITY
Insufficient reliable information is available.

ADVERSE REACTIONS
Gastrointestinal discomfort, gout, skin rashes and a case of granulomatous hepatitis has been reported (Ahern et al 1980, Brooks 1980).

SIGNIFICANT INTERACTIONS
Insufficient reliable information is available.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindicated in people with allergies to shellfish — use with caution in people with hypertension, as the sodium content could theoretically raise blood pressure.

PREGNANCY USE
Insufficient reliable information is available to assess safety.

PRACTICE POINTS/PATIENT COUNSELLING
- New Zealand green-lipped mussel has been used to treat arthritis by the Maoris for many years.
- Significant anti-inflammatory activity has been observed in both animals and humans.
- Although a controlled study in dogs showed significant symptom relief for OA, clinical studies have produced inconsistent results.
- One controlled study has identified possible benefits in asthma.
- Insufficient reliable information is available to determine the safety of green-lipped mussel.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this supplement do for me?
Some studies have showed that NZ green-lipped mussel exerts significant anti-inflammatory activity, but it is uncertain whether it will relieve symptoms of OA. One small study suggests that it may relieve some symptoms of asthma.
When will it start to work?
Effects in asthma were seen after 8 weeks' use in one study.
Are there any safety issues?
It should not be taken by people with allergies to shellfish and should be used with caution by people with high blood pressure.

REFERENCES

Ahern MJ, Milazzo SC, Dymock R. Granulomatous hepatitis and Seatone. Med J Aust 2.3 (1980): 151-2.

Bierer TL, Bui LM. Improvement of arthritic signs in dogs fed green-lipped mussel (Perna canaliculus). J Nutr 132.6 Suppl 2 (2002): 1634-6S.

Brooks PM. Side effects from Seatone. Med J Aust 2.3 (1980): 158.

Emelyanov A et al. Treatment of asthma with lipid extract of New Zealand green-lipped mussel: a randomised clinical trial. Eur Respir J 20.3 (2002): 596-600.

Halpern GM. Anti-inflammatory effects of a stabilized lipid extract of Perna canaliculus (Lyprinol). Allerg Immunol (Paris) 32.7 (2000): 272-8.

Larkin JG, Capell HA, Sturrock RD. Seatone in rheumatoid arthritis: a six-month placebo-controlled study. Ann Rheum Dis 44.3 (1985): 199-201.

Lau CS et al. Treatment of knee osteoarthritis with Lyprinol®, lipid extract of the green-lipped mussel: A double-blind placebo-controlled study. Prog Nutr 6.1 (2004): 17-31

Miller T, Wu H. In vivo evidence for prostaglandin inhibitory activity in New Zealand green-lipped mussel extract. NZ Med J 97.757 (1984): 355-7.

Miller TE et al. Anti-inflammatory activity of glycogen extracted from Perna canaliculus (NZ green-lipped mussel). Agents Actions 38 (1993): C139-42.

Miller TE, Ormrod D. The anti-inflammatory activity of Perna canaliculus (NZ green lipped mussel). NZ Med J 92.667 (1980): 187-93.

Scotti PD et al. Pernin: a novel, self-aggregating haemolymph protein from the New Zealand green-lipped mussel, Perna canaliculus (Bivalvia: Mytilidae). Comp Biochem Physiol B Biochem Mol Biol 128.4 (2001): 767-79.

Sinclair AJ, Murphy KJ, Li D. Marine lipids: overview news insights and lipid composition of Lyprinol. Allerg Immunol (Paris) 32.7 (2000): 261-71.

Tenikoff D et al. Lyprinol (stabilized lipid extract of New Zealand green-lipped mussel): a potential preventative treatment modality for inflammatory bowel disease. J Gastroenterol 40.4 (2005): 361-5.

Noni

Historical note Noni has been used throughout South-East Asia and Polynesia for more than 2000 years as a food source, a medicine and a dye. Polynesian legends tell of heroes and heroines that used noni to survive from famine (Wang et al 2002).

COMMON NAME
Noni

OTHER NAMES
Ba Ji Tian, cheese fruit, Indian mulberry, mengkudu, nhau, nono, nonu

BOTANICAL NAME/FAMILY
Morinda citrifolia (family Rubiaceae)

PLANT PARTS USED
Roots, stems, bark, leaves, flowers, fruit and juice

CHEMICAL COMPONENTS
Noni contains terpenoids, alkaloids, anthraquinones (e.g. damnacanthal, morindone and rubiadin), the coumarin scopoletin, beta sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, the orange-red pigment alizarin, L-asperuloside, caproic acid, caprylic acid, ursolic acid, octoanoic acid, potassium, vitamin C, rutin (Hiramatsu et al 1993, Wang et al 2002), as well as a natural precursor for xeronine named proxeronine (Heinicke 1985, 2001).

MAIN ACTIONS
Noni is purported to have many different effects including analgesic, anti-inflammatory, antioxidant, anticancer, antimicrobial, immune enhancement and antihypertensive activity.

ANALGESIC
Noni root extract has exhibited opioid-like properties, with dose-dependent analgesic properties in mice that were reversible by naloxone, together with sedative effects at higher doses (Younos et al 1990). Analgesic activity has also been reported in controlled trials using rats and mice (Wang et al 2002).

ANTIOXIDANT/ANTI-INFLAMMATORY

Fruit, leaf and root extracts have all been shown to exhibit antioxidant activity (Kamiya et al 2004, Zin et al 2006) and NO scavenging activity in vitro (Jagetia & Baliga 2004), with some extracts showing comparable antioxidant activity to tocopherol (Zin et al 2002, 2006), grape seed powder and pycnogenol (Wang et al 2002). The neolignan, americanin A, has shown to be a particularly potent antioxidant in vitro (Su et al 2005).

Noni juice has been shown to reduce free radicals and liver damage in the livers of carbon-tetrachloride treated rats (Wang et al 2002). A 1-month double-blind, randomised, placebo-controlled trial involving 68 smokers found that 50 mL of noni juice twice daily significantly reduced plasma superoxide radicals and lipid peroxides (Wang et al 2002). Noni juice inhibits the enzymatic activity of COX-1 (Li et al 2003) and COX-2 in vitro (Wang et al 2002). The clinical significance of these findings is yet to be determined.

ANTITUMOUR

An alcoholic precipitate of noni juice significantly prolonged the life of mice with implanted tumors (Furusawa et al 2003, Hirazumi et al 1994). It is suggested that this antitumour activity is due to immunostimulatory activity, because the noni precipitate was not directly cytotoxic to tumour cells, but did activate immune cells in vitro with its activity reduced by immunosuppressant drugs (Furusawa et al 2003, Hirazumi et al 1996). Noni juice has also been observed to increase the wet weight of thymus tissue in animals (Wang et al 2002) and protect against DMBA-induced DNA adduct formation in rats (Wang & Su 2001).

Noni also improved survival times in cancer-implanted mice when combined with suboptimal doses of standard chemotherapeutic agents (Hirazumi & Furusawa 1999) and this is supported by in vitro studies demonstrating synergistic effects with chemotherapeutic agents (Furusawa et al 2003, Wang et al 2002).

In vitro studies have also found that noni fruit has antiproliferative activity against SKBR3 human breast adenocarcinoma cells (Moongkarndi et al 2004), and that glycosides extracted from noni inhibit cell transformation (Liu et al 2001) and UVB-induced activator protein-1 activity (Sang et al 2001, 2003). The anthraquinone, damnacanthal, is reported to stimulate UV-induced apoptosis in vitro (Hiwasa et al 1999).

ANTIMICROBIAL

Constituents of noni have been reported to have in vitro activity against *Escherichia coli* (Duncan et al 1998) and *Mycobacterium tuberculosis* (Anon 2001), as well as the

parasite *Ascaris lumbricoides* (Raj 1977); however, the clinical significance of this is undetermined.

ANTIHYPERTENSIVE

The antihypertensive effects of the root extract of noni were first investigated in the 1950s (Ho 1955) and a hot-water extract of noni root is reported to have lowered the blood pressure of an anaesthetised dog (Youngken 1958).

OTHER ACTIONS

Noni has been shown to inhibit gastric emptying in male rats via a mechanism involving stimulation of cholecystokinin (CCK) secretion and CCK1 receptor activation (Pu et al 2004).

CLINICAL USE

Noni has been reported to have benefits for people suffering from arthritis, diabetes, high blood pressure, muscle aches and pains, menstrual difficulties, headache, heart disease, atherosclerosis, AIDS, cancers, gastric ulcers, poor digestion, depression, senility and drug addiction (Wang et al 2002). Noni has not been significantly investigated under clinical trial conditions, so evidence for its use is derived from traditional, in vitro and animal studies.

ANTICANCER

There are anecdotal reports of noni being used as an adjuvant immunotherapy for cancer (Wong 2004); however, further research is required to determine its role in clinical practice.

HEARING AND MENTAL HEALTH

A small placebo-controlled pilot study involving nine hearing impaired osteopenic or osteoporotic women found that ingestion of approximately 50 mL of noni juice over 3 months resulted in improved mental health and a mild protective effect on hearing. Further studies are required to determine the clinical significance of these findings (Langford et al 2004).

OTHER USES

Noni fruit has been used as a food source.

DOSAGE RANGE

- There is little human research upon which to make dosage recommendations.
- Juice 25 mL (1 oz.) twice daily (Wang et al 2002).

TOXICITY

No toxic effects have been found in rats (Mancebo et al 2002) even when given doses up to 80 mL/kg (Wang et al 2002). No allergic responses were reported from allergenicity studies using guinea pigs (Wang et al 2002).

Three case of hepatotoxicity related to noni juice consumption have been reported, with one case requiring urgent liver transplantation (Millonig et al 2005, Stadlbauer et al 2005) and the others recovering spontaneously after ceasing noni consumption (Millonig et al 2005, Stadlbauer et al 2005).

ADVERSE REACTIONS

There is insufficient reliable information available about the safety of noni.

SIGNIFICANT INTERACTIONS

There is one case report of noni juice consumption causing resistance to warfarin (Carr et al 2004).

CONTRAINDICATIONS AND PRECAUTIONS

Not known.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Noni has been traditionally used as food and medicine for a wide range of medical conditions.
- Noni has not been significantly investigated in clinical studies, so its use is based on traditonal evidence and laboratory and animal studies.
- Although it is likely to be safe, it is prudent to avoid using noni in amounts greater than those ingested as a food during pregnancy and to monitor clotting profiles if noni is used with anticoagulant medications.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Noni has not been significantly investigated under clinical trial conditions, so its use is based on traditional evidence and laboratory and animal studies.

When will it start to work?

There is little published evidence to indicate its speed of action, which will depend on the clinical use.

Are there are any safety issues?

Noni is generally considered safe and can be consumed as a food; however, the safety of large intakes is unknown.

REFERENCES

Anon. Noni plant may help TB. AIDS Patient Care STDs 15(3) (2001): 175.

Carr ME et al. Coumadin resistance and the vitamin supplement Noni [1]. Am J Hematol 77(1) (2004): 103.

Duncan SH et al. Inhibitory activity of gut bacteria against Escherichia coli O157 mediated by dietary plant metabolites. FEMS Microbiol Lett 164(2) (1998): 283-8.

Furusawa E et al. Antitumour potential of a polysaccharide-rich substance from the fruit juice of Morinda citrifolia (Noni) on sarcoma 180 ascites tumour in mice. Phytother Res 17(10) (2003): 1158-64.

Heinicke R. The pharmacologically active ingredient of Noni. Bull Ntl Trop Bot Gardens; as cited in Wang MY et al. (2002). Morinda citrifolia (Noni): A literature review and recent advances in Noni Res. Acta Pharmacol Sin 23(12) (1985): 1127-41.

Heinicke R. The Xeronine System: A Nex Cellular Mechanism That Explains the Health Promoting Action of NONI and Bromelain. USA: Direct Source Publishing [online] 2001.

Hiramatsu T et al. Induction of normal phenotypes in ras-transformed cells by damnacanthal from Morinda citrifolia. Cancer Lett 73(2-3) (1993): 161-6.

Hirazumi A, Furusawa E. An immunomodulatory polysaccharide-rich substance from the fruit juice of Morinda citrifolia (noni) with antitumour activity. Phytother Res 13(5) (1999): 380-7.

Hirazumi A et al. Anticancer activity of Morinda citrifolia (noni) on intraperitoneally implanted Lewis lung carcinoma in syngeneic mice. Proc West Pharmacol Soc 37 (1994): 145-6.

Hirazumi A et al. Immunomodulation contributes to the anticancer activity of morinda citrifolia (noni) fruit juice. Proc West Pharmacol Soc 39 (1996): 7-9.

Hiwasa T et al. Stimulation of ultraviolet-induced apoptosis of human fibroblast UVr-1 cells by tyrosine kinase inhibitors. FEBS Lett 444(2-3) (1999): 173-6.

Ho DV. Treatment and prevention of hypertension and its cerebral complications by total root extracts of Morinda citrifolia. Press Med 63(72) (1955): 1478.

Jagetia GC, Baliga MS. The evaluation of nitric oxide scavenging activity of certain Indian medicinal plants in vitro: a preliminary study. J Med Food 7(3) (2004): 343-8.

Kamiya K et al. Chemical constituents of Morinda citrifolia fruits inhibit copper-induced low-density lipoprotein oxidation. J Agric Food Chem 52(19) (2004): 5843-8.

Langford J et al. Effects of Morinda citrifolia on quality of life and auditory function in postmenopausal women [1]. J Altern Complement Med 10(5) (2004): 737-9.

Li RW et al. A cross-cultural study: anti-inflammatory activity of Australian and Chinese plants. J Ethnopharmacol 85(1) (2003): 25-32.

Liu G et al. Two novel glycosides from the fruits of Morinda Citrifolia (noni) inhibit AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line. Cancer Res 61(15) (2001): 5749-56.

Mancebo A et al. Repeated dose oral toxicity assay (28 days) of the aqueous extract of Morinda citrifolia in Sprague Dawley rats. Rev Toxicol 19(2) (2002): 73-8.

Millonig G et al. Herbal hepatotoxicity: Acute hepatitis caused by a Noni preparation (Morinda citrifolia). Eur J Gastroenterol Hepatol 17(4) (2005): 445-7.

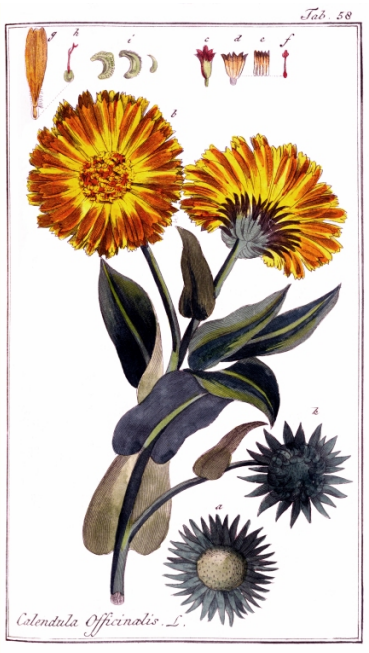
Moongkarndi P et al. Antiproliferative activity of Thai medicinal plant extracts on human breast adenocarcinoma cell line. Fitoterapia 75(3-4) (2004): 375-7.

Pu HF et al. Effects of juice from Morinda citrifolia (Noni) on gastric emptying in male rats. Chin J Physiol 47(4) (2004): 169-74.

Raj RK Screening of indigenous plants for anthelmintic action against human Ascaris lumbricoides: Part II. Indian J Physiol Pharmacol 19(1), 1997.

Sang S et al. Citrifolinin A, a new unusual iridoid with inhibition of Activator Protein-1 (AP-1) from the leaves of noni (Morinda citrifolia L.). Tetrahedron Lett 42(10) (2001): 1823-5.
Sang S et al. New unusual iridoids from the leaves of noni (Morinda citrifolia L.) show inhibitory effect on ultraviolet B-induced transcriptional activator protein-1 (AP-1) activity. Bioorg Med Chem 11(12) (2003): 2499-502.
Stadlbauer V et al. Hepatotoxicity of NONI juice: report of two cases. World J Gastroenterol 11(30) (2005): 4758-60.
Su BN et al. Chemical constituents of the fruits of Morinda citrifolia (Noni) and their antioxidant activity. J Nat Prod 68(4) (2005): 592-5.
Wang MY, Su C. Cancer preventive effect of Morinda citrifolia (Noni). Ann NY Acad Sci 952 (2001): 161-8.
Wang MY et al. Morinda citrifolia (Noni): A literature review and recent advances in Noni Res. Acta Pharmacol Sin 23(12) (2002): 1127-41.
Wong DKW. Are immune responses pivotal to cancer patient's long term survival? Two clinical case-study reports on the effects of Morinda citrifolia (Noni). Hawaii Med J 63(6) (2004): 182-4.
Youngken HW Sr. A study of the root of Morinda citrifolia Linne. I. J Am Pharm Assoc Am Pharm Assoc (Baltim) 47(3) (1958): 162-5.
Younos C et al. Analgesic and behavioural effects of Morinda citrifolia. Planta Med 56(5) (1990): 430-4.
Zin ZM et al. Antioxidative activity of extracts from Mengkudu (Morinda citrifolia L.) root, fruit and leaf. Food Chem 78(2) (2002): 227-31.
Zin ZM et al. Antioxidative activities of chromatographic fractions obtained from root, fruit and leaf of Mengkudu (Morinda citrifolia L.). Food Chem 94(2) (2006): 169-78.

Oats



Historical note Culpeper (1652) recommended that 'a poultice made of meal of oats and some oil of bay helpeth the itch and the leprosy'. By the end of the 18th century oats was the main grain used by all levels of the population in Scotland. Students would arrive at university after the summer with a bag of oatmeal to live on during the term. The older Scottish universities still call the autumn mid-term break 'Meal Monday' because traditionally at that time the students would return home to replenish their supplies.

OTHER NAMES

Groats, green oats, green tops, haver, oat herb, oatmeal

BOTANICAL NAME/FAMILY

Avena sativa (family Poaceae (Graminaceae))

PLANT PARTS USED

The whole flowering plant, including the oat straw and the seed (also used for porridge). Oat bran is also used in some clinical trials.

CHEMICAL COMPONENTS

Beta-glucan (soluble fibre), triterpenoid saponins (including avenacosides A and B), phenolic compounds (avenanthramides A, B, C), alkaloids (including indole alkaloid, gramine, trigonelline, avenine), sterol (avenasterol), flavonoids, starch, phytates, protein (including gluten) and coumarins.

Nutrients such as silicic acid, calcium, potassium, phosphorus, iron (39 mg/kg), manganese (8.5 mg/kg), zinc (19.2 mg/kg) (Witchl & Bisset 1991), vitamins A, B-complex, C, E and K, and amino acids.

MAIN ACTIONS

LIPID LOWERING

Beta-glucans increase bile acid synthesis and thus decrease serum cholesterol (Andersson et al 2002). The fibre binds to cholesterol, preventing initial absorption and enterohepatic recirculation of cholesterol, and the two are excreted together.

Clinical trials have shown that oat bran contains soluble fibres, such as beta-glucan (e.g. 75 g extruded oat bran, equivalent to 11 g beta-glucan), which nearly

double the serum alpha-HC concentration within 8 hours, indicating increased bile acid synthesis and thus decreased serum cholesterol (Andersson et al 2002).

ANTIATHEROGENIC EFFECTS

In vitro studies suggest that the phenolic anti-oxidants known as avenanthramides, present in oats, may exert anti-inflammatory and anti-atherogenic effects (Liu et al 2004) by inhibiting smooth muscle cell proliferation and increasing nitric oxide production (Nie et al 2005).

ANTIHYPERTENSIVE EFFECTS

A reduction in blood pressure has been observed in clinical trials; however, the mechanism of action has not been fully elucidated (Pins et al 2002, Saltzman et al 2001).

HYPOGLYCAEMIC (BLOOD SUGAR CONTROL)

Oats have been shown in clinical trials to reduce the postprandial glycaemic response (Jenkins et al 2002, Pins et al 2002, Tapola et al 2005). Whilst the mechanism of action is unclear, the ability of beta-glucans to slow stomach emptying and increase the viscosity of food in the small intestine, resulting in delayed glucose absorption, is most likely a factor (Rakel 2003).

ANTIPRURITIC EFFECTS

External application of oat preparations has been shown to relieve itch (Matheson et al 2001).

OTHER ACTIONS

Due to its vitamin, mineral and amino acid content, oats are a nutritious food. Internally, oats also act as a bulk-forming laxative.

CLINICAL USE

Oats are not usually used as a stand-alone treatment and tend to form part of an overall management program.

HYPERLIPIDAEMIA

Several clinical trials have shown a marked reduction in total and LDL-cholesterol using oat-based cereals (Karmally et al 2005, Saltzman et al 2001) and also oat milk (6% reduction) (Onning et al 1999).

Oat bran has been shown to reduce LDL-cholesterol by 16% in 140 hypercholesterolaemic subjects consuming 56 g oat bran/day for 12 weeks (Davidson et al 1991). In overweight men consuming an oat-based cereal (14 g dietary fibre) for 12 weeks, LDL-cholesterol was most significantly affected, with a reduction in

concentrations of small, dense LDL-cholesterol and LDL particle number. No adverse changes occurred in blood triacylglycerol or HDL-cholesterol concentration (Davy et al 2002). In another clinical trial, a group consuming wholegrain oat-based cereals experienced a 24.2 mg/dL reduction in total cholesterol levels and a 16.2 mg/dL decrease in LDL-cholesterol levels (Pins et al 2002). Oats do not generally affect total and LDL-cholesterol levels in people with normal serum cholesterol levels (Chen et al 2005). (See Clinical note: Major lipids affecting cardiovascular disease risk, in monograph on Vitamin B3.)

The lipid-lowering effects of a hypocaloric diet containing oats has been shown in a clinical trial to result in significantly greater decreases in total and LDL-cholesterol than a hypocaloric diet alone (Saltzman et al 2001). In addition, a RCT of moderately hypercholesterolaemic men consuming oat milk, deprived of insoluble fibre but still containing 0.5 g/100 g beta-glucan (750 mL/day) for 5 weeks, also showed a 6% reduction in total and LDL-cholesterol (Onning et al 1999).

HYPERTENSION

Results of RCT suggest that consumption of oat-based cereals may reduce SBP and reduce or eliminate requirements for antihypertensive medications in some people (Pins et al 2002, Saltzman et al 2001).

The inclusion of wholegrain oat-based cereals was found in a RCT to decrease blood pressure in hypertensive patients and reduce requirements for antihypertensive medications. 'Seventy-three percent of participants in the oats group versus 42% in the control group were able to stop or reduce their medication by half. Treatment group participants whose medication was not reduced had substantial decreases in blood pressure' (Pins et al 2002). In another RCT, overweight subjects consuming a hypocaloric diet containing oats (45 g/4.2 MJ dietary energy/day) for 6 weeks experienced a reduction in SBP that was more significant than a hypocaloric diet alone (oats –6 ± 7 mmHg, control –1 ± 10 mmHg, $P = 0.026$). Lipid-lowering effects were also noted (Saltzman et al 2001).

PRURITIS

A clinical trial assessing the itch experienced by burns patients found that the group using a product with 5% colloidal oatmeal reported significantly less itch and requested significantly less antihistamine treatment than the control group (Matheson et al 2001).

Commission E approves topical use in baths for inflammatory and seborrhoeic skin disease, especially with itch (Blumenthal et al 2000).

BLOOD SUGAR REGULATION

The ability of oats to delay glucose absorption, and therefore reduce the postprandial glycaemic response, provides a theoretical basis for their use as part of an overall treatment protocol in diabetes and hypoglycaemic conditions. A RCT of 12 patients with type 2 diabetes demonstrated that 30 g oat bran flour, high in beta-glucan, had a low glycaemic response and decreased the postprandial glycaemic response of an oral glucose load in a series of 2-hour meal glucose tolerance tests (Tapola et al 2005).

A RCT has shown that in a 50 g portion of carbohydrate, each gram of beta-glucan reduces the GI by 4 units, making it a useful adjunct to reduce the postprandial glycaemic response without affecting palatability (Jenkins et al 2002). Another trial showed a 15.03 mg/dL drop in plasma glucose levels versus controls when consuming wholegrain oat-based cereals (Pins et al 2002).

OTHER USES

Traditionally, oats are considered a nervous system nutritive and therefore used during times of convalescence. More specifically, the straw is prescribed for nervous debility and exhaustion, whereas the seed is considered more stimulating and said to gently improve energy and support an overly stressed nervous system (Chevallier 1996).

Preliminary trials have suggested an improvement in sexual interest and performance in people taking oats in combination with nettles. The effects were more consistent in males than females. Further trials are required to confirm the benefits of oats in isolation (Haroian et al 1987).

Interestingly, oats are also used as supportive therapy during nicotine (Beglinger et al 1977, Schmidt & Geckeler 1976) and morphine withdrawal; however, reliable clinical evidence is currently limited and does not fully support these recommendations.

Due to its high soluble fibre content, oats are also used as an aid to weight loss. Taken before meals, they increase satiety and therefore enable smaller food portions to satisfy hunger.

DOSAGE RANGE

- 1–4 g three times daily of oatmeal or straw (Mills 1991).
- Australian manufacturers recommend 20–40 mL/week 1:2 tincture.
- Topically for itch: 5% colloidal oatmeal in a suitable carrier (Matheson et al 2001) or 100 g cut herb in a bath (Blumenthal et al 2000).

- The inclusion of wholegrain oat-based cereals or oat bran may be a useful adjunct to the treatment of hyperlipidaemia and hypertension and to delay glucose absorption. 75 g dried oatmeal (equivalent to ≈3 g soluble fibre daily) (Rakel 2003).

ADVERSE REACTIONS

Excessive intake of fibre from oats or oat bran may cause flatulence and anal irritation.

SIGNIFICANT INTERACTIONS

Controlled studies are largely unavailable; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

ANTIHYPERTENSIVES

Additive effects are theoretically possible (Pins et al 2002); beneficial interaction is possible — observe. Patients taking oats, oat milk or oat bran should be monitored, as medication requirements may alter.

LIPID-LOWERING MEDICATIONS

Additive effects are theoretically possible — beneficial interaction is possible. Patients taking oats, oat milk or oat bran should be monitored, as medication requirements may alter. Conversely, two case reports exist of a reduced effect of lovastatin in patients taking 50–100 g oatbran daily (Richter et al 1991). As this is likely to be due to the fibre inhibiting absorption of the drug doses should be separated by 2–3 hours.

Clinical note — Do oats interfere with nutrient absorption?
Although the high phytate content of oats would indicate a potential for reduced absorption of trace elements such as zinc, calcium and iron, one clinical trial investigating the effects of oat bran on zinc absorption found no evidence of reduced absorption (Sandstrom et al 2000).

CONTRAINDICATIONS AND PRECAUTIONS

COELIAC DISEASE

Although oats are generally considered to be contraindicated in patients with coeliac disease, a moderate amount as part of an otherwise gluten-free diet may improve the nutritional value of the diet (Storsrud et al 2003a) and is generally well tolerated by the majority of adults (Lundin et al 2003) and children (Hogberg et al 2004) with coeliac disease. Both short- and longer-term studies have found no adverse immunological effects associated with the regular consumption of moderate

amounts of oats in patients with coeliac disease (Janatuinen et al 2002, Thompson 2003), although some may experience intestinal discomfort, diarrhoea, bloating and subtotal villous atrophy (Lundin et al 2003, Peraaho et al 2004, Storsrud et al 2003b).

Dietary oats should not be used in cases of intestinal obstruction (Skidmore-Roth 2001).

PREGNANCY USE

Oral use is considered to be safe in pregnancy and lactation (NMCD 2003).

PRACTICE POINTS/PATIENT COUNSELLING

- Oats are a rich source of nutrients, such as calcium, potassium, phosphorus, iron, manganese, zinc; vitamins A, B-complex, C, E and K, and amino acids. Dietary oats also contain a significant amount of soluble fibre.
- Regular intake of wholegrain oat-based cereals may have positive effects on cardiovascular disease risk factors such as hypertension, hyperlipidaemia and glucose regulation.
- Topical use of the cut herb in the bath or 5% colloidal oatmeal in a suitable carrier is used to relieve itch.
- Traditionally, oats are viewed as a nervous system nutritive and therefore used during times of convalescence.
- Patients with coeliac disease should be able to tolerate moderate amounts of oats in the diet.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Oats are a concentrated nutrient source and also contain soluble fibre. They not only provides a range of vitamins and minerals, but can reduce blood pressure, cholesterol and improve blood sugar regulation.

When will it start to work?

Scientific studies have shown that oatbran and oat-based cereals can reduce cholesterol levels and blood pressure within 5–6 weeks.

Are there any safety issues?

Dietary oats should be avoided in cases of intestinal obstruction.

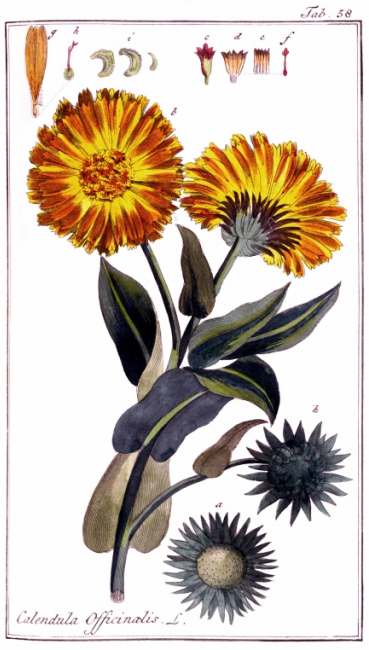
REFERENCES

Andersson M, Ellegard L, Andersson H. Oat bran stimulates bile acid synthesis within 8 h as measured by 7alpha-hydroxy-4-cholesten-3-one. Am J Clin Nutr 76(5) (2002): 1111–16.

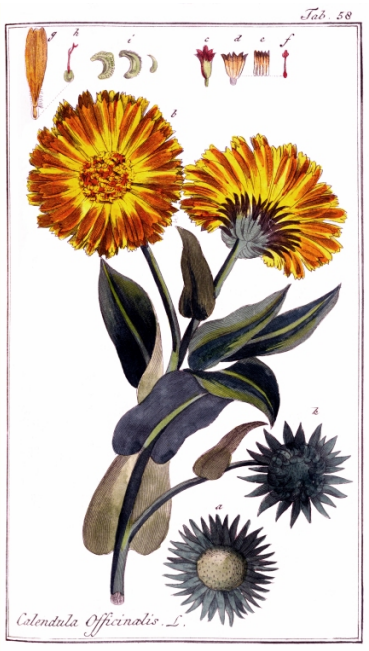
Beglinger C, Frey C, Abelin T. Modification of smoking behavior using long-distance methods. Soz Praventivmed 22(4) (1977): 182–3 [in German].

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Chen J et al. A randomized controlled trial of dietary fiber intake on serum lipids. Eur J Clin Nutr, 2005; [Epub ahead of print].
Chevallier A. The Encyclopedia of Medicinal Plants. London, UK: Dorling Kindersley, 1996.
Culpeper N. The English Physician, 1652.
Davidson MH et al. The hypocholesterolaemic effects of beta-glucan in oatmeal and oat bran: A dose-controlled study. JAMA 265 (1991): 1833-9.
Davy BM et al. High-fiber oat cereal compared with wheat cereal consumption favorably alters LDL-cholesterol subclass and particle numbers in middle-aged and older men. Am J Clin Nutr 76(2) (2002): 351-8.
Haroian L et al. Institute for Advanced Study of Human Sexuality research report: The exsativa project (Swiss formula A111). Specific Press, 1987.
Hogberg L et al. Oats to children with newly diagnosed coeliac disease: a randomised double blind study. Gut 53(5) (2004): 649-54.
Janatuinen EK et al. No harm from five year ingestion of oats in coeliac disease. Gut 50(3) (2002): 332-5.
Jenkins AL et al. Depression of the glycemic index by high levels of beta-glucan fiber in two functional foods tested in type 2 diabetes. Eur J Clin Nutr 56(7) (2002): 622-8.
Karmally W et al. Cholesterol-lowering benefits of oat-containing cereal in Hispanic Americans. J Am Diet Assoc 105(6) (2005): 967-70.
Liu L et al. The antiatherogenic potential of oat phenolic compounds. Atherosclerosis 175(1) (2004): 39-49.
Lundin KE et al. Oats induced villous atrophy in coeliac disease. Gut 52(11) (2003): 1649-52.
Matheson JD, Clayton J, Muller MJ. The reduction of itch during burn wound healing. J Burn Care Rehabil 22(1) (2001): 76-81.
Mills S. The Essential Book of Herbal Medicine. Middlesex, UK: Penguin, 1991.
Natural medicines comprehensive database (NMCD online). Oats, 2003. Available from: http://www.naturaldatabase.com
Nie L et al. Avenanthramide, a polyphenol from oats, inhibits vascular smooth muscle cell proliferation and enhances nitric oxide production. Atherosclerosis 186(2) (2005): 260-6.
Onning G et al. Consumption of oat milk for 5 weeks lowers serum cholesterol and LDL cholesterol in free-living men with moderate hypercholesterolemia. Ann Nutr Metab 43(5) (1999): 301-9.
Peraaho M et al. Effect of an oats-containing gluten-free diet on symptoms and quality of life in coeliac disease: A randomized study. Scand J Gastroenterol 39(1) (2004): 27-31.
Pins JJ et al. Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? J Fam Pract 51(4) (2002): 353-59.
Rakel D. Integrative Medicine. Philadelphia: Saunders, 2003.
Richter W, Jacob B, Schwandt P. Interaction between fibre and lovastatin. Lancet 338(8768) (1991): 706.
Saltzman E et al. An oat-containing hypocaloric diet reduces systolic blood pressure and improves lipid profile beyond effects of weight loss in men and women. J Nutr 131(5) (2001): 1465-70.
Sandstrom B et al. A high oat-bran intake does not impair zinc absorption in humans when added to a low-fiber animal protein-based diet. J Nutr 130(3) (2000): 594-9.
Schmidt K, Geckeler K. Pharmacotherapy with avena sativa: a double blind study. Int J Clin Pharmacol Biopharm 14(3) (1976): 214-16.
Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. St Louis: Mosby, 2001.
Storsrud S et al. Beneficial effects of oats in the gluten-free diet of adults with special reference to nutrient status, symptoms and subjective experiences. Br J Nutr 90(1) (2003a): 101-7.
Storsrud S et al. Adult coeliac patients do tolerate large amounts of oats. Eur J Clin Nutr 57(1) (2003b): 163-9.
Tapola N et al. Glycemic responses of oat bran products in type 2 diabetic patients. Nutr Metab Cardiovasc Dis 15(4) (2005): 255-61.
Thompson T. Oats and the gluten-free diet. J Am Diet Assoc 103(3) (2003): 376-9.
Witchl M, Bisset NG (eds). Herbal Drugs and Phytopharmaceuticals. Stuttgart: Medpharm Scientific Publishers, 1991.



Olive



Historical note The olive tree is among the oldest known cultivated trees in the world. Several biblical references to olive suggest its use dates back to ancient times and victors in the early Olympic Games were crowned with its leaves. Olives and its associated products have been used widely as folk medicines in countries such as Spain, Italy, France, Greece, Israel, Morocco, Tunisia, Turkey and the Mediterranean islands. Today, the olive plant is most well known for its fruit crop and oil. The Mediterranean region produces approximately 98% of the world's total olive crop (≈11 million tons) (Delgado-Pertinez 2000), although the plant is also widespread on the Arabian peninsula, the Indian subcontinent and Asia. More recently, olive plantations have been developed in Australia and research is now being undertaken to identify the best species suited to the subtropical climate.

BOTANICAL NAME/FAMILY

Olea europaea L. (family Oleaceae)

PLANT PARTS USED

Fruit and leaf.

Olive oil is made from the fruit and widely used in cooking. This review will focus on olive oil and olive leaf extracts.

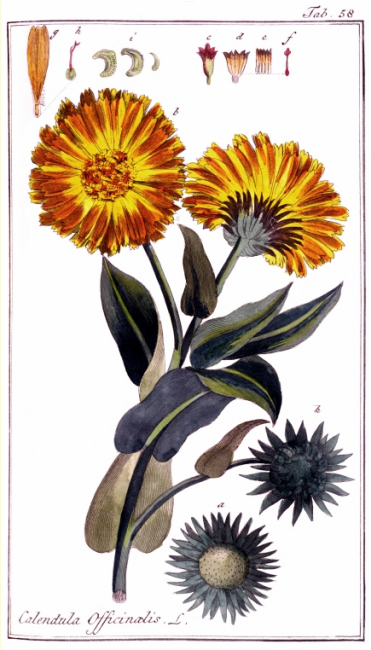
CHEMICAL COMPONENTS

Olive oil contains high levels of monounsaturated fatty acids (chiefly oleic acid) and is also a source of at least 30 phenolic compounds including oleuropein, hydroxytyrosol and tyrosol and also flavonoids, squalene, beta-carotene, and alpha-tocopherol (Stark & Madar 2002).

Olive leaf extract also contains a variety of phenolic compounds, most importantly oleuropein, hydroxytyrosol and tyrosol, and also rutin, luteolin, catechin and apigenin, and various nutrients such as selenium, chromium, iron, zinc, vitamin C, beta-carotene and a wide range of amino acids (Polzonetti et al 2004). Unlike the olive fruit, olive leaf does not contain significant amounts of monounsaturated fatty acids, oleic acid or squalene (Stark & Madar 2002).

It is important to note that not all olive products contain the same concentration of phenolic compounds. Olive leaf extract and extra virgin olive oil (acidity <1%) are

considered superior sources of phenolic compounds (Owen et al 2000), with extra virgin olive oil containing higher amounts than refined virgin olive oil (Visioli & Galli 2002). Of these, olive leaf extract is the most concentrated. According to one test, total phenol levels ranging from 6360 to 8190 mg/L were identified in olive leaf extract (samples from Olive Products Australia) compared to 200–800 mg/L for extra virgin olive oil (unpubl data, Department of Primary Industries Laboratory, Wagga Wagga, NSW, Australia).



MAIN ACTIONS

Most of the pharmacological effects for olive oil and olive leaf extract can be attributed to their main phenolic constituents, in particular oleuropein, hydroxytyrosol and tyrosol; however, several other biologically active constituents are also present.

ANTIOXIDANT

Numerous olive phenolics have strong free radical scavenging capacity and show a synergistic behaviour when combined, as occurs naturally in the fruit and leaf (Benavente-Garcia et al 2000). According to in vitro tests, the flavonoids, rutin, catechin and luteolin exert antioxidant effects almost 2.5-fold those of vitamin C and E and are comparable to that of lycopene (Benavente-Garcia et al 2000).

ANTI-INFLAMMATORY AND ANTITHROMBOTIC

Several constituents within olive oil and/or leaf have demonstrated anti-inflammatory properties, chiefly oleuropein, hydroxytyrosol, oleic acid, luteolin and apigenin (de la Puerta et al 2000, Makin et al 2003).

Oleuropein and hydroxytyrosol are found in both the oil and leaf and inhibit leukotriene B4 generation, which is involved in a wide range of pro-inflammatory pathways (Petroni et al 1997). These polyphenols are able to inhibit platelet aggregation and lipoxygenases and eicosanoid production (Andrikopoulos et al 2002, Manna et al 2004).

Olive oil also contains large amounts of oleic acid, which is an omega-9 monounsaturated fatty acid that is converted to eicosatrienoic acid, which is then converted to leukotriene A3, which is a potent inhibitor of leukotriene B4 synthesis.

ANTI-ATHEROGENIC

The oleic acid component modifies the vascular response to pro-atherogenic chemicals (such as high levels of cholesterol and the advanced glycation end-products of diabetes) and inhibits endothelial adhesion molecule expression, according to test tube studies (Massaro & Caterina 2002).

ANTIMICROBIAL

Oleuropein has antimicrobial activity against a variety of viruses, bacteria, yeasts and fungi (Aziz et al 1998, Bisignano et al 1999, Furneri et al 2002, Koutsoumanis et al 1998, Ma et al 2001, Markin et al 2003, Tassou & Nychas 1995, Tassou et al 1991); however, one study suggests that hydroxytyrosol has stronger broad-spectrum effects (Bisignano et al 1999).

ANTIHYPERTENSIVE

Studies have identified the Mediterranean diet, as an entity, and the olive oil in particular, as significantly reducing arterial blood pressure in humans (Ferrara et al 2000, Fito et al 2005, Perona et al 2004, Psaltopoulou et al 2004).

The hypotensive effect of olive leaves has been well documented in vivo (Cherif et al 1996, Fehri et al 1994, Khayyal et al 2002, Somova et al 2003). One of the more recent studies tested a specially prepared olive leaf extract (EFLA 943) and confirmed dose-dependent hypotensive activity when given orally to animals (Khayyal et al 2002).

HYPOGLYCAEMIC ACTIVITY

Olive leaf extract has demonstrated hypoglycaemic activity in animal models and one of the compounds responsible for this activity is oleuropeoside, which produced antidiabetic activity in animals with alloxan-induced diabetes (Gonzalez et al 1992, Manna 2004). The researchers have suggested potentiation of glucose-induced insulin release and increased peripheral uptake of glucose as the most likely mechanisms of action.

OTHER ACTIONS

Traditional texts describe the leaves as astringent and antiseptic and useful when boiled in water to create a decoction for the treatment of obstinate fevers. The oil is described as a nourishing demulcent with laxative properties. Oleuropein is the phenolic constituent responsible for the typically bitter and pungent aroma associated with olives, olive oil and leaf (Manna et al 2004).

ANTIMUTAGENIC

Luteolin possesses antimutagenic and antitumorigenic properties (Kim et al 2003).

HYPO-URICAEMIA

In vivo tests report that olive leaf extract has a hypo-uricaemic effect in treated animals (Serra-Majem L et al 2003).

CLINICAL USE

Olive oil has been studied as a stand-alone entity in some studies; however, it is generally studied as part of the Mediterranean diet where it is the principal source of fat and considered a key contributor to the diet's many healthy benefits (Serra-Majem et al 2003). As a reflection of this, research into the Mediterranean diet is included in this monograph; however, the contribution of olive oil to these results remains unclear. In contrast, olive leaf extract has not been significantly tested under clinically controlled conditions, so evidence is mainly derived from traditional, in vitro and animal studies.

Clinical note — What is the Mediterranean diet?
The Mediterranean diet studied in most trials is based on the traditional diet of Greece. It is low in saturated fat and high in monounsaturated fat (oleic acid:omega-9 = 18:1), mainly from olive oil; high in complex carbohydrates, from legumes; and high in fibre, mostly from vegetables and fruits. Total fat may be high (>40% of total energy intake), but the monounsaturated to saturated fat ratio is around 2. The high content of vegetables, fresh fruits, cereals, and olive oil guarantees a high intake of beta-carotene, vitamins B6, B12, C, and E, polyphenols, and various minerals.

CARDIOVASCULAR DISEASE

Prevention It has been speculated that consumption of olive oil reduces the incidence of coronary heart disease, based on the observation that countries where the Mediterranean diet is consumed, chiefly Greece, Italy and Spain, have a lower incidence of coronary heart disease.

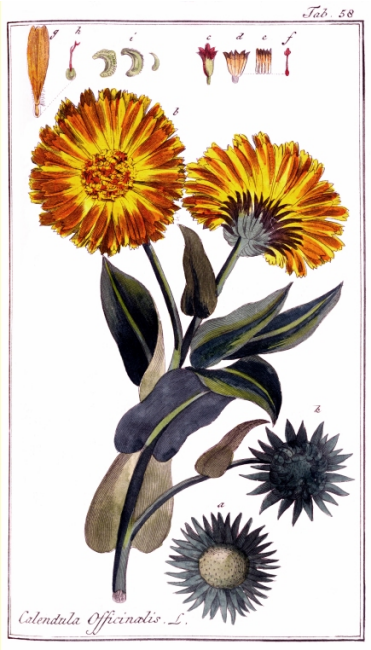
In 1999, the Lyon Diet Heart Study was published and is widely claimed to be a landmark study investigating whether a Mediterranean type diet could reduce the rate of myocardial infarction (de Lorgeril et al 1999). It was a randomised secondary prevention trial that used a Mediterranean-type diet (with butter and cream replaced by a margarine based on rapeseed/canola oil and rich in alpha-linolenic acid). At a mean follow-up of 27 months, there was a 73% decrease in combined end-points of cardiac death and non-fatal myocardial infarction, with a 70% decrease in cardiac death in the group eating the Mediterranean-style diet. Benefits were maintained for nearly 4 years after follow-up, which translates to 12 lives saved per 300 people in 27 months. Interestingly, these impressive results were obtained without lowering blood pressure, LDL-cholesterol and triglycerides, or raising HDL-cholesterol.

Several years later, data from the CARDIO2000 multicentre study was used to investigate the association between acute coronary syndromes (ACS) and a

Mediterranean-style diet. Once again it was shown that the Mediterranean diet reduced the risk of developing ACS regardless of the presence of other risk factors such as hyperlipidaemia, type 2 diabetes or a sedentary lifestyle (Panagiotakos et al 2002). In this instance, primary prevention benefits were observed.

Positive results were also seen with the Indo-Mediterranean diet, which has increased intakes of whole grains, walnuts and almonds, fruit and vegetables (Singh et al 2002). The randomised trial involving 1000 patients with angina pectoris, myocardial infarction or other risk factors for coronary artery disease compared the Indo-Mediterranean diet to the Step I National Cholesterol Education Program diet and found total cardiac end-points were significantly fewer with the Indo-Mediterranean diet, as were sudden cardiac deaths and non-fatal myocardial infarctions.

Overall, these results suggest the Mediterranean diet has both primary and secondary prevention effects.



HYPERTENSION

Both olive oil and olive leaf extract have demonstrated blood pressure lowering ability in small intervention trials, and long-term dietary intake of olive oil is associated with reduced incidence of hypertension.

Olive oil One randomised, double-blind, crossover study compared the effects of monounsaturated (MUFA) (extra-virgin olive oil) and polyunsaturated fatty acids (PUFA) (sunflower oil) in 23 hypertensive patients over 6 months (Ferrara et al 2000). MUFA intake resulted in significantly reduced resting blood pressure compared to the PUFA diet, but most impressively, daily drug dosage was significantly reduced with the MUFA diet (–48% vs –4%, $P < 0.005$).

A randomised, placebo-controlled, crossover study of 40 subjects with stable coronary heart disease compared the antioxidant and antihypertensive effects of two different olive oil supplements with different phenolic compound levels (refined: 14.7 mg/kg vs virgin: 161.0 mg/kg) (Fito et al 2005). Treatment with virgin olive oil rich in phenolic compounds resulted in significantly lower plasma oxidised LDL and lipid peroxide levels, together with higher activities of glutathione peroxidiase. Additionally, SBP was significantly decreased in the hypertensive patients; however, no changes in DBP were observed.

Another randomised study involving elderly patients found that increased dietary intake of virgin olive oil significantly reduced total and LDL-cholesterol in normotensive but not hypertensive volunteers, whereas virgin olive oil consumption normalised SBP in this group (136 ± 10 mmHg) compared to treatment with sunflower oil (150 ± 8 mmHg) (Perona et al 2004).

In 2004, results from two large observational studies were published that further suggested olive oil intake has significant effects on blood pressure.

One study involved assessing data from the Greek arm of the European Prospective Investigation into Cancer and Nutrition study, which included 20,343 participants (Psaltopoulou et al 2004). Intakes of olive oil, vegetables, and fruit were significantly inversely associated with both SBP and DBP, whereas cereals, meat and meat products, and ethanol intake were positively associated with arterial blood pressure. Mutual adjustment between olive oil and vegetables indicated that olive oil has the dominant beneficial effect on arterial blood pressure in this population.

Another study investigated whether dietary olive oil consumption over time affected the incidence of hypertension (Alonso & Martinez-Gonzalez 2004). Data from 6863 participants with at least 2 years follow-up was used and the study found that olive oil consumption was associated with a reduced risk of hypertension among men; no association was observed among women. The researchers suggested this might be attributed to the overall lower incidence of hypertension among females and the resulting lower statistical power.

Olive leaf A study of olive leaf extract involving 30 subjects with essential hypertension was conducted by the Service de Cardiologie, Hospital Militaire in Tunis (Cherif et al 1996). Olive leaf extract (1600 mg daily) was administered for 3 months, after 15 days treatment with a placebo. Active treatment resulted in a statistically significant decrease in blood pressure ($P < 0.001$) in all patients and was considered well tolerated. Other interesting observations were that patients previously treated with beta-blockers noted a disappearance of gastric symptoms during treatment with olive leaf extract.

INFLAMMATORY CONDITIONS

Olive leaf extract is used to promote symptomatic relief in various inflammatory conditions, such as osteoarthritis and asthma, and as a gargle in tonsillitis and pharyngitis. The anti-inflammatory effects demonstrated by several major components in olive leaf provide a theoretical basis for its use; however, clinical trials are not yet available to determine whether effects are significant and efficacy remains speculative.

Alternately, olive oil supplementation has been tested in some clinical studies.

Rheumatoid arthritis In some studies of RA in which fish oil supplements have been investigated, olive oil has been used as a placebo because it was generally regarded as containing neutral fatty acids; however, in some instances olive oil produced significant improvements in disease activity, prompting further research.

Supplementation for 12 weeks with olive oil resulted in a significant decrease in pain intensity, duration of morning stiffness, time taken to walk 18 metres, and fibrinogen levels and improved trends in erythrocyte sedimentation rate, C3, and right grip strength according to an early study (Darlington & Ramsey 1987). A later double-blind study found subjective measures of mean duration of morning stiffness and analogue pain score improved to the same extent as treatment with fish oil supplements after 12 weeks (Cleland et al 1988).

A 24-week double-blind, randomised study of two different dosages of fish oil (3 g/day and 6 g/day) and a single dosage of olive oil (6.8 g/day of oleic acid) was conducted with 49 subjects with active RA (Kremer et al 1990). The fish oil treatment produced better results overall; however, improvement in patients' global assessment was only observed with olive oil supplementation.

Another double-blind study of 90 patients comparing treatment with fish oils (2.6 g/day), or fish oils and olive oil (1.3 g/day and 3 g/day, respectively) or olive oil (6 g/day) over 12 months found a significant decrease in Ritchie's articular index of pain and the number of painful joints after 12 months of olive oil and also after the combined use of fish oil (1.3 g/day) and olive oil (3 g/day) (Geusens et al 1994).

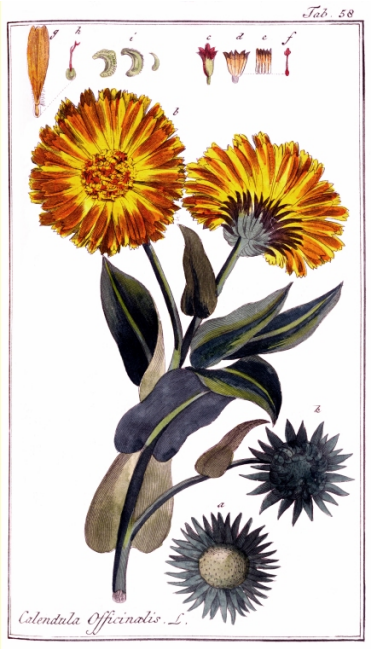
More recently, a study of 43 patients investigated the effects of placebo (soy oil), fish oil (3 g/day), and a combination of fish oil (3 g/day) and 9.6 mL/day of olive oil as an adjunct to standard treatment (Berbert et al 2005). The groups receiving fish oil and the fish oil/olive oil combination experienced a statistically significant improvement in joint pain intensity, hand grip strength, duration of morning stiffness, and onset of fatigue compared with placebo. Parameters that responded after 24 weeks were Ritchie's articular index for pain joints, the ability to bend down to pick up clothing from the floor, and getting in and out of a car. The group using the fishoil/olive oil combination also experienced improved ability to turn taps on and off and decreased rheumatoid factor after 24 weeks. When groups were compared, the combination treatment was found to be superior, showing a significant improvement in patient global assessment after 12 weeks.

CANCER PREVENTION

It has been speculated that consumption of olive oil, chiefly as an ingredient of the Mediterranean diet, may reduce the incidence of some cancers, based on the observation that the incidence of cancer overall in Mediterranean countries is lower than in Scandinavian countries, the United Kingdom, and the United States (Trichopoulou et al 2000, Visoli et al 2004).

One review calculated that up to 25% of the incidence of colorectal cancer, approximately 15% of the incidence of breast cancer, and approximately 10% of the

incidence of prostate, pancreas, and endometrial cancers could be prevented if the populations of highly developed Western countries shifted to the traditional healthy Mediterranean diet (Trichopoulou et al 2000). Although these figures are only estimates, data from observational studies are now considered strong enough to suggest that the traditional Mediterranean diet should be actively promoted in order to reduce the incidence of cancer (Visoli et al 2004).



DIABETES

There is anecdotal evidence that people with type 2 diabetes are using olive leaf extract as an adjunct to dietary modification. One report from Morocco found that 80% of people surveyed used herbal medicines for diabetes, hypertension and cardiac disease, and olive leaf was one of the most popular treatments (Eddouks et al 2002). Once again, hypoglycaemic activity reported in animal models provides a theoretical basis for its use; however, clinical testing is not yet available to determine whether effects are significant and efficacy remains speculative.

LONGEVITY

In 2002, Panagiotakos et al found that adherence to a Mediterranean diet and healthy lifestyle (non-smoking, physically active, moderate drinking) is associated with a greater than 50% lower rate of all-cause and cause-specific mortality, such as from coronary heart disease, cardiovascular diseases, and cancer (Knoop et al 2004). The cohort study involved 1507 apparently healthy men and 832 women, aged 70–90 years in 11 European countries and was conducted from 1988 until 2000.

A year later, Trichopoulou et al (2003) also reported a positive association between longevity and the Mediterranean diet, with their study showing that the benefits are significant in people aged 55 years and older.

More recently, a 2004 review of five cohort studies further confirmed these findings and concluded that there is now sufficient evidence to show that diet does indeed influence longevity and that the optimal diet for the prevention of both coronary heart disease and cancer is likely to extensively overlap with the traditional Mediterranean diet (Trichopoulou & Critselis 2004). Although it is uncertain which specific components in the Mediterranean diet are most important for its protective health benefits, olive oil, fish, plant foods and moderate wine consumption are likely candidates.

ANTIBACTERIAL, ANTIFUNGAL AND ANTIVIRAL

Based on evidence of its broad-spectrum antimicrobial activity, olive leaf extract is used for the treatment of common bacterial infections such as bronchitis and tonsillitis, common fungal infections such as vaginal candidiasis, *Tinea pedis* and

Tinea capitis, and viral infections such as herpes simplex. Currently, controlled studies are not available to determine whether treatment is effective.

OTHER USES

Olive oil is an emollient and used externally to relieve pruritis and inflamed surfaces and is used to soften and remove dry scales in eczema and psoriasis. Taken internally, it is used as a laxative to soften impacted faeces. As a folk remedy, the plant is used as a diuretic, hypotensive, emollient, febrifuge and tonic, for urinary and bladder infections and for headaches (Somova et al 2003). Olive leaf extract is also used as a general tonic to improve energy and provide a sense of wellbeing.

DOSAGE RANGE

GENERAL RECOMMENDATIONS

- Olive leaf extract (according to manufacturer's recommendations): 5 mL three times daily diluted with water or juice if necessary (Olive Leaf Australia)
- Olive oil: should replace dietary intake of saturated fats and be consumed as part of a Mediterranean style diet

ACCORDING TO CLINICAL STUDIES

- Hypertension: 1600 mg/day of olive leaf extract or 50 mL/day of virgin olive oil.
- Rheumatoid arthritis: 6–10 g/day of olive oil long term

ADVERSE REACTIONS

Allergenic pollen is produced by the Oleaceae family, including the olive tree, which causes seasonal respiratory allergies in Mediterranean countries.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

HYPOGLYCAEMIC AGENTS

Theoretically, an additive hypoglycaemic effect is possible but is speculative — possible beneficial interaction under professional supervision.

HYPERTENSIVE AGENTS

Theoretically, an additive hypotensive effect is possible but is speculative — possible beneficial interaction under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

People with known allergies to the Oleaceae family of plants should avoid this herb.

PREGNANCY USE

Olive oil is likely to be safe when consumed in dietary amounts; however, the safety of olive leaf extract is not known.

PRACTICE POINTS/PATIENT COUNSELLING

- Consumption of olive oil has beneficial effects on arterial blood pressure and reduces the risk of cardiovascular disease when ingested as part of the Mediterranean diet.
- Several studies have demonstrated that supplemental olive oil produces significant improvements in disease activity in rheumatoid arthritis.
- When used as part of the Mediterranean diet, olive oil may reduce the incidence of some cancers and increases longevity.
- Olive leaf extract contains a greater concentration of biologically active phenolic compounds than olive oil; however, it has not been significantly studied in clinical trials.
- Preliminary studies with olive leaf extract show it has significant anti-inflammatory and antioxidant activity and possibly hypoglycemic effects.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Long-term consumption of olive oil as part of a Mediterranean diet is likely to reduce the incidence of heart disease and promote longevity. It may also reduce the risk of cancer; however, this is less well established. Used as a stand-alone supplement, it may reduce blood pressure and improve symptoms in rheumatoid arthritis. Olive leaf extract may also be useful in hypertension and inflammatory conditions; however, little research has been conducted to confirm effectiveness.

When will it start to work?

In rheumatoid arthritis, benefits start to appear after 12 weeks, with further improvement noticed after 24 weeks. In regards to other health benefits, olive oil should be used long term.

Are there any safety issues?

Dietary amounts of olive oil are well tolerated and considered safe in healthy individuals; however, the safety of olive leaf extract has not been well studied and it should be avoided in pregnancy until safety is established.

REFERENCES

Alonso A, Martinez-Gonzalez MA. Olive oil consumption and reduced incidence of hypertension: the SUN study. Lipids 39 (2004): 1233-8.

Andrikopoulos NK et al. Oleuropein inhibits LDL oxidation induced by cooking oil frying by-products and platelet aggregation induced by platelet-activating factor. Lebensmittel-Wissensch Technol 35 (2002): 479-84.
Aziz NH et al. Comparative antibacterial and antifungal effects of some phenolic compounds. Microbios 93 (1998): 43-54.
Benavente-Garcia O et al. Antioxidant activity of phenolics extracted from Olea europaea L. leaves. Food Chem 68 (2000): 457-62.
Berbert AA et al. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 21 (2005): 131-6.
Bisignano G et al. On the in-vitro antimicrobial activity of oleuropein and hydroxytyrosol. J Pharm Pharmacol 51 (1999): 971-4.
Cherif S et al. [A clinical trial of a titrated Olea extract in the treatment of essential arterial hypertension]. J Pharm Belg 51 (1996): 69-71.
Cleland LG et al. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. J Rheumatol 15 (1988): 1471-5.
Darlington L, Ramsey N. Olive oil for rheumatoid patients? (Abstract). Br J Rheumatol 24(2) (1987): 215.
de la Puerta R et al. Effect of minor components of virgin olive oil on topical antiinflammatory assays. Z Naturforsch C 55 (2000): 814-19.
de Lorgeril M et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 99 (1999): 779-85.
Delgado-Pertinez M et al. Predicting the nutritive value of the olive leaf (Olea europaea): digestibility and chemical composition and in vitro studies. Animal Feed Sci Technol 87 (2000): 187-201.
Eddouks M et al. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol 82 (2002): 97-103.
Fehri B et al. [Hypotension, hypoglycemia and hypouricemia recorded after repeated administration of aqueous leaf extract of Olea europaea L.]. J Pharm Belg 49 (1994): 101-8.
Ferrara LA et al. Olive oil and reduced need for antihypertensive medications. Arch Intern Med 160 (2000): 837-42.
Fito M et al. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. Atherosclerosis 181 (2005): 149-58.
Furneri PM et al. In vitro antimycoplasmal activity of oleuropein. Int J Antimicrob Agents 20 (2002): 293-6.
Geusens P et al. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis: A 12-month, double-blind, controlled study. Arthritis Rheum 37 (1994): 824-9.
Gonzalez M et al. Hypoglycemic activity of olive leaf. Planta Med 58 (1992): 513-15.
Khayyal MT et al. Blood pressure lowering effect of an olive leaf extract (Olea europaea) in L-NAME induced hypertension in rats. Arzneimittelforschung 52 (2002): 797-802.
Kim SH et al. Luteolin inhibits the nuclear factor-[kappa]B transcriptional activity in rat-1 fibroblasts. Biochem Pharmacol 66 (2003): 955-63.
Knoops KT et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA 292 (2004): 1433-9.
Koutsoumanis K et al. Modelling the effectiveness of a natural antimicrobial on Salmonella enteritidis as a function of concentration, temperature and pH, using conductance measurements. J Appl Microbiol 84 (1998): 981-7.
Kremer JM et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis: Clinical and immunologic effects. Arthritis Rheum 33 (1990): 810-20.
Ma SC et al. In vitro evaluation of secoiridoid glucosides from the fruits of Ligustrum lucidum as antiviral agents. Chem Pharm Bull (Tokyo) 49 (2001): 1471-3.
Manna C et al. Oleuropein prevents oxidative myocardial injury induced by ischemia and reperfusion. J Nutr Biochem 15 (2004): 461-6.

Markin D et al. In vitro antimicrobial activity of olive leaves. Mycoses 46 (2003): 132-6.
Massaro M, De Caterina R. Vasculoprotective effects of oleic acid: epidemiological background and direct vascular antiatherogenic properties. Nutr Metab Cardiovasc Dis 12 (2002): 42-51.
Olive Leaf Australia. Available at: www.envirolea.com (accessed 16-2-06).
Owen RW et al. Olive-oil consumption and health: the possible role of antioxidants. Lancet Oncol 1 (2000): 107-12.
Panagiotakos DB et al. Primary prevention of acute coronary events through the adoption of a Mediterranean-style diet. East Mediterr Health J 8 (2002): 593-602.
Perona JS et al. Virgin olive oil reduces blood pressure in hypertensive elderly subjects. Clin Nutr 23 (2004): 1113-21.
Petroni A et al. Inhibition of leukocyte leukotriene B4 production by an olive oil-derived phenol identified by mass-spectrometry. Thromb Res 87 (1997): 315-22.
Polzonetti V et al. Involvement of oleuropein in (some) digestive metabolic pathways. Food Chem 88 (2004): 11-15.
Psaltopoulou T et al. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. Am J Clin Nutr 80 (2004): 1012-18.
Serra-Majem L et al. Mediterranean diet and health: is all the secret in olive oil? Pathophysiol Haemost Thromb 33 (2003): 461-5.
Singh RB et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet 360 (2002): 1455-61.
Somova LI et al. Antihypertensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from Olea europaea, subspecies africana leaves. J Ethnopharmacol 84 (2003): 299-305.
Stark AH, Madar Z. Olive oil as a functional food: epidemiology and nutritional approaches. Nutr Rev 60 (2002): 170-6.
Tassou CC, Nychas GJ. Inhibition of Salmonella enteritidis by oleuropein in broth and in a model food system. Lett Appl Microbiol 20 (1995): 120-4.
Tassou CC et al. Effect of phenolic compounds and oleuropein on the germination of Bacillus cereus T spores. Biotechnol Appl Biochem 13 (1991): 231-7.
Trichopoulou A. Traditional Mediterranean diet and longevity in the elderly: a review. Public Health Nutr 7 (2004): 943-7.
Trichopoulou A, Critselis E. Mediterranean diet and longevity. Eur J Cancer Prev 13 (2004): 453-6.
Trichopoulou A et al. Cancer and Mediterranean dietary traditions. Cancer Epidemiol Biomarkers Prev 9 (2000): 869-73
Visioli F, Galli C. Biological properties of olive oil phytochemicals. Crit Rev Food Sci Nutr 42 (2002): 209-21.
Visioli F et al. The role of antioxidants in the mediterranean diets: focus on cancer. Eur J Cancer Prev 13 (2004): 337-43.

Passionflower

Historical note Legend has it that this herb received its name because the corona resembles the crown of thorns worn by Christ during the crucifixion. A popular sedative medicine in the early 20th century, it was listed in the United States National Formulary until 1936.

COMMON NAME
Passionflower

OTHER NAMES
Apricot vine, granadilla, Jamaican honeysuckle, Maypop passion flower, passion vine, water lemon

BOTANICAL NAME/FAMILY
Passiflora incarnata (family Passifloraceae)

PLANT PARTS USED
Aerial parts, particularly leaves

CHEMICAL COMPONENTS
Flavonoids (including apigenin, quercetin and kaempferol), maltol, coumarin derivatives, indole alkaloids (mainly harman, harmaline, harmine), phytosterols (stigmasterol), sugars and small amounts of essential oil.

HARMAN
Numerous in vitro and in vivo trials have been conducted on the constituent known as harman. Some of these studies have suggested:

- mild monoamine oxidase A inhibition (Adell et al 1996)
- inhibition of HIV replication (Ishida et al 2001)
- vasorelaxant activity (Shi et al 2000)
- effects on GABA release (Dolzhenko & Komissarov 1984).

Harman is not considered to be one of the main active constituents in the herb and is not present in biologically active concentrations in the dosage range used for passionflower. As such, results obtained using isolated harman in vitro and in vivo cannot necessarily be extrapolated to the use of passionflower in humans.

Harman has also been identified in beer, and to a lesser extent in wine, both of which contain levels far in excess of those found in passionflower at therapeutic doses.

MAIN ACTIONS

ANXIOLYTIC AND SEDATIVE ACTIVITY

Several in vivo studies have demonstrated the anxiolytic effects of *Passiflora* extract (Della et al 1981, Dhawan et al 2001, Soulimani et al 1997). Behavioural tests in mice have also demonstrated that high doses have a sedative effect (Soulimani et al 1997).

The mechanism of action is currently unclear, as some research suggests stimulation of GABA release or an interaction with GABA receptors, and other research observes no interaction with GABA-benzodiazepine receptors (Zanolil et al 2000). One in vitro study also showed inhibition of GABA-A binding with *Passiflora* extract (Simmen et al 1999).

CLINICAL USE

ANXIETY AND NERVOUS RESTLESSNESS

Passiflora extract is a popular herb for nervousness and is most often prescribed in combination with other herbs such as valerian. A 2001 double-blind, randomised controlled study involving 36 outpatients diagnosed with GAD found that *Passiflora* extract was as effective as oxazepam 30 mg/day over a 4-week period and better tolerated (Akhondzadeh et al 2001a).

Commission E approved for this indication (Blumenthal et al 2000).

INSOMNIA

Currently, in vivo evidence supports the sedative activity of *Passiflora* when used in high doses; however, controlled studies are not available to confirm the clinical efficacy (Soulimani et al 1997).

OTHER USES

TRADITIONAL USES

Traditionally, passionflower has been used to treat neuralgia, generalised seizures, hysteria and insomnia. It has also been used to treat diarrhoea, dysentery and dysmenorrhoea by acting on the nervous system.

APHRODISIAC

Recent tests in mice have identified significant aphrodisiac properties associated with high doses of *Passiflora* extract (Dhawan et al 2003a). A benzoflavone moiety may be

chiefly responsible, as tests with this isolated compound were found to increase libido and fertility of males rats after 30 days' treatment (Dhawan et al 2002a).

ANTITUSSIVE AND ANTIASTHMATIC ACTIVITY

Passiflora incarnata was as effective as codeine phosphate in suppressing a sulfur-dioxide-induced cough in mice (Dhawan & Sharma 2002). Passionflower (100 mg/kg) was also able to prevent dyspnoea-related convulsions in guinea pigs with acetylcholine-induced bronchospasm (Dhawan et al 2003b).

CANNABIS, ALCOHOL AND OPIATE WITHDRAWAL

A randomised double-blind study involving 65 subjects with opiate addiction compared the effects of clonidine and placebo with clonidine and *Passiflora* extract over a 14-day period. The combination treatment of clonidine and *Passiflora* extract showed significant superiority for alleviating the psychological symptoms associated with withdrawal; however, no differences in physical symptoms were seen (Akhondzadeh et al 2001b).

Although no clinical studies are available for *Passiflora* extract, preliminary results from animal studies testing the benzoflavone moiety isolated from *Passiflora* has found it to be a useful adjunct during cannabis and alcohol withdrawal, reducing dependence and attenuating withdrawal symptoms (Dhawan et al 2002b, c).

DOSAGE RANGE

- Dried herb: 2 g three to four times daily.
- Infusion of dried herb: 0.25–2 g three to four times daily.
- Fluid extract (1:1) (g/mL): 2 mL three to four times daily in 150 mL of water.
- Tincture (1:5) (g/mL): 10 mL three to four times daily.

TOXICITY

Not known.

ADVERSE REACTIONS

Drowsiness is theoretically possible with excessive doses.

One human study found that *Passiflora* extract has a significantly lower incidence of impairment of job performance compared with oxazepam (Akhondzadeh et al 2001b). One case reports a 34-year-old woman who developed severe nausea, vomiting, drowsiness and episodes of non-sustained ventricular tachycardia following administration of passionflower at therapeutic doses (Fisher et al 2000).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of pharmacological activity and are theoretical.

BENZODIAZEPINES
Additive effects are theoretically possible at high doses. Use with caution and monitor drug dosage — possible beneficial interaction under medical supervision.

BARBITURATES
Additive CNS sedation is theoretically possible. Use with caution and monitor drug dosage — possible beneficial interaction under medical supervision.

ANTICOAGULANTS
Increased risk of bleeding is theoretically possible owing to the coumarin content of the herb — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS
None known

PREGNANCY USE
Passionflower has demonstrated the ability to increase uterine contractions in an isolated rat uterus model when compared to control tissue (Sadraei et al 2003). It is not advisable to use passionflower in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING
- Both human and animal studies confirm passionflower has significant anxiolytic activity.
- One randomised study found that it has significantly less negative effects on performance than 30 mg oxazepam, yet is as effective for GAD.
- Maximal effects may require several days of regular intake.
- It is not known whether physical tolerance develops.
- One study has shown it improves psychological symptoms during opiate withdrawal when used together with clonidine.
- In practice, it is often prescribed with other herbs for stronger anxiolytic effect.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Passionflower has an anxiolytic effect that can relieve restlessness and nervous tension. In higher doses, it is used for insomnia.
When will it start to work?
When being used for anxiety, it may take 3–4 weeks before significant effects are seen.
Are there any safety issues?
Overall, passionflower does not appear to impair job performance. However, it may theoretically interact with other sedative medicines when used in high doses. Other

interactions are theoretically possible, so use should be monitored by a healthcare professional.

REFERENCES

Adell A, Biggs TA, Myers RD. Action of harman (1-methyl-beta-carboline) on the brain: body temperature and in vivo efflux of 5-HT from hippocampus of the rat. Neuropharmacology 35(8) (1996): 1101-7.

Akhondzadeh S et al. Passionflower in the treatment of opiates withdrawal: a double-blind randomized controlled trial. J Clin Pharm Ther 26.5 (2001a): 369-73.

Akhondzadeh S et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 26.5 (2001b): 363-7.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Della Loggia R, Tubaro A, Redaelli C. Evaluation of the activity on the mouse CNS of several plant extracts and a combination of them. Riv Neurol 51.5 (1981): 297-310.

Dhawan K, Sharma A. Antitussive activity of the methanol extract of Passiflora incarnata leaves. Fitoterapia 73.5 (2002): 397-9.

Dhawan K, Kumar S, Sharma A. Anxiolytic activity of aerial and underground parts of Passiflora incarnata. Fitoterapia 72.8 (2001): 922-6.

Dhawan K, Kumar S, Sharma A. Beneficial effects of chrysin and benzoflavone on virility in 2-year-old male rats. J Med Food 5.1 (2002a): 43-8.

Dhawan K, Kumar S, Sharma A. Reversal of cannabinoids (delta9-THC) by the benzoflavone moiety from methanol extract of Passiflora incarnata Linneaus in mice: a possible therapy for cannabinoid addiction. J Pharm Pharmacol 54.6 (2002b): 875-81.

Dhawan K, Kumar S, Sharma A. Aphrodisiac activity of methanol extract of leaves of Passiflora incarnata Linn. in mice. Phytother Res 17.4 (2003a): 401-3.

Dhawan K, Kumar S, Sharma A. Antiasthmatic activity of the methanol extract of leaves of Passiflora incarnate. Phytother Res 17.7 (2003b): 821-2.

Dhawan K, Kumar S, Sharma A. Suppression of alcohol-cessation-oriented hyper-anxiety by the benzoflavone moiety of Passiflora incarnata Linneaus in mice. J Ethnopharmacol 81.2 (2002c): 239-44.

Dolzhenko AT, Komissarov IV. GABA-ergic effects of harman independent of its influence on benzodiazepine receptors. Bull Eksp Biol Med 98.10 (1984): 446-8.

Fisher AA, Purcell P, Le Couteur DG. Toxicity of Passiflora incarnata L. J Toxicol Clin Toxicol 38.1 (2000): 63-6.

Ishida J et al. Anti-AIDS agents. 46: Anti-HIV activity of harman, an anti-HIV principle from Symplocos setchuensis, and its derivatives. Nat Prod 64.7 (2001): 958-60.

Sadraei H, Ghannadi A, Takei-Bavani M. Extract of Zataria multiflora and Carum carvi essential oils and hydroalcoholic extracts of Passiflora incarnata, Berberis intejerrimat and Crocus sativus on rat isolated uterus contractions. Int J Aromather 13.2-3 (2003): 121-7.

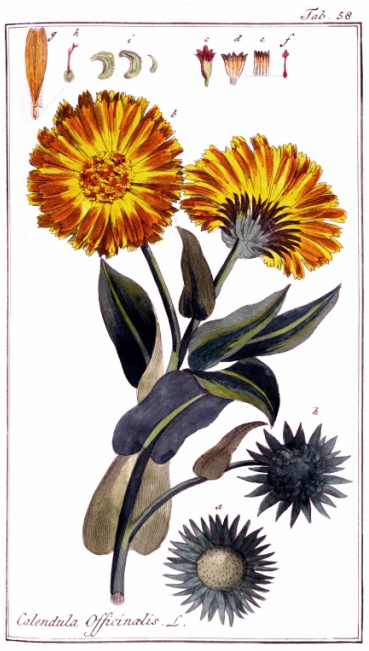
Shi CC et al. Vasorelaxant effect of harman. Eur J Pharmacol 390.3 (2000): 319-25.

Simmen U et al. Extracts and constituents of Hypericum perforatum inhibit the binding of various ligands to recombinant receptors expressed with the Semliki Forest virus system. J Recept Signal Transduct Res 19.1-4 (1999): 59-74.

Soulimani R et al. Behavioural effects of Passiflora incarnata L. and its indole alkaloid and flavonoid derivatives and maltol in the mouse. J Ethnopharmacol 57.1 (1997): 11-20.

Zanolil P, Avallone R, Baraldi M. Behavioral characterisation of the flavonoids apigenin and chrysin. Fitoterapia 71 (Suppl 1) (2000): S117-23.

Peppermint



Historical note The written record of mint dates back to an ancient Greek myth in which the Greek god Pluto was said to have affections for a beautiful nymph named Minthe. His jealous wife Persephone cast a spell on the nymph, transforming her into a plant. When Pluto could not reverse the spell, he gave her a sweet scent that would emanate throughout the garden (Murray & Pizzorno 1999). Peppermint has been used medicinally for generations as a digestive aid and carminative. More recently, enteric-coated peppermint oil capsules have been widely prescribed for the relief of IBS.

BOTANICAL NAME/FAMILY

Mentha x *piperita* (family [Labiatae] Lamiaceae)

PLANT PARTS USED

Leaf or stem — essential oil is distilled from the aerial parts.

CHEMICAL COMPONENTS

Peppermint leaves contain about 2.5% essential oil, 19% total polyphenolic compounds, 12% total flavonoid compounds (eriocitrin, luteolin-7-O-rutinoside, hesperidoside) and 7% total hydroxycinnamic compounds (including rosmarinic acid) (Duband et al 1992). The biochemistry, organisation, and regulation of essential oil metabolism in the epidermal oil glands of peppermint have been defined and research is underway to create 'super' transgenic peppermint plants with improved oil composition and yield (Wildung & Croteau 2005).

Essential oil Over 100 constituents have been identified in peppermint oil. The principal constituents are menthol (35–55%), menthones (10–35%), isomenthone, menthyl acetate, menthofuran and cineole. To comply with the European Pharmacopoeia, the oil must not contain more than 4% pulegone and not more than 1% carvone.

MAIN ACTIONS

The actions of the leaf as an infusion or liquid extract are largely dependent on the essential oil content. Other compounds, such as the flavonoids, also contribute to the overall activity, especially the antioxidant and anti-allergic activities. Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile (Grigoleit & Grigoleit 2005a).

ANTISPASMODIC

Peppermint oil, ethanol extracts and flavonoids isolated from the leaf have all been shown to have antispasmodic (spasmolytic) effects in vitro (ESCOP 1997) with the effect mediated via smooth muscle calcium channels (Hills & Aaronson 1991).

In healthy volunteers, intragastric administration of a dose equivalent to 180 mg peppermint oil reduced intraoesophageal pressure within 1–7 minutes of infusion (Kingham 1995), while in nine human studies involving 269 subjects peppermint oil produced substantial spasmolytic effects on the smooth muscles of the gastrointestinal tract when used topically (intraluminal) or orally in doses of 0.1–0.24 mL (Grigoleit & Grigoleit 2005b). Enteroplant, an enteric-coated capsule containing 90 mg peppermint and 50 mg caraway oil, has also been shown to act locally in the stomach and duodenum to produce smooth muscle relaxation (Micklefield et al 2003). Peppermint oil has also been shown to have similar anti-spasmodic activity on the colon to the Chinese herbal medicine Shakuyaku-kanzo-to (TJ-68), as observed by direct observation during colonoscopy (Ai et al 2005).

CARMINATIVE

Peppermint has a carminative activity, which refers to its ability to relax the gastrointestinal sphincters. Carminatives are thought to alleviate symptoms of bloating and gas by facilitating eructation and passage of flatus. The classic carminatives are essential oils, such as spearmint and peppermint. Studies from the 1950s on the effect of carminatives on the gut suggest that they work by inducing relaxation of the lower oesophageal sphincter (Massey 2001). A later study has shown that peppermint oil canalised into the gall bladder and duodenal areas was able to counteract morphine hydrochloride-induced constriction of the sphincter of Oddi (Giachetti et al 1988).

CHOLERETIC

Choleretic activity has been demonstrated for peppermint tea, flavonoids and the essential oil in dogs and rats (ESCOP 1997). Hydrophilic compounds may contribute to the gastrointestinal effects, with aqueous extracts from peppermint leaves having anti-ulcerogenic and choleretic effects (Grigoleit & Grigoleit 2005c, Van Rensen 2004). Peppermint oil has been shown to have a relaxing effect on the gall bladder and small intestine, producing complete inhibition of gall-bladder emptying and prolonged orocaecal transit time comparable to that produced by n-butylscopolamine (Goerg & Spilker 2003).

ANTIMICROBIAL

Antibacterial Peppermint oil has been shown to have significant antibacterial activity (Mimica-Dukic et al 2003), as has the juice of peppermint leaves (Saeed & Tariq 2005). Peppermint oil has been shown to inhibit *Helicobactor pylori*, *Staphylococcus aureus* (Imai et al 2001), *Escherichia coli* (Pattnaik et al 1995), *Salmonella enteritidis*, *Listeria monocytogenes* and multiresistant strains of *Shigella sonnei* and *Micrococcus flavus* (Mimica-Dukic et al 2003).

Fungistatic, fungicidal Peppermint is also fungistatic and fungicidal (Anon 1998, Pattnaik et al 1996) with its activity against *Trichophyton tonsurans* and *Candida albicans* being considerably greater than the commercial fungicide bifonazole (Mimica-Dukic et al 2003). Peppermint oil and its main constituent menthol has also been shown to have significant antibacterial, antifungal and antiplasmid activity and to potentiate the antibiotic effect of oxytetracycline (Schelz et al 2006).

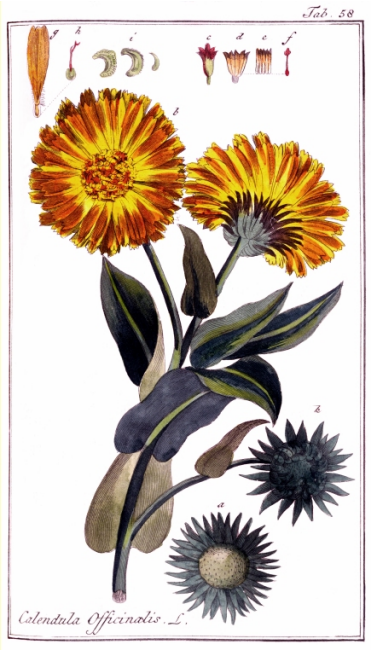
Peppermint oil has further been shown to have significant antimycobacterial activity in vitro and inhalation of peppermint oil has been successfully used as a supplement to combined multidrug therapy for pulmonary tuberculosis (Shkurupi et al 2002).

Antiviral Peppermint oil also has virucidal activity against HSV -1 and -2, including activity against an acyclovir-resistant strain of HSV-1 with a 50% inhibitory concentration determined at 0.002% and 0.0008% for HSV-1 and HSV-2, respectively. The oil was also found to affect the virus before, but not after, penetration into the host cell (Schuhmacher et al 2003).

ANTI-ALLERGIC

A 50% hydro-ethanolic extract of peppermint leaves inhibited chemically induced histamine release from rat peritoneal mast cells in vitro. The peppermint extract was also shown to reduce nasal symptoms (sneezing and nasal rubbing) in rats with experimentally induced allergic rhinitis. Significant inhibition of sneezing and nasal rubbing was observed at oral doses of 300 and 1000 mg/kg, respectively (Inoue et al 2001).

The flavonoid luteolin-7-O-rutinoside isolated from the aerial parts of peppermint has been shown to inhibit histamine release from rat peritoneal mast cells in a dose-dependent manner (100–300 mg/kg) and to reduce antigen-induced allergic nasal symptoms (Inoue et al 2002), although it would be difficult to achieve such doses of luteolin with a commercially available peppermint extract or oil. An extract of the whole herb, however, may be beneficial in alleviating nasal symptoms associated with allergic rhinitis in association with other medicines.



ANTIOXIDANT

The polyphenolic compounds in peppermint, such as luteolin-7-O-rutinoside, eriocitrin and rosmarinic acid, have been shown to have antioxidant and free radical scavenging activity (Sroka et al 2005). Peppermint oil, and its constituents menthone and isomenthone, exert antioxidant activity (Mimica-Dukic et al 2003). It has been suggested that this antioxidant effect confers chemopreventive and antigenotoxic effects (Samarth et al 2006).

STIMULANT

Intraperitoneal and intravenous injections of peppermint oil and its constituents, 1,8-cineol, menthone, isomenthone, menthol, pulegone, menthyl acetate and caryophyllene, dramatically increased ambulatory activity in mice. It is thought that the effect is mediated via a dopaminergic effect of menthol. This may explain the traditional use of peppermint for mental fatigue (Umezu & Morita 2003, Umezu et al 2001). Inhalation of peppermint oil has also been shown to have a stimulant effect on mice in a forced swimming test, with the effect remaining when over-agitation was induced by intraperitoneal caffeine (Lim et al 2005).

COOLANT

Peppermint oil interacts with smooth muscle calcium channels (Hills & Aaronson 1991). In the peripheral nerves this effect may be responsible for the characteristic cooling sensation experienced on oral ingestion of mint.

ANALGESIC

Peppermint and caraway oil have been shown to synergistically modulate post-inflammatory visceral hyperalgesia in a rat model (Adam et al 2006). A significant analgesic effect, with a reduction in sensitivity to headache, was observed in a double-blind, placebo-controlled, randomised, 7-day cross-over study that used a combination of peppermint oil and ethanol applied externally in 32 healthy males undergoing artificial pain stimulation (Gobel et al 1994).

OTHER ACTIONS

A spray-dried peppermint infusion has been found to be mildly diuretic and produce weak sedative action in several tests when administered orally to mice (Della et al 1990). Peppermint tea has been found to significantly increase FSH and LH levels and reduce total testosterone levels in rats (Akdogan et al 2004).

CLINICAL USE

In practice, peppermint and its derivatives are used in many forms and administered by various routes. This review will focus only on those methods that are commonly

used by the public and preparations that are available OTC, such as oral dose forms, topical applications and inhalations.

IRRITABLE BOWEL SYNDROME

There have been several studies examining the effects of peppermint oil in the treatment of IBS (Dew et al 1984, Rees et al 1979). Newer studies have tended to use pH-triggered, enteric-coated peppermint oil capsules that prevent dissolution of the capsules until they have reached the small intestine, and release into the colon is extended over 10–12 hours (Grigoleit & Grigoleit 2005c). Enteric coating allows administration of a higher dose than would otherwise be possible to tolerate and, importantly, avoids the risk of excessively relaxing the lower oesophageal sphincter and causing reflux.

A recent review identified 15 clinical trials investigating peppermint oil in IBS. Of these, 8 of 12 placebo-controlled studies show statistically significant effects in favour of peppermint oil, with average response for 'overall success' being 58% for peppermint oil and 29% for placebo. Three studies that compared peppermint oil to smooth muscle relaxants showed no difference between these treatments (Grigoleit & Grigoleit 2005a). A critical review and meta-analysis of peppermint oil for IBS performed in 1998, which included five double-blind trials, concluded that peppermint oil is efficacious for symptom relief in IBS (Pittler & Ernst 1998).

Since then, one randomised, double-blind controlled trial of 42 children with IBS, treatment with enteric-coated peppermint oil capsules reduced the severity of the pain in 75% of the children (Kline et al 2001), and another recent randomised, double-blind study involving 48 patients with IBS without bacterial overgrowth found that treatment with two enteric-coated capsules of peppermint oil twice daily (Mintoil) for 4 weeks produced statistically significant improvement in diarrhoea, abdominal bloating, constipation, lower abdomen pain, pain on defecation, feeling of incomplete evacuation and difficulty on evacuation (Cappello et al 2006).

Another randomised, double-blind, placebo-controlled clinical study of 110 outpatients with IBS found that one enteric-coated peppermint oil capsule (Colpermin) taken 3–4 times daily, 15–30 minutes before meals, significantly reduced symptoms compared to placebo. Of the 41 patients taking the capsule, 79% experienced alleviation of the severity of abdominal pain (29 were pain free), 83% had less abdominal distension, 83% had reduced stool frequency, 73% had less borborygmi, and 79% had less flatulence, with treatment producing minimal side-effects and no significant changes in liver function tests (Liu et al 1997).

Bacterial overgrowth of the small intestine is associated with a number of functional somatic disorders, including IBS, fibromyalgia and CFS. There have been

two reports of successful treatment of IBS due to intestinal overgrowth with enteric-coated peppermint oil capsules. This clinical effect may in part be associated with the antimicrobial activities of peppermint oil (Gaby 2003, Logan & Beaulne 2002).

Clinical note — Pathophysiology of IBS

The pathophysiology of IBS is poorly understood, but it is believed to occur when the intestinal muscles are contracting faster or more slowly than normal. Colonic contractions cause abdominal pain, cramping, wind and diarrhoea or constipation. It has been proposed that IBS may result from dysregulation of gastrointestinal motor and enhanced sensory functions, as modulated by the CNS. However, clinical and laboratory investigations have failed to uncover any histological, microbiological or biochemical abnormalities in IBS patients. Patients with IBS demonstrate increased motility and abnormal contractions of the intestinal muscles when faced with an emotionally or physically stressful situation (Greenberg et al 2002). It is likely that IBS is also associated with dietary habits, poor upper digestion and intestinal dysbiosis (bacterial overgrowth of the bowels).

Common symptoms of IBS are (Greenberg et al 2002):

- cramping pain in the lower abdomen
- bloating and excess gas (wind)
- changes in bowel habits
- diarrhoea or constipation, either one dominant or both alternating
- immediate need for a bowel movement on awakening or during or after meals
- relief of pain after bowel movements
- feeling of incomplete emptying after bowel movements
- mucus in the stool.

DYSPEPSIA

In a systematic review of herbal medicines for functional dyspepsia, Coon and Ernst (2002) found 17 randomised clinical trials, 9 of which involved peppermint and caraway combination preparations with 60–95% of patients reporting improvements in symptoms.

An enteric-coated capsule (Enteroplant) containing 90 mg peppermint oil (WS-1340) and 50 mg caraway oil (WS-1520) has been shown in a double-blind, placebo-controlled multicentre trial with 45 patients to significantly improve symptoms of non-ulcer dyspepsia. Nearly 90% of patients experienced a reduction in pain, and after 4 weeks nearly 95% had improved their Clinical Global Impression scores. Before the start of treatment all patients in the test preparation group reported moderate to

severe pain, while by the end of the study 63.2% of these patients were free of pain. The peppermint and caraway oil combination was well tolerated (May et al 1996).

Since then there have been three further randomised, placebo-controlled trials of this particular peppermint–caraway oil combination. In one trial with 223 patients with non-ulcer dyspepsia and IBS, the peppermint oil combination was found to significantly reduce pain compared to placebo ($P < 0.001$) (Freise & Kohler 1999). In a further study of 96 outpatients, the same peppermint formulation was found to significantly improve symptoms of functional dyspepsia. After 4 weeks, the average intensity of pain was reduced by 40% versus baseline in the active group and by 22% in the placebo group. The peppermint combination also reduced pressure, heaviness and fullness (May et al 2000). A subgroup analysis from this study revealed that *Helicobacter pylori*-positive patients had a substantially better treatment response, although those who were negative to *H. pylori* also showed significant improvements compared to those receiving placebo (May et al 2003). In a further double-blind, placebo-controlled trial the same oil combination was found to significantly improve disease-specific QOL, as measured by the validated Nepean Dyspepsia Index (NDI) compared to placebo (Holtmann et al 2003).

The same peppermint and caraway oil combination has been compared with cisapride (Prepulsid), which increases the lower oesophageal sphincter pressure, thereby reducing the risk of reflux. Cisapride is also used to treat IBS dominated by constipation, but has been linked to serious cardiac arrhythmias and should be used with caution. In the 4-week study, the peppermint and caraway oil combination (Enteroplant, 2 capsules daily) was shown to be as effective as cisapride in reducing both the magnitude and frequency of pain. Physicians rated the two treatments comparable in regard to other dyspeptic symptoms, in addition to intestinal and extra-intestinal autonomic symptoms. Corresponding results were also found in *H. pylori*-positive patients and patients who initially presented with intense epigastric pain in the two treatment groups. Both medications were well-tolerated (Madisch et al 1999).

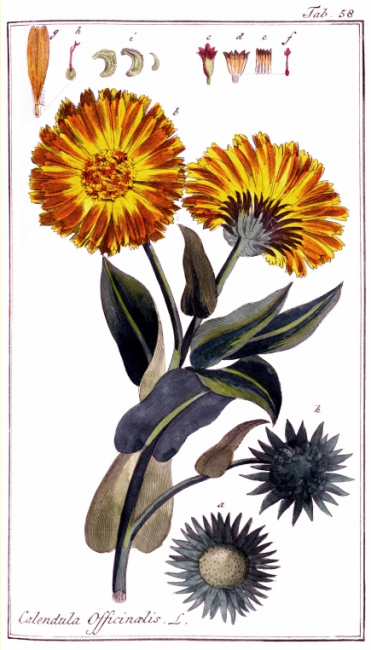
A combination herbal preparation (Iberogast) that includes peppermint leaf extract and eight other plant extracts (*Iberis amara, Chelidonii herba*, *Cardui mariae fructus*, *Melissae folium*, *Carvi fructus*, *Liquiritiae radix, Angelicae radix, Matricariae flos*) has been demonstrated to significantly relieve dyspepsia in a number of RCTs, including a meta-analysis of three trials (Melzer et al 2004), with a fourth RCT showing similar effects to cisapride (Rosch et al 2002).

DIFFUSE OESOPHAGEAL SPASM

Diffuse oesophageal spasm (DES) is a relatively rare motor disorder. Associated manometric abnormalities may include hypertensive and repetitive contractions. The lower oesophageal sphincter (LES) may also be hypertensive. Although LES relaxation with deglutition is generally normal, disturbances in LES function are often seen. These abnormalities are, however, not required for the diagnosis (Massey 2001). In a study of eight DES patients with chest pain or dysphagia, peppermint oil had no effect on LES pressures or contractile pressures and durations in the oesophagus, yet completely eliminated simultaneous oesophageal contractions in all patients ($P < 0.01$). The number of multiphasic, spontaneous and missed contractions also improved. Two of the eight patients had their chest pain resolved after taking the peppermint oil (Pimentel et al 2001).

ANTISPASMODIC

The results from a randomised double-blind, double-dummy, controlled trial suggest that the antispasmodic properties of peppermint oil can be utilised intraluminally during upper endoscopy with superior efficacy and fewer side-effects than hyoscine-N-butylbromide (buscopan) administered by intramuscular injection (Hiki et al 2003a, b). The use of peppermint oil solution was subsequently used to successfully extend an endoscope past an area of severe antral stenosis in a case that was unresponsive to buscopan. In a further study of 383 patients receiving double-contrast barium enemas, which compared peppermint oil in the barium, peppermint in the enema tube, buscopan and no treatment, found that peppermint oil in the barium or the enema tube could be safely and effectively used instead of buscopan and that the oil had a stronger antispasmodic effect in the caecum and the ascending colon than a buscopan injection (Asao et al 2003).



HEADACHE

A solution of 10% peppermint oil in ethanol has been shown in a randomised, placebo-controlled, double-blind crossover study to efficiently alleviate tension-type headache. The study analysed 164 headache attacks in 41 patients of both sexes ranging between 18 and 65 years of age, suffering from tension-type headache. The peppermint oil was spread largely across forehead and temples and repeated after 15 and 30 minutes. Using a headache diary, the headache parameters were assessed after 15, 30, 45 and 60 minutes. Compared with the application of a placebo, the peppermint oil significantly reduced the intensity of the headache after 15 minutes ($P < 0.01$). The analgesic effect of the peppermint oil was comparable to 1000 mg paracetamol (acetaminophen). Simultaneous ingestion of 1000 mg of paracetamol

and application of 10% peppermint oil in ethanol solution led to a slight additive effect (Gobel et al 1996).

Postoperative nausea Inhalation of peppermint oil vapours has been shown in a study to reduce postoperative nausea in gynaecological patients in a placebo-controlled trial in which patients were free to inhale peppermint oil as frequently as desired (Tate 1997). A hot peppermint oil compress is used in China to prevent abdominal distension in postoperative gynaecological patients (Feng 1997). In another placebo-controlled trial, a reduction in postoperative nausea was seen equally with inhalation of isopropyl alcohol, peppermint oil or saline, with the authors attributing the effect to the controlled breathing used during inhalation (Anderson & Gross 2004).

RESPIRATORY TRACT INFECTIONS

Peppermint and menthol have an established tradition in the treatment of respiratory infections. Chest rubs containing menthol are frequently used to treat coughs and bronchitis. Inhalation of various antiseptic and anti-inflammatory essential oils is often used in the treatment of respiratory infections, including bronchitis (Shubina et al 1990). Peppermint oil has been found to have a pronounced antimycobacterial effect in vitro, and long-term use of peppermint oil in a humidifier has been used in the Ukraine as an adjunctive treatment to multidrug therapy for pulmonary tuberculosis (Shkurupi et al 2002).

ENHANCE COGNITIVE PERFORMANCE

A combination of peppermint oil, eucalyptus oil and ethanol was shown in a crossover double-blind study to increase cognitive performance, and promote relaxation in 32 healthy subjects (Gobel et al 1994). Peppermint odour has also been shown to reduce daytime sleepiness (Norrish & Dwyer 2005) and fatigue, and to improve mood (Goel & Lao 2006), as well as significantly improve performance in difficult tactile tasks (Ho & Spence 2005) and promote a general arousal of attention with improved typing speed and accuracy (Barker et al 2003).

OTHER USES

Peppermint or pure menthol is commonly used in heat rub ointments for arthritis, fibromyositis, tendonitis and other musculoskeletal conditions. Commission E approved peppermint oil externally for neuralgia and myalgia (Blumenthal et al 2000).

An oral spray or gargle containing a range of essential oils including peppermint oil is reported to reduce snoring in one double blind study (Prichard 2004). A case report describes the treatment of post-herpetic neuralgia with the direct application of undiluted peppermint oil containing 10% menthol to the affected area. The pain

relief persisted for 4–6 hours after application of the oil. At a 2-month follow-up the patient had only minor side-effects and continued to use the medication (Davies et al 2002).

TRADITIONAL USES

Traditionally, peppermint was believed to increase libido, and used to stop hiccups, relieve pain in childbirth, reduce bleeding and treat menorrhagia (Fisher & Painter 1996). It was also used externally to repress lactation, to treat dermatological conditions, as a mouthwash for painful gums and mouth and applied to the temples to relieve headaches.

DOSAGE RANGE

LEAF

- Infusion: 3–6 g three times daily (Blumenthal et al 2000).
- Liquid extract (1:2): 1.5–4.5 mL/day.

These dosages are for adults; adjust according to size for children.

ESSENTIAL OIL

- Digestive disorders: 0.2–0.4 mL three times daily in dilute preparations or in suspension (ESCOP 1997).
- IBS: 0.2–0.4 mL three times daily in enteric-coated capsules or tablets (Dew et al 1984, Rees et al 1979).
- Inhalation: 3–4 drops added to hot water.
- Lozenge: 2–10 mg.
- External use (for analgesic, anaesthetic or antipruritic activity): 0.1–1.0% m/m (ESCOP 1997).
- External use (counterirritant): 1.25–16% m/m (ESCOP 1997).

ADVERSE REACTIONS

A single dose of 4000 mg/kg of a spray-dried infusion did not produce any macroscopic signs of toxicity in mice (Della et al 1990). Peppermint oil has been shown to be minimally toxic in acute oral studies. Short-term and subchronic oral studies reported brain lesions in rats that were given very large doses of peppermint oil containing pulegone, pulegone alone or large amounts (> 200 mg/kg/day) of menthone. Pulegone is also a recognised hepatotoxin and large doses of peppermint oil have been shown to be hepatotoxic in cultured human hepatoma cells (Vo et al 2003). Peppermint oil was negative in an Ames test and a mouse lymphoma mutagenesis assay, but gave equivocal results in a Chinese hamster fibroblast cell

chromosome aberration assay. There is a case report of acute lung injury following IV injection of peppermint oil (Behrends et al 2005).

Although sensitisation to peppermint oil and/or its constituents has been reported, a solution containing 8% peppermint oil was shown not to be a sensitiser (Nair 2001). Contact dermatitis to peppermint and menthol has been reported (Morton et al 1995) and there is a case report of chemical burn after peppermint oil ingestion (Tamir et al 2005); however, as long as the pulegone content is kept to a minimum, peppermint oil and peppermint extract are considered to have a very good safety profile.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

FELODIPINE

Peppermint oil has been shown to increase the oral bioavailability of felodipine in animal studies (Anon 2002) — use this combination with caution.

SIMVASTATIN

Peppermint oil has been shown to increase the oral bioavailability of simvastatin in animal studies (Anon 2002). Observe the patient and monitor drug requirements — possible beneficial interaction.

CYCLOSPORIN

Peppermint oil has been shown to increase the oral bioavailability of cyclosporin in animal studies (Anon 2002) — avoid concurrent use, unless under medical supervision.

DRUGS METABOLISED BY CYP3A4 LIVER ENZYME

Peppermint may increase the oral bioavailability of certain drugs by inhibition of CYP3A4-mediated drug metabolism, which has been demonstrated in vitro but not in test animals (Dresser et al 2002, Maliakal & Wanwimolruk 2001). Although these studies seem to suggest that peppermint may modulate drug metabolising enzymes, the clinical significance of this is unknown and requires further investigation. Caution is advised.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to peppermint oil (Morton et al 1995).

Non-enteric-coated peppermint may be best avoided in patients with reflux oesophageal symptoms. Avoid chewing enteric-coated capsules as it may cause heartburn (Liu et al 1997). Avoid the use of peppermint oil on the face of infants and

small children. Capsules containing peppermint oil are contraindicated in biliary duct occlusion, gall bladder inflammation and severe liver damage (Blumenthal et al 2000).

PREGNANCY USE

Safe dosages in pregnant women have not been determined; however, external use is likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Peppermint oil and/or peppermint leaf extracts can be used for IBS, dyspepsia, flatulence, intestinal colic and biliary disorders. Note, however, that peppermint oil is contraindicated in inflammation of the gall bladder and severe liver disease.
- Although enteric-coated peppermint oil capsules may prevent side-effects such as reflux and allow higher doses to be used, traditional extracts of peppermint, including hydro-ethanolic extracts and infusions, may also be effective.
- Peppermint leaf extract combines well with chamomile, caraway, licorice, lemon balm, angelica, St Mary's thistle and the bitter candytuft (*Iberis amara*) in the treatment of functional dyspepsia (Madisch et al 2001).
- Peppermint oil can be used as an inhalation or chest rub for coughs, sinusitis and bronchitis. Commission E approved peppermint oil for internal use in the treatment of respiratory tract inflammation (Blumenthal et al 2000) and hot peppermint leaf infusion is used as a diaphoretic tea in the treatment of colds and influenza.
- Peppermint oil can be inhaled to reduce nausea and may enhance cognitive performance and tactile tasks.
- 10% peppermint oil in ethanol solution can be applied externally for tension headaches and applied over affected areas for post-herpetic neuralgia.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Peppermint is a safe herb for gastrointestinal disorders, including dyspepsia and IBS. It is also safe for children, particularly as a herbal tea.

When will it start to work?

Peppermint will generally have an immediate effect, with the condition continuing to improve with long-term use.

Are there any safety issues?

Concentrated peppermint oil preparations may theoretically interact with a number of different medications. It is unlikely any interaction will occur with peppermint tea or simple liquid extracts. Avoid the use of peppermint oil on the face of infants and small children.

REFERENCES

Adam B et al. A combination of peppermint oil and caraway oil attenuates the post-inflammatory visceral hyperalgesia in a rat model. Scandinavian J Gastroenterol 41.2 (2006): 155-60.

Ai M et al. Assessment of the antispasmodic effect of peppermint oil and Shakuyaku-Kanzo-To (TJ-68), a Chinese herbal medicine, on the colonic wall. Gastrointest Endosc 61.5 (2005): AB107.

Akdogan M et al. Effects of peppermint teas on plasma testosterone, follicle-stimulating hormone, and luteinizing hormone levels and testicular tissue in rats. Urology 64.2 (2004): 394-8.

Anderson LA, Gross JB. Aromatherapy with peppermint, isopropyl alcohol, or placebo is equally effective in relieving postoperative nausea. J Perianesth Nurs 19.1 (2004): 29-35.

Anon. Essential oils of peppermint, orange or lemongrass kill most strains of fungal and bacterial infections. Posit Health News no. 17 (1998): 26-7.

Anon. Peppermint oil increases the oral bioavailability of felodipine and simvastatin, Clin Pharmacol Ther 71.2 (2002): P67.

Asao T et al. Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with buscopan. Clin Radiol 58.4 (2003): 301-5.

Barker S et al. Improved performance on clerical tasks associated with administration of peppermint odor. Percept Motor Skills 97.3 (2003): 1007-10.

Behrends M et al. Acute lung injury after peppermint oil injection. Anesth Analgesia 101.4 (2005): 1160-2.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Cappello G et al. Peppermint oil (Mintoil(R)) in the treatment of irritable bowel syndrome: A prospective double blind placebo controlled randomized trial. Dig Liver Dis 38 (Suppl 1) (2006): S201-2.

Coon JT, Ernst E. Systematic Review: Herbal medicinal products for non-ulcer dyspepsia. Aliment Pharmacol Ther 16.10 (2002): 1689-99.

Davies SJ, Harding LM, Baranowski AP. A novel treatment of postherpetic neuralgia using peppermint oil. Clin J Pain 18.3 (2002): 200-2.

Della LR, Tubaro A, Lunder TL. Evaluation of some pharmacologica activities of a peppermint extract. Fitoterapia 61.3 (1990): 215-21.

Dew MJ, Evans BK, Rhodes J. Peppermint oil for the irritable bowel syndrome: a multicentre trial. Br J Clin Pract 38.11-12 (1984): 394, 398.

Dresser GK et al. Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. Clin Pharmacol Ther 72.3 (2002): 247-55.

Duband F et al. Aromatic and polyphenolic composition of infused peppermint, Mentha x piperita L. Ann Pharm Fr 50.3 (1992): 146-55.

ESCOP Menthae Piperitae Folium: peppermint leaf. European Scientific Co-operative On Phytomedicine (ESCOP), 2nd edn. Stuttgart: Thieme, 1997.

Feng XZ. Effect of peppermint oil hot compresses in preventing abdominal distension in postoperative gynecological patients. Zhonghua Hu Li Za Zhi 32.10 (1997): 577-8.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

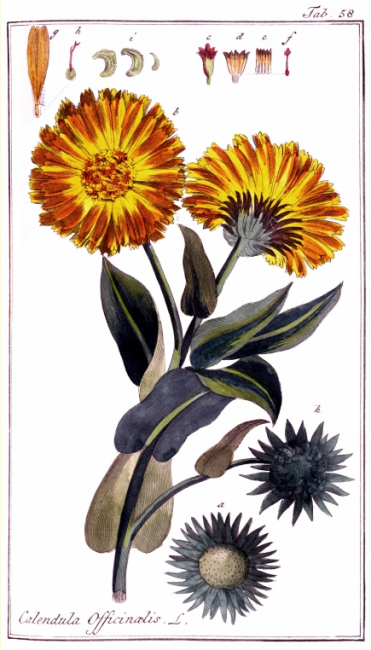
Freise J, Kohler S. Peppermint oil-caraway oil fixed combination in non-ulcer dyspepsia: comparison of the effects of enteric preparations. Pharmazie 54.3 (1999): 210-15.

Gaby AR. Treatment with enteric-coated peppermint oil reduced small-intestinal bacterial overgrowth in a patient with irritable bowel syndrome. Alt Med Rev 8.1 (2003): 3; author reply 4-5.

Giachetti D, Taddei E, Taddei I. Pharmacological activity of essential oils on Oddi's sphincter. Planta Med 54.5 (1988): 389-92.

Gobel H, Schmidt G, Soyka D. Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters. Cephalalgia 14.3 (1994): 228-34.

Gobel H et al. Effectiveness of Oleum menthae piperitae and paracetamol in therapy of headache of the tension type. Nervenarzt 67.8 (1996): 672-81.



Goel N, Lao RP. Sleep changes vary by odor perception in young adults. Biol Psychol 71.3 (2006): 341-9.
Goerg KJ, Spilker T. Effect of peppermint oil and caraway oil on gastrointestinal motility in healthy volunteers: a pharmacodynamic study using simultaneous determination of gastric and gall-bladder emptying and orocaecal transit time. Aliment Pharmacol Ther 17.3 (2003): 445-51.
Greenberg MM, Amitrone HP-CA, Galiczynski JEMB. A contemporary review of irritable bowel syndrome. Physician Assist 26.8 (2002): 26-33.
Grigoleit H-G, Grigoleit P. Gastrointestinal clinical pharmacology of peppermint oil. Phytomedicine 12.8 (2005a): 607-11.
Grigoleit H-G, Grigoleit P. Peppermint oil in irritable bowel syndrome. Phytomedicine 12.8 (2005b): 601-6.
Grigoleit H-G, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. Phytomedicine 12.8 (2005c): 612-16.
Hiki N et al. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. Gastrointest Endosc 57.4 (2003a): 475-82.
Hiki N et al. Case of gastric outlet stenosis with features of pyloric stenosis diagnosed by using peppermint oil solution as a new antispasmodic. Dig Endosc 15.3 (2003b): 224-7.
Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle: An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. Gastroenterology 101.1 (1991): 55-65.
Ho C, Spence C. Olfactory facilitation of dual-task performance. Neurosci Lett 389.1 (2005): 35-40.
Holtmann G et al. Effects of a fixed combination of peppermint oil and caraway oil on symptoms and quality of life in patients suffering from functional dyspepsia. Phytomedicine 10 (Suppl 4) (2003): 56-7.
Imai H et al. Inhibition by the essential oils of peppermint and spearmint of the growth of pathogenic bacteria. Microbios 106 (Suppl 1) (2001): 31-9.
Inoue T et al. Effects of peppermint (Mentha piperita L.) extracts on experimental allergic rhinitis in rats. Biol Pharm Bull 24.1 (2001): 92-95.
Inoue T et al. Antiallergic effect of flavonoid glycosides obtained from Mentha piperita L. Biol Pharm Bull 25.2 (2002): 256-9.
Kingham JGC. Peppermint oil and colon spasm. Lancet 346.8981 (1995): 986.
Kline RM et al. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 138.1 (2001): 125-8.
Lim WC et al. Stimulative and sedative effects of essential oils upon inhalation in mice. Arch Pharmacol Res 28.7 (2005): 770-4.
Liu JH et al. Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol 32.6 (1997): 765-8.
Logan AC, Beaulne TM. The treatment of small intestinal bacterial overgrowth with enteric-coated peppermint oil: a case report. Alt Med Rev 7.5 (2002): 410-17.
Madisch A et al. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride: A multicenter, reference-controlled double-blind equivalence study. Arzneimittelforschung 49.11 (1999): 925-32.
Madisch A et al. A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study. Z Gastroenterol 39.7 (2001): 511-17.
Maliakal PP, Wanwimolruk S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol 53.10 (2001): 1323-9.
Massey BT. Diffuse esophageal spasm: a case for carminatives? J Clin Gastroenterol 33.1 (2001): 8-10.
May B et al. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. Arzneimittelforschung 46.12 (1996): 1149-53.
May BL, Kohler S, Schneider B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment Pharmacol Ther 14.12 (2000): 1671-7.
May B et al. Peppermint oil and caraway oil in functional dyspepsia: Efficacy unaffected by H. pylori. Aliment Pharmacol Ther 17.7 (2003): 975-6.

Melzer J et al. Meta-analysis: Phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 Iberogast. Aliment Pharmacol Ther 20.11-12 (2004): 1279-17.
Micklefield G et al. Effects of intraduodenal application of peppermint oil (WS(R) 1340) and caraway oil (WS(R) 1520) on gastroduodenal motility in healthy volunteers. Phytother Res 17.2 (2003): 135-40.
Mimica-Dukic N et al. Antimicrobial and antioxidant activities of three Mentha species essential oils. Planta Med 69.5 (2003): 413-19.
Morton CA et al. Contact sensitivity to menthol and peppermint in patients with intra-oral symptoms. Contact Dermatitis 32.5 (1995): 281-4.
Murray MT, Pizzorno JE. Mentha piperita peppermint. In: Textbook of Natural Medicine. Philadelphia, Churchill Livingstone, 827–9, 1999.
Nair B. Final report on the safety assessment of Mentha piperita (peppermint) oil, Mentha piperita (Peppermint) leaf extract, Mentha piperita (peppermint) leaf, and Mentha piperita (peppermint) leaf water. Int J Toxicol 20 (Suppl 3) (2001): 61-73.
Norrish MIK, Dwyer KL. Preliminary investigation of the effect of peppermint oil on an objective measure of daytime sleepiness. Int J Psychophysiol 55.3 (2005): 291-8.
Pattnaik S, Subramanyam VR, Rath CC. Effect of essential oils on the viability and morphology of Escherichia coli (SP-11). Microbios 84.340 (1995): 195-9.
Pattnaik S, Subramanyam VR, Kole C. Antibacterial and antifungal activity of ten essential oils in vitro. Microbios 86.349 (1996): 237-46.
Pimentel M et al. Peppermint oil improves the manometric findings in diffuse esophageal spasm. J Clin Gastroenterol 33.1 (2001): 27-31.
Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. Am J Gastroenterol 93.7 (1998): 1131-5.
Prichard AJN. The use of essential oils to treat snoring. Phytother Res 18.9 (2004): 696-9.
Rees WD, Evans BK, Rhodes J. Treating irritable bowel syndrome with peppermint oil. BMJ 2.6194 (1979): 835-6.
Rosch W, Vinson B, Sassin I. A randomised clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. Z Gastroenterol 40 (2002): 401-8.
Saeed S, Tariq P. Antibacterial activities of Mentha piperita, Pisum sativum and Momordica charantia. Pakistan J Botany 37.4 (2005): 997-1001.
Samarth RM et al. Modulatory effects of Mentha piperita on lung tumor incidence, genotoxicity, and oxidative stress in benzo[a]pyrene-treated Swiss albino mice. Environ Mol Mutagen 47.3 (2006): 192-8.
Schelz Z et al. Antimicrobial and antiplasmid activities of essential oils. Fitoterapia 77.4 (2006): 279-85.
Schuhmacher A et al. Virucidal effect of peppermint oil on the enveloped viruses herpes simplex virus type 1 and type 2 in vitro. Phytomedicine 10.6-7 (2003): 504-10.
Shkurupi VA et al. [Efficiency of the use of peppermint (Mentha piperita L.) essential oil inhalations in the combined multi-drug therapy for pulmonary tuberculosis]. Probl Tuberkul (4) (2002): 36-9.
Shubina LP, Siurin SA, Savchenko VM. [Inhalations of essential oils in the combined treatment of patients with chronic bronchitis.] Vrach Delo no. 5 (1990): 66-7.
Sroka Z et al. Antiradical and anti-H_2O_2 properties of polyphenolic compounds from an aqueous peppermint extract. Z Naturforsch Section C J Biosci 60.11-12 (2005): 826-32.
Tamir S et al. Peppermint oil chemical burn. Otolaryngol Head Neck Surg 133.5 (2005) 801-2.
Tate S. Peppermint oil: a treatment for postoperative nausea. J Adv Nurs 26.3 (1997): 543-9.
Umezu T, Morita M. Evidence for the involvement of dopamine in ambulation promoted by menthol in mice. J Pharmacol Sci 91.2 (2003): 125-35.
Umezu T, Sakata A, Ito H. Ambulation-promoting effect of peppermint oil and identification of its active constituents. Pharmacol Biochem Behav 69.3-4 (2001): 383-90.
Van Rensen I. Mentha x piperita: Peppermint in indigestion. Z Phytother 25.3 (2004): 118-27.

Vo LT et al. Investigation of the effects of peppermint oil and valerian on rat liver and cultured human liver cells. Clin Exp Pharmacol Physiol 30.10 (2003): 799-804.
Wildung MR, Croteau RB. Genetic engineering of peppermint for improved essential oil composition and yield. Transgenic Res 14.4 (2005): 365-72.

Perilla

Historical note Perilla is an annual plant native to Eastern Asia. It was introduced to Japan from China and is now cultivated extensively in Japan, India and Korea. The seed is mainly used for its high oil content, and the leaves of *Perilla frutescens* var. *crispa* are used as a vegetable and food colouring. The salty umeboshi plum is coloured by the addition of special red perilla leaves. In China perilla has been used to reduce the risk of food poisoning by cooking seafood with the leaf (Bensky & Gamble 1986). In recent times, certain compounds (monoterpines) isolated from the oil are being investigated as an anticancer treatment, and the defatted seed extract is used in the treatment of allergies.

COMMON NAME
Perilla

OTHER NAMES
Beefsteak plant, Chinese basil, Purple perilla, wild sesame (English common names), Ban Tulsi (Bengali), Su Zi (Mandarin), Shosi, Egoma (Japanese). Different names are used for the different parts of the perilla plant used as foods or medicines.

BOTANICAL NAME/FAMILY
Perilla frutescens (L.) Britt.

There are several botanical variants that seem to be used interchangeably: *P. frutescens* var. *crispa*, *P. frutescens* var. *japonica* (family Lamiaceae or Labiatae [mint family]).

PLANT PARTS USED
Leaf, stem and the fruit (seed) are used.

CHEMICAL COMPONENTS
As different parts of the plant are used, this section will deal with each part individually.

RAW OIL
Perilla seed contains 25–51% lipids. The raw perilla oil has been used as a drying oil in paints, varnishes, linoleum, printing ink, lacquers and for protective waterproof coatings on cloth. It has also been used for cooking and as a fuel.

REFINED OIL

The purified oil is rich in fatty acids including palmitic acid, linoleic acid, alpha-linolenic acid, stearic acid, eicosenoic acid and arachidic acid. The n-3 essential fatty acid, alpha-linolenic acid, comprises over 60% of the oil (Tan et al 1998).

DEFATTED PERILLA SEED EXTRACT

Defatted perilla seed extract is a concentrated ethanolic extract rich in polyphenolic compounds including rosmarinic acid, rosmarinic acid methyl ester and the flavones apigenin, luteolin and chrysoeriol. Normally flavonoids exist as glycosides in plants; however, in perilla seed extract they occur as aglycones (free flavonoids), which have more potent activity. The defatted extract is free of perillyl ketone, perillyl aldehyde and perillyl alcohol (Oryza Co. 2003).

LEAF

The leaf contains flavones, including apigenin and luteolin, flavone glycosides, anthocyanins, phenolic compounds including rosmarinic acid, and aldehydes including perillyl aldehyde (Makino et al 2003a).

ESSENTIAL OIL

The volatile oil is distilled from the dried foliage of perilla. It contains perillyl aldehyde, elsholtziaketone, perillyl ketone, citral and perillene, in addition to more than 70 other compounds (Ito et al 1999). Perillyl aldehyde is used as a sweetener and flavouring agent. One of the aldehyde isomers is 2000-fold sweeter than sugar and 4–8-fold sweeter than saccharin. Perillyl alcohol, prepared from perillyl aldehyde, is used in fragrances (Misra & Husain 1987). There are different chemotypes of perilla; one genotype lacks perillyl aldehyde but has perillyl ketone (Brenner 1993).

MAIN ACTIONS

The herb has several different actions and the part of the plant used will determine which is exhibited. As such, this review includes information about which part of the herb is responsible for the activity listed. Additionally, much research has been conducted with the rosmarinic acid and luteolin components isolated from perilla.

ANTI-INFLAMMATORY ACTION

Both the refined oil and seed extract demonstrate anti-inflammatory activity in vitro.

Refined oil The pharmacological effects of the refined oil are associated with its high level of alpha-linolenic acid, which is metabolised in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA is a precursor of the series-3 prostaglandins, the series-5 leukotrienes and the series-3 thromboxanes, which have anti-inflammatory and anti-atherogenic properties. The effects have been

shown clinically, as perilla seed oil significantly suppressed the generation of leukotrienes in asthma patients in an observational study comparing two groups of asthma patients, one of which received perilla oil for 4 weeks. Ventilatory parameters, such as PEF, FVC and FEV_1, increased significantly after 4 weeks' dietary supplementation in the treated group (Okamoto et al 2000).

Seed extract Perilla seed extract, as well as its constituents luteolin, rosmarinic acid and chrysoeriol, have been shown to inhibit 5-lipoxygenase in vitro, and therefore leukotriene synthesis. Leukotrienes are associated with both allergic and inflammatory disorders, including hay fever, asthma and inflammatory bowel disorders.

ANTI-ALLERGIC ACTIVITY

In both in vitro and animal models of allergy, perilla preparations have demonstrated anti-allergic effects. Luteolin and rosmarinic and caffeic acids are chiefly responsible for this activity.

Seed extract The defatted seed extract has been shown to inhibit chemically induced type IV allergy and inflammation in vivo, with the luteolin constituent exhibiting the most potent activity.

Perilla seed extract has also been shown to inhibit histamine release from mast cells in a dose-dependent manner. The effect is more potent than for isolated flavonoids including catechin, quercetin and caffeic acid. Additionally, in a case report of perilla seed extract, 150 mg/day for 2 weeks selectively inhibited the production of serum IgE in two human subjects suffering allergic symptoms including sneezing, nasal obstruction and itchy eyes (Oryza Co. 2003).

Leaf Perilla leaf extract is thought to downregulate Th2-type cytokine production and prevent the Th1/Th2 balance from shifting toward Th2-type immune responses. A study on the effects of perilla leaf extract on cytokine production in allergic reaction in mice found that it suppressed IgE and IgG antibodies as well as IL-4, IL-5 and IL-10 (Ishihara et al 1999).

An aqueous extract of perilla leaf was shown in vitro and in vivo to inhibit local and systemic reactions in a mast cell-mediated immediate-type allergic reaction. Plasma histamine levels and cyclic AMP were reduced in a dose-dependent manner. Perilla also inhibited IgE-induced TNF-alpha production (Shin et al 2000). Oral administration of a hot water extract of perilla leaf was also shown to inhibit histamine release from mast cells and reduce scratching in an animal model of dermatitis (Wakame et al 2000).

Oral administration of a perilla leaf extract inhibited the inflammatory response in an induced allergic reaction in animals. Luteolin, rosmarinic and caffeic acids were isolated and identified as active constituents. Luteolin has been shown in vivo to

inhibit TNF-alpha and arachidonic acid and reduce oedema (Ueda et al 2002). In another inflammatory model, perilla dose-dependently reduced the allergic response in mice by over 40%. Rosmarinic acid was identified as the main active constituent (Makino et al 2001) and has been shown to decrease the inflammatory response and increase superoxide radical scavenging in vivo (Osakabe et al 2004a). An extract of perilla leaf with high levels of rosmarinic acid decreased cytokine activity in asthma-induced rats (Sanbongi et al 2004). A perilla leaf decoction was found to suppress IgA nephropathy in genetically predisposed rats, possibly through modulation of the intestinal mucosal immune system. Perilla suppressed proteinuria, proliferation of glomerular cells, serum levels of IgA, glomerular IgA and IgG depositions in the mice. Rosmarinic acid seems to produce this effect synergistically with other constituents (Makino et al 2003b).

ANTIOXIDANT ACTIVITY

A methanolic extract of roasted defatted perilla seed has been shown to exert strong antioxidant activity and, upon fractionation, luteolin was identified as one of the active antioxidant constituents (Jung et al 2001). Rosmarinic acid inhibits NO and iNOS in vitro (Qiao et al 2005, Renzulli et al 2004).

IMMUNOSTIMULANT

Perilla leaf extract stimulates phagocytosis in vitro and in vivo (Simoniene et al 2005). An increase in neutrophil phagocytosis was noted after 7 days, but was strongest after 4 weeks of treatment. A polysaccharide extract from perilla leaf has also demonstrated phagocytic ability both in vitro and in vivo (Kwon et al 2002).

ANTIMICROBIAL ACTIVITY

Perilla may help prevent dental caries and periodontal disease. Perilla seed extract has been shown to have antimicrobial activity against oral cariogenic streptococci and periodontopathic *Porphyromonas gingivalis*. The luteolin constituent showed the strongest antimicrobial effect amongst the phenolic compounds tested (Yamamoto & Ogawa 2002).

HEPATOPROTECTIVE EFFECTS

Perilla extract and its constituent rosmarinic acid have both been shown to be hepatoprotective against lipopolysaccharide-induced liver damage in mice, possibly due to the antioxidant activity (Osakabe et al 2002).

HYPOCHOLESTEROLAEMIC

Hypocholesterolaemic effects of perilla have been demonstrated in vivo. Perilla oil lowers cholesterol by suppressing hepatic HMG-CoA reductase activity (Du et al

2003). Perilla oil also lowers plasma triacylglycerol by suppressing fatty acid synthase (Kim et al 2004) and stimulating acyl-CoA oxidase (Kim & Choi 2005) in the liver.

Perilla oil mixed with borage and evening primrose oil has been shown to reduce cholesterol in older rats (Fukushima et al 2001).

ANTICANCER EFFECTS

Several constituents found in perilla have demonstrated anticancer effects in vitro and in experimental cancer models. This has prompted phase I and phase II clinical testing with one key active constituent, perillyl alcohol.

Conjugated alpha-linolenic acid from perilla oil has been shown to reduce the rate of carcinogenesis in a chemically induced rat mammary cancer model (Futakuchi et al 2002). The fibrinolytic and antioxidative activities of rosmarinic acid suppress the proliferation of mesangial cells in vivo (Makino et al 2002, Osakabe et al 2004b). Animal studies have demonstrated the ability of perillyl alcohol to inhibit tumorigenesis in the mammary gland (Yuri et al 2004) and skin (Lluria-Prevatt et al 2002). The precise mechanism of action is unclear. Perillyl alcohol has been shown to inhibit part of the signal transduction cascade involved in uncontrolled cell proliferation, upregulate the mannose-6-phosphate receptor and induce apoptosis (Liston et al 2003, Xu et al 2004). Perillyl alcohol has also demonstrated an ability to decrease the release of vascular endothelial growth factor from cancer cells and encourage the expression of angiopoietin-2 by endothelial cells (Loutrari et al 2004). This indicates that perilla may play a role in decreasing the vascularisation of tumours and inducing regression.

Perillyl alcohol increases the sensitivity of cancer cells in vitro to radiation treatment of prostate cancer (Rajesh & Howard 2003), glioma (Rajesh et al 2003) and certain neck and head cancers (Samaila et al 2004).

ANTIDEPRESSANT ACTIVITY

Several different constituents within perilla leaf have demonstrated effects on behaviour in vivo, most notably antidepressant effects.

Rosmarinic acid and caffeic acid have demonstrated antidepressant activity in a forced swimming test in mice. The activity is thought to be via some mechanism other than the inhibition of monoamine transporters and monoamine oxidase (Takeda et al 2002a). Apigenin from perilla significantly reduced immobility in a forced swimming test in mice, an effect mediated by dopaminergic mechanisms (Nakazawa et al 2003).

Rosmarinic acid and caffeic acid have been shown to decrease the duration of the defensive freezing behaviour caused by fear and stress in animals (Takeda et al 2002b).

OTHER ACTIONS

Perilla oil has been shown to reduce the excessive growth of visceral adipose tissue in rats by downregulating adipocyte differentiation in animals (Okuno et al 1997). This has direct relevance to obesity, as a high-fat diet not only accelerates the filling process of pre-existing pre-adipocytes but also stimulates the proliferation of adipose precursor cells. Adipocyte differentiation, from adipoblasts to adipocytes, is a key factor underlying obesity.

A glycoprotein isolated from perilla oil has been shown to inhibit an early stage of HIV-1 replication without blocking viral adsorption in vitro (Kawahata et al 2002, Yamasaki et al 1998).

Perilla-aldehyde has demonstrated vasodilatory activity in isolated rat aorta and appears to work by blocking Ca^{2+} channels (Takagi et al 2005).The clinical significance of this is currently unknown.

CLINICAL USE

The form most commonly used at the moment is the perilla seed defatted extract; however, this review will also include information regarding other forms.

CANCER

Phase I clinical trials have shown a favourable toxicity profile and preliminary data have indicated some chemotherapeutic efficacy in advanced cancers. However, perillyl alcohol (1200 mg/m^2 four times daily) failed to extend the time-to-progression in three phase II studies in patients with advanced ovarian carcinoma (Bailey et al 2002), prostate cancer (Liu et al 2003) and colorectal cancer. All trials were very small and had to contend with high drop-out rates due to intolerability of the medicine. Despite encouraging preclinical results, perilla does not appear to be an effective treatment for advanced cancer.

ALLERGY

Based on traditional use, in vitro and in vivo studies, and human trials, perilla leaf and defatted seed extracts are used for allergic respiratory disorders including hay fever, asthma and sinusitis. The refined oil may also help allergic and inflammatory respiratory conditions by regulating the arachidonic acid metabolism pathways.

A double-blind, randomised, placebo-controlled clinical trial showed a significant reduction in symptoms such as watery eyes, itchy eyes and itchy nose in 29 patients with seasonal allergic rhinoconjunctivitis, taking 50 or 200 mg of rosmarinic acid enriched perilla for 21 days (Takano et al 2004). Responder rates were 55.6% and 70%, respectively. A drastic reduction in the number of neutrophils and eosinophils in nasal fluid was also demonstrated.

An open clinical trial of 20 human subjects suffering allergic symptoms, including sneezing, nasal obstruction and itchy eyes and skin, were treated with 100–150 mg perilla seed extract daily (higher dose for persons over 60 kg) for 2 weeks. The subjects themselves evaluated changes in the severity of symptoms. Significant improvement was noted in 80% of the subjects for nasal obstructive symptoms, 40% reported a significant improvement in sneezing, and half reported a significant reduction of itchy eyes (Oryza Co. 2003).

Perilla leaf extract cream Open studies of more than 100 children with atopic dermatitis found that perilla leaf extract cream improved symptoms in 80% of cases after 3 months' treatment (Yu & Kosuna 1997). Another open study with 20 allergic patients, using perilla leaf cream topically and perilla leaf extract orally, showed a general improvement in 90% of the patients after 2 months, with 30% reporting significant improvements (Yu & Kosuna 1997).

DENTAL CARIES AND PERIODONTAL DISEASE

Perilla seed extract inhibits the growth of cariogenic and inflammatory microorganisms including oral streptococci and *Porphyromonas gingivalis* (Yamamoto & Ogawa 2002). Perilla seed extract also reduces inflammation through inhibition of leukocyte production and radical scavenging activity. As such, application of the extract in the oral cavity is used to reduce dental caries and pericoronitis.

OTHER USES

Perilla refined oil is a good source of n-3 series alpha-linolenic acid.

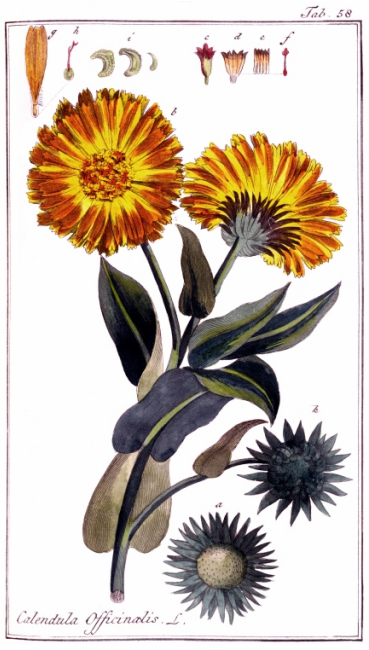
Clinical note — Perilla and TCM

Perilla is an important ingredient of several TCM formulas. Perilla leaf is a key ingredient in Saiboku-to, a traditional Chinese formulation used in the treatment of type 1 hypersensitivity disorders including asthma (Nishiyori et al 1985). Saiboku-to contains *Bupleurum falcatum*, *Pinellia ternata*, *Poria cocus*, *Scutellaria baicalensis*, *Magnolia officinalis*, *Zizyphus spinosa*, *Panax ginseng*, *Glycyrrhizae uralensis*, *Zingiber officinale* and perilla.

Banxia Houpu Decoction used for depression. It contains *Pinellia ternata*, *Poria cocos*, *Magnolia officinalis*, *Perilla frutescens* and *Zingiber officinale* (Luo et al 2000).

DOSAGE RANGE

- Perilla leaf: extract equivalent to 4–9 g/day (Bensky & Gamble 1986).
- Perilla refined oil: 1000 mg capsules taken 3–6 times daily.



- Perilla seed extract (containing min. 3.0% polyphenols):100–150 mg/day (Oryza Co. 2003).
- External use (dental caries and periodontal disease): 80–160 mg defatted perilla seed daily delivered directly into the oral cavity in the form of toothpaste, chewing gum or mouth rinse.

ADVERSE REACTIONS

Perilla defatted seed extract has very low toxicity. After administering 2000 mg/kg to mice for 2 weeks, no toxic effects were observed (LD_{50} for mice is therefore more than 2000 mg/kg). Dosage of 7.0 g/kg for 2 weeks did not produce any toxic effects in humans.

In Japan, 20–50% of long-term workers in the perilla industry develop dermatitis on their hands due to contact with perillyl aldehyde (Brenner 1993).

A 13-week subchronic oral toxicity study of perilla leaf extracts in drinking water did not show any acute toxicity. There were no treatment-related changes in body weight gain or in haematological or blood biochemistry values. Nor were there any treatment-related histopathological changes observed in the highest dose group (Yun et al 1999).

There has been a report of lipoid pneumonia in a 57-year-old man who had a history of ingesting green perilla oil, and there was also residual neurologic deficit of cerebral infarction with right hemiparesis (Kwang et al 1999).

Phase I and II clinical trials of perillyl alcohol for certain cancers have shown that gastrointestinal side-effects and fatigue are the most common adverse reactions (Azzoli et al 2003, Bailey et al 2002, 2004, Liu et al 2003, Meadows et al 2002). Gastrointestinal effects are usually mild and include nausea, vomiting, bloating and belching. Doses were usually between 1200 and 1600 mg/m^2 four times daily.

The refined perilla oil is clear golden yellow. It is fully refined (neutralised, bleached and deodorised) and should be free of perillyl ketone, which is a potent lung toxin that causes increased microvascular permeability and pulmonary oedema in grazing animals (Waters et al 1993).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

ANTIHISTAMINE AGENTS

Theoretical additive effect is possible. Patients taking perilla concurrently with antihistaminic should be observed and drug doses modified if required.

CONTRAINDICATIONS AND PRECAUTIONS

None reported for perilla seed extract or refined oil; however, perilla leaf extract is contraindicated in diarrhoea (Bensky & Gamble 1986).

PREGNANCY USE

Insufficient information is available to determine the safety of perilla during pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Perilla exhibits anti-inflammatory, anti-allergic, antioxidant and anticariogenic activity. Preliminary evidence also suggests hepatoprotective and behavioural effects.
- Perilla leaf and defatted seed extracts are specifically used for allergic respiratory disorders including hay fever, asthma and sinusitis.
- Perilla leaf and defatted seed extract may downregulate Th2-type cytokine production and prevent the Th1/Th2 balance from shifting toward Th2-type immune responses that may be associated with a range of allergic reactions and autoimmune disorders.
- Perilla refined oil is a good source of n-3 series alpha-linolenic acid and extracts should be free of perillyl ketones and aldehydes.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What can this herb do for me?

Perilla is used in the treatment of allergic respiratory conditions, such as hay fever, asthma and sinusitis. Preliminary evidence suggests that it may be beneficial; however, more rigorous studies are still required to confirm effectiveness.

When will it start to work?

Relief of symptoms should be noticed within the first week, although it may take a couple of weeks to show a significant effect. For hay fever, it would be beneficial to start taking perilla at least 1 month before the onset of the hay fever season.

Are there any safety issues?

Perilla is very well tolerated and non-toxic. It can be used long term if indicated.

REFERENCES

Azzoli CG et al. A phase I trial of perillyl alcohol in patients with advanced solid tumors. Cancer Chemother Pharmacol 51.6 (2003) : 493-8.

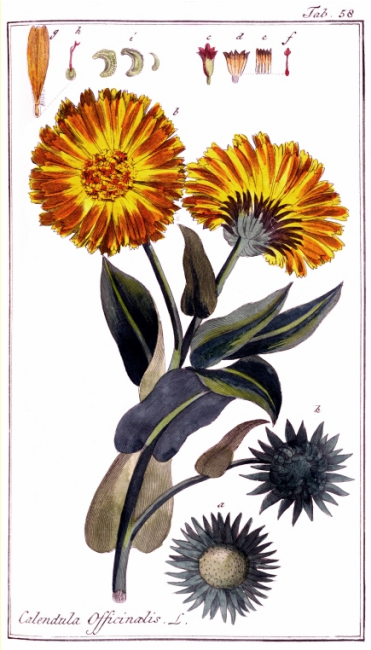
Bailey HH et al. Phase II trial of daily perillyl alcohol in patients with advanced ovarian cancer: Eastern Cooperative Oncology Group Study E2E96. Gynecol Oncol 85 (2002): 464-8.

Bailey HH et al. A phase I trial of perillyl alcohol administered four times daily for 14 days out of 28 days. Cancer Chemother Pharmacol 54.4 (2004): 368-76.

Bensky D, Gamble A. Chinese Herbal Medicine: Materia Medica. Seattle: Eastland Press, 294-5, 1986.

Brenner DM. New Crops. New York: Wiley, 322-8, 1993.

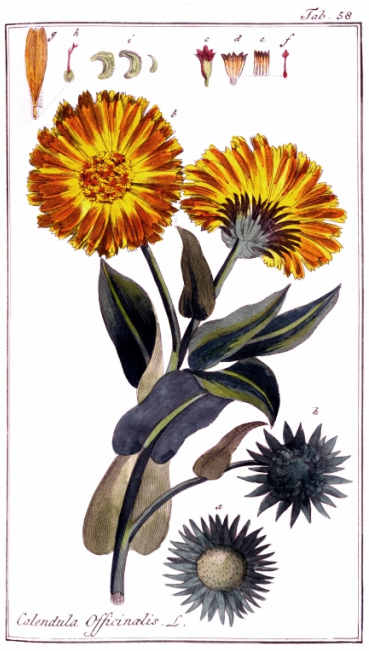
Du C et al. Cholesterol synthesis in mice is suppressed but lipofuscin formation is not affected by long-term feeding of n-3 fatty acid-enriched oils compared with lard and n-6 fatty acid-enriched oils. Biol Pharm Bull 26.6 (2003): 766-70.
Fukushima M et al. Effects of diets enriched in n-6 or n-3 fatty acids on cholesterol metabolism in older rats chronically fed a cholesterol-enriched diet. Lipids 36(3) (2001): 261-6.
Futakuchi M et al. Inhibition of conjugated fatty acids derived from safflower or perilla oil of induction and development of mammary tumors in rats induced by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). Cancer Lett 178(2) (2002): 131-9.
Ishihara T et al. Inhibition of antigen-specific T helper type 2 responses by Perilla frutescens extract. Jpn J Allergol 48(4) (1999): 443-50 [in Japanese].
Ito M, Toyoda M, Honda G. Chemical composition of the essential oil of Perilla frutescens. Nat Med 53(1) (1999): 32-6.
Jung MJ, Chung HY, Choi JS. Antioxidant activity of roasted defatted perilla seed. Nat Prod Sci 7(3) (2001): 72-5.
Kawahata T et al. A novel substance purified from Perilla frutescens Britton inhibits an early stage of HIV-1 replication without blocking viral adsorption. Antiviral Chem Chemother 13.5 (2002): 283-8.
Kim HK, Choi H. Stimulation of acyl-CoA oxidase by alpha-linolenic acid-rich perilla oil lowers plasma triacylglycerol level in rats. Life Sci 77.12 (2005): 1293-306.
Kim HK, Choi S, Choi H. Suppression of hepatic fatty acid synthase by feeding alpha-linolenic acid rich perilla oil lowers plasma triacylglycerol level in rats. J Nutr Biochem 15.8 (2004): 485-92.
Kwang JJ et al. A case of lipoid pneumonia after ingestion of green perilla oil. Tuberculosis Resp Dis 47(1) (1999): 123-6 [in Korean].
Kwon KH et al. In vitro and in vivo effects of macrophage-stimulatory polysaccharide from leaves of Perilla frutescens var. crispa. Biol Pharm Bull 25.3 (2002): 367-71.
Liston BW et al. Perillyl alcohol as a chemopreventive agent in N-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis. Cancer Res 63 (2003): 2399-403.
Liu G et al. Phase II trial of perillyl alcohol (NSC 641066) administered daily in patients with metastatic androgen independent prostate cancer. Invest New Drugs 21.3 (2003): 367-72.
Lluria-Prevatt M et al. Effects of perillyl alcohol on melanoma in the TPras mouse model. Cancer Epidemiol Biomarkers Prev 11.6 (2002): 573-9.
Loutrari H et al. Perillyl alcohol is an angiogenesis inhibitor. J Pharmacol Exp Ther 311.2 (2004): 568-75.
Luo L et al. Antidepressant effects of Banxia Houpu decoction, a traditional Chinese medicinal empirical formula. J Ethnopharmacol 73(1-2) (2000): 277-81.
Makino T et al. Effect of oral treatment of Perilla frutescens and its constituents on type-I allergy in mice. Biol Pharm Bull 24(10) (2001): 1206-9.
Makino T et al. Suppressive effects of rosmarinic acid on mesangioproliferative glomerulonephritis in rats. Nephron 92(4) (2002) : 898-904.
Makino T et al. Anti-allergic effect of Perilla frutescens and its active constituents. Phytother Res 17 (2003a): 240-3.
Makino T et al. Suppressive effects of Perilla frutescens on IgA nephropathy in HIGA mice. Nephrol Dialysis Transplant 18(3) (2003b): 484-90.
Meadows SM et al. Phase II trial of perillyl alcohol in patients with metastatic colorectal cancer. Int J Gastrointest Cancer 32.2-3 (2002): 125-8.
Misra LN, Husain A. The essential oil of Perilla ocimoides: A rich source of rosefuran. Planta Med 53(4) (1987): 379-80.
Nakazawa T et al. Antidepressant-like effects of apigenin and 2,4,5-trimethoxycinnamic acid from Perilla frutescens in the forced swimming test. Biol Pharm Bull 26 (2003): 474-80.
Nishiyori T et al. Effect of Saiboku-to, a blended Chinese traditional medicine, on type I hypersensitivity reactions, particularly on experimentally-caused asthma. Nippon Yakurigaku Zasshi 85(1) (1985): 7-16.



Okamoto M et al. Effects of perilla seed oil supplementation on leukotriene generation by leucocytes in patients with asthma associated with lipometabolism. Int Arch Allergy Immunol 122(2) (2000): 137-42.
Okuno M et al. Perilla oil prevents the excessive growth of visceral adipose tissue in rats by down-regulating adipocyte differentiation. J Nutr 127 (1997): 1752-7.
Oryza Co. Perilla seed extract: Product Monograph. Version 5.0 TS edn. Japan: Oryza Oil & Fat Chemical Co, 2003.
Osakabe N et al. Rosmarinic acid, a major polyphenolic component of Perilla frutescens, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice. Free Radical Biol Med 33(6) (2002): 798-806.
Osakabe N et al. Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA); inhibition of seasonal allergic rhinoconjunctivitis (SAR) and its mechanism. Biofactors 21.1-4 (2004a): 127-31.
Osakabe N et al. Rosmarinic acid inhibits epidermal inflammatory responses: anticarcinogenic effect of Perilla frutescens extract in the murine two-stage skin model. Carcinogenesis 25.4 (2004b): 549-57.
Qiao S et al. Rosmarinic acid inhibits the formation of reactive oxygen and nitrogen species in RAW264.7 macrophages. Free Radic Res 39.9 (2005): 995-1003.
Rajesh D, Howard SP. Perillyl alcohol mediated radiosensitization via augmentation of the Fas pathway in prostate cancer cells. Prostate 57.1 (2003): 14-23.
Rajesh D, Stenzel RA, Howard SP. Perillyl alcohol as a radio-chemosensitizer in malignant glioma. J Biol Chem 278.38 (2003): 35968-78.
Renzulli C et al. Effects of rosmarinic acid against aflatoxin B1 and ochratoxin-A-induced cell damage in a human hepatoma cell line (Hep G2). J Appl Toxicol 24.4 (2004): 289-96.
Samaila D et al. Monoterpenes enhanced the sensitivity of head and neck cancer cells to radiation treatment in vitro. Anticancer Res 24.5A (2004): 3089-95.
Sanbongi C et al. Rosmarinic acid in perilla extract inhibits allergic inflammation induced by mite allergen, in a mouse model. Clin Exp Allergy 34.6 (2004): 971-7.
Shin TY et al. Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by Perilla frutescens. Immunopharmacol Immunotoxicol 22(3) (2000): 489-500.
Simoniene G et al. [The influence of common perilla (Perilla frutescens (L.) Britton) on non-specific cell-mediated immunity: phagocytosis activity]. Medicina (Kaunas) 41.12 (2005): 1042-7.
Takagi S et al. Vasodilative effect of perillaldehyde on isolated rat aorta. Phytomedicine 12.5 (2005): 333-7.
Takano H et al. Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic rhinoconjunctivitis in humans. Exp Biol Med (Maywood) 229.3 (2004): 247-54.
Takeda H et al. Rosmarinic acid and caffeic acid produce antidepressive-like effect in the forced swimming test in mice. Eur J Pharmacol 449(3) (2002a): 261-7.
Takeda H et al. Rosmarinic acid and caffeic acid reduce the defensive freezing behavior of mice exposed to conditioned fear stress. Psychopharmacology 164(2) (2002b): 233-5.
Tan YF, Lai BS, Yan XL. Analysis of fatty acids in Perilla frutescens seed oil. Chin Pharm J 33(7) (1998): 400-2 [in Chinese].
Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. Biol Pharm Bull 25 (2002) 1197-202.
Wakame K et al. Effects of perilla extracts on compound 48/80 - Induced scratching behavior in mice and histamine release from peritoneal cells. Dokkyo J Med Sci 27(2) (2000): 373-8.
Waters CM et al. Perilla ketone increases endothelial cell monolayer permeability in vitro. J App Physiol 74(5) (1993): 2493-501.
Xu M et al. Perillyl alcohol-mediated inhibition of lung cancer cell line proliferation: potential mechanisms for its chemotherapeutic effects. Toxicol Appl Pharmacol 195.2 (2004): 232-46.
Yamamoto H, Ogawa T. Antimicrobial activity of perilla seed polyphenols against oral pathogenic bacteria. Biosci Biotechnol Biochem 66 (2002): 921-4.
Yamasaki K et al. Anti-HIV-1 activity of herbs in Labiatae. Biol Pharm Bull 21(8) (1998): 829-33.

Yun L et al. A 13-week subchronic oral toxicity study of Perilla extracts in F344 rats. Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku 117 (1999): 104-7 [in Japanese].
Yuri T et al. Perillyl alcohol inhibits human breast cancer cell growth in vitro and in vivo. Breast Cancer Res Treat 84.3 (2004): 251-60.

Policosanol



BACKGROUND AND RELEVANT PHARMACOKINETICS

Policosanol is isolated from the waxes of plants such as sugar cane. The main component, octacosanol, has variable absorption from the small intestine and is chiefly metabolised by the liver and excreted in the faeces.

CHEMICAL COMPONENTS

Policosanol is a mixture of long-chain primary aliphatic alcohols (Arruzazabala et al 1993a).

MAIN ACTIONS

LOWERS TOTAL CHOLESTEROL LEVELS, INCREASES HDL-CHOLESTEROL AND REDUCES LDL-CHOLESTEROL LEVELS

The exact mechanism of action responsible for this activity has not been fully elucidated; however, several theories exist. One observation that appears to be agreed on by researchers is that policosanol does not inhibit the activity of HMG-CoA reductase, although it produces similar clinical results to HMG-CoA reductase inhibitors.

Some data indicate that policosanol inhibits cholesterol synthesis at an earlier point in the cholesterol biosynthetic pathway and increases LDL-cholesterol processing (Menendez et al 1994, 1996, 2000). Other evidence indicates that policosanol downregulates the cellular expression of HMG-CoA reductase by up to 50%, thereby suppressing biosynthesis of the enzyme (McCarty 2002). It has also been suggested that policosanol may stimulate the degradation of HMG-CoA reductase (Menendez et al 2001). Furthermore, animal studies suggest that LDL catabolism may be enhanced (Gouni-Berthold & Berthold 2002).

REDUCES OXIDATION OF LDL-CHOLESTEROL

This has been demonstrated in vitro at an equivalent dose of 5 and 10 mg/day (Menendez et al 2000).

REDUCES PLATELET AGGREGATION

This has been confirmed in animal models and randomised double-blind studies, with effects starting at 10 mg/day (Castano et al 1999a, Arruzazabala et al 1993b, 2002). One clinical study found that a dose of 20 mg/day policosanol produces the same inhibitory effects on platelet aggregation as 100 mg aspirin daily (Arruzazabala et al 1997). A higher dose of 40 mg policosanol does not appear to produce any further

antiplatelet effects according to another double-blind study (Arruzazabala et al 2002). Thromboxane, but not prostacyclin, generation induced by collagen is also inhibited by policosanol in clinical studies (Carbajal et al 1998a).

OTHER ACTIONS

ENDOTHELIAL PROTECTION

Oral administration of policosanol to spontaneously hypertensive rats resulted in a significant reduction in circulating endothelial cells compared with controls. Moreover, comparison between groups revealed a lower frequency of aortic lesions in policosanol-treated animals than in untreated animals (Noa et al 1997).

ANTIHYPERTENSIVE EFFECTS AT VERY HIGH DOSES

Tests in animal models have identified enhancement of propranolol-induced hypotensive effects with pretreatment at 200 mg/kg policosanol (Molina et al 1999), which is an extremely high dose and clinically irrelevant in humans.

REDUCES ATHEROSCLEROTIC LESION DEVELOPMENT

According to one animal study, most policosanol-treated animals did not develop atherosclerotic lesions compared with an untreated group, and the thickness of fatty streaks that did develop with treatment had fewer foam cell layers than in controls (Arruzazabala et al 2000).

CLINICAL USE

Most clinical studies have been conducted in Cuba with policosanol derived from sugar cane.

HYPERLIPIDAEMIA

Numerous randomised, double-blind clinical trials conducted prior to 2006 demonstrated significant cholesterol-lowering effects of oral policosanol (Castano et al 2001b, Mas et al 1999, Menendez et al 2000, Pons et al 1944, Torres et al 1995); however, one recent study has produced negative results (Berthold et al 2006). Several previous studies conducted with postmenopausal women have confirmed efficacy in this population (Castano et al 2000, Mas et al 1999, Menendez et al 2000, Mirkin et al 2001, Pons et al 1994, Torres et al 1995). Overall, these results show that a daily dose of 5 mg policosanol may:

- reduce LDL-cholesterol by 11–18%
- reduce total cholesterol by 8–15%
- increase HDL by 8–15%

Whereas a higher dose of 20 mg policosanol daily can:

- reduce LDL-cholesterol by 31%

- reduce total cholesterol by 23%
- increase HDL by 27%.

Recent controversy It is important to note that previous research had been conducted almost entirely by the same research group in Cuba and involved Hispanic patients. In 2006, Berthold et al conducted a 12-week randomised study of 143 Caucasian subjects with hypercholesterolaemia or combined hyperlipidaemia. In contrast to previous studies, policosanol failed to significantly reduce LDL-cholesterol, total cholesterol, HDL-cholesterol, triglycerides and other lipid parameters at all test doses (10, 20, 40, 80 mg/day). It has been proposed that these results differed from previous studies because of possible differences between test subjects and/or bias, which could have influenced the conduct of previous studies, leading to erroneous positive findings.

Studies of type 2 diabetes Policosanol has proven effects in dyslipidaemia secondary to type 2 diabetes mellitus according to two studies (Crespo et al 1999, Torres et al 1995).

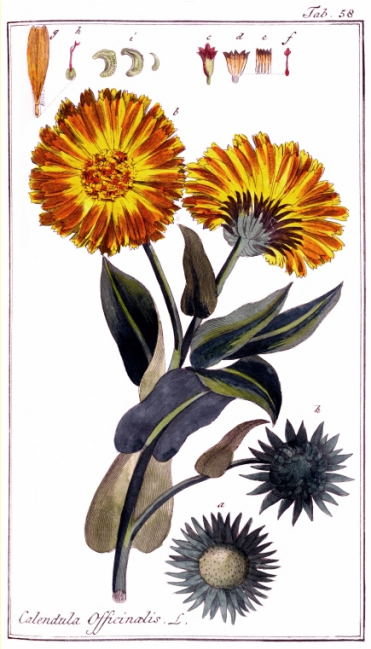
Comparative trials with HMG-CoA reductase inhibitor Several randomised, double-blind studies comparing the effects of policosanol with standard hyperlipidaemic treatment (with statin drugs such as simvastatin and pravastatin) have produced favourable results (Alcocer et al 1999, Castano et al 1999b, Crespo et al 1999, Prat et al 1999, Torres et al 1995). A dose of 10 mg policosanol daily reduced LDL-cholesterol by 24%, compared with 22% reduction with lovastatin and 15% reduction with simvastatin. Additionally, policosanol treatment reduced HDL significantly, whereas the other treatments had no effect (Prat et al 1999, Torres et al 1995). Another study demonstrated better cholesterol- and LDL-lowering effects for 10 mg policosanol compared with 20 mg lovastatin (Crespo et al 1999). Additionally, policosanol significantly raised HDL-cholesterol levels, was better tolerated and had a superior safety profile. A trial comparing pravastatin 10 mg/day with policosanol 10 mg/day found that the policosanol treatment produced greater reductions in total cholesterol and LDL levels and was the only treatment to increase HDL (Castano et al 1999a). Additionally, policosanol was more effective than pravastatin in inhibiting platelet aggregation.

More recently, policosanol (10 mg/day) taken for 8 weeks was found to be less effective than atorvastatin (10 g/day) in reducing serum LDL-cholesterol and total cholesterol levels in older patients with type II hypercholesterolaemia (Castano et al 2003b). Policosanol, but not atorvastatin, however, significantly increased serum HDL-cholesterol levels, whereas both drugs similarly reduced atherogenic ratios and serum triglycerides.

Concurrent use with omega-3 essential fatty acids Due to the favourable effects of omega-3 fatty acids (FAs) in cardiovascular disease, in practice clinicians have recommended policosanol together with fish-oil supplements. According to an 8-week, double-blind, randomised study, the combination effectively reduced total cholesterol, LDL-cholesterol and triglycerides and increased HDL-cholesterol (Castano et al 2005). The study of 90 patients with type II hypercholesterolaemia found that when omega-3 FAs (2 g/day) were combined with policosanol (10 mg/day), there was a significant decrease in total cholesterol (15.3%) and triglycerides (14.7%), and a significant increase in HDL-cholesterol (15.5%).

Concurrent use with beta-blockers A 3-year randomised study of 205 older hypercholesterolaemic patients taking beta-blockers to showed that after 1 year of therapy, policosanol significantly reduced LDL-cholesterol (20.9%), total cholesterol (19.3%) and triglycerides (25.7%) and increased HDL-cholesterol levels (4.1%), effects that lasted for the duration of the study (Castano et al 2004a). The frequency of mild, moderate or severe adverse events was lower in the policosanol group than in the placebo group; however, an additional reduction in SBP and DBP was observed in the policosanol patients compared with those in the placebo group.

Wheat-germ-derived policosanol No beneficial effects on blood lipid profiles were observed in a double-blind, randomised study of 58 subjects with normal to mildly elevated plasma cholesterol who were given 20 mg wheat-germ policosanol in the short 4-week study (Lin et al 2004).



INTERMITTENT CLAUDICATION

Policosanol treatment for intermittent claudication has produced encouraging results in several randomised studies (Castano et al 1999b, 2001b, 2003a). Policosanol 10 mg/day taken for 6 months significantly increased initial claudication distance by approximately 70 metres and absolute claudication by approximately 140 metres in one double-blind study, whereas placebo produced no changes (Castano et al 1999b). A single-blind study using 20 mg policosanol daily showed significant improvements after 6 months' treatment, which further increased after 12 months (Castano et al 2001b). In both studies patients in the policosanol group reported improvements in lower limb symptoms that were greater than those in the placebo group.

More recently, policosanol (10 mg twice daily) was shown to be as effective as ticlopidine (250 mg twice daily) for improving walking distances of claudicant patients (Castano et al 2004a). In the 20-week double-blind, randomised study of 28 subjects, policosanol significantly increased mean values of initial and absolute claudication distances from 162.1 to 273.2 metres and from 255.8 to 401.0 metres,

respectively, which was not significantly different to ticlopidine. Both treatments were well tolerated.

OTHER USES

PRE-EXISTING CORONARY HEART DISEASE (CHD)

A randomised double-blind study of 45 subjects with documented CHD found that a dose of 10 mg policosanol daily increased maximum oxygen uptake and exercise ECG responses. The effects were further enhanced by co-administration of 125 mg aspirin (Stusser et al 1998).

CEREBROVASCULAR DISEASE

In two different experimental models policosanol had anti-ischaemic activity when administered after induction of cerebral ischaemia, suggesting a possible therapeutic effect in CVD (Molina et al 1999).

DOSAGE RANGE

- The doses tested in clinical trials range from 5–20 mg/day.
  More specific doses are:
- hypercholesterolaemia: 5–20 mg/day
- intermittent claudication: 10–20 mg/day; 3 months' continual use may be required before effects are observed
- platelet inhibition: 10 mg/day
- policosanol is usually taken after the evening meal.

TOXICITY

Studies using several animal models have confirmed no carcinogenic effects and no signs of toxicity at doses as high as 500 mg/kg (Aleman et al 1994a, 1994b). This dose is hundreds of times greater than the maximal recommended therapeutic dose (20 mg/day), thereby indicating an excellent safety profile (Mesa et al 1994).

ADVERSE REACTIONS

A pharmacovigilance study of 2252 subjects aged 60 or more years with coronary, cerebrovascular, and peripheral artery disease and treated with policosanol (5, 10 or 20 mg/day) at seven major medical centres found that long-term tolerability of policosanol in elderly patients at high vascular risk was very good (Fernandez et al 2004).

SIGNIFICANT INTERACTIONS

CHOLESTEROL-LOWERING MEDICATION

Additive effects are likely — caution is advised.

Considering the mode of action of policosanol, it is likely to increase the cholesterol-lowering effects of statin drugs. However, a theoretical concern exists as to whether concurrent use will also increase the likelihood of adverse effects.

ASPIRIN

Increased antiplatelet effects may develop — patients taking aspirin and policosanol concurrently should be observed for increased bleeding or bruising.

WARFARIN

Current evidence suggests that there is no interaction between policosanol and warfarin. One clinical study confirmed that the addition of policosanol to warfarin therapy does not enhance the prolongation of the bleeding time induced by warfarin alone (Carbajal et al 1998b). Caution with doses > 10 mg/day.

CONTRAINDICATIONS AND PRECAUTIONS

Suspend use of high doses 1 week before major surgery.

PREGNANCY USE

Safety has been investigated in animal tests with no evidence of teratogenicity or any other embryonal toxicity (Rodriguez & Garcia 1994, 1998, Rodriguez et al 1997).

PRACTICE POINTS/PATIENT COUNSELLING

- Policosanol can be considered an efficacious lipid-lowering treatment that may be used in cases where other treatment has been either ineffective or poorly tolerated. Numerous, randomised double-blind trials confirm activity.
- Comparative studies with statin drugs have generally produced positive results.
- It does not appear to significantly reduce triglyceride levels; however, it has been used successfully with omega-3 essential fatty acids to reduce total cholesterol levels and triglycerides.
- It is also a safe and potentially useful treatment in claudication.
- Policosanol has significant platelet aggregation inhibitor activity.
- Safety studies indicate that it is well tolerated and has a wide safety margin.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What can this supplement do for me?

Policosanol can significantly lower cholesterol levels. Studies suggest this effect is as strong as conventional cholesterol-lowering medications. It also has some blood-thinning activity, is effective in intermittent claudication and can increase total walking distance.

When will it start to work?

Generally, results are observed after approximately 8 weeks' continuous use.

Are there any safety issues?

Policosanol has a wide safety margin and is well tolerated.

REFERENCES

Alcocer L et al. A comparative study of policosanol versus acipimox in patients with type II hypercholesterolemia. Int J Tissue React 21.3 (1999): 85-92.

Aleman CL et al. Carcinogenicity of policosanol in Sprague Dawley rats: a 24 month study. Teratog Carcinog Mutagen 14.5 (1994a): 239-49.

Aleman CL et al. A 12-month study of policosanol oral toxicity in Sprague Dawley rats. Toxicol Lett 70.1 (1994b): 77-87.

Arruzazabala ML et al. Comparative study of policosanol, aspirin and the combination therapy policosanol-aspirin on platelet aggregation in healthy volunteers. Pharmacol Res 36.4 (1997): 293-7.

Arruzazabala ML et al. Effect of policosanol on cerebral ischemia in Mongolian gerbils: role of prostacyclin and thromboxane A2. Prostaglandins Leukot Essent Fatty Acids 49.3 (1993a): 695-7.

Arruzazabala ML et al. Effects of Policosanol on platelet aggregation in rats. Thromb Res 69.3 (1993b): 321-7.

Arruzazabala ML et al. Protective effect of policosanol on atherosclerotic lesions in rabbits with exogenous hypercholesterolemia. Braz J Med Biol Res 33.7 (2000): 835-40.

Arruzazabala ML et al. Antiplatelet effects of policosanol (20 and 40 mg/day) in healthy volunteers and dyslipidaemic patients. Clin Exp Pharmacol Physiol 29.10 (2002): 891-7.

Berthold HK et al. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. JAMA 295.19 (2006): 2262-9.

Carbajal D et al. Effect of policosanol on platelet aggregation and serum levels of arachidonic acid metabolites in healthy volunteers. Prostaglandins Leukot Essent Fatty Acids 58.1 (1998a): 61-4.

Carbajal, D et al. Interaction policosanol-warfarin on bleeding time and thrombosis in rats. Pharmacol Res 38.2 (1998b): 89-91.

Castano G et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelemia in older hypercholesterolemic patients. Int J Clin Pharmacol Res 19.4 (1999a): 105-16.

Castano G et al. A double-blind, placebo-controlled study of the effects of policosanol in patients with intermittent claudication. Angiology 50.2 (1999b): 123-30.

Castano G et al. Effects of policosanol on postmenopausal women with type II hypercholesterolemia. Gynecol Endocrinol 14.3 (2000): 187-95.

Castano G et al. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. J Gerontol A Biol Sci Med Sci 56.3 (2001a): M186-92.

Castano G et al. A long-term study of policosanol in the treatment of intermittent claudication. Angiology 52.2 (2001b): 115-25.

Castano G et al. Comparison of the efficacy and tolerability of policosanol with atorvastatin in elderly patients with type II hypercholesterolaemia. Drugs Aging 20.2 (2003a): 153-63.

Castano G et al. Effects of policosanol and lovastatin in patients with intermittent claudication: a double-blind comparative pilot study. Angiology 54.1 (2003b): 25-38.

Castano G et al. Concomitant use of policosanol and beta-blockers in older patients. Int J Clin Pharmacol Res 24.2-3 (2004a): 65-77.

Castano G et al. Effects of policosanol and ticlopidine in patients with intermittent claudication: a double-blinded pilot comparative study. Angiology 55.4 (2004b): 361-71.

Castano G et al. Effects of addition of policosanol to omega-3 fatty acid therapy on the lipid profile of patients with type II hypercholesterolaemia. Drugs RD 6.4 (2005): 207-19.

Crespo N et al. Comparative study of the efficacy and tolerability of policosanol and lovastatin in patients with hypercholesterolemia and noninsulin dependent diabetes mellitus. Int J Clin Pharmacol Res 19.4 (1999): 117-27.

Fernandez S et al. A pharmacological surveillance study of the tolerability of policosanol in the elderly population. Am J Geriatr Pharmacother 2.4 (2004): 219-29.
Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. Am Heart J 143.2 (2002): 356-65.
Lin Y et al. Wheat germ policosanol failed to lower plasma cholesterol in subjects with normal to mildly elevated cholesterol concentrations. Metabolism 53.10 (2004): 1309-14.
Mas R et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. Clin Pharmacol Ther 65.4 (1999): 439-47.
McCarty MF. Policosanol safely down-regulates HMG-CoA reductase: potential as a component of the Esselstyn regimen. Med Hypotheses 59.3 (2002): 268-79.
Menendez R et al. Policosanol inhibits cholesterol biosynthesis and enhances low density lipoprotein processing in cultured human fibroblasts. Biol Res 27.3-4 (1994): 199-203.
Menendez R et al. Effect of policosanol on the hepatic cholesterol biosynthesis of normocholesterolemic rats. Biol Res 29.2 (1996): 253-7.
Menendez R et al. Effects of policosanol treatment on the susceptibility of low density lipoprotein (LDL) isolated from healthy volunteers to oxidative modification in vitro. Br J Clin Pharmacol 50.3 (2000): 255-62.
Menendez R et al. Policosanol modulates HMG-CoA reductase activity in cultured fibroblasts. Arch Med Res 32.1 (2001): 8-12.
Mesa AR et al. Toxicity of policosanol in beagle dogs: one-year study. Toxicol Lett 73.2 (1994): 81-90.
Mirkin A et al. Efficacy and tolerability of policosanol in hypercholesterolemic postmenopausal women. Int J Clin Pharmacol Res 21.1 (2001): 31-41.
Molina V et al. Effect of policosanol on cerebral ischemia in Mongolian gerbils. Braz J Med Biol Res 32.10 (1999): 1269-76.
Noa M, Mas R, Mesa R. Effect of policosanol on circulating endothelial cells in experimental models in Sprague-Dawley rats and in rabbits. J Pharm Pharmacol 49.10 (1997): 999-1002.
Pons P et al. Effects of successive dose increases of policosanol on the lipid profile of patients with type II hypercholesterolaemia and tolerability to treatment. Int J Clin Pharmacol Res 14.1 (1994): 27-33.
Prat H, Roman O, Pino E. Comparative effects of policosanol and two HMG-CoA reductase inhibitors on type II hypercholesterolemia. Rev Med Chil 127.3 (1999): 286-94.
Rodriguez MD, Garcia H. Teratogenic and reproductive studies of policosanol in the rat and rabbit. Teratog Carcinog Mutagen 14.3 (1994): 107-13.
Rodriguez MD, Garcia H. Evaluation of peri- and post-natal toxicity of Policosanol in rats. Teratog Carcinog Mutagen 18.1 (1998): 1-7.
Rodriguez MD, Sanchez M, Garcia H. Multigeneration reproduction study of policosanol in rats. Toxicol Lett 90.2-3 (1997): 97-106.
Stusser R et al. Long-term therapy with policosanol improves treadmill exercise-ECG testing performance of coronary heart disease patients. Int J Clin Pharmacol Ther 36.9 (1998): 469-73.
Torres O et al. Treatment of hypercholesterolemia in NIDDM with policosanol. Diabetes Care 18.3 (1995): 393-7.

Probiotics

Historical note Eating foods containing microorganisms to improve health has a long tradition. As far back as 1908, Metchnikoff, the Nobel laureate, stated that 'ingested lactobacilli can displace toxin-producing bacteria, promoting health and prolonging life' (Elmer 2001). The term 'probiotics' was first coined in 1965 in reference to substances produced by protozoa that stimulated the growth of other organisms. It has since been applied to those microorganisms found naturally in foods that are able to improve health by stimulating the growth of beneficial organisms. Although it has taken the most part of a century for scientists to investigate their health benefits, there are now several thousand studies on probiotics available on Medline, the majority published since 2000.

BACKGROUND AND RELEVANT PHARMACOKINETICS

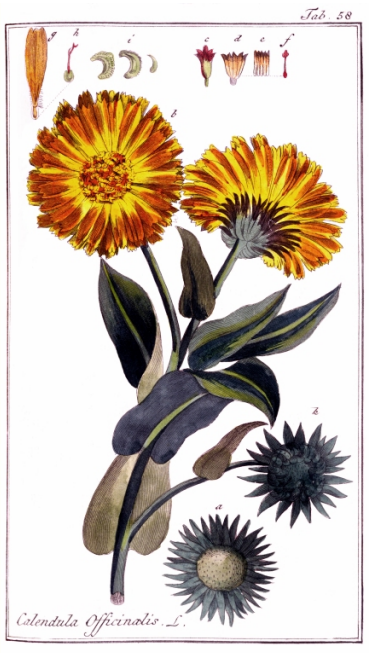
The generally accepted definition of a probiotic is 'a live microbial food supplement which beneficially affects the host animal by improving its intestinal microbial balance'. This definition is, however, rather limited as some probiotics are transient and do not take up residence in the intestinal tract. A better definition may be '[a] microbial dietary supplement that beneficially affect the host physiology by modulating mucosal and systemic immunity, as well as improving nutritional and microbial balance of the intestinal tract' (Salminen et al 1998).

The gastrointestinal tract is sterile at birth. Normal gut flora develops gradually over time and is influenced by factors such as composition of the maternal gut microflora, diet, degree of hygiene, use of antibiotics or other medication, the environment and possibly genetic aspects. Once established, a person's individual gut flora remains surprisingly constant throughout life. This is likely to be due to the fact that the gut immune system learns to recognise and tolerate those bacterial species acquired during early infancy. It is therefore very difficult to alter the composition of the gut flora after this time. Successful colonisation with probiotics is therefore most often transient, as the gastrointestinal tract has many defences that inhibit this process (Vanderhoof & Young 2002). The intestines are host to 10^{14} microbes representing 400–500 different species (Ouwehand et al 2002).

Clinical note — Prebiotics

There is another concept associated with the microflora and intestinal health: prebiotics, which are compounds that modify the environment of the gastrointesti-

nal tract to favour proliferation of the beneficial intestinal microflora (Gibson & Roberfroid 1995). Herbal and nutritional prebiotics include the fibre-supplement known as slippery elm (*Ulmus fulva*), oligofructose and inulin. The prebiotic approach, while promising, has not been thoroughly tested by controlled clinical trials.



CHEMICAL COMPONENTS

Probiotics include *Bifidobacteria* (e.g. *B. bifidum*), *Lactobacillus acidophilus*, *L. bulgaricus*, *L. casei*, *L. gassen*, *L. plantarum*, *L. reuteri*, *L. GG* (variant of *L. casei* subsp. *rhamnosus*, named after Drs Gorbach and Goldin who first isolated the strain in 1980), *Lactobacillus* strain LB, *Saccharomyces boulardii* (a yeast), *Streptococcus thermophilus* and *Streptococcus salivarius*.

FOOD SOURCES

Fermented foods of dairy or vegetable origin, such as yoghurt and sauerkraut respectively, are a source of probiotics. Of these, dairy sources such as yoghurt are most popular and may contain probiotics, especially *Lactobacillus acidophilus* and bifidobacteria strains.

DEFICIENCY SIGNS AND SYMPTOMS

Clear deficiency signs are difficult to establish because the symptoms may vary enormously. Local signs and symptoms of an imbalance of the intestinal flora (intestinal dysbiosis) include bloating, flatulence, abdominal pain, diarrhoea and/or constipation and fungal overgrowth (such as *Candida*).

Imbalance of the intestinal flora may result from the use of antibiotics, chronic diarrhoea or constipation. Additionally, babies exclusively fed on infant formulas will have slower colonisation of the gut than those who are breastfed, as breast milk allows for the transfer of oligosaccharides to the baby. This appears to be of particular concern in premature babies requiring intensive care as they acquire intestinal organisms slowly, which allows for the colonisation of bacterial species that tend to be virulent. It has been suggested that the aberrant colonisation of the premature infant's gut may contribute to the development of necrotising enterocolitis and, therefore, probiotics supplementation may be a useful approach for prevention (Dai & Walker 1999).

MAIN ACTIONS

The positive effects of probiotics are a result of several different mechanisms.

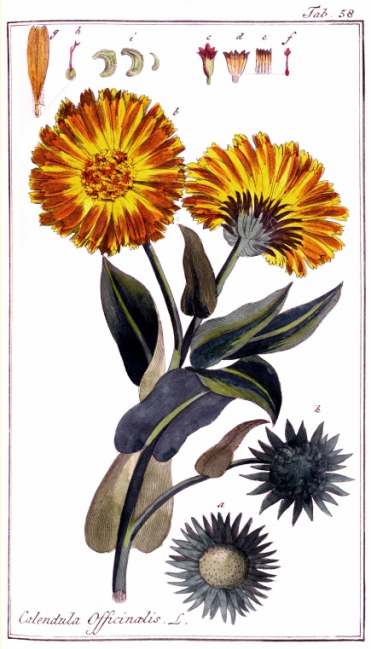
ENHANCED IMMUNE RESPONSE

Immune system modulation and the prevention of gastrointestinal tract colonisation by a variety of pathogens are perhaps the most important actions of probiotics.

Probiotics bind to intestinal epithelial cells and inhibit the binding of pathogenic bacteria to the gut wall by production of inhibitory substances such as bacteriocins, lactic acid and toxic oxygen metabolites. Of the toxic oxygen metabolites, hydrogen peroxide is of major importance as it exerts a bactericidal effect on many pathogens (Kaur et al 2002). The ability to produce bacteriocins, hydrogen peroxide and other antimicrobial compounds is strain-dependent and requires the presence of folic acid and riboflavin in the case of lactobacilli. Binding to the gut wall also initiates signalling events that result in the synthesis of cytokines (Vanderhoof & Young 2003). Studies in germ-free mice have proven that intestinal bacteria are essential for a healthy systemic immune system (Falk et al 1998).

Lactobacillus GG has been well studied in this regard and shown to modulate intestinal immunity by increasing the number of IgA and other immunoglobulin-secreting cells in the intestinal mucosal and stimulates the local release of IFNs.

***Helicobacter pylori* infection** Several in vitro studies have shown that certain probiotics inhibit or kill *H. pylori*, prevent its adhesion to mammalian epithelial cells and prevent IL-8 release. In vivo models demonstrate that pretreatment with a probiotic can prevent *H. pylori* infections and/or that administration of probiotics markedly reduces an existing infection. Clinical efficacy has also been established for the use of probiotics as prevention or treatment, according to a review of six clinical studies (Hamilton-Miller 2003).



DIGESTIVE PROCESSES

The gut bacteria carry out a number of biochemical functions, including deconjugation and dehydroylation of bile acids, the conversion of bilirubin to urobilinogen, the metabolism of cholesterol to coprostanol, production of vitamins K, B1, B2, B6, B12 and generation of short-chain fatty acids. Probiotics are involved in balancing colonic microbiota and aid in the treatment of diarrhoea associated with travel and antibiotic therapy, and control of rotavirus and *Clostridium difficile*-induced colitis.

CHEMOPREVENTATIVE EFFECTS

Antimutagenic activity against chemical mutagens and promutagens has been demonstrated for different strains of *Lactobacillus acidophilus*, *Bifidobacteria* and the organic acids usually produced by these probiotics, with live cells producing the most positive results (Lankaputhra & Shah 1998). Some probiotics also reduce faecal

enzymes implicated in cancer initiation, by producing butyric acid, which affects the turnover of enterocytes and neutralises the activity of dietary carcinogens, such as nitrosamines. Additionally, enhancing host immunity and qualitative and quantitative changes to the intestinal microflora and physicochemical conditions are important contributing factors (Hirayama and Rafter 1999).

OTHER ACTIONS

CHOLESTEROL-LOWERING ACTIVITY

This has been established in several clinical trials (see 'Clinical Use' below)

ALLERGY

High-level antigen exposure during the first few months of life is suspected of predisposing individuals to allergic sensitisation and, therefore, various atopic conditions. The intestinal microflora plays a major protective role against the development of allergy because it reduces antigen transport through the intestinal mucosa.

CLINICAL USE

It is generally agreed that a probiotic must be capable of colonising the intestinal tract to influence human health. Currently, one of the most extensively studied probiotics is *Lactobacillus GG*. Probiotic supplements are usually standardised in terms of the amount of living organisms per unit of volume and dosages range from 1 billion colonies to as high as 450 billion daily.

DIARRHOEA

Infectious diarrhoea A Cochrane review analysed results from 23 RCTs that compared a specified probiotic agent with placebo or no probiotic in people with acute diarrhoea proven or presumed to be caused by an infectious agent (Allen et al 2004). Overall, 1917 volunteers were involved, of whom 1449 were infants or children (age <18 years). The review concluded that probiotics reduced the risk of diarrhoea at 3 days and the mean duration of diarrhoea by 30.5 hours and supplementation was a useful adjunct to rehydration therapy in treating acute, infectious diarrhoea in adults and children. Several different probiotics were tested: all were lactic acid bacilli, except in two studies that tested the yeast *Saccharomyces boulardii*. With the exception of a trial of live *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, a beneficial effect in the probiotic group compared to controls was observed in all trials. Due to the variation in treatment regimens, further investigation is required to clarify which particular one is best in specific patient groups.

Travellers' diarrhoea Travellers' diarrhoea is the most common health problem in those visiting developing countries, affecting 20% to more than 50% of tourists. Although it is usually benign, travellers' diarrhoea represents a considerable socioeconomic burden for both the traveller and the host country. The most common enteropathogen is *Escherichia coli*.

Some clinical studies have found various probiotics somewhat effective against travellers' diarrhoea; however no probiotic has been able to demonstrate clinically relevant protection worldwide (Rendi-Wagner & Kollaritsch 2002).

A large, randomised, placebo-controlled double-blind study of the efficacy of *Lactobacillus GG* in preventing travellers' diarrhoea involved 820 people on holiday to Turkey to two destinations. The group was randomly assigned either *L. GG* or placebo in identical sachets. On the return flight each participant completed a questionnaire indicating the incidence of diarrhoea and related symptoms during the trip. Of the original group, 756 (92%) subjects completed the study. The overall incidence of diarrhoea was 43.8% (331 cases) and the total incidence of diarrhoea in the *L. GG* group was 41.0% compared with 46.5% in the placebo group, indicating an overall protection of 11.8%. Protection rates varied between two different destinations, with the maximum protection rate reported as 39.5% and no side-effects reported (Oksanen et al 1990).

In another placebo-controlled double-blind study, two doses (250 mg and 1000 mg) of *Saccharomyces boulardii* were administered prophylactically to 3000 Austrian travellers. A significant reduction in the incidence of diarrhoea was observed, with success depending directly on the rigorous use of the preparation. A tendency was noted for *S. boulardii* to have a regional effect, which was particularly marked in North Africa and in Turkey. The effect was dose-dependent, with participants taking the higher dose of probiotics experiencing the lowest incidence of travellers' diarrhoea (29%) and little difference observed between low-dose *S. boulardii* supplementation (34%) and placebo (39%). Treatment was considered very safe (Kollaritsch et al 1993).

AIDS-related diarrhoea Two studies have found probiotics beneficial in the treatment of AIDS-related diarrhoea. In patients given *S. boulardii* (3 g/day of the yeast) for 1 week, 10 of 18 improved compared with 1 of 11 patients given placebo. In another study, a similar protocol improved the condition of 7 of 11 patients (Elmer 2001).

Antibiotic-induced diarrhoea According to a 2002 meta-analysis, *Lactobacillus* spp. and *Saccharomyces boulardii* are superior to placebo in preventing antibiotic-associated diarrhoea. Of nine randomised, double-blind placebo-controlled trials of

probiotics, two of which involved children, four used the yeast *S. boulardii*, four used lactobacilli, one used a strain of *Enterococcus*-producing lactic acid, and three used a combination of probiotics.

In all nine trials, probiotics were given in combination with antibiotics, whereas the control groups received placebo with the antibiotic treatment. The odds ratio in favour of active treatment over placebo in preventing diarrhoea associated with antibiotics was 0.39 for *S. boulardii* and 0.34 for lactobacilli (D'Souza et al 2002).

***Clostridium difficile*-associated diarrhoea (CDAD)** *Clostridium difficile* is a common cause of diarrhoea associated with treatment with antimicrobial and/or antibiotic medication and can potentially progress to colitis, pseudomembranous colitis, toxic megacolon and death. In spite of antimicrobial therapy, recurrence is common. The *S. boulardii* strain of bacteria is being used to restore microbial balance and inhibit *C. difficile* proliferation (Elmer 2001) and has been used as an adjunct to vancomycin treatment.

A 2005 systematic review of RCTs conducted to assess the effectiveness of probiotic therapy in the prevention or treatment of *C. difficile*-associated diarrhoea (CDAD) reported that the benefit of probiotic therapy was seen in two studies and restricted to subgroups characterised by severe CDAD and increased use of vancomycin (Dendukuri et al 2005). Due to the heterogeneity in choice and dose of probiotic and in the criteria for diagnosing CDAD, synthesising further information from the eight studies was difficult, leaving the authors to conclude that better designed and larger studies are required.

UROGENITAL INFECTIONS

Probiotics are widely used to decrease the frequency of recurrent bacterial vaginosis and candidal vulvovaginitis, and have undergone clinical testing that supports this use. They are administered both orally and intravaginally. Additionally, lactobacilli play a significant role in the prevention of UTIs. One study using intravaginal administration of probiotics such as *Lactobacillus* GR-1 and B-54 or RC-14 strains twice weekly for 2 weeks and then monthly for 2 months demonstrated that treatment resulted in 45% less UTIs than placebo and improved the maintenance of normal flora (Reid & Burton 2002). A significant reduction in UTI rate was also reported in a randomised double-blind study involving 55 premenopausal women (Reid 2001b). The study investigated the effectiveness of treatment for 1 year with a weekly suppository containing either 0.5 g *L. rhamnosus* GR-1 and *L. fermentum* B-54 or a *Lactobacillus* growth factor. Treatment resulted in the UTI rate decreasing by 73% and 79%, respectively, with no adverse effects reported.

The mechanisms by which *Lactobacillus* spp. reduce bacterial vaginosis and UTIs appear to involve anti-adhesion factors, byproducts such as hydrogen peroxide and bacteriocins lethal to pathogens, and perhaps immune modulation or signalling effects. Bifidobacteria in particular are considered well suited to this activity and have, therefore, been investigated for their effects in the treatment of female genitourinary infections (Korshunov et al 1999).

Oral supplementation Several studies have confirmed that lactobacilli administered orally can survive the gastrointestinal tract and colonise the genitourinary tract, thus enhancing the normal vaginal lactobaccilli.

In a study of 10 women whose vaginal bacterial flora was abnormal and who had suffered repeated bacterial vaginosis, yeast infections and/or UTIs, a regimen was prescribed of ingesting 10^9 viable *Lactobacillus* GR-1 and RC-14 bacteria each day. In a majority of patients with symptoms of suprapubic and micturition pain, frequency, dysuria and urgency, or vaginal irritation, the symptoms disappeared within 1–2 weeks and all the patients remained healthy for several months following treatment (Reid 2001a).

A randomised study of 42 healthy women compared treatment with either *L. rhamnosus* GR-1 plus *L. fermentum* RC-14 or *L. rhamnosus GG* alone. On assessment, the vaginal flora was normal in 40% of cases and 14 patients had asymptomatic bacterial vaginosis. Oral treatment with 10^8 viable *L. rhamnosus* GR-1 and *L. fermentum* RC-14 once and twice daily re-established a healthy vaginal flora in up to 90% of patients, and 7 of 11 patients with bacterial vaginosis converted to normal or intermediate scores within 1 month. Treatment with *L. rhamnosus GG* failed to have an effect (Reid et al 2001). Another study by Reid and Bruce (2001) suggests that oral administration of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 can result in vaginal colonisation even more quickly: within 7 days. Their study also found that colonisation can be maintained for up to 10 weeks after treatment cessation in some individuals.

Similar results were obtained in a randomised placebo-controlled study of 64 healthy women testing oral administration of *L. rhamnosus* GR-1 and *L. fermentum* RC-14, which found that the probiotics can restore asymptomatic bacterial vaginosis microflora to normal lactobacilli colonised microflora and reduce pathogenic bacteria. Significant results were obtained after 60 days' treatment with no adverse effects reported (Reid et al 2003).

Probiotic-enriched dairy products A small randomised study of 46 participants showed that ingestion of 150 mL *L. acidophilus*-enriched yoghurt was associated with an increased prevalence of colonisation of the rectum and vagina by the bacteria

and may have contributed to reduced episodes of bacterial vaginosis (Dorren 2002). Another crossover study of 33 women with recurrent vaginitis found that daily ingestion of 240 mg yoghurt containing *L. acidophilus* for 1 year decreased both candidal colonisation and infection (Hilton et al 1992).

IRRITABLE BOWEL SYNDROME

People suffering from IBS sometimes experience symptoms of abdominal cramping and either diarrhoea or constipation or a combination of both. Although the aetiology of IBS is still unknown, there is growing suspicion that there is a persistent, mild inflammatory state with changes in mucosal function or structure and an associated imbalance of intestinal flora (Camilleri 2006). This imbalance can lead to inefficient metabolism of nutrients and the formation of gas and short-chain fatty acids, both of which induce propulsive contractions and accelerate colonic transit or enhance fluid and sodium absorption in the colon. As such, clinical trials have been conducted to clarify the role of probiotics in this condition, so far producing promising results.

In a 4-week, double-blind placebo-controlled trial, 60 people with IBS were treated with *L. plantarum* or placebo. The patients recorded their own gastrointestinal function, starting 2 weeks before the study and continuing throughout the study period. Twelve months after the end of the study, all patients were asked to complete a questionnaire. The study showed significant reductions in intestinal flatulence in the treatment group compared with placebo. At the 12-month follow-up, patients in the test group maintained a better overall gastrointestinal function than control patients (Nobaek et al 2000).

In another study, 40 patients were randomly assigned either *L. plantarum* 299V in liquid suspension or placebo over a period of 4 weeks. All patients treated with the probiotic reported resolution of their abdominal pain as compared with 11 patients from the placebo group. There was also a trend towards normalisation of stool frequency in constipation for 6 of 10 patients treated with the probiotic compared with 2 of 11 treated with placebo. With regard to all IBS symptoms, an improvement was noted in 95% of patients in the active group compared with 15% of patients in the placebo group ($P < 0.0001$) (Niedzielin et al 2001).

INFLAMMATORY BOWEL DISEASES

Probiotics are also being used as adjunctive therapy for Crohn's disease and inflammatory bowel disease (Goh & O'Morain 2003, Guslandi 2003a, 2003b, Jonkers & Stockbrugger 2003, Kanauchi et al 2003, Karthik 2003, Marteau et al 2003, Rutgeerts 2003).

Pouchitis Pouchitis is the most common long-term complication of ileal pouch–anal anastomosis in patients with underlying ulcerative colitis. Clinical symptoms of pouchitis are not specific, and they can be caused by other conditions such as rectal cuff inflammation and irritable pouch syndrome. Therefore, to make an accurate diagnosis, endoscopic evaluation, together with symptom assessment, is necessary. Although antibacterial therapy can induce and maintain remission, probiotics can also be used to maintain clinical remission and prevent relapse in patients with relapsing or chronic pouchitis (Kailasapathy & Chin 2000). According to one review, there is now strong evidence to support the therapeutic use of probiotics in postoperative pouchitis (Penner et al 2005).

HELICOBACTER PYLORI INFECTION

A review (Hamilton-Miller 1997) of 13 clinical trials of probiotics and *H. pylori* infection summarises the results as follows.

- In six trials involving a total of 180 patients, sole treatment with probiotics produced positive results in five studies. In three trials, there were significantly reduced breath-test readings and in two others some patients were cleared of infection.
- In seven further trials of 682 patients, probiotics were added to a therapeutic regimen of antibiotics, resulting in an increased cure rate in two studies, and reduced side-effects in four. Trials in which fermented milk products or whole cultures of lactobacilli were used tended to show better results than when the probiotic was taken in the form of bacteria alone.

It must be noted that not all the studies were randomised, double-blind and placebo-controlled, and some involved only small numbers of patients. However, the positive results obtained suggest that probiotics may have a place as adjunctive treatment in *H. pylori* infections and possibly in prophylaxis.

ATOPIC DERMATITIS AND ECZEMA

Probiotics have the potential to moderate inflammatory and immune responses and strengthen the intestinal barrier function, three actions that are useful in addressing the underlying pathophysiological processes involved in atopic dermatitis (AD) and eczema (Rosenfeldt et al 2004). The use of probiotic therapy to prevent allergic disease has been demonstrated in studies using *L. rhamnosus GG* in neonates, whereas studies in infants and children with established AD have found that probiotics reduce the severity of the condition (Furrie 2005, Weston et al 2005).

Prevention of allergy A randomised, double-blind placebo-controlled study showed that perinatal administration of probiotics (*L. rhamnosus GG*) reduced the

development of atopic eczema in children by 50% during the first 2 years of life. Some 159 mothers were randomly allocated to receive 2 capsules of placebo or 10^{10} viable *L. rhamnosus GG* daily for 4 weeks before expected delivery. After delivery, capsules were taken for 6 months. During lactation either the mother or the infant consumed the preparations. In a 4-year follow-up study, it was revealed that the preventive effect of the probiotic on atopic eczema extended beyond infancy (Kalliomaki et al 2003).

Treatment of established allergy A randomised, double-blind study of 56 young children (aged 6–18 months) with moderate or severe atopic AD found that treatment with *L. fermentum* VRI-033 PCC (1×10^9; Probiomics) twice daily produced a significant reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index (Weston et al 2005). At week 16, 92% of children receiving probiotics had a SCORAD index that was significantly better than baseline compared with the placebo group ($n = 17$, 63%) ($P = 0.01$). Another randomised double-blind study has found that supplementation of infant formulas with viable but not heat-inactivated *L. GG* may have benefits for the management of atopic eczema and cow's milk allergy (Kirjavainen et al 2003).

According to two other placebo-controlled studies, it appears that people with greater allergic responses may be better suited to treatment and experience superior effects. Rosenfeldt et al found that treatment with two *Lactobacillus* strains (lyophilised *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460) given in combination for 6 weeks to children aged 1–13 years with AD resulted in 56% experiencing improvement (Rosenfeldt et al 2003). Interestingly, the total SCORAD score did not change significantly. Allergic patients with a positive skin prick test response and increased IgE levels experienced a more pronounced response to treatment. Similarly, a study by Sistek et al (2006) found that a combination of two probiotics (*Lactobacillus rhamnosus* and *Bifidobacteria lactis*) given to children with established AD effectively reduced the SCORAD index among the food-sensitised children, but not in other children (Sistek et al 2006). Children in this study received 2×10^{10} colony-forming units/g of probiotic or placebo daily as a powder mixed with food or water.

HIGH CHOLESTEROL

Probiotics modestly reduce cholesterol levels in healthy subjects and may have stronger effects in people with hyperlipidaemia.

A meta-analysis of six studies of a probiotic dairy product containing *Enterococcus faecium* found that the fermented yoghurt product produced a 4% decrease in total cholesterol and a 5% decrease in LDL-cholesterol (Agerholm-Larsen et al 2000).

In another study, 32 subjects with serum total cholesterol ranging from 5.7 to 7.25 mg/dL were randomly assigned to two treatments: (1) intake of a low-fat drinking yoghurt prepared with two ordinary yoghurt starters (*Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *Bulgaricus*: placebo group); and (2) intake of a low-fat drinking yoghurt prepared with the two yoghurt starters plus *Bifidobacterium longum* strain BL1 (probiotic group). After intake for 4 weeks at 3×100 mL/day, reduction of serum total cholesterol was observed in approximately half of the probiotic group subjects; a particularly significant decrease in serum total cholesterol was found among subjects with moderate hypercholesterolaemia (serum total cholesterol > 6.2 mg/dL). The serum lipid concentrations in the placebo group subjects were almost stable during the experimental periods (Xiao et al 2003).

A crossover study of 29 healthy women, aged 19–56 years, found that the long-term daily consumption of 300 g of two different types of yoghurt over a period of 21 weeks increased the serum concentration of HDL-cholesterol and led to the desired improvement of the LDL:HDL-cholesterol ratio. The normal yoghurt contained 3.5% fat and starter cultures of *S. thermophilus* and *L. lactis*, whereas the probiotic yoghurt was enriched with *L. acidophilus* 145, *B. longum* 913 and 1% oligofructose. The mean serum concentration of total cholesterol and the LDL-cholesterol was not influenced by the normal yoghurt ($P > 0.05$). However, both the normal and the probiotic yoghurt increased the HDL concentration significantly, by 0.3 mmol/L ($P = 0.002$) and decreased the LDL:HDL ratio from 3.24 to 2.48 ($P = 0.001$) (Kiessling et al 2002).

A recent controlled, randomised double-blind study of 36 heavy smokers found that 400 mL/day of a rose hip drink containing *L. plantarum* 299v (5×10^7 colony-forming units/mL) led to a reduction in cardiovascular disease risk factors. Significant decreases in SBP, leptin, and fibrinogen ($P < 0.001$) were recorded in the experimental group. No such changes were observed in the control group. Decreases in F(2)-isoprostanes (markers of oxidative stress) (37%) and IL-6 (42%) were also noted in the experimental group in comparison with baseline. Monocytes isolated from subjects treated with *L. plantarum* showed significantly reduced adhesion ($P < 0.001$) to endothelial cells (Naruszewicz et al 2002).

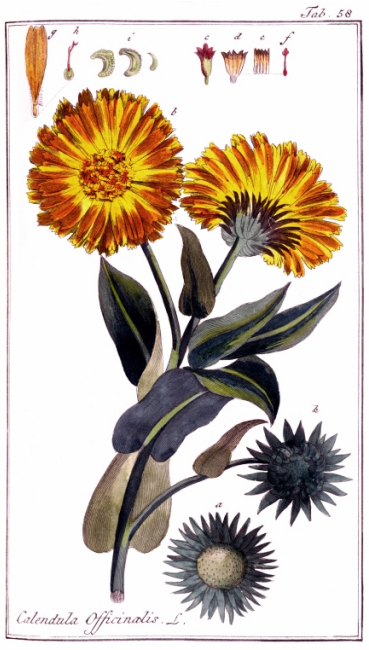
OTHER USES

FOOD ALLERGIES

High-level antigen exposure during the first few months of life is suspected of predisposing individuals to allergic sensitisation and, therefore, various atopic conditions such as skin reactions and even systemic or respiratory manifestations.

Intestinal inflammation seems to be a predisposing factor in increased sensitisation of a subject (Holt 1994), which in turn promotes further inflammation when antigen exposure occurs.

Considering that the gut microflora is an important factor in regulating both the intestinal and systemic immune system, probiotics are used to promote endogenous barrier mechanisms, reduce gut permeability and alleviate intestinal inflammation in patients with atopic dermatitis and food allergy (Majamaa & Isolauri 1997). A 1-month study of 10 breastfed infants who had atopic eczema and cow's milk allergy found that *L. GG* reduced certain faecal inflammatory markers.



Clinical note — The hygiene hypothesis

The intestinal tract is the largest immune organ of the body. It produces more antibodies than any other part of the body and contains 80% of all antibody-producing cells. The intestinal mucosa functions as a barrier against infections, but it also provides communication between the different mucosal surfaces of the body (Ouwehand et al 2002).

At birth, the gastrointestinal tract is sterile. Normal gut flora develops gradually over time and is influenced by factors such as composition of the maternal gut microflora, diet, degree of hygiene, use of antibiotics or other medication, the environment and possibly genetic aspects. Studies in germ-free mice have shown that without these bacteria, the systemic immune system will not function normally (Vanderhoof & Young 2002).

In the absence of microbes, a mammal develops fewer Peyer's patches (part of the gut-associated lymphoid tissue) and less than 10% of the number of IgA-producing B cells compared with normal. However, on exposure to a normal microflora, previously germ-free animals develop their immune system very much like other animals. This indicates that the intestinal microflora is instrumental in the proper development of the immune system (Ouwehand et al 2002) and has led to the emergence of the 'hygiene theory of immune disorders'.

More specifically, the hygiene hypothesis suggests that improved hygienic conditions and vaccinations, which reduce early-life exposure to microbes, are associated with a heightened risk of allergic disease and other immune disorders. This is because reduced exposure may result in reduced stimulation of the immune system. As a result, lymphocytes that would normally differentiate to become Th1 type, differentiate to Th2-type cells and produce inflammatory cytokines in the allergic response in much greater quantities. As such, very early stimulation of the immune system is important in dampening the Th2 dominance and reducing the development of IgE-mediated food reactions as well as other allergic reactions. In a

closely observed cohort of 329 Finnish children it was shown that the earlier an acute respiratory infection occurred, the greater the protective effect was against atopic eczema (Vanderhoof & Young 2003).

The obvious solution for increasing microbial exposure without increasing the health risk is the use of prebiotics and probiotics. Supplementation with probiotics has been shown to both reduce the risk and treat the symptoms of childhood eczema (see later).

Modulating the intestinal microflora with probiotics and prebiotics (fibre) may be an effective and safe therapy for the natural development of a balanced immune defence in infants and children. In adults and the elderly, prebiotics and probiotics may be used to improve the general functioning of the immune system.

IMMUNE STIMULATION

In a 12-week, double-blind, placebo-controlled, three-stage before-and-after intervention trial of 25 healthy elderly individuals, one-half were given milk containing a specific strain of *Bifidobacterium lactis* HN019, while the other half were given milk alone. Dietary consumption of the probiotic enhanced immune function of two different types of leucocytes; the degree of enhancement was increased by consuming *B. lactis* in an oligosaccharide-rich substrate (Chiang et al 2000).

In another 7-month, double-blind placebo-controlled study of 571 children in daycare centres in Finland, milk fortified with *L. GG* reduced the number and severity of respiratory infections. The effects of the probiotic were modest but consistent (Hatakka et al 2001).

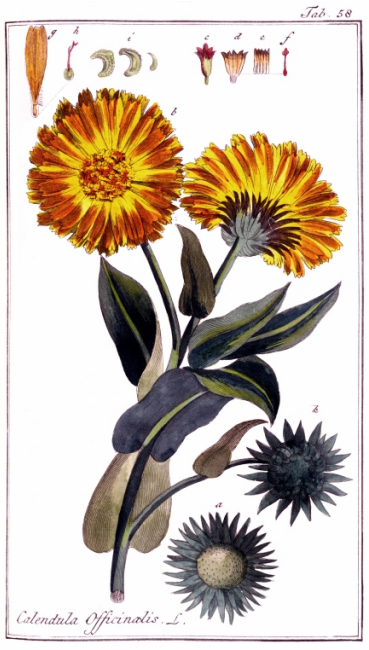
A 9-week, three-stage, pre- and post-intervention trial with 52 healthy middle-aged and elderly volunteers found that dietary consumption of *L. rhamnosus* HN001, in a base of low-fat milk or lactose-hydrolysed low-fat milk, enhanced systemic cellular immune responses. The phagocytic activity of peripheral blood polymorphonuclear leucocytes and in vitro tumouricidal activity of NK leucocytes increased by 19% and 15%, respectively. The relative level of NK-cell tumour killing activity increased by 71% and 147% (Sheih et al 2001).

DOSAGE RANGE

- As more information is gathered from probiotic research, it is becoming evident that certain strains or combination of strains are suitable for different conditions. Different strains of probiotics are chosen and combined to produce specific products for diarrhoea in children, antibiotic-induced diarrhoea, travellers' diarrhoea, inflammatory bowel diseases etc.

- Probiotic doses are usually standardised in terms of the amount of living bacteria per unit of volume. A quality product may contain between 1×10^9 and 1×10^{11} colony-forming units/g; however, the dose required to achieve therapeutic effects varies between strains. If a product contains multiple strains then each strain should be present at levels of 10^9 to be effective. The viable bacteria are mixed in a suitable matrix, which may contain maltodextrin, amylase and prebiotics such as fructo-oligosaccharides and inulin.
- Supplements are best taken with meals to enhance bacterial survival.
- Diarrhoea: generally *Saccharomyces boulardii* and sometimes lactobacilli.
- Atopic dermatitis: generally lactobacilli, sometimes together with bifidobacteria.
- Cholesterol-lowering: lactobacilli are used.
- Urinary tract infection: lactobacilli are used.
- Vaginal candidiasis: lactobacilli are used.

* A serving of yoghurt containing less than 10^8 viable bacteria is unlikely to have any therapeutic activity beyond acting as a nutritional source.



Clinical note — Dosages tailored to increase probiotic survival

Several attempts have been made to ensure the survival of the probiotics through the acid environment of the stomach and exposure to bile acid. Microencapsulating the probiotics is one method that has been used (Kailasapathy 2002). Enteric-coated tablets containing probiotics that are gastric-acid resistant have also been produced (Stadler & Viernstein 2003). More studies, however, are needed to examine the efficacy of these administration forms to deliver and release the probiotic at the appropriate target sites in the gastrointestinal tract. Studies are also needed to establish if such measures are actually necessary. With a suitable matrix, a probiotic powder may survive the passage through the digestive tract without either microencapsulation or enteric-coating of tablets.

ADVERSE REACTIONS

There have only been two documented adverse reactions. In a 74-year-old diabetic patient with hypertension, and in a 67-year-old patient with endocarditis undergoing tooth extraction, *L. rhamnosus* preparations caused adverse reaction. The causality was not established (Sanders 2003) and details are scant.

SIGNIFICANT INTERACTIONS

No adverse drug interactions have been reported.

ANTIBIOTICS

Concomitant administration of probiotics (lactobacilli and *Saccharomyces boulardii*) reduces gastrointestinal and genitourinary side effects according to clinical studies — combination can be safely used together and a beneficial interaction is likely.

CONTRAINDICATIONS AND PRECAUTIONS

Specific strains of probiotics are appropriated for different disorders. Certain strains are suitable for children.

Probiotics are contraindicated in those people who are hypersensitive to any component of the probiotics-containing product.

PREGNANCY USE

Likely to be safe in pregnancy; however, use of concentrated forms should be supervised by a healthcare professional.

PRACTICE POINTS/PATIENT COUNSELLING

- There is good clinical evidence that probiotics may be beneficial in the treatment of infant diarrhoea, travellers' diarrhoea, acute diarrhoea, antibiotic-induced diarrhoea, urogenital infections, irritable bowel syndrome, inflammatory bowel diseases, *H. pylori* infections, food intolerances and allergies, leaky gut and eczema.
- There is also some evidence that probiotics are essential for both the development and maintenance of a healthy immune system.
- There is some evidence that probiotics have a modest effect improving the LDL:HDL-cholesterol ratio.
- Probiotics can be administered orally or intravaginally. They can also be taken as yoghurt or other cultured dairy products. It should be noted that only products containing actual probiotic strains will be beneficial. The so-called starter cultures do not necessarily have the same beneficial effects.
- Although probiotics may improve the long-term bowel flora, probiotic supplementation has other benefits not associated with direct colonisation of the gastrointestinal tract.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What can probiotics do for me?

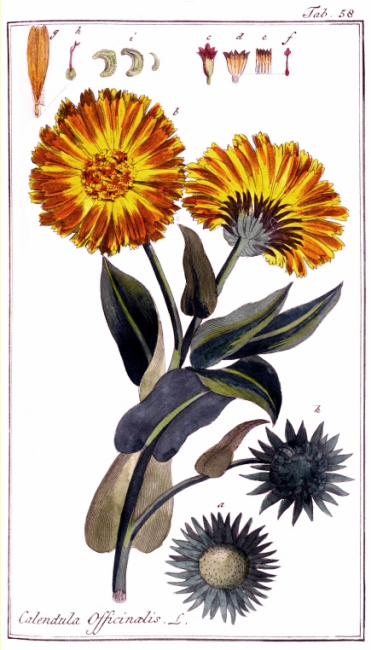
Probiotics are beneficial in the treatment of digestive disorders such as diarrhoea and inflammatory bowel diseases and other conditions not directly connected with the digestive tract. Clinical studies have found probiotics to be beneficial in the treatment of antibiotic-induced and travellers' diarrhoea, for vaginal thrush and recurrent cystitis, irritable bowel syndrome, colitis, food allergies and eczema.

When will they start to work?

Probiotics can start to exert beneficial effects in digestive disorders within a few days. Long-term benefits are seen after weeks to months of continuous use. Greater results may be obtained if the so-called prebiotics are also added to the diet. Prebiotics refer to the use of compounds that modify the environment of the gastrointestinal tract to favour proliferation of the intestinal microflora. Herbal and nutritional prebiotics include the fibre known as slippery elm (*Ulmus fulva*), oligofructose and inulin.

Are there any safety issues?

Many species of probiotics are integral to the production of fermented foods and have been consumed safely as part of the daily diet for millennia. Other probiotics used as supplements are actually normal, non-pathogenic inhabitants of the human intestinal tract. There have been no reports of probiotics interacting with prescription medication.



REFERENCES

Agerholm-Larsen L et al. The effect of a probiotic milk product on plasma cholesterol: a meta-analysis of short-term intervention studies. Eur J Clin Nutr 54.11 (2000): 856-60.

Allen SJ et al. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev 2 (2004): CD003048.

Camilleri M. Probiotics and irritable bowel syndrome: rationale, putative mechanisms, and evidence of clinical efficacy. J Clin Gastroenterol 40.3 (2006): 264-9.

Chiang BL et al. Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium (Bifidobacterium lactis HN019): optimization and definition of cellular immune responses. Eur J Clin Nutr 54.11 (2000): 849-55.

D'Souza AL et al. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ 324.7350 (2002): 1361.

Dai D, Walker WA. Protective nutrients and bacterial colonization in the immature human gut. Adv Pediatr 46 (1999): 353-82.

Dendukuri N et al. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. Can Med Assoc J 173.2 (2005): 167-70.

Elmer GW. Probiotics: living drugs. Am J Health Syst Pharm 58.12 (2001): 1101-9.

Falk PG et al. Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology. Microbiol Mol Biol Rev 62.4 (1998): 1157-70.

Furrie E. Probiotics and allergy. Proc Nutr Soc 64.4 (2005): 465-9.

Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 125.6 (1995): 1401-12.

Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 17.3 (2003): 307-20.

Guslandi M. Of germs in inflammatory bowel disease and of how to fight them. J Gastroenterol Hepatol 18.1 (2003a): 115-16.

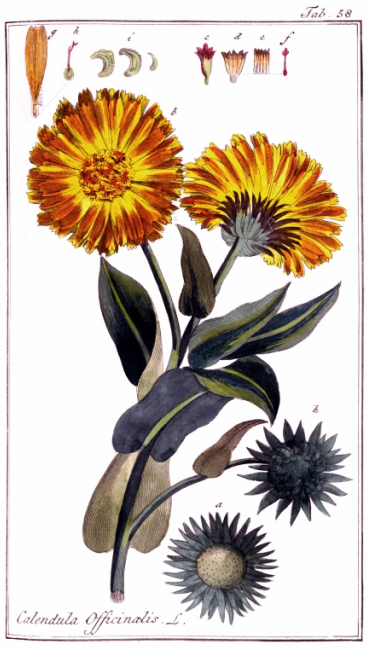
Guslandi M. Probiotics for chronic intestinal disorders. Am J Gastroenterol 98.3 (2003b): 520-1.

Hamilton-Miller JM. Living in the 'post-antibiotic era': could the use of probiotics be an effective strategy? Clin Microbiol Infect 3.1 (1997): 2-3.

Hamilton-Miller JM. The role of probiotics in the treatment and prevention of Helicobacter pylori infection. Int J Antimicrob Agents 22.4 (2003): 360-6.

Hatakka K et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ 322.7298 (2001): 1327.

Hilton E et al. Ingestion of yogurt containing Lactobacillus acidophilus as prophylaxis for candidal vaginitis. Ann Intern Med 116.5 (1992): 353-7.
Hirayama K, Rafter J. The role of lactic acid bacteria in colon cancer prevention: mechanistic considerations. Antonie Van Leeuwenhoek 76.1-4 (1999): 391-4.
Holt P. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. Lancet 344.8920 (1994): 456-8.
Jonkers D, Stockbrugger R. Probiotics and inflammatory bowel disease. J R Soc Med 96.4 (2003): 167-71.
Kailasapathy K., Microencapsulation of probiotic bacteria: technology and potential applications. Curr Issues Intest Microbiol 3.2 (2002): 39-48.
Kailasapathy K, Chin J. Survival and therapeutic potential of probiotic organisms with reference to Lactobacillus acidophilus and Bifidobacterium spp. Immunol Cell Biol 78.1 (2000): 80-8.
Kalliomaki M et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 361.9372 (2003): 1869-71.
Kanauchi O et al. Modification of intestinal flora in the treatment of inflammatory bowel disease. Curr Pharm Des 9.4 (2003): 333-46.
Karthik SV. Probiotics in inflammatory bowel disease. J R Soc Med 96.7 (2003): 370.
Kaur IP, Chopra K, Saini A. Probiotics: potential pharmaceutical applications. Eur J Pharm Sci 15.1 (2002): 1-9.
Kiessling G, Schneider J, Jahreis G. Long-term consumption of fermented dairy products over 6 months increases HDL cholesterol. Eur J Clin Nutr 56.9 (2002): 843-9.
Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. J Pediatr Gastroenterol Nutr 36.2 (2003): 223-7.
Kollaritsch H et al. [Prevention of traveler's diarrhea with Saccharomyces boulardii: Results of a placebo controlled double-blind study]. Fortschr Med 111.9 (1993): 152-6.
Korshunov VM et al. The vaginal Bifidobacterium flora in women of reproductive age. Zh Mikrobiol Epidemiol Immunobiol 4 (1999): 74-8.
Lankaputhra WE, Shah NP. Antimutagenic properties of probiotic bacteria and of organic acids. Mutat Res 397.2 (1998): 169-82.
Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. J Allergy Clin Immunol 99.2 (1997): 179-85.
Marteau P, Seksik P, Shanahan F. Manipulation of the bacterial flora in inflammatory bowel disease. Best Pract Res Clin Gastroenterol 17.1 (2003): 47-61.
McFarland LV et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA 271.24 (1994): 1913-18.
Naruszewicz M et al. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. Am J Clin Nutr 76.6 (2002): 1249-55.
Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 13.10 (2001): 1143-7.
Nobaek S et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 95.5 (2000): 1231-8.
Oksanen PJ et al. Prevention of travellers' diarrhoea by Lactobacillus GG. Ann Med 22.1 (1990): 53-6.
Ouwehand A, Isolauri E, Salminen S. The role of the intestinal microflora for the development of the immune system in early childhood. Eur J Nutr 41 (Suppl 1) (2002): 132-7.
Penner R, Fedorak RN, Madsen KL. Probiotics and nutraceuticals: non-medicinal treatments of gastrointestinal diseases. Curr Opin Pharmacol 5.6 (2005): 596-603.
Reid G. Could probiotics be an option for treating and preventing urogenital infections? Medscape Gen Med 3.4, 2001a
Reid G. Probiotic agents to protect the urogenital tract against infection. Am J Clin Nutr 73.2 (Suppl) (2001b): 437-43S.



Reid G, Bruce AW. Selection of lactobacillus strains for urogenital probiotic applications. J Infect Dis 183 (Suppl 1) (2001): S77-80.
Reid G, Burton J. Use of Lactobacillus to prevent infection by pathogenic bacteria. Microbes Infect 4.3 (2002): 319-24.
Reid G et al. Probiotic Lactobacillus dose required to restore and maintain a normal vaginal flora. FEMS Immunol Med Microbiol 32.1 (2001): 37-41.
Reid G et al. Oral use of Lactobacillus rhamnosus GR-1 and L. fermentum RC-14 significantly alters vaginal flora: randomized, placebo-controlled trial in 64 healthy women. FEMS Immunol Med Microbiol 35.2 (2003): 131-4.
Rendi-Wagner P, Kollaritsch H. Drug prophylaxis for travelers' diarrhea. Clin Infect Dis 34.5 (2002): 628-33.
Rosenfeldt V et al. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. J Allergy Clin Immunol 111.2 (2003): 389-95.
Rosenfeldt V et al. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. J Pediatr 145.5 (2004): 612-16.
Rutgeerts P. Modern therapy for inflammatory bowel disease. Scand J Gastroenterol Suppl 237 (2003): 30-3.
Salminen S et al. Demonstration of safety of probiotics: a review. Int J Food Microbiol 44.1-2 (1998): 93-106.
Sanders ME. Probiotics: considerations for human health. Nutr Rev 61.3 (2003): 91-9.
Sheih YH et al. Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium Lactobacillus rhamnosus HN001. J Am Coll Nutr 20.2 (Suppl) (2001): 149-56.
Sistek D et al. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? Clin Exp Allergy 36.5 (2006): 629-33.
Stadler M, Viernstein H. Optimization of a formulation containing viable lactic acid bacteria. Int J Pharm 256.1-2 (2003): 117-22.
Vanderhoof JA, Young RJ. Probiotics in pediatrics. Pediatrics 109.5 (2002): 956-8.
Vanderhoof JA, Young RJ. Role of probiotics in the management of patients with food allergy. Ann Allergy Asthma Immunol 90.6 (Suppl 3) (2003): 99-103.
Weston S et al. Effects of probiotics on atopic dermatitis: a randomised controlled trial. Arch Dis Child 90.9 (2005): 892-7.
Xiao JZ et al. Effects of milk products fermented by Bifidobacterium longum on blood lipids in rats and healthy adult male volunteers. J Dairy Sci 86.7 (2003): 2452-61.

Psyllium

Historical note Psyllium has a long history of use in both conventional and traditional medical systems and has been listed in various pharmacopoeias around the world.

OTHER NAMES

Psyllium, plantain or ispaghula.

White or blond psyllium, also known as Indian plantago or isphaghula, is produced from the seeds of *Plantago ovata*.

Black, French or Spanish psyllium comes from *P. psyllium* (syn. *P. afra*) and *P. arenaria* (*P. indica*).

Plantago mucilage refers to psyllium husk (isphaghula, *P. ovata*).

BOTANICAL NAME/FAMILY

Plantago ovata, *P. psyllium*, *P. arenaria* (family Plantago)

PLANT PART USED

Seed coat

CHEMICAL COMPONENTS

Plantago ovata has the highest amount of seed coat.

Constituents of the seed husk include 10–30% mucilage (arabinoxylans), iridoid glycosides (≈0.14% aucubin), trace monoterpene alkaloids, sugars, protein, sterols, triterpenes, fatty acids and tannins.

MAIN ACTIONS

BULKING AGENT

The husk is a water-soluble fibre that forms a mucilaginous gel on contact with aqueous fluids and is degraded by human intestinal flora.

PROMOTES SATIETY

A placebo-controlled study of a *P. ovata* preparation administered in water found a significant difference in satiety 1 hour after consumption (Turnbull & Thomas 1995). Increased satiety was apparent up to 6 hours after consumption.

LIPID-LOWERING

Two main theories have been proposed to explain the lipid-lowering effect of psyllium. First, psyllium sequesters bile salts during passage through the intestinal

lumen and second, it physically disrupts the intraluminal formation of micelles, thereby reducing the absorption of cholesterol and re-absorption of bile salts. In both cases, bound bile acids are moved to the terminal ileum and colon, thereby interrupting the enterohepatic circulation so that more cholesterol is converted into newly produced bile acids. Reduced cholesterol biosynthesis results in upregulation of LDL receptors and enhanced uptake of LDL-cholesterol. Overall, the combined effects result in decreased serum LDL-cholesterol and total cholesterol (Rodriguez-Moran et al 1998).

SLOWS GLUCOSE ABSORPTION

Psyllium supplementation delays gastric emptying and small-bowel motility and reduces intestinal mixing, thereby slowing and reducing glucose absorption.

CLINICAL USE

Psyllium is used mainly for its mucilage content, which comes from the seed coat.

BULKING AGENT

Psyllium is commonly used as a bulking agent to treat constipation or diarrhoea and to regulate stool consistency in people with a colostomy or ileostomy. As a bowel regulator, psyllium husk absorbs water in the colon to increase faecal bulk, which stimulates peristaltic activity. Alternatively, the antidiarrhoeal effect is promoted when taken with minimal fluids but can give rise to abdominal discomfort.

Commission E approves the use of black psyllium seed and blond psyllium seed for chronic constipation and when a soft stool is desirable, such as in patients with haemorrhoids, anal fissures or post-rectal surgery (Blumenthal et al 2000).

WEIGHT LOSS AID

Psyllium is used to increase the subjective feeling of satiety before and between meals in an attempt to reduce total caloric intake. One study comparing *Plantago ovata* preparation (20 g granules with 200 mL water) to water or a placebo preparation found a significant difference in fullness 1 hour after consumption (Turnbull & Thomas 1995). Other studies have confirmed a suppressant effect on hunger and increased satiety that remains apparent up to 6 hours after consumption. Psyllium also significantly delays gastric emptying from the third hour after a meal (Bergmann et al 1992, Delargy et al 1997).

HYPERLIPIDAEMIA

Psyllium is also used as a cholesterol-lowering agent, usually as an adjunct to a low-fat diet (Reid et al 2002). Soluble fibres, such as psyllium husk, increase the cholesterol-lowering effect of a low-fat diet in people with elevated cholesterol

(Anderson et al 2000). A meta-analysis of eight studies evaluating the cholesterol-lowering effects of psyllium (10.2 g/day) as an adjunct to a low-fat diet for at least 8 weeks found it lowered serum total cholesterol by 4%, LDL-cholesterol by 7% and the ratio of apolipoprotein (apo) B to apo A-I by 6% relative to placebo. It has also been used with some success in the paediatric population and is easy to incorporate into various foods (Davidson et al 1996).

DIABETES

Fibre products such as psyllium have been used as an aid to metabolic control in patients with diabetes (Pittler & Ernst 2004, Sierra et al 2002). Epidemiological and clinical data suggests a role for both soluble and insoluble fibre products in the management of hyperglycaemia. It appears that soluble fibre has a dose-dependent effect on serum glucose levels and the insulin response to a meal, improves glycaemic control in type 2 diabetes and can reduce the amount of medication required (Pastors et al 1991). One clinical study using 14 g/day of psyllium (Plantaben, ALTANA Pharma, Mexico) showed a significant 12.2% reduction in glucose absorption, as well as a significant reduction in total cholesterol and LDL-cholesterol and also uric acid (Sierra et al 2002). Another study identified that a higher dose (20 g/day in divided doses) may produce better results and significantly lowers both basal and postprandial hyperglycaemia (Frati-Munari et al 1989).

IRRITABLE BOWEL SYNDROME

In recent years, high-fibre diets and fibre supplements have been commonly recommended in primary- and secondary- care management of IBS. This has been particularly the case for people with IBS characterised by constipation. However, a systematic review of the role of different types of fibre in IBS concluded that insoluble fibre can exacerbate IBS symptoms and that although soluble fibre can benefit patients with constipation, it does not have a significant effect on abdominal pain (Bijkerk et al 2004).

Black and blond psyllium seed is approved for use by Commission E in IBS and recommended when a soft stool is desired (Blumenthal et al 2000).

OTHER USES

In the confectionery industry, it is used as a thickening agent in ice cream and frozen desserts.

DOSAGE RANGE

GENERAL RECOMMENDATIONS

- Blond psyllium seed: 12–40 g of whole seeds or equivalent taken in divided doses daily.
- Black psyllium seed: 10–30 g of whole or ground seeds or equivalent taken in divided doses daily.

  Seeds should be presoaked in 100–150 mL of warm water for several hours before ingestion. Each dose should be followed by another full glass of water.
- Powdered blond psyllium seed husk: 4–5 g taken up to four times daily. Stir desired dose into 150 mL of water and drink immediately. Follow each dose with ½–1 glass of water.

ACCORDING TO CLINICAL STUDIES

- Weight loss: *Plantago ovata* preparation (20 g granules with 200 mL water)
- Hyperlipidaemia: 10.2 g daily
- Diabetes: 14–20 g daily (in divided doses)

SIGNIFICANT INTERACTIONS

CALCIUM

Animal studies suggest that soluble fibre from sources of purified psyllium negatively impact calcium balance by decreasing the bioavailability of calcium from the diet (Luccia & Kunkel 2002) — psyllium and other soluble fibre supplements should be taken at least 1 hour before or after calcium.

IRON

Soluble fibre may decrease the bioavailability of iron (EMEA 2003) — take psyllium at least 1 hour before or after iron.

ZINC

Soluble fibre may decrease the bioavailability of zinc (EMEA 2003) — take psyllium at least 1 hour before or after zinc.

LITHIUM

Soluble fibre may decrease the bioavailability of lithium (EMEA 2003) — take psyllium at least 1 hour before or after lithium.

COUMARIN DERIVATIVES

Soluble fibre may decrease the bioavailability of coumarin derivatives (EMEA 2003) — take psyllium at least 1 hour before or after coumarin derivatives.

VITAMIN B12
Soluble fibre may decrease the bioavailability of vitamin B12 (EMEA 2003) — take psyllium at least 1 hour before or after vitamin B12.

CARDIAC GLYCOSIDES
Soluble fibre may decrease the bioavailability of cardiac glycosides (EMEA 2003) — take psyllium at least 1 hour before or after cardiac glycosides.

HYPOGLYCAEMIC AGENTS
Additive hypoglycaemic effects are theoretically possible — drug dose may need modification and the outcome can be favourable under professional supervision.

ADVERSE REACTIONS
Allergy is possible, although rare and is characterised by tightness in the chest, wheezing and urticaria. Psyllium should not be consumed dry as it may cause oesophageal obstruction. In practice, it is not unusual for people to experience flatulence, bloating and mild abdominal discomfort when they start to use psyllium; however, these symptoms can reduce with long-term use.

CONTRAINDICATIONS AND PRECAUTIONS
Although psyllium is considered a safe substance, it should not be used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

According to Commission E, blond psyllium seed is contraindicated if there is difficulty regulating diabetes mellitus.

PREGNANCY USE
May be used during pregnancy and lactation.

PRACTICE POINTS/PATIENT COUNSELLING
- Psyllium seed husk is a water-soluble fibre that forms a mucilaginous gel on contact with aqueous fluids and is degraded by human intestinal flora.
- It is most commonly used to treat constipation or diarrhoea and to regulate stool consistency.
- It is also used to promote satiety and weight loss, and as an aid to metabolic control in diabetes and hyperlipidaemia when combined with a low-fat diet.
- The seeds should be presoaked in warm water for several hours before ingestion and each dose should be followed by a full glass of water. Ingesting it dry may cause oesophageal obstruction.
- Although generally safe, it should not be used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Psyllium is a bulking agent that can regulate stool consistency, increase satiety, improve metabolic control in diabetes and reduce cholesterol when combined with a low-fat diet.

When will it start to work?

As a bulking agent, it will start to have an effect within several hours. It will improve satiety within 30–60 minutes and has a mild cholesterol lowering effect after 8 weeks of use.

Are there any safety issues?

Although generally safe, it should not be ingested dry or used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

REFERENCES

Anderson JW et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. Am J Clin Nutr 71 (2000): 472-9.

Bergmann JF et al. Correlation between echographic gastric emptying and appetite: influence of psyllium. Gut 33 (1992): 1042-3.

Bijkerk CJ et al. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 19 (2004): 245-51.

Blumenthal M et al (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Davidson MH et al. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. Am J Clin Nutr 63 (1996): 96-102.

Delargy HJ et al. Effects of amount and type of dietary fibre (soluble and insoluble) on short-term control of appetite. Int J Food Sci Nutr 48 (1997): 67-77.

EMEA (European agency for the evaluation of medicinal products). London UK: EMEA, 1995-2006. Available at: www.emea.eu.int (accessed 03-03).

Frati-Munari AC et al. [Effect of different doses of Plantago psyllium mucilage on the glucose tolerance test]. Arch Invest Med (Mex) 20 (1989): 147-52.

Luccia BHD, Kunkel ME. Psyllium reduces relative calcium bioavailability and induces negative changes in bone composition in weanling Wistar rats. Nutr Res 22 (2002): 1027-40.

Pastors JG et al. Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes. Am J Clin Nutr 53 (1991): 1431-5.

Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. Am J Clin Nutr 79 (2004): 529-36.

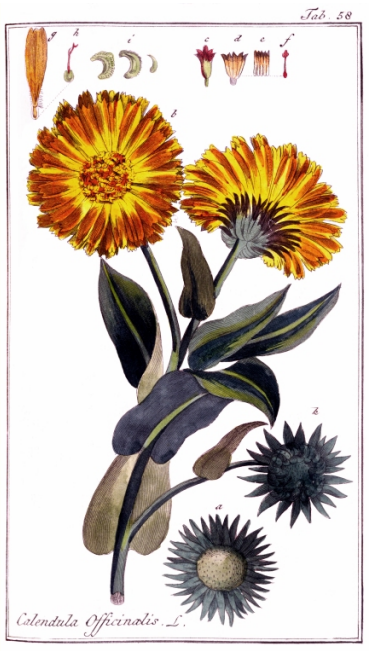
Reid R et al. Dietary counselling for dyslipidemia in primary care: results of a randomized trial. Can J Diet Pract Res 63 (2002): 169-75.

Rodriguez-Moran M et al. Lipid- and glucose-lowering efficacy of plantago psyllium in type II diabetes. J Diabetes Complications 12 (1998): 273-8.

Sierra M et al. Therapeutic effects of psyllium in type 2 diabetic patients. Eur J Clin Nutr 56 (2002): 830-42.

Turnbull WH, Thomas HG. The effect of a Plantago ovata seed containing preparation on appetite variables, nutrient and energy intake. Int J Obes Relat Metab Disord 19 (1995): 338-42.

Pygeum



Historical note *Pygeum africanum* is a large, evergreen tree native to Africa. Its bark has been used medicinally for thousands of years by traditional African healers to treat bladder disorders, kidney disease, prostate disorders, and malaria, as well as male baldness and to enhance sexual functioning. Since the late 1960s, the extract has been used in clinical practice in Europe; however, because of over-harvesting, the plant is now considered an endangered species and efforts are underway to protect it.

COMMON NAME
Pygeum

OTHER NAMES
African plum tree, African prune tree, alumty, iluo, kirah, natal tree, Pigenil, Pronitol, Provol, Tadenan

BOTANICAL NAME/FAMILY
Prunus africana (Hook. f.) KalRm (family Rosaceae)

PLANT PART USED
Bark

Clinical note — Popular to the point of extinction?
For the past 35 years, pygeum has been used in Europe for the treatment of BPH and other disorders. The bark is entirely wild-collected, mainly from Cameroon, Madagascar, Equatorial Guinea and Kenya, and exported principally to Europe for production into commercial medicinal extracts (Stewart 2003). Since 1995, it has been considered an endangered species so attempts at cultivation are underway to protect the plant from extinction. Prior to 1966 when it was discovered to have significant medicinal effects, *Prunus africana* was a relatively common, but never abundant species. The reasons for its demise include economic, social, and ecological factors. Currently, wild-crafting is no longer commercially viable in Cameroon and harvest has ceased in both Uganda and Kenya.

CHEMICAL COMPONENTS
Phytosterols (beta-sitosterol, beta-sitostenone), pentacyclic triterpenes (oleanolic and ursolic acids), and ferulic esters (*n*-docosanol and *n*-tetracosanol) (Stewart 2003).

MAIN ACTIONS

Pygeum has demonstrated several different pharmacological effects according to in vitro and in vivo data; however, these are not well defined.

HORMONAL EFFECTS

In vivo studies have shown that orally administered pygeum extract has a significant effect on dihydrotestosterone (DHT)-induced prostatic enlargement (Choo et al 2000, Yoshimura et al 2003). Pretreatment with pygeum extract counteracted the effect of DHT-induced prostate enlargement (Choo et al 2000), and the more recent study found that oral administration of pygeum extract suppressed the effects of DHT on micturition (Yoshimura et al 2003) and effectively suppressed prostatic growth when co-administered with DHT; however, it did not reverse established prostatic growth when administered after DHT.

Phytoestrogens found in pygeum can exert either an oestrogenic or anti-oestrogenic effect depending on the dose, according to other in vivo tests (Mathe et al 1995) and may also contribute to its effects in the prostate.

ANTI-INFLAMMATORY

Phytosterols (beta-sitosterol, beta-sitostenone) reportedly inhibit the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms associated with BPH and chronic prostatitis. The pentacyclic triterpenes (oleanolic and ursolic acids) are believed to inhibit the activity of glucosyl-transferase, an enzyme involved in the inflammation process (Stewart 2003).

Studies with pygeum extract confirm that it decreases production of leukotrienes and other 5-lipoxygenase metabolites (Cristoni et al 2000).

BLADDER EFFECTS

Pygeum protects the bladder from contractile dysfunction induced by ischaemia and reperfusion according to in vivo studies. Studies with rabbit models have shown that pretreatment can prevent the bladder from developing contractile and biochemical dysfunctions induced by partial outlet obstruction, possibly by protecting the bladder from ischaemic injury (Levin et al 2005). It has also been shown that treatment can reverse these dysfunctions when started 2 weeks post obstruction. Past studies have used very high doses to achieve these results; however, the recent study using a clinically relevant dose found treatment was still effective (Levin et al 2005).

INHIBITION OF FIBROBLAST PROLIFERATION

Pygeum is a potent inhibitor of prostatic fibroblast proliferation, as demonstrated in an animal model (Yablonsky et al 1997). As a result, it has been suggested that part

of the herb's therapeutic effect may be due to the inhibition of growth factors responsible for prostatic overgrowth.

OTHER ACTIONS

Ferulic esters (*n*-docosanol and *n*-tetracosanol) reportedly lower blood levels of cholesterol, from which testosterone is produced (Stewart 2003).

CLINICAL USE

The most commonly studied product is Tadenan (Laboratoires DEBAT, Garches, France), which is a lipophilic extract standardised to contain 12–13% total sterols.

BENIGN PROSTATIC HYPERTROPHY

A Cochrane systematic review analysed the results of 18 clinical trials that involved a total of 1562 participants (Wilt et al 2002). Seventeen studies were double-blinded and the mean treatment duration was 61 ± 21 days (range 30–122 days). Most studies used a standardised extract of *P. africanum* in doses ranging from 75 to 200 mg/day.

Twelve of the 13 placebo-controlled studies reported a beneficial effect on at least one parameter (overall symptoms, nocturia, peak urine flow, or residual volume), whereas one study found no significant effects. The overall summary effect size indicated a large and statistically significant improvement with *P. africanum*. More specifically, active treatment increased peak urine flow by 23%, reduced residual urine volume by 24% and physicians were twice as likely to report their patients were experiencing an overall improvement in symptoms when pygeum was being used. The authors report that these findings are similar to other widely used treatment options and that treatment was well tolerated.

It is believed that the phytosterols, pentacyclic triterpenes and ferulic esters found within the extract work synergistically to counteract the structural and biochemical changes associated with BPH.

OTHER USES

FERTILITY DISORDERS

Pygeum extract was used experimentally in the treatment of 22 men with reduced fertility and diminished prostatic secretion and proved to have a beneficial effect (Lucchetta et al 1984). Treatment was administered daily over 2 months and was most effective in men who did not have prostatitis.

DOSAGE RANGE

ACCORDING TO CLINICAL STUDIES

- BPH: 50–100 mg twice daily of extract standardised to 12–13% total sterols

ADVERSE REACTIONS
Pygeum is well tolerated with side-effects similar to placebo (Wilt et al 2002). Mild gastrointestinal discomfort has been reported.

SIGNIFICANT INTERACTIONS
None known.

CONTRAINDICATIONS AND PRECAUTIONS
People with known allergies should avoid use.

PREGNANCY USE
Safety not scientifically established; however, it is not used for any indication that would cause a pregnant woman to use it.

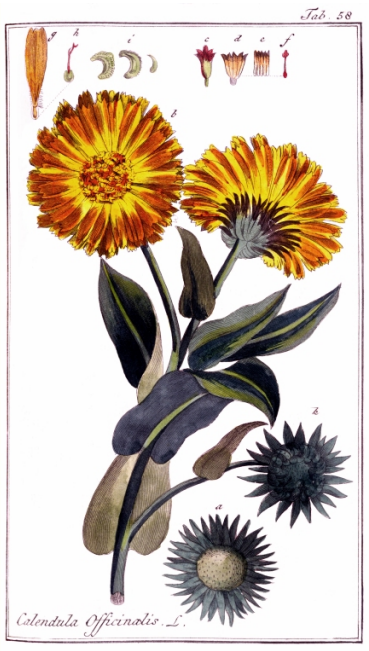
PRACTICE POINTS/PATIENT COUNSELLING
- Pygeum is a popular treatment in Europe for benign prostatic hypertrophy.
- A systematic review of 18 clinical studies found it has significant effects in BPH such as increasing peak urine, reducing residual urine volume and producing an overall improvement in symptoms.
- Several different mechanisms of action have been identified using animal models which would explain its effectiveness in BPH.
- According to clinical studies the dose used is 50–100 mg twice daily of standardised extract for BPH and the treatment is well tolerated.
- Over-harvesting has meant the tree is now considered endangered and efforts are being made to protect it from extinction.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Standardised pygeum extract is an effective treatment in benign prostate enlargement or inflammation and improves several symptoms.
When will it start to work?
Some men will notice an improvement in symptoms after 4 weeks; however, others will require longer term treatment.
Are there any safety issues?
It is a well tolerated treatment but should not be used by people with a known allergy to the plant. If symptoms worsen, seek professional advice.

REFERENCES
Choo MS et al. Functional evaluation of Tadenan on micturition and experimental prostate growth induced with exogenous dihydrotestosterone. Urology 55 (2000): 292-8.
Cristoni A et al. Botanical derivatives for the prostate. Fitoterapia 71 (Suppl 1) (2000): S21-8.

Levin RM et al. Low-dose tadenan protects the rabbit bladder from bilateral ischemia/ reperfusion-induced contractile dysfunction. Phytomedicine 12 (2005): 17-24.
Lucchetta G et al. Reactivation of the secretion from the prostatic gland in cases of reduced fertility. Biological study of seminal fluid modifications. Urol Int 39 (1984): 222-4.
Mathe G et al. The so-called phyto-estrogenic action of Pygeum africanum extract. Biomed Pharmacother 49 (1995): 339-40.
Stewart KM. The African cherry (Prunus africana): Can lessons be learned from an over-exploited medicinal tree? J Ethnopharmacol 89 (2003): 3-13.
Wilt T et al. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst Rev CD001044, 2002.
Yablonsky F et al. Antiproliferative effect of Pygeum africanum extract on rat prostatic fibroblasts. J Urol 157 (1997): 2381-7.
Yoshimura Y et al. Effect of Pygeum africanum tadenan on micturition and prostate growth of the rat secondary to coadministered treatment and post-treatment with dihydrotestosterone. Urology 61 (2003): 474-8.

Quercetin



BACKGROUND AND RELEVANT PHARMACOKINETICS

Quercetin is a flavonol belonging to a group of polyphenolic substances known as flavonoids or bioflavonoids. The first flavonoids were identified in 1936 by Albert Szent-Györgyi, who was awarded the Nobel Prize for his discovery of vitamin C (Challem 1998).

Studies on the absorption, bioavailability, and metabolism of quercetin after oral intake in humans have produced contradictory results (Graefe et al 1999). The nature of quercetin metabolites in plasma is currently unclear and requires further elucidation (Day & Williamson 2001), which may in part explain these inconsistencies.

There appears to be marked individual variation in absorption rates ranging from 0% to over 50% (Erlund 2004, Graefe et al 1999). Factors that may improve bioavailability include: gender (especially females taking oral contraceptives), gastrointestinal flora (Erlund 2004), and concurrent intake of bromelain and papain (Shoskes et al 1999). Absorption from onions is three times that of apples (Hollman et al 1997) and twice that of black tea (deVries et al 1998).

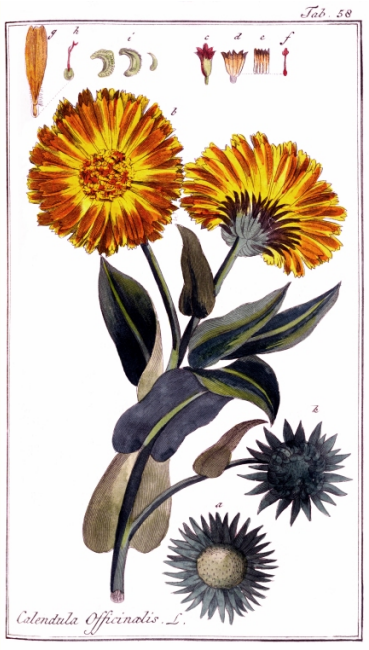
The main determinant for the absorption of quercetin conjugates is the nature of the sugar moiety. Glucose-bound glycosides (quercertin glucosides) are effectively absorbed from the small intestine because the cells possess glucoside-hydrolysing activity and their glucose transport system is capable of participating in glucoside absorption, whereas quercetin glycosides are subject to deglycosidation by enterobacteria before absorption in the large intestine (Murota & Terao 2003).

After absorption, quercetin is transported to the liver via the portal circulation, where it undergoes significant first pass metabolism. Peak plasma levels of quercetin occur from 0.7 to 9 hours following ingestion, and the elimination half-life of quercetin is approximately 23–28 hours (Hollman et al 1997, PDRHealth 2005). Due to its long half-life, repeated consumption of quercetin-containing foods should cause accumulation of quercetin in the body. Excretion is likely to be via the biliary system (Erlund 2004).

CHEMICAL COMPONENTS

Quercetin, also known as meletin and sophretin, is known chemically as 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one and 3,3′,4′5,7-penthydroxyflavone. It is typically found in plants as a glycone or carbohydrate conjugate, but does not in itself possess a carbohydrate moiety in its structure.

Quercetin glycone conjugates include rutin (quercetin-3-rutinoside) and quercitrin (thujin, quercetin-3-L-rhamnoside, or 3-rhamnosylquercetin) (Erlund et al 2000, PDRHealth).



FOOD SOURCES

Apples, berries (blackcurrants, lingonberries and bilberries), beans, black tea, green tea, onions, red wine.

Herbal medicines such as St John's wort, *Ginkgo biloba*, *Vaccinium macrocarpon* (cranberry) and *Oenothera biennis* (evening primrose) also contain quercetin and this may help to explain some of their therapeutic benefits.

MAIN ACTIONS

ANTIOXIDANT

Quercetin is a phenolic antioxidant and has been shown to inhibit lipid peroxidation, protecting the lens of the eye (Cornish et al 2002) and renal tubular epithelial cells from oxidant-induced injury (Pietruck et al 2003). The antioxidant activity may be the result of free radical scavenging, metal chelation, enzyme inhibition or the induction of protective enzymes (Erlund 2004).

Quercetin treatment for short periods exerts an antioxidant effect whereas long-term treatment may produce an increase in oxidant activity due to a reduction in glutathione (GSH) levels (Ferraresi et al 2005). In the absence of GSH, potentially harmful oxidation products such as orthoquinone may be produced when quercetin exerts its antioxidant activity. Therefore, adequate GSH levels should be maintained when quercetin is supplemented (Boots et al 2003).

ANTI-INFLAMMATORY

In animal and in vitro studies quercetin inhibits inflammation by modulating neutrophil function, prostanoid synthesis, cytokine production, and iNOS expression via the inhibition of the NF-kappa-B pathway (Busse et al 1984, Comalada et al 2005, Morikawa et al 2003).

ANTIVIRAL

Quercetin causes a dose-dependent reduction in the infectivity and intracellular replication of HSV-1, polio-virus type 1, parainfluenza virus type 3 and respiratory syncytial virus in vitro (Kaul et al 1985); however, pretreatment with quercetin does not appear to provide any additional benefit. Animal studies have also suggested that the antioxidant effects of quercetin may protect the lungs from the deleterious effects of oxygen-derived free radicals released during influenza infection (Kumar et al 2005).

IMMUNOMODULATION

Results from animal and in vitro studies have produced contradictory results suggesting both an induction and inhibition of Th1 cytokines (Muthian & Bright 2004, Nair et al 2002).

According to in vitro data quercetin induces Th1-derived cytokines (promoting cellular immunity) and inhibits Th2-derived cytokines, which exert negative effects on cellular immunity (Nair et al 2002). An excess of Th2 cytokines has also been implicated in allergic tendencies, which provides a theoretical basis for the use of quercetin as an anti-allergic substance. Conversely animal studies have demonstrated that quercetin is able to inhibit Th1 differentiation and signalling of IL-12 (Muthian & Bright 2004). As this occurred in the presence of a Th1 cell-mediated inflammatory demyelinating autoimmune disease model of multiple sclerosis suggestive of Th1 excess, a possibility exists that quercetin actually exerts an immunomodulatory effect on these cells. Further trials are required to elucidate the exact effects of quercetin under different conditions.

ANTI-ALLERGY

Quercetin is structurally similar to the anti-allergic drug disodium cromoglycate (cromolyn). In vitro and animal studies demonstrate that quercetin stabilises mast cells, neutrophils and basophils inhibiting antigen- as well as mitogen-induced histamine release (Blackburn et al 1987, Busse et al 1984, Middleton & Drzewiecki 1982, Middleton et al 1981, Ogasawara et al 1996, Pearce et al 1984). Inhibition of inflammatory enzymes, prostaglandins and leukotrienes, and modulation of Th2 excess may further contribute to the anti-allergic effects. Pretreatment with quercetin does not appear to produce any additional benefits.

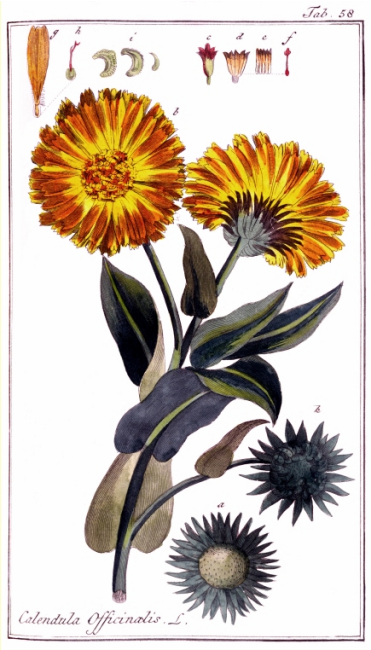
ANTIHYPERTENSIVE

Chronic treatment with quercetin lowers blood pressure and restores endothelial dysfunction in animal models of hypertension (Garcia-Saura et al 2005, Sanchez et al 2006).

CARDIOPROTECTIVE

During inflammation, circulating conjugates of quercetin pass through the endothelium to reach vascular smooth muscle cells where they exert their biological effects and are then deconjugated (Mochizuki et al 2004).

The cardioprotective effects of quercetin may be related to its vasorelaxant (Ke Chen & Pace-Asciak 1996, Roghani et al 2004), anti-inflammatory and antioxidant properties and inhibition of vascular smooth muscle cell proliferation and migration (Alcocer et al 2002, Moon et al 2003) as demonstrated in animal and in vitro models.



Animal experiments indicate that doses of quercetin equivalent to 1–2 glasses of red wine exerts a cardioprotective effect following ischaemia–reperfusion by improving the function of mitochondria, which play a critical role in myocardial recovery (Brookes et al 2002) and may also prevent the development of atherosclerosis through several indirect mechanisms (Auger et al 2005). In humans quercetin inhibits platelet aggregation and signalling and thrombus formation at doses of 150 mg or 300 mg quercetin-4′-O-beta-D-glucoside (Hubbard et al 2004). This effect, however, may not occur with clinically relevant doses.

NEUROPROTECTIVE

Quercetin protects neuronal cells from oxidative stress-induced neurotoxicity (Heo & Lee 2004) and inflammatory-related neuronal injury (Chen et al 2005).

GASTROPROTECTIVE

It has been suggested that the gastroprotective effect of quercetin in animal models may be due to its antiperoxidative, antioxidant and antihistaminic effects, resulting in a significant reduction in the number of mast cells and size of gastric erosions (Kahraman et al 2003).

HEPATOPROTECTIVE

In vitro and animal studies have demonstrated the hepatoprotective effects of quercetin. It protects the liver from oxidative damage and may reduce biliary obstruction (Alia et al 2006, Peres et al 2000). Pretreatment of rats with quercetin (10 mg/kg) reduced the mortality rate from paracetamol (1 g/kg) from 100% to 30% and prevented liver damage at sublethal doses (640 mg/kg) (Janbaz et al 2004).

CHEMOPROTECTIVE

In the 1970s quercetin was considered to be carcinogenic after demonstrating mutagenicity in the Ames test; however subsequent long-term studies have refuted this and demonstrated an anticarcinogenic effect in laboratory animals (Erlund 2004).

In vitro and preliminary animal and human data indicate that quercetin inhibits tumour growth and induces apoptosis. The anticarcinogenic effects may be due to its antioxidant properties, protection against DNA damage, inhibition of angiogenesis, effects on gene expression, effects on cell cycle regulation, phyto-oestrogen-like activity, interaction with type II oestrogen binding sites and tyrosine kinase inhibition (Duraj et al 2005, Erlund 2004, Igura et al 2001, Lamson & Brignall 2000, Lee et al 2003, 2006, Tan et al 2003, van der Woude et al 2005, Wilms et al 2005).

ALDOSE REDUCTASE INHIBITION

Quercetin has been shown to inhibit human lens aldose reductase by 50% in vitro (Chaudhry et al 1983) and may be responsible for the reduction in cataract formation observed in diabetic rats receiving either dietary or topical quercetin (Beyer-Mears & Farnsworth 1979).

PREVENTING BONE LOSS

Quercetin is claimed to play an important role in preventing bone loss by affecting osteoclastogenesis and regulating many systemic and local factors, including hormones and cytokines (Son et al 2006), providing a theoretical basis for its use in the prevention of postmenopausal bone loss. In vitro studies demonstrate that bone resorption is mediated by oestrogen-receptor proteins through the inhibition of RANK protein or the activation of caspases (Rassi et al 2005, Wattel et al 2003). However, in vitro studies also suggest that quercetin inhibits the metabolism of not only osteoclasts (bone-resorption cells), but also osteoblasts (bone-forming cells) and therefore further research is required to elucidate whether quercetin increases or decreases bone mass in vivo (Notoya et al 2004).

OTHER ACTIONS

Possible modulation of P-glycoprotein (Choi & Li 2005, Hsiu et al 2002, Limtrakul et al 2005) and inhibition of CYP1A1 (Schwarz et al 2005), CYP1A2 (Chang et al 2005) and CYP 3A4 (Choi & Li 2005) activity have been reported.

CLINICAL USE

ALLERGIES

Quercetin is used in the treatment of acute and chronic allergic symptoms, such as hayfever and chronic rhinitis. The anti-inflammatory activity of quercetin and its ability to stabilise mast cells, neutrophils and basophils and inhibit histamine release (Blackburn et al 1987, Busse et al 1984, Middleton & Drzewiecki 1982, Middleton et al 1981, Ogasawara et al 1996, Pearce et al 1984) provides a rationale for its use in these indications.

In a study of 123 patients sensitised to house dust mite and displaying nasal symptoms of mild to severe perennial allergic rhinitis (Otsuka et al 1995), nasal scrapings were taken and histamine release measured as a percentage of the total content in the specimen. Antigen exposure resulted in an increase in mast cells of the epithelial layer of the nasal mucosa resulting in nasal hypersensitivity. Quercetin inhibited histamine release by 46–96% in a dose-dependent manner.

Large-scale human trials are required to fully elucidate the potential for quercetin to inhibit allergic symptoms caused by the release of histamine.

ASTHMA

Quercetin has also been used as an adjunct in the management of asthma, often in combination with vitamin C because of its anti-allergic activity and ability to inhibit leukotriene synthesis (Formica & Regelson 1995). Controlled studies are still required to determine its effectiveness.

PREVENTING DIABETIC COMPLICATIONS

As quercetin has been shown to inhibit aldose reductase, the first enzyme in the polyol pathway, a theoretical basis exists for its use in the prevention of long-term diabetic complications such as cataracts, nephropathy, retinopathy and neuropathy (Chaudhry et al 1983). Quercetin may also provide beneficial effects in people with diabetes by decreasing oxidative stress and preserving pancreatic beta-cell integrity (Coskun et al 2005).

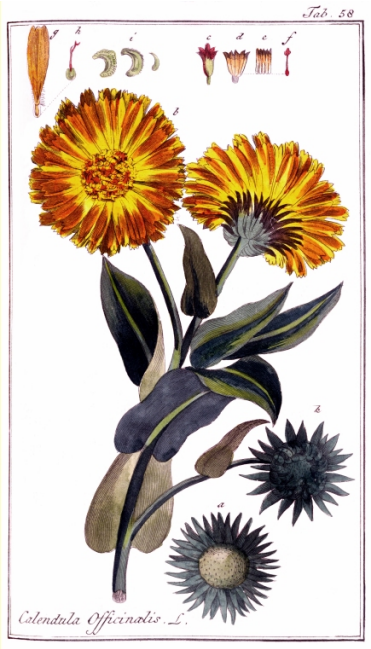
Preliminary evidence suggests a possible antinociceptive activity of quercetin, probably through modulation of opioidergic mechanism, suggesting a potential for the treatment of diabetic neuropathic pain (Anjaneyulu & Chopra 2003). Topical application of quercetin in combination with ascorbyl palmitate and vitamin D3 has been tested in a randomised, placebo-controlled, double-blind trial of 34 men and women (age 21–71 years) with diabetic neuropathy. The QR-333 preparation or placebo was applied three times daily for 4 weeks to each foot experiencing symptoms. QR-333 was well tolerated and reduced the severity of numbness, jolting pain, and irritation from baseline values and improved QOL scores (Valensi et al 2005).

The diabetic status of rats fed high-dose quercetin (1 g/kg) was found to be ameliorated by approximately 25%; however, the amounts used were considerably higher than those commonly used in humans (Shetty et al 2004). Intraperitoneal injection of quercetin has also demonstrated an ability to improve glucose tolerance, and cholesterol and triglyceride levels in diabetic, but not normoglycaemic, rats and increase the number of pancreatic islets in both groups (Vessal et al 2003). However, these results cannot necessarily be applied to oral doses in humans and further research is required to confirm any potential benefits.

CATARACTS

In addition to the potential reduction in diabetic cataract formation afforded by the inhibition of aldose reductase (Chaudhry et al 1983), quercetin may also reduce oxidative stress associated with the initiation of maturity onset cataracts.

Cataracts may result from oxidative damage to the lens, which causes a disruption of the redox system, membrane damage, proteolysis, protein aggregation and a loss



of lens transparency. Quercetin has been shown to inhibit oxidative damage to the lens and maintain lens transparency in vitro (Cornish et al 2002, Sanderson et al 1999). Further trials are warranted to confirm the effects of oral doses in humans.

PREVENTING CARDIOVASCULAR DISEASE

The cardioprotective properties of quercetin, demonstrated in animal and in vitro studies, provide a theoretical basis for the use of quercetin in the prevention of cardiovascular disease; however, current human data is less encouraging.

A double-blind, placebo-controlled study investigating the effects of a quercetin-containing supplement on plasma quercetin status, risk factors for heart disease and serum/platelet fatty acid levels was conducted on 27 healthy men and women with cholesterol levels of 4.0–7.2 mmol/L (Conquer et al 1998). The subjects consumed a quercetin-containing supplement (1 g quercetin/day) or rice flour placebo for 28 days. Quercetin intakes were approximately 50-fold greater than dietary intakes previously associated with lower coronary heart disease mortality in epidemiologic studies. Plasma quercetin concentrations were approximately 23-fold greater in subjects consuming the quercetin capsules than in the placebo group. Quercetin supplementation did not alter serum total, LDL- or HDL-cholesterol or triglyceride levels, or other cardiovascular disease or thrombogenic risk factors such as platelet thromboxane B2 production, blood pressure or resting heart rate. This is in contrast to a previous trial (Hubbard et al 2004), which demonstrated inhibition of platelet aggregation and signalling and thrombus formation at doses of 150 mg or 300 mg quercetin-4′-O-beta-D-glucoside, were not reproduced using the dose and form in this study. There was also no effect on the levels of omega-3 or omega-6 polyunsaturated fatty acids in serum or platelet phospholipids (Conquer et al 1998). Further investigation with larger and longer term trials is required to determine the effects and safety of quercetin in the prevention of cardiovascular disease in humans.

CHRONIC PROSTATITIS

Thirty men with category IIIa or IIIb chronic pelvic pain syndrome received either placebo or quercetin 500 mg twice daily for 1 month. Sixty seven percent of the treated subjects had at least a 25% improvement in symptoms, compared to 20% of the placebo group. In a follow-up, unblinded, open-label study, 17 additional men received the same dose of quercetin (combined with bromelain and papain to enhance absorption) for 1 month. The combination increased the response rate from 67% to 82% (Shoskes et al 1999). The anti-inflammatory, antioxidant and immunomodulating activities of quercetin may help to explain these results.

CANCER

Early concerns that quercetin may be carcinogenic have not been supported by recent research. Quercetin is primarily found in fruit and vegetables, which have been shown to decrease the risk of certain human cancers when consumed regularly (Morrow et al 2001), thereby casting doubt on this proposition. In fact, the anticarcinogenic effects of quercetin seen in laboratory animals suggest a possible preventative role (Erlund 2004), and in vitro and epidemiological studies have suggested potential benefits in the prevention of colon (Kim et al 2005, Park et al 2005), lung (Schwarz et al 2005), prostate (Yuan et al 2004) and breast cancer (Otake et al 2000).

Human studies using extremely low dose supplementation of quercetin (30 mg/day) have so far provided more questions than answers about the exact mechanism/s by which quercetin may exert its effects but much remains unknown (Morrow et al 2001).

OTHER USES

Although the potential benefits of quercetin in allergic conditions have yet to be elucidated by human trials, quercetin is often used to treat conditions such as hayfever and other respiratory allergies and histamine-related conditions. In practice, quercetin is also commonly used to stabilise the integrity of blood vessel walls and address conditions resulting from capillary fragility and used in conjunction with vitamin C for the treatment of viral infections.

DOSAGE RANGE

GENERAL DOSE RANGE

- 200–1500 mg daily taken in divided doses (PDRHealth 2005, Spoerke & Rouse 2004)

SPECIFIC DOSES

- Chronic prostatitis: 500 mg (combined with bromelain and papain to enhance absorption) twice daily (Shoskes et al 1999)
- Acute allergies: 2 g every 2 hours for 2 days (often used with vitamin C)
- Chronic allergies: 2 g daily
- Asthma: as an adjunct to standard treatment 2 g daily

ADVERSE REACTIONS

Quercetin is generally well tolerated and appears to be associated with little toxicity when administered orally or intravenously (Lamson and Brignall 2000). Adverse effects may include nausea, dyspnoea, headache and mild tingling of the extremities (PDRHealth 2005, Spoerke & Rouse 2004).

SIGNIFICANT INTERACTIONS

Possible modulation of P-glycoprotein (Choi & Li 2005, Hsiu et al 2002, Limtrakul et al 2005) and inhibition of CYP1A1 (Schwarz et al 2005), CYP1A2 (Chang et al 2005) and CYP 3A4 (Choi & Li 2005) activity should be considered when prescribing.

CISPLATIN

Quercetin pretreatment may sensitise human cervix carcinoma cells to cisplatin-induced apoptosis (Jakubowicz-Gil et al 2005) — beneficial interaction theoretically possible under professional supervision.

CYCLOSPORIN

Animal studies demonstrate that coadministration of quercetin significantly decreases the oral bioavailability of cyclosporin (Hsiu et al 2002) — avoid concurrent use.

DIGOXIN

An increase in drug bioavailability is theoretically possible and has been observed in an in vivo study. Although human studies at lower doses are not available, the narrow therapeutic range of digoxin and the serious nature of the interaction should not be underestimated. Avoid concurrent use.

DILTIAZEM

Pretreatment of rabbits with quercetin resulted in an increased bioavailability of the calcium channel blocker, diltiazem, which may be the result of inhibition of P-glycoprotein and CYP 3A4 (Choi & Li 2005). Caution — use under professional supervision; doses may need to be adjusted accordingly

HALOPERIDOL

Tardive dyskinesia (rhythmical involuntary movements of the tongue, face, mouth or jaw e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements) may result from long-term therapy with the antipsychotic medication haloperidol and may be irreversible in some individuals with no known effective treatment. Oxidative stress and the products of lipid peroxidation have been implicated in the pathophysiology of tardive dyskinesia and co-administration of quercetin (25–100 mg/kg) has been shown to dose-dependently reduce haloperidol-induced vacuous chewing movements and tongue protrusions in animal models (Naidu et al 2003). Beneficial interaction theoretically possible under professional supervision.

PACLITAXEL
Pretreatment with quercetin may increase the bioavailability of paclitaxel according to animal studies (Choi et al 2004). Caution — use under professional supervision; doses may need to be adjusted accordingly.

PARACETAMOL
According to animal data, pretreatment with quercetin may reduce the risk of mortality from paracetamol overdose (Janbaz et al 2004). However, effects in humans have not been studied — beneficial interaction theoretically possible.

QUINOLONE ANTIBIOTICS
In vitro, quercetin binds to the DNA gyrase site in bacteria and therefore may theoretically compete with quinolone antibiotics that also bind to this site (PDRHealth 2005) — caution.

STIBANATE
Concurrent use of quercetin with the antileishmanial drug stibanate appears to improve the efficacy of the drug and reduce the anaemia and parasitaemia associated with the condition (Sen et al 2005) — beneficial interaction theoretically possible.

CONTRAINDICATIONS AND PRECAUTIONS
Hypersensitivity to quercetin.

PREGNANCY USE
Safety in pregnancy has not been established.

PRACTICE POINTS/PATIENT COUNSELLING
- Quercetin is a flavonol belonging to a group of polyphenolic substances known as flavonoids or bioflavonoids and is found in many fruits, vegetables and some herbal medicines.
- According to experimental studies, it has antioxidant, anti-inflammatory, antiviral, mast cell stabilisation, neuroprotective, gastroprotective, hepatoprotective and possibly cardioprotective actions.
- In practice, it is used for respiratory allergies such as hayfever, as an adjunct in asthma management, preventing diabetic complications such as cataracts and symptom relief in prostatitis; however, large controlled studies are not available to determine its effectiveness.
- Numerous drug interactions are theoretically possible, mainly due to P-glycoprotein and CYP inhibition.
- Quercetin is generally well tolerated. Adverse effects may include nausea, dyspnoea, headache and mild tingling of the extremities

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Quercetin has several pharmacological effects and may provide some symptom relief in allergic conditions and prostatitis, and be beneficial in diabetes and cardiovascular disease; however, further research is required to clarify its effectiveness.

When will it start to work?

This will depend on the indication it is being used to treat.

Are there any safety issues?

Although it is generally well tolerated, numerous drug interactions are possible, so seek professional advice if taking other medication.

REFERENCES

Alcocer F et al. Quercetin inhibits human vascular smooth muscle cell proliferation and migration. Surgery 131(2) (2002): 198-204.

Alia M et al.Quercetin protects human hepatoma HepG2 against oxidative stress induced by tert-butyl hydroperoxide. Toxicol Applied Pharmacol 212(2) (2006): 110-18.

Anjaneyulu M, Chopra K. Quercetin, a bioflavonoid, attenuates thermal hyperalgesia in a mouse model of diabetic neuropathic pain. Prog Neuro-Psychopharmacol Biol Psychiatr 27(6) (2003): 1001-5.

Auger C et al. Dietary wine phenolics catechin, quercetin, and resveratrol efficiently protect hypercholesterolemic hamsters against aortic fatty streak accumulation. J Agric Food Chem 53(6) (2005): 2015-21.

Beyer-Mears A, Farnsworth PN. Diminished sugar cataractogenesis by quercetin. Exp Eye Res 28(6) (1979): 709-16.

Blackburn W, Heck L, Wallace R. The bioflavonoid quercetin inhibits neutrophil degranulation, superoxide production, and the phosphorylation of specific neutrophil proteins. Biochem Biophys Res Commun 144(3) (1987): 1229-36.

Boots AW et al. Oxidized quercetin reacts with thiols rather than with ascorbate: implication for quercetin supplementation. Biochem Biophys Res Commun 308(3) (2003): 560-5.

Brookes PS et al. Mitochondrial function in response to cardiac ischemia-reperfusion after oral treatment with quercetin. Free Radic Biol Med 32(11) (2002): 1220-8.

Busse W, Kopp D, Middleton E. Flavonoid modulation of human neutrophil function. J Allergy Clin Immunol 73(6) (1984): 801-9.

Challem J. The power of flavonoids: antioxidant nutrients in fruits, vegetables, and herbs. The Nutrition Reporter, 1998.

Chang TK, Chen J, Yeung EY. Effect of Ginkgo biloba extract on procarcinogen-bioactivating human CYP1 enzymes: Identification of isorhamnetin, kaempferol, and quercetin as potent inhibitors of CYP1B1. Toxicol Appl Pharmacol, 2005 (Epub ahead of print).

Chaudhry PS et al. Inhibition of human lens aldose reductase by flavonoids, sulindac and indomethacin. Biochem Pharmacol 32(13) (1983): 1995-8.

Chen J-C et al. Inhibition of iNOS gene expression by quercetin is mediated by the inhibition of I(kappa)B kinase, nuclear factor-kappa B and STAT1, and depends on heme oxygenase-1 induction in mouse BV-2 microglia. Eur J Pharmacol 521(1-3) (2005): 9-20.

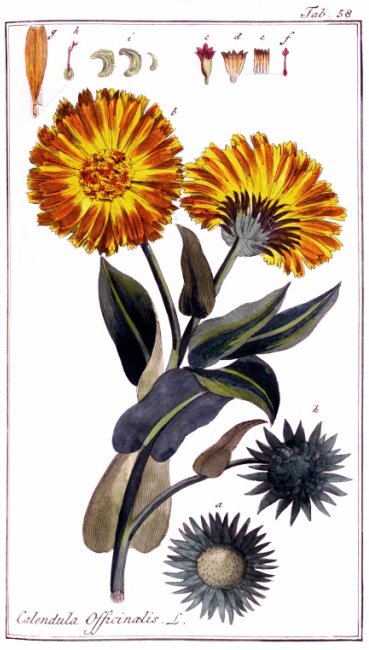
Choi J-S, Li X. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. Int J Pharm 297(1-2) (2005): 1-8.

Choi J-S, Jo B-W, Kim Y-C. Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin. Eur J Pharm Biopharm 57(2) (2004): 313-18.

Comalada M et al. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-kappaB pathway. Eur J Immunol 35(2) 2005(): 584-92.
Conquer JA et al. Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. J Nutr 128(3) (1998): 593-7.
Cornish KM, Williamson G, Sanderson J. Quercetin metabolism in the lens: role in inhibition of hydrogen peroxide induced cataract. Free Radic Biol Med 33(1) (2002): 63-70.
Coskun O et al. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and (beta)-cell damage in rat pancreas. Pharmacol Res 51(2) (2005): 117-23.
Day AJ, Williamson G. Biomarkers for exposure to dietary flavonoids: a review of the current evidence for identification of quercetin glycosides in plasma. Br J Nutr 86 (Suppl 1) (2001): S105-10.
deVries J et al. Plasma concentrations and urinary excretion of the antioxidant flavonols quercetin and kaempferol as biomarkers for dietary intake. Am J Clin Nutr 68(1) (1998): 60-5.
Duraj J et al. Flavonoid quercetin, but not apigenin or luteolin, induced apoptosis in human myeloid leukemia cells and their resistant variants. Neoplasma 52(4) (2005): 273-9.
Erlund I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. Nutr Res 24(10) (2004): 851-74.
Erlund I et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol 56(8) (2000): 545-53.
Ferraresi R et al. Essential requirement of reduced glutathione (GSH) for the anti-oxidant effect of the flavonoid quercetin. Free Radic Res 39(11) (2005): 1249-58.
Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. Food Chem.Toxicol 33 (1995): 1061-80.
Garcia-Saura MF et al. Effects of chronic quercetin treatment in experimental renovascular hypertension. Mol Cell Biochem 270(1-2) (2005): 147-55.
Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther 37(5) (1999): 219-33.
Heo HJ, Lee CY. Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration. J Agric Food Chem 52(25) (2004): 7514-17.
Hollman PCH et al. Bioavailability of the dietary antioxidant flavonol quercetin in man. Cancer Lett 114(1-2) (1997): 139-40.
Hsiu S-L et al. Quercetin significantly decreased cyclosporin oral bioavailability in pigs and rats. Life Sci 72(3) (2002): 227-35.
Hubbard GP et al. Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. J Thromb Haemost 2(12) (2004): 2138-45.
Igura K et al. Resveratrol and quercetin inhibit angiogenesis in vitro. Cancer Lett 171(1) (2001): 11-16.
Jakubowicz-Gil J et al. The effect of quercetin on pro-apoptotic activity of cisplatin in HeLa cells. Biochem Pharmacol 69(9) (2005): 1343-50.
Janbaz KH, Saeed SA, Gilani AH. Studies on the protective effects of caffeic acid and quercetin on chemical-induced hepatotoxicity in rodents. Phytomedicine 11(5) (2004): 424-30.
Kahraman A et al. The antioxidative and antihistaminic properties of quercetin in ethanol-induced gastric lesions. Toxicology 183(1-3) (2003): 133-42.
Kaneider NC et al. Inhibition of thrombin-induced signaling by resveratrol and quercetin: effects on adenosine nucleotide metabolism in endothelial cells and platelet-neutrophil interactions. Thrombosis Res 114(3) (2004): 185-94.
Kaul T, Middleton E, Ogra P. Antiviral effect of flavonoids on human viruses. J Med Virol 15(1) (1985): 71-9.
Ke Chen C, Pace-Asciak CR. Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta. Gen Pharmacol Vasc Syst 27(2) (1996): 363-6.
Kim WK et al. Quercetin decreases the expression of ErbB2 and ErbB3 proteins in HT-29 human colon cancer cells. J Nutr Biochem 16(3) (2005): 155-62.

Kumar P et al. Effect of quercetin supplementation on lung antioxidants after experimental influenza virus infection. Exp Lung Res 31(5) (2005): 449-59.
Lamson DW, Brignall MS. Antioxidants and cancer. Part 3: quercetin. Altern Med Rev 5(3) (2000): 196-208.
Lee J-C et al. The antioxidant, rather than prooxidant, activities of quercetin on normal cells: quercetin protects mouse thymocytes from glucose oxidase-mediated apoptosis. Exp Cell Res 291(2) (2003): 386-97.
Lee T-J et al. Quercetin arrests G2/M phase and induces caspase-dependent cell death in U937 cells. Cancer Lett [Epub ahead of print] 2005.
Limtrakul P, Khantamat O, Pintha K. Inhibition of P-glycoprotein function and expression by kaempferol and quercetin. J Chemother 17(1) (2005): 86-95.
Middleton E, Drzewiecki G. Effects of flavonoids and transitional metal cations on antigen-induced histamine release from human basophils. Biochem Pharmacol 31(7) (1982): 1449-53.
Middleton C, Drzewiecki G, Krishnararao D. Quercetin: an inhibitor of antigen-induced human basophil histamine release. J Immunol 127 (1981): 546-50.
Mochizuki M et al. Effect of quercetin conjugates on vascular permeability and expression of adhesion molecules. Biofactors 22(1-4) (2004): 201-4.
Moon S-K et al. Quercetin exerts multiple inhibitory effects on vascular smooth muscle cells: role of ERK1/2, cell-cycle regulation, and matrix metalloproteinase-9. Biochem Biophys Res Commun 301(4) (2003): 1069-78.
Morikawa K et al. Inhibitory effect of quercetin on carrageenan-induced inflammation in rats. Life Sci 74(6) (2003): 709-21.
Morrow DM et al. Dietary supplementation with the anti-tumour promoter quercetin: its effects on matrix metalloproteinase gene regulation. Mutat Res 480-1 (2001): 269-76.
Murota K, Terao J. Antioxidative flavonoid quercetin: implication of its intestinal absorption and metabolism. Arch Biochem Biophys 417(1) (2003): 12-17.
Muthian G, Bright JJ. Quercetin, a flavonoid phytoestrogen, ameliorates experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK-STAT pathway in T lymphocyte. J Clin Immunol 24(5) (2004): 542-52.
Naidu PS, Singh A, Kulkarni SK. Quercetin, a bioflavonoid, attenuates haloperidol-induced orofacial dyskinesia. Neuropharmacology 44(8) (2003): 1100-6.
Nair MPN et al. The flavonoid, quercetin, differentially regulates Th-1 (IFN(gamma)) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. Biochim Biophys Acta Mol Cell Res 1593(1) (2002): 29-36.
Notoya M et al H. Quercetin, a flavonoid, inhibits the proliferation, differentiation, and mineralization of osteoblasts in vitro. Eur J Pharmacol 485(1-3) (2004): 89-96.
Ogasawara H et al. The role of hydrogen peroxide in basophil histamine release and the effect of selected flavonoids. J Allergy Clin Immunol 78 (1996): 321-8.
Otake Y et al. Quercetin and resveratrol potently reduce estrogen sulfotransferase activity in normal human mammary epithelial cells. J Steroid Biochem Mol Biol 73(5) (2000): 265-70.
Otsuka H et al. Histochemical and functional characteristics of metachromatic cells in the nasal epithelium in allergic rhinitis: Studies of nasal scrapings and their dispersed cells. J Allergy Clin Immunol 96(4) (1995): 528-36.
Park CH et al. Quercetin, a potent inhibitor against (beta)-catenin/Tcf signaling in SW480 colon cancer cells. Biochem Biophys Res Commun 328(1) (2005): 227-34.
PDRHealth [online]. Thomson Healthcare, 2005 . Available from: http://www.pdrhealth.com. Accessed 04-02-06.
Pearce FL, Dean Befus A, Bienenstock J. Mucosal mast cells: Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal mast cells. J Allergy Clin Immunol 73(6) (1984): 819-23.
Peres W et al. The flavonoid quercetin ameliorates liver damage in rats with biliary obstruction. J Hepatol 33(5) (2000): 742-50.

Pietruck F et al. Effect of quercetin on hypoxic injury in freshly isolated rat proximal tubules. J Lab Clin Med 142(2) (2003): 106-12.
Rassi CM et al. Modulation of osteoclastogenesis in porcine bone marrow cultures by quercetin and rutin. Cell Tissue Res 319(3) (2005): 383-93.
Roghani M et al. Mechanisms underlying quercetin-induced vasorelaxation in aorta of subchronic diabetic rats: an in vitro study. Vasc Pharmacol 42(1) (2004): 31-5.
Sanchez M et al. Quercetin downregulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats. J Hypertens 24(1) (2006): 75-84.
Sanderson J, McLauchlan WR, Williamson G. Quercetin inhibits hydrogen peroxide-induced oxidation of the rat lens. Free Radic Biol Med 26(5-6) (1999): 639-45.
Schwarz D, Kisselev P, Roots I. CYP1A1 genotype-selective inhibition of benzo(a)pyrene activation by quercetin. Eur J Cancer 41(1) (2005): 151-8.
Sen G et al. Therapeutic use of quercetin in the control of infection and anemia associated with visceral leishmaniasis. Free Radic Biol Med 38(9) (2005): 1257-64.
Shetty AK et al. Antidiabetic influence of quercetin in streptozotocin-induced diabetic rats. Nutr Res 24(5) (2004): 373-81.
Shoskes DA et al. Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. Urology 54(6) (1999): 960-3.
Son Y-O et al. Quercetin, a bioflavonoid, accelerates TNF-(alpha)-induced growth inhibition and apoptosis in MC3T3-E1 osteoblastic cells. Eur J Pharmacol 529(1-3) (2006): 24–32.
Spoerke D, Rouse J. Quercetin: Alternative Medicine Summary. Micromedex, 2004. Available from: www.micromedex.com. Accessed 04-02-06.
Tan W-F et al. Quercetin, a dietary-derived flavonoid, possesses antiangiogenic potential. Eur J Pharmacol 459(2-3) (2003): 255-62.
Valensi P et al. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy: A preliminary report. J Diabetes Complications 19(5) (2005): 247-53.
van der Woude H et al. The stimulation of cell proliferation by quercetin is mediated by the estrogen receptor. Mol Nutr Food Res 49(8) (2005): 763-71.
Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C Toxicol Pharmacol 135(3) (2003): 357-64.
Wattel A et al. Potent inhibitory effect of naturally occurring flavonoids quercetin and kaempferol on in vitro osteoclastic bone resorption. Biochem Pharmacol 65(1) (2003): 35-42.
Wilms LC et al. Protection by quercetin and quercetin-rich fruit juice against induction of oxidative DNA damage and formation of BPDE-DNA adducts in human lymphocytes. Mutat Res 582(1-2) (2005): 155-62.
Yuan H, Pan Y, Young CYF. Overexpression of c-Jun induced by quercetin and resverol inhibits the expression and function of the androgen receptor in human prostate cancer cells. Cancer Lett 213(2) (2004): 155-63.



Raspberry leaf

Historical note Although the fruits of the raspberry are used as a luxury food source, midwives have used raspberry leaves since ancient times to prepare the uterus for childbirth. Raspberry has also been used as an antidiarrhoeal and an astringent to treat inflammations of the mucous membranes of the mouth and throat. It has also been used for disorders of the gastrointestinal and respiratory tracts and as an ingredient in dietary drinks.

COMMON NAME
Red raspberry

OTHER NAMES
Framboise, *Rubi idaei folium*, rubus

BOTANICAL NAME/FAMILY
Rubus idaeus (synonym: *Rubus strigosus*) (family Rosaceae [roses])

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Raspberry leaves have a tannin content of between 13% and 15%, as well as flavonoids such as rutin and quercetin, volatile oils, organic acids and vitamin C.

MAIN ACTIONS
Raspberry leaf contains a number of active constituents and their therapeutic actions have been reviewed (Patel et al 2004). Currently, evidence of activity comes from in vitro and in vivo studies.

UTERINE EFFECTS
Raspberry leaf has demonstrated a variable effect on uterine muscle tone. It contains a smooth muscle stimulant, an anticholinesterase and an antispasmodic. The results of animal studies indicate that raspberry can either reduce or initiate uterine contractions (Bamford et al 1970). It appears to inhibit uterine contractions in samples from pregnant test animals, but has no effect in non-pregnant ones. Samples from human pregnant uteri respond with contraction effects; however, no effect was seen on non-pregnant uteri samples. Overall, it appeared that raspberry leaf extract promoted more regular contractions that generally became less frequent (Newell et al

1996). A more recent preliminary study produced similar results with fractions of raspberry leaf extract, both stimulating and relaxing uterine muscle in pregnant rats (Briggs & Briggs 1997). There is evidence of at least two components of raspberry leaf extract that exhibit relaxant activity in an in vitro guinea pig ileum preparation (Rojas-Vera et al 2002).

ANTIDIARRHOEAL

In addition to the high tannin content, which may exert an antidiarrhoeal action, raspberry cordial and juice were found to significantly reduce the growth of several species of bacteria, including *Salmonella*, *Shigella* and *Escherichia coli*, but no antimicrobial activity was detected in the leaf extract or tea (Ryan et al 2001).

ANTI-INFLAMMATORY

Raspberry leaf exhibits anti-inflammatory activity because of its high tannin content, which has been found to inhibit COX (Duke 2003). When applied topically to mucous membranes, tannins have a local anti-inflammatory effect, produce capillary vasoconstriction and decrease vascular permeability (Halvorsen et al 2001).

ASTRINGENT

The high tannin content of the leaf is responsible for the astringent activity.

OTHER ACTIONS

Raspberry ketone, which is an aromatic compound with similar structure to capsaicin and synephrine, has been shown in vivo to prevent and improve obesity and fatty liver though increasing norepinephrine-induced lipolysis in white adipocytes (Morimoto et al 2005).

CLINICAL USE

The therapeutic effects of raspberry have not been significantly investigated under clinical trial conditions, so most evidence is derived from traditional, in vitro and animal studies.

UTERINE TONIC

Raspberry leaf is commonly used as a 'partus preparator' to prepare the uterus for delivery and to facilitate labour, as well as for morning sickness, dysmenorrhoea, leukorrhoea and menorrhagia (McFarlin et al 1999).

In vitro studies using pregnant rat and human uteri preparations suggest that raspberry may increase the regularity and decrease the frequency of uterine contractions (Bamford et al 1970). In a double-blind trial of 192 low-risk nulliparous women, raspberry leaf (2 × 1.2 g/day), consumed from 32 weeks' gestation until labour, was associated with a lower rate of interventions with no adverse effects for

mother or baby (Simpson et al 2001). Raspberry leaf did not shorten the first stage of labour; however, it did significantly reduce the second stage. A retrospective, observational study of 108 mothers also found that treatment with raspberry leaf was associated with a lower rate of medical intervention (Parsons et al 1999). This study further suggested that treatment may shorten labour, and reduce the incidence of pre- and post-term labour. Some pregnant women commenced use of raspberry leaf from 8 weeks' gestation; however, most chose to start it between 30 and 34 weeks' gestation.

TOPICAL INFLAMMATORY CONDITIONS

The high tannin content of raspberry supports its traditional use as a topical treatment for inflammation of the mouth, throat, eye and skin, as well as to treat cuts and wounds.

DIARRHOEA

Once again, the high tannin content of raspberry supports its traditional use as an antidiarrhoeal agent.

DYSPEPTIC COMPLAINTS

Traditionally understood to act as a choleretic, raspberry is used to improve digestion and detoxifying processes, but controlled studies are not available to determine effectiveness.

OTHER USES

As well as a long tradition of use as a 'women's tonic' to facilitate childbirth, cold infusions of raspberry leaf have been used to treat diarrhoea, loose bowels and stomach complaints in children. Raspberry leaf has traditionally been incorporated into mouthwashes to treat inflammation of the mouth and throat, used as a diaphoretic for fever, as a choleretic to improve digestion and detoxification, and as a food and flavouring agent. In a small, uncontrolled, prospective pilot study of eight women, raspberry leaf in combination with 11 other botanical extracts was found to relieve menopausal symptoms (Smolinski et al 2005).

DOSAGE RANGE

INTERNAL USE

- Infusion of dried leaf: 4–8 g taken up to three times daily.
- Liquid extract: (1:1): 4–8 mL three times daily.

EXTERNAL USE

- Topically, the tea can be used as a mouth or eye wash, or to clean wounds.

TOXICITY
There is no evidence that raspberry leaf tea is toxic.

ADVERSE REACTIONS
Owing to the tannin content of the herb, it may cause gastrointestinal discomfort.

SIGNIFICANT INTERACTIONS
IRON, CALCIUM, MAGNESIUM
Due to its high tannin content, raspberry leaf may decrease absorption of iron, calcium and magnesium, as well as some drugs. As such, it is advised to separate the administration of these substances by at least 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS
The high tannin concentration within the herb means it should be avoided in constipation and used cautiously in active peptic ulcer and gastrointestinal conditions associated with inflammation.

PREGNANCY USE
Clinical studies suggest that it is safe to use after the first trimester, although it is prudent to ensure close professional supervision.

PRACTICE POINTS/PATIENT COUNSELLING
- Raspberry leaves have been traditionally used to prepare the uterus for childbirth, with some modern research suggesting it may be useful.
- When used in this way, it is often combined with other herbs and used during the last 6–8 weeks of pregnancy while under close supervision.
- Raspberry leaves are high in tannins, which may make them useful as a mouthwash and to treat diarrhoea, although this has not been confirmed in clinical trials.
- As tannins may reduce the absorption of other substances, it is recommended to take raspberry leaf preparations separately from other medications. Raspberry leaf preparations can be considered safe and non-toxic.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Raspberry leaf preparations have been used since ancient times to prepare the uterus for birth in an attempt to facilitate a complication-free labour. It is also used to treat diarrhoea and dyspeptic complaints, and incorporated into a mouthwash to reduce inflammation of the mouth and throat.

When will it start to work?
Currently, there is insufficient research to answer this question. However, it is used in increasing doses during the last few weeks of pregnancy. Symptomatic relief of

diarrhoea and inflammation of the oral cavity is likely to occur within the first few doses.

Are there any safety issues?

Considering raspberry leaf has uterine activity, it is recommended that pregnant women wanting to use it do so under the careful supervision of an experienced healthcare professional.

REFERENCES

Bamford DS et al. Raspberry leaf tea: a new aspect to an old problem. Br J Pharmacol 40.1 (1970): 161-2.

Briggs CJ, Briggs K. Raspberry. Can Pharm J 130.3 (1997): 41-3.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003. www.ars-grin.gov/duke.

Halvorsen BL et al. A systematic screening of total antioxidants in dietary plants. J Nutr 142.3 (2001): 461-71.

McFarlin BL et al. A national survey of herbal preparation use by nurse-midwives for labor stimulation: Review of the literature and recommendations for practice. J Nurse Midwifery 44.3 (1999): 205-16.

Morimoto C et al. Anti-obese action of raspberry ketone. Life Sci 77.2 (2005): 194-204.

Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.

Parsons M et al. Raspberry leaf and its effect on labour: safety and efficacy. Aust Coll Midwives Inc J 12.3 (1999): 20-5.

Patel A et al. Therapeutic constituents and actions of Rubus species. Curr Med Chem 11.11 (2004): 1501-12.

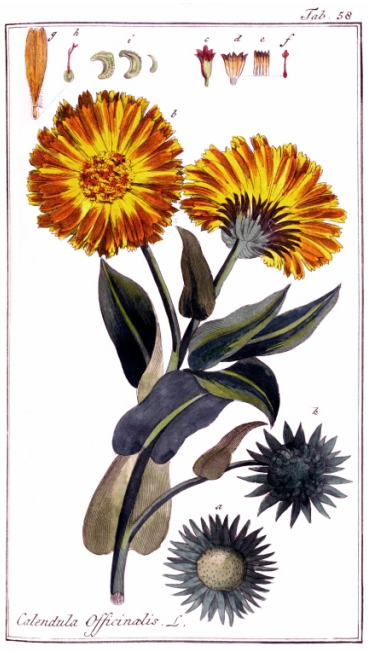
Rojas-Vera J, Patel AV, Dacke CG. Relaxant activity of raspberry (Rubus idaeus) leaf extract in guinea-pig ileum in vitro. Phytother Res 16.7 (2002): 665-8.

Ryan T et al. Antibacterial activity of raspberry cordial in vitro. Res Vet Sci 71.3 (2001): 155-9.

Simpson M et al. Raspberry leaf in pregnancy: its safety and efficacy in labor. J Midwifery Women's Health 46.2 (2001): 51-9.

Smolinski D et al. A pilot study to examine a combination botanical for the treatment of menopausal symptoms. J Alt Complement Med 11.3 (2005): 483-9.

Red clover



Historical note Red clover has been used for a long time as an animal fodder as well as a human medicine. Traditionally, it is considered an alternative remedy with good cleansing properties useful in the treatment of skin diseases such as psoriasis, eczema and rashes. A strong infusion was used to ease whooping cough and other spasmodic coughs due to measles, bronchitis and laryngitis. It was recommended for 'ulcers of every kind, and deep, ragged-edged, and otherwise badly-conditioned burns. It possesses a peculiar soothing property, proves an efficient detergent, and promotes a healthful granulation'. Combined with other herbs, red clover was recommended for syphilis, scrofula, chronic rheumatism, glandular and various skin affections (Felter & Lloyd 1983). Interestingly, red clover was not traditionally used for the treatment of menopausal symptoms.

OTHER NAMES
Cow clover, meadow clover, purple clover, trifoil

BOTANICAL NAME/FAMILY
Trifolium pratense L. (family Fabaceae)

PLANT PARTS USED
Flower head or leaf

CHEMICAL COMPONENTS

FLOWER HEAD
Flavonoids, including formononetin; flavonols, including isorhamnetin and quercetin glucosides; phenolic acids, including salicylic and p-coumaric acids; volatile oils and other constituents, including sitosterol, starch, fatty acids (BHMA 1983).

LEAF
Isoflavones, including biochanin A, daidzein, formononetin and genistein; caffeic acid derivatives; and coumestrol (trace) (Clifton-Bligh et al 2001, He et al 1996).

In the plant, the isoflavones are attached to a sugar molecule, usually glucose. The chemical term for any compound attached to a sugar is 'glycoside'. The free isoflavone form is known as an 'aglycone'. The active aglycone is liberated in the gut. Isoflavones are readily absorbed from the gut; they circulate freely in the blood and

are excreted in the urine; 50% of ingested isoflavones are eliminated within 12 hours (Joannou et al 1995).

The glycoside and aglycone forms of the four main oestrogenic isoflavones are as follows:

Glycoside	Aglycone
Ononin	Formononetin
Daidzin	Daidzein
Sissotrin	Biochanin
Genistin	Genistein

Clinical note — Phyto-oestrogens and isoflavones

Phyto-oestrogens are plant-based compounds that are structurally similar to oestradiol. The term phyto-oestrogen encompasses isoflavone compounds, such as genistein and daidzein, found predominantly in soya and red clover, and the lignans, such as matairesinol and secoisolariciresinol, found in many fruits, cereals and in linseed. Phyto-oestrogens have been investigated for their potential to reduce the risk of hormone-dependent diseases such as breast and prostate cancers and osteoporosis. The metabolism of isoflavones and lignans is complex and involves gut microbial processes. Isoflavones are present predominantly as glucosides; however, their bioavailability requires initial hydrolysis of the sugar moiety by intestinal [beta]-glucosidases. After absorption, phyto-oestrogens are reconjugated predominantly to glucuronic acid and to a lesser degree to sulfuric acid. There is further metabolism of isoflavones (to equol and *O*-desmethyl-angolensin) and lignans (to enterodiol and enterolactone) by gut bacteria. In humans, even those on controlled diets, there is large interindividual variation in the metabolism of isoflavones and lignans, particularly in the production of the gut bacterial metabolite equol (from daidzein). Dietary factors and gut microflora directly influence the absorption and metabolism of phyto-oestrogens and is likely to influence the clinical benefits of supplementation with phyto-oestrogens (Rowland et al 2003).

MAIN ACTIONS

OESTROGENIC ACTIVITY

The pharmacological investigation of red clover has mainly centred around the activity of the isoflavone constituents, especially their oestrogenic activity (Miksicek 1994). The isoflavones biochanin A, genistein and daidzein have varying levels of subtle oestrogenic activity, biochanin A having the strongest effect. Formononetin, however, has very little or no oestrogenic activity (Wong & Flux 1962). Red clover isoflavones have been shown to have an affinity for oestrogen alpha- and beta-receptors and may act as both agonists and antagonists, depending on the level of endogenous oestrogens (Nelson et al 2002, Zava et al 1998). Red clover extract, standardised to contain 15% isoflavones, produced a dose-dependent increase in uterine weight and differentiated vaginal cells, but did not stimulate cell proliferation in mammary glands in an ovariectomised rat model. The extract did not produce any anti-oestrogenic or additive oestrogenic effects when combined with 17-beta-oestradiol. These data suggest that red clover extract is weakly oestrogenic in the ovariectomised rat model (Burdette et al 2002).

REDUCING CANCER RISK

Phyto-oestrogens and isoflavones may reduce the risk of cancer, including breast cancer (Adlercreutz et al 1995, Clarke et al 1996, Ingram et al 1997, Pagliaaci et al 1994). Biochanin A isolated from red clover has been shown to be antimutagenic, as well as protective against chemically-induced DNA damage in vitro (Chan et al 2003). Genistein has been shown to inhibit cell proliferation and in vitro angiogenesis (Fotsis et al 1995).

An animal study has found that red clover isoflavones significantly increase oestrogen beta-receptor and E-cadherin expression, but decrease transforming growth factor beta-1. These proteins are markers of oestrogen-induced proliferation, preservation of cell phenotype and reduction of the potential for neoplastic and metastatic transformation. These results suggest that red clover isoflavones may be useful in the treatment of prostatic hyperplasia and reduce the risk of neoplastic transformation (Slater et al 2002). A recent study has reported that red clover-derived isoflavones significantly reduced non-malignant prostatic growth in mice by acting as anti-androgenic agents rather than weak oestrogenic substances (Jarred et al 2003).

CLINICAL USE

Considerable research has been carried out on the constituents of red clover. However, most of the investigations have been undertaken for agricultural rather

than medicinal purposes. Very few investigations have concentrated specifically on the flower heads and the traditional uses.

RELIEF OF MENOPAUSAL SYMPTOMS

Although extracts standardised for soy isoflavone levels may help relieve symptoms, such as hot flushes and other symptoms frequently associated with menopause (Adlercreutz & Mazur 1997, Cassidy et al 1994), the evidence from red clover isoflavones is less convincing.

A 2004 systematic review that included data from five trials published between 1966 until March 2004 concluded that phyto-oestrogens from red clover have not been shown to reduce hot flushes (Krebs et al 2004). The trials were placebo-controlled, involved a total of 400 women and tested a standardised red clover isoflavone extract available commercially as Promensil (Novogen Ltd, Sydney, NSW, Australia), which contains 40 mg isoflavones. Two of the smallest trials ($n = 30$ each) (Jerri & de Roma 2001, van de Weijer & Barentsen 2002) reported a significant decrease in hot flush frequency; however, three, double-blind placebo-controlled trials found little effect in reducing the incidence or severity of hot flushes (Baber et al 1999, Knight et al 1999, Tice et al 2003). The largest and highest quality study involved 252 menopausal women, aged 45–60 years, who were experiencing at least 35 hot flushes per week (Tice et al 2003). After a 2-week placebo run-in, participants were randomly assigned to Promensil (82 mg total isoflavones per day), Rimostil (57 mg total isoflavones per day) or a placebo. The reductions in mean daily hot flushes at 12 weeks were similar for all three groups. However, Promensil (but not Rimostil) reduced hot flushes more rapidly than placebo. Although the study provides some evidence for a biological effect of Promensil, neither supplement had a clinically important effect on hot flushes or other symptoms of menopause.

One study not included in this review was an American open study of 23 postmenopausal women (aged 40–65 years) suffering vasomotor hot flushes, which found that Promensil (standardised red clover isoflavone extract) containing 40 mg isoflavones taken daily for 2–3 months significantly reduced the self-rated intensity of hot flushes ($P < 0.001$). The mean endometrial thickness was unchanged and there was no significant change in the mean fasting total cholesterol, LDL, HDL, glucose, oestradiol, sex hormone binding globulin or FSH levels. There were no adverse effects (Nachtigall et al 1999).

Two new randomised studies have been published since the 2004 review. One was a double-blind placebo controlled trial of 60 menopausal women using 80 mg/day of red clover isoflavones for 90 days and they reported significant reductions in menopausal symptoms as compared to placebo and a positive effect on

vaginal cytology (Hidalgo et al 2005). The other double-blind, placebo-controlled trial found no effects on breast density, oestradiol, FSH, LH or lymphocyte tyrosine kinase activity after 12 months of treatment with red clover isoflavones (43.5 mg/day) in 205 women aged between 49 and 65 years (Atkinson et al 2004a).

CARDIOVASCULAR EFFECTS

Lipid levels Because oestrogens have been reported to favourably alter lipid levels, there has been some investigation into the effects of red clover isoflavones in this regard. Currently, the evidence remains inconclusive and most studies report no significant effect.

In a double blind, placebo-controlled, randomised trial of red clover-derived isoflavones (43.5 mg/day), with 205 women aged between 49 and 65 years, active treatment had no significant effect on total cholesterol or HDL- and LDL-cholesterol levels or triglycerides (Atkinson et al 2004b). A single-blind, randomised crossover study of 21 healthy premenopausal women (aged 18–45 years) found that tablets containing 86 mg/day isoflavones for two menstrual cycles did not significantly change total cholesterol, HDL- or LDL-cholesterol or triglyceride levels (Samman et al 1999). Another study of postmenopausal women with mild to moderate hypercholesterolaemia also found red clover did not significantly affect plasma lipids (Howes et al 2000). A recent double-blind, randomised parallel study found that 86 mg/day purified isoflavones derived from red clover also had no effect on cholesterol homeostasis or insulin resistance in 25 premenopausal women (Blakesmith et al 2003).

However, there have been some positive findings. A randomised, placebo-controlled, crossover pilot study in 23 healthy pre- and postmenopausal women taking 86 mg/day isoflavones derived from red clover demonstrated an increase in HDL-cholesterol as compared to placebo after 1 month (Campbell et al 2004). A 12-week randomised, double-blind, placebo-controlled trial with 252 menopausal women investigated the possible benefits of isoflavones from red clover on cholesterol and triglyceride levels (Schult et al 2004). Two products were investigated, Rimostil (57.2 mg total isoflavones) and Promensil (82 mg total isoflavones) and both extracts induced a statistically significant decrease in triglyceride levels. Additionally, a small but statistically insignificant increase in HDL-cholesterol was noted.

Blood pressure and endothelial function Red clover isoflavones (approximately 50 mg/day) have been shown to favourably influence blood pressure and endothelial function in postmenopausal type 2 diabetic women in a randomised, double-blind crossover trial of 16 women. Mean daytime SBP and DBP were significantly lower during isoflavone therapy compared with placebo (Howes et al 2003).

Alternatively, no effect on blood pressure was observed in a double-blind, placebo-controlled, randomised trial of red clover derived isoflavones (43.5 mg/day) in 205 women aged between 49 and 65 years (Atkinson et al 2004b).

Negative results were also seen in another study of healthy subjects (46 men, 34 women, age 45–75 years) who received isoflavones enriched in either biochanin or formononetin (precursors of genistein and daidzein; 80 mg/day) crossed over randomly with placebo in two 6-week periods. The red clover isoflavones reduced arterial stiffness and total vascular resistance, but had no effect on blood pressure (Teede et al 2003). Previously, a double-blind, placebo-controlled trial of Promensil (40 mg and 80 mg) found that the isoflavone extract significantly improved arterial compliance compared with placebo (Nestel et al 1999). However, the large drop-out rate and poor study design means that the results are not compelling (Fugh-Berman & Kronenberg 2001).

REDUCING CANCER RISK

Biochanin A, daidzein and genistein have demonstrated antiproliferative activity in vitro (Hempstock et al 1998). Red clover isoflavones (50 mg total isoflavones), however, were found not to be antiproliferative in a double-blind randomised study of 30 perimenopausal women (Hale et al 2001).

Prostate cancer A non-randomised non-blinded trial of 38 men with clinically significant prostate cancer found that 160 mg/day red clover-derived dietary isoflavones, containing a mixture of genistein, daidzein, formononetin and biochanin A, significantly increased apoptosis compared with matched controls ($P = 0.0018$). There were no significant differences between pre- and post-treatment serum levels of prostate-specific antigen, testosterone or biochemical factors or Gleason score in the treated patients ($P > 0.05$). The study was performed in men undergoing radical prostatectomy; however, it indicates that the isoflavones may halt the progression of prostate cancer by inducing apoptosis in low to moderate-grade tumours (Gleason grade 1–3) (Jarred et al 2002).

BENIGN PROSTATIC HYPERTROPHY

Isoflavone-containing supplements are widely used in patients with BPH. Recently, an in vivo study using mice showed that red clover-derived isoflavones have a significant effect on prostatic growth, and are capable of reducing the tendency to enlarged non-malignant prostate, by acting as anti-androgenic agents rather than weak oestrogenic substances (Jarred et al 2003). A case series ($n = 29$) presented at the Endocrine Society's 82nd Annual Meeting in 2000 suggested that 3 months of treatment with 1 or 2 tablets of Trinovin (standardised to 40 mg red clover

isoflavones per tablet) significantly decreased nocturia frequency, the International Prostate Symptom Score, increased urinary flow rates and QOL score. The PSA values and prostate size did not alter from baseline (Ulbricht & Basch 2005).

OSTEOPOROSIS PREVENTION

Pharmaceutical HRT is sometimes used for preventing loss of bone following menopause; however, a growing number of users are concerned about the increased risk of breast cancer associated with long-term HRT. As such, phyto-oestrogens have been used as an alternative to prevent osteoporosis. Most research has focused on soy isoflavones, although there is some evidence that red clover-derived isoflavones may also be of benefit.

In a recent trial by Atkinson et al, loss of lumbar spine bone mineral content and bone mineral density was significantly reduced in women taking red clover-derived isoflavones (43.5 mg/day) compared to placebo in a double-blind, placebo-controlled, randomised trial in 205 women over 12 months (Atkinson et al 2004c). Bone formation markers were also significantly increased; however, no improvement in hip-bone mineral content or bone mineral density was noted. A double-blind study of 46 postmenopausal women investigated the effects of a red clover isoflavone preparation (Rimostil) containing genistein, daidzein, formononetin and biochanin A after a single-blind placebo phase and followed by a single-blind washout phase. Patients were randomly assigned to receive 28.5 mg, 57 mg or 85.5 mg phyto-oestrogens daily for a 6-month period. After the test period, the bone mineral density of the proximal radius and ulna rose significantly, by 4.1% with a dose of 57 mg/day and by 3.0% with a dose of 85.5 mg/day isoflavones. The response with 28.5 mg/day isoflavones was not significant (Clifton-Bligh et al 2001).

No significant difference in bone turnover markers was apparent after 12 weeks of treatment with Promensil and Rimostil in a double-blind, placebo-controlled, randomised clinical trial in 252 menopausal women aged between 45 and 60 years (Schult et al 2004).

OTHER USES

Red clover flower heads are still used in the traditional manner for indications not related to the potential hormonal activity of the herb.

The British Herbal Pharmacopoeia lists red clover as a dermatological agent, mild antispasmodic and expectorant (British Herbal Medicine Association 1983). The specific indications are for eczema and psoriasis. Red clover is said to combine well with yellow dock for treatment of chronic skin disease.

DOSAGE RANGE

- 4 g as infusion or extract.
- Liquid extract (1:1) in 25% alcohol: 1.5–3.0 mL/day.
- Concentrated isoflavone extract: extract containing 40–80 mg total isoflavones daily.

ACCORDING TO CLINICAL REPORTS

Menopausal symptoms: 40–82 mg daily of red clover-derived isoflavones.

Lipid-lowering: 40–86 mg daily of red clover-derived isoflavones.

Osteoporosis prevention: 44–86 mg daily of red clover-derived isoflavones.

BPH symptom relief: 40–80 mg daily of red clover-derived isoflavones.

ADVERSE REACTIONS

The oestrogenic potency of the isoflavones has been well documented. Overgrazing cattle or sheep on red clover can be detrimental to their fertility. In 'clover disease', ewes are made permanently infertile by clover consumption. In animals with clover disease, the uterine response to oestrogen is reduced, as is the surge in LH. Clover disease has not been observed with normal therapeutic doses in humans. None of the trials has reported adverse effects. An isoflavone preparation from soya bean, and red clover extracts containing genistein, daidzein, biochanin A and formononetin, did not modify the endometrial architecture in 25 postmenopausal women taking the preparation for 1 year (Aguilar et al 2002).

SIGNIFICANT INTERACTIONS

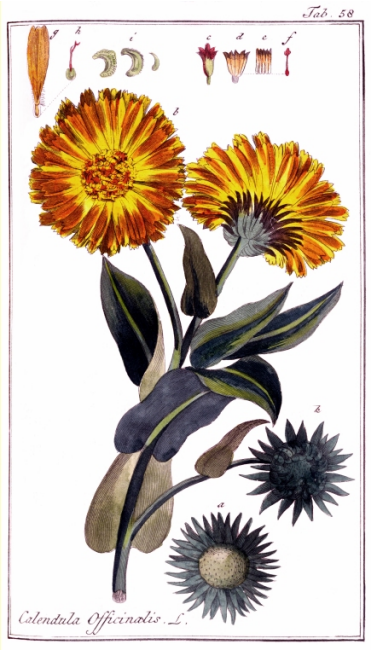
Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

ANTICOAGULANT AGENTS

Red clover contains coumarin, which could theoretically exert anticoagulant activity and therefore increase the clinical effects of warfarin. However, it is only the byproduct, dicoumarol (produced by microorganism in poorly dried sweet clover) that has established anticoagulant effects. Interaction with anticoagulant medication is not likely for extracts from properly dried red clover. Observe patients taking red clover and anticoagulants concurrently.

OESTROGENS

Theoretically, if taken in large quantities, phyto-oestrogens may compete with synthetic oestrogens for receptor binding, but the clinical significance of this remains unknown. A recent review concluded that up to 2 mg of red clover-derived isoflavones per kg should be considered a safe dose for most patient groups (Barnes 2003).



CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for the flower head extracts. Concentrated isoflavone extracts should only be used by people with oestrogen-sensitive cancers under professional supervision because of the possible proliferative effects. Additionally, people with conditions that may be aggravated by increased oestrogen levels, such as endometriosis or uterine fibroids, should use this herb under professional supervision only.

PREGNANCY USE

Scientific evidence for the use of red clover during pregnancy has not been established. No teratogenicity data are available. Use is not recommended.

PRACTICE POINTS/PATIENT COUNSELLING

- Red clover flower heads are traditionally considered a dermatological agent, mild antispasmodic and expectorant and specifically used for eczema and psoriasis. In practice, it is often combined with yellow dock for treatment of chronic skin disease.
- In recent years, red clover isoflavones have been studied and shown to have an affinity for oestrogen alpha- and beta-receptors and may act as both agonists and antagonists, depending on the level of endogenous oestrogens.
- Evidence that red clover-derived isoflavones reduce hot flush frequency in menopause is unconvincing.
- Preliminary evidence suggests a possible preventative role in osteoporosis; however, further research is required.
- Concentrated isoflavone extracts from red clover are used in cardiovascular disease as there is weak evidence that it may reduce arterial stiffness.
- Evidence from animal studies and case series suggests a potential role in BPH.
- Cancer (there is weak evidence that red clover isoflavone extracts may reduce risk of hormone-sensitive cancers and that they may be beneficial in the treatment of prostate cancer).

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Red clover is traditionally used for skin disorders. In recent years, concentrated red clover isoflavone extracts have been promoted for use in the treatment of menopausal symptoms, although clinical studies have produced inconsistent results.

When will it start to work?

Red clover tea or extract for skin diseases requires long-term use. Improvement may occur within several weeks with the condition continuing to improve with long-term

use. Improvement in menopausal symptoms from the use of concentrated isoflavone extracts may take 2–3 months, although results are inconsistent.

Are there any safety issues?

Short- or long-term use of red clover tea or flower head extract is not thought to be associated with any adverse reactions and its use is considered safe. Concentrated red clover isoflavone extracts may have subtle oestrogenic activity and little is known about drug interactions or long-term use. As a result, they should not be used by people with oestrogen-sensitive tumours or conditions that may be aggravated by increased oestrogen levels such as endometriosis, unless under professional supervision.

REFERENCES

Adlercreutz H, Goldin BR, Gorbach SL. Soybean phytoestrogen intake and cancer risk. J Nutr 125 (1995): 757-70.

Adlercreutz H, Mazur W. Phytoestrogens and western diseases. Ann Med 29 (1997): 95-120.

Aguilar JG et al. Histeroscopic prospective study of the action of isoflavones on the endometrium. Acta Ginecologica 59.7 (2002): 217-20.

Atkinson C et al. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 79.2 (2004a): 326-33.

Atkinson C et al. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65-year-old women. J Nutr 134.7 (2004b): 1759-64.

Atkinson C et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. Breast Cancer Res 6.3 (2004c): R170-9.

Baber RJ, Templeman C, Mortton T. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. Climacteric 2 (1999): 85-93.

Barnes S. Phyto-oestrogens and osteoporosis: what is a safe dose? Br J Nutr 89 (Suppl 1) (2003): S101-8.

Blakesmith SJ et al. Effects of supplementation with purified red clover (Trifolium pratense) isoflavones on plasma lipids and insulin resistance in healthy premenopausal women. Br J Nutr 89.4 (2003): 467-74.

British Herbal Medicine Association Scientific Committee. British Herbal Pharmacopoeia. Lane House, Cowling, UK: BHMA, 1983.

Burdette JE et al. Trifolium pratense (red clover) exhibits estrogenic effects in vivo in ovariectomized sprague-dawley rats. J Nutr 132.1 (2002): 27-30.

Campbell MJ et al. Effect of red clover-derived isoflavone supplementation on insulin-like growth factor, lipid and antioxidant status in healthy female volunteers: a pilot study. Eur J Clin Nutr 58.1 (2004): 173-9.

Cassidy A, Bingham S, Setchell KDR. Biological effects of a diet of soyprotein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr 60 (1994): 333-40.

Chan HY, Wang H, Leung LK. The red clover (Trifolium pratense) isoflavone biochanin A modulates the biotransformation pathways of 7,12-dimethylbenz[a]anthracene. Br J Nutr 90.1 (2003): 87-92.

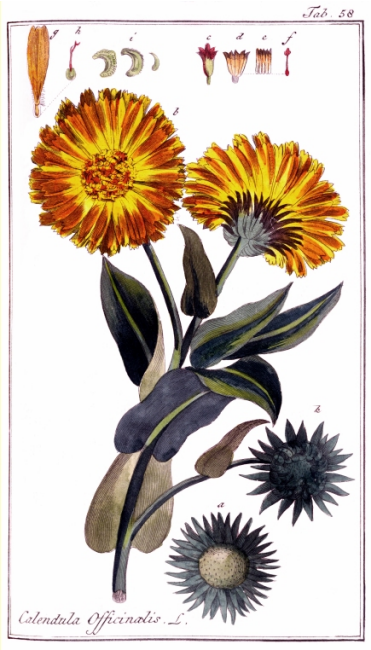
Clarke R, Hilakivi-Clarke L, Cho E. Estrogens, phytoestrogens and breast cancer. Adv Exp Med Biol 401 (1996): 63-85.

Clifton-Bligh PB et al. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause 8.4 (2001): 259-65.

Felter HW, Lloyd JU. King's American Dispensatory, 18th edn. Portland: Eclectic Medical Publications, 1983.

Fotsis T, Pepper M, Adlercreutz H. Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. J Nutr 125 (1995): 790-7.

Fugh-Berman A, Kronenberg F. Red clover (Trifolium pratense) for menopausal women: Current state of knowledge. Menopause 8.5 (2001): 333-7.
Hale GE et al. A double-blind randomized study on the effects of red clover isoflavones on the endometrium. Menopause 8.5 (2001): 338-46.
He X, Lin Z, Lian L.Analysis of flavonoids from red clover by liquid chromatography-electrospray mass spectrometry. J Chromatogr A 755.1 (1996): 127-32.
Hempstock JP, Kavanagh JP, George NJR. Growth inhibition of prostate cell lines in vitro by phyto-oestrogens. Br J Urol 82.4 (1998): 560-3.
Hidalgo LA et al. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study. Gynecol Endocrinol 21.5 (2005): 257-64.
Howes JB et al. The effects of dietary supplementation with isoflavones from red clover on the lipoprotein profiles of post menopausal women with mild to moderate hypercholesterolaemia. Atherosclerosis 152.1 (2000): 143-7.
Howes JB et al. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. Diabetes Obes Metab 5.5 (2003): 325-32.
Ingram D et al. Case control study of phyto-oestrogens and breast cancer. Lancet 350 (1997): 990-4.
Jarred RA et al. Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones. Cancer Epidemiol Biomarkers Prev 11.12 (2002): 1689-96.
Jarred RA et al. Anti-androgenic action by red clover-derived dietary isoflavones reduces non-malignant prostate enlargement in aromatase knockout (ArKo) mice. Prostate 56.1 (2003): 54-64.
Joannou GE, Kelly GE, Reeder AY. A urinary profile study of dietary phytoestrogens: the identification and mode of metabolism of new isoflavonoids. J Steroid Biochem Mol Biol 54 (1995): 167-84.
Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric 2.2 (1999): 79-84.
Krebs EE et al. Phytoestrogens for treatment of menopausal symptoms: a systematic review. Obstet Gynecol 104.4 (2004): 824-36.
Miksicek RJ. Interaction of naturally occurring nonsteroidal estrogens with expressed recombinant human estrogen receptor. J Steroid Biochem Mol Biol 49.2-3 (1994): 153-60.
Nachtigall LB et al. The effects of isoflavone derived red clover on vasomotor symptoms, endometrial thickness, and reproductive hormone concentrations in menopausal women. In; Proceedings of 81st Annual Meeting of the Endocrine Society, San Diego, California, 1999.
Nestel PJ et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. J Clin Endocrinol Metab 84.3 (1999): 895-8.
Pagliaaci MC, Smacchia M, Migliorati G. Growth inhibitory effects of the natural phyto-oestrogen genistein in MCF-7 human breast cancer cells. Eur J Cancer 30A (1994): 1675-82.
Rowland I et al. Bioavailability of phyto-oestrogens. Br J Nutr 89 (Suppl 1) (2003): S45-58.
Samman S et al. The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women. Atherosclerosis 147.2 (1999): 277-83.
Schult TM et al. Effect of isoflavones on lipids and bone turnover markers in menopausal women. Maturitas 48.3 (2004): 209-18.
Slater M, Brown D, Husband A. In the prostatic epithelium, dietary isoflavones from red clover significantly increase estrogen receptor beta and E-cadherin expression but decrease transforming growth factor beta1. Prostate Cancer Prostatic Dis 5.1 (2002): 16-21.
Teede HJ et al. Isoflavones reduce arterial stiffness: A placebo-controlled study in men and postmenopausal women. Arteriosclerosis Thromb Vasc Biol 23.6 (2003): 1066-71.
Tice JA et al. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA 290.2 (2003): 207-14.
Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.



van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. Maturitas 42.3 (2002): 187-93.
Wong E. The oestrongenic activity of red clover isoflavones and some of their degradation products. J Endocrinol 24 (1962): 341-8.
Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217.3 (1998): 369-78.

Rosemary

Historical note Since ancient times rosemary has been used as a tonic and stimulant. The ancient Greeks used it to strengthen memory function and scholars wore garlands of rosemary during examinations in order to improve their memory and concentration (Blumenthal et al 2000). It is widely used as a food spice and as an antioxidant to preserve foods.

COMMON NAME
Rosemary

OTHER NAMES
Compass plant, compass-weed, garden rosemary, old man, polar plant, *Rosmarini folium*

BOTANICAL NAME/FAMILY
Rosmarinus officinalis (family Labiatae or Lamiaceae)

PLANT PART USED
Fresh or dried leaf

CHEMICAL COMPONENTS
Phenolic acids and diterpenoid bitter substances, including carnosic acid and carnosol (Aruoma et al 1992, Bicchi et al 2000, Wei & Ho 2006), triterpenoid acids, flavonoids, tannins and volatile oils (0.5–2.5%) that consist of cineole, pinene, terpineol, camphor, camphene, borneol and bornyl acetate (Blumenthal et al 2000). Rosemary has also been found to contain high amounts of salicylates (Swain et al 1985).

MAIN ACTIONS

ANTIOXIDANT
Rosemary has strong antioxidant activity and is widely used to preserve food and cosmetics (Etter 2004). Rosemary leaf extract has been shown to enhance superoxide dismutase activity (Kim et al 1995) and to have an effect stronger than vitamin E in scavenging oxygen radicals (Zhao et al 1989). It is suggested that carnosol and carnosic acid account for over 90% of its antioxidant properties (Aruoma et al 1992, 1996). Carnosic acid has been shown to have a photoprotective action on human dermal fibroblasts exposed to UVA light in vitro (Offord et al 2002) and rosemary extract inhibits oxidative alterations to skin surface lipids, both in vitro and in vivo

(Calabrese et al 2000), as well as enhancing cell-mediated immunity in rats under oxidative stress (Babu et al 1999). In a study of 150 patients with bronchitis exposed to essential oils of rosemary, basil, fir and eucalyptus, an antioxidant effect was observed (Siurin 1997).

ANTIBACTERIAL

Rosemary extract demonstrates in vitro antibacterial activity against a variety of bacteria (Del Campo et al 2000, Erdogrul 2002, Ouattara et al 1997) including *Helicobacter pylori* (Mahady et al 2005) and *Staphylococcus aureus* (Oluwatuyi et al 2004). Topical application of rosemary essential oil preparations has been found to have antifungal activity (Ouraini et al 2005, Steinmetz et al 1988, Suleimanova et al 1995) and to inhibit the growth and aflatoxin production of *Aspergillus* spp. at concentrations between 0.2% and 1% (Tantaoui-Elaraki & Beraoud 1994). Carnosol has been found to have anti-HIV activity (Aruoma et al 1996) and carnosic acid has also been shown to have an inhibitory effect on HIV-1 protease in cell-free assays (Paris et al 1993). Rosemary extract has some antiviral activity against HSV (Vijayan et al 2004). Powdered rosemary leaves are said to be effective as a natural flea and tick repellent and rosemary essential oil has been found to be ovicidal and repellent towards mosquito (Prajapati et al 2005).

ANTI-INFLAMMATORY

In vitro studies have found that rosemary extracts inhibited inflammatory-induced peroxynitrite radical and nitrite production (Chan et al 1995, Choi et al 2002) and that carnosol suppresses NO production (Lo et al 2002). Rosmarinic acid has been found to increase the production of PGE_2, reduce the production of leukotriene B_4 in human polymorphonuclear leucocytes, and inhibit the complement system (al-Sereiti et al 1999).

HEPATOPROTECTIVE

The hepatoprotective properties of rosemary extract are attributed to its antioxidant properties and improving detoxification systems dependent on glutathione S-transferase (Sotelo-Felix et al 2002). Rosemary extract has been shown to reduce thioacetamide-induced cirrhosis (Galisteo et al 2000) and azathioprine-induced toxicity in rats (Amin & Hamza 2005), as well as partially prevent carbon tetrachloride induced liver damage in both rats (Sotelo-Felix et al 2002) and mice (Fahim et al 1999, Sotelo-Felix et al 2002).

CHEMOPROTECTION AND ANTIMUTAGENIC EFFECTS

In vivo studies suggest that rosemary extract may reduce the effects of carcinogenic or toxic agents on many cell lines, including rat mammary gland (Amagase et al 1996, Singletary et al 1996), mouse liver and stomach (Singletary & Rokusek 1997), bone marrow (Fahim et al 1999) and skin (Huang et al 1994).

An in vitro study on human bronchial cells found that rosemary extract and its constituents, carnosol and carnosic acid, may have chemoprotective activity through decreasing carcinogen activation via inhibition of the enzyme cytochrome P450 (CYP1A1) and increasing carcinogen detoxification by induction of phase II enzymes (Offord et al 1995). Carnosol has been found to also restrict the invasive ability of mouse melanoma cells in vitro by reducing MMP-9 expression and activity (Huang et al 2005).

INCREASES OESTROGEN METABOLISM

Feeding female mice a 2% rosemary diet enhanced the liver microsomal metabolism of endogenous oestrogens (Zhu et al 1998), thereby reducing oestrogen levels.

OTHER ACTIONS

Carnosic acid and carnosol, which are major components of rosemary, have been found to markedly enhance synthesis of nerve growth factor in vitro (Kosaka & Yokoi 2003). Rosemary has been also demonstrated to have significant antithrombotic activity in vitro and in vivo, possibly through a direct inhibitory effect on platelets (Yamamoto et al 2005). Rosemary essential oil and its constituent monoterpenes, such as borneol, have been found to inhibit bone resorption in the rat (Muhlbauer et al 2003). Aqueous and ethanol extracts of rosemary have been found to produce significant antinociceptive activity and diminish morphine withdrawal syndrome in rats (Hosseinzadeh & Nourbakhsh 2003).

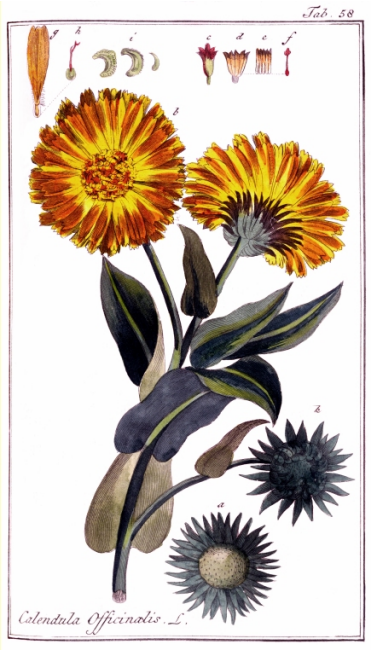
Rosemary extract may delay and inhibit tumour formation in women with breast cancer (Abascal & Yarnell 2001) and prevent mesangial cell proliferation in cultured murine mesangial cells (Makino et al 2000).

When used topically, rosemary essential oil is said to stimulate the skin and increase blood circulation (Blumenthal et al 2000).

CLINICAL USE

INCREASED MENTAL CONCENTRATION

One of the main traditional uses of rosemary oil is to increase mental concentration and memory. This is supported by a RCT of 140 subjects that found that rosemary produced a significant enhancement of performance for overall quality of memory and secondary memory factors, with an impairment of speed of memory compared



with controls (Moss et al 2003). Further support comes from an observational study in 40 adults where 3 minutes' exposure to rosemary essential oil was seen to decrease frontal alpha and beta power, suggesting increased alertness. Subjects felt more relaxed and alert, had lower anxiety scores and were faster, but not more accurate, at completing maths computations (Diego et al 1998). A small, case series of 10 subjects also found that rosemary essential oil had positive effects on mood concentration and memory (Svoboda et al 2002).

ALOPECIA

The traditional use of rosemary to stimulate hair growth is supported by a 7-month, randomised double-blind study of 86 patients that found rubbing oils (thyme, rosemary, lavender and cedarwood) into the scalp helped with alopecia for 44% of patients versus 15% of controls (Hay et al 1998). Although promising, the role of rosemary as a stand-alone substance in achieving these results is unclear.

ANTISPASMODIC

Rosemary is widely acknowledged to be a carminative and is used internally as an antispasmodic for mild cramp-like gastrointestinal and biliary upsets, as well as for tension headache, renal colic and dysmenorrhoea (Blumenthal et al 2000). It is also used to relax bronchial smooth muscle in the treatment of asthma (al-Sereiti et al 1999), but controlled studies are unavailable to determine clinical efficacy.

CHEMOPROTECTIVE AND ADJUNCT IN CANCER THERAPY

Rosemary was used topically to treat cancer in ancient Greece and South America. Although controlled trials are yet to be conducted, it has been suggested that rosemary may delay and inhibit tumour formation in women with breast cancer (Abascal & Yarnell 2001) and that it has potential as a preventive agent or as an adjunct in cancer therapy. An in vitro study in human breast cancer cells found that rosemary extract increased the intracellular accumulation of commonly used chemotherapeutic agents, including doxorubicin and vinblastine via inhibition of P-glycoprotein, thereby overcoming multidrug resistance in tumour cells (Plouzek et al 1999). Clinical studies are required to determine whether the effect is significant.

OTHER USES

When applied topically, rosemary oil may stimulate the blood supply and act as supportive therapy for rheumatic conditions and circulatory problems (Blumenthal et al 2000). Topically, rosemary has also been used for wound healing, as an insect repellent, and to treat toothache and eczema. Rosemary extract cream preparations

have been shown to protect against sodium-lauryl-sulfate-induced irritant contact dermatitis (Fuchs et al 2005).

In a small, uncontrolled, prospective pilot study of eight women, rosemary in combination with 11 other botanical extracts was found to relieve menopausal symptoms (Smolinski et al 2005).

DOSAGE RANGE

- Infusion of dried leaf: 2–4 g three times daily.
- Fluid extract (45%): 1–4 mL three times daily.
- Topical preparations containing 6–10% essential oil can be applied directly to skin. Often a carrier oil, such as almond oil, is used as a vehicle for the essential oil.
- Bath additive: 10 drops essential oil added to bath.

ADVERSE REACTIONS

Rosemary is generally recognised as safe for human consumption in quantities used as food. Consuming large amounts of rosemary may cause stomach and intestinal irritation, as well as seizures, owing to the high content of highly reactive monoterpene ketones, such as camphor (Burkhard et al 1999). Topically, rosemary is not considered to be highly allergenic; however allergic contact dermatitis from rosemary has been reported (Fernandez et al 1997, Hjorther et al 1997, Inui & Katayama 2005), as has asthma from repeated occupational exposure (Lemiere et al 1996). Rosemary essential oil should be diluted before topical application to minimise irritation.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

IRON

Rosemary extracts are widely used as an antioxidant to preserve foods; however, the phenolic-rich extracts may reduce the uptake of dietary iron (Samman et al 2001). Separate doses by 2 hours.

ANTICOAGULANTS

Increased bruising and bleeding theoretically possible — use caution.

DRUGS DEPENDENT ON P-GLYCOPROTEIN TRANSPORT

Theoretically, increased drug uptake can occur with those drugs dependent on P-glycoprotein transport. The clinical significance of this finding remains to be tested, although it has been suggested that this activity may be used to enhance the effects of chemotherapeutic agents (Plouzek et al 1999).

CONTRAINDICATIONS AND PRECAUTIONS

None known

PREGNANCY USE

Rosemary has been shown to have an anti-implantation effect in rats, without interfering with normal fetal development post-implantation (Lemonica et al 1996). It has been used as an abortive in Brazilian folk medicine and is not recommended for use in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Rosemary is widely used as a food seasoning and preservative.
- Rosemary extract exhibits antioxidant, antibacterial, anti-inflammatory, hepatoprotective and chemoprotective activity in various in vitro and experimental models.
- Rosemary oil is widely used to assist in concentration and memory and to stimulate blood flow.
- Traditionally, it has been used to relieve stomach, gall bladder and menstrual cramps, but its internal use has not yet been significantly investigated in controlled studies.
- Rosemary is generally safe when the leaves are consumed in dietary amounts, although excessive intake may cause stomach irritation and seizures in susceptible people.

REFERENCES

Abascal K, Yarnell E. Herbs and breast cancer: Research review of seaweed, rosemary, and ginseng. Alt Complement Ther 7(1) (2001): 32-6.

al-Sereiti MR et al. Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol 37(2) (1999): 124-30.

Amagase H et al. Dietary rosemary suppresses 7,12-dimethylbenz(a)anthracene binding to rat mammary cell DNA. J Nutr 126(5) (1996): 1475-80.

Amin A, Hamza AA. Hepatoprotective effects of Hibiscus, Rosmarinus and Salvia on azathioprine-induced toxicity in rats. Life Sci 77(3) (2005): 266-78.

Aruoma OI et al. Antioxidant and pro-oxidant properties of active rosemary constituents: carnosol and carnosic acid. Xenobiotica 22(2) (1992): 257-68.

Aruoma OI et al. An evaluation of the antioxidant and antiviral action of extracts of rosemary and Provencal herbs. Food Chem Toxicol 34(5) (1996): 449-56.

Babu US et al. Effect of dietary rosemary extract on cell-mediated immunity of young rats. Plant Foods Hum Nutr 53(2) (1999): 169-74.

Bicchi C et al. Determination of phenolic diterpene antioxidants in Rosemary (Rosmarinus officinalis L.) with different methods of extraction and analysis. Phytochem Anal 11(4) (2000): 236-42.

Blumenthal M et al. Herbal Medicine: Expanded Commission E Monographs. American Botanical Council, 2000.

Burkhard PR et al. Plant-induced seizures: reappearance of an old problem. J Neurol 246(8) (1999): 667-70.

Calabrese V et al. Biochemical studies of a natural antioxidant isolated from rosemary and its application in cosmetic dermatology. Int J Tissue React 22(1) (2000): 5-13.
Chan M-Y et al. Effects of three dietary phytochemicals from tea, rosemary and turmeric on inflammation-induced nitrite production. Cancer Lett 96(1) (1995): 23-9.
Choi HR et al. Peroxynitrite scavenging activity of herb extracts. Phytother Res 16(4) (2002): 364-7.
Del Campo J et al. Antimicrobial effect of rosemary extracts. J Food Protect 63(10) (2000): 1359-68.
Diego MA et al. Aromatherapy positively affects mood, EEG patterns of alertness and math computations. Int J Neurosci 96(3-4) (1998): 217-24.
Erdogrul OT. Antibacterial activities of some plant extracts used in folk medicine. Pharm Biol 40(4) (2002): 269-73.
Etter SC. Rosmarinus officinalis as an antioxidant. J Herbs Spices Med Plants 11(1-2) (2004): 121-59.
Fahim FA et al. Allied studies on the effect of Rosmarinus officinalis L. on experimental hepatotoxicity and mutagenesis. Int J Food Sci Nutr 50(6) (1999): 413-27.
Fernandez L et al. Allergic contact dermatitis from rosemary (Rosmarinus officinalis L.). Contact Dermatitis 37(5) (1997): 248-9.
Fuchs SM et al. Protective effects of different marigold (Calendula officinalis L.) and rosemary cream preparations against sodium-lauryl-sulfate-induced irritant contact dermatitis. Skin Pharmacol Physiol 18(4) (2005): 195-200.
Galisteo M et al. Antihepatotoxic activity of Rosmarinus tomentosus in a model of acute hepatic damage induced by thioacetamide. Phytother Res 14(7) (2000): 522-6.
Hay IC et al. Randomized trial of aromatherapy: Successful treatment for alopecia areata [Comment]. Arch Dermatol 134(11) (1998): 1349-52.
Hjorther AB et al. Occupational allergic contact dermatitis from carnosol, a naturally-occurring compound present in rosemary. Contact Dermatitis 37(3) (1997): 99-100.
Hosseinzadeh H, Nourbakhsh M. Effect of Rosmarinus officinalis L. aerial parts extract on morphine withdrawal syndrome in mice. Phytother Res 17(8) (2003): 938-41.
Huang MT et al. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. Cancer Res 54(3) (1994): 701-8.
Huang S-C et al. Carnosol inhibits the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9 through down-regulating nuclear factor-kappaB and c-Jun. Biochem Pharmacol 69(2) (2005): 221-32.
Inui S, Katayama I. Allergic contact dermatitis induced by rosemary leaf extract in a cleansing gel. J Dermatol 32(8) (2005): 667-9.
Kim SJ et al. Measurement of superoxide dismutase-like activity of natural antioxidants. Biosci Biotech Biochem 59(5) (1995): 822-6.
Kosaka K, Yokoi T. Carnosic acid, a component of rosemary (Rosmarinus officinalis L.), promotes synthesis of nerve growth factor in T98g human glioblastoma cells. Biol Pharm Bull 26(11) (2003): 1620-2.
Lemiere C et al. Occupational asthma caused by aromatic herbs. Allergy 51(9) (1996): 647-9.
Lemonica IP et al. Study of the embryotoxic effects of an extract of rosemary (Rosmarinus officinalis L.). Braz J Med Biol Res 29(2) (1996): 223-7.
Lo AH et al. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-kappaB in mouse macrophages. Carcinogenesis 23(6) (2002): 983-91.
Mahady GB et al. In vitro susceptibility of Helicobacter pylori to botanical extracts used traditionally for the treatment of gastrointestinal disorders. Phytother Res 19(11) (2005): 988-91.
Makino T et al. Inhibitory effects of rosmarinic acid on the proliferation of cultured murine mesangial cells. Nephrol Dial Transplant 15(8) (2000): 1140-5.
Moss M et al. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci 113(1) (2003): 15-38.
Muhlbauer RC et al. Common herbs, essential oils, and monoterpenes potently modulate bone metabolism. Bone 32(4) (2003): 372-80.

Offord EA et al. Rosemary components inhibit benzo[a]pyrene-induced genotoxicity in human bronchial cells. Carcinogenesis 16(9) (1995): 2057-62.
Offord EA et al. Photoprotective potential of lycopene, beta-carotene, vitamin E, vitamin C and carnosic acid in UVA-irradiated human skin fibroblasts. Free Radic Biol Med 32(12) (2002): 1293-303.
Oluwatuyi M et al. Antibacterial and resistance modifying activity of Rosmarinus officinalis. Phytochemistry 65(24) (2004): 3249-54.
Ouattara B et al. Antibacterial activity of selected fatty acids and essential oils against six meat spoilage organisms. Int J Food Microbiol 37(2-3) (1997): 155-62.
Ouraini D et al. Therapeutic approach to dermatophytoses by essential oils of some Moroccan aromatic plants. Phytotherapie 3(1) (2005): 3-12.
Paris A et al. Inhibitory effect of carnosic acid on HIV-1 protease in cell-free assays [corrected][erratum appears in J Nat Prod 57(4) (1994): 552]. J Nat Prod 56(8) (1993): 1426-30.
Plouzek CA et al. Inhibition of P-glycoprotein activity and reversal of multidrug resistance in vitro by rosemary extract. Eur J Cancer 35(10) (1999): 1541-5.
Prajapati V et al. Insecticidal, repellent and oviposition-deterrent activity of selected essential oils against Anopheles stephensi, Aedes aegypti and Culex quinquefasciatus. Bioresource Technol 96(16) (2005): 1749-57.
Samman S et al. Green tea or rosemary extract added to foods reduces nonheme-iron absorption. Am J Clin Nutr 73(3) (2001): 607-12.
Singletary KW, Rokusek JT. Tissue-specific enhancement of xenobiotic detoxification enzymes in mice by dietary rosemary extract. Plant Foods Hum Nutr 50(1) (1997): 47-53.
Singletary K et al. Inhibition by rosemary and carnosol of 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumorigenesis and in vivo DMBA-DNA adduct formation. Cancer Lett 104(1) (1996): 43-8.
Siurin SA. Effects of essential oil on lipid peroxidation and lipid metabolism in patients with chronic bronchitis. Klin Med 75(10) (1997): 43-5.
Smolinski D et al. A pilot study to examine a combination botanical for the treatment of menopausal symptoms. J Alt Complement Med 11(3) (2005): 483-9.
Sotelo-Felix JI et al. Evaluation of the effectiveness of Rosmarinus officinalis (Lamiaceae) in the alleviation of carbon tetrachloride-induced acute hepatotoxicity in the rat. J Ethnopharmacol 81(2) (2002): 145-54.
Steinmetz MD et al. Transmission and scanning electronmicroscopy study of the action of sage and rosemary essential oils and eucalyptol on Candida albicans. Mycoses 31(1) (1988): 40-51.
Suleimanova AB et al. Experimental assessment of fungicidal activity of 3% ointment with wild rosemary ether oil in external therapy of T. rubrum-induced mycosis of the soles. [Russian]. Vestn Dermatol Venerol 71(1) (1995): 17-18.
Svoboda KP et al. Case study: The effects of selected essential oils on mood, concentration and sleep in a group of 10 students monitored for 5 weeks. Int J Aromather 12(3) (2002): 157-61.
Swain AR et al. Salicylates in foods. J Am Diet Assoc 85(8) (1985): 950-60.
Tantaoui-Elaraki A, Beraoud L.Inhibition of growth and aflatoxin production in Aspergillus parasiticus by essential oils of selected plant materials. J Environ Pathol Toxicol Oncol 13(1) (1994): 67-72.
Vijayan P et al. Antiviral activity of medicinal plants of Nilgiris. Indian J Med Res 120(1) (2004): 24-9.
Wei G-J, Ho C-T. A stable quinone identified in the reaction of carnosol, a major antioxidant in rosemary, with 2,2-diphenyl-1-picrylhydrazyl radical. Food Chem 96(3) (2006): 471-6.
Yamamoto J et al.Testing various herbs for antithrombotic effect. Nutrition 21(5) (2005): 580-7.
Zhao BL et al. Scavenging effect of extracts of green tea and natural antioxidants on active oxygen radicals. Cell Biophys 14(2) (1989): 175-85.
Zhu BT et al. Dietary administration of an extract from rosemary leaves enhances the liver microsomal metabolism of endogenous estrogens and decreases their uterotropic action in CD-1 mice. Carcinogenesis 19(10) (1998): 1821-7.

Sage

Historical note Sage has been used since ancient times as an antiseptic, astringent and to reduce sweating. The name 'Salvia' derives from the Latin salvere (to be saved) (Blumenthal et al 2000). Sage oil is used as a culinary spice and as a fragrance in soaps and perfumes. The fragrance is said to suppress the odour of fish.

OTHER NAMES
Broad-leafed sage, common sage, dalmatian sage, garden sage, meadow sage, Spanish sage, true sage

BOTANICAL NAME/FAMILY
Salvia officinalis, Salvia lavandulaefolia (family Labiatae or Lamiaceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
The leaves contain up to 2.5% essential oil, which contains thujone, cineol and camphor, as well as humulene, pinene, camphene, limonene, carnosol and rosmarinic acid. In addition, the leaves contain catechin-type tannins, diterpene bitter principles, triterpenes, steroids, flavones, and flavonoid glycosides, together with polysaccharides. Sage is a rich source of beta-carotene, vitamins C and B-complex (Fisher & Painter 1996). Pharmacopoeial grade sage leaf must contain not less than 1.5% thujone-rich volatile oil (Blumenthal et al 2000).

MAIN ACTIONS
ANTIMICROBIAL
Sage is reported to have antimicrobial activity attributed to the thujone, thymol and eugenol content of the volatile oil (Shapiro 1994), as well as its rosmarinic acid content (Petersen & Simmonds 2003). The phenolic acids, salvins and monomethyl ethers have also been attributed with antimicrobial activity. Overall, activity has been reported in vitro against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., *Shigella sonnei*, *Klebsiella ozanae*, *Bacillus subtilis* and various fungi including *Candida albicans* (Newell et al 1996). Phenolic extracts have also shown antibacterial activity against *Enterococcus* (Feres et al 2005). Sage had some in vitro antimicrobial

effects on saliva samples from periodontally healthy and diseased subjects, although it had less activity than clove or propolis (Feres et al 2005). Sage essential oil has been shown to have effective inhibitory activity against microorganisms, such as *Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus mirabilis* and *Morganella morganii*, isolated from urinary tract infection (Santos Pereira et al 2004). There are also reports that sage may also be fungistatic and virustatic (Eidi et al 2005).

ANTIOXIDANT

Sage extracts have been shown to have strong anti-oxidant activity (Matsingou et al 2003, Pizzale et al 2002), with labiatic acid and carnosic acid reported to be the active compounds (Perry et al 2003). According to in vivo studies with animal models, ingestion of sage infusion improves the liver's antioxidant status (Lima et al 2005) and protects against azathioprine-induced toxicity (Amin & Hamza 2005). However, sage essential oil did not show protective effects against toxicity from an oxidative compound in isolated rat hepatocytes (Lima et al 2004).

ASTRINGENT

The high tannin content of sage supports its reported astringent activity.

ANTISPASMODIC

Sage oil has antispasmodic effects in laboratory animals (Newell et al 1996) and this is likely due to the irritating effects of the volatile oil. There is some evidence that sage oil may also exert a centrally mediated antisecretory action.

ANXIOLYTIC

Rosmarinic acid, which is a component of sage essential oil, produces an anxiolytic-like effect without exerting locomotor alterations or DNA damage in the brain tissue of rats (Pereira et al 2005). According to in vitro tests, compounds in the methanolic extract have an affinity for human brain benzodiazepine receptors (Kavvadias et al 2003).

OTHER ACTIONS

In vitro and in vivo studies suggest that sage essential oil and some individual monoterpenoid constituents inhibit acetylcholinesterase activity, as well as exert anti-oxidant, anti-inflammatory and oestrogenic effects (Perry et al 2003). The water soluble polysaccharide complex from sage has demonstrated immunomodulatory activity (Capek & Hribalova 2004) and the terpenoid fractions have shown antimutagenic properties in vivo (Vujosevicacute et al 2004).

Sage extract has been found to also significantly decrease serum glucose in diabetic rats without affecting insulin release, suggesting a possible role in diabetes

(Eidi et al 2005). It has been suggested that extracts of sage containing carnosic acid may act as a new class of lipid absorption inhibitor. A methanolic extract of sage has also shown significant inhibitory effect on serum triglyceride elevation in olive oil-loaded mice, and inhibitory activity against pancreatic lipase, mainly because of the carnosic acid content. Carnosic acid was also found to reduce the weight gain and accumulation of epididymal fat in high-fat-diet fed mice after 14 days (Ninomiya et al 2004).

CLINICAL USE

Although sage has not been the subject of many clinical studies, many of its constituents demonstrate significant pharmacological effects, providing a theoretical basis for some of its uses.

REDUCES SECRETIONS

Sage has been traditionally used to treat excessive perspiration and salivation, as well as dysmenorrhoea, diarrhoea, galactorrhoea, sweats associated with menopause and to cease lactation (Fisher & Painter 1996). An open study of 80 patients confirmed that it can reduce perspiration (Blumenthal et al 2000). The high tannin content of the herb provides a theoretical basis for its use.

DYSPEPSIA AND LACK OF APPETITE

Sage's reported antispasmodic action and bitter constituents support its use in treating loss of appetite, gastritis, flatulence, bloating and dyspepsia. These uses await support from clinical research.

INFLAMMATION OF MUCOUS MEMBRANES

Topically, sage is used as a gargle for laryngitis, pharyngitis, stomatitis, gingivitis, glossitis, minor oral injuries and inflammation of the nasal mucosa (Blumenthal et al 2000). These uses can be based on the pharmacological activity of its chemical components. In an open-label, single-blind, RCT of 420 patients, the non-steroidal anti-inflammatory drug, benzydamine hydrochloride, was found to be more effective than sage in relieving postoperative pain when used as a mouthwash after tonsillectomy in children and adults (Lalicevic & Djordjevic 2004).

Sage has been found to have less antitussive effects than codeine, but a significantly higher or similar effect to dropropizine (Nosalova et al 2005). A small, double-blind study has suggested that use of an essential oil spray or gargle formulation that includes sage may help relieve snoring (Prichard 2004).

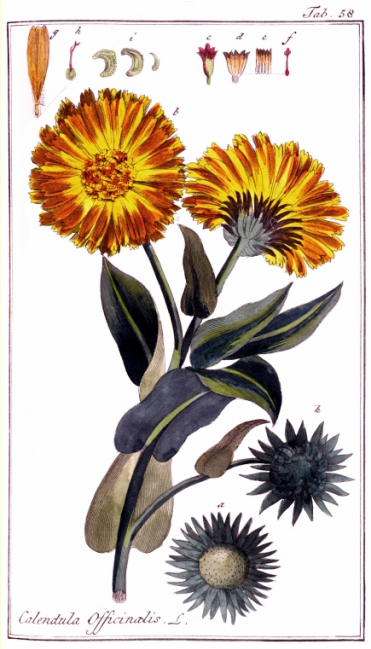
MEMORY ENHANCEMENT

Since ancient times sage has been used to enhance memory and treat dementia. More recently, cholinergic activities have been demonstrated in vitro and in vivo, suggesting that it may be useful in treating Alzheimer's disease (Perry et al 2001). A randomised placebo-controlled study undertaken at three centres assessed the effects of sage extract (60 drops/day) in 42 subjects with mild to moderate Alzheimer's disease (Akhondzadeh et al 2003). Initially, subjects had a score of 12 or less on the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and two or less on the Clinical Dementia Rating (CDR). At 4 months, sage extract produced a significantly better outcome on cognitive functions than placebo in both test scales and was well tolerated.

In 2003, two placebo-controlled, double-blind crossover studies involving 44 healthy young adults investigated the effects of different strengths of standardised essential oil of *S. lavandulaefolia* on memory (Tildesley et al 2003). Both studies found that a 50-microlitre dose of *Salvia* essential oil significantly improved immediate word recall and was able to modulate cognition. In another placebo-controlled, double-blind, crossover study involving 24 subjects, Spanish sage (*S. lavandulaefolia*) essential oil was found to enhance cognitive performance and mood in healthy young adults (Tildesley et al 2005).

MENOPAUSAL SYMPTOMS

Sage is commonly used by modern herbalists in prescriptions for menopause in order to treat hot flushes, night sweats, and for its oestrogenic effect. As yet there is no clinical evidence available to confirm effectiveness for these indications (Blumenthal et al 2000).



OTHER USES

As an inhalant, sage is used for asthma. In foods, it is used as a culinary spice. In manufacturing, sage is used as a fragrance component in soaps and cosmetics.

DOSAGE RANGE

INTERNAL USE

- Infusion of dried herb: 1–4 g three times daily.
- Tincture (1:1): 1–4 mL three times daily.
- Essential oil: 2–3 drops in 100 mL water several times daily.
- Gargle or rinse (use warm infusion): 2.5 g cut leaf in 100 mL water; or 2–3 drops essential oil in 100 mL water; or use 5 mL fluid extract diluted in a glass of water, several times daily.

TOXICITY

Sage is likely to be safe when taken in amounts typically found in foods, although sage oil contains thujone, which may be toxic in large doses. In large amounts, the camphor and thujone content of sage oil have been shown to have convulsant properties in rats (Millet et al 1981) and when taken internally in large amounts, sage may cause restlessness and seizures in humans (Blumenthal et al 2000, Newell et al 1996). Sage tea has also been reported to cause cheilitis and stomatitis, dry mouth and local irritation.

ADVERSE REACTIONS

One, double-blind randomised trial found that it was well tolerated and produced fewer side-effects than placebo (Akhondzadeh et al 2003). Occasional allergic reactions with topical use have been reported.

SIGNIFICANT INTERACTIONS

IRON, CALCIUM, MAGNESIUM

Due to the tannin content, sage may reduce the absorption of these minerals — separate doses by 2–3 hours.

CONTRAINDICATIONS AND PRECAUTIONS

Sage oil can irritate the skin when used topically. Internal use of the essential oil should be closely monitored.

PREGNANCY USE

Traditionally, sage is reported to have abortifacient properties. Its use in pregnancy is therefore not recommended (Mills & Bone 2000, Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Sage is a widely used, popular spice and sage oil is used in a variety of culinary applications.
- Sage has a long history of use in traditional medicine as an antispasmodic and carminative, to relieve excess sweating and as a gargle for inflammations of the mouth.
- It is also commonly prescribed in combination with other herbs to relieve menopausal symptoms such as night sweats.
- Sage contains volatile oils and tannins that are thought to be the key constituents responsible for most of its pharmacological actions.
- It also has antibacterial and some antifungal activity.
- A recent double-blind study suggests it may be useful in mild to moderate Alzheimer's disease. Other studies report it improves memory in healthy subjects.

- Sage is likely to be safe when taken in amounts typically found in foods.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Sage is used to reduce symptoms of menopause such as night sweats; however, scientific testing has not been conducted to confirm whether it is effective. Recent research suggests it may improve memory in Alzheimer's disease and in healthy subjects.

When will it start to work?

The study in Alzheimer's disease found effects established within 4 months' use. In the case of menopause, a time frame is unknown.

Are there any safety issues?

When used in appropriate doses, it appears to be a safe herbal medicine; however, it should not be used in pregnancy.

REFERENCES

Akhondzadeh S et al. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther 28.1 (2003): 53-9.

Amin A, Hamza AA. Hepatoprotective effects of Hibiscus, Rosmarinus and Salvia on azathioprine-induced toxicity in rats. Life Sci 77.3 (2005): 266-78.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Capek P, Hribalova V. Water-soluble polysaccharides from Salvia officinalis L. possessing immunomodulatory activity. Phytochemistry 65.13 (2004): 1983-92.

Eidi M et al. Effect of Salvia officinalis L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats. J Ethnopharmacol 100.3 (2005): 310-13.

Feres ML et al. In vitro antimicrobial activity of plant extracts and propolis in saliva samples of healthy and periodontally-involved subjects. J Int Acad Periodontol 7.3 (2005): 90-6.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Kavvadias D et al. Constituents of sage (Salvia officinalis) with in vitro affinity to human brain benzodiazepine receptor. Plant Med 69.2 (2003): 113-17.

Lalicevic S, Djordjevic I. Comparison of benzydamine hydrochloride and Salvia officinalis as an adjuvant local treatment to systemic nonsteroidal anti-inflammatory drug in controlling pain after tonsillectomy, adenoidectomy, or both: an open-label, single-blind, randomized clinical trial. Curr Ther Res 65.4 (2004): 360-72.

Lima CF et al. Evaluation of toxic/protective effects of the essential oil of Salvia officinalis on freshly isolated rat hepatocytes. Toxicol In Vitro 18.4 (2004): 457-65.

Lima CF et al. The drinking of a Salvia officinalis infusion improves liver antioxidant status in mice and rats. J Ethnopharmacol 97.2 (2005): 383-9.

Matsingou TC et al. Antioxidant activity of organic extracts from aqueous infusions of sage. J Agric Food Chem 51.23 (2003): 6696-701.

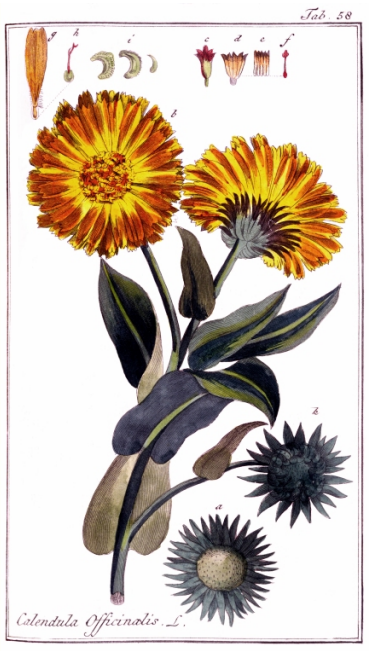
Millet Y et al. Toxicity of some essential plant oils: Clinical and experimental study. Clin Toxicol 18.12 (1981): 1485-98.

Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.

Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.

Ninomiya K et al. Carnosic acid, a new class of lipid absorption inhibitor from sage. Bioorg Med Chem Lett 14.8 (2004): 1943-6.
Nosalova G et al. Efficacy of herbal substances according to cough reflex. Minerva Biotecnol 17.3 (2005): 141-52.
Pereira P et al. Neurobehavioral and genotoxic aspects of rosmarinic acid. Pharmacol Res 52.3 (2005): 199-203.
Perry N et al. In-vitro activity of S. lavandulaefolia (Spanish sage) relevant to treatment of Alzheimer's disease. J Pharm Pharmacol 53.10 (2001): 1347-56.
Perry N et al. Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacol Biochem Behav 75.3 (2003): 651-9.
Petersen M, Simmonds MSJ. Rosmarinic acid. Phytochemistry 62.2 (2003): 121-5.
Pizzale L et al. Antioxidant activity of sage (Salvia officinalis and S. fruticosa) and oregano (Origanum onites and O. indercedens) extracts related to their phenolic compound content. J Sci Food Agric 82.14 (2002): 1645-51.
Prichard AJN. Use of essential oils to treat snoring. Phytother Res 18.9 (2004): 696-9.
Santos Pereira R et al. Antibacterial activity of essential oils on microorganisms isolated from urinary tract infection. Rev Saude Pub 38.2 (2004): 326-8.
Tildesley NT et al. Salvia lavandulaefolia (Spanish Sage) enhances memory in healthy young volunteers Pharmacol Biochem Behav 75.3 (2003): 669-74.
Tildesley NT et al. Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers. Physiol Behav 83.5 (2005): 699-709.
Vujosevicacute M et al. Antimutagenic effects of extracts from sage (Salvia officinalis) in mammalian system in vivo. Acta Vet Hung 52.4 (2004): 439-43.

St John's wort



Historical note St John's wort (SJW) has been used medicinally since ancient Greek times when, it is believed, Dioscorides and Hippocrates used it to rid the body of evil spirits. Since the time of the Swiss physician Paracelsus (*c.* 1493–1541), it has been used to treat neuralgia, anxiety, neurosis and depression. Externally, it has also been used to treat wounds, bruises and shingles. The name 'St John's wort' is related to its yellow flowers, traditionally gathered for the feast of St John the Baptist and the term 'wort' is the old English word for plant. St John's wort has enjoyed its greatest popularity in Europe and comprises 25% of all antidepressant prescriptions in Germany (Schrader 2000). In the past few decades its popularity has also grown in countries such as Australia and the United States.

OTHER NAMES

Amber, balsana, devil's scourge, goatweed, hardhay, hartheu, herb de millepertuis, hierba de San Juan, hypericum, iperico, johanniskraut, klamath weed, konradskraut, millepertuis, rosin rose, sonnenwendkraut, St Jan's kraut, tipton weed, witch's herb

BOTANICAL NAME/FAMILY

Hypericum perforatum (family Clusiaceae or Guttiferae)

PLANT PARTS USED

Aerial parts, flowering tops

CHEMICAL COMPONENTS

Naphthodianthrones (including hypericin and pseudohypericin). Flavonoids, mostly hyperoside, rutin, quercetin, isoquercitrin, quercetin and kaemferol, phenolics including hyperforin, procyanidins, essential oil, sterols (beta-sitosterol), vitamins C and A, xanthones and choline.

Manufactured products will vary in the concentrations and proportions of the different plant constituents present because these are influenced by the plant's place of origin, its harvest time and drying, extraction processes and storage conditions. Hyperforin, in particular, can be present in variable concentrations because it is unstable in light, air and most organic solvents (Mennini & Gobbi 2004). This is extremely important to remember when comparing studies, as variations in chemical

composition could be responsible for differences in results. It also provides a rationale for lack of interchangeability between brands.

Clinical note — Pharmacologically important constituents
It has generally been considered that most of the pharmacological activities of SJW are attributable to hypericin and the flavonoid constituent, hyperforin. Besides contributing to the antidepressant activity, hypericin is the primary constituent responsible for the photosensitivity reactions reported with high intakes. Hyperforin is also a major contributor to the herb's antidepressant activity (Butterweck et al 2003a, Mennini & Gobbi 2004) and considered the main constituent responsible for inducing the cytochrome P-glycoprotein and thereby producing drug interactions. Besides this, it demonstrates many other pharmacological effects such as antibacterial, anti-inflammatory and antineoplastic activities. Components previously considered void of activity have also been identified as important for pharmacological activity. For example, both procyanidin B2 and hyperoside increase the oral bioavailability of hypericin by 58% and 34%, respectively, and therefore, its clinical effects (Butterweck et al 2003b). A report published in June 2003 demonstrated that an extract devoid of both hyperforin and hypericin still exhibited antidepressant activity (Butterweck et al 2003a). Other constituents with antidepressant activity were identified and include hyperoside, isoquercitrin and miquelianin, and the 3-O-galactoside, 3-O-glucoside and 3-O-glucuronide of quercetin.

MAIN ACTIONS

Due to the combined effect of several active constituent groups, SJW has many pharmacological actions.

ANTIDEPRESSANT

Although SJW has been investigated extensively in scientific studies, there are still many questions about its pharmacology and mechanisms of action.

Collectively, the data show that SJW extract exerts significant pharmacological activity within several neurochemical systems believed to be implicated in the pathophysiology of depression.

Inhibits synaptic reuptake of several neurotransmitters Preclinical animal studies have found that SJW inhibits the synaptic reuptake system for serotonin, noradrenaline and dopamine (Nathan 1999, Wonnemann et al 2001). Studies using specific isolated constituents have demonstrated potent uptake inhibition of GABA and L-glutamate in vivo (Bilia et al 2002, Chatterjee et al 1998). These effects appear to be non-competitive, dose-dependent and mediated via sodium channels (Roz &

Rehavi 2004). Studies with hyperforin have shown it acts by reducing the pH gradient across the synaptic vesicle membrane, resulting in diffusion of uncharged monoamines out of the vesicular compartment into the cytoplasm. The increase in cytoplasmic concentration in turn decreases the transmembrane gradient of the neurotransmitters causing an 'apparent' inhibition of synaptosomal uptake by hyperforin. This is a novel mechanism of action, which differs from conventional antidepressant drugs.

Although hyperforin is the main constituent responsible for these effects, tests now show that a number of others are also involved (Gobbi et al 2001), such as adhyperforin, which has demonstrated a strong inhibitory effect on neurotransmitter uptake, and the oligomeric procyanidins fraction, which has demonstrated weak to moderate effects (Wonnemann et al 2001).

GABA receptor binding SJW extracts have been shown to bind at GABA-A and -B receptors, to inhibit GABA reuptake, to evoke GABA release from synaptosomes and to exert an anxiolytic effect that is blocked by the benzodiazepine antagonist flumazenil (Perfumi et al 2002).

Upregulation of serotonin receptors SJW significantly up-regulates both 5-HT_{1A} and 5-HT_{2A} receptors and has a significant affinity for opiate sigma-receptors, which may contribute to the antidepressant effect (Teufel-Mayer & Gleitz 1997).

Dopamine beta-hydroxylase inhibition Studies on isolated constituents showed that hypericin and pseudohypericin can inhibit the enzyme dopamine-beta-hydroxylase in vitro (Bilia et al 2002).

Inhibition of catechol-o-methyltransferase This has been demonstrated in test tube studies (Thiede & Walper 1994).

Suppresses IL-6 synthesis Various extracts from SJW produce a potent and dose-dependent inhibition of substance-P-induced IL-6 synthesis (Fiebich et al 2001), which may also contribute to the herb's overall antidepressant effect.

Monoamine oxidase (MAO) inhibition Inhibition of MAO by hypericin demonstrated in vitro was believed to be the primary mode of action; however, this has not been confirmed in several subsequent studies that have shown only weak inhibitory activity at doses in excess of usual therapeutic levels (Di Carlo et al 2001).

ANTIRETROVIRAL AND ANTIBACTERIAL

Although in vitro and studies in animal models have identified antiretroviral activity for hypericin and pseudohypericin (Meruelo et al 1988), two clinical trials could not confirm these effects, even when larger doses of hypericin were administered (Gulick et al 1999, Jacobson et al 2001).

The mechanism involved is not known; however, it is suspected to involve direct inactivation of the virus or prevention of virus shedding, budding or assembly at the cell membrane (Meruelo et al 1988). The presence of light is an important requirement for antiretroviral activity to be demonstrated as the effect appears to be photoactivated (Hudson et al 1993, Miskovsky 2002).

Hyperforin has also demonstrated antiviral and antibacterial activity (Medina et al 2006). Hyperforin exhibits effective antibacterial activity against MRSA and other Gram-positive bacteria, but no growth-inhibitory effect on Gram-negative bacteria or *Candida albicans* (Schempp et al 1999).

ANXIOLYTIC

Several in vivo studies confirm the anxiolytic effects of SJW extract (Beijamini & Andreatini 2003, Jakovljevic et al 2000, Vandenbogaerde et al 2000). Activity at the GABA receptors and an increase in circulating GABA levels are likely to be involved.

ANTI-INFLAMMATORY AND ANALGESIC

Both in vitro and in vivo testing has identified anti-inflammatory and analgesic activities for SJW (Jakovljevic et al 2000, Raso et al 2002). It potently inhibits binding to mu-, delta- and kappa-opioid receptors (Simmen et al 1998). In vivo tests also identify modulation of COX-2 expression for hypericum extract (Raso et al 2002). Studies with the isolated constituent hyperforin have shown it potently inhibits COX-1 and 5-lipo-oxygenase in vitro (Albert et al 2002). Quercetin and other flavonoids contribute to the anti-inflammatory effect.

ANTICANCER EFFECTS

Emerging evidence clearly indicates that hypericin is a promising tool in the photodynamic treatment of cancers. St John's wort appears to selectively photosensitise tumour cells. More recently, evidence suggests that when hyperthermia is combined with this approach, the antitumour effects of hypericin are strengthened (Chen et al 2002). Hyperforin also exhibits antineoplastic potential based on the sum of its anticarcinogenic, antiproliferant, pro-apoptotic, anti-invasive and antimetastasic effects (Medina et al 2006). Hyperforin has been shown to effectively decrease the proliferation rates of a number of mammalian cancer cell lines, induce apoptosis of tumour cells and inhibit angiogenesis both in vitro and in vivo. Besides hypericin and hyperforin, polyphenolic procyanidin B2 has also demonstrated an inhibitory effect on the growth of leukaemia cells, brain glioblastoma cells and normal human astrocytes in vitro (Hostanska et al 2003). Further, the inhibitory effects on leukaemic cell growth were synergistically strengthened when hypericin and hyperforin were tested together.

Clinical note — Photodynamic therapy for tumour cells
Photodynamic therapy is primarily an experimental treatment designed to destroy tumour cells without damaging surrounding normal tissues. This treatment involves the combination of a photosensitising substance, which is taken up and stored within tumour cells, and then the application of visible light at a wavelength matching the absorption spectrum of the photosensitising substance (Agostinis et al 2002). This combination approach results in the production of cytotoxic oxygen singlets within the tumour that cause irreversible cellular damage and tumour destruction.

REDUCES ALCOHOL INTAKE
Several reports indicate comorbidity between depression and ethanol abuse and that depressive disorders and ethanol abuse may be associated with similar changes in the activity of central neurotransmitters (Markou et al 1998). In vivo studies using SJW in animal models of alcoholism have found that it does not alter food and water intakes, or the pharmacokinetics of alcohol, but a reduction in ethanol intake occurs (Panocka et al 2000).

COGNITIVE EFFECTS
St John's wort extracts and hyperforin improve cognitive function in experimental models (Kiewert et al 2004); however, clinical studies have been less convincing (Siepmann et al 2002, Timoshanko et al 2001). In vivo studies with hyperforin have found it induces release of acetycholine from cholinergic terminals in the hippocampus and striatum, providing an explanation for the observed effects.

OTHER ACTIONS

INDUCTION OF CYP3A4 ACTIVITY IN THE INTESTINAL WALL
Human studies have identified CYP3A4 and 2C19 induction effects for standard SJW extracts (e.g. LI 160), but no effects on CYP1A2, CYP2C9 or CYP2D6 (Durr et al 2000, Jiang et al 2004, Wang et al 2001, 2004a).

Human studies have failed to identify significant CYP3A4, 2D6, 2C9, 1A2 or 2C19 induction for low-hyperforin SJW extracts, such as ZE 117, using the appropriate probe drugs (Arold et al 2005, Madabushi et al 2006, Mueller et al 2004).

Hyperforin is a potent ligand for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the CYP3A4 mono-oxygenase (Moore et al 2000). Although it is considered the chief constituent responsible for the pharmacokinetic interactions reported, there are other, less potent constituents in SJW which also modulate cytochrome enzymes (Obach 2000).

Results from an open label clinical study suggest that the effects of standard SJW (LI 160) on CYP3A4 enzymes may be biphasic, where the initial dose leads to a minor inhibition, followed by significant induction during long-term use (Rengelshausen et al 2005).

INCREASES LEVELS OF INTESTINAL P-GLYCOPROTEIN

SJW extract produced a 3.8-fold increase of intestinal P-glycoprotein (P-gp) expression in vivo (Durr et al 2000). Hyperforin has been identified as the key constituent responsible for P-gp induction effects (Tian et al 2005), although in vitro tests suggest other less potent constituents also exist such as quercetin, hypericin, biapigenin and kaempferol (Patel et al 2004, Weber et al 2004).

Once again, low hyperforin SJW extracts do not appear to significantly induce P-gp (Arold et al 2005, Madabushi et al 2006, Mueller et al 2004).

In vitro and in vivo tests further indicate that P-gp effects caused by standard SJW (LI 160) are biphasic with an initial inhibitory effect followed by induction after longer exposure (Rengelshausen et al 2005, Wang et al 2004a).

ANTISPASMODIC

St John's wort exhibits antispasmodic activity, according to research conducted with an experimental animal model (Jakovljevic et al 2000), most likely mediated via GABA activity.

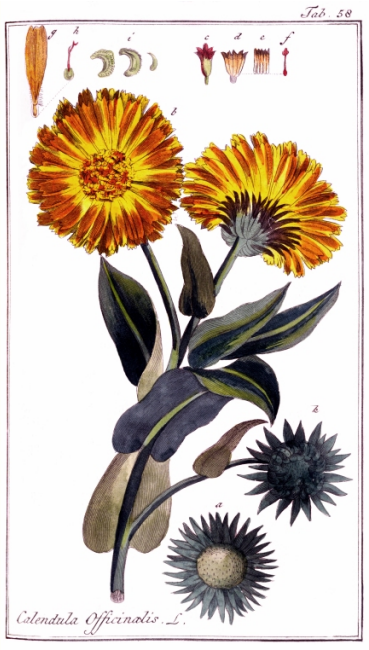
CLINICAL USE

Up until recently, most trials conducted with SJW used a 0.3% hypericin water and alcohol extract known as LI 160. Subsequently, studies using different preparations, such as WS 5573 (standardised to hyperforin) or ZE 117 (a low concentration hyperforin preparation), have been tested.

DEPRESSION AND ANXIETY

Clinical note — The Hamilton Depression Scale
The HDS is an observer-rated scale that focuses mainly on somatic symptoms of depression. Although the original version included 21 items, a similar version using 17 items is more commonly used in clinical trials. Most studies using the HDS report the number of 'treatment responders' (patients achieving a score less than 10 and/or less than 50% of the baseline score) (Linde et al 2005).

Mild to moderate depression St John's wort has shown efficacy as a successful treatment for mild to moderate depression in numerous double-blind placebo-controlled trials, confirmed by several meta-analyses.



The most recent Cochrane review released in 2005 analysed data from 37 double-blind, randomised studies ($n = 4925$) that used monopreparations of SJW over a treatment period of at least 4 weeks (Linde et al 2005). It concluded that hypericum extracts improved symptoms more than placebo and produced effects similar to synthetic antidepressants (tricyclics and SSRIs) in adults with mild to moderate depression. This confirms the results obtained in two earlier meta-analyses (Linde & Mulrow 2000, Whiskey et al 2001).

Subsequently, a double-blind study of 388 patients with moderate depression has found SJW extract (900 mg daily of extract STW3-VI) to be as effective as citalopram (20 mg daily) ($P < 0.0001$) (Gastpar et al 2006). The HDS scores were reduced to 10.3 ± 6.4 for SJW extract, 10.3 ± 6.4 for citalopram and 13.0 ± 6.9 for placebo and both antidepressants were significantly more effective than placebo. At the end of treatment 54.2% of the SJW group and 55.9% of the citalopram group were assessed as responders compared with 39.2% for placebo. In regards to safety, significantly more adverse events were documented in the citalopram group (53.2%) than for SJW (17.2%) or placebo (30%).

Low hyperforin extracts effective? Considering that hyperforin demonstrates significant antidepressant activity, it is important to evaluate whether low-hyperforin containing SJW preparations remain effective. Three randomised, double-blind studies that have compared low hyperforin extracts (ZE 117) to fluoxetine or imipramine suggest the absence of hyperforin does not hinder the antidepressant effect (Friede et al 2001, Schrader 2000, Woelk 2000).

Paediatric use Results from a post-marketing surveillance study of 101 children under 12 years with mild to moderate depression has suggested that SJW may be an effective and well tolerated treatment in this population (Hubner & Kirste 2001). The number of physicians rating effectiveness of treatment with SJW as 'good' or 'excellent' was 72% after 2 weeks, 97% after 4 weeks and 100% after 6 weeks, and ratings by parents were similar. Although encouraging, it is difficult to interpret the clinical significance of the results, as there was no placebo group and the final evaluation included only 76% of the initial sample.

More recently, an 8-week open pilot study was conducted with SJW (300 mg three times daily) in 26 adolescents with major depressive disorders (Simeon et al 2005). The subjects were aged 12–17 years (mean, 14.8 years). Only 11 patients completed the study of which 9 (82%) showed significant clinical improvement based on Clinical Global Improvement change scores. Once again, interpretation of these results is hampered by a large drop-out rate.

Major depression Although a 2005 Cochrane review stated that SJW shows only minimal benefits over placebo in major depression (Linde et al 2005), two subsequent randomised, double-blind trials found SJW to be as effective as treatment doses of fluoxetine and paroxetine (Fava et al 2005, Szegedi et al 2005).

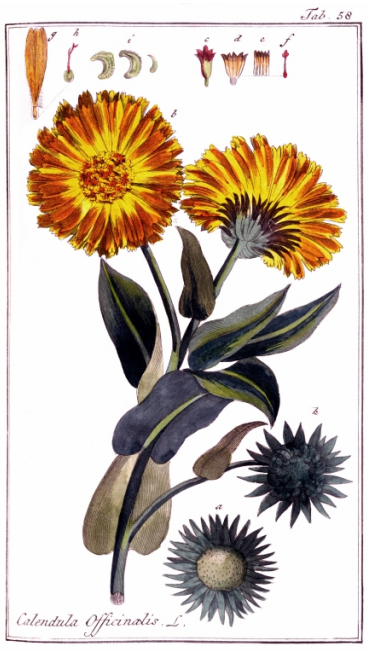
Fava et al compared SJW (LI 160 900 mg/day) to fluoxetine 20 mg/day or placebo in 135 patients with major depression in a 12-week study. Mean HDS scores reduced to 10.2 with SJW compared with 13.3 for fluoxetine and 12.6 for placebo. There was also a trend toward higher rates of remission (HDS <8) in the SJW group (38%) compared with fluoxetine (30%) or placebo (21%). According to another randomised, double-blind study, SJW (WS 5570 900 mg/day) was as effective as paroxetine 20 mg/day in 251 outpatients with acute moderate to severe depression (Szegedi et al 2005). The HDS scores decreased by a mean 14.4 (SD8.8) with SJW compared with a decrease of 11.4 (SD8.6) with paroxetine and herbal treatment was better tolerated. The study took place at 21 centres in Germany.

Commission E approves the use of SJW for psychovegetative disturbances, depressive moods, anxiety and nervous unrest (Blumenthal et al 2000).

Clinical note — Relative safety of St John's wort compared with pharmaceutical antidepressants

Much has been made of the known or suspected risks associated with the use of SJW, with far too little discussion focusing on the decisive question of its relative safety compared with pharmaceutical antidepressants. It has been estimated that approximately 1 in 30,000 people using SJW will experience an adverse reaction, including those attributed to drug interactions (Schulz 2006). An overview of 16 post-marketing surveillance studies involving different SJW preparations and 34,804 patients found that side-effect incidence varied from 0 to 2.8% in short-term studies (4–6 weeks) and 3.4–5.7% in long-term studies (52 weeks) (Linde & Knuppel 2005). Gastrointestinal symptoms, sensitivity to light and other skin conditions, and agitation were the most commonly reported side-effects and were generally described as mild. The review found that serious side-effects or interactions were not reported by any study. Taking this into account, the incidence of side-effects to SJW is approximately 10-fold lower than for conventional antidepressants (SSRIs) (Schulz 2006). The most common adverse event among spontaneous reports is photosensitivity, which is estimated to occur in 1 in 300,000 treated cases. This can occur with a dose of 5–10 mg/day hypericin, which is 2–4-fold higher than the recommended dose. St John's wort has no significant effect on blood pressure or heart rate (Siepmann et al 2002), making it a safer choice than tricyclic antidepressants in patients with cardiovascular disease. It also lacks atropinic

activity, so side-effects such as dry mouth, urinary retention and blurred vision do not occur. In addition, the common side-effects reported for SSRIs, such as anorexia, insomnia, sexual dysfunction, excessive sweating and visual disturbance, have not been reported for SJW. Similar to all standard antidepressants, SJW can interact with other medicines and needs to be judiciously prescribed.



OBSESSIVE COMPULSIVE DISORDER

Treatment with a fixed dose of 450 mg of SJW containing 0.3% hypericin twice daily over 12 weeks improved the condition in 5 of 12 patients, according to an open study (Taylor & Kobak 2000).

POLYNEUROPATHY

Although SJW is sometimes used for nerve pain, a randomised, double-blind, crossover study of 54 patients identified a trend toward lower total pain score with SJW treatment, although none of the individual pain ratings were significantly changed (Sindrup et al 2000). The dose of SJW used provided 2.7 mg/day total hypericin and was taken over 5 weeks.

MENOPAUSE: PSYCHOLOGICAL AND PSYCHOSOMATIC SYMPTOMS

In at least one trial, SJW has been investigated as sole therapy in menopausal and premenopausal women with psychological and psychosomatic symptoms. After 12 weeks' treatment with 900 mg hypericum (Kira 300 mg three times daily) symptoms diminished or disappeared completely in the majority of women (76.4% by patient evaluation and 79.2% by physician evaluation). Interestingly, sexual wellbeing also improved in 80% of cases (Grube et al 1999).

Another study investigated a fixed combination of isopropanolic black cohosh (Remifemin; standardised to 1 mg triterpene glycosides) and ethanolic SJW (standardised to 0.25 mg total hypericin) in 301 women with menopausal symptoms with pronounced psychological symptoms (Uebelhack et al 2006). The double-blind, randomised study found that 16 weeks of herbal treatment produced a significant 50% reduction in the Menopause Rating Scale score compared to 20% with placebo and a significant 42% reduction in the HDS score compared to only 13% in the placebo group.

SEASONAL AFFECTIVE DISORDER

Wheatley found that people with mild to moderate SAD experienced significant improvements with anxiety, loss of libido and insomnia after 8 weeks' treatment with SJW (Wheatley 1999). The test group receiving SJW extract (Kira 300 mg) three times

daily plus light therapy experienced superior sleep compared with the group receiving SJW as stand-alone treatment.

PREMENSTRUAL SYNDROME

An open study in patients with PMS found that a low dose of 300 mg SJW daily produced significant reductions in all outcome measures. The degree of improvement in overall PMS scores between baseline and the end of the trial was 51%, with over two-thirds experiencing at least a 50% decrease in symptom severity (Stevinson & Ernst 2000).

HERPES INFECTION

Based on its antiviral activity, SJW is also used clinically in the treatment of herpes virus infections. One study of unknown design found that oral extract LI 160 (over a period of 3 months) reduced the frequency and severity of episodes of recurrent herpes labialis and herpes genitalis (Mannel et al 2000).

SMOKING CESSATION

Preliminary evidence from experimental models suggests that SJW may be of use in reducing nicotine withdrawal signs. In the study, SJW significantly and dose-dependently reduced the total nicotine abstinence score (Catania et al 2003). Further studies are required to determine its usefulness for smoking cessation treatment in humans.

TOPICAL USE

Atopic dermatitis A cream containing SJW extract (standardised to 1.5% hyperforin) was shown to reduce the intensity of eczematous lesions when used twice daily in a prospective double-blind study (Schempp et al 2003a). Beneficial effects were already observed at the first review, which was on day 7.

Treatment of acute and contused injuries No controlled studies are available, but anti-inflammatory, analgesic and bactericidal activities provide a theoretical basis for its use.

Commission E approves the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

Myalgia Although no controlled studies are available, anti-inflammatory and analgesic activity provide a theoretical basis for its use in this condition.

Commission E approved the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

First-degree burns Although no controlled studies are available, anti-inflammatory, analgesic and bactericidal activity provide a theoretical basis for its use in this condition.

Commission E approves the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

OTHER USES

In practice, SJW is also used to treat fibrositis, nervous exhaustion, sciatica and gastrointestinal conditions, such as oesophagitis and peptic ulcers. Traditionally, SJW has been used for wound healing, diuretic, melancholy, pain relief, treatment for snake bites, bedwetting in children, malaria and psychosis.

DOSAGE RANGE

- Dried herb: 2–5 g/day.
- Liquid extract (1:2): 3–6 mL/day.
- Tincture (1:5): 7.5–15 mL/day.
- Standardised extract containing 1.0–2.7 mg total hypericin daily.
- It is advised that patients using SJW long term should have their doses reduced slowly when discontinuing use.

EXTERNAL USE

- Oily macerate: macerate flowering tops in olive oil for several weeks and stir often, then drain through a gauze. Store in a dark bottle out of direct light. Apply oil directly to the affected area. To promote extraction of flavonoids, store in a sunny area for 6 weeks (oil will turn red).

ACCORDING TO CLINICAL STUDIES

(Doses are for dried herb or equivalent).

- Mild to moderate depression: adult — doses ranging from 350–1800 mg/day have been used; children (aged 6–12 years) — 200–400 mg/day in divided doses.

The extract most often studied is LI 160, although others have also been tested, such as WS 5573 (standardised to hyperforin), ZE 117 (a low concentration hyperforin preparation), WS 550 and STW3-V1.

- Major depression: 1800 mg/day in divided doses.
- OCD: 450 mg twice daily of an extract containing 0.3% hypericin.
- Menopausal symptoms: 900 mg/day in divided doses.
- PMS: 300 mg/day (standardised to 900 μg hypericin).
- SAD: 900 mg/day in divided doses.

ADVERSE REACTIONS

It has been estimated that approximately 1 in 30,000 people using SJW will experience an adverse reaction, including those attributed to drug interactions (Schulz 2006). The incidence of side-effects to SJW is approximately 10-fold lower than for conventional antidepressants (SSRIs). According to an overview of 16 post-marketing surveillance studies, gastrointestinal symptoms, sensitivity to light and other skin conditions and agitation were the most commonly reported side-effects and were generally described as mild (Linde & Knuppel 2005).

PHOTOSENSITIVITY (UNLIKELY AT THERAPEUTIC DOSES)

The most common adverse event among spontaneous reports is photosensitivity, which is estimated to occur in 1 in 300,000 treated cases. This can occur with a dose of 5–10 mg/day hypericin, which is 2–4-fold higher than the recommended dose. Commission E has noted the possibility of photosensitivity reactions, particularly in fair-skinned people.

SIGNIFICANT INTERACTIONS

St John's wort is one of the few herbal medicines that has been subjected to controlled studies in order to determine the significance of its interaction with numerous drugs. Although this can be reassuring, the clinical significance of many interactions is still unpredictable because of the variable chemical composition of products.

It is important to note that interactions due to CYP and P-gp induction do not appear significant with low hyperforin extracts (ZE 117).

Clinical note — Mechanisms responsible for reported interactions

Based on the herb's pharmacology, there are several mechanisms by which it may interact with drugs. Considering SJW has significant serotonin reuptake inhibitor activity and significantly upregulates both 5-HT_{1A} and 5-HT_{2A} receptors, concomitant use of drugs that elevate serotonin levels, such as tricyclic antidepressants or SSRIs, may result in additive or synergistic effects and increase the risk of serotonergic syndrome. As the constituent hyperforin has a significant and selective induction effect on CYP3A4 and 2C19 activity (Durr et al 2000, Wang et al 2001) and induces the drug transporter P-glycoprotein, a number of pharmacokinetic interactions are possible with those drugs that are substrates for CYP3A4 or 2C19 and/or rely on P-gp transport. Refer to Chapter 8 for further information on interactions with herbs and natural supplements.

ALPRAZOLAM
Decreases serum levels of alprazolam via CYP induction — monitor for signs of reduced drug effectiveness and adjust the dose if necessary.

AMITRIPTYLINE
Although SJW decreases serum levels of amitriptyline via CYP induction in vivo (Johne et al 2002), theoretically it could also induce increases in serotonin availability, which has an opposite effect; the clinical outcome of these two interacting mechanisms is unknown — monitor for signs of changed drug effectiveness and adjust the dose if necessary or avoid concurrent use.

ANTIDEPRESSANTS
Increased risk of serotonin syndrome possible; however, increased antidepressant activity also possible with appropriate doses — avoid concurrent use unless under medical supervision, so that doses may be altered appropriately.

ANTICONVULSANTS
Phenobarbitone, phenytoin: SJW may increase drug metabolism resulting in reduced drug efficacy — avoid concurrent use unless under medical supervision, so that doses may be altered appropriately.

ANTINEOPLASTIC DRUGS
Irinotecan (Mathijssen et al 2002), imatinib mesylate etc. which are P-gp and/or CYP3A4 substrates — avoid (see Chapter 10 for more information on safety of complementary medicines and cancer).

CYCLOSPORIN
Decreases plasma levels of cyclosporin significantly within 3 days of concomitant use via CYP induction (Bauer et al 2003) — avoid concurrent use.

A pharmacokinetic study with kidney graft recipients suggests the effect is not significant when low hyperforin products are used (Madabushi et al 2006).

DIGOXIN
Decreases serum digoxin levels significantly within 10 days of concomitant use (Johne et al 1999), chiefly due to induction of the P-glycoprotein — monitor patient for signs of reduced drug effectiveness and adjust the dose if necessary or avoid concurrent use.

HIV NON-NUCLEOSIDE TRANSCRIPTASE INHIBITORS
Decreases serum levels — avoid concurrent use.

HIV PROTEASE INHIBITORS
Decreases serum levels — avoid concurrent use.

METHADONE
Decreases serum levels via CYP induction — avoid concurrent use (Eich-Hochli et al 2003).

MIDAZOLAM
Decreases serum levels of midazolam via CYP induction — monitor for signs of reduced drug effectiveness and adjust the dose if necessary.

OMEPRAZOLE
Decreases serum levels via CYP induction (Wang et al 2004b) — monitor for signs of reduced drug effectiveness and adjust the dose if necessary.

ORAL CONTRACEPTIVES
Breakthrough bleeding has been reported, which can indicate decreased effectiveness of oral contraceptives. In 2003, a controlled study confirmed that standard doses of SJW cause an induction of ethinyl oestradiol-norethindrone metabolism consistent with increased CYP3A activity (Hall et al 2003) — use this combination with caution.

In 2002, a pharmacokinetic study found no significant interaction between low hyperforin SJW and low-dose oral contraceptives (Madabushi et al 2006) — appears to be safe.

PUVA THERAPY
High-dose hypericin may increase sensitivity to UV radiation — caution is advised.

SIMVASTATIN
Decreases serum levels of simvastatin via CYP induction (Sugimoto et al 2001) — monitor for signs of reduced drug effectiveness and adjust the dose if necessary (no interaction is expected with pravastatin).

TACROLIMUS
Decreases serum levels of tacrolimus via CYP induction (Mai et al 2003) — avoid this combination.

VERAPAMIL
Decreases serum levels of verapamil via CYP induction — monitor for signs of reduced drug effectiveness and adjust the dose if necessary.

WARFARIN

Metabolism of warfarin is chiefly by CYP2C9, and a minor metabolic pathway is CYP3A4, so theoretically it may interact with SJW. A clinical study found no change to INR or platelet aggregation (Jiang et al 2004), but there are case reports suggesting SJW may lower the INR — caution is advised.

CONTRAINDICATIONS AND PRECAUTIONS

People with fair skin undergoing UV treatment should use high doses of SJW with caution. Suspend use of SJW 2 weeks prior to major surgery.

PREGNANCY USE

A study conducted in an experimental animal model found no adverse effects on offspring with maternal use; however, safe doses in pregnant women have not been determined. In practice, it is not used in pregnancy.

St John's appears to be relatively safe in lactation. A study of breast feeding mothers indicated that low levels of hyperforin are excreted into breast milk; however, infant exposure is comparable to levels reported in most studies assessing antidepressants or neuroleptics and no side-effects were seen in the mothers or infants (Klier et al 2006). The doses used were 300 mg of SJW (LI 160, three times daily).

PRACTICE POINTS/PATIENT COUNSELLING

- St John's wort contains numerous constituents with pharmacological activity, including antidepressant, analgesic, anti-inflammatory, antispasmodic, anxiolytic, antineoplastic, antiviral and bactericidal activities.
- Numerous clinical studies support the use of SJW as an effective treatment for mild to moderate depression. The most commonly studied extract is LI 160 although others have also been tested (e.g. WS 5573 (standardised to hyperforin), ZE 117 (a low concentration hyperforin preparation), WS 550 and STW3-V1). Clinical effects are comparable to tricyclic antidepressants and SSRIs.
- In regards to safety, SJW is better tolerated than standard antidepressants; however, it still needs to be prescribed judiciously to avoid interactions.
- Low-hyperforin-containing SJW extracts do not have the same interaction potential as standard SJW extracts and may present a safer option for some individuals.
- Efficacy in severe depression has not been established, with mixed results reported so far.
- Preliminary human studies have suggested a possible role in PMS, SAD, OCD and in menopausal and premenopausal women with psychological and psychosomatic symptoms.

- Oily preparations have been used to treat burns, acute and contused injuries, atopic dermatitis and myalgia.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

St John's wort is an effective treatment for mild to moderate depression. It may also be useful for PMS symptoms, SAD, OCD and for menopausal and premenopausal women with psychological and psychosomatic symptoms. The oily preparations are also used to treat burns, injuries, allergic dermatitis and muscle pain.

When will it start to work?

It often starts to exert beneficial effects in depression within 2–4 weeks of continuous use.

Are there any safety issues?

St John's wort is well tolerated and has far less side-effects than pharmaceutical antidepressant drugs, but it can interact with a number of different medications.

REFERENCES

Agostinis P et al. Hypericin in cancer treatment: more light on the way. Int J Biochem Cell Biol 34.3 (2002): 221-41.

Albert D et al. Hyperforin is a dual inhibitor of cyclooxygenase-1 and 5-lipoxygenase. Biochem Pharmacol 64.12 (2002): 1767-75.

Anon. Final report on the safety assessment of Hypericum perforatum extract and Hypericum perforatum oil. Int J Toxicol 20 (Suppl 2) (2001): 31-9.

Anon. Effect of Hypericum perforatum (St John's Wort) in major depressive disorder: a randomized controlled trial. JAMA 287.14 (2002): 1807-14.

Arold G et al. No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. Planta Med 71.4 (2005): 331-7.

Bauer S et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol 55.2 (2003): 203-11.

Beijamini V, Andreatini R. Effects of Hypericum perforatum and paroxetine on rat performance in the elevated T-maze. Pharmacol Res 48.2 (2003): 199-207.

Bilia AR, Gallori S, Vincieri FF. St John's wort and depression: efficacy, safety and tolerability: an update. Life Sci 70.26 (2002): 3077-96.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Brenner R et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther 22.4 (2000): 411-19.

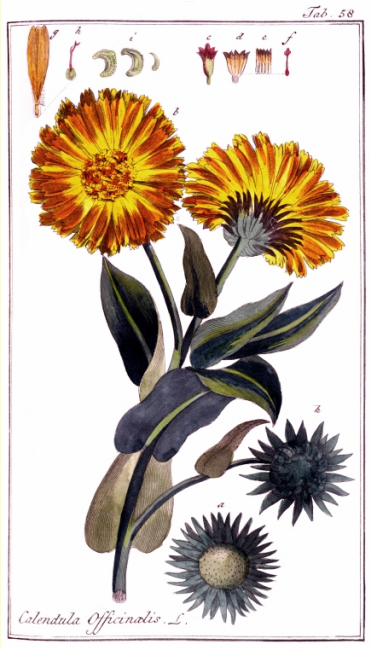
Butterweck V et al. Step by step removal of hyperforin and hypericin: activity profile of different Hypericum preparations in behavioral models. Life Sci 73.5 (2003a): 627-39.

Butterweck V et al. Plasma levels of hypericin in presence of procyanidin B2 and hyperoside: a pharmacokinetic study in rats. Planta Med 69.3 (2003b): 189-92.

Catania MA et al. Hypericum perforatum attenuates nicotine withdrawal signs in mice. Psychopharmacology (Berl) 169.2 (2003): 186-9.

Chatterjee SS et al. Hyperforin as a possible antidepressant component of hypericum extracts. Life Sci 63.6 (1998): 499-510.

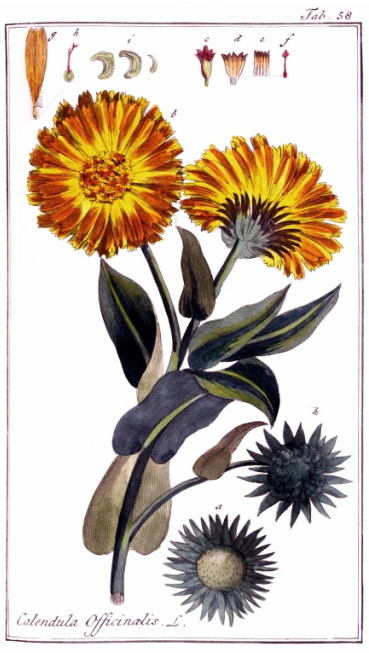
Chen B, Roskams T, de Witte PA. Enhancing the antitumoral effect of hypericin-mediated photodynamic therapy by hyperthermia. Lasers Surg Med 31.3 (2002): 158-63.
Di Carlo G et al. St John's wort: Prozac from the plant kingdom. Trends Pharmacol Sci 22.6 (2001): 292-7.
Durr D et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 68.6 (2000): 598-604.
Eich-Hochli D et al. Methadone maintenance treatment and St John's Wort: a case report. Pharmacopsychiatry 36.1 (2003): 35-7.
Fava M et al. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol 25.5 (2005): 441-7.
Fiebich B, Hollig A, Lieb K. Inhibition of substance P-induced cytokine synthesis by St John's wort extracts. Pharmacopsychiatry 34 (Suppl 1) (2001): S26-8.
Friede M, Henneicke von Zepelin HH, Freudenstein J. Differential therapy of mild to moderate depressive episodes (ICD-10 F 32.0; F 32.1) with St John's wort. Pharmacopsychiatry 34 Suppl 1 (2001): S38-41.
Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry 39.2 (2006): 66-75.
Gobbi M et al. In vitro binding studies with two hypericum perforatum extracts (hyperforin, hypericin and biapigenin) on 5-HT6, 5-HT7, GABA(A)/benzodiazepine, sigma, NPY-Y1/Y2 receptors and dopamine transporters. Pharmacopsychiatry 34 (Suppl 1) (2001): S45-8.
Grube B, Walper A, Wheatley D. St John's Wort extract: efficacy for menopausal symptoms of psychological origin. Adv Ther 16.4 (1999): 177-86.
Gulick RM et al. Phase I studies of hypericin, the active compound in St John's Wort, as an antiretroviral agent in HIV-infected adults AIDS Clinical Trials Group Protocols 150 and 258. Ann Intern Med 130.6 (1999): 510-14.
Hall SD et al. The interaction between St John's wort and an oral contraceptive. Clin Pharmacol Ther 74.6 (2003): 525-35.
Hostanska K et al. Hyperforin a constituent of St John's wort (Hypericum perforatum L) extract induces apoptosis by triggering activation of caspases and with hypericin synergistically exerts cytotoxicity towards human malignant cell lines. Eur J Pharm Biopharm 56.1 (2003): 121-32.
Hubner WD, Kirste T. Experience with St John's Wort (Hypericum perforatum) in children under 12 years with symptoms of depression and psychovegetative disturbances. Phytother Res 15.4 (2001): 367-70.
Hudson JB, Harris L, Towers GH. The importance of light in the anti-HIV effect of hypericin. Antiviral Res 20.2 (1993): 173-8.
Jacobson JM et al. Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St John's wort plant, in patients with chronic hepatitis C virus infection. Antimicrob Agents Chemother 45.2 (2001): 517-24.
Jakovljevic V et al. Pharmacodynamic study of Hypericum perforatum L. Phytomedicine 7.6 (2000): 449-53.
Jiang X et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 57.5 (2004): 592-9.
Johne A et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). Clin Pharmacol Ther 66.4 (1999): 338-45.
Johne A et al. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St John's wort (Hypericum perforatum). J Clin Psychopharmacol 22.1 (2002): 46-54.
Kiewert C et al. Stimulation of hippocampal acetylcholine release by hyperforin, a constituent of St John's Wort. Neurosci Lett 364.3 (2004): 195-8.
Klier CM et al. St John's wort (Hypericum perforatum) and breastfeeding: plasma and breast milk concentrations of hyperforin for 5 mothers and 2 infants. J Clin Psychiatry 67.2 (2006): 305-9.
Linde K, Knuppel L. Large-scale observational studies of hypericum extracts in patients with depressive disorders: a systematic review. Phytomedicine 12.1-2 (2005): 148-57.
Linde K, Mulrow CD. St John's wort for depression. Cochrane Database Syst Rev 2 (2000): CD000448.



Linde K et al. St John's wort for depression. Cochrane Database Syst Rev 2 (2005): CD000448.
Madabushi R et al. Hyperforin in St John's wort drug interactions. Eur J Clin Pharmacol 62.3 (2006): 225-33.
Mai I et al. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. Nephrol Dial Transplant 18.4 (2003): 819-22.
Mannel M, Koytchev R, Dundarov S. Oral hypericum extract LI 160 is an effective treatment of recurrent herpes genitalis and herpes labialis: 3rd International Congress on Phytomedicine. Phytomedicine 7 (II) (2000).
Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18.3 (1998): 135-74.
Mathijssen RH et al. Effects of St John's wort on irinotecan metabolism. J Natl Cancer Inst 94.16 (2002): 1247-9.
Medina MA et al. Hyperforin: More than an antidepressant bioactive compound? Life Sci 79.2 (2006): 105-11.
Mennini T, Gobbi M. The antidepressant mechanism of Hypericum perforatum. Life Sci 75.9 (2004): 1021-7.
Meruelo D, Lavie G, Lavie D. Therapeutic agents with dramatic antiretroviral activity and little toxicity at effective doses: aromatic polycyclic diones hypericin and pseudohypericin. Proc Natl Acad Sci USA 85.14 (1988): 5230-4.
Miskovsky P. Hypericin: a new antiviral and antitumor photosensitizer: mechanism of action and interaction with biological macromolecules. Curr Drug Targets 3.1 (2002): 55-84.
Moore LB et al. St John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. Proc Natl Acad Sci USA 97.13 (2000): 7500-2.
Mueller SC et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. Clin Pharmacol Ther 75.6 (2004): 546-57.
Nathan, P. The experimental and clinical pharmacology of St John's Wort (Hypericum perforatum L). Mol Psychiatry 4.4 (1999): 333-8.
Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St John's Wort, an herbal preparation used in the treatment of depression. J Pharmacol Exp Ther 294.1 (2000): 88-95.
Panocka I et al. Effects of Hypericum perforatum extract on ethanol intake, and on behavioral despair: a search for the neurochemical systems involved. Pharmacol Biochem Behav 66.1 (2000): 105-11.
Patel J et al. In vitro interaction of the HIV protease inhibitor ritonavir with herbal constituents: changes in P-gp and CYP3A4 activity. Am J Ther 11.4 (2004): 262-77.
Perfumi M et al. Blockade of gamma-aminobutyric acid receptors does not modify the inhibition of ethanol intake induced by Hypericum perforatum in rats. Alcohol Alcohol 37.6 (2002): 540-6.
Raso GM et al. In-vivo and in-vitro anti-inflammatory effect of Echinacea purpurea and Hypericum perforatum. J Pharm Pharmacol 54.10 (2002): 1379-83.
Rengelshausen J et al. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 78.1 (2005): 25-33.
Roz N, Rehavi M. Hyperforin depletes synaptic vesicles content and induces compartmental redistribution of nerve ending monoamines. Life Sci 75.23 (2004): 2841-50.
Schempp CM et al. Antibacterial activity of hyperforin from St John's wort against multiresistant Staphylococcus aureus and Gram-positive bacteria. Lancet 353.9170 (1999): 2129.
Schempp CM et al. Topical treatment of atopic dermatitis with St John's wort cream: a randomized, placebo controlled, double blind half-side comparison. Phytomedicine 10 (Suppl 4) (2003a): 31-7.
Schempp CM et al. Effect of oral administration of Hypericum perforatum extract (St John's Wort) on skin erythema and pigmentation induced by UVB, UVA, visible light and solar simulated radiation. Phytother Res 17.2 (2003b): 141-6.
Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol 15.2 (2000): 61-8.
Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. Phytomedicine 8.2 (2001): 152-60.

Schulz V. Safety of St. John's Wort extract compared to synthetic antidepressants. Phytomedicine 13.3 (2006): 199-204.
Siepmann M et al. The effects of St John's wort extract on heart rate variability, cognitive function and quantitative EEG: a comparison with amitriptyline and placebo in healthy men. Br J Clin Pharmacol 54.3 (2002): 277-82.
Simeon J et al. Open-label pilot study of St John's wort in adolescent depression. J Child Adolesc Psychopharmacol 15.2 (2005): 293-301.
Simmen U et al. Hypericum perforatum inhibits the binding of mu- and kappa-opioid receptor expressed with the Semliki Forest virus system. Pharm Acta Helv 73.1 (1998): 53-6.
Sindrup SH et al. St John's wort has no effect on pain in polyneuropathy. Pain 9.3 (2001): 361-5.
Stevinson C, Ernst E. A pilot study of Hypericum perforatum for the treatment of premenstrual syndrome. Br J Obstet Gynaecol 107.7 (2000): 870-6.
Sugimoto K et al. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. Clin Pharmacol Ther 70.6 (2001): 518-24.
Szegedi A et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ 330.7490 (2005): 503.
Taylor LH, Kobak KA. An open-label trial of St John's Wort (Hypericum perforatum) in obsessive-compulsive disorder. J Clin Psychiatry 61.8 (2000): 575-8.
Teufel-Mayer R, Gleitz J. Effects of long-term administration of hypericum extracts on the affinity and density of the central serotonergic 5-HT1A and 5-HT2A receptors. Pharmacopsychiatry 30 (Suppl 2) (1997): 113-16.
Thiede HM, Walper A. Inhibition of MAO and COMT by hypericum extracts and hypericin. J Geriatr Psychiatry Neurol 7 (Suppl 1) (1994): S54-6.
Tian R et al. Functional induction and de-induction of P-glycoprotein by St John's wort and its ingredients in a human colon adenocarcinoma cell line. Drug Metab Dispos 33.4 (2005): 547-54.
Timoshanko A et al. A preliminary investigation on the acute pharmacodynamic effects of hypericum on cognitive and psychomotor performance. Behav Pharmacol 12.8 (2001): 635-40.
Uebelhack R et al. Black cohosh and St. John's wort for climacteric complaints: a randomized trial. Obstet Gynecol 107.2 (2006): 247-55.
Vandenbogaerde A et al. Evidence that total extract of Hypericum perforatum affects exploratory behavior and exerts anxiolytic effects in rats. Pharmacol Biochem Behav 65.4 (2000): 627-33.
Wang EJ et al. Quantitative characterization of direct P-glycoprotein inhibition by St John's wort constituents hypericin and hyperforin. J Pharm Pharmacol 56.1 (2004a): 123-8.
Wang LS et al. St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. Clin Pharmacol Ther 75.3 (2004b): 191-7.
Wang Z et al. The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. Clin Pharmacol Ther 70.4 (2001): 317-26.
Weber CC et al. Modulation of P-glycoprotein function by St John's wort extract and its major constituents. Pharmacopsychiatry 37.6 (2004): 292-8.
Wheatley D. Hypericum in seasonal affective disorder (SAD). Curr Med Res Opin 15.1 (1999): 33-7.
Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of Hypericum perforatum in depression: a comprehensive clinical review. Int Clin Psychopharmacol 16.5 (2001): 239-52.
Woelk H. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. BMJ 321.7260 (2000): 536-9.
Wonnemann M et al. Evaluation of synaptosomal uptake inhibition of most relevant constituents of St John's wort. Pharmacopsychiatry 34 (Suppl 1) (2001): S148-51.

St Mary's thistle



Historical note St Mary's thistle has a long history of traditional use since ancient times. Over the centuries, it has been touted as a remedy for snake bite, melancholy, liver conditions and promoting lactation. The name 'milk thistle' derives from its characteristic spiked leaves with white veins, which according to legend, were believed to carry the milk of the Virgin Mary.

OTHER NAMES

Carduus marianus, cardo blanco, cardo de burro, chandon marie, holy thistle, lady's milk, lady's thistle, Mariendistel, Marian thistle, Mary thistle, milk thistle, silybum, true thistle

BOTANICAL NAME/FAMILY

Silybum marianum (family [Compositae] Asteraceae)

PLANT PART USED

Ripe seed

CHEMICAL COMPONENTS

The major active constituents are the flavolignans, collectively named 'silymarin'. The principal components of silymarin are silybin, isosilybin, silychristin and silydianin. Silybin makes up approximately 50% of silymarin and is regarded as one of the most biologically active constituents (Jacobs et al 2002). There is also a fixed oil comprising linoleic, oleic and palmitic acids, tocopherol and sterols, including cholesterol, campesterol, stigmasterol and sitosterol.

MAIN ACTIONS

Most investigation has used standardised preparations of St Mary's thistle, the silymarin constituent group or silybin.

HEPATOPROTECTIVE EFFECT

Protection of liver cells has been demonstrated against the following substances in vitro or in vivo:

- carbon tetrachloride-induced liver cirrhosis (Chrungoo et al 1997, Mourelle et al 1989, Muriel & Mourelle 1990)
- paracetamol-induced liver peroxidation (Chrungoo et al 1997, Muriel et al 1992)
- cyclosporin (von Schonfeld et al 1997)

- phenothiazine (Palasciano et al 1994)
- butyrophenone (Palasciano et al 1994)
- erythromycin (Davila et al 1989)
- amitriptyline and nortriptyline (Davila et al 1989)
- oestradiol (Morazzoni & Bombardelli 1995)
- amanita phalloides (Floersheim 1976, Vogel et al 1984)
- tacrine (Galisteo et al 2000)
- iron overload (Masini et al 2000, Pietrangelo et al 1995).

The exact mechanism of action has not been fully elucidated; however, several observations have been made.

Toxin blockade Silymarin and silybin alter the structure of hepatocyte cell membranes by being incorporated into the hydrophobic-hydrophilic interface of the microsomal bilayer (Parasassi et al 1984). Additionally, inhibition of cyclic AMP-dependent phosphodiesterase by silybin has been shown in vitro, which results in increased cAMP and stabilisation of lysosomal membranes (Koch et al 1985). Both actions alter cell membrane function and may be important for protecting the cell from toxin-induced damage. Alternatively, components in St Mary's thistle may bind to the hepatocyte cell membrane receptor site and inhibit binding of toxins to these sites (Jacobs et al 2002).

Antioxidant activity Both a direct and an indirect free radical scavenging activity has been observed, with silymarin shown to increase the redox state and total glutathione content of the liver, intestine and stomach in vivo (Liu et al 2001, Gonzalez-Correa et al 2002, Hagymasi et al 2002, Valenzuela et al 1989). As such, enhanced antioxidant activity further adds to the herb's hepatoprotective effects, particularly when hepatic injury involves free radical molecules.

Chelates iron Hepatic iron toxicity and fibrosis due to iron overload is mediated by lipid peroxidation of biological membranes and the associated organelles (Masini et al 2000). Both silymarin and silybin demonstrate protective effects against hepatic iron toxicity in vivo, primarily owing to antioxidant mechanisms. However, there is some evidence that iron chelation may also be involved (Borsari et al 2001, Masini et al 2000, Pietrangelo et al 1995, Psotova et al 2002).

LIVER REGENERATION

Silymarin accelerates the regeneration of hepatocytes after liver damage, according to an in vivo study. Silymarin was shown to increase hepatocyte protein synthesis by stimulating the activity of ribosomal RNA polymerase (Kropacova et al 1998).

GASTROPROTECTIVE EFFECT

St Mary's thistle extract produces a dose-dependent anti-ulcerogenic activity against indomethacin-induced ulcers, which can be histologically confirmed, according to research with test animals (Khayyal et al 2001). This is associated with reduced acid output, increased mucin secretion, increased PGE_2 release and decreased leukotriene release.

Experiments with the silymarin constituent group have found it to be effective in the prevention of gastric ulceration induced by cold-restraint stress in rats (Alarcon et al 1992) and post-ischaemic gastric mucosal injury (Alarcon et al 1995).

ANTI-INFLAMMATORY

The anti-inflammatory activity of silymarin is due to several different mechanisms, such as antioxidant and membrane-stabilising effects, and inhibition of the production or release of inflammatory mediators, such as arachidonic acid metabolites. Inhibitory activity on lipo-oxygenase, COX and PG synthetase has been demonstrated in several in vitro assays and animal studies (Alarcon et al 1992, Dehmlow et al 1996, Fiebrich & Koch 1979, Rui et al 1990, Zhao et al 1999).

NEPHROPROTECTIVE EFFECT

In vitro experiments with kidney cells damaged by paracetamol, cisplatin or vincristin demonstrate that administration of silybin before or after the chemical-induced injury can lessen or avoid the nephrotoxic effects (Sonnenbichler et al 1999). Animal studies have confirmed the nephroprotective effect for cisplatin-induced injury (Karimi et al 2005). In one study, the effects of cisplatin on glomerular and proximal tubular function as well as proximal tubular morphology were totally or partly ameliorated by silybin (Gaedeke et al 1996).

MAST-CELL STABILISATION

Silybin has shown mast-cell-stabilisation activity in vivo (Lecomte 1975), which was confirmed some years later and found to be dose-dependent (Fantozzi et al 1986). More recently, silymarin has been shown to exert protective effects in the early phase of asthma, most likely due to its influence on histamine release (Breschi et al 2002).

ANTIFIBROTIC

Silymarin reduces markers for collagen accumulation in the liver and exerts antifibrotic activity, according to an animal model of liver fibrosis (Boigk et al 1997).

ANTITUMOUR EFFECTS

In a variety of experimental tumour models and cell systems, silymarin and silybin have been found to have both cancer preventive and anticancer activity.

In vitro studies have shown that silymarin possesses exceptionally high cancer-preventive effects in different mouse skin carcinogenesis models and affords strong anticancer effects in human skin, cervical, prostate, bladder and breast carcinoma cells (Vinh et al 2002, Zi & Agarwal 1999, Zi et al 1998a,b, Zhao et al 1999, Zhu et al 2001). Recent investigation has also identified that silibinin is biologically active against hepatocellular carcinoma cells (Varghese et al 2005).

Two studies involving the use of topical silymarin in hairless mice before chemical carcinogenesis and photocarcinogenesis have shown a protective effect that resulted in a statistically significant decrease in tumour incidence, tumour multiplicity, and tumour volume per mouse in the treated groups (Wright et al 2006). Furthermore, this chemopreventive effect was found to be dose-dependent in one of the studies, in which the topical application ranged from 3 to 12 mg per mouse, with the 12-mg application conferring the most protection.

It appears that several mechanisms are responsible, besides an antioxidant effect. Anti-angiogenic activity has been observed in vitro, and is likely to be involved (Jiang et al 2000). Additionally, in vivo research has demonstrated chemopreventive effects for silymarin, by inhibiting endogenous tumour promoter TNF-alpha (Zi et al 1997). In regard to skin cancer, silymarin provides substantial protection against different stages of UVB-induced carcinogenesis, possibly via its strong antioxidant properties (Katiyar et al 1997) and a selective action on NF-kappa-B activation (Saliou et al 1999).

OTHER ACTIONS

CHOLESTEROL-LOWERING

Cholesterol reduction has been demonstrated for silymarin in two studies of rats fed a high cholesterol diet (Krecman et al 1998, Sobolova et al 2006). Although the mechanism of action is unknown, it has been suggested that inhibition of HMG-CoA reductase is involved (Skottova & Krecman 1998a) and inhibition of cholesterol absorption from dietary sources (Sobolova et al 2006).

Considering that the herb also contains phytosterols, these too may play a role in cholesterol reduction.

NEUROPROTECTIVE

Silymarin demonstrated neuroprotective activity according to preliminary research. A study by Wang et al (2002) demonstrated that silymarin could effectively protect dopaminergic neurons against lipopolysaccharide-induced neurotoxicity by inhibiting activation of the microglia that represent resident macrophage-like population of brain cells acting in host defence and tissue repair in the CNS. Silymarin induced an

increase of reduced glutathione and ascorbic acid levels and superoxide dismutase activity in the brain of treated rats (200 mg/kg/day PO) for 3 days, showing a protective effect on antioxidant defence systems.

LIVER CYP ENZYMES

Conflicting results from different studies make it difficult to determine what effect silymarin has on liver enzymes. However, there is some in vitro evidence of CYP3A4 inhibition and, possibly, inhibition of other CYP enzymes (Venkataramanan et al 2000, Zuber et al 2002). At the time of writing, no clinical studies were available to determine the significance of this.

Results published in 2002 suggest that the flavolignans silybin, silydianin and silycristin display a dose-dependent inhibition of CYP3A4, CYP2E1 and CYP2D6 (Zuber et al 2002). Two other in vitro studies could not confirm inhibitory effects for silymarin on CYP2E1, with one study actually reporting induction activity (Kim et al 1997, Miguez et al 1994). In regard to CYP2C9, one early clinical study showed that a daily dose of 210 mg silymarin over 28 days had no influence on the metabolism phenylbutazone (Leber & Knauff 1976).

In 2003, a crossover study of healthy volunteers found that silymarin (160 mg three times daily) had no apparent effect on indinavir plasma concentrations, suggesting no significant effect on CYP3A4 in humans (DiCenzo et al 2003). More recently, a clinical study found no evidence of an interaction between St Mary's thistle and indinavir when administered in commonly used therapeutic doses (DiCenzo et al 2003).

P-GLYCOPROTEIN

An in vitro study identified that silymarin inhibited P-glycoprotein (P-gp) ATPase activity in such a way as to suggest direct interaction with P-gp substrate binding (Zhang & Morris 2003).

CLINICAL USE

DYSPEPSIA

Although St Mary's thistle has been most commonly investigated for its effects as a hepatoprotective agent, it is commonly used to treat dyspeptic complaints, such as loss of appetite, poor digestion and upper gastrointestinal discomfort. Animal studies have identified a dose-dependent increase in bile flow and bile salt secretion for silymarin, achieved by stimulating the synthesis of bile salts (Crocenzi et al 2000).

Commission E approves the use of crude milk thistle preparations for dyspeptic complaints (Blumenthal et al 2000).

TOXIC LIVER DAMAGE

Mushroom poisoning (*Amanita phalloides*) One of the best documented uses of milk thistle is in the treatment of poisoning by the mushroom *Amanita phalloides* (death cap). Nausea, vomiting, abdominal cramps and severe diarrhoea usually occur 8–12 hours after ingestion with extensive hepatic necrosis occurring 1–2 days later. A mortality rate of 20–30% has been observed but can be as high as 50% in children under 10 years of age (Floersheim et al 1982). Several clinical studies have shown silybin (20–50 mg/kg/day IV) to protect against hepatotoxicity when administered within 48 hours. One report of pooled data from 452 case reports of *A. phalloides* poisoning showed a highly significant difference in mortality in favour of silybin (Saller et al 2001).

Environmental toxins and drugs In animals, milk thistle reduces acute liver injury caused by paracetamol (Ali et al 2001, Muriel et al 1992), carbon tetrachloride (Favari & Perez-Alvarez 1997, Letteron et al 1990), radiation (Hakova & Misurova 1996, Kropacova et al 1998), iron overload (Masini et al 2000, Pietrangelo et al 1995), phenylhydrazine (Valenzuela & Guerra 1985) and D-galactosamine (Tyutyulkova et al 1981, 1983).

One, randomised double-blind study involving 222 patients showed that silymarin improves the tolerability of tacrine without altering the drug's cognitive effects (Allain et al 1999). Two other clinical trials have documented the effectiveness of silymarin in improving or preventing hepatotoxicity from chronic administration of phenothiazines or butyrophenone (Anon 1989).

Hepatocyte repair The effects of a commercial silymarin product (Legalon 120 mg three times daily) on liver function tests and liver histology were studied in 36 patients with chronic alcoholic liver disease in a 6-month, double-blind clinical trial (Feher et al 1989). Treatment not only produced significant improvements in liver function test results, but also positive effects on histology, while these parameters remained unchanged in the placebo group. Salmi and Sarna (1982) found similar results in a RCT of 106 patients with liver disease. After just 4 weeks' treatment, histological changes began to normalise significantly more often in the treated group than in controls.

Commission E approves the use of standardised St Mary's thistle extracts (70–80% silymarin content) for toxic liver damage (Blumenthal et al 2000).

SUPPORTIVE TREATMENT IN CHRONIC LIVER DISEASES

Numerous clinical trials have been conducted with St Mary's thistle preparations in various chronic liver diseases. The most studied treatments are Legalon (Madaus Corporation, Cologne, Germany) and Silipide (Inverni Della Beffa Research and

Development Laboratories, Milan, Italy) designed to improve oral absorption of silymarin.

Clinical note — Hepatic fibrosis
Hepatic fibrosis is a pathological wound-healing process that occurs when the liver is injured chronically, such as in chronic alcohol abuse. The oxidative metabolite of ethanol, acetaldehyde, often in conjunction with viral or metabolic liver disease, is implicated as the major cause for liver fibrogenesis, which ultimately leads to cirrhosis (Schuppan et al 1995). Antifibrotic agents, which interrupt the continuous process of wound healing in the liver, are being investigated as strategies to prevent or reverse liver cirrhosis.

A 1998 clinical review of St Mary's thistle concluded that it may be effective in improving the clinical courses of both acute and chronic viral, drug-induced, toxin-induced and alcoholic hepatitis (Flora et al 1998). A more recent systematic review of efficacy for St Mary's thistle in chronic liver diseases stated that data are still too limited to detect a substantial benefit on mortality or recommend the herb in liver disease (Jacobs et al 2002).

Eleven clinical studies were located in which researchers have attempted to clarify the role of St Mary's thistle in the treatment of various liver diseases (Angulo et al 2000, Benda et al 1980, Buzzelli et al 1993, Ferenci et al 1989, Lucena et al 2002, Magliulo et al 1978, Par et al 2000, Pares et al 1998, Salmi and Sarna 1982, Trinchet et al 1989, Velussi et al 1997). Much of the research focuses on the different forms of hepatitis and alcoholic liver cirrhosis with doses ranging from 100–300 mg three times daily, usually given in a standardised extract of 70–80% silymarin. Overall, results have been mixed, with eight trials showing generally positive results and three negative, suggesting more research is still required.

A 2005 Cochrane review of 13 randomised clinical trials assessed milk thistle in 915 patients with alcoholic and/or hepatitis B or C virus liver diseases (Rambaldi et al 2005). The authors stated that the methodological quality of the trials was low and although liver-related mortality was significantly reduced by milk thistle in patients with alcoholic liver disease, milk thistle versus placebo or no intervention had no significant effect on complications of liver disease, or liver histology. Milk thistle was not associated with a significantly increased risk of adverse events.

Acute viral hepatitis Several studies have investigated the use of milk thistle in this disease, reporting beneficial effects on serological outcomes (Bode et al 1977, Magliulo et al 1978, Tkacz & Dworniak 1983). However, several studies were not

clearly blinded and further research is required to determine whether St Mary's thistle can provide significant benefits in this population.

Hepatitis C infection A 2003 systematic review of medicinal herbs for hepatitis C virus (HCV) infection concluded that compared with placebo, none of the herbs showed effects on HCV RNA or liver enzyme, except for silybin, which showed a significant reduction of serum AST and gamma-glutamyltranspeptidase levels in one trial (Liu et al 2003). Overall, the review concluded that further randomised trials are justified.

Commission E approves the use of standardised St Mary's thistle extracts (70–80% silymarin content) as supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis (Blumenthal et al 2000).

Diabetes Silymarin has also been investigated in diabetic patients with cirrhosis. Velussi et al (1997) investigated whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis. The 6-month open trial found that silymarin treatment had several benefits. After the first month's treatment, fasting glucose levels showed a progressive and significant decline that, interestingly, did not lead to an increase in the frequency of hypoglycaemic episodes. Other observations revealed decreased glucosuria and levels of glycosylated haemoglobin also decreased significantly, indicating an overall improvement in glucose control. The dose used was 600 mg/day silymarin.

OTHER USES

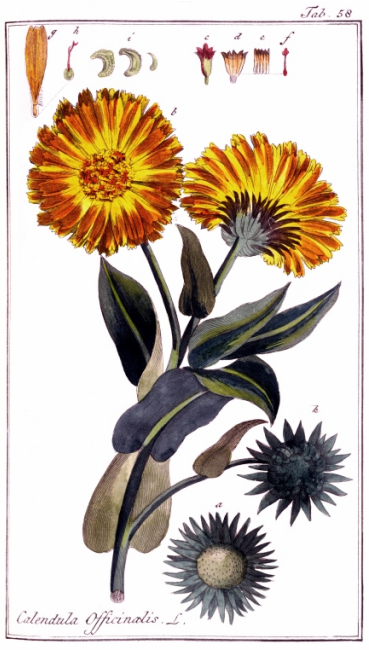
Traditionally, the seeds have been used to treat jaundice, hepatitis, haemorrhoids and psoriasis, as a tonic for nursing mothers, and as a general 'liver cleansing' agent.

HYPERCHOLESTEROLAEMIA

In clinical practice, it is not unusual to find treatment with St Mary's thistle at the higher end of the dose range results in cholesterol lowering effects. Several in vivo studies confirm that St Mary's thistle increases LDL-cholesterol clearance and raises HDL-cholesterol levels; however, only one clinical trial is available to determine whether the effect is clinically significant (Krecman et al 1998, Skottova & Krecman 1998b, Somogyi et al 1989). An open trial involving 14 subjects with type 2 hyperlipidaemia found that treatment with silymarin (420 mg/day) slightly reduced total cholesterol and HDL-cholesterol levels (Somogyi et al 1989).

SKIN CANCER PREVENTION

In vivo research suggests that silymarin and/or its major active constituent silibinin could be an effective agent for prevention and/or supportive treatment of human skin cancer (Singh et al 2002, Zhao et al 2000). Topical application of silymarin provided



significant protection against different stages of UV-B induced skin carcinogenesis in mouse skin tumorigenesis models (Ahmad et al 1998, Lahiri-Chatterjee et al 1999).

CHEMOTHERAPY SUPPORT

The role of St Mary's thistle as adjunctive therapy in a range of cancer treatments has received much interest in the past few years. Silybin appears to have nephroprotective activity effective against cisplatin and vincristine toxicity in vitro (Sonnenbichler et al 1999). Protection against cisplatin nephrotoxicity has been confirmed in vivo by Gaedeke et al (1996), who showed the adverse effects of cisplatin on creatinine clearance and proteinuria were totally prevented by silybin pretreatment. Bokemeyer et al (1996) confirmed the nephroprotection afforded by silybin in a rat animal model and observed that it did not alter the clinical efficacy of cisplatin. According to an in vivo study by Karimi et al (2005), both silymarin and St Mary's thistle extract are also effective when given as pretreatment before cisplatin.

In vitro and in vivo research has further shown that a combination of silybin with cisplatin produces a dose-dependent and statistically significant increase of drug activity, resulting in a potentiation of antitumour activity (Giacomelli et al 2002, Scambia et al 1996).

Clinical note — Cisplatin

Cisplatin is one of the most active cytotoxic agents in the treatment of testicular cancer, but its clinical use is associated with side-effects, such as severe nausea, ototoxicity, neurotoxicity and nephrotoxicity (Giacomelli et al 2002). It is also used in the treatment of head and neck, gastrointestinal, cervical, lung and bladder cancer.

DOSAGE RANGE

- The average daily recommended dose is 12–15 g (practitioners have used doses as high as 18 g/day) of milk thistle seed, usually in divided doses (equivalent to 200–400 mg silymarin) (Anon 2003).
- Liquid extract (1:1): 4–9 mL/day (Mills & Bone 2000).
- Liquid extract (1:2): 30–60 mL/week.

TOXICITY

Extremely low. Toxicity studies in rats and mice have shown that silymarin, even at daily doses as high as 2500–5000 mg/kg, produced no adverse toxic effects (Anon 1998). In a 12-month study in rats and dogs given up to 2500 mg/day, no signs of toxicity were seen.

ADVERSE REACTIONS

A review of studies involving more than 7000 participants identified three cases of serious adverse reactions (two anaphylaxis and one gastroenteritis symptoms) (Jacobs et al 2002).

Overall, adverse effect frequency was the same as for placebo and had a low frequency, ranging from 2% to 10% in controlled trials. In practice, loose bowels have been reported, although the reaction is considered rare.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative. Preliminary evidence of CYP3A4 inhibition suggests it could theoretically increase levels of drugs metabolised, although a 2003 crossover study found no evidence of significant effect (DiCenzo et al 2003).

WARFARIN

Elevation of serum warfarin levels is theoretically possible owing to CYP inhibition seen in vitro — use this combination with caution.

CISPLATIN

Preliminary research has shown this combination may reduce toxic effects, yet enhance antitumour activity — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with known allergy to the Asteraceae (Compositae) family of plants.

PREGNANCY USE

Insufficient reliable information is available to determine safety in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- St Mary's thistle has hepatoprotective activity and has been shown to reduce the hepatotoxic effects of a variety of environmental toxins and medicines, such as paracetamol, erythromycin, carbon tetrachloride and death cap mushrooms.
- It has direct and indirect antioxidant activity, accelerates the regeneration of hepatocytes after liver damage, has significant gastroprotective and nephroprotective activity, anti-inflammatory and antihistamine activity according to in vitro and animal studies.
- Numerous clinical studies have investigated its effects in a variety of liver diseases. However, a recent review concluded that current data are still insufficient to recommend the herb in chronic liver diseases.

- In clinical practice, it is used to treat dyspepsia, toxic liver damage, as supportive therapy in chronic liver diseases and hypercholesterolaemia.
- Preliminary evidence suggests a possible role as adjunctive therapy with cisplatin and as a skin cancer preventative agent when applied topically.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

St Mary's thistle may improve digestion, particularly of fatty foods, and afford protection against the toxic effects of a number of drugs and environmental poisons. It is also used as supportive treatment in chronic liver diseases and high cholesterol states.

When will it start to work?

This varies, depending on the indication.

Are there any safety issues?

St Mary's thistle is considered a very safe and well tolerated herb.

REFERENCES

Ahmad N et al. Skin cancer chemopreventive effects of a flavonoid antioxidant silymarin are mediated via impairment of receptor tyrosine kinase signaling and perturbation in cell cycle progression. Biochem Biophys Res Commun 247.2 (1998): 294-301.

Alarcon de la Lastra AC et al. Gastric anti-ulcer activity of silymarin, a lipoxygenase inhibitor, in rats. J Pharm Pharmacol 44.11 (1992): 929-31.

Alarcon de la Lastra AC et al. Gastroprotection induced by silymarin, the hepatoprotective principle of Silybum marianum in ischemia-reperfusion mucosal injury: role of neutrophils. Planta Med 61.2 (1995): 116-19.

Ali BH, Bashir AK, Rasheed RA. Effect of the traditional medicinal plants Rhazya stricta, Balanitis aegyptiaca and Haplophylum tuberculatum on paracetamol-induced hepatotoxicity in mice. Phytother Res 15.7 (2001): 598-603.

Allain H et al. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. Dement Geriatr Cogn Disord 10.3 (1999): 181-5.

Angulo P et al. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology 32.5 (2000): 897-900.

Anon. Legalon Booklet. Madaus AG D-5000 Koln, West Germany 91 (1989): 3-42 (as cited in Combest WL. Milk thistle. US Pharmacist. 23.9 (1998)).

Anon. Fructis Silybi Mariae. WHO Herbal Monographs. Geneva: WHO, 2003; 300-16.

Benda L et al. The influence of therapy with silymarin on the survival rate of patients with liver cirrhosis (author's transl). Wien Klin Wochenschr 92.19 (1980): 678-83.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bode JC, Schmidt U, Durr HK. [Silymarin for the treatment of acute viral hepatitis? Report of a controlled trial. (author's transl)] Med Klin 72.12 (1977): 513-18.

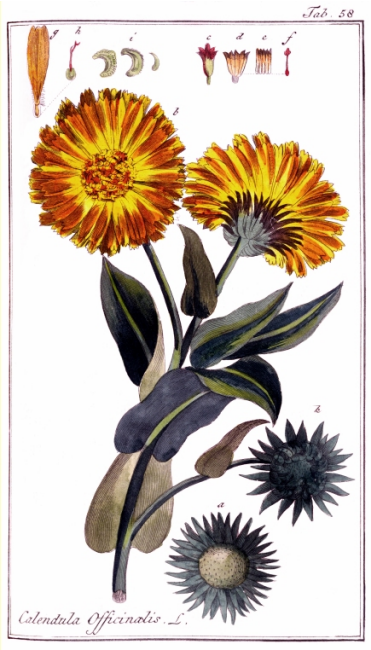
Boigk G et al. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. Hepatology 26.3 (1997): 643-9.

Bokemeyer C et al. Silibinin protects against cisplatin-induced nephrotoxicity without compromising cisplatin or ifosfamide anti-tumour activity. Br J Cancer 74.12 (1996): 2036-41.

Borsari M et al. Silybin, a new iron-chelating agent. J Inorg Biochem 85.2-3 (2001): 123-9.

Breschi MC et al. Protective effect of silymarin in antigen challenge- and histamine-induced bronchoconstriction in in vivo guinea-pigs. Eur J Pharmacol 437.1-2 (2002): 91-5.
Buzzelli G et al. A pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB1016) in chronic active hepatitis. Int J Clin Pharmacol Ther Toxicol 31.9 (1993): 456-60.
Chrungoo VJ, Singh K, Singh J. Silymarin mediated differential modulation of toxicity induced by carbon tetrachloride, paracetamol and D-galactosamine in freshly isolated rat hepatocytes. Indian J Exp Biol 35.6 (1997): 611-17.
Crocenzi FA et al. Effect of silymarin on biliary bile salt secretion in the rat. Biochem Pharmacol 59.8 (2000): 1015-22.
Davila JC, Lenherr A, Acosta D. Protective effect of flavonoids on drug-induced hepatotoxicity in vitro. Toxicology 57.3 (1989): 267-86.
Dehmlow C, Murawski N, de Groot H. Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells. Life Sci 58.18 (1996): 1591-600.
DiCenzo R et al. Coadministration of milk thistle and indinavir in healthy subjects. Pharmacotherapy 23.7 (2003): 866-70.
Fantozzi R et al. FMLP-activated neutrophils evoke histamine release from mast cells. Agents Actions 18.1-2 (1986): 155-8.
Favari L, Perez-Alvarez V. Comparative effects of colchicine and silymarin on CCl4-chronic liver damage in rats. Arch Med Res 28.1 (1997): 11-17.
Feher J et al. Liver-protective action of silymarin therapy in chronic alcoholic liver diseases. Orv Hetil 130.51 (1989): 2723-7.
Ferenci P et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J Hepatol 9.1 (1989): 105-13.
Fiebrich F, Koch H. Silymarin, an inhibitor of lipoxygenase. Experientia 35.12 (1979): 1548-60.
Floersheim GL. Antagonistic effects against single lethal doses of Amanita phalloides. Naunyn Schmiedebergs Arch Pharmacol 293.2 (1976): 171-4.
Floersheim GL et al. Clinical death-cap (Amanita phalloides) poisoning: prognostic factors and therapeutic measures. Analysis of 205 cases. Schweiz Med Wochenschr 112.34 (1982): 1164-77.
Flora K et al. Milk thistle (Silybum marianum) for the therapy of liver disease. Am J Gastroenterol 93.2 (1998): 139-43.
Gaedeke J et al. Cisplatin nephrotoxicity and protection by silibinin. Nephrol Dial Transplant 11.1 (1996): 55-62.
Galisteo M et al. Hepatotoxicity of tacrine: occurrence of membrane fluidity alterations without involvement of lipid peroxidation. J Pharmacol Exp Ther 294.1 (2000): 160-7.
Giacomelli S et al. Silybin and its bioavailable phospholipid complex (IdB 1016) potentiate in vitro and in vivo the activity of cisplatin. Life Sci 70.12 (2002): 1447-59.
Gonzalez-Correa JA et al. Effects of silymarin MZ-80 on hepatic oxidative stress in rats with biliary obstruction. Pharmacology 64.1 (2002): 18-27.
Hagymasi K et al. Extrahepatic biliary obstruction: can silymarin protect liver function? Phytother Res 16 Suppl 1 (2002): 78-80.
Hakova H, Misurova E. Therapeutical effect of silymarin on nucleic acids in the various organs of rats after radiation injury. Radiats Biol Radioecol 36.3 (1996): 365-70.
Jacobs BP et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. Am J Med 113.6 (2002): 506-15.
Jiang C, Agarwal R, Lu J. Anti-angiogenic potential of a cancer chemopreventive flavonoid antioxidant, silymarin: inhibition of key attributes of vascular endothelial cells and angiogenic cytokine secretion by cancer epithelial cells. Biochem Biophys Res Commun 276.1 (2000): 371-8.
Karimi G, Ramezani M, Tahoonian Z. Cisplatin nephrotoxicity and protection by milk thistle extract in rats. Evid Based Complement Altern Med 2.3 (2005): 383-6.

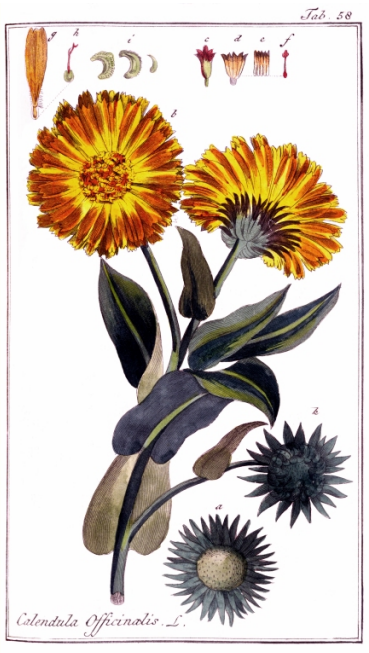
Katiyar SK et al. Protective effects of silymarin against photocarcinogenesis in a mouse skin model. J Natl Cancer Inst 89.8 (1997): 556-66.
Khayyal MT et al. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung 51.7 (2001): 545-53.
Kim HJ et al. Protection of rat liver microsomes against carbon tetrachloride-induced lipid peroxidation by red ginseng saponin through cytochrome P450 inhibition. Planta Med 63.5 (1997): 415-18.
Koch HP, Bachner J, Loffler E. Silymarin: potent inhibitor of cyclic AMP phosphodiesterase. Methods Find Exp Clin Pharmacol 7.8 (1985): 409-13.
Krecman V et al. Silymarin inhibits the development of diet-induced hypercholesterolemia in rats. Planta Med 64.2 (1998): 138-42.
Kropacova K, Misurova E, Hakova H. Protective and therapeutic effect of silymarin on the development of latent liver damage. Radiats Biol Radioecol 38.3 (1998): 411-15.
Lahiri-Chatterjee M et al. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. Cancer Res 59.3 (1999): 622-32.
Leber HW, Knauff S. Influence of silymarin on drug metabolizing enzymes in rat and man. Arzneimittelforschung 26.8 (1976): 1603-5.
Lecomte J. General pharmacologic properties of silybin and silymarin in the rat. Arch Int Pharmacodyn Ther 214.1 (1975): 165-76.
Letteron P et al. Mechanism for the protective effects of silymarin against carbon tetrachloride-induced lipid peroxidation and hepatotoxicity in mice: Evidence that silymarin acts both as an inhibitor of metabolic activation and as a chain-breaking antioxidant. Biochem Pharmacol 39.12 (1990): 2027-34.
Liu J et al. Medicinal herbs for hepatitis C virus infection. Cochrane Database Syst Rev 4 (2001): CD003183.
Liu J et al. Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials. Am J Gastroenterol 98.3 (2003): 538-44.
Lucena MI et al. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis: Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Ther 40.1 (2002): 2-8.
Magliulo E, Gagliardi B, Fiori GP. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres (author's transl). Med Klin 73.28-29 (1978): 1060-5.
Masini A et al. Iron-induced oxidant stress leads to irreversible mitochondrial dysfunctions and fibrosis in the liver of chronic iron-dosed gerbils: The effect of silybin. J Bioenerg Biomembr 32.2 (2000): 175-82.
Miguez MP et al. Hepatoprotective mechanism of silymarin: no evidence for involvement of cytochrome P450 2E1. Chem Biol Interact 91.1 (1994): 51-63.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Morazzoni P, Bombardelli E. Silybum marianum (Carduus marianus). Fitoterapia 66 (1995): 3-42.
Mourelle M et al. Prevention of CCL4-induced liver cirrhosis by silymarin. Fundam Clin Pharmacol 3.3 (1989): 183-91.
Muriel P, Mourelle M. Prevention by silymarin of membrane alterations in acute CCl4 liver damage. J Appl Toxicol 10.4 (1990): 275-9.
Muriel P et al. Silymarin protects against paracetamol-induced lipid peroxidation and liver damage. J Appl Toxicol 12.6 (1992): 439-42.
Palasciano G et al. The effect of silymarin on plasma levels of malondialdehyde in patients receiving long-term treatment with psychotropic drugs. Curr Ther Res 55 (1994): 537-45.
Par A et al. Oxidative stress and antioxidant defense in alcoholic liver disease and chronic hepatitis C. Orv Hetil 141.30 (2000): 1655-9.
Parasassi T et al. Drug-membrane interactions: silymarin, silybin and microsomal membranes. Cell Biochem Funct 2.2 (1984): 85-8.
Pares A et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol 28.4 (1998): 615-21.
Pietrangelo A et al. Antioxidant activity of silybin in vivo during long-term iron overload in rats. Gastroenterology 109.6 (1995): 1941-9.



Psotova J et al. Influence of silymarin and its flavonolignans on doxorubicin-iron induced lipid peroxidation in rat heart microsomes and mitochondria in comparison with quercetin. Phytother Res 16 (Suppl 1) (2002): 63-7.
Rui YC et al. Effects of silybin on production of oxygen free radical, lipoperoxide and leukotrienes in brain following ischemia and reperfusion. Zhongguo Yao Li Xue Bao 11.5 (1990): 418-21.
Saliou C et al. Antioxidants modulate acute solar ultraviolet radiation-induced NF-kappa-B activation in a human keratinocyte cell line. Free Radic Biol Med 26.1-2 (1999): 174-83.
Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs 61.14 (2001): 2035-63.
Salmi HA, Sarna S. Effect of silymarin on chemical, functional, and morphological alterations of the liver. A double-blind controlled study. Scand J Gastroenterol 17.4 (1982): 517-21.
Scambia G et al. Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin. Eur J Cancer 32A.5 (1996): 877-82.
Schuppan D et al. Alcohol and liver fibrosis: pathobiochemistry and treatment. Z Gastroenterol 33.9 (1995): 546-50.
Singh RP et al. Silymarin inhibits growth and causes regression of established skin tumors in SENCAR mice via modulation of mitogen-activated protein kinases and induction of apoptosis. Carcinogenesis 23.3 (2002): 499-510.
Skottova N, Krecman V. Dietary silymarin improves removal of low density lipoproteins by the perfused rat liver. Acta Univ Palacki Olomuc Fac Med 141 (1998a): 39-40.
Skottova N, Krecman V. Silymarin as a potential hypocholesterolaemic drug. Physiol Res 47.1 (1998b): 1-7.
Somogyi A et al. Short term treatment of type II hyperlipoproteinaemia with silymarin. Acta Med Hung 46.4 (1989): 289-95.
Sonnenbichler J et al. Stimulatory effects of silibinin and silicristin from the milk thistle Silybum marianum on kidney cells. J Pharmacol Exp Ther 290.3 (1999): 1375-83.
Trinchet JC et al. Treatment of alcoholic hepatitis with silymarin: A double-blind comparative study in 116 patients. Gastroenterol Clin Biol 13.2 (1989): 120-4.
Tyutyulkova N et al. Hepatoprotective effect of silymarin (carsil) on liver of D-galactosamine treated rats: Biochemical and morphological investigations. Methods Find Exp Clin Pharmacol 3.2 (1981): 71-7.
Tyutyulkova N et al. Effect of silymarin (Carsil) on the microsomal glycoprotein and protein biosynthesis in liver of rats with experimental galactosamine hepatitis. Methods Find Exp Clin Pharmacol 5.3 (1983): 181-4.
Valenzuela A, Guerra R. Protective effect of the flavonoid silybin dihemisuccinate on the toxicity of phenylhydrazine on rat liver. FEBS Lett 181.2 (1985): 291-4.
Valenzuela A et al. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. Planta Med 55.5 (1989): 420-2.
Velussi M et al. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol 26.4 (1997): 871-9.
Venkataramanan R et al. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. Drug Metab Dispos 28.11 (2000): 1270-3.
Vinh PQ et al. Chemopreventive effects of a flavonoid antioxidant silymarin on N-butyl-N-(4-hydroxybutyl)nitrosamine-induced urinary bladder carcinogenesis in male ICR mice. Jpn J Cancer Res 93.1 (2002): 42-9.
Vogel G et al. Protection by silibinin against Amanita phalloides intoxication in beagles. Toxicol Appl Pharmacol 73.3 (1984): 355-62.
von Schonfeld J, Weisbrod B, Muller MK. Silibinin, a plant extract with antioxidant and membrane stabilizing properties, protects exocrine pancreas from cyclosporin A toxicity. Cell Mol Life Sci 53.11-12 (1997): 917-20.

Zhao J et al. Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradecanoylphorbol 13-acetate-caused modulation of antioxidant and inflammatory enzymes, and cyclooxygenase 2 and interleukin-1alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumor promotion. Mol Carcinog 26.4 (1999): 321-33.
Zhao J et al. Inhibitory effect of a flavonoid antioxidant silymarin on benzoyl peroxide-induced tumor promotion, oxidative stress and inflammatory responses in SENCAR mouse skin. Carcinogenesis 21.4 (2000): 811-16.
Zhu W, Zhang JS, Young CY. Silymarin inhibits function of the androgen receptor by reducing nuclear localization of the receptor in the human prostate cancer cell line LNCaP. Carcinogenesis 22.9 (2001): 1399-403.
Zi X, Agarwal R. Modulation of mitogen-activated protein kinase activation and cell cycle regulators by the potent skin cancer preventive agent silymarin. Biochem Biophys Res Commun 263.2 (1999): 528-36.
Zi X et al. Novel cancer chemopreventive effects of a flavonoid antioxidant silymarin: inhibition of mRNA expression of an endogenous tumor promoter TNF alpha. Biochem Biophys Res Commun 239.1 (1997): 334-9.
Zi X et al. A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells. Cancer Res 58.9 (1998a): 1920-9.
Zi X et al. Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins. Clin Cancer Res 4.4 (1998b): 1055-64.
Zuber R et al. Effect of Silybin and its congeners on human liver microsomal cytochrome P450 activities. Phytother Res 16.7 (2002): 632-8.

S-Adenosyl-L-Methionine (SAMe)



Historical note SAMe was first discovered in Italy in 1952. About 20 years later, a stable salt was commercially manufactured and produced for injectable use. At first, it was investigated as a treatment for schizophrenia, for which it proved inappropriate; however, successful trials in depressed patients began in the 1970s and it was inadvertently found to improve symptoms of arthritis. Since then, numerous studies have been undertaken to examine the role of SAMe in both depression and osteoarthritis. To date, more than 75 clinical trials have been conducted using SAMe as a therapeutic agent, involving over 23,000 people.

BACKGROUND AND RELEVANT PHARMACOKINETICS

SAMe is synthesised in the cytosol of every cell, but the liver plays a central role in its homeostasis and is the major site of biosynthesis and degradation. Up to half the daily intake of methionine is converted to SAMe in the liver, where it is metabolised to *S*-adenosylhomocysteine and then homocysteine. Being a central part of the one carbon metabolism cycle, SAMe is intrinsically linked with the other methyl donors such as folate and B12.

SAMe naturally exists as diastereoisomers and it is presently unclear whether both the R and S forms are biologically active in humans. Evidence from a rat model suggests they are equi-potent (Dunne et al 1998). Oral doses achieve peak plasma concentrations within 3–5 hours after ingestion of an enteric-coated tablet (400–1000 mg). Enteric coating of SAMe supplements is essential to ensure product stability and potency. The half-life is reported to be 100 minutes, and excretion occurs via both urine and faeces (Najim et al 2004).

MAIN ACTIONS

SAMe is involved in myriad biochemical processes and metabolic pathways, chiefly as a methyl donor. It is a methyl donor involved in the synthesis of many important biochemicals, such as creatine, melatonin, glutathione, RNA and DNA, phospholipids, proteins, adrenaline and amino acids L-cysteine and taurine. SAMe is closely linked with the metabolism of folate and vitamin B12, which accounts for its ability to lower excessive homocysteine serum concentrations resulting from a deficiency of one or both of these nutrients.

This review will only discuss those actions that have been confirmed clinically.

ANTIDEPRESSANT ACTIVITY

SAMe supplementation produces a clinically significant antidepressant activity that has been demonstrated in numerous trials.

The mode of antidepressant action is unknown, but is likely to involve several mechanisms. As a methyl donor, SAMe plays a role in the metabolism of various CNS neurotransmitters that play an integral part in synaptic transmission and behaviour, such as noradrenaline, dopamine and serotonin (Bottiglieri 1996). Supplementation with SAMe in depressed patients raises serotonin, dopamine and phosphatidylserine and improves neurotransmitter binding to receptor sites, resulting in increased activity (Pizzorno & Murray 2006). More recent evidence suggests that the dopaminergic activity is most prominent. One human study confirmed that 7 days of supplemental SAMe (400 mg/day) decreased the exaggerated plasma noradrenaline levels found in depressed patients (Sherer et al 1986). It is also involved in the formation of phosphatidylcholine, a major component of cell membranes and neurotransmission (Carney et al 1987).

Interestingly, significantly low levels of SAMe in cerebrospinal fluid have been observed in severely depressed patients compared with controls (Bottiglieri et al 1990); however, the significance of this finding is unknown.

ANTI-INFLAMMATORY

A substantial body of evidence has identified clinically significant anti-inflammatory activity for SAMe with comparative trials showing it to be as effective as standard NSAIDs.

Although the mechanism of action remains unclear, it does not appear to be mediated by PG. SAMe stimulates the synthesis of proteoglycans by articular chondrocytes and exerts a chondroprotective effect according to in vitro research and tests with experimental animals (Barcelo et al 1987, 1990, Harmand et al 1987). In vitro studies using cultured rabbit synovial cells has found that SAMe reduces TNF-alpha and fibronectin RNA expression (Gutierrez et al 1997).

HEPATOPROTECTIVE EFFECTS

SAMe indirectly reduces oxidative stress in the liver by serving as a precursor for glutathione. Glutathione is particularly important for reducing the toxic effects of free radical molecules generated by various substances, including alcohol. SAMe also acts as the main methylating agent in the liver. Research with people with alcoholic and non-alcoholic liver diseases confirms that SAMe supplementation significantly increases hepatic glutathione levels (Vendemiale et al 1989). Additionally, in vitro research has identified antifibrotic activity and recently, enhanced production of IL-6,

a key anti-inflammatory cytokine in the liver that assists regeneration and downregulation of TNF (Arteel et al 2003, Casini et al 1989, Song et al 2004). Research using animal models demonstrate that SAMe is a natural growth regulator in hepatocytes and is anti-apoptotic in healthy liver cells, but pro-apoptotic in hepatic carcinoma cells (Lu & Mato 2005).

OTHER ACTIONS

PROLACTIN AND TSH EFFECTS

A double-blind, placebo-controlled study involving 20 subjects with depression identified a significant reduction in prolactin concentrations after 14 days' treatment with SAMe (Thomas et al 1987). The results of a study conducted in 1990, however, suggest that the effects on these hormones may be gender specific, with women demonstrating an augmented response of thyroid stimulating hormone (TSH) and no effect on prolactin levels, whereas release of both TSH and prolactin was inhibited in male subjects (Fava et al 1990). If SAMe does exert dopaminergic effects, as presently suspected, then it should also be taken into consideration that dopamine naturally inhibits both TSH and prolactin secretion in humans.

ANTIOXIDANT

SAMe exhibited direct antioxidant activity in vitro (Caro & Cederbaum 2004).

CLINICAL USE

Although SAMe is administered as an oral supplement in Australia, it is also used in injectable dose forms in Europe. This discussion will mainly focus on oral use.

OSTEOARTHRITIS

A 2004 meta-analysis of 11 RCTs involving almost 1500 patients, comparing SAMe with either placebo or NSAIDs, concluded that SAMe is as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA of the knee. In addition, SAMe-treated patients were 58% less likely to experience adverse effects than those treated with NSAIDs (Soeken 2004).

The longest clinical trial to date was conducted over 2 years and found that a loading dose of oral SAMe 600 mg/day taken over the first 2 weeks, followed by a maintenance dose of 400 mg, produced an improvement in symptoms within the first month and no serious adverse effects (Konig 1987).

Comparative studies Comparative studies in humans have found that oral SAMe (1200 mg) produces similar symptom-relieving effects as piroxicam (20 mg), ibuprofen (1200 mg), indomethacin (150 mg) or naproxen (750 mg) (Caruso &

Pietrogrande 1987, Glorioso et al 1985, Maccagno et al 1987, Muller-Fassbender 1987, Vetter 1987).

More recently, a 16-week randomised, double-blind crossover study of 61 individuals with OA of the knee compared the efficacy of SAMe (1200 mg/day) with celecoxib (200 mg/day). At this dose SAMe was as effective as celecoxib in providing significant symptom relief; however, it had a slower onset of action, requiring 1 month of continuous use before benefits were felt (Najm et al 2004). The same study was unable to detect an antidepressant effect for SAMe.

DEPRESSION

Several reviews and at least two meta-analyses have examined the available evidence for SAMe in the treatment of depression for trials completed prior to 1994 and concluded that SAMe is superior to placebo, as effective as standard tricyclic antidepressants, and it is better tolerated in the treatment of depressive disorders (Bressa 1994, Fetrow & Avila 2001).

The most recent review conducted in 2005 assessed results from 11 studies and concluded that the evidence for SAMe was positive in depression, but currently hampered by the short duration of trials and questions over the oral bioavailability of the products used (Williams et al 2005). Advantages consistently noted by reviewers include the faster onset of action observed with SAMe treated patients (10 days) compared to treatment with SSRIs (21 days) and the lack of many side-effects that plague the pharmaceutical antidepressants (Mischoulon & Fava 2002).

A trial implementing 800–1600 mg/day SAMe as an adjunctive agent in 30 treatment-resistant patients over a 6-week trial revealed a staggering 50% response rate, with 43% of the sample experiencing remission of symptoms (Alpert et al 2004). Positive results such as these warrant further investigation of SAMe in this adjunctive role with more stringent trial designs.

Parkinson's disease and depression High-dose SAMe (800–3600 mg/day) treatment was investigated in a pilot study involving 11 depressed patients with Parkinson's disease, all of whom had been previously treated with other antidepressant agents and had no significant benefit or intolerable side-effects. After 10 weeks, 10 patients had at least a 50% improvement on the Hamilton Depression Scale, with only one patient showing no improvement. The mean score before treatment was 27.09 and was 9.55 after SAMe treatment (Di Rocco et al 2000).

FIBROMYALGIA

Four double-blind trials have investigated the effects of SAMe in fibromyalgia, with all reporting positive findings (Jacobsen et al 1991, Tavoni et al 1987, 1998, Volkmann et al 1997). Two studies used injectable SAMe (200 mg daily).

The largest study involved 44 patients with primary fibromyalgia and found that during week 5, the group receiving SAMe (800 mg/day) experienced improvements in clinical disease activity, pain, fatigue, morning stiffness and one measurement of mood. Although encouraging, not all parameters were improved beyond placebo, such as tender point score and isokinetic muscle strength (Jacobsen et al 1991).

These results should not be surprising, given that one-third of all fibromyalgia patients are reported to suffer from depression and a meta-analysis of the effectiveness of antidepressants (including SAMe) in fibromyalgia deemed them a successful treatment strategy (O'Malley et al 2000). It concluded that tricyclic antidepressants, SSRIs and SAMe all improved sleep, fatigue, pain and wellbeing, but not trigger points.

LIVER CIRRHOSIS

It is now generally accepted that in alcoholic patients with advanced liver cirrhosis, hepatic SAMe concentration is greatly decreased (Lieber 2002). While transient SAMe depletion is necessary for the liver to regenerate, chronic hepatic SAMe depletion may lead to malignant transformation (Lu & Mato 2005). Studies with primates have found that the decreased hepatic SAMe concentrations and the associated liver lesions, including mitochondrial injury, can be corrected with SAMe supplementation (Lieber et al 1990).

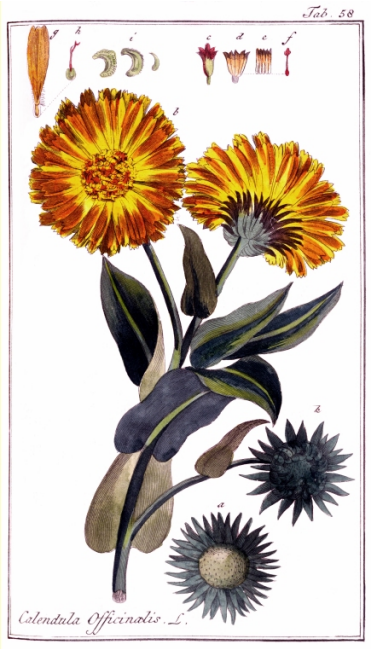
A 2006 Cochrane review of SAMe in alcoholic liver disease analysed results from nine randomised clinical trials that included a heterogeneous sample of 434 patients (Rambaldi & Gluud 2006). The methodological quality was considered low; however, eight of the trials were placebo controlled. As a result, the analysis was based mainly on one trial that found no significant effects of SAMe on all-cause mortality, liver-related mortality, liver transplantation or complications. The authors concluded that based on such limited evidence, more long-term, high-quality randomised trials of SAMe for these patients are required before SAMe may be recommended for clinical practice.

HEPATIC CANCER

Due to its role in the regulation of growth and apoptosis of hepatocytes, SAMe is being investigated as a possible preventative or treatment agent in hepatocellular carcinoma (Lu & Mato 2005).

OTHER USES

SAMe is used to reduce pain in migraine headache because analgesic activity was reported at a dose of 400–800 mg/day in a group of migraine sufferers (Gatto et al 1986). It is also used in AIDS-related myelopathy and coronary artery disease, as these conditions have been associated with depleted SAMe levels. Supplementation has also been prescribed in cases of general fatigue, poor digestion, allergies and elevated homocysteine levels.



DOSAGE RANGE

BASED ON CLINICAL STUDIES

- Depression: 400–1600 mg/day in divided doses. Sometimes it is started as 200 mg twice daily, increased on day 2 to 400 mg twice daily and then increased again to 400 mg three times daily on day 10 until reaching the full therapeutic dose of 400 mg four times daily by day 20, if necessary (Pizzorno & Murray 2006).
- Osteoarthritis: 1200 mg/day in divided doses, taken as above, with a reduced dose of 400 mg/day used as a maintenance dose once a response occurs.
- Fibromyalgia: 600–800 mg/day in divided doses.
- Liver diseases: 400–1200 mg/day in divided doses, although larger doses have been used.
- Parkinson's disease: 800–3600 mg/day in divided doses.
- Migraine: 400–800 mg/day in divided doses.

ADVERSE REACTIONS

Mild gastrointestinal discomfort is the most common side-effect reported in clinical studies, although anxiety, headache, urinary frequency and pruritis have also been reported. It has been reported that side effects may be minimised by consuming SAMe before food.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

TRICYCLIC ANTIDEPRESSANTS AND OTHER SEROTONERGIC AGENTS

Theoretically, co-administration may result in an increased risk of serotonin syndrome. However, one experimental study found that brain SAMe levels were significantly reduced after chronic treatment with imipramine (Taylor & Randall 1975) — use this combination with caution.

HEPATOTOXIC DRUGS
SAMe may reduce hepatic injury caused by such agents as paracetamol, alcohol and oestrogens — potentially beneficial interaction.

THYROXINE
Caution and monitoring may be warranted.

BETAINE
In studies supplementing mice with betaine, significant increases in SAMe were observed with a three-fold elevation of the activity of methionine adenosyltransferase — observe.

CONTRAINDICATIONS AND PRECAUTIONS
SAMe should be used with caution in people with bipolar disorder, schizophrenia or schizoaffective disorder, or Parkinson's disease (Pizzorno & Murray 2006).

PREGNANCY USE
SAMe has been used intravenously in the last trimester of pregnancy with no adverse effects to mother or fetus. However, safety has not yet been conclusively established for either injectable or oral dose forms and possible effects on prolactin levels need to be considered.

PRACTICE POINTS/PATIENT COUNSELLING
- SAMe is involved in myriad biochemical reactions within the body and found within every cell.
- Clinically, it has anti-inflammatory, analgesic, antidepressant and hepatoprotective activity.
- A 2002 meta-analysis concluded that SAMe is as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA without the adverse effects associated with NSAIDs. A recent study has found it is as effective as celecoxib for providing symptom relief; however, SAMe has a slower onset of action.
- Clinical trials have also shown it to be a safe and effective treatment for depression, comparable to tricyclic antidepressant drugs, yet with a faster onset of action.
- SAMe also appears to be useful in fibromyalgia, and possibly migraine headache. Its usefulness in alcoholic liver disease is unclear. Other uses include general fatigue, elevated homocysteine levels, allergies and poor digestion.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

SAMe has anti-inflammatory, analgesic, antidepressant and protective effects on the liver. It effectively reduces pain and inflammation in OA and elevates mood in depression. In fibromyalgia, SAMe reduces pain, fatigue and morning stiffness and may also reduce pain in migraine headache.

When will it start to work?

Beneficial effects are usually seen within 4–5 weeks for OA, whereas antidepressant effects are experienced within 1 week. Benefits in fibromyalgia can take up to 6 weeks to establish.

Are there any safety issues?

SAMe should be used with caution by people with bipolar disorder, schizophrenia or schizoaffective disorder, Parkinson's disease or taking antidepressant medicines. Monitoring of homocysteine levels may be required with long term supplementation.

REFERENCES

Alpert JE et al. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 24.6 (2004): 661-4.

Arteel G et al. Advances in alcoholic liver disease. Best Pract Res Clin Gastroenterol 17 (2003): 625-47.

Barcelo HA et al. Effect of S-adenosylmethionine on experimental osteoarthritis in rabbits. Am J Med 83.5A (1987): 55-9.

Barcelo HA et al. Experimental osteoarthritis and its course when treated with S-adenosyl-L-methionine. Rev Clin Esp 187.2 (1990): 74-8.

Bell KM et al. S-adenosylmethionine blood levels in major depression: changes with drug treatment. Acta Neurol Scand Suppl 154 (1994): 15-18.

Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. Nutr Rev 54.12 (1996): 382-90.

Bottiglieri T et al. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry 53.12 (1990): 1096-8.

Bressa GM. S-adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neurol Scand Suppl 154 (1994): 7-14.

Carney MW, Toone BK, Reynolds EH. S-adenosylmethionine and affective disorder. Am J Med 83.5A (1987): 104-6.

Caro AA, Cederbaum AI. Antioxidant properties of S-adenosyl-methionine in Fe^{2+}-initiated oxidations. Free Radical Biol Med 36.10 (2004): 1303-16.

Caruso I, Pietrogrande V. Italian double-blind multicenter study comparing S-adenosylmethionine, naproxen, and placebo in the treatment of degenerative joint disease. Am J Med 83.5A (1987): 66-71.

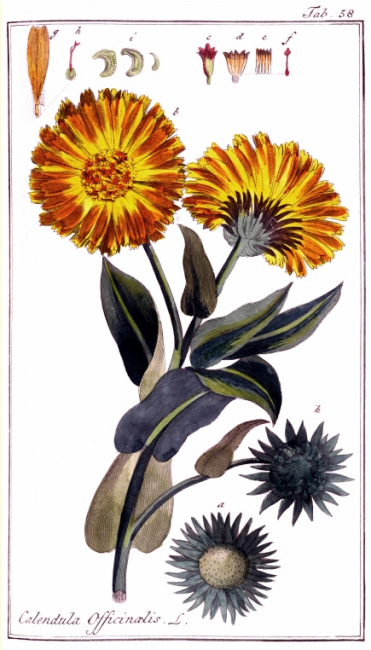
Casini A et al. S-adenosylmethionine inhibits collagen synthesis by human fibroblasts in vitro. Methods Find Exp Clin Pharmacol 11.5 (1989): 331-4.

Di Rocco A et al. S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial. Mov Disord 15.6 (2000): 1225-9.

Dunne JB et al. Evidence that S-adenosyl-L-methionine diastereoisomers may reduce ischaemia-reperfusion injury by interacting with purinoceptors in isolated rat liver. Br J Pharmacol 125 (1998): 225-33.

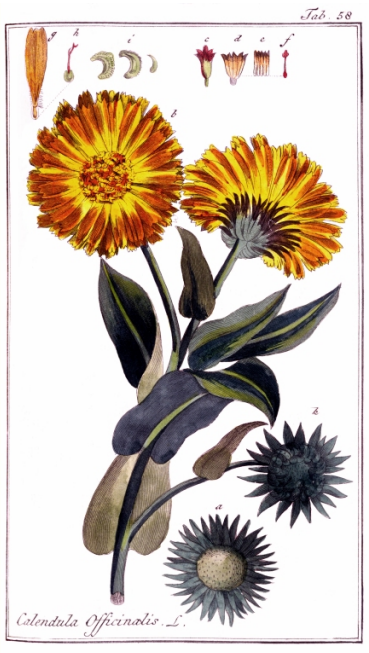
Fava M et al. Neuroendocrine effects of S-adenosyl-L-methionine: a novel putative antidepressant. J Psychiatr Res 24.2 (1990): 177-84.

Fetrow CW, Avila JR. Efficacy of the dietary supplement S-adenosyl-L-methionine. Ann Pharmacother 35.11 (2001): 1414-25.
Gatto G et al. Analgesizing effect of a methyl donor (S-adenosylmethionine) in migraine: an open clinical trial. Int J Clin Pharmacol Res 6.1 (1986): 15-17.
Glorioso S et al. Double-blind multicentre study of the activity of S-adenosylmethionine in hip and knee osteoarthritis. Int J Clin Pharmacol Res 5.1 (1985): 39-49.
Gutierrez S et al. SAMe restores the changes in the proliferation and in the synthesis of fibronectin and proteoglycans induced by tumour necrosis factor alpha on cultured rabbit synovial cells. Br J Rheumatol 36 (1997): 27-31.
Harmand MF et al. Effects of S-adenosylmethionine on human articular chondrocyte differentiation. An in vitro study. Am J Med 83.5A (1987): 48-54.
Jacobsen S, Danneskiold-Samsoe B, Andersen RB. Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. Scand J Rheumatol 20.4 (1991): 294-302.
Konig B. A long-term (two years) clinical trial with S-adenosylmethionine for the treatment of osteoarthritis. Am J Med 83.5A (1987): 89-94.
Lieber CS et al. S-adenosyl-L-methionine attenuates alcohol-induced liver injury in the baboon. Hepatology 11.2 (1990): 165-72.
Lieber CS. S-Adenosyl-L-methionine and alcoholic liver disease in animal models: implications for early intervention in human beings. Alcohol 27.3 (2002): 173-7.
Lu SC, Mato JM. Role of methionine adenosyltransferase and S-adenosylmethionine in alcohol-associated liver cancer. Alcohol 35.3 (2005): 227-34.
Maccagno A et al. Double-blind controlled clinical trial of oral S-adenosylmethionine versus piroxicam in knee osteoarthritis. Am J Med 83.5A (1987): 72-7.
Mato JM et al. S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. J Hepatol 30.6 (1999): 1081-9.
Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. Am J Clin Nutr 76.5 (2002): 1158-61S.
Muller-Fassbender H. Double-blind clinical trial of S-adenosylmethionine versus ibuprofen in the treatment of osteoarthritis. Am J Med 83.5A (1987): 81-3.
Najm WI et al. S-adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. [ISRCTN36233495]. BMC Musculoskelet Disord 5 (2004): 6.
O'Malley PG et al. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 15.9 (2000): 659-66.
Pizzorno J, Murray M. Textbook of Natural Medicine, 3rd edn. St Louis: Elsevier, 2006.
Rambaldi A, Gluud C. S-adenosyl-L-methionine for alcoholic liver diseases. Cochrane Database Syst Rev 2 (2006): CD002235.
Sherer MA et al. Effects of S-adenosyl-methionine on plasma norepinephrine, blood pressure, and heart rate in healthy volunteers. Psychiatry Res 17.2 (1986): 111-18.
Soeken KL et al. Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. J Fam Pract 51.5 (2002): 425-30.
Song Z et al. Modulation of endotoxin stimulated Interleukin 6 production in moncytes and Kupffer cells by S-adenosylmethionine (SAMe). Cytokine 28.6 (2004): 214-23.
Tavoni A et al. Evaluation of S-adenosylmethionine in primary fibromyalgia: A double-blind crossover study. Am J Med 83.5A (1987): 107-10.
Tavoni A et al. Evaluation of S-adenosylmethionine in secondary fibromyalgia: a double-blind study. Clin Exp Rheumatol 16.1 (1998): 106-7.
Taylor KM, Randall PK. Depletion of S-adenosyl-L-methionine in mouse brain by antidepressive drugs. J Pharmacol Exp Ther 194.2 (1975): 303-10.
Thomas CS et al. The influence of S-adenosylmethionine (SAM) on prolactin in depressed patients. Int Clin Psychopharmacol 2.2 (1987): 97-102.



Vendemiale G et al. Effects of oral S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease. Scand J Gastroenterol 24.4 (1989): 407-15.
Vetter G. Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis. Am J Med 83.5A (1987): 78-80.
Volkmann H et al. Double-blind, placebo-controlled cross-over study of intravenous S-adenosyl-L-methionine in patients with fibromyalgia. Scand J Rheumatol 26.3 (1997): 206-11.
Williams AL et al. S-adenosylmethionine (SAMe) as treatment for depression: a systematic review. Clin Invest Med 28.3 (2005):132-9.

Saw palmetto



Historical note Saw palmetto was used traditionally as a treatment for urogenital irritations, impotence and male infertility, among other conditions, and was described by the American Eclectic physicians as the 'old man's friend'. Between 1906 and 1917 saw palmetto was listed in the US Pharmacopoeia and between 1926 and 1950 it was in the National Formulary as a treatment for urogenital ailments; however, it fell out of favour for several decades as pharmaceutical medicines came to the forefront of mainstream medicine. Not so in Europe where, in the 1960s, French researchers began to chemically analyse the saw palmetto berry, and a breakthrough lipophilic preparation was eventually developed and subjected to countless clinical trials.

COMMON NAME
Serenoa or saw palmetto

OTHER NAMES
American dwarf palm tree, cabbage palm, dwarf palmetto, fan palm, sabal fructus, sabal, serenoa

BOTANICAL NAME/FAMILY
Sabal serrulata, Serenoa repens (family Arecaceae or Palmaceae)

PLANT PART USED
Dried ripe fruit

CHEMICAL COMPONENTS
An ethanol extract of the berry contains free fatty acids rich in shorter chain-length fatty acids, such as capric, caprylic, lauric and myristic acid (Nemecz 2003). Palmitic, stearic, oleic, linoleic and linolenic acid are also present in the extract. There are also lesser amounts of phytosterols (such as beta-sitosterol, stigmasterol, ampesterol, and cycloartenol), aliphatic alcohols and polyprenic compounds. The lipophilic extract is used medicinally.

MAIN ACTIONS
The mechanism of action is not fully elucidated; however, it appears that several mechanisms are at work.

INHIBITION OF 5-ALPHA REDUCTASE

In different cell systems, the lipid-sterolic extract acts as a non-competitive inhibitor of both type 1 and type 2 5-alpha reductase activity, thereby preventing the conversion of testosterone to dihydrotestosterone (Bayne et al 2000, Raynaud et al 2002, Sultan et al 1984). However, it is currently unclear whether the effect is apparent in humans, as contradictory evidence exists. Raynaud et al (2002) explained that the discrepancies found by different authors were due to different experimental conditions and selectivity for fatty acids, as only specific aliphatic unsaturated fatty acids have been shown to inhibit 5-alpha reductase activity.

One study that analysed and compared BPH samples taken from both untreated and treated subjects (320 mg saw palmetto extract taken for 3 months) found that local levels of testosterone were raised, whereas dihydrotestosterone levels were reduced, suggestive of local 5-alpha reductase inhibition (Di Silverio et al 1998). An earlier, short-term study found that a dose of 160 mg of a liposterolic extract (Permixon) produced no changes to serum dihydrotestosterone levels, whereas finasteride 5 mg induced a significant reduction (Strauch et al 1994). Since prostate levels were untested in this study, it is not known whether a local effect occurred, even though serum levels remained unchanged.

Unlike other 5-alpha reductase inhibitors, there is no interference with the cell's capacity to secrete prostate-specific antigens because it does not affect the transcription of the gene for prostate-specific antigen (PSA), as demonstrated both in vitro and in vivo (Maccagnano et al 2006). Although having an obvious clinical advantage in regard to PSA screening for prostate cancer, this also suggests that 5-alpha reductase inhibition is not a major activity.

INHIBITS BINDING OF DIHYDROTESTOSTERONE AND TESTOSTERONE TO ANDROGEN RECEPTORS

Saw palmetto reduces receptor binding of dihydrotestosterone and testosterone by an average of 41%, as tested in 11 different tissue specimens from BPH patients (el Sheikh et al 1988). In 2003, results from two animal studies showed that saw palmetto (whole berry and extract) influenced prostatic hyperplasia via effects on androgen metabolism (Talpur et al 2003).

INHIBITS PROLACTIN

In vivo research has identified not only an inhibitory effect on androgens, but also on the trophic effect of prolactin in the rat prostate (Van Coppenolle et al 2000). The inhibitory effect on prolactin activity appears to be due to inhibition of several steps in

prolactin receptor signal transduction, according to one animal model (Vacher et al 1995).

ANTI-INFLAMMATORY

Saw palmetto is a dual inhibitor of the COX and 5-lipoxygenase pathways, according to in vitro research (Breu et al 1992, Paubert-Braquet et al 1997). More recently, decreased expression of COX-2 has been identified, providing a further explanation for the observed anti-inflammatory activity (Goldmann et al 2001).

ANTISPASMODIC

Both the lipid and saponifiable fractions have demonstrated antispasmodic activity in several in vitro studies (WHO 2003).

CYTOCHROMES

Saw palmetto failed to have a significant effect on CYP3A4 or CYP2D6 when tested in healthy individuals (Markowitz et al 2003).

ANTIPROLIFERATIVE EFFECTS

In recent years, there has been interest in determining whether saw palmetto may have a role in prostate cancer, as an inhibitory activity has been observed in several test tube studies for prostatic cancer cell lines (Goldmann et al 2001, Ishii et al 2001).

OTHER ACTIONS

Although alpha-1 adrenoreceptor activity has been reported in vitro, a clinical study found no evidence of this activity (Goepel et al 1999, 2001).

Traditionally, saw palmetto is believed to act as a mild diuretic, urinary antiseptic and expectorant.

CLINICAL USE

The most studied saw palmetto preparation is a commercial product known as Permixon (Pierre Fabre Médicament, Castres, France), which is a liposterolic extract consisting of 80% free (e.g. 94 g/100 g extract) and 7% esterified fatty acids, as well as small amounts of sterols (beta-sitosterol, campesterol, stigmasterol, cycloartenol), and a minimum percentage of polyprenic compounds, arabinose, glucose, galactose, uronic acid, and flavonoids.

BENIGN PROSTATIC HYPERTROPHY

Saw palmetto extracts are extremely popular in Europe where herbal preparations represent approximately one-third of total sales of all therapeutic agents sold for the treatment of BPH (Levin & Das 2000).

Substantial evidence suggests that saw palmetto is an effective treatment for stages 1 and 2 of BPH. A 2002 Cochrane review assessing the results from 21 randomised trials involving 3139 men concluded that saw palmetto improves urinary scores, symptoms and urinary flow measures compared with placebo, with effects on symptoms scores and peak urine flow similar to the pharmaceutical drug finasteride (Wilt et al 2002). Additionally, its use is associated with fewer adverse effects compared with finasteride and typically, symptomatic relief is reported more quickly.

In 2004, an updated meta-analysis of 14 randomised studies and three open-label studies was published (Boyle et al 2004). The analysis used data from 4280 patients derived from clinical studies that had used Permixon. Peak urinary flow rate and nocturia were the two common end-points. Active treatment was associated with a mean reduction in the International Prostate Symptom Score (IPSS) of 4.78 (0.41). A significant improvement in peak flow rate and reduction in nocturia was also reported.

Since then, a double-blind study of 1 year of continuous treatment with saw palmetto extract (160 mg twice daily) failed to produce significant differences compared with placebo for the American Urological Association Symptom Index, maximal urinary flow rate, prostate size, residual volume after voiding, quality of life, or serum PSA levels (Bent et al 2006). A closer look at the study reveals that some subjects with moderate to severe BPH were also included in the sample, which may have contributed to the results observed; however, this is speculative.

Comparisons with alpha-adrenoreceptor antagonists Although several comparative trials have been undertaken with finasteride, only a few have compared it with alpha-adrenoreceptor antagonist drugs, which are also commonly used in BPH (Adriazola et al 1992, Debruyne et al 2002). The most recent was a large, randomised, double-blind study involving 811 men with symptomatic BPH, who were recruited from 11 European countries, which showed that Permixon 320 mg/day produced similar results to tamsulosin 0.4 mg/day (Omnic) (Debruyne et al 2002). More specifically, both treatments reduced the IPSS by an average of 4.4 in 80% of subjects. Those patients with the most severe disease experienced the greatest improvement in IPSS total score, with mean changes greater in the Permixon group than in the tamsulosin group (–8.0 and –6.8, respectively). In regard to safety, both treatments were considered well tolerated; however, ejaculation disorders were significantly more frequent with tamsulosin (4.2%) than with Permixon (0.6%). Although these results are promising, this study has been criticised for not including a placebo group as a comparator.

In a short 3-week study, Grasso et al (1995) compared the effects of alfuzosin (7.5 mg/day) with saw palmetto (320 mg/day) in 63 BPH subjects under double-blind test conditions. Both treatments were found to be as effective in regard to improving irritative score; with maximum and mean urine flow, however, alfuzosin was shown to more rapidly reduce symptoms of obstruction. Considering most studies have shown that 4–8 weeks' treatment with the herb is required to produce maximal effects, the effect seen at 3 weeks is encouraging.

An earlier study compared the effects of prazosin with saw palmetto in 45 patients with BPH over a 12-week period (Adriazola et al 1992). This study found that although both treatments reduced symptoms, prazosin was slightly more effective.

Changes to prostate size It is still open to speculation as to whether saw palmetto affects prostate size, because studies have produced contradictory results (Aliaev et al 2002, Bent et al 2006, Pytel et al 2002). One open study of 155 men tested the effectiveness and tolerability of Permixon (160 mg twice daily) over 2 years (Pytel et al 2002), and not only detected a significant improvement in the IPSS and QOL marker, but also a decrease in prostate size and significant improvement in sexual function after the first year of treatment.

A longer 5-year study using Permixon in 26 subjects with BPH showed that a total daily dose of 320 mg twice daily also significantly reduced disease symptoms and improved QOL, while reducing prostate size by an average of 30% (Aliaev et al 2002). In 2003, results from two animal studies showed that saw palmetto (whole berry and extract) significantly diminished prostatic hyperplasia (Talpur et al 2003). In contrast, the 2006 study discussed earlier failed to find a significant effect on prostate size (Bent et al 2006).

Commission E approves the use of saw palmetto for stages 1 and 2 of BPH (Blumenthal et al 2000).

Clinical note — Benign prostatic hypertrophy
BPH occurs in more than 50% of men over the age of 50 years. It is a slow, progressive enlargement of the fibromuscular and epithelial structures of the prostate gland, which can lead to obstruction of the ureter and urine retention. Symptoms such as frequent and/or painful urination, painful perineal stress, and a decrease in urine volume and flow can develop. The condition has four stages, with stage 1 considered mild, stages 2 and 3 considered more severe and often requiring pharmacological treatment, and stage 4 as severe and necessitating surgery.

ANDROGENETIC ALOPECIA

The idea of using saw palmetto for androgenetic alopecia (AGA) arose from the observation that finasteride appears to have some effect on this condition. One double-blind study has investigated the effects of saw palmetto as a potential therapeutic option, finding a highly positive response in 60% of subjects (Prager et al 2002). A second double-blind study of 48 men and women with AGA noted that mean hair density increased by 17% after 10 weeks of treatment with a topical lotion containing saw palmetto and by 27% after 50 weeks of treatment compared to baseline (Morganti et al as reported in Linde et al 2006, Ulbricht & Basch 2006).

CHRONIC PROSTATITIS AND PELVIC PAIN

Evidence to support the herb's use in prostatitis is scarce. However, in April 2003 positive findings from a preliminary study using Permixon to treat symptoms of chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS) were presented at the annual meeting of the American Urological Association (Anon 2003). The RCT involving 61 patients with category IIIB CP/CPPS found that 75% receiving active treatment experienced at least mild improvement in symptoms, compared with 20% of the control group. Furthermore, 55% of patients receiving Permixon reported moderate or marked improvement, compared with 16% of the control group. In contrast, results from a 2004 prospective, randomised, open-label study failed to find benefits for saw palmetto (325 mg daily) in men diagnosed with category III CP/CPPS (Kaplan et al 2004). After 1 year, the mean total National Institutes of Health Chronic Prostatitis Symptom Index score decreased from 24.7 to 24.6 ($P = 0.41$) and no benefits were seen for QOL or pain with saw palmetto treatment.

OTHER USES

Traditionally, saw palmetto has been used to treat a variety of urogenital conditions, such as impotence, male infertility and also as an aphrodisiac. It has also been used in female hirsutism, although its effectiveness in this condition is unknown.

DOSAGE RANGE

- Liposterolic extract: 320 mg/day in divided doses.
- Dried berry: 2–4 g.
- Liquid extract (1:2): 2–4.5 mL/day.

ACCORDING TO CLINICAL STUDIES

- 160 mg twice daily of liposterolic extract taken long term.

ADVERSE REACTIONS

The herb is generally well tolerated, with only non-specific symptoms reported, such as gastrointestinal upset, constipation, nausea, abdominal pain and diarrhoea. These minor complaints are generally resolved by taking the herb in association with meals (Maccagnano et al 2006).

One large clinical study identified headache and rhinitis as the most common side-effects associated with use (Adriazola et al 1992).

SIGNIFICANT INTERACTIONS

No controlled studies are available and theoretical interactions are difficult to predict, due to the poorly understood nature of the herb's mechanism of action.

FINASTERIDE (AND OTHER 5-ALPHA REDUCTASE INHIBITOR AGENTS)

Additive effect theoretically possible — potential beneficial effect, although the clinical significance is unknown.

ANDROGENIC DRUGS

Theoretically, saw palmetto may reduce effectiveness of therapeutic androgens such as testosterone — observe patient for lack of drug effect.

CONTRAINDICATIONS AND PRECAUTIONS

If symptoms of BPH worsen, blood is detected in the urine, or acute urinary retention occurs, professional reassessment is required.

PREGNANCY USE

Use of saw palmetto during pregnancy is contraindicated due to the herb's hormonal effects. In clinical practice, it is not used in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Substantial scientific evidence has shown that saw palmetto is an effective treatment for stages 1 and 2 of BPH in cases where the diagnosis of cancer is negative. It is as effective as finasteride and alpha-adrenoreceptor antagonist drugs such as tamsulosin and alfuzosin, although prazosin may be slightly more effective.
- Typically, symptom reduction is experienced within 1–2 months' treatment, which is well tolerated, and associated with fewer side effects than finasteride and tamsulosin.
- The herb does not affect PSA levels therefore PSA test results will be unaffected.
- If symptoms worsen, blood is detected in the urine or acute urinary retention occurs, seek professional advice.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Saw palmetto has been investigated in numerous scientific studies and shown to reduce symptoms of enlarged prostate with few side-effects. There is also some early research suggesting it may be useful in some forms of hair loss and prostatitis.

When will it start to work?

Symptom relief for enlarged prostate is generally experienced within 4–8 weeks.

Are there any safety issues?

Saw palmetto is well tolerated; however, occasionally mild gastrointestinal disturbances, headaches and rhinitis have been reported.

REFERENCES

Adriazola SM et al. Symptomatic treatment of benign hypertrophy of the prostate. Comparative study of prazosin and serenoa repens. Arch Esp Urol 45.3 (1992): 211-13.

Aliaev IG et al. Five-year experience in treating patients with prostatic hyperplasia patients with permixone (Serenoa repens Pierre Fabre Medicament). Urologiia 1 (2002): 23-5.

Anon. Abstract 103937. In: Proceedings of American Urological Association 98th Annual Meeting, 26 April, 2003.

Bayne CW et al The selectivity and specificity of the actions of the lipido-sterolic extract of Serenoa repens (Permixon) on the prostate. J Urol 164.3 (2000): 876-81.

Bent S et al. Saw palmetto for benign prostatic hyperplasia. N Engl J Med 354.6 (2006): 557-66.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Boyle P et al. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. BJU Int 93.6 (2004): 751-6.

Breu W et al. Anti-inflammatory activity of sabal fruit extracts prepared with supercritical carbon dioxide: In vitro antagonists of cyclooxygenase and 5-lipoxygenase metabolism. Arzneimittelforschung 42.4 (1992): 547-51.

Debruyne F et al. Comparison of a phytotherapeutic agent (Permixon) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomized international study. Eur Urol 41.5 (2002): 497-506.

Di Silverio F et al. Effects of long-term treatment with Serenoa repens (Permixon) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia. Prostate 37.2 (1998): 77-83.

el Sheikh MM, Dakkak MR, Saddique A. The effect of Permixon on androgen receptors. Acta Obstet Gynecol Scand 67.5 (1988): 397-9.

Goepel M et al. Saw palmetto extracts potently and noncompetitively inhibit human alpha1-adrenoceptors in vitro. Prostate 38.3 (1999): 208-15.

Goepel M et al. Do saw palmetto extracts block human alpha1-adrenoceptor subtypes in vivo? Prostate 46.3 (2001): 226-32.

Goldmann WH et al. Saw palmetto berry extract inhibits cell growth and COX-2 expression in prostatic cancer cells. Cell Biol Int 25.11 (2001): 1117-24.

Grasso M et al. Comparative effects of alfuzosin versus Serenoa repens in the treatment of symptomatic benign prostatic hyperplasia. Arch Esp Urol 48.1 (1995): 97-103.

Ishii K et al. Extract from Serenoa repens suppresses the invasion activity of human urological cancer cells by inhibiting urokinase-type plasminogen activator. Biol Pharm Bull 24.2 (2001): 188-90.

Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 171.1 (2004): 284-8.
Levin RM, Das AK. A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. Urol Res 28.3 (2000): 201-9.
Linde K et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev 1 (2006): CD000530.
Maccagnano C et al. A critical analysis of permixon (TM) in the treatment of lower urinary tract symptoms due to benign prostatic enlargement. Eur Urol Suppl 5.4 (2006): 430-40.
Markowitz JS et al. Multiple doses of saw palmetto (Serenoa repens) did not alter cytochrome P450 2D6 and 3A4 activity in normal volunteers 74.6 (2003): 536-42.
Nemecz G. Saw palmetto. US Pharmacist (2003); available at: www.uspharmacist.com.
Prager N et al. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. J Altern Complement Med 8.2 (2002): 143-52.
Pytel YA et al. Long-term clinical and biologic effects of the lipidosterolic extract of Serenoa repens in patients with symptomatic benign prostatic hyperplasia. Adv Ther 19.6 (2002): 297-306.
Raynaud JP, Cousse H, Martin PM. Inhibition of type 1 and type 2 5alpha-reductase activity by free fatty acids, active ingredients of Permixon. J Steroid Biochem Mol Biol 82.2-3 (2002): 233-9.
Strauch G et al. Comparison of finasteride (Proscar) and Serenoa repens (Permixon) in the inhibition of 5-alpha reductase in healthy male volunteers. Eur Urol 26.3 (1994): 247-52.
Sultan C et al. Inhibition of androgen metabolism and binding by a liposterolic extract of Serenoa repens B in human foreskin fibroblasts. J Steroid Biochem 20.1 (1984): 515-19.
Talpur N et al. Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats. Mol Cell Biochem 250.1-2 (2003): 21-6.
Ulbricht C, Basch E. Natural Standards Herb and Supplement Reference. St Louis: Mosby, 2006.
Vacher P et al. The lipidosterolic extract from Serenoa repens interferes with prolactin receptor signal transduction. J Biomed Sci 2.4 (1995): 357-65.
Van Coppenolle F et al. Pharmacological effects of the lipidosterolic extract of Serenoa repens (Permixon) on rat prostate hyperplasia induced by hyperprolactinemia: comparison with finasteride. Prostate 43.1 (2000): 49-58.
Wilt T et al. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev 3 (2002): CD001423.
World Health Organization. Monographs on Selected Medicinal Plants. Geneva: WHO (update January 2003).

Schisandra

Historical note Schisandra has an extensive history of use in TCM. It has sour and warm qualities and is used to treat spleen and kidney 'deficiency', restore Qi and also as a treatment for chronic cough, wheezing, diabetes, insomnia and palpitations.

OTHER NAMES
Chinese magnolia vine, gomishi, sheng-mai-san, wuweizi

BOTANICAL NAME/FAMILY
Schisandra chinensis (family Schisandraceae)

PLANT PART USED
Fruit

CHEMICAL COMPONENTS
Dibenzocyclooctene lignans (schisandrin, schisandrins A-C, schizabdrols, schisantherins and gomisin A), essential oil, malic, tartaric, nigranoic and citric acids, resins, pectin, vitamins A, C and E, niacin, beta-carotene, sterols, tannins and several minerals.

MAIN ACTIONS
Studies have been conducted with schisandra and a number of its constituents in isolation, such as schisandrin B and gomisin A. Currently, most evidence is derived from in vitro and animal studies, as it has not been significantly investigated in clinical studies.

ANTIOXIDANT
In vitro tests have identified antioxidant activity (Ohsugi et al 1999). More specifically, seven lignans isolated from schisandra have demonstrated stronger antioxidant activity than vitamin E at the same concentrations, with schisanhenol exhibiting the strongest effects (Lu & Liu 1992). An extract of schisandra and the isolated constituent schisandrin B have both demonstrated the ability to significantly decrease ALT and increase glutathione levels in CCL4 damaged liver in vivo (Chiu et al 2002). It appears that several constituents also have indirect antioxidant activity and can increase hepatic and myocardial glutathione levels (Yim & Ko 1999).

HEPATOPROTECTIVE ACTIVITY

Decreases hepatotoxic damage Several in vitro and in vivo studies have identified hepatoprotective effects with schisandra against carbon tetrachloride toxicity (Ip et al 1995, Mak & Ko 1997, Zhu et al 1999, 2000). Research with schisandrin B suggests it is the main constituent responsible for these beneficial effects (Ip et al 1995, Mak et al 1996, Pan et al 2002). Further investigation reveals that schisandrin B increases the efficiency of the hepatic glutathione antioxidant system, thereby inhibiting carbon tetrachloride induced lipid peroxidation; however, additional mechanisms appear likely (Ip et al 1995).

Protection against paracetamol-induced liver damage has been demonstrated in animal models using gomisin A (Yamada et al 1993). Gomisin A inhibited not only the elevation of serum aminotransferase activity and hepatic lipoperoxide content, but also the appearance of histological changes such as degeneration and necrosis of hepatocytes.

In 2003, protection against paracetamol-induced liver damage and D-galactosamine-induced liver damage was confirmed for a fractionated extract of *S. chinensis* in an experimental model (Nakagiri et al 2003).

Liver regeneration Two animal studies have demonstrated that oral administration of gomisin A, a lignan isolated from *S. chinensis*, accelerates liver regeneration after partial hepatectomy and hastens recovery of liver function (Kubo et al 1992, Takeda et al 1987). The mechanism for these effects is not fully elucidated; however, gomisin A increases ornithine decarboxylase activity, which is important during the early stages of regeneration and suppresses fibrosis proliferation.

OTHER ACTIONS

INHIBITS LEUKOTRIENE FORMATION

Gomisin A has been found to inhibit the biosynthesis of leukotrienes by preventing the release of arachidonic acid in vitro (Ohkura et al 1990).

PLATELET-ACTIVATING-FACTOR ANTAGONIST

Several lignans inhibit platelet-activating-factor in vitro (Lee et al 1999).

ANTI-INFLAMMATORY

Animal studies have identified anti-inflammatory activity for gomisin A, gomisin J, and wuweizi C isolated from *S. chinensis* (Yasukawa et al 1992). Several lignans from schisandra, including gomisin N and schisandrol A, have shown potent inhibition of nuclear factor of activated T cells (NFAT) in vitro (Lee et al 2003). Excessive activation of NFAT has a significant role to play in autoimmune disease, but further study is needed to assess schisandra's usefulness in immunopathological disease states.

CARDIOPROTECTIVE EFFECTS

Schisandrin B demonstrated protective effects against ischaemia–reperfusion-induced myocardial damage in a dose-dependent manner in an animal model (Yim & Ko 1999). The myocardial protection was associated with an enhancement in myocardial glutathione antioxidant status.

NEUROPROTECTIVE

Preliminary in vitro data suggests that certain lignans from schisandra are protective against l-glutamate induced neurotoxicity in rat cortical cells (Kim et al 2004). Schisandrin B appears to also improve cognition and hepatic function in mice treated with tacrine, the common Alzheimer's dementia medication (Pan et al 2002).

CYTOCHROMES AND P-GLYCOPROTEIN

Conflicting in vivo data suggests that certain constituents from schisandra, in particular gomisin C, may inhibit CYP450 3A4 activity (Iwata et al 2004). Schisandrin B has demonstrated an inhibitory effect on P-glycoprotein in vitro (Qiangrong et al 2005). The clinical importance of this is as yet unknown.

CLINICAL USE

The therapeutic activity of schisandra has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

LIVER DAMAGE, HEPATOPROTECTION

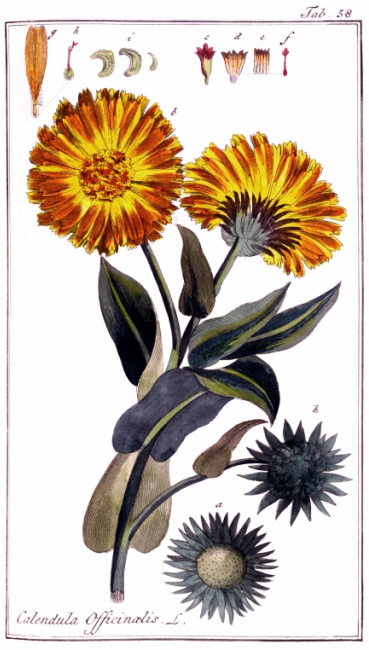
Traditionally, schisandra has been used to treat a variety of liver disorders. Hepatoprotective effects have been observed in test tube and animal studies; however, the clinical significance of these findings in humans remains unknown. Several encouraging clinical reports using an analogue of schisandrin C are available; however, it is not known whether these effects will be seen with *S. chinensis* (Akbar et al 1998).

ADAPTOGEN

In TCM, schisandra is viewed as an adaptogen and prescribed with other herbs to increase resistance to physical and emotional stressors and improve allostasis (see monographs on Korean ginseng and Siberian ginseng for further information about adaptogenic activity and allostasis).

OTHER USES

Traditionally, schisandra has been used to treat chronic cough and dyspnoea, diarrhoea, night sweats, irritability, palpitations and insomnia. Based on the herb's



inhibitory effects on leukotriene biosynthesis and platelet-activating-factor activity and anti-inflammatory effects, it is also used for asthmatic symptoms.

INFECTION

Schisandra is also used in combination with other herbal medicines to treat infection. One double-blind, randomised, placebo-controlled pilot study found that a commercial product known as ImmunoGuard significantly reduced the duration, frequency and severity of attacks in patients with familial Mediterranean fever (Amaryan et al 2003). The dose regimen used was four tablets taken three times daily for 1 month. The ImmunoGuard product contains a fixed combination of *Andrographis paniculata* Nees., *Eleutherococcus senticosus* Maxim., *Schisandra chinensis* Bail., and *Glycyrrhiza glabra* L. special extracts, which are standardised for the content of andrographolide (4 mg/tablet), eleuteroside E, schisandrins and glycyrrhizin, respectively. Although these results are encouraging, it is not known to what extent schisandra contributed to the outcome.

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturers' recommendations.

- Dried fruit: 1.5–6 g/day.
- Liquid extract (1:2): 3.5–8.5 mL/day or 25–60 mL/week.

TOXICITY

Insufficient reliable information is available.

ADVERSE REACTIONS

Mild gastrointestinal discomfort.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are speculative.

DRUGS METABOLISED BY CYP 3A4

In vivo evidence suggests an inhibitory effect on CYP 3A4 activity, particularly for the gomisin C constituent; however, clinical studies have not yet confirmed the effect (Iwata et al 2004). Based on this observation, serum levels of drugs chiefly metabolised by CYP 3A4 may increase — observe patient.

P-GLYCOPROTEIN SUBSTRATES

Schisandrin B has demonstrated an inhibitory effect on P-glycoprotein in vitro (Qiangrong et al 2005); however, the effect has not been confirmed clinically. Theoretically, the bioavailability of P-gp substrates could be increased — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Not recommended.

PRACTICE POINTS/PATIENT COUNSELLING

- *Schisandra chinensis* is popular in TCM and is used to increase resistance to physical and emotional stressors and regarded as an adaptogen.
- Traditionally, schisandra has been used to treat chronic cough and dyspnoea, diarrhoea, night sweats, irritability, palpitations and insomnia.
- It is commonly used as a liver tonic, and preliminary evidence has identified significant hepatoprotective effects.
- Schisandra exerts direct antioxidant activity and increases hepatic and myocardial glutathione levels, thereby increasing antioxidant systems within the heart and liver.
- Overall, little clinical evidence is available; therefore, much information is still speculative and based on in vitro and animal research and traditional use.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

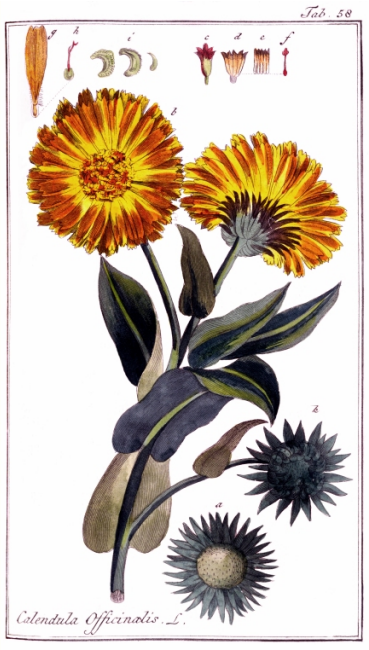
Schisandra is often prescribed to increase physical and emotional resilience and as a liver tonic. It has antioxidant activity, and early research suggests it may have significant protective benefits for the liver.

When will it start to work?

This is uncertain due to insufficient research being available.

Are there any safety issues?

This is uncertain due to insufficient research being available.



REFERENCES

Akbar N et al. Effectiveness of the analogue of natural Schisandrin C (HpPro) in treatment of liver diseases: an experience in Indonesian patients. Chin Med J (Engl) 111.3 (1998): 248-51.

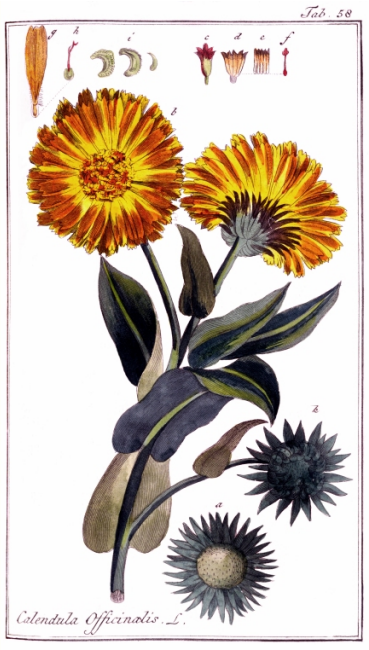
Amaryan G et al. Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard: a standardized fixed combination of Andrographis paniculata Nees, with Eleutherococcus senticosus Maxim, Schizandra chinensis Bail. and Glycyrrhiza glabra L. extracts in patients with Familial Mediterranean Fever. Phytomedicine 10.4 (2003): 271-85.

Chiu PY et al. In vivo antioxidant action of a lignan-enriched extract of Schisandra fruit and an anthraquinone-containing extract of Polygonum root in comparison with schisandrin B and emodin. Planta Med 68.11 (2002): 951-6.

Ip SP et al. Effect of schisandrin B on hepatic glutathione antioxidant system in mice: protection against carbon tetrachloride toxicity. Planta Med 61.5 (1995): 398-401.

Iwata H et al. Identification and characterization of potent CYP3A4 inhibitors in Schisandra fruit extract. Drug Metab Dispos 32.12 (2004): 1351-8.

Kim SR et al. Dibenzocyclooctadiene lignans from Schisandra chinensis protect primary cultures of rat cortical cells from glutamate-induced toxicity. J Neurosci Res 76.3 (2004): 397-405.
Kubo S et al. Effect of Gomisin A (TJN-101) on liver regeneration. Planta Med 58.6 (1992): 489-92.
Lee IS et al. Structure-activity relationships of lignans from Schisandra chinensis as platelet activating factor antagonists. Biol Pharm Bull 22.3 (1999): 265-7.
Lee IS et al. Lignans with inhibitory activity against NFAT transcription from Schisandra chinensis. Planta Med 69.1 (2003): 63-4.
Lu H, Liu GT. Anti-oxidant activity of dibenzocyclooctene lignans isolated from Schisandraceae. Planta Med 58.4 (1992): 311-13.
Mak DH, Ko KM. Alterations in susceptibility to carbon tetrachloride toxicity and hepatic antioxidant/detoxification system in streptozotocin-induced short-term diabetic rats: effects of insulin and Schisandrin B treatment. Mol Cell Biochem 175.1-2 (1997): 225-32.
Mak DH et al. Effects of Schisandrin B and alpha-tocopherol on lipid peroxidation, in vitro and in vivo. Mol Cell Biochem 165.2 (1996): 161-5.
Nakagiri R, Oda H, Kamiya T. Small scale rat hepatocyte primary culture with applications for screening hepatoprotective substances. Biosci Biotechnol Biochem 67.8 (2003): 1629-35.
Ohkura Y et al. Effect of gomisin A (TJN-101) on the arachidonic acid cascade in macrophages. Jpn J Pharmacol 52.2 (1990): 331-6.
Ohsugi M et al. Active-oxygen scavenging activity of traditional nourishing-tonic herbal medicines and active constituents of Rhodiola sacra. J Ethnopharmacol 67.1 (1999): 111-19.
Pan SY et al. Schisandrin B protects against tacrine- and bis(7)-tacrine-induced hepatotoxicity and enhances cognitive function in mice. Planta Med 68.3 (2002): 217-20.
Qiangrong P et al. Schisandrin B: a novel inhibitor of P-glycoprotein. Biochem Biophys Res Commun 335.2 (2005): 406-11.
Takeda S et al. Effects of TJN-101, a lignan compound isolated from Schisandra fruits, on liver fibrosis and on liver regeneration after partial hepatectomy in rats with chronic liver injury induced by CCl4. Nippon Yakurigaku Zasshi 90.1 (1987): 51-65.
Yamada S, Murawaki Y, Kawasaki H. Preventive effect of gomisin A, a lignan component of shizandra fruits, on acetaminophen-induced hepatotoxicity in rats. Biochem Pharmacol 46.6 (1993): 1081-5.
Yasukawa K et al. Gomisin A inhibits tumor promotion by 12-O-tetradecanoylphorbol-13-acetate in two-stage carcinogenesis in mouse skin. Oncology 49.1 (1992): 68-71.
Yim TK, Ko KM. Schisandrin B protects against myocardial ischemia-reperfusion injury by enhancing myocardial glutathione antioxidant status. Mol Cell Biochem 196.1-2 (1999): 151-6.
Zhu M et al. Evaluation of the protective effects of Schisandra chinensis on Phase I drug metabolism using a CCl4 intoxication model. J Ethnopharmacol 67.1 (1999): 61-8.
Zhu M et al. Improvement of phase I drug metabolism with Schisandra chinensis against CCl4 hepatotoxicity in a rat model. Planta Med 66.6 (2000): 521-5.



Selenium

Historical note During his travels in the 13th century, Marco Polo first reported what is thought to be selenium toxicity in grazing animals. He observed that certain grazing areas in China were associated with horses developing diseased hooves (Hendler et al 2001). It is now known that parts of China have the highest selenium soil concentrations in the world and diseased hooves were likely to be due to selenium toxicity. It was not until nearly 500 years later, in 1817, that selenium was actually discovered (Tinggi 2003) and the fact that it is essential in mammals was not discovered until 1957 (Navarro-Alarcon & Lopez-Martinez 2000). In 1979, the importance of selenium in human nutrition was further reinforced when Chinese researchers reported that selenium supplementation prevented the development of Keshan disease, a cardiomyopathy seen in children living in selenium replete areas, and New Zealand workers reported a clinical response to selenium supplementation in a selenium-depleted patient (Shils et al 2006).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Selenium is an essential trace element that enters the food chain through incorporation into plants from the soil. Selenium is mainly present in the form of selenite in acid soils, which is poorly assimilated by crops, whereas for alkaline soils, it is in the form of selenate, which is more soluble and assimilated by crops. When taken in supplement form, animal and human trials demonstrate that bioavailability of organic forms of selenium (Se-methionine and Se-cysteine) is higher than that obtained for inorganic forms (selenite and selenate) (Navarro-Alarcon & Lopez-Martinez 2000).

The variation in selenium content of adult humans living in different parts of the world is testimony to the influence of the natural environment on the selenium content of soils, crops and human tissues. According to a WHO report, adults in New Zealand have approximately 3 mg selenium in their bodies compared with 14 mg in some Americans (WHO 2002).

Selenium is readily absorbed, especially in the duodenum but also in the caecum and colon. Vitamins A, E, and C can modulate selenium absorption, and there is a complex relationship between selenium and vitamin E that has not been entirely elucidated for humans (Bates 2005). Selenium enters the body in two major forms:

Se-methionine, which is derived from plants, and Se-cysteine, which is mainly derived from animal selenoproteins (Shils et al 2006). Metabolism is complex and occurs via several routes for the different selenoproteins. Se-methionine enters the methionine pool where it undergoes the same fate as methionine until catabolised. Once the selenium from Se-methionine is liberated by the trans-sulfuration pathway in the liver or kidney, it is able to be used by peripheral cells. Ingested selenite, selenate and selenocysteine are metabolised to selenide. Urinary excretion accounts for 50–60% of total excretion of selenium and homeostasis is achieved through regulation in the kidney. Volatile forms of selenium are exhaled when intake is very high and presents a significant route of excretion at this level.

CHEMICAL COMPONENTS

In human tissues, it is found as either L-selenomethionine or L-selenocysteine.

FOOD SOURCES

The most concentrated food sources are brewer's yeast, wheatgerm, meats, fish and seafood, brazil nuts, garlic and organ meats.

DEFICIENCY SIGNS AND SYMPTOMS

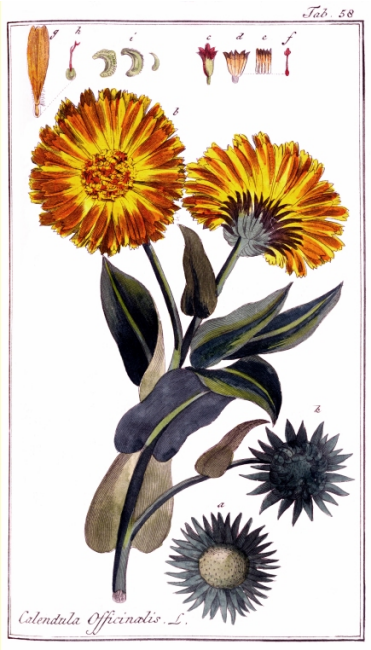
Selenium deprivation reduces the activity of selenium-dependent enzymes and has widespread effects. Characteristic signs of selenium deficiency have not been described in humans, but very low selenium status is a factor in the aetiologies of a juvenile cardiomyopathy (Keshan disease) and a chondrodystrophy (Kashin-Beck disease) that occur in selenium-deficient regions of China.

Low selenium status has been associated with:

- loss of immunocompetence (Ongele et al 2002)
- increased risk of developing certain cancers (Clark et al 1998)
- reduced male fertility (Scott et al 1998, Xu et al 2003)
- poorer prognosis in HIV infection and AIDS (Baum et al 1997, Campa et al 1999)
- greater incidence of depression, anxiety, confusion and hostility (Rayman 2000)
- compromised thyroid hormone metabolism (particularly when iodine deficiency is also present) (Gartner et al 2002)
- asthma and atopy (Kadrabova et al 1996, Misso et al 1996, Omland et al 2002)
- rheumatoid arthritis (Zamamiri-Davis et al 2002)
- possibly, increased inflammatory processes (Zamamiri-Davis et al 2002)
- changes to drug metabolising enzymes including the cytochrome P450 system, with some activities increasing and others decreasing (Shils et al 2006).

Low selenium status may contribute to the aetiology of several diseases, while in others this state exacerbates disease progression, such as in HIV infection.

People at risk of marginal selenium deficiency include those living in areas of low environmental selenium, such as some regions of New Zealand, people receiving long-term TPN, alcoholics, and those with liver cirrhosis, malabsorption syndromes, cystic fibrosis, coeliac disease and AIDS.



MAIN ACTIONS

ANTIOXIDANT

Selenium is an integral part of thioredoxin reductase and the glutathione peroxidases and therefore is intimately involved in the body's antioxidant systems. These enzymes are involved in controlling tissue levels of free radical molecules and maintain cell-mediated immunity.

CHEMOPREVENTATIVE

Chemoprotective effects of selenium have been indicated by an epidemiological relationship, RCTs and by experimental studies of selenium and known carcinogens in the development of specific cell lines. Overall, it appears that selenium works by inhibiting important early steps in carcinogenesis.

Several mechanisms have been postulated to explain the chemopreventative effect of selenium, including protection against oxidative damage, alterations to immune and metabolic systems, alterations to carcinogen metabolism, production of cytotoxic selenium metabolites, inhibition of protein synthesis, stabilisation of genetic material and stimulation of apoptosis (Clark et al 1996, El Bayoumy 2001, Schrauzer 2000). One study demonstrated that combining vitamin E succinate and methylselenic acid produces a synergistic effect on cell growth suppression, primarily mediated by augmenting apoptosis (Zu & Ip 2003).

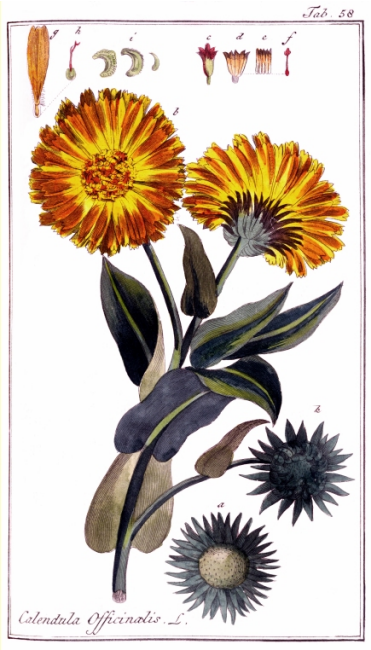
In humans, the chemopreventative effect is strongest for individuals with the lowest selenium status; however, it is still unclear whether low selenium status is implicated in the aetiology of cancer or whether it produces a state of increased susceptibility to the effects of carcinogens.

IMMUNOMODULATION

Confirmed in both animal studies and human trials, immunomodulation is in part due to improved activation and proliferation of B-lymphocytes and enhanced T-cell function (Hawkes et al 2001, Gazdik et al 2002a, b, Kiremidjian-Schumacher & Roy 1998, Ongele et al 2002). Interestingly, selenium concentrations significantly decrease during stages of acute infection, suggesting increased use and/or excretion or decreased absorption during this period (Sammalkorpi et al 1988).

THYROID HORMONE MODULATION

Selenium is required for normal thyroid hormone synthesis, activation and metabolism (Sher 2001). Three different selenium-dependent iodothyronine deiodinases (types I, II, and III) can both activate and inactivate thyroid hormone, making selenium an essential element for normal development, growth and metabolism through the regulation of thyroid hormones.



OTHER ACTIONS

MALE FERTILITY

Selenium is required for testosterone synthesis, normal sperm maturation and sperm motility (Rayman & Rayman 2002). Two clinical studies have confirmed this association (Scott et al 1998, Vezina et al 1996) and identified selenium supplements as able to increase sperm motility.

ANTI-INFLAMMATORY

Selenium deficiency produces a significantly increased COX-2 protein expression, as well as higher PGE_2 levels, according to one in vitro study (Zamamiri-Davis et al 2002). It has also been theorised that selenium may decrease leukotriene production (McCarty 1984). In vivo tests have identified anti-inflammatory activity in the lung with selenium, which is thought to relate to an increase in glutathione levels and immune parameters (Jeong et al 2002).

REDUCES HEAVY METAL TOXICITY

Selenium protects against toxicity of some heavy metals such as cadmium, arsenic, lead, silver and mercury (Berry & Galle 1994, Lindh et al 1996, Navarro-Alarcon & Lopez-Martinez 2000, Yiin et al 1999a, b, 2000, 2001). A physiological role for selenium in counteracting heavy metal poisoning has been proposed (Shils et al 2006). It appears that the form of selenium is important, as inorganic selenium has been shown to enhance the toxic effects of inorganic arsenic by increasing its retention in tissues and suppressing its metabolism in vitro (Styblo & Thomas 2001).

ANTI-ATHEROGENIC ACTIVITY

Selenium supplementation reduces high-fat diet induced atherosclerosis, according to an in vivo study (Kang et al 2001).

CLINICAL USE

DEFICIENCY STATES: PREVENTION AND TREATMENT

Traditionally, selenium supplementation has been used to treat deficiency or prevent deficiency in conditions such as malabsorption syndromes.

CANCER: PREVENTION AND POSSIBLE ADJUNCT TO TREATMENT

Selenium supplementation is used to reduce total cancer incidence and mortality.

Chemoprevention Collectively, geographical studies, epidemiological data, laboratory bioassays, studies in over 12 different animal models and human intervention trials generally support a protective role for selenium against the development of cancer. Populations who live in low selenium environments and have low selenium intakes tend to have higher cancer mortality rates. However, the results from epidemiological studies have been less consistent and show the effect is strongest in males.

Total cancer incidence and mortality The Nutritional Prevention of Cancer Trial was a large multicentre, double-blind, randomised, placebo-controlled trial conducted with 1312 patients with a history of basal cell or squamous cell carcinomas of the skin, which investigated the effects of 200 μg selenium daily (as 500 mg brewer's yeast) as a cancer protective agent (Clark et al 1998). Selenium supplementation in this population did not alter future incidence of skin cancer; however, it significantly reduced total cancer mortality, total cancer incidence by 37% and the incidences of lung, colorectal and prostate cancers by 46%, 58% and 63%, respectively. Results from further continuation of the trial has continued to find a protective effect for selenium in total cancer incidence and the individual cancers; however, this now appears to be restricted to people with low baseline plasma levels and most pronounced for colorectal cancer and current smokers, whereas protective effects in prostate cancer was further restricted to lower baseline levels of prostate-specific antigen (PSA: ≤4 ng/mL) (Duffield-Lillico et al 2002, 2003, Reid et al 2002, 2006).

Liver cancer A trial involving 130,471 individuals living in a high-risk area for viral hepatitis and liver cancer (Quidong, China) found that table salt enriched with sodium selenite reduced the incidence of liver cancer by 35% during the 8-year follow-up period, whereas no changes were observed for the control groups (Yu et al 1997). Additionally, incidences of liver cancer began to rise after withdrawal of selenium supplementation.

Prostate cancer Epidemiological and clinical data suggest that selenium may prevent prostate cancer. To date, the largest case control study involved 33,737 males and identified an association between higher selenium status and a reduced risk of prostate cancer (Yoshizawa et al 1998). The study showed that men consuming the most dietary selenium (assessed indirectly by measuring toenail selenium levels) developed 65% fewer cases of advanced prostate cancer than those with the lowest intake.

Strong evidence for a protective effect of selenium against prostate cancer comes from the Nutritional Prevention of Cancer Trial, as described above, in which the incidence of prostate cancer was reduced in the selenium group by two-thirds as compared to placebo. Further follow-up has revealed that selenium supplementation continues to show a marked reduction on the incidence of prostate cancer with strongest effects seen in men with a PSA <4 ng/ml and those with the lowest serum selenium levels at study entry (Duffield-Lillico et al 2003).

Currently under way is the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is a randomised, prospective, double-blind study designed to determine whether 200 μg l-selenomethionine, 400 mg of racemic alpha-tocopheryol and an optional multivitamin containing no selenium or vitamin E can reduce the risk of prostate cancer among healthy men. It is anticipated that over 32,000 men will be involved in the study and final results will be available in 2013 (Klein et al 2001).

Stomach and oesophageal cancer A large study of nearly 30,000 people demonstrated a protective effect for a combination of selenium, beta-carotene and vitamin E against the development of cancer of the gastric cardia and oesophagus (Mark et al 2000). Supplementation also reduced the cancer mortality rate compared with those not receiving supplementation. Protective effects on total cancer deaths developed slowly, appearing after 1 year of treatment and the effect on stomach cancer appeared after 2 years.

REDUCING MORTALITY FROM HIV INFECTION

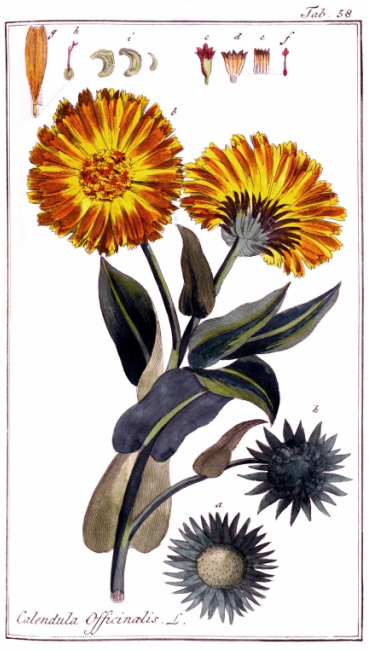
Selenium appears to be important in HIV infection, with plasma selenium a strong predictor of disease outcome in both adults and children (Baum & Shor-Posner 1998, Baum et al 1997, Campa et al 1999).

Low selenium status is common in HIV-positive patients and is associated with a decline in Th (CD4) cell counts (Bates 2005). It is also associated with an increased incidence of mycobacterial diseases in HIV-1-seropositive drug users (Shor-Posner et al 2002, Dworkin 1994, Dworkin et al 1986, 1989). One small intervention trial using low-dose selenium supplements (80 μg/day with 25 mg vitamin E) over 2 months has shown an improvement in general symptoms but no alterations to immunological or haemotological parameters (Cirelli et al 1991).

CARDIOVASCULAR DISEASE PREVENTION

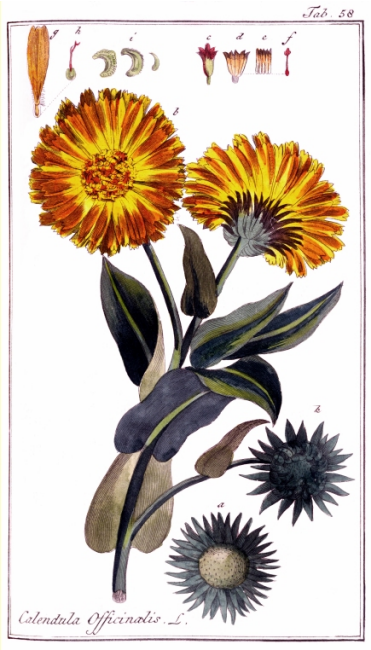
Selenium may decrease cardiovascular disease mortality; however, epidemiological studies have produced mixed results.

A case-control study from a population of 11,000 people found that individuals with low serum selenium levels had a two- to three-fold increase in cardiovascular



morbidity and mortality (Salonen et al 1982). A more recent study of just over 3000 middle-aged and elderly men also established an association between low serum selenium levels and a significantly increased risk of ischaemic heart disease (Suadicani et al 1992). Alternatively, no association was identified between serum selenium levels and coronary deaths or myocardial infarctions in a study of 1110 men; however, a significant association with stroke mortality was detected (Virtamo et al 1985). No significant primary preventative effect was seen for selenium supplementation (200 μg/day) and incidence of cardiovascular disease, myocardial infarction, stroke or all cardiovascular disease mortality in the Nutritional Prevention of Cancer study (Stranges et al 2006). Lack of association was confirmed when analyses were further stratified by tertiles of baseline plasma selenium concentrations.

With regard to secondary prevention, an intervention study conducted by Korpela et al (1989) in subjects having suffered acute myocardial infarction has produced encouraging results. The randomised, double-blind trial compared the effects of selenium-rich yeast (100 μg/day) with placebo, concurrently with standard treatment in 81 patients with acute myocardial infarction. During the 6-month follow-up period, there were no cardiac deaths in the selenium-treated group compared with four receiving placebo, and two non-fatal re-infarctions in the placebo group compared with only one receiving selenium supplementation.

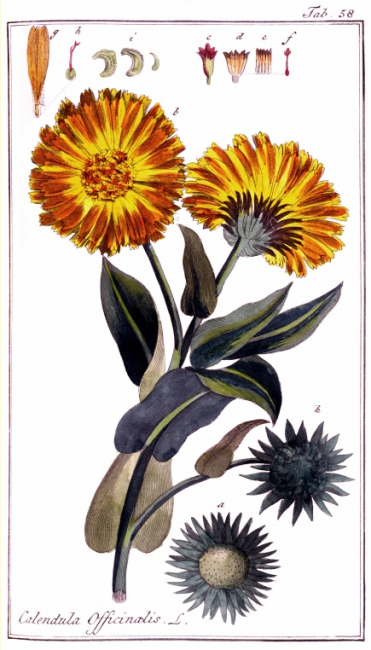


ASTHMA

Asthma, respiratory symptoms and ventilatory function have been associated with lowered circulatory selenium status and glutathione peroxidase activity (Devereux & Seaton 2005, Hasselmark et al 1990, Kadrabova et al 1996, Misso et al 1996, Omland et al 2002). When these observations are coupled with in vivo evidence of anti-inflammatory activity in the lung for selenium, it is not surprising that there is growing interest in using selenium supplementation to improve asthmatic symptoms and disease management. A small number of intervention studies have been conducted, producing mixed results (Gazdik et al 2002a, b, Hasselmark et al 1993).

Hasselmark et al conducted a randomised double-blind study involving 24 patients with intrinsic asthma. A dose of 100 μg sodium selenite was administered for 14 weeks, resulting in significant increases in serum selenium and platelet glutathione peroxidase activity, while no changes were observed with placebo. Clinical results varied, with significantly more treated patients improving on several parameters of lung function such as airway responsiveness, clinical examination, medication use, and subjective patient impressions. However, there were no significant improvements over baseline in any individual clinical parameter. A small pilot study of 17 asthmatics dependent on corticosteroid medication found that a dose of 200 μg selenium daily

taken over a 96-week period reduced both inhaled and systemic corticosteroid requirements. The same study observed selenium supplementation enhancing immunity (Gazdik et al 2002a, b).



AUTOIMMUNE THYROIDITIS

Selenium supplementation may improve inflammatory activity in chronic autoimmune thyroiditis patients, as evidenced by a significant reduction in the concentration of thyroid peroxidase antibodies (TPO-Ab) to 63.8% in selenium-supplemented subjects versus 88% ($P = 0.95$) in placebo subjects (Gartner et al 2002). The randomised study of 70 females (mean age 47.5 years) compared 200 μg sodium selenium daily orally for 90 days to placebo. A follow-up crossover study of 47 patients from the initial 70 was conducted for a further 6 months (Gartner & Gasnier 2003). The group that continued to take sodium selenite (200 μg/day) experienced further significant decreases whereas the group that ceased selenium use experienced a significant increase. The patients who received 200 μg sodium selenite after placebo also experienced a significant decrease in levels of TPO-Ab.

RHEUMATOID ARTHRITIS

Selenium supplements have been used in RA because of its antioxidant activity and the observation that some patients with RA have been reported with low selenium status (O'Dell et al 1991, Rosenstein & Caldwell 1999). One double-blind, placebo-controlled intervention study of 55 patients with moderate RA found that both placebo and selenium appeared to have significant effects on a number of symptoms; however, only selenium significantly improved arm movements and sense of wellbeing (Peretz et al 2001).

LOWERED MALE FERTILITY

Xu et al (2003) identified a significantly positive correlation between selenium levels and sperm density, sperm number, sperm motility and sperm viability in human volunteers. Supplementation with selenium in selenium-replete subfertile men has been shown to improve sperm motility and the chance of successful conception in over half of treated patients (Scott et al 1998). When taken with vitamin E over 6 months, selenium produces a statistically significant increase in sperm motility, per cent live and per cent normal spermatozoa, with effects reversing after supplement cessation (Vezina et al 1996). Although results are encouraging, particularly for subfertile men with low selenium status, one negative intervention trial was located that found that supplementation had no effect (Iwanier & Zachara 1995).

GENERAL IMMUNE ENHANCEMENT

Several intervention trials of either double-blind or open design have shown selenium supplementation can enhance immune function and decrease the risk of developing certain infections in selenium-replete subjects, healthy adults and the elderly (Girodon et al 1999, Kiremidjian-Schumacher et al 1994, Roy et al 1994, Yu et al 1989).

The largest was a 3-year study of 20,847 people that showed that substituting conventional table salt with table salt fortified with sodium selenite significantly reduced the incidence of viral hepatitis compared with controls provided with normal table salt (Yu et al 1989).

MOOD ELEVATION AND REDUCED ANXIETY

Considering that low dietary intakes of selenium have been linked with greater incidence of anxiety, depression and tiredness, several research groups have investigated whether higher dietary intakes or selenium supplementation will elevate mood and/or reduce anxiety. Currently, results are equivocal; however, it appears that selenium-replete individuals are most likely to respond to supplementation, if a response is observed.

An early double-blind, crossover, study showed that short-term selenium supplementation (100 μg/day for 5 weeks) significantly elevated mood and decreased anxiety, depression and tiredness, with effects most marked in people with low dietary intake (Benton & Cook 1991). A study of 30 selenium replete men who were fed either a low (32.6 μg/day) or a high (226.5 μg/day) selenium diet for 15 weeks found that the mood of those with the higher selenium intake increased whereas mood worsened with low intake (Finley & Penland 1998 as reported in Rayman 2005). Alternatively, another study involving 11 men of adequate selenium intake failed to show effects on mood when high (356 μg/day) and low (13 μg/day) selenium diets were followed for 99 days (Hawkes & Hornbostel 1996). Most recently, a large (n = 448), 2-year, randomised study also failed to find evidence that additional selenium enhanced mood or any of its subscales, despite significant increases in plasma selenium levels (Rayman et al 2006). This study compared the effects of 100, 200 or 300 μg/day of selenium to placebo for effects on mood and QOL. Selenium supplementation was given as high-selenium yeast, SelenoPrecise™ (Pharma Nord, Vejle, Denmark).

REDUCING MORBIDITY IN PRE-TERM BABIES

Preterm infants are born with slightly lower selenium and glutathione peroxidase concentrations than term infants and have low hepatic stores of selenium. In very preterm infants low selenium concentrations have been associated with an increased

risk of chronic neonatal lung disease and retinopathy of prematurity (Darlow & Austin 2003). Although the full consequences of low selenium concentrations in this population are not fully known, observation from animal studies has found an association between selenium deficiency and increased susceptibility to oxidative lung injury. This has special significance for sick, very preterm infants as they are exposed to many possible sources of oxygen radical products, including high concentrations of inspired oxygen. A Cochrane review of three randomised studies that reported outcomes on 297 infants receiving selenium supplements and 290 control infants concluded that selenium supplementation in very preterm infants is associated with benefit in terms of a reduction in one or more episodes of late-onset sepsis, but is not associated with improved survival, a reduction in neonatal chronic lung disease or retinopathy of prematurity (Darlow & Austin 2003). It should be noted that most of the evidence derives from research conducted in New Zealand, a country with low soil and population selenium concentrations, and may not be readily translated to other populations.

OTHER USES

Used in combination with other antioxidants or administered intravenously, selenium has been used in pancreatitis and as adjunctive therapy in cancer patients.

RADIATION-ASSOCIATION LYMPHOEDEMA

Oral sodium selenite (350 μg/m^2 body surface area) was given daily for 4–6 weeks to 52 patients with extensive, persistent or progressive lymphoedema from radiation and resulted in the majority experiencing some reduction in oedema (Micke et al 2002). A further study (Micke et al 2003) of 48 patients found that sodium selenite supplementation had a positive effect on secondary lymphoedema caused by radiation therapy alone or by irradiation after surgery. The group consisted of 12 patients with oedema of the arm and 36 with oedema of the head-and-neck region.

DOSAGE RANGE

AUSTRALIAN RDI

Children

- 1–3 years: 25 μg
- 4–8 years: 30 μg
- 9–13 years: 50 μg
- 14–18 years:
  Boys: 70 μg
  Girls: 60 μg

Adults

- Males >18 years: 70 μg
- Females >18 years: 60 μg
- Pregnancy: 65 μg
- Lactation: 75 μg

ACCORDING TO CLINICAL STUDIES

- Asthma: 100–200 μg/day of sodium selenite.
- Cancer prophylaxis: 200 μg/day selenium (supplied as 500 mg brewer's yeast).
- Infertility: 100 μg/day.
- Mood disturbances: 100 μg/day.
- Post myocardial infarction: selenium-rich yeast 100 μg/day.
- Rheumatoid arthritis: 200 μg/day.
- Autoimmune thyroiditis: 200 μg/day sodium selenite.
- HIV positive status: 80 μg/day has been used but it is most likely that higher doses are required.

TOXICITY

Long-term ingestion of excessive levels of selenium (> 1000 μg/day) may produce fatigue, depression, arthritis, hair or fingernail loss, garlicky breath or body odour and gastrointestinal disorders or irritability (Fan & Kizer 1990).

ADVERSE REACTIONS

Nausea, vomiting, nail changes, irritability and fatigue have been reported.

The organic form of selenium found in high-selenium yeast is often preferred because it is less toxic.

The National Health and Medical Research Council of Australia states that selenium intake should not exceed 600 μg/day.

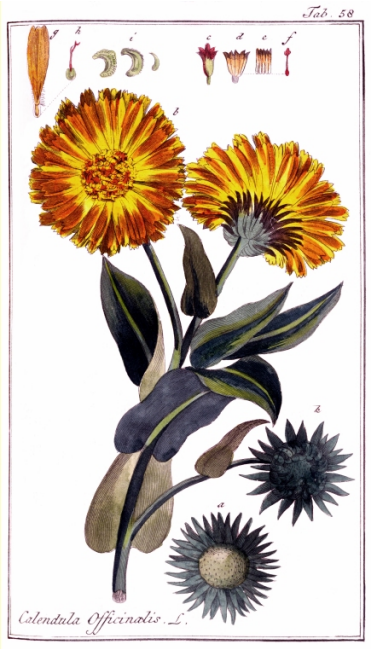
SIGNIFICANT INTERACTIONS

CISPLATIN

Selenium may reduce associated nephrotoxicity, myeloid suppression and weight loss, according to in vitro and in vivo tests (Camargo et al 2001, Ohkawa et al 1988) — beneficial interaction.

HEAVY METALS (E.G. MERCURY, LEAD, ARSENIC, SILVER AND CADMIUM)

Selenium reduces toxicity of heavy metals such as mercury, lead, arsenic, silver and cadmium by forming inert complexes — beneficial interaction.



CONTRAINDICATIONS AND PRECAUTIONS

Sensitivity to selenium.

PREGNANCY USE

Considered safe in usual dietary doses; safety at higher levels is unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- Selenium is a trace element that is essential for health.
- Low selenium states have been associated with a variety of conditions, such as cardiovascular disease, cancer, asthma, atopy, male subfertility, rheumatoid arthritis, depression and anxiety and compromised immune function.
- Studies have identified selenium deficiency in a significant number of people with the HIV infection and suggested a link between selenium levels and mortality rate.
- It is also involved in the detoxification of some heavy metals and xenobiotics.
- Selenium-enriched yeast is the safest way to supplement the diet, but other forms are also used.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Selenium supplementation may reduce the risk of developing certain cancers and heart disease and help to improve a range of conditions such as rheumatoid arthritis, asthma, autoimmune thyroiditis, male subfertility, depression and anxiety.

When will it start to work?

If a protective effect is to occur with selenium against cancer or cardiovascular disease, the effect appears to develop slowly over several years' consistent intake.

Are there any safety issues?

High intakes of selenium above 1000 μg/day have been associated with a number of adverse effects and should be avoided.

REFERENCES

Bates CJ. Selenium. In: Benjamin C (ed.). Encyclopedia of Human Nutrition. Oxford: Elsevier (2005): 118-25.

Baum MK, Shor-Posner G. Micronutrient status in relationship to mortality in HIV-1 disease. Nutr Rev 56.1 (1998): S135-9.

Baum MK et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol 15.5 (1997): 370-4.

Benton D, Cook R. The impact of selenium supplementation on mood. Biol Psychiatry 29.11 (1991): 1092-8.

Berry JP, Galle P. Selenium-arsenic interaction in renal cells: role of lysosomes: Electron microprobe study. J Submicrosc Cytol Pathol 26.2 (1994): 203-10.

Camargo SM et al. Oral administration of sodium selenite minimizes cisplatin toxicity on proximal tubules of rats. Biol Trace Elem Res 83.3 (2001): 251-62.

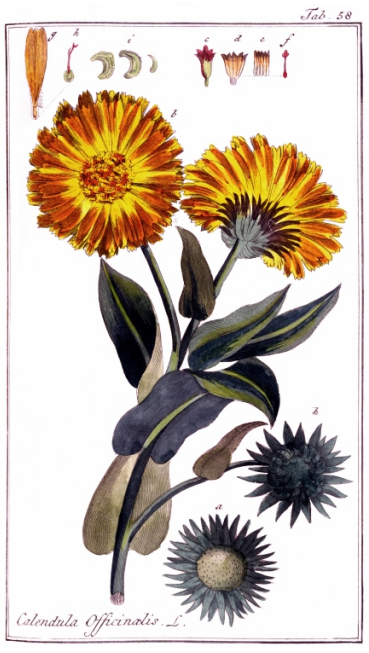
Campa A et al. Mortality risk in selenium-deficient HIV-positive children. J Acquir Immune Defic Syndr Hum Retrovirol 20.5 (1999): 508-13.

Cirelli A et al. Serum selenium concentration and disease progress in patients with HIV infection. Clin Biochem 24.2 (1991): 211-14.
Clark LC et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: A randomized controlled trial (Nutritional Prevention of Cancer Study Group). JAMA 276.24 (1996): 1957-63.
Clark LC et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 81.5 (1998): 730-4.
Darlow BA, Austin NC. Selenium supplementation to prevent short-term morbidity in preterm neonates. Cochrane Database Syst Rev 4 (2003): CD003312.
Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 115.6 (2005): 1109-17.
Duffield-Lillico AJ et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev 11.7 (2002): 630-9.
Duffield-Lillico AJ et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 91.7 (2003): 608-12.
Dworkin BM et al. Reduced cardiac selenium content in the acquired immunodeficiency syndrome. J Parenter Enteral Nutr 13.6 (1989): 644-7.
Dworkin BM et al. Selenium deficiency in the acquired immunodeficiency syndrome. J Parenter Enteral Nutr 10.4 (1986): 405-7.
Dworkin BM. Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS). Chem Biol Interact 91.2-3 (1994): 181-6.
El Bayoumy K. The protective role of selenium on genetic damage and on cancer. Mutat Res 475.1-2 (2001): 123-39.
Fan AM, Kizer KW. Selenium: Nutritional, toxicologic, and clinical aspects. West J Med 153.2 (1990): 160-7.
Gartner R, Gasnier BC. Selenium in the treatment of autoimmune thyroiditis. Biofactors 19.3-4 (2003): 165-70.
Gartner R et al. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. J Clin Endocrinol Metab 87.4 (2002): 1687-91.
Gazdik F et al. Decreased consumption of corticosteroids after selenium supplementation in corticoid-dependent asthmatics. Bratisl Lek Listy 103.1 (2002a): 22-5.
Gazdik F et al. The influence of selenium supplementation on the immunity of corticoid-dependent asthmatics. Bratisl Lek Listy 103.1 (2002b): 17-21.
Girodon F et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. Arch Intern Med 159.7 (1999): 748-54.
Hasselmark L et al. Lowered platelet glutathione peroxidase activity in patients with intrinsic asthma. Allergy 45.7 (1990): 523-7.
Hasselmark L et al. Selenium supplementation in intrinsic asthma. Allergy 48.1 (1993): 30-6.
Hawkes WC, Hornbostel L. Effects of dietary selenium on mood in healthy men living in a metabolic research unit. Biol Psychiatry 39.2 (1996): 121-8.
Hawkes WC, Kelley DS, Taylor PC. The effects of dietary selenium on the immune system in healthy men. Biol Trace Elem Res 81.3 (2001): 189-213.
Iwanier K, Zachara BA. Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men. J Androl 16.5 (1995): 441-7.
Jeong DW et al. Protection of mice from allergen-induced asthma by selenite: prevention of eosinophil infiltration by inhibition of NF-kappa B activation. J Biol Chem 277.20 (2002): 17871-6.
Kadrabova J et al. Selenium status is decreased in patients with intrinsic asthma. Biol Trace Elem Res 52.3 (1996): 241-8.

Kang BP, Mehta U, Bansal MP. Selenium supplementation protects from high fat diet-induced atherogenesis in rats: role of mitogen stimulated lymphocytes and macrophage NO production. Indian J Exp Biol 39.8 (2001): 793-7.
Kiremidjian-Schumacher L et al. Supplementation with selenium and human immune cell functions. II: Effect on cytotoxic lymphocytes and natural killer cells. Biol Trace Elem Res 41.1-2 (1994): 115-27.
Kiremidjian-Schumacher L, Roy M. Selenium and immune function. Z Ernahrungswiss 37 (Suppl 1) (1998): 50-6.
Klein EA et al. SELECT: the next prostate cancer prevention trial (Selenium and Vitamin E Cancer Prevention Trial). J Urol 166.4 (2001): 1311-15.
Korpela H et al. Effect of selenium supplementation after acute myocardial infarction. Res Commun Chem Pathol Pharmacol 65.2 (1989): 249-52.
Lindh U, Danersund A, Lindvall A. Selenium protection against toxicity from cadmium and mercury studied at the cellular level. Cell Mol Biol (Noisy-le-grand) 42.1 (1996): 39-48.
Mark SD et al. Prospective study of serum selenium levels and incident esophageal and gastric cancers. J Natl Cancer Inst 92.21 (2000): 1753-63.
McCarty M. Can dietary selenium reduce leukotriene production? Med Hypotheses 13.1 (1984): 45-50.
Micke O et al. Selenium in the treatment of radiation-associated lymphedema. In: Prog Radio-Oncol VII Proc (2002): 533-46.
Micke O et al. Selenium in the treatment of radiation-associated secondary lymphedema. Int J Radiat Oncol Biol Phys 56.1 (2003): 40-9.
Misso NL et al. Reduced platelet glutathione peroxidase activity and serum selenium concentration in atopic asthmatic patients. Clin Exp Allergy 26.7 (1996): 838-47.
Navarro-Alarcon M, Lopez-Martinez MC. Essentiality of selenium in the human body: relationship with different diseases. Sci Total Environ. 249.1-3 (2000): 347-71.
O'Dell JR et al. Serum selenium concentrations in rheumatoid arthritis. Ann Rheum Dis 50.6 (1991): 376-78.
Ohkawa K et al. The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumour activity. Br J Cancer 58.1 (1988): 38-41.
Omland O et al. Selenium serum and urine is associated to mild asthma and atopy: The SUS study. J Trace Elem Med Biol 16.2 (2002): 123-7.
Ongele EA et al. Effects of selenium deficiency in the development of trypanosomes and humoral immune responses in mice infected with Trypanosoma musculi. Parasitol Res 88.6 (2002): 540-5.
Peretz A, Siderova V, Neve J. Selenium supplementation in rheumatoid arthritis investigated in a double blind, placebo-controlled trial. Scand J Rheumatol 30.4 (2001): 208-12.
Rayman MP. The importance of selenium to human health. Lancet 356.9225 (2000): 233-41.
Rayman MP. Selenium in cancer prevention: a review of the evidence and mechanism of action. Proc Nutr Soc 64.4 (2005): 527-42.
Rayman MP, Rayman MP. The argument for increasing selenium intake. Proc Nutr Soc 61.2 (2002): 203-15.
Rayman M et al. Impact of selenium on mood and quality of life: a randomized, controlled trial. Biol Psychiatry 59.2 (2006): 147-54.
Reid ME et al. Selenium supplementation and lung cancer incidence: an update of the nutritional prevention of cancer trial. Cancer Epidemiol Biomarkers Prev 11.11 (2002): 1285-91.
Reid ME et al. Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial. Int J Cancer 118.7 (2006): 1777-81.
Rosenstein ED, Caldwell JR. Trace elements in the treatment of rheumatic conditions. Rheum Dis Clin North Am 25.4 (1999): 929-35, viii.
Roy M et al. Supplementation with selenium and human immune cell functions. I. Effect on lymphocyte proliferation and interleukin 2 receptor expression. Biol Trace Elem Res 41.1-2 (1994): 103-14.
Salonen JT et al. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. Lancet 2.8291 (1982): 175-9.
Sammalkorpi K et al. Serum selenium in acute infections. Infection 16.4 (1988): 222-4.

Schrauzer GN. Anticarcinogenic effects of selenium. Cell Mol Life Sci 57.13-14 (2000): 1864-73.
Scott R et al. The effect of oral selenium supplementation on human sperm motility. Br J Urol 82.1 (1998): 76-80.
Sher L. Role of thyroid hormones in the effects of selenium on mood, behavior, and cognitive function. Med Hypotheses 57.4 (2001): 480-3.
Shils M et al (eds). Modern Nutrition in Health and Disease. Baltimore: Lippincott Williams and Wilkins. 2006. Available at: Clinicians health channel gateway.ut.ovid.com/gw1/ovidweb.cgi (accessed 13-06-06).
Shor-Posner G et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 29.2 (2002): 169-73.
Stranges S et al. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. Am J Epidemiol 163.8 (2006): 694-9.
Styblo M, Thomas DJ. Selenium modifies the metabolism and toxicity of arsenic in primary rat hepatocytes. Toxicol Appl Pharmacol 172.1 (2001): 52-61.
Suadicani P, Hein HO, Gyntelberg F. Serum selenium concentration and risk of ischaemic heart disease in a prospective cohort study of 3000 males. Atherosclerosis 96.1 (1992): 33-42.
Tinggi U. Essentiality and toxicity of selenium and its status in Australia: a review. Toxicol Lett 137.1-2 (2003): 103-10.
Vezina D et al. Selenium-vitamin E supplementation in infertile men: Effects on semen parameters and micronutrient levels and distribution. Biol Trace Elem Res 53.1-3 (1996): 65-83.
Virtamo J et al. Serum selenium and the risk of coronary heart disease and stroke. Am J Epidemiol 122.2 (1985): 276-82.
Xu DX et al. The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma. Mutat Res 534.1-2 (2003): 155-63.
Yiin SJ et al. Cadmium induced lipid peroxidation in rat testes and protection by selenium. Biometals 12.4 (1999a): 353-9.
Yiin SJ et al. Cadmium-induced renal lipid peroxidation in rats and protection by selenium. J Toxicol Environ Health A 57.6 (1999b): 403-13.
Yiin SJ et al. Cadmium-induced liver, heart, and spleen lipid peroxidation in rats and protection by selenium. Biol Trace Elem Res 78.1-3 (2000): 219-30.
Yiin SJ et al. Lipid peroxidation in rat adrenal glands after administration cadmium and role of essential metals. J Toxicol Environ Health A 62.1 (2001): 47-56.
Yoshizawa K et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. J Natl Cancer Inst 90.16 (1998): 1219-24.
Yu SY et al. Chemoprevention trial of human hepatitis with selenium supplementation in China. Biol Trace Elem Res 20.1-2 (1989): 15-22.
Yu SY et al. Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong. Biol Trace Elem Res 56.1 (1997): 117-24.
Zamamiri-Davis F et al. Nuclear factor-kappaB mediates over-expression of cyclooxygenase-2 during activation of RAW 264.7 macrophages in selenium deficiency. Free Radic Biol Med 32.9 (2002): 890-7.
Zu K, Ip C. Synergy between selenium and vitamin E in apoptosis induction is associated with activation of distinctive initiator caspases in human prostate cancer cells. Cancer Res 63.20 (2003): 6988-95.

Shark cartilage



Historical note Shark cartilage became a popular supplement in the 1980s, largely based around the claim that sharks rarely get cancer and therefore must have some protection against the disease. By 1995, the annual world market for shark-cartilage products exceeded US$30 million and dozens of shark cartilage products were available in retail stores and usually sold as food supplements (Ernst 1998). Over the past few decades, some progress has been made in identifying the various unusual compounds present in shark cartilage and it is clearly known that it contains some anti-angiogenic compounds, which increase resistance to tumours. Previously, much work had been conducted with bovine cartilage, which also exhibits anti-angiogenic properties, although to a lesser extent.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Although there has been some investigation into its actions and potential role as a therapeutic agent, little information is available about its pharmacokinetics.

CHEMICAL COMPONENTS

Shark cartilage is mainly composed of proteins, calcium, phosphorus, water, collagen and proteoglycans, chiefly chondroitin sulfates. Collagen imparts tensile strength and proteoglycans impart resilience to cartilage.

MAIN ACTIONS

ANALGESIC AND ANTI-INFLAMMATORY

Both analgesic and anti-inflammatory activities have been reported for shark cartilage preparations in animal studies (Fontenele et al 1996, 1997). The mechanism of action is unknown; however, tests with the opioid antagonist naloxone have found it does not involve the opioid system (Fontenele et al 1997).

ANTI-ANGIOGENIC

Shark cartilage extract appears to block the two main pathways that contribute to the process of angiogenesis, matrix metalloproteases and the vascular endothelial growth factor signalling pathway (Anon 2004). The effect is due to several different constituents that have been isolated from shark cartilage and identified as exerting anti-angiogenic activity (Dupont et al 1998, Gonzalez et al 2001, Shen et al 2001, Sheu et al 1998) in various experimental models.

ANTINEOPLASTIC EFFECTS

Due to its anti-angiogenic activity, shark cartilage has been investigated for antineoplastic effects. In one study, oral administration of powdered shark cartilage significantly delayed the development of papillary and solid tumours in a murine renal tumour model in experimental animals (Barber et al 2001).

IMMUNOSTIMULANT

A complex mixture of constituents is responsible for the immunostimulating properties of shark cartilage, according to in vitro research (Kralovec et al 2003). Of these, a protein fraction composed of two proteins with molecular weights of approximately 14 and 15 kDa has exhibited the most immunostimulatory effects (Hassan et al 2005).

OTHER ACTIONS

ANTIBIOTIC

Squalamine, isolated from dogfish shark cartilage, is a broad-spectrum antibiotic with activity against protozoa, fungi and both Gram-positive and Gram-negative bacteria (Moore 1993).

ANTIOXIDANT

Antioxidant activity has been demonstrated in vitro (Gomes et al 1996).

CLINICAL USE

OSTEOARTHRITIS

Based on its analgesic and anti-inflammatory activities, shark cartilage has been used to relieve symptoms in OA. To date, no clinical studies are available to determine its effectiveness; however, positive results have been obtained in several clinical studies for one of its constituents, chondroitin sulfate (see Chondroitin monograph for details).

CANCER

Shark cartilage is a popular supplement with cancer patients (Bernstein & Grasso 2001), although results from the few clinical trials conducted using shark cartilage in people with advanced cancers have generally produced negative findings.

One study of 60 people with advanced, previously treated cancer (breast, colorectal, lung, prostate, non-Hodgkin's lymphoma, brain) failed to demonstrate an effect for orally administered shark cartilage (1 g/kg) on tumour growth or QOL (Miller et al 1998). A larger study of 83 patients with advanced breast and colorectal cancers, which was published in 2005, also found that shark cartilage failed to improve survival or QOL (Loprinzi et al 2005). This study was a two-arm, randomised,

placebo-controlled, double-blind, clinical trial. Of note, there was a high drop-out rate as only half the patients receiving shark cartilage powder continued with treatment beyond 1 month and only 10% were still using the treatment by 6 months. It was thought that gastrointestinal symptoms may have contributed to the poor patient compliance.

Several smaller preliminary studies have produced positive results, with some patients experiencing less tumour progression and weight loss, improved appetite or decreased pain (Couzin et al 2003). Unfortunately, details of these studies are difficult to locate and much remains unanswered, such as doses used, time frames for use and criteria for improvement.

Investigation with Neovastat (AE-941), a standardised shark cartilage extract, has produced more promising results and demonstrated inhibitory effects on the growth and metastasis of tumors; however, research has mainly been conducted in animal models (Hassan et al 2005). One clinical study conducted with Neovastat did report a significant survival advantage for the patients with unresectable stage IIIA, IIIB, or IV non-small-cell lung cancers receiving treatment (Hassan et al 2005).

Clinical note — Angiogenesis and tumour growth

Angiogenesis is defined as the formation of new capillary blood vessels from existing microvessels and is a process regulated by inducers and inhibitors. It is critical for development, reproduction and repair and dominates many pathological conditions (Folkman 2003). In 1971, the hypothesis that tumour growth is angiogenesis-dependent was first proposed and since then, the study of angiogenesis inhibitors in cancer research has developed. It has now been demonstrated that solid tumours secrete angiogenic substances to set up an internal network of blood vessels to support further growth and there is a correlation between tumour microvessel density and the risk of metastases. In the absence of angiogenesis, tumour growth is restricted to a microscopic size and tumour cells do not shed into the circulation. Several clinical studies have been conducted with various anti-angiogenic therapies, generally indicating that despite an initial increase in tumour blood flow, long-term treatment causes total tumour blood flow to reach a steady state or to gradually decrease.

OTHER USES

There is one case report of a man with Kaposi's sarcoma, whose lesion disappeared after taking shark cartilage (3.75–4.5 g/day for 9 months) (Hillman et al 2001).

DOSAGE RANGE

- Depending on the purity of the supplement, 500–4500 mg/day in divided doses.
- Various doses of cartilage have been used in different studies, ranging from 2.5 mg to 100 g/day (Simone et al 1998).

ADVERSE REACTIONS

A clinical study of 60 patients with advanced cancer reported the most common adverse reactions as gastrointestinal related, such as nausea, vomiting and constipation (Miller et al 1998).

SIGNIFICANT INTERACTIONS

Controlled studies and sufficient reliable information is not available to predict or determine interactions.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with seafood allergy.

HYPERCALCAEMIA

Due to the high calcium content of this supplement, it should be used with caution in people with hypercalcaemia.

THEORETICAL CAUTIONS BASED ON THE SUPPLEMENT'S ANTI-ANGIOGENIC ACTIVITY

- Suspend use 3 weeks before surgery and for 6 weeks after surgery.
- Not recommended for children or teenagers still experiencing growth.

PREGNANCY USE

Although not scientifically investigated in this population, it is not recommended in pregnancy based on theoretical considerations.

PRACTICE POINTS/PATIENT COUNSELLING

- Shark cartilage is mainly composed of calcium, phosphorus, water, collagen and proteoglycans, chiefly chondroitin sulfates.
- Anti-angiogenic, antineoplastic, immunostimulant and broad-spectrum antibiotic activities have been reported in preliminary studies.
- Both analgesic and anti-inflammatory activities have been reported for shark cartilage preparations in animal studies, most likely due to its chondroitin content. As a result, it is used to relieve symptoms in arthritic conditions.
- It is a popular supplement among cancer patients; however, the few clinical trials conducted so far with people with advanced cancers have generally produced negative results, suggesting no benefit.

- Its use is contraindicated in people with seafood allergy, and in pregnancy. Do not use 3 weeks before and 6 weeks after surgery, or in children or teenagers still experiencing growth.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Shark cartilage has a number of different actions, such as anti-inflammatory, antibiotic, anti-tumour and pain-relieving effects. However, these have not been confirmed in controlled human studies. As a result, it is difficult to determine what effects will be experienced.

When will it start to work?

Due to the lack of human research, this is unknown.

Are there any safety issues?

Shark cartilage products are not to be used in people with seafood allergy or in pregnancy. They should not be used by children or teenagers still experiencing growth or 3 weeks before and for 6 weeks after surgery.

REFERENCES

Anon. AE 941. Drugs R D 5.2 (2004): 83-9.

Barber R et al. Oral shark cartilage does not abolish carcinogenesis but delays tumor progression in a murine model. Anticancer Res 21.2A (2001): 1065-9.

Bernstein BJ, Grasso T. Prevalence of complementary and alternative medicine use in cancer patients. Oncology (Huntingt) 15.10 (2001): 1267-72.

Couzin J. Beefed-up NIH center probes unconventional therapies. Science 282.5397 (1998): 2175-6 as cited in Microdex (Thomson 2003). Available at: www.micromedex.com (accessed 07-03).

Dupont E et al. Antiangiogenic properties of a novel shark cartilage extract: potential role in the treatment of psoriasis. J Cutan Med Surg 2.3 (1998): 146-52.

Ernst E. Shark cartilage for cancer? Lancet 351.9098 (1998): 298.

Folkman J. Angiogenesis and apoptosis. Semin Cancer Biol 13.2 (2003): 159-67.

Fontenele JB et al. Anti-inflammatory and analgesic activity of a water-soluble fraction from shark cartilage. Braz J Med Biol Res 29.5 (1996): 643-6.

Fontenele JB et al. The analgesic and anti-inflammatory effects of shark cartilage are due to a peptide molecule and are nitric oxide (NO) system dependent. Biol Pharm Bull 20.11 (1997): 1151-4.

Gomes EM, Souto PR, Felzenszwalb I. Shark-cartilage containing preparation protects cells against hydrogen peroxide induced damage and mutagenesis. Mutat Res 367.4 (1996): 204-8.

Gonzalez RP et al. Demonstration of inhibitory effect of oral shark cartilage on basic fibroblast growth factor-induced angiogenesis in the rabbit cornea. Biol Pharm Bull 24.2 (2001): 151-4.

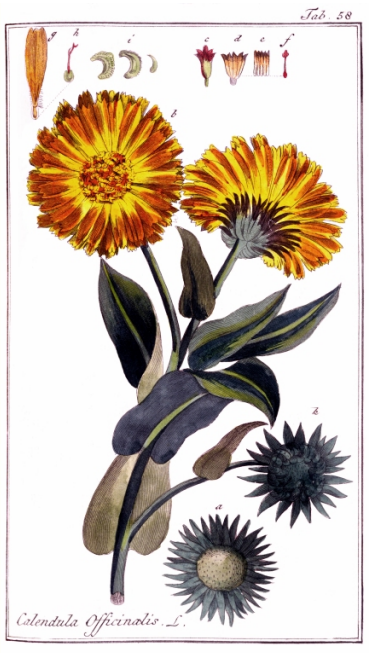
Hassan ZM et al. Low molecular weight fraction of shark cartilage can modulate immune responses and abolish angiogenesis. Int Immunopharmacol 5.6 (2005): 961-70.

Hillman JD et al. Treatment of Kaposi sarcoma with oral administration of shark cartilage in a human herpesvirus 8-seropositive, human immunodeficiency virus-seronegative homosexual man. Arch Dermatol 137.9 (2001): 1149-52.

Kralovec JA et al. Immunomodulating principles from shark cartilage. Part 1. Isolation and biological assessment in vitro. Int Immunopharmacol 3.5 (2003): 657-69.

Loprinzi CL et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. Cancer 104.1 (2005): 176-82.
Miller DR et al. Phase I/II trial of the safety and efficacy of shark cartilage in the treatment of advanced cancer. J Clin Oncol 16.11 (1998): 3649-55.
Moore KS et al. Squalamine: an aminosterol antibiotic from the shark Proc Natl Acad Sci USA 90.4 (1993): 1354-8.
Shen XR et al. SCAIF80, a novel inhibitor of angiogenesis, and its effect on tumor growth. Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao (Shanghai) 33.1 (2001): 99-104.
Shepherd FA. Angiogenesis inhibitors in the treatment of lung cancer. Lung Cancer 34 Suppl 3 (2001): S81-9.
Sheu JR et al. Effect of U-995, a potent shark cartilage-derived angiogenesis inhibitor, on anti-angiogenesis and anti-tumor activities. Anticancer Res 18.6A (1998): 4435-41.
Simone CB, Simone NL, Simone CB II. Shark cartilage for cancer. Lancet 351.9113 (1998): 1440.

Slippery elm



Historical note The dried inner bark of the slippery elm tree was a popular remedy used by many Native American tribes, and subsequently taken up by European settlers. It was mixed with water and applied topically to treat wounds, bruises and skin irritations, and used internally for sore throat, coughs and gastrointestinal conditions. When mixed with milk, it was used as a nutritious gruel for children and convalescents. It also gained a reputation as an effective wound healer among soldiers during the American Civil War. From 1820 until 1960 it was listed in the US Pharmacopeia as a demulcent, emollient and antitussive (Ulbricht & Basch 2005). The name 'slippery elm' refers to the slippery consistency of the inner bark when it comes into contact with water.

COMMON NAME
Slippery elm

OTHER NAMES
American elm, Indian elm, moose elm, red elm, sweet elm, winged elm

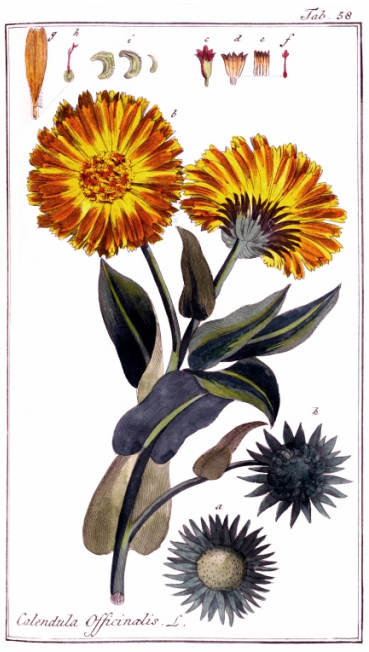
BOTANICAL NAME/FAMILY
Ulmus fulvus or *Ulmus rubra* (family Ulmaceae)

According to current botanical nomenclature, it should now be referred to as *Ulmus rubra.*

PLANT PART USED
Dried inner bark

CHEMICAL COMPONENTS
The inner bark chiefly contains mucilage (various hexoses, pentoses, methylpentoses), glucose, polyuronides, tannins, galacturonic acid, L-rhamnose, D-galactose, starches, fat, phytosterols, sesquiterpenes, and cholesterol (Beveridge et al 1969; IM Gateway Database 2003; Newall et al 1996; US Department of Agriculture Phytochemical Database 2003). The bark provides 2740 kilocalories per kilogram. It contains a variety of nutritional factors such as glucose, calcium, iron, vitamin C, thiamin, zinc, magnesium and potassium, providing support for its traditional use as a nutritious gruel.

Clinical note — Mucilages
Mucilages are hydrophilic structures, capable of trapping water, which causes them to swell in size and develop a gel-like consistency. The gels tend to have soothing properties and can be broken down by bowel flora when taken internally (Mills & Bone 2000). Mucilages are known to have beneficial effects on burns, wounds and ulcers when applied externally and on gastric inflammation, irritations and diarrhoea when taken internally.



MAIN ACTIONS

The pharmacological actions of slippery elm have not been significantly investigated in clinical studies. Therefore, information is generally based on what is known about key constituents found within the herb.

SOOTHES IRRITATED AND INFLAMED TISSUE

The large amount of mucilage found in slippery elm bark will coat the surface of mucous membranes or wounds and sores when it comes in contact with water, and form a gel-like layer. Laboratory research has shown that mucilaginous medicinal plants, such as slippery elm, can decrease local irritation in acute gastritis.

NUTRITIVE DEMULCENT

A number of constituents, such as starch, glucose, calcium, iron, vitamin C, thiamine, zinc, magnesium and potassium are present in slippery elm, making it a source of many nutritional factors (Duke 2003).

ANTIOXIDANT

In vitro studies show a free radical scavenging activity that may relate to its anti-inflammatory action (Langmead et al 2002).

CLINICAL USE

The therapeutic effectiveness of slippery elm has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

GASTROINTESTINAL CONDITIONS

Based on traditional evidence, slippery elm is taken internally to relieve the symptoms of gastritis, acid dyspepsia, gastric reflux, peptic ulcers, irritable bowel syndrome and Crohn's disease.

It is widely accepted that the mucilage acts as a barrier against the damaging effects of stomach acid on the oesophagus and may also exert mild anti-inflammatory activity locally. Currently, clinical research is not available to determine the effectiveness of slippery elm in these conditions; however, anecdotally the treatment appears

to be very successful and patients report rapid improvement in upper gastrointestinal symptoms.

Solid dose tablets and capsules are used in the treatment of diarrhoea when it is believed the fibre will slow down gastric transit time and act as a bulking agent. Although clinical studies are not available to determine its effectiveness, the high mucilaginous content and presence of tannins in the herb provide a theoretical basis for its use.

DERMATITIS AND WOUNDS

Slippery elm has also been used as a topical agent to soothe irritated and/or inflamed skin conditions, wounds and burns and draw out boils and abscesses (Fisher & Painter 1996). When applied, it forms a protective gel-like layer, which is considered to have soothing properties.

OTHER USES

Traditionally, slippery elm is used to treat bronchitis, cystitis and intestinal parasites. Externally, it has been used to treat gout, inflamed joints and toothache (Fisher & Painter 1996).

Clinical note – Essiac tea

Slippery elm is one of the key ingredients in Essiac tea, which was reportedly developed by the Ojibwa tribe of Canada and named after an Ontario nurse (Rene Caisse) to whom the formula for the herbal tea was given by an Ojibwa healer in 1922 (Smith & Boon 1999). It is used to treat a variety of diverse conditions such as allergies, hypertension, and osteoporosis. The tea is made up of a mixture of four herbs, *Arctium lappa* (burdock root), *Rumex acetosella* (sheep sorrel), *Ulmus rubra* (slippery elm) and *Rheum officinale* (rhubarb) and is considered to possess antioxidant and possibly anticancer activity (Leonard et al 2006). As a result, it is used widely by North American cancer patients during chemo- and radiotherapy (Cheung et al 2005) for reduction in symptoms associated with cancer treatment and as a possible adjunctive treatment. In vitro tests with Essiac have identified anticancer activity, although its effects in vivo are controversial and evidence of efficacy is anecdotal (Leonard et al 2006). A recent study demonstrated that Essiac tea effectively scavenges several types of radicals and possesses DNA-protective effects (Leonard et al 2006).

DOSAGE RANGE

Owing to insufficient data available from clinical studies, doses have been derived from Australian manufacturers' recommendations.

GASTROINTESTINAL SYMPTOMS

- One to two capsules containing 150 mg of slippery elm before meals.
- Fluid extract (60%): 5 mL three times daily.
- Half a teaspoon of slippery elm bark powder is mixed with one cup of hot water and taken up to three times daily. For added flavouring, cinnamon or nutmeg can be added.

EXTERNAL USE

- Mix the coarse powdered bark with enough boiling water to make a paste and use as a poultice (Hoffman 1983).

TOXICITY

Insufficient reliable information is available.

ADVERSE REACTIONS

Insufficient reliable information is available.

SIGNIFICANT INTERACTIONS

Controlled studies are unavailable, but interactions are theoretically possible with some medicines.

Since slippery elm forms an inert barrier over the gastrointestinal lining, it may theoretically alter the rate and/or extent of absorption of medicines with a narrow therapeutic range (e.g. barbiturates, digoxin, lithium, phenytoin, warfarin). The clinical significance of this is unclear. Separate doses by 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Insufficient reliable information is available.

PRACTICE POINTS/PATIENT COUNSELLING

- Slippery elm inner bark is a highly mucilaginous substance, which has been traditionally used as a topical application to soothe irritated and inflamed skin conditions and promote wound healing.
- It is used internally to soothe an irritated throat and is often combined with antiseptic herbs.
- Slippery elm is used to provide symptomatic relief in acid dyspepsia, gastrointestinal reflux and inflammatory bowel diseases, but has not been scientifically studied to any significant extent.

- Overall, slippery elm has not been significantly investigated in clinical studies, so most information is derived from traditional sources.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

The inner bark of slippery elm is highly mucilaginous, meaning that it forms a thick gel-like substance when combined with water. Traditionally, it has been used internally to relieve symptoms of dyspepsia and inflamed bowel conditions and topically to soothe irritated skin and promote wound healing.

When will it start to work?

Whether used internally for upper gastrointestinal symptoms (such as reflux and dyspepsia) or applied topically to irritated skin, it should theoretically provide quick symptomatic relief; however, research to confirm this is not available.

Are there any safety issues?

Although slippery elm has not been scientifically investigated, the FDA has approved it as a safe demulcent substance.

REFERENCES

Beveridge RJ, Stoddart JF, Szarek WA, Jones JKN. Some structural features of the mucilage from the bark of Ulmus fulvus. Carbohydr Res 9 (1969): 429-39.

Cheung S, Lim KT, Tai J. Antioxidant and anti-inflammatory properties of ESSIAC and Flor-essence. Oncol Rep 14 (2005): 1345-50.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. www.ars-grin.gov/duke.

Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Hoffman D. The New Holistic Herbal. Dorset: Element Books, 1983.

IM Gateway Database. Slippery elm review. (Accessed 2003 at www.imgateway.com)

Langmead L et al. Antioxidant effects of herbal therapies used by patients with inflammatory bowel disease: an in vitro study. Aliment Pharmacol Ther 16.2 (2002): 197-205.

Leonard SS, Keil D, Mehlman T, Proper S, Shi X, Harris GK. Essiac tea: Scavenging of reactive oxygen species and effects on DNA damage. J Ethnopharmacol 103.2 (2006): 288-96.

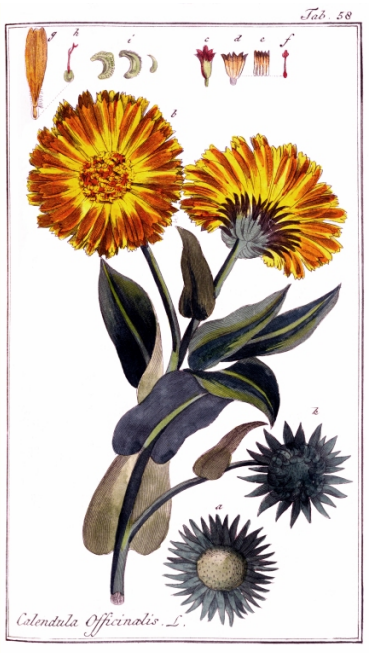
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.

Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London, UK: The Pharmaceutical Press, 1996.

Smith M, Boon HS. Counseling cancer patients about herbal medicine. Patient Educ Counsel 38 (1999): 109-20.

Ulbricht CE, Basch EM. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.

Soy



Historical note Soybeans were one of the first crops grown by humans and have been consumed for approximately 5000 years in China where they are regarded as both a food and a medicine. During the Chou dynasty 1134–246 BC fermentation techniques were developed to produce tempeh, miso and tamari soy sauce, with tofu being invented around the second century BC. Soy first reached the West as imported soy sauce, and soy bean cultivation began in the 1770s, primarily for animal feed. It was not until World War I that soy became a significant crop for human consumption (Natural Standard Patient Monograph 2005). Soy protein was first produced in the 1930s for its functional properties and used as a pigment binder for paper, a foam for fire extinguishers and a fibre for making artificial silk before being used as a food supplement in the 1960s (Wikipedia 2006).

COMMON NAME
Glycine max

OTHER NAMES
Glycine soja, dolichos soja, glycine gracilis, glycine hispida, phaseolus max, soja hispida, soja max

BOTANICAL NAME/FAMILY
Glycine max (family Fabaceae [Leguminosae])

PLANT PART USED
Bean

CHEMICAL COMPONENTS
Soybeans are a high nutrient food containing up to 50% protein. Soy protein contains all of the essential amino acids in sufficient quantities to act as a sole protein source with methionine (a precursor of homocysteine) being the limiting amino acid (Young 1991).

Soy is a major food source of phytoestrogens (isoflavones and lignans), with each gram of soy protein containing approximately 1–3 mg of isoflavones, including glycosides of genistein, daidzein and glycitein (Erdman 2000). Soy also contains the lignans secoisolariciresinol, matairesinol, syringaresinol, lariciresinol, isolariciresinol, and pinoresinol (Penalvo et al 2004), as well as soy lecithin (a phospholipid containing

linoleic and linolenic acid), vitamin E (in its four isomeric forms as alpha, beta, gamma, and delta-tocopherol), oligosaccharides, the phytosterols beta-sitosterol, campesterol and stigmasterol, phytates and protease inhibitors, inositol hexaphosphate, saponins and oligosaccharides (Mazur et al 1998, Tripathi & Misra 2005).

MAIN ACTIONS

Daidzein, an isoflavone found in soy, is metabolised to the more metabolically active equol and O-desmethylangolensin (O-DMA) by as yet unspecified intestinal bacteria. Following soy or daidzein consumption, approximately 30–50% of the human population produce equol, and approximately 80–90% produce O-DMA; however, the significance of this is uncertain, despite some studies suggesting that the ability to produce equol and O-DMA may be associated with reduced risk of certain diseases including breast and prostate cancers (Atkinson et al 2005).

Predicting the effects of isoflavones in vivo is difficult because the route of administration, chemical form of the phyto-oestrogen, its metabolism, bioavailability, half-life, timing and level of exposure, intrinsic oestrogenic state and non-hormonal secondary mediated actions of isoflavones may all influence their biological and clinical effects (Setchell & Cassidy 1999) and the mechanisms for the clinical effects of soy are yet to be fully evaluated (Balk et al 2005, Setchell & Cassidy 1999).

OESTROGEN RECEPTOR/HORMONAL MODULATION

Soy isoflavones and lignans share structural similarities with oestrogen and are referred to as phyto-oestrogens and/or selective oestrogen receptor modulators (Sliva 2005). Soy isoflavones have weak oestrogenic activity. The order of activity in in-vivo assays is glycitein > genistein > daidzein (PDRHealth 2004). Soy isoflavone glycosides bind weakly to both oestrogen receptors, with the binding affinity of genistein, dihydrogenistein and equol being comparable to the binding affinity of 17-beta-estradiol (Morito et al 2001).

Isoflavones have complex actions that may be tissue specific and may act as partial oestrogen agonists and antagonists, as well as having non-classical affects on plasma membranes and cell signalling pathways (Setchell & Cassidy 1999).

The oestrogenic effects of soy are postulated to contribute to protective effects against cardiovascular disease, cancer and menopausal symptoms. Although a review of 861 studies on the effects of phyto-oestrogens suggests they are indeed biologically active in humans (Knight & Eden 1996), major gaps in knowledge still exist regarding the effects of phyto-oestrogen supplements on bone diseases, various cancers, menopausal symptoms, and cognitive function (Lu et al 2001, Stark & Madar

2002). Interestingly, soy has a greater affinity for the oestrogen beta-receptor than the alpha-receptor. The beta-receptor is found in brain, bone, bladder and vascular epithelia, tissues in which isoflavones purportedly have activity (Setchell & Cassidy 1999).

Genistein has been found to have an oestrogen-like effect on the serum lipid profile (Yildiz et al 2005); however, in a double-blind, placebo-controlled trial in 40 healthy postmenopausal women aged 50–75 years, 40 g of soy protein containing 118 mg isoflavones did not produce biologically significant oestrogenic effects on coagulation, fibrinolysis, or endothelial function (Teede et al 2005). In another 12-month double-blind randomised trial of soy protein containing 99 mg isoflavones/day in 202 postmenopausal women, SBP and DBP decreased and endothelial function improved in the equol producers, with increased blood pressure and deterioration in endothelial function seen in the equol non-producers (Kreijkamp-Kaspers et al 2005).

A review of 50 RCTs of soy and endocrine function suggest that there are no consistent statistically significant effects of soy on FSH or TSH levels or on oestradiol levels at the follicular phase, or on menstrual cycle length. Similarly, there was not a consistent significant effect on testosterone levels in healthy males (Balk et al 2005).

MENOPAUSAL SYMPTOMS

The natural oestrogen-receptor activity of soy is popularly considered an alternative to controversial HRT for postmenopausal women (Sliva 2005). A recent analysis of 17 trials, however, found mixed results for the effects of soy isoflavone extracts on menopausal symptoms (Nelson et al 2006). Although some data seem to support the efficacy of isoflavones in reducing the incidence and severity of hot flushes, many studies have not found any difference between the isoflavone recipients and the controls. Inadequate data exist to evaluate the effect of isoflavones on bone mass and vaginal dryness (Greenwood et al 2000).

CARDIOVASCULAR DISEASE

There are many potential mechanisms by which soy may improve cardiovascular outcomes, including reduction in total cholesterol, LDL, HDL, triglycerides, lipoprotein a, blood pressure, C-reactive protein, homocysteine, endothelial function, systemic artery compliance, and oxidised LDL (Balk et al 2005). A review by the North American Menopause Society suggests that the most convincing health effects of soy can be attributed to the actions of isoflavones on lipids, with studies finding statistically significant reductions in LDL and triglycerides, as well as increases in HDL (Greenwood et al 2000). It is unclear how soy exerts its beneficial effects on lipid metabolism or which are the active components of soy, which may include soy protein, bioactive

peptides, interaction of isoflavones within the intact soy matrix, or other compounds (Cassidy & Hooper 2006, Torres et al 2006).

Consumption of soy protein may produce cardiovascular benefits through multiple mechanisms, including the low methionine content reducing serum homocysteine concentration (Nagata et al 2003), reduction of the insulin/glucagon ratio (Sanchez & Hubbard 1991), downregulation of the hepatic transcription factor sterol regulatory element binding protein-1, which in turn reduces lipotoxicity in the liver (Torres et al 2006), regulation of hepatic lipid metabolism through upregulation of LDL receptors and increase in bile acid secretion (Potter 1995), reducing hepatic fatty acid and triglyceride biosynthesis and increasing fatty acid oxidation (Tovar et al 2005), preventing the transfer of fatty acids to extra adipose tissues by increasing the adipocyte hormone adiponectin (Nagasawa et al 2003), and increasing bile acid secretion and bacterial conversion of cholesterol to the non-absorbable coprostanol (Huff & Carroll 1980). Soy protein peptides may also act to decrease intestinal cholesterol absorption and bile acid uptake, reduce aortic accumulation of cholesterol esters and suppress food intake and gastric emptying by increasing cholecystokinin, and inhibiting angiotensin-converting enzyme (Torres et al 2006).

Soy protein is also reported to have beneficial effects on renal function, with suggestions that the isoflavones genistein and daidzein reduce glomerular damage by protecting LDL from oxidation and the high arginine content acts as a precursor for NO thus improving renal flow (Torres et al 2006).

Although it has been suggested that there is no evidence of beneficial effects of phyto-oestrogens on blood pressure, arterial compliance or oxidation of LDL-cholesterol, there may be beneficial effects on endothelial function and homocysteine concentrations in postmenopausal women (Cassidy & Hooper 2006). Soy isoflavones have, however, been found to improve systemic arterial compliance in perimenopausal and menopausal women (Nestel 1997). Soy protein, regardless of isoflavone content, modulates serum lipid ratios in a direction beneficial for cardiovascular disease risk in healthy young men (McVeigh et al 2006).

ANTI-OSTEOPOROTIC

It has been suggested that the oestrogenic effects of soy isoflavone may help prevent osteoporosis (Setchell & Cassidy 1999). A recent review of in vitro and in vivo studies suggests that soy protein prevents bone loss and that soy isoflavones stimulate the synthesis and the expression of alkaline phosphatases in osteoblasts, and food enriched with isoflavones prevented the reduction of bone mineral density (BMD) in ovariectomised rats or mice and inhibited excretion of urinary deoxypyridinoline (Horiuchi 2005). Animal studies have also found a synergy between soy isoflavones

and supplemental calcium in improving BMD, particularly in the lumbar spine (Ward 2005).

In human trials, 35 g/day soy protein for 12 weeks was found to significantly reduce urinary deoxypyridinoline and increase total alkaline phosphatase in a small study of 15 women aged 45–64 years (Roudsari et al 2005); however, randomised trials in humans suggest that soy protein and soy isoflavones do not significantly affect calcium metabolism in postmenopausal women (Spence et al 2005) or improve BMD (Horiuchi 2005), despite having an effect on markers of bone formation (Arjmandi et al 2005).

It has been suggested that the beneficial effects of soy isoflavones on bone may be life-stage specific and dependent on the number of oestrogen receptors and the endogenous hormone milieu. Perimenopausal and early menopausal women may therefore be more receptive to the therapeutic effects of isoflavones on bone loss prior to the diminution of oestrogen receptors that occurs in the postmenopausal years (Reinwald & Weaver 2006).

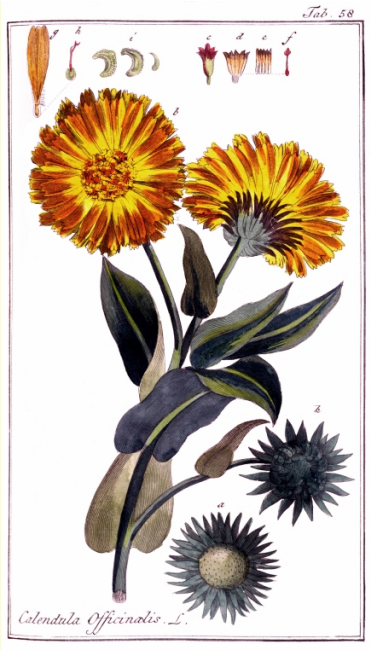
ANTICANCER

To date there have been no positive human intervention studies and the evidence of soy's anticancer effects is based on epidemiological data, as well as in vitro and animal studies.

Soy phyto-oestrogens are converted by gut bacteria to derivatives with weak oestrogenic and antioxidative activity, and epidemiological studies suggest that the highest plasma levels of their metabolites are found in individuals living in countries or regions with low incidence of both cancer and cardiovascular disease (Mazur et al 1998). Although soy phyto-oestrogens have been implicated in soy's anticarcinogenic activity, a causal relation to disease prevention is hypothetical, as the exact mechanisms have not been elucidated (Adlercreutz 2002a, b).

There are multiple mechanisms by which soy protein may protect against cancer, as there is evidence for soy isoflavones having oestrogenic, anti-oestrogenic, antioxidant, antiproliferative, and anti-angiogenic activities (Barnes et al 2000). Soy also contains other putative anticarcinogenic compounds such as lignans, saponins, phytates, protease inhibitors, and phytosterols (Greenwood et al 2000) and it is possible that soy consumption may be a marker for other dietary factors.

It has been suggested that soy isoflavones may reduce breast-cancer risk by affecting endogenous sex-hormone concentrations and the menstrual cycle (Adlercreutz 2002a, b, Setchell & Cassidy 1999) and that soy phyto-oestrogens may influence cancer growth through effects on oestrogen receptors, as well as through inhibition of tyrosine and other protein kinases, and other enzymes such as



aromatase, alteration of growth-factor activity and inhibition of angiogenesis (Adlercreutz 2002a, b).

Genistein is the most studied of the phyto-oestrogens and has weak oestrogenic activity. It has also been found to cause apoptosis in cancer cells both in vitro and in vivo (Bylund et al 2000), stimulate several antioxidative enzymes, such as catalase, superoxide dismutase, glutathione peroxidase and reductase, induce tumour cell differentiation, downregulate the epidermal-growth-factor receptor and erbB2/Neu receptors in cancer cells, and also possibly inhibit tumour cell invasion by inhibiting MMP9 (92 kDa type IV collagenase) (Adlercreutz 2002a, b). Genistein is also reported to inhibit angiogenesis, DNA topoisomerase II, protein tyrosine kinases, aromatase, NF-kappa-B, and to downregulate TGF-beta and stimulate the sex-hormone-binding globulin (PDRHealth 2004). Isoflavones have also been shown to inhibit the activity of aromatase (CYP19), thus decreasing oestrogen biosynthesis and producing anti-oestrogenic effects, which may be important in breast and prostate cancers (Moon et al 2006).

Soy isoflavones also demonstrate a variety of oestrogen-independent activities, and some of them are directly associated with the suppression of the invasive behaviour of breast cancer cells (Sliva 2005). Furthermore, it is suggested that variability in xenobiotic metabolising enzymes and the effect of flavonoid ingestion on enzyme activity may contribute to individual variations in susceptibility to diseases such as cancer (Moon et al 2006).

Although in vitro and animal models point to several pathways by which isoflavones may reduce incidence of cancer (Rosenberg Zand et al 2002), and experimental evidence also exists for an inhibitory effect of soy bran on prostate cancer growth and of isolated lignans on colon cancer (Adlercreutz 2002a, b), clinical trial data supporting this are still lacking.

OTHER ACTIONS

ANTIOXIDANT

Oxygen stress is believed to contribute to menopause and degenerative changes associated with ageing and it is suggested that antioxidants such as soy isoflavones may help to protect mitochondria against premature oxidative damage (Miquel et al 2006). Although several clinical trials have suggested that soy intake decreases oxidative stress and that soy isoflavones, such as genistein, have antioxidant properties in vitro, results of supplementation in clinical trials are inconclusive. Furthermore, diets relatively high in soy protein or soy-derived isoflavones are

reported to have little effect on plasma antioxidant capacity or biomarkers of oxidative stress (Vega-Lopez et al 2005).

COGNITIVE FUNCTION

Soy isoflavones may mimic the actions and functions of oestrogen on the brain, and they have been shown to have positive effects on the cognitive function in females, whereas results in males are inconsistent. Soy isoflavones, and particularly genistein, have been suggested to influence cognitive function via an oestrogen-receptor-mediated pathway and via the inhibition of tyrosine kinase; however, definitive data are still lacking (Lee et al 2005).

CLINICAL USE

Soybeans are usually consumed as fermented and non-fermented soy foods such as tofu, miso and tempeh, as well as whole soybeans, soynuts, soymilk or soy cheese, and soy flour is a common ingredient in foods, beverages and condiments (Sliva 2005). Wide variability has been reported in the total amount of isoflavones in commercial soy products with levels being generally lower than the values on the product labels (Nurmi et al 2002).

CARDIOVASCULAR DISEASE

Substantial data from epidemiological surveys and nutritional interventions in humans and animals indicate that soy protein reduces serum total and LDL-cholesterol and triglycerides, as well as hepatic cholesterol and triglycerides (Torres et al 2006). Based on this data the US FDA has approved a food label health claim stating that a diet with a daily intake of 25 g of soy protein, and low in saturated fat and cholesterol may reduce the risk of heart disease (Balk et al 2005). This claim, however, is only based on studies demonstrating beneficial effects on lipids and other biomarkers of risk, as there have been no published trials on the effects of soy on mortality or cardiovascular events (Cassidy & Hooper 2006).

Although it has been suggested that soy improves lipoprotein levels, a critical analysis of investigations to date suggest that the effects are not impressive and questions the clinical importance of the observed hypocholesterolaemic effects (Dewell et al 2006).

At least six systematic reviews have assessed the effects of soy isoflavones on lipid levels, and suggest that a diet supplemented with soy protein isolate containing isoflavones reduces LDL-cholesterol by approximately 0.15 mmol/L, but without clear effects on triglycerides or HDL-cholesterol (Cassidy & Hooper 2006). In one of the most recent systematic reviews that included a total of 68 RCTs, it is suggested that soy has small to moderate effects on lipids with significant reductions in total

cholesterol (by 2.5%), LDL (3%), triglycerides (6%) and no significant change on HDL, and that the effect is independent of isoflavone content. This review further suggests that higher doses of soy protein are associated with greater LDL reduction in those with elevated baseline LDL levels (Balk et al 2005).

In a meta-analysis of 23 RCTs published from 1995 to 2002, soy protein with isoflavones was associated with significant decreases in total cholesterol (by 3.8%), LDL (by 5.25%), and triacylglycerols (by 7.27%) and significant increases in serum HDL-cholesterol (by 3.03%), with the observed changes being greater for those having higher baseline cholesterol levels or taking more than >80 mg/day isoflavone and the greatest lowering effects on total cholesterol and LDL-cholesterol occurred within short time frames, whereas improvements in HDL-cholesterol were only observed in studies of longer than 12 weeks duration (Zhan & Ho 2005).

Since these reviews a number of studies have confirmed the effects of soy on blood lipids, yet results continue to be mixed. In a double-blind RCT of 117 patients with hypercholesterolaemia 15 or 25 g/day soy protein was found to significantly reduce LDL, total serum cholesterol and apolipoprotein B levels without affecting HDL, triglycerides, homocysteine, folic acid, or vitamin B12, with 25 g/day of soy protein being twice as effective as 15 g/day (Hoie et al 2005a). Similar results were obtained in a similar study, with a preparation combining isolated soy protein with soy fibres and phospholipids showing twice the lipid-lowering effect of a preparation containing isolated soy protein alone (Hoie et al 2005b). A soy protein substitution was also reported to have lipid-lowering effects in hyperlipidaemic but not normolipidaemic haemodialysis patients (Chen et al 2005).

These results contrast with those from studies that have not found lipid-lowering effects with soy supplementation. In a RCT of 55 postmenopausal women, 6 weeks of supplementation with either phytate or isoflavones in soy protein isolate was not found to have a significant effect of reducing oxidative damage or favourably altering blood lipids (Engelman et al 2005). Similarly, in two other RCTs no difference in plasma lipids were found with soy-based supplements (Hermansen et al 2005, Ma et al 2005).

BLOOD PRESSURE

In addition to beneficial effects on lipids, epidemiological data suggest that soy may affect blood pressure. In an observational study of 45,694 participants of the Shanghai Women's Health Study, aged 40–70 years with no history of hypertension, diabetes or cardiovascular disease, the intake of soy foods over 2–3 years was inversely associated with both SBP and DBP, particularly among elderly women. Results of this study found that compared to women consuming less than 2.5 g/day

of soy, consumption of more than 25 g/day was associated with a significant reduction in SBP of 1.9 mmHg and a significant reduction in DBP of 0.9 mmHg and that the inverse association between soy consumption and blood pressure became stronger with increasing age, with significant reductions of –4.9 mmHg for SBP and –2.2 mmHg for DBP in women aged over 60 years (Yang et al 2005). A recent review of 22 RCTs on the effect of soy consumption on blood pressure, however, suggests that there is no discernible effect on either SBP or DBP (Balk et al 2005).

CANCER PREVENTION

High levels of phyto-oestrogens (lignans and isoflavonoids) are frequently associated with low risk of breast, prostate and colon cancer, and breast cancer has been found to be associated with low lignan levels in the USA, Finland, Sweden and Australia. It is not clear, however, if these compounds are cancer protective or are simply biomarkers of a 'healthy' diet (Adlercreutz 1998).

A review of the role of phyto-oestrogens, such as soy containing isoflavones, for the prevention of breast cancer concluded that a soy-containing diet in adult women is not or only slightly protective with regard to breast cancer, but may be beneficial if consumed in early life before puberty or during adolescence and that negative effects on the breast cannot be excluded (Adlercreutz 2002a, b).

A more recent meta-analysis of published epidemiologic studies associating cancer risk with soy intake suggests statistically significant reductions in the mean overall risk estimate for breast (0.78), colon (0.70) and prostate (0.66) cancer for soy consumers (Badger et al 2005).

Soy proteins, common in the Asian diet, have been shown to inhibit prostate cancer cell growth (Sonn et al 2005). In RCTs in men aged 50–80 years, 12 months' supplementation with 83 mg/day isoflavones did not alter serum levels of prostate-specific antigen (PSA) in healthy men (Adams 2004), and 60 mg/day of soy isoflavone did alter serum PSA and free testosterone in some men with early stage prostate cancer (Kumar 2004).

In another RCT involving 29 men with prostate cancer and scheduled to undergo a radical prostatectomy, supplementation with bread containing 50 g of soy grits was found to significantly reduce PSA levels (Dalais 2004).

MENOPAUSAL SYMPTOMS

A systematic review of 21 trials of soy and/or isoflavones on hot flushes and night sweats suggest that, although results were inconsistent, most RCTs of isoflavone supplements found reductions in weekly hot flushes of between 7% and 40%; however, the quality of studies was generally low (Balk et al 2005). Another

systematic review and meta-analysis that included 17 trials found that isoflavone supplementation significantly reduced flushes, with the percentage reduction being related to the number of baseline flushes per day and the dose of isoflavone studied (Howes et al 2006). The fact that the composition and dose of soy supplements varies widely across studies, however, means that making comparisons and definitive conclusions is difficult (Low Dog 2005). In two separate RCTs, soy consumption did not significantly alleviate hot flushes in women with breast cancer (MacGregor et al 2005, Van Patten et al 2002).

OSTEOPOROSIS PREVENTION

The clinical data suggest that approximately 80 mg/day isoflavones are needed to derive skeletal benefits, whereas limited epidemiologic data among Asian populations generally suggests that lower amounts are efficacious (Messina et al 2004). The relationship between usual soy food consumption and fracture incidence was studied in 24,403 postmenopausal women aged 40–70 years who had no history of fracture or cancer in the Shanghai Women's Health Study. During a mean follow-up of 4.5 years a statistically significant association was found between soy or isoflavone consumption and fracture risk, with the association being more pronounced among women in early menopause (Zhang et al 2005).

A recent systematic review found 31 studies that evaluated the effect of soy on markers of bone health; however, few of these were long term studies and they involved a wide variety of interventions making overall conclusions difficult. Of the 5 studies longer than 1 year, no consistent effect was seen on BMD or makers of bone formation (Balk et al 2005). Another systematic review that evaluated 15 clinical trials looking at the effects of isoflavones or isoflavone-rich soy protein on BMD suggests that isoflavones reduce bone loss in younger postmenopausal women (Messina et al 2004).

COGNITIVE FUNCTION

Although not all studies have consistently shown benefits of soy on cognitive function, there have been a number of double-blind RCTs showing that soy improves memory and frontal lobe function in young volunteers (File et al 2001) and postmenopausal women (Duffy et al 2003, File et al 2005).

In one 6-week double-blind trial in 50 postmenopausal women, 60 mg/day total isoflavone equivalents significantly improved non-verbal short-term memory and performance on tests of frontal lobe function with no effects on long-term memory, category generation, or sustained attention (File et al 2005). Similarly, another double-blind controlled trial of 33 postmenopausal women found that 12 weeks'

supplementation with the same supplement significantly improved recall of pictures, sustained attention, learning rule reversals and planning at 12 weeks without affecting menopausal symptoms, self-rating of mood, bodily symptoms or sleepiness (Duffy et al 2003). A further double-blind, randomised, placebo-controlled trial in healthy postmenopausal women aged 55–74 years found that 6 months' supplementation with 110 mg/day total isoflavones significantly improved category fluency compared with baseline scores and the placebo group responses at 6 months (Kritz-Silverstein et al 2003). In contrast to these studies a double-blind, randomised, placebo-controlled trial of 202 healthy postmenopausal women aged 60–75 years found that 25 g/day of soy protein containing 99 mg of isoflavones for 12 months did not affect cognitive function, BMD or plasma lipids (Kreijkamp-Kaspers et al 2004).

OTHER USES

SOY INFANT FORMULA

Soy has been used as an alternative for cow's milk in infant feeding for more than 30 years and may account for as much as 25% of infant formula (Mendez et al 2002). Soy formula is commonly used for infants with cow's milk allergy and there is evidence to suggest that soy milk may be effective in reducing infant colic (Garrison & Christakis 2000). There are few studies, however, examining the effects of phyto-oestrogens in infants. Although infants consuming soy formula may be exposed to 6–11 mg/kg/day of phyto-oestrogens and have plasma levels of isoflavones an order of magnitude higher than adults consuming soy foods (Setchell & Cassidy 1999), there is no obvious evidence to suggest any negative effects (Mendez et al 2002, Setchell & Cassidy 1999).

DIABETES AND DIABETIC NEPHROPATHY

Replacing animal protein with soy protein has been found to improve various disease markers in patients with type 1 or type 2 diabetes and people with obesity. In a RCT of 104 patients with type 2 diabetes, 12 months of a soy-based meal replacement was found to significantly improve weight loss, HbAlc and high-sensitivity C-reactive protein levels and significantly reduce the use of sulfonylureas and metformin compared to the use of individual diet plans (Li et al 2005). Another randomised trial involving 90 obese (non-diabetic) subjects suggests that 6 months on a low-fat, high-soy-protein diet can help to reduce fat while preserving muscle mass and improving glycaemic control and the lipid profile (Deibert et al 2004).

Soy protein supplementation is also reported to be of benefit in a number of pilot studies of diabetic nephropathy. In a controlled crossover trial, 8 weeks of

substituting soy protein for animal protein significantly reduced glomerular filtration rates in 12 young adults with type 1 diabetes mellitus (Stephenson et al 2005). In another crossover trial, isolated soy protein significantly reduced urinary albumin and improved lipid profiles in 14 men with type 2 diabetes and nephropathy (Teixeira et al 2004). Similarly, improvement in lipid profile and renal function was observed in another randomised crossover clinical trial of 14 patients with type 2 diabetes and nephropathy consuming a 35% soy protein and 30% vegetable protein diet for 7 weeks (Azadbakht et al 2003).

SEASONAL ALLERGIC RHINITIS

Polysaccharides from soy sauce have been shown to have anti-allergic activities in vitro and in vivo and an 8-week double blind study involving 51 subjects with seasonal allergic rhinitis found that oral supplementation with 600 mg of soy polysaccharides was effective in significantly improving symptom scores such as sneezing, nasal stuffiness, and hindrance of daily life, as well as significantly improving the appearance and state of the nasal mucosa (Kobayashi 2005, Kobayashi et al 2005).

PREMENSTRUAL SYNDROME

Isolated soy protein containing 68 mg/day (aglycone equivalents) soy isoflavones was found to significantly improve specific PMS symptoms, including headache, breast tenderness, cramps and swelling in a seven-menstrual cycle, double-blind, placebo-controlled, crossover intervention study in 23 women (Bryant et al 2005).

DOSAGE RANGE

Soy foods contain variable amounts of isoflavones. Soy flour contains 1.3 mg/g of isoflavones, with tofu containing 0.4 mg/g, soy milk 0.25 mg/g, tempeh 0.4 mg/g, miso 0.92 mg/g, soy sauce 0.023 mg/g, soybean paste 0.57 mg/g and soy cheese 0.05 mg/g (Coward et al 1993). Soy isoflavones are also available in some functional food products. Although soy oils and lecithin are used in many food ingredients, the typical Western diet provides negligible isoflavones, whereas the typical Asian diet has 20–50 mg (Nagata et al 1998). The optimal dose required to have clinical effects is yet to be established; however, the benefits seen in epidemiological studies are achieved with approximately 50 mg/day of isoflavones (Setchell & Cassidy 1999).

TOXICITY

Soy and soy isoflavones are considered non-toxic in the doses that are generally consumed as foods. Soy may interfere with the absorption of synthetic thyroid hormone, and there is a theoretical concern based on in vitro and animal data that in

individuals with compromised thyroid function and/or whose iodine intake is marginal, soy foods may increase risk of developing clinical hypothyroidism. Thus soy food consumers should ensure their intake of iodine is adequate (Messina & Redmond 2006).

Although the phyto-oestrogens may have hormonal activity, they have relatively short half-lives of approximately 6–8 hours, which is contrasted with the environmental xeno-oestrogens that may persist for years in fat tissue and hence bio-accumulate (Setchell & Cassidy 1999).

ADVERSE REACTIONS

There is little suggestion of adverse effects of soy or isoflavones at physiological doses, although those taking soy isoflavone supplements do appear to have higher levels of gastrointestinal and menstrual complaints (Cassidy & Hooper 2006).

Women with breast cancer (especially oestrogen-positive tumours) and men with prostate cancer should avoid the use of soy isoflavone supplements pending long-term safety studies.

SIGNIFICANT INTERACTIONS

Antibiotic administration blocks metabolism of isoflavones to equol through inhibition of the intestinal microflora, whereas a high carbohydrate milieu increases intestinal fermentation and results in more extensive bio-transformation of phyto-oestrogens (Setchell & Cassidy 1999).

It has been suggested that isoflavones can inhibit the oxidative and conjugative metabolism of drugs in vitro and interact with transporters such as P-glycoprotein; however, their ability to interact with drugs remains uncertain (Evans 2000).

CALCIUM, MAGNESIUM, ZINC, COPPER AND IRON

Soy contains phytic acid, which may bind with certain minerals, such as calcium, magnesium, manganese, zinc, copper and iron, reducing their availability (PDRHealth 2004).

TAMOXIFEN

The soy isoflavone genistein may theoretically compete with tamoxifen for oestrogen receptors, thereby reducing drug efficacy — use caution.

In vivo studies suggest the isoflavone daidzein may enhance the effect of tamoxifen against breast cancer burden and incidence — possible beneficial effect under professional supervision.

PREGNANCY USE

Soy is likely to be safe when used as a food; however, pregnant women and nursing mothers should avoid the use of soy isoflavone supplements pending long-term safety studies.

PRACTICE POINTS/PATIENT COUNSELLING

- Soy is a component of many foods and a nutritious source of protein.
- There are many different types and formulations of soy and people may react differently to soy products depending on their diet and the activity of their gut bacteria.
- In countries where people regularly consume soy products there appears to be lower incidence of cardiovascular disease, menopausal symptoms and some cancers; however, these effects have not yet been definitely attributed to soy consumption.
- The most active agents in soy are the isoflavones, which are used to treat menopausal symptoms, and prevent osteoporosis, cancer and heart disease; however, their use is not yet based on large-scale clinical trials.
- The ability of soy to reduce menopausal symptoms is uncertain at present.
- Although there has not been much research on the use of soy in infants, there does not appear to be any adverse effects of feeding infants with soy formula.
- The long-term benefits of soy may relate to the lifetime exposure to the use of soy products.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Soy is a nutritious food and a good source of protein that appears to have beneficial effects on cholesterol, and possible activity against cancer, heart disease osteoporosis and may positively affect cognitive function.

When will it start to work?

Clinical studies suggest the effects of soy take between 6 and 12 weeks to appear.

Are there any safety issues?

Soy is generally considered safe when taken as a food source or protein substitute; however, soy isoflavone supplements should be taken with caution in pregnancy, and in those with breast cancer or prostate cancer.

REFERENCES

Adams K et al. Soy isoflavones do not modulate prostate-specific antigen concentrations in older men in a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 13(4) (2004): 644-8.

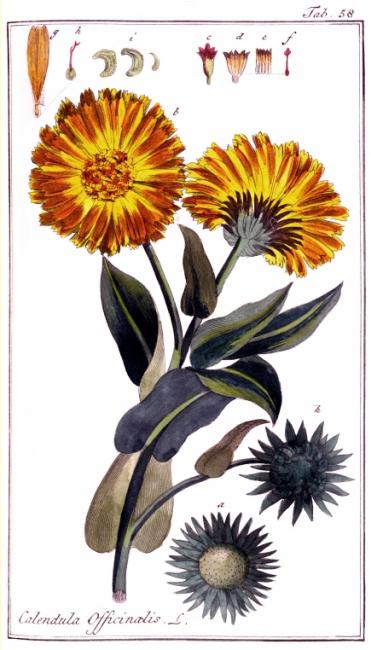
Adlercreutz H. Phytoestrogens and breast cancer. J Steroid Biochem Mol Biol 83 (2002a): 113-18.

Adlercreutz H. Phyto-oestrogens and cancer. Lancet Oncol 3(6) (2002b): 364-73.

Adlercreutz H. Epidemiology of phytoestrogens. Bailliere's Clin Endocrinol Metab 12 (1998): 605-23.
Arjmandi BH et al. One year soy protein supplementation has positive effects on bone formation markers but not bone density in postmenopausal women. Nutr J 4, 2005 [Epub ahead of print].
Atkinson C et al. Gut bacterial metabolism of the soy isoflavone daidzein: Exploring the relevance to human health. Exp Biol Med 230(3) (2005): 155-70.
Azadbakht L et al. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr 57(10) (2003): 1292-4.
Badger TM et al. Soy protein isolate and protection against cancer. J Am Coll Nutr 24(2) (2005): 146-9S.
Balk E et al. Effects of soy on health outcomes. Evidence Report/Technology Assessment (Summary). Report no. 126. Agency for Healthcare Research and Quality; (2005): 1-8.
Barnes S et al. Beyond ER[alpha] and ER[beta]: Estrogen receptor binding is only part of the isoflavone story. J Nutr 130(3) (2000): 656-7S.
Bryant M et al. Effect of consumption of soy isoflavones on behavioural, somatic and affective symptoms in women with premenstrual syndrome. Br J Nutr 93(5) (2005): 731-9.
Bylund A et al. Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. Prostate 42(4) (2000): 304-14.
Cassidy A, Hooper L. Phytoestrogens and cardiovascular disease. J Br Menopause Soc 12(2) (2006): 49-56.
Chen ST et al. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. Am J Kidney Dis 46(6) (2005): 1099-106.
Coward L et al. Genistein, daidzein, and their beta-glycoside conjugates - Antitumor isoflavones in soybean foods from Am and Asian diets. J Agric Food Chem 41(11) (1993): 1961-7.
Dalais F et al. Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. Urology 64(3) (2004): 510-15.
Deibert P et al. Weight loss without losing muscle mass in pre-obese and obese subjects induced by a high-soy-protein diet. Int J Obesity Relat Metab Dis 28(10) (2004): 1349-52.
Dewell A et al. Clinical review a critical evaluation of the role of soy protein and isoflavone supplementation in the control of plasma cholesterol concentrations. J Clin Endocrinol Metab 91(3) (2006): 772-80.
Duffy R et al. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav 75(3) (2003): 721-9.
Engelman HM et al. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. Am J Clin Nutr 81(3) (2005): 590-6.
Erdman JW Jr. Soy protein and cardiovascular disease: A Statement for Healthcare Professionals From the Nutrition Committee of the AHA. Circulation 102(20) (2000): 2555-9.
Evans A. Influence of dietary components on the gastrointestinal metabolism and transport of drugs. Ther Drug Monit 22(1) (2000): 131-6.
File S et al. Eating soya improves human memory. Psychopharmacology 157 (2001): 430-6.
File SE et al. Cognitive improvement after 6 weeks of soy supplements in postmenopausal women is limited to frontal lobe function. Menopause 12(2) (2005): 193-201.
Garrison MM, Christakis DA. A systematic review of treatments for infant colic. Pediatrics 106(1 Pt 2) (2000): 184-90.
Greenwood S et al. The role of isoflavones in menopausal health: Consensus opinion of the North American Menopause Society. Menopause 7(4) (2000): 215-29.
Hermansen K et al. Effects of soy supplementation on blood lipids and arterial function in hypercholesterolaemic subjects. Eur J Clin Nutr 59(7) (2005): 843-50.
Hoie LH et al. Lipid-lowering effect of 2 dosages of a soy protein supplement in hypercholesterolemia. Adv Ther 22(2) (2005a): 175-86.
Hoie LH et al. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. Eur J Nutr 44(2) (2005b): 65-71.
Horiuchi T. Soy protein intake and bone mineral density. Clin Calcium 15(9) (2005): 1507-13.

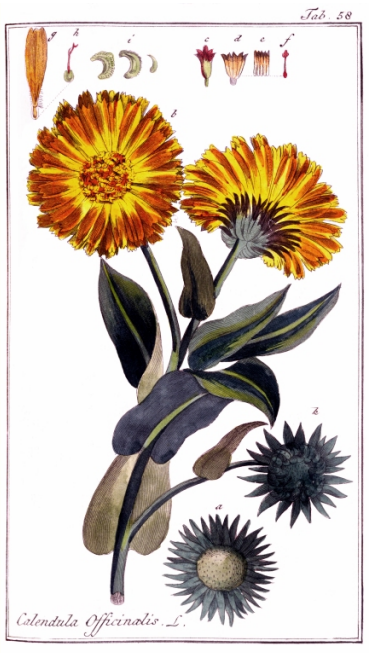
Howes LG et al. Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis. Maturitas, 2006 (in press).
Huff MW, Carroll KK. Effects of dietary protein on turnover, oxidation, and absorption of cholesterol, and on steroid excretion in rabbits. J Lipid Res 21(5) (1980): 546-8.
Knight DC, Eden JA. A review of the clinical effects of phytoestrogens. Obstet Gynecol 87(5 Pt 2) (1996): 897-904.
Kobayashi M. Immunological functions of soy sauce: hypoallergenicity and antiallergic activity of soy sauce. J Biosci Bioeng 100(2) (2005): 144-51.
Kobayashi M et al. Shoyu polysaccharides from soy sauce improve quality of life for patients with seasonal allergic rhinitis a double-blind placebo-controlled clinical study. Int J Mol Med 15(3) (2005): 463-7.
Kreijkamp-Kaspers S et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: A randomized controlled trial. J Am Med Assoc 292(1) (2004): 65-74.
Kreijkamp-Kaspers S et al. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. Am J Clin Nutr 81(1) (2005): 189-95.
Kritz-Silverstein D et al. Isoflavones and cognitive function in older women: The soy and postmenopausal health in aging (SOPHIA) study. Menopause 10(3) (2003): 196-202.
Kumar N et al. The specific role of isoflavones in reducing prostate cancer risk. Prostate 59(2) (2004): 141-7.
Lee YB et al. Soy isoflavones and cognitive function. J Nutr Biochem 16(11) (2005): 641-9.
Li Z et al. Long-term efficacy of soy-based meal replacements vs an individualized diet plan in obese type II DM patients: Relative effects on weight loss, metabolic parameters, and C-reactive protein. Eur J Clin Nutr 59(3) (2005): 411-18.
Low Dog T. Menopause: A review of botanical dietary supplements. Am J Med 118(12, Suppl 2) (2005): 98-108S.
Lu LJ et al. Phytoestrogens and healthy aging: gaps in knowledge. A workshop report [Comment]. Menopause. 8(3) (2001):157-70.
Ma Y et al. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: a randomized controlled trial. J Am Coll Nutr 24(4) (2005): 275-85.
MacGregor CA et al. A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. Eur J Cancer 41(5) (2005): 708-14.
Mazur WM et al. Isoflavonoids and lignans in legumes: nutritional and health aspects in humans. J Nutr Biochem 9(4) (1998): 193-200.
McVeigh BL et al. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. Am J Clin Nutr 83(2) (2006): 244-51.
Mendez MA et al. Soy-based formulae and infant growth and development: a review. J Nutr 132(8) (2002): 2127-30.
Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: A review of the relevant literature. Thyroid 16(3) (2006): 249-58.
Messina M et al. Skeletal benefits of soy isoflavones: A review of the clinical trial and epidemiologic data. Curr Opin Clin Nutr Metab Care 7(6) (2004): 649-58.
Miquel J et al. Menopause: A review on the role of oxygen stress and favorable effects of dietary antioxidants. Arch Gerontol Geriatrics 42(3) (2006): 289-306.
Moon YJ et al. Dietary flavonoids: Effects on xenobiotic and carcinogen metabolism. Toxicol In Vitro 20(2) (2006): 187-210.
Morito K et al. Interaction of phytoestrogens with estrogen receptors alpha and beta. Biol Pharm Bull 24(4) (2001): 351-6.
Nagasawa A et al. Divergent effects of soy protein diet on the expression of adipocytokines. Biochem Biophys Res Commun 311(4) (2003): 909-14.
Nagata C et al. Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women. J Nutr 128(2) (1998): 209-13.

Nagata C et al. Soy product intake is inversely associated with serum homocysteine level in premenopausal Japanese women. J Nutr 133(3) (2003): 797-800.
Natural Standard Patient Monograph. Herbal/plant therapies: Soy (Glycine max [L.] Merr.) 2005. Available at: www.naturalstandard.com/naturalstandard/monographs/herbssupplements/patient-soy.asp (accessed 18-08-06).
Nelson HD et al. Nonhormonal therapies for menopausal hot flushes: systematic review and meta-analysis. JAMA 295(17) (2006): 2057-71.
Nestel P et al. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. Arterioscler Thromb Vasc Biol 17(12) (1997): 3392-8.
Nurmi T et al. Isoflavone content of the soy based supplements. J Pharm Biomed Anal 28(1) (2002): 1-11.
PDRHealth [online]. Soy Isoflavones. Thomson Healthcare, 2004. Available at: http://www.pdrhealth.
Penalvo JL et al. Plant lignans in soy-based health supplements. J Agric Food Chem 52(13) (2004): 4133-8.
Potter SM. Overview of proposed mechanisms for the hypocholesterolemic effect of soy. J Nutr 125(3) (1995): 606-11S.
Reinwald S, Weaver CM. Soy isoflavones and bone health: A double-edged sword? J Nat Prod 69(3) (2006): 450-9.
Rosenberg Zand RS et al. Flavonoids and steroid hormone-dependent cancers. J Chromatogr B 777(1-2) (2002): 219-32.
Roudsari AH et al. Assessment of soy phytoestrogens' effects on bone turnover indicators in menopausal women with osteopenia in Iran: a before and after clinical trial. Nutr J 4 (2005): 30.
Sanchez A, Hubbard RW. Plasma amino acids and the insulin/glucagon ratio as an explanation for the dietary protein modulation of atherosclerosis. Med Hypotheses 36(1) (1991): 27-32.
Setchell KDR, Cassidy A. Dietary isoflavones: biological effects and relevance to human health. J Nutr 129(3) (1999): 758-67S.
Sliva D. Soy isoflavones and the invasiveness of breast cancer. Agric Food Industry Hi-Tech 16(1) (2005): 40-1.
Sonn GA et al. Impact of diet on prostate cancer: A review. Prostate Cancer Prostat Dis 8(4) (2005): 304-10.
Spence LA et al. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: a randomized crossover study. Am J Clin Nutr 81(4) (2005): 916-22.
Stark A, Madar Z. Phytoestrogens: a review of recent findings. J Pediatr Endocrinol Metab 15(5) (2002): 561-72.
Stephenson TJ et al. Effect of soy protein-rich diet on renal function in young adults with insulin-dependent diabetes mellitus. Clin Nephrol 64(1) (2005): 1-11.
Teede HJ et al. Dietary soy containing phytoestrogens does not activate the hemostatic system in postmenopausal women. J Clin Endocrinol Metab 90(4) (2005): 1936-41.
Teixeira SR et al. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy. J Nutr 134(8) (2004): 1874-80.
Torres N et al. Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders. J Nutr Biochem 17(6) (2006): 365-73.
Tovar AR et al. Soy protein reduces hepatic lipotoxicity in hyperinsulinemic obese Zucker fa/fa rats. J Lipid Res 46(9) (2005): 1823-32.
Tripathi AK, Misra AK. Soybean: A consummate functional food: A review. J Food Sci Technol 42(2) (2005): 111-19.
Van Patten CL et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial [Comment]. J Clin Oncol 20(6) (2002): 1449-55.
Vega-Lopez S et al. Plasma antioxidant capacity in response to diets high in soy or animal protein with or without isoflavones. Am J Clin Nutr 81(1) (2005): 43-9.
Ward WE. Potential synergy of soy isoflavones and supplemental calcium on bone health. Agric Food Industry Hi-Tech 16(1) (2005): 37-8.
Wikipedia. Soy protein. Wikimedia Foundation Inc. 2001-2006 Available at: www.en.wikipedia.org (accessed 18-08-06).



Yang G et al. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. Am J Clin Nutr 81(5) (2005): 1012-17.
Yildiz MF et al. Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive C-reactive protein in postmenopausal women. Int J Gynecol Obstet 90(2) (2005): 128-33.
Young VR. Soy protein in relation to human protein and amino acid nutrition. J Am Diet Assoc 91 (1991): 828-35.
Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr 81(2) (2005): 397-408.
Zhang X et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Arch Intern Med 165(16) (2005): 1890-5.

Stinging nettle



Historical note Stinging nettle has been used since ancient times, with Dioscorides and Galen in ancient Greece reporting diuretic and laxative effects for nettle leaf. It is also widely used for gynaecological complaints by North American Indians and in Ayurvedic medicine in India (Blumenthal et al 2000). The Latin root of *urtica* is *uro*, meaning 'I burn', indicative of the small stings caused by the hairs on the leaves of nettle when contact is made with the skin.

OTHER NAMES

Common nettle, brenessel, brennesselkraut, brennesselwurzel, urtica ortie, great stinging nettle, haarnesselkraut, haarnesselwurzel

BOTANICAL NAME/FAMILY

Urtica dioica and *Urtica urens* (family Urticaceae)

PLANT PARTS USED

Leaf and root

CHEMICAL COMPONENTS

Constituents found within the leaf include vitamins A and C, beta-carotene, calcium and potassium, phosphorus, chlorophyll, magnesium and tannins, flavonoids, sterols and amines (US Department of Agriculture 2003).

Constituents found chiefly in the root include polysaccharides, lectins, lignans, fatty acids, terpenes and coumarin (Ernst 2001).

MAIN ACTIONS

ANTI-INFLAMMATORY AND ANALGESIC

In vitro studies have identified anti-inflammatory activity for *Urtica* extract (Obertreis et al 1996a, b, Riehemann et al 1999). The mechanism of action has not been fully elucidated, but test tube studies have demonstrated inhibitory effects on NF-kappa B activation and partial inhibitory effects on cyclo-oxygenase and 5-lipoxygenase derived reactions. Additionally, isolated phenolic acid from nettle has been shown to inhibit leukotriene B4 synthesis in a concentration-dependent manner in vitro.

Although extensive investigation has not been conducted in humans to confirm anti-inflammatory mechanisms, one study of 20 volunteers showed that oral ingestion of 1.34 g nettle extract for 3 weeks significantly decreased

lipopolysaccharide stimulated TNF-alpha and IL-1-beta when tested ex vivo but had no effects on cytokine levels (Teucher et al 1996).

In vitro data has shown that nettle leaf extract (IDS 30) reduces the induction of primary T-cell responses and TNF-alpha in T-cell mediated diseases such as RA (Broer & Behnke 2002). Faecal IL-1-beta and TNF-alpha concentrations were significantly reduced in mice with induced Crohn's disease treated with IDS 30 (Konrad et al 2005). Mice treated with nettle extract displayed fewer histological changes and general disease symptoms. The authors conclude that the effect may be due to a decrease in Th1 response and may constitute a new treatment option for prolonging remission in inflammatory bowel disease.

HYPOTENSIVE AND DIURETIC

When administered intravenously to test animals, *Urtica* extract exerts an acute hypotensive action accompanied by diuretic and natriuretic effects (Tahri et al 2000). It is uncertain whether the same effects are seen with oral administration.

A review of in vitro and in vivo studies concluded that the hypotensive action of *U. dioica* is due in part to negative inotropic activity and a vasodilatory effect (Testai et al 2002).

HYPOGLYCAEMIC

A 33% reduction in blood glucose was noted in rats administered 250 mg/kg of nettle leaf extract orally, 30 minutes before glucose loading (Bnouham et al 2003). Nettle was shown to decrease glucose absorption in the small intestine of rats under anaesthesia; however, 500 mg/kg failed to modify blood glucose levels in alloxan-induced diabetic rats.

A six-fold increase in blood insulin levels occurred after intravenous administration of a nettle leaf fraction in streptozotocin diabetic rats, with a corresponding drop in blood sugar levels as compared to control (Farzami et al 2003). Details of the isolated fraction were not given.

ANTIPROLIFERATIVE EFFECTS ON PROSTATE CELLS

The exact mechanism of action of the antiproliferative effects of nettle extract on prostate cells has not been fully elucidated (Hirano et al 1994, Hryb et al 1995, Lichius & Muth 1997, Lichius et al 1999). Results from several in vitro studies suggest that several mechanisms are responsible.

Reduced prostate cell metabolism and growth may result from inhibition of membrane ATPase activity and decreased binding capacity of sex hormone binding globulin to its receptor on human prostatic membranes (Hirano et al 1994, Hryb et al

1995). Additionally, reduced 5-alpha dihydrotestosterone binding to proteins in humans has been demonstrated (Schmidt 1983).

Prostate cancer One study found that a methanolic extract of stinging nettle roots slows the progression of prostate cancer in both an in vivo model and an in vitro system (Konrad et al 2000). One study involving 20 males with prostatic adenoma found that treatment for 7 days with nettle produced a significant drop in zinc level, thought to be a result of altering zinc-testosterone metabolism and diminishing zinc secretion in adenomatous tissue (Romics & Bach 1991).

ANTIVIRAL

A lectin extracted from nettle had inhibitory effects against HIV-1, HIV-2, human cytomegalovirus, respiratory syncytial virus and influenza A virus in vitro (Balzarini et al 1992).

ANTIOXIDANT

Nettle has shown potent antioxidant activity in a range of in-vitro tests (Gulcin et al 2004): 50, 100 and 250 μg inhibited peroxidation of linoleic acid by 39%, 66% and 98%, respectively, as compared to 30% inhibition demonstrated by 60 μg/mL of alpha-tocopherol.

In the same study, nettle was shown to scavenge free radicals, hydrogen peroxide and superoxide anion radicals and to chelate heavy metals. Ozen and Korkmaz (2003) reported that constituents from nettle can regulate glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase in vivo.

The fixed oil of nettle has demonstrated strong antioxidant activity in mice treated with carbon tetrachloride, by decreasing lipid peroxidation and increasing antioxidant status (Kanter et al 2003). Nettle extract is significantly effective in preventing fibrosis in liver tissue from carbon tetrachloride damage in vivo (Turkdogan et al 2003). Dried nettle added to the diet of rats decreased cerebral free radicals after forced-swim tests (Toldy et al 2005).

OTHER ACTIONS

Nettle has a mild diuretic action (ESCOP 2003).

CLINICAL USE

Different parts of the nettle herb have been used for different indications. Most evidence comes from traditional usage as nettle has not been significantly investigated under controlled conditions as a stand-alone treatment.

ARTHRITIC CONDITIONS

Traditionally, nettle herb and leaf have been used to treat painful joint diseases, and scientific investigation now shows there is a demonstrable benefit with its use.

One randomised, double-blind crossover study involving 27 patients with OA pain at the base of the thumb or index finger compared topical applications of stinging nettle leaf with placebo, used daily for 1 week. After a 5-week washout period, treatments were then reversed. Nettle application used for 1 week showed reduction in pain and disability and produced significantly superior results to placebo (Randall et al 2000). An open study of 17 patients reporting beneficial effects with the nettle sting of *U. dioica* showed that a transient urticarial rash can be associated with topical use (Randall et al 1999). It is suspected that a counterirritant effect is chiefly responsible.

In a multicentre study of 152 subjects with degenerative rheumatic conditions, 1.54 g dried nettle herb extract produced a subjective improvement in 70% of cases after 3 weeks (Ramm & Hansen 1995).

Four other studies using a nettle-leaf extract reported that most subjects rated the treatment as good or very good (ESCOP 2003).

Commission E approved as supportive therapy for rheumatic ailments when used internally or applied externally (Blumenthal et al 2000).

BENIGN PROSTATIC HYPERPLASIA

In practice, nettle root preparations are often prescribed in combination with other herbal medicines, such as saw palmetto or pygeum. Representative of clinical practice, most studies have investigated the effects of nettle in combination with other herbs and have generally yielded positive results.

Open studies involving a total of over 15 000 men with BPH have found significant improvements in prostate size, night-time urination, frequency of urination, urine flow and residual urine (ESCOP 1996–97). One double-blind study over 9 weeks of nettle extract in 50 men with BPH showed a significant decrease in sex hormone binding globulin and non-significant improvements in micturition volume and maximum urinary flow (Vontobel et al 1985); however, the authors explain that the results were due to inappropriate length and dosage of therapy. In another double-blind, placebo-controlled study, treatment of 67 men with nettle produced a 14% improvement in urine flow and a 53% decrease in residual urine (Dathe & Schmid 1987). An open study of 30 patients with BPH showed that nettle root extract over an average of 3.5 months significantly decreased residual urine volume and increased maximal urinary flow in 50% of cases (Romics 1987). Marked subjective relief was also reported.

Urtica* and *Pygeum In one study, 134 patients with BPH were randomly assigned an *Urtica* and *Pygeum* preparation (300 mg *U. dioica* root extract combined with 25 mg *P. africanum* bark extract) or a preparation containing half that dose under double-blind test conditions for 8 weeks. Both treatments significantly increased urine flow, and reduced residual urine and nocturia after 28 days, whereas after 56 days, further significant decreases were found in residual urine (half-dose group) and in nocturia (both groups) (Krzeski et al 1993).

Nettle and saw palmetto extract In 1995, an open, prospective, multicentre observational study involving 419 specialist urological practices investigated the efficacy and tolerability of a saw palmetto and nettle combination in 2080 patients with BPH (Schneider et al 1995). Herbal treatment was seen to improve pathological findings and obstructive and irritative symptoms. Both efficacy and tolerability were assessed by physicians as very good or good and most patients reported an improvement in general QOL and reduction in symptoms of BPH.

A randomised, multicenter, double-blind study involving 543 patients with early stage BPH found that a combination of nettle and saw palmetto extract was as effective as finasteride at increasing maximum urinary flow and improving International Prostate Symptom Scores (IPSS) after 24 weeks' treatment, which continued to improve by week 48 (Sokeland 2000). Improvement in QOL scores were similarly observed with both treatments, regardless of prostate size. Overall, the two treatments only differed in regard to adverse reaction incidence, with the herbal combination much better tolerated (Sokeland & Albrecht 1997). A 2003 review concluded that a combination of nettle and saw palmetto is safe and effective for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia, comparable to the alpha-blocker tamsulosin (Bondarenko et al 2003).

A randomised, placebo controlled, double-blind, multicentre trial in 2005 further demonstrated the effectiveness of saw palmetto fruit (160 mg) and nettle root (120 mg) for lower urinary tract symptoms due to prostate enlargement (Lopatkin et al 2005): 257 men aged 50 years or more were randomised to take either two capsules of the study medication (320 mg saw palmetto and 240 mg nettle root) daily or placebo for 24 weeks. Men on the treatment experienced a 35% reduction in symptoms, most notably intermittency, hesitancy, urgency and nocturia, compared to 24% for placebo. At the end of the 24-week period an open trial was conducted for an additional 24 weeks and all men were given the herbal medicine. Those previously taking placebo reported significant improvements when switched to the study medication.

Commission E approved the use of *Urtica* root for difficulty in urination in BPH stages 1 and 2 (Blumenthal et al 2000).

ALLERGIC RHINITIS

A double-blind randomised study showed that a freeze-dried preparation of nettles improved global assessments of allergic rhinitis after 1 week's therapy (Mittman 1990).

OTHER USES

Diarrhoea, dysentery and diseases of the colon, internal bleeding, chronic skin eruptions such as eczema, discharges and arthritic conditions.

DOSAGE RANGE

LEAF

- Dry extract: 0.6–2.1 g/day in divided doses; or
- Liquid extract (1:2): 2–6 mL/day.

ROOT

- Although Commission E recommend 4–6 g/day cut root for symptoms of BPH, doses up to 18 g/day have been used (www.phytotherapies.org June 2003).

TOXICITY

Insufficient reliable evidence is available.

ADVERSE REACTIONS

One report states that gastrointestinal discomfort, allergic reactions, urticaria, pruritus, oedema and decreased urine volume are possible (Ernst 2001).

Clinical studies in BPH with herbal combinations containing nettle have found only 0.72% to 3.7% experience mild adverse effects.

URTICARIA DUE TO STINGING NETTLE

A frequent cause of contact urticaria is skin exposure to the stinging nettle. The urticaria is accompanied by a stinging sensation lasting longer than 12 hours. Part of the immediate reaction to nettle stings is due to histamine introduced by the nettle (Oliver et al 1991). It has also been found that both hair and plant extracts of nettle contain high levels of leukotrienes B4 and C4, besides histamine, which add to the irritant effects (Czarnetzki et al 1990).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

DIURETIC MEDICINES
Potentiated effects are theoretically possible observe — patients taking this combination.

ANTIHYPERTENSIVE MEDICINES
Additive effects are theoretically possible observe — patients taking this combination.

FINASTERIDE
Additive effects are theoretically possible, although the interaction may be beneficial.

CONTRAINDICATIONS AND PRECAUTIONS
People with known sensitivities or allergies to stinging nettle should use this herb cautiously. If symptoms of BPH worsen, seek professional advice.

PREGNANCY USE
Use of nettle during pregnancy is contraindicated because of its effects on hormones (WHO 2003).

PRACTICE POINTS/PATIENT COUNSELLING
- Preliminary research has demonstrated anti-inflammatory, analgesic and antiviral activity for nettle.
- Several test tube studies have shown that it reduces prostate cell proliferation and slows the progression of prostate cancer in both an in vivo model and in vitro system.
- The aerial parts are most commonly used to relieve symptoms of arthritis, whereas the root is used for BPH symptom relief, and both uses are supported by clinical evidence.
- Application of nettle leaf for 1 week reduced pain and disability in arthritis under double-blind test conditions.
- One double-blind study found that nettle reduced symptoms of allergic rhinitis.
- Studies using nettle root in combination with saw palmetto or pygeum have shown positive results in BPH.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this herb do for me?
Nettle leaf appears to reduce pain in OA when applied topically for 1 week, whereas oral preparations of nettle root alone or in combination with saw palmetto or pygeum reduces symptoms of BPH. Internal preparations of the leaf reduce symptons in arthritis and may also reduce symptoms of allergic rhinitis.

When will it start to work?

Topical applications of the leaf in OA have been shown to work after 1 week, whereas benefits in BPH require at least 28 days' treatment.

Are there any safety issues?

Local application of nettle can be irritating and cause contact urticaria, but preparations taken internally seem generally well tolerated.

REFERENCES

Balzarini J et al. The mannose-specific plant lectins from Cymbidium hybrid and Epipactis helleborine and the (N-acetylglucosamine) n-specific plant lectin from Urtica dioica are potent and selective inhibitors of human immunodeficiency virus and cytomegalovirus replication in vitro. Antiviral Res 18.2 (1992): 191-207.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Bnouham M, Merhfour FZ, Ziyyat A, Mekhfi H, Aziz M, Legssyer A. Antihyperglycemic activity of the aqueous extract of Urtica dioica. Fitoterapia 74.7-8 (2003): 677-81.

Bondarenko B, Walther C, Funk P, Schlafke S, Engelmann U. Long-term efficacy and safety of PRO 160/120 (a combination of sabal and urtica extract) in patients with lower urinary tract symptoms (LUTS). Phytomedicine 10 (Suppl 4) (2003): 53-5.

Broer J, Behnke B. Immunosuppressant effect of IDS 30, a stinging nettle leaf extract, on myeloid dendritic cells in vitro. J Rheumatol 29.4 (2002): 659-66.

Czarnetzki BM, Thiele T, Rosenbach T. Immunoreactive leukotrienes in nettle plants (Urtica urens). Int Arch Allergy Appl Immunol 91.1 (1990): 43-6.

Dathe G, Schmid H. Phytotherapy of benign prostate hyperplasia (BPH); double-blind study with stinging nettle root extract (Extractum Radicis Urticae – ERU). Urologe B (1987) 27: 223-6 [translated from German].

Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.

European Scientific Cooperative on Phytotherapy (ESCOP). Urticae radix. Monographs on the Uses of Plant Drugs, Fascicule 2. Exeter, UK: ESCOP (1996-1997): 4-5.

European Scientific Cooperative on Phytotherapy (ESCOP). Urticae folium/herba, 2nd edn Exeter, UK: ESCOP (2003): 521-7.

Farzami B, Ahmadvand D, Vardasbi S, Majin FJ, Khaghani S. Induction of insulin secretion by a component of Urtica dioica leaf extract in perifused Islets of Langerhans and its in vivo effects in normal and streptozotocin diabetic rats. J Ethnopharmacol 89.1 (2003): 47-53.

Gulcin I, Kufrevioglu OI, Oktay M, Buyukokuroglu ME. Antioxidant, antimicrobial, antiulcer and analgesic activities of nettle (Urtica dioica L.). J Ethnopharmacol 90.2-3 (2004): 205-15.

Hirano T, Homma M, Oka K. Effects of stinging nettle root extracts and their steroidal components on the Na^{+},$K^{(+)}$-ATPase of the benign prostatic hyperplasia. Planta Med 60.1 (1994): 30-3.

Hryb DJ et al. The effect of extracts of the roots of the stinging nettle (Urtica dioica) on the interaction of SHBG with its receptor on human prostatic membranes. Planta Med 61.1 (1995): 31-2.

Kanter M et al. Effects of Nigella sativa L. and Urtica dioica L. on lipid peroxidation, antioxidant enzyme systems and some liver enzymes in CCl4-treated rats. J Vet Med A Physiol Pathol Clin Med 50.5 (2003): 264-8.

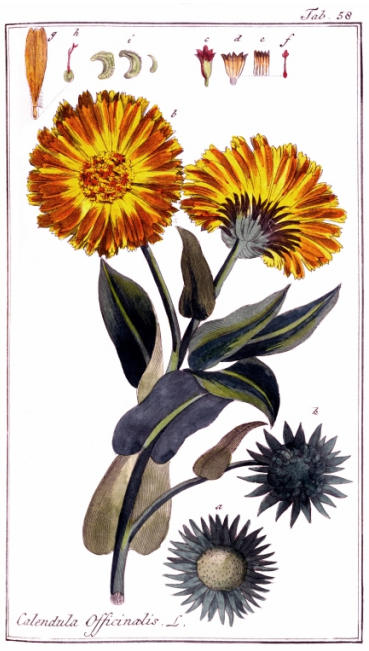
Konrad A, Mahler M, Arni S, Flogerzi B, Klingelhofer S, Seibold F. Ameliorative effect of IDS 30, a stinging nettle leaf extract, on chronic colitis. Int J Colorectal Dis 20.1 (2005): 9-17.

Konrad L et al. Antiproliferative effect on human prostate cancer cells by a stinging nettle root (Urtica dioica) extract. Planta Med 66.1 (2000): 44-7.

Krzeski T et al. Combined extracts of Urtica dioica and Pygeum africanum in the treatment of benign prostatic hyperplasia: double-blind comparison of two doses. Clin Ther 15.6 (1993): 1011-20.
Lichius JJ, Muth C. The inhibiting effects of Urtica dioica root extracts on experimentally induced prostatic hyperplasia in the mouse. Planta Med 63.4 (1997): 307-10.
Lichius JJ et al. Antiproliferative effect of a polysaccharide fraction of a 20% methanolic extract of stinging nettle roots upon epithelial cells of the human prostate (LNCaP). Pharmazie 54.10 (1999): 768-71.
Lopatkin N et al. Long term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms–a placebo controlled, double-blind, multicentre trial. World J Urol 23 (2005): 139-46.
Mittman P. Randomized, double-blind study of freeze-dried Urtica dioica in the treatment of allergic rhinitis. Planta Med 56.1 (1990): 44-7.
Obertreis B et al. Anti-inflammatory effect of Urtica dioica folia extract in comparison to caffeic malic acid. Arzneimittelforschung 46.1 (1996a): 52-6.
Obertreis B et al. Ex-vivo in-vitro inhibition of lipopolysaccharide stimulated tumor necrosis factor-alpha and interleukin-1 beta secretion in human whole blood by extractum urticae dioicae foliorum. Arzneimittelforschung 46.4 (1996b): 389-94.
Oliver F et al. Contact urticaria due to the common stinging nettle (Urtica dioica) – histological, ultrastructural and pharmacological studies. Clin Exp Dermatol 16.1 (1991): 1-7.
Ozen T, Korkmaz H. Modulatory effect of Urtica dioica L. (Urticaceae) leaf extract on biotransformation enzyme systems, antioxidant enzymes, lactate dehydrogenase and lipid peroxidation in mice. Phytomedicine 10.5 (2003): 405-15.
Randall C et al. Nettle sting of Urtica dioica for joint pain – an exploratory study of this complementary therapy. Complement Ther Med 7.3 (1999): 126-31.
Randall C et al. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. J R Soc Med 93.6 (2000): 305-9.
Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. FEBS Lett 442.1 (1999): 89-94.
Romics I. Observations with Bazoton in the management of prostatic hyperplasia. Int Urol Nephrol 19.3 (1987): 293-7.
Romics I, Bach D. Zn, Ca and Na levels in the prostatic secretion of patients with prostatic adenoma. Int Urol Nephrol 23.1 (1991): 45-9.
Schmidt K. Effect of radix urticae extract and its several secondary extracts on blood SHBG in benign prostate hyperplasia. Fortschr Med 101.15 (1983): 713-16.
Schneider HJ, Honold E, Masuhr T. Treatment of benign prostatic hyperplasia. Results of a treatment study with the phytogenic combination of Sabal extract WS 1473 and Urtica extract WS 1031 in urologic specialty practices. Fortschr Med 113.3 (1995): 37-40.
Sokeland J, Albrecht J. Combination of Sabal and Urtica extract vs. finasteride in benign prostatic hyperplasia (Aiken stages I to II). Comparison of therapeutic effectiveness in a one year double-blind study. Urologe A 36.4 (1997): 327-33.
Sokeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. BJU Int 86.4 (2000): 439-42.
Tahri A et al. Acute diuretic, natriuretic and hypotensive effects of a continuous perfusion of aqueous extract of Urtica dioica in the rat. J Ethnopharmacol 73.1-2 (2000): 95-100.
Testai L et al. Cardiovascular effects of Urtica dioica L. (Urticaceae) roots extracts: in vitro and in vivo pharmacological studies. J Ethnopharmacol 81.1 (2002): 105-9.
Teucher T et al. Cytokine secretion in whole blood of healthy subjects following oral administration of Urtica dioica L. plant extract. Arzneimittelforschung 46.9 (1996): 906-10.
Toldy A et al. The effect of exercise and nettle supplementation on oxidative stress markers in the rat brain. Brain Res Bull 65.6 (2005): 487-93.

Turkdogan MK, Ozbek H, Yener Z, Tuncer I, Uygan I, Ceylan E. The role of Urtica dioica and Nigella sativa in the prevention of carbon tetrachloride-induced hepatotoxicity in rats. Phytother Res 17.8 (2003): 942-6.
US Department of Agriculture. Phytochemical Database. Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003.
Vontobel HP et al. Results of a double-blind study on the effectiveness of ERU (extractum radicis Urticae) capsules in conservative treatment of benign prostatic hyperplasia. Urologe A 24.1 (1985): 49-51.
World Health Organization, Department of Essential Drugs and Medicines (EDM). Essential Drugs and Medicines Policy. Geneva. WHO: 2003.

Tea tree oil



Historical note The Bundjalong Australian Aboriginal people of northern New South Wales knew of the medicinal qualities of the leaves of this plant for many centuries and used it to treat burns, cuts and insect bites. It was not until the 1700s that it became known in the Western world as 'tea tree' because Captain Cook found its aromatic leaves an enjoyable substitute for real tea. The first official report of its medicinal use appeared in the *Medical Journal of Australia* in 1930 when a Sydney surgeon wrote of its impressive wound healing and antiseptic qualities (Murray 1995). In modern times, tea tree oil has become widely accepted as a standard treatment for wounds and minor skin infections.

COMMON NAME
Tea tree

OTHER NAMES
Australian tea tree oil, melaleuca, melasol, narrow-leaved paperbark, paperbark tree oil, punk tree, ti tree oil

BOTANICAL NAME/FAMILY
Melaleuca alternifolia (family Myrtaceae)

PLANT PARTS USED
Essential oil from leaves and branches

CHEMICAL COMPONENTS
Tea tree oil contains many active constituents, including cineole, alpha cadinine, terpinenes, pinenes, alpha terpineol, aromadendrene, terpinenols and terpinolene (Duke 2003).

MAIN ACTIONS

ANTIFUNGAL AND ANTIBACTERIAL
The in vitro evidence of antifungal and antibacterial activity is overwhelming. In vitro results find that tea tree oil has activity against a range of yeasts and fungi found in common mucosal and skin infections such as *Corynebacterium* spp., *Klebsiella pneumoniae*, *Micrococcus* spp. (*M. luteus*, *M. varians*), *Propionibacterium acnes*, *Streptococcus pyogenes*, *Trichomonas vaginalis*, *Pseudomonas aeruginosa*, *A. baumannii*, *Staphylococcus* spp. (*S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*,

S. hominis, *S. marcescens*, *S. saprophyticus*, *S. warneri*, and *S. xylosus*) and *Candida* spp. (Bagg et al 2006, Carson et al 2006, Concha et al 1998, De Mondello et al 2003, Hada et al 2001, Hammer et al 1996, 1998, Messager et al 2005, Murray 1995, Papadopoulos et al 2006).

Tea tree oil disrupts the permeability barrier of cell membrane structures of microorganisms and denatures proteins (Carson et al 2002, Cox et al 2000, Gustafson et al 1998). This activity is similar to disinfectants such as chlorhexidine and quaternary ammonium compounds.

ANTIVIRAL

An in vitro study has identified activity against HSV types 1 and 2 (Schnitzler et al 2001).

HEAD LICE ERADICATION

Topical application of tea tree oil was extremely effective against head lice, with 93% of lice and 83% of eggs destroyed, in test tube studies (Veal 1996). Phenols, phenolic ethers, ketones and oxides appear to be the major toxic components responsible for this activity.

DERMATITIS

Tea tree oil may be an effective treatment for dermatitis in dogs. Tea tree oil cream (10%) was applied twice daily for 4 weeks to 53 dogs suffering from chronic dermatitis, allergic dermatitis, interdigital pyoderma, acral lick dermatitis and skinfold pyoderma (Fitzi et al 2002). At the end of the trial 82% of the animals had a good or very good response to treatment with most symptoms disappearing, although two dogs experienced local irritation. Another trial by the same research team again evaluated the tea tree cream and blinded the study with a commercial skin care cream (Reichling et al 2004). Fifty-seven dogs were involved in this study and again the results were similar, with drastically reduced dermatitis in 71% of animals as compared to 41% using the control cream. A local reaction was reported in one dog.

CLINICAL USE

Tea tree oil preparations have been investigated in a number of clinical studies, either as the oil itself or as an ingredient of gels, creams or ointments.

ACNE VULGARIS

A single-blind, randomised clinical trial involving 124 patients with mild to moderate acne showed that a 5% tea tree oil gel significantly improved the condition and reduced the number of acne lesions. These effects were similar to 5% benzoyl

peroxide lotion, but tea tree oil gel was better tolerated and produced fewer side-effects (Bassett et al 1990).

TINEA PEDIS

Under double-blind, randomised test conditions 104 subjects with tinea pedis (athlete's foot) used 10% w/w tea tree oil cream or 1% tolnaftate or placebo creams as treatment (Tong et al 1992). In this study, significantly more tolnaftate-treated patients (85%) than tea tree oil (30%) and placebo-treated (21%) patients showed conversion to negative culture at the end of therapy. However, tea tree oil cream reduced symptoms as effectively as tolnaftate 1%. A more recent randomised, double-blinded, controlled study by the same group used a higher concentration of tea tree oil (25% and 50%) for the treatment of interdigital tinea pedis in 158 patients over 4 weeks (Satchell et al 2002a). In the 50% tea tree oil group 68% of patients had a significant response and 64% achieved negative mycology. In the 25% tea tree group, 72% of patients responded and 50% were cured. The placebo responder rates were 39% and 31% respectively, with 3% of patients using tea tree developing dermatitis.

TOENAIL INFECTION (ONYCHOMYCOSIS)

A randomised, double-blind multicentre study involving 177 volunteers found that 6 months' treatment with 1% clotrimazole solution (applied twice daily) or 100% tea tree oil (applied twice daily) produced similar results, improving nail appearance and associated symptoms (Buck et al 1994). Additionally, 3 months after either treatment ceased, continued improvement or complete resolution was observed in approximately half of participants.

One randomised, double-blind placebo-controlled study investigated the effects of a combined tea tree oil (5%) and butenafine hydrochloride (2%) cream in chronic toenail onychomycosis and found that after 6 weeks, 80% of patients achieved a cure compared with none using placebo cream (Syed et al 1999).

MRSA INFECTION

A combination of 4% tea tree oil nasal ointment and 5% tea tree oil body wash was found to be superior to the standard 2% mupirocin nasal ointment and triclosan body wash used for the eradication of methicillin-resistant *Staphylococcus aureus* (Caelli et al 2000). A recent review concluded that tea tree oil was not statistically superior to the standard treatment mupirocin for MSRA (Flaxman & Griffiths 2005). The paper reported on two RCTs ($n = 30$, $n = 224$), both of which demonstrated that tea tree oil was as effective as mupirocin. In the larger trial 224 patients were given either mupirocin 2% nasal ointment, chlorhexidine gluconate 4% soap and silver

sulfadiazine 1% cream or tea tree 10% cream and tea tree 5% body wash for five days (Dryden et al 2004). Rates of MRSA clearance were similar: 41% in the tea tree group and 49% using standard treatment. Mupirocin was significantly more effective at clearing nasal carriage (78%) than tea tree cream (47%); however, tea tree treatment was more effective than both chlorhexidine and silver sulfadiazine at clearing superficial skin sites and skin lesions. Although encouraging, more large clinical trials are needed to examine the efficacy of tea tree against MRSA.

VAGINITIS AND CERVICITIS

Clinical data support the use of tea tree oil for vaginitis and cervicitis caused by *Trichomonas vaginalis* or *Candida albicans* (WHO 2003). An open study found that intravaginal application of tampons saturated in a diluted emulsified solution successfully healed vaginitis and cervicitis ($n = 130$) caused by *T. vaginalis*. Vaginal pessaries containing 0.2 g essential oil inserted nightly eradicated symptoms of leucorrhoea and burning in 86% of women with *C. albicans* vaginitis after 30 days in with 75% becoming free of infection.

A case report shows that a 5-day course of 200 mg tea tree oil in a vegetable oil base inserted into the vagina may also be successful at treating vaginal candidiasis (Blackwell 1991). As used here, tea tree oil treatment eradicated anaerobic bacterial vaginosis, confirmed upon examination 1 month later.

CYSTITIS

A randomised, double-blind study investigated the effects of tea tree oil, administered as 8 mg essential oil (taken three times daily) in an enteric-coated capsule, in 26 women with chronic idiopathic colibacillary cystitis (Belaiche 1988). After the 6-month test period, 54% of women receiving active treatment were symptom free compared with only 15% receiving placebo. Although symptom free, 50% of women in the tea tree group still showed evidence of infection.

GINGIVITIS

Tea tree oil was as effective as chlorhexidine against *Streptococcus mutans*, the bacteria that causes gingivitis, in a controlled study of 30 individuals (Groppo et al 2002). A more recent double-blind, randomised, longitudinal, study evaluated and compared the effects of tea tree oil gel (2.5%) and chlorhexidine gel (0.2%) in 49 patients with severe chronic gingivitis (Soukoulis & Hirsch 2004). Subjects brushed with the tea tree, chlorhexidine or placebo gel twice daily for a period of 8 weeks. Tea tree oil significantly reduced the papillary bleeding index and gingival index, but did not reduce plaque.

DANDRUFF

Tea tree oil is effective for the treatment of dandruff. A randomised, single-blind, parallel-group study investigated the efficacy of tea tree oil shampoo (5%) and placebo in 126 patients with mild to moderate dandruff over 4 weeks (Satchell et al 2002b). The tea tree oil group achieved a 41% improvement as compared to 11% in the placebo group with no adverse effects.

OTHER USES

COLD SORES

Since tea tree oil exhibits antiviral activity in vitro, tea tree oil preparations have been used in the treatment of herpes simplex. Clinical trials investigating tea tree oil for this indication are not available, so it is unknown whether effects are clinically significant.

HEAD LICE

Based on successful test tube results, preparations containing tea tree oil are used to eradicate head lice (Veal 1996).

DOSAGE RANGE

Tea tree oil is used in a variety of forms, such as gels, creams, ointments, oral rinses, soaps, shampoos and paints. Minimum bactericidal concentrations are generally 0.25%.

- Onychomycosis: 100% essential oil applied twice daily.
- Tinea pedis: 10% essential oil in cream base applied twice daily.
- Acne: 5% essential oil in cream or gel base applied daily.
- Vaginitis (*Candida albicans* or *Trichomonas vaginalis*): intravaginally applied tampons saturated in a 1% emulsified solution, vaginal pessaries containing 0.2 g essential oil.
- Cervicitis (*Candida albicans* or *Trichomonas vaginalis*): intravaginally applied tampons saturated in a 20% emulsified solution.

TOXICITY

Tea tree oil should not be ingested. Accidental ingestion has resulted in confusion, disorientation, general malaise and coma, according to case reports (WHO 2003).

One case has been reported of an infant ingesting less than 10 mL of 100% oil, which resulted in confusion and an inability to walk within 30 minutes, followed by a full recovery within 5 hours (Jacobs & Hornfeldt 1994).

ADVERSE REACTIONS

Contact dermatitis is possible in sensitive individuals (Hammer et al 2006).

SIGNIFICANT INTERACTIONS
None known.

CONTRAINDICATIONS AND PRECAUTIONS
Caution should be exercised if applying the oil to eczematous or inflamed skin as it may cause irritation. It is suggested that a small amount be first applied to a test patch, to determine whether irritation will occur, as contact dermatitis has been reported.

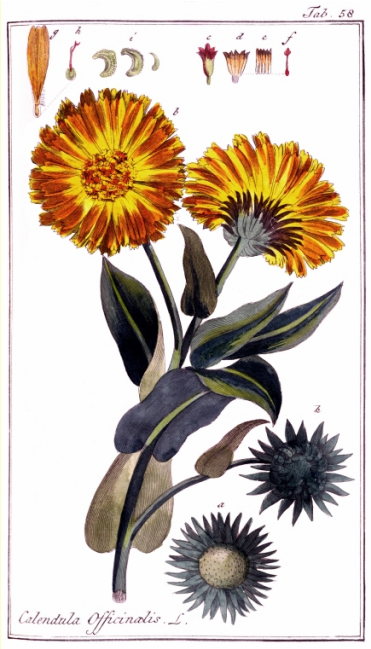
PREGNANCY USE
Insufficient reliable information is available to determine safety.

PRACTICE POINTS/PATIENT COUNSELLING
- 100% tea tree oil is a safe and effective alternative to clotrimazole for the treatment of toenail onychomycosis.
- Extensive in vitro testing has found significant activity against a wide range of bacterial and fungal microorganisms, such as common skin pathogens.
- 5% tea tree oil gel has been shown to significantly improve acne vulgaris, with effects similar to 5% benzoyl peroxide lotion.
- Clinical evidence supports the use of tea tree oil preparations in *Candida albicans* or *Trichomonas vaginalis* vaginitis and cervicitis, cystitis and MRSA infection. It may also be useful in herpes simplex and head lice, but clinical data are unavailable.
- Tea tree oil should not be ingested other than in capsule form under professional supervision and a test patch is advised before widespread topical application.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will tea tree oil do for me?
Tea tree oil is an antiseptic substance that is effective against a wide range of common bacterial and fungal organisms. Scientific evidence shows that it is an effective treatment for acne, fungal infections of the toenails, *Candida albicans* or *Trichomonas vaginalis* vaginitis and cervicitis, cystitis and MRSA infection. It is also used to treat cold sores and head lice.

When will it start to work?
This will depend on the indication it is being used to treat. In some cases, clinical tests are not available, so it is uncertain when, if any, effects are seen.

Are there any safety issues?
Tea tree oil should not be ingested orally and used with caution on inflamed and sensitive skin.



REFERENCES

Bagg J et al. Susceptibility to Melaleuca alternifolia (tea tree) oil of yeasts isolated from the mouths of patients with advanced cancer. Oral Oncol 42.5 (2006): 487-92.

Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Med J Aust 153.8 (1990): 455-8.

Belaiche P. Letter to the editor. Phytotherapy Res 2 (1988): 157.

Blackwell AL. Tea tree oil and anaerobic (bacterial) vaginosis. Lancet 337.8736 (1991): 300.

Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole. J Fam Pract 38.6 (1994): 601-5.

Caelli M et al. Tea tree oil as an alternative topical decolonization agent for methicillin-resistant Staphylococcus aureus. J Hosp Infect 46.3 (2000): 236-7.

Carson CF, Mee BJ, Riley TV. Mechanism of action of Melaleuca alternifolia (tea tree) oil on Staphylococcus aureus determined by time-kill, lysis, leakage, and salt tolerance assays and electron microscopy. Antimicrob Agents Chemother 46.6 (2002): 1914-20.

Carson CF, Hammer KA, Riley TV. Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev 19.1 (2006): 50-62.

Concha JM, Moore LS, Holloway WJ. 1998 William J. Stickel Bronze Award: Antifungal activity of Melaleuca alternifolia (tea-tree) oil against various pathogenic organisms. J Am Podiatr Med Assoc 88.10 (1998): 489-92.

Cox SD et al. The mode of antimicrobial action of the essential oil of Melaleuca alternifolia (tea tree oil). J Appl Microbiol 88.1 (2000): 170-5.

De Mondello F et al. In vitro and in vivo activity of tea tree oil against azole-susceptible and -resistant human pathogenic yeasts. J Antimicrob Chemother 51.5 (2003): 1223-9.

Dryden MS, Dailly S, Crouch M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. J Hosp Infect 56.4 (2004): 283-6.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003. www.ars-grin.gov/duke.

Fitzi J et al. Phytotherapy of chronic dermatitis and pruritus of dogs with a topical preparation containing tea tree oil (Bogaskin). Schweiz Arch Tierheilkd 144.5 (2002): 223-31.

Flaxman D, Griffiths P. Is tea tree oil effective at eradicating MRSA colonization? A review. Br J Community Nurs 10.3 (2005): 123-6.

Groppo FC et al. Antimicrobial activity of garlic, tea tree oil, and chlorhexidine against oral microorganisms. Int Dent J 52.6 (2002): 433-7.

Gustafson JE et al. Effects of tea tree oil on Escherichia coli. Lett Appl Microbiol 26.3 (1998): 194-8.

Hada T et al. Comparison of the effects in vitro of tea tree oil and plaunotol on methicillin-susceptible and methicillin-resistant strains of Staphylococcus aureus. Microbios 106 (Suppl 2) (2001): 133-41.

Hammer KA, Carson CF, Riley TV. In-vitro activity of essential oils, in particular Melaleuca alternifolia (tea tree) oil and tea tree oil products, against Candida spp. J Antimicrob Chemother 42.5 (1998): 591-5.

Hammer KA et al. A review of the toxicity of Melaleuca alternifolia (tea tree) oil. Food Chem Toxicol 44.5 (2006): 616-25.

Hammer KA et al. Susceptibility of transient and commensal skin flora to the essential oil of Melaleuca alternifolia (tea tree oil). Am J Infect Control 24.3 (1996): 186-9.

Jacobs MR, Hornfeldt CS. Melaleuca oil poisoning. J Toxicol Clin Toxicol 32.4 (1994): 461-4.

Messager S et al. Assessment of the antibacterial activity of tea tree oil using the European EN 1276 and EN 12054 standard suspension tests. J Hosp Infect 59.2 (2005): 113-25.

Murray M. The Healing Power of Herbs. Rocklin, CA: Prima Health, 1995.

Papadopoulos CJ et al. Susceptibility of pseudomonads to Melaleuca alternifolia (tea tree) oil and components. J Antimicrob Chemother 58.2 (2006): 449-51.

Reichling J et al. Topical tea tree oil effective in canine localised pruritic dermatitis: a multi-centre randomised double-blind controlled clinical trial in the veterinary practice. Dtsch Tierarztl Wochenschr 111.10 (2004): 408-14.
Satchell AC et al. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. Aust J Dermatol 43.3 (2002a): 175-8.
Satchell AC et al. Treatment of dandruff with 5% tea tree oil shampoo. J Am Acad Dermatol 47.6 (2002b): 852-5.
Schnitzler P, Schon K, Reichling J. Antiviral activity of Australian tea tree oil and eucalyptus oil against herpes simplex virus in cell culture. Pharmazie 56.4 (2001): 343-7.
Soukoulis S, Hirsch R. The effects of a tea tree oil-containing gel on plaque and chronic gingivitis. Aust Dent J 49.2 (2004): 78-83.
Syed TA et al. Treatment of toenail onychomycosis with 2% butenafine and 5% Melaleuca alternifolia (tea tree) oil in cream. Trop Med Int Health 4.4 (1999): 284-7.
Tong MM, Altman PM, Barnetson RS. Tea tree oil in the treatment of tinea pedis. Aust J Dermatol 33.3 (1992): 145-9.
Veal L. The potential effectiveness of essential oils as a treatment for headlice, Pediculus humanus capitis. Complement Ther Nurs Midwifery 2.4 (1996): 97-101.
World Health Organization, Department of Essential Drugs and Medicines Policy (EDM). Essential drugs and medicines policy: Herba Thymi. Geneva: WHO, 2003: 259-66.

Thyme

Historical note Although thyme has been used as a cooking spice for centuries in Europe, it is also used medicinally to treat common infections, coughs, bronchitis and asthma. The 17th century herbalist Nicholas Culpeper recommended thyme for whooping cough, gout, stomach pains and shortness of breath. It was also used in perfumes and embalming oils. In medieval times the plant was seen as imparting courage and vigour (Blumenthal et al 2000).

COMMON NAME
Thyme

OTHER NAMES
Common thyme, garden thyme, farigola, folia thymi, gartenthymian, herba thymi, almindelig timian, thym, thymian, thymianblätter, timo

BOTANICAL NAME/FAMILY
Thymus vulgaris (family Lamiaceae or Labiatae)

PLANT PARTS USED
Leaves and flowering tops

CHEMICAL COMPONENTS
The primary constituents are the volatile oils (1–2.5%), which include phenols (0.5%), namely thymol (30–70%), eugenol, and carvacrol (3–15%), also flavonoids, apigenin, luteolin and saponins and tannins. Rosmarinic acid, caffeic acid and calcium are also found in significant quantities (Duke 2003). The herb also contains bitter principles and salicylates.

MAIN ACTIONS
Although thyme has not been significantly investigated in human studies, there has been some investigation into the activity of thymol and the volatile oil component of the herb. It is not known whether results obtained for these constituents are representative for the crude herb, but they provide some further understanding. Both the essential oil and thymol are ingredients in many proprietary products.

ANTITUSSIVE AND ANTISPASMODIC EFFECTS
These actions have been attributed to the phenolic compounds in thyme (WHO 2003). Antispasmodic effects on trachea and guinea pig ileum have been demon-

strated for these constituents. The saponin content is believed to have expectorant activity, as demonstrated in animal studies.

ANTIMICROBIAL

In vitro tests have demonstrated activity against *Escherichia coli*, *Listeria monocytogenes* and *Salmonella enterica* for thyme extract (Friedman et al 2002). A review of the antibacterial and antifungal properties of the essential oil of thyme in vitro has demonstrated effectiveness against a wide range of pathogens including *Clostridium botulinum*, *E. coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Staphylococcus aureus* and *Candida albicans* (Kalemba & Kunicka 2003). Effects are most likely due to the eugenol, thymol and carvacrol constituents. Aqueous thyme extract also exhibited a significant inhibitory effect on *Helicobacter pylori*, reducing both its growth and its potent urease activity in vitro (Tabak et al 1996).

Thymol and eugenol have demonstrated antifungal activity by establishing the ability to alter the cell wall and membrane of the yeast *Saccharomyces cervisiae* (Bennis et al 2004).

ANTIOXIDANT

Eugenol, carvacrol, thymol and 4-allylphenol (5 μg/mL) all inhibited the oxidation of hexanal for a period of 30 days, demonstrating potent antioxidant activity comparable to alpha-tocopherol (Lee et al 2005).

ASTRINGENT

The tannin content of the herb is chiefly responsible for its astringent activity.

ANTHELMINTIC

Thymol possesses anthelmintic activity, demonstrated in vitro (Newell et al 1996).

OTHER ACTIONS

Anti-inflammatory due to thymol and carvacrol.

CLINICAL USE

Thyme has not been significantly investigated in controlled studies, therefore information is generally derived from evidence of activity and traditional use and the clinical significance is unknown.

RESPIRATORY TRACT INFECTIONS

Thyme extract has been used to treat the common cold, bronchitis, laryngitis and tonsillitis. It is orally ingested or used in a gargle for local activity, based on the herb's suspected antimicrobial and antitussive activities.

Bronchitis Encouraging data have been reported for chronic bronchitis treated by thyme in combination with other herbs in large ($n > 3000$) comparative clinical trials, although no data are available for thyme as a stand-alone treatment (Ernst et al 1997).

Thyme is approved by Commission E in the treatment of bronchitis, whooping cough and upper respiratory tract catarrh (Blumenthal et al 2000).

DIARRHOEA

The astringent activity of thyme provides a theoretical basis for its application in this condition.

GASTRITIS AND DYSPEPSIA

The bitter principles present in the herb and its antispasmodic activity provide a theoretical basis for its use in these conditions.

SKIN DISINFECTION (TOPICAL USE)

Thyme extract has been used topically for infection control in minor wounds. The herb's antimicrobial and astringent activity provides a theoretical basis for this use.

OTHER USES

Traditionally, it has been used to aid in labour and delivery, promote menstruation and topically for warts and inflamed swellings (Fisher & Painter 1996). It has also been used to treat enuresis in children.

DOSAGE RANGE

INTERNAL USE

- Fluid extract (1:1): 1–2 mL up to three times daily.
- Fluid extract (1:2): 15–40 mL/week.
- Tincture (1:5): 2–6 mL three times daily.
- Infusion of dried herb: 1–4 g three times daily.

EXTERNAL USE

- 5% infusion used as a compress.

ADVERSE REACTIONS

The volatile oil is considered an irritant topically and can cause nausea and vomiting, headache, dizziness, convulsions, cardiac or respiratory arrest if taken internally (Newell et al 1996). As such, the crude herb is considered far safer.

Contact dermatitis reactions have been reported with topical use (Lorenzi et al 1995).

SIGNIFICANT INTERACTIONS

Thyme may induce enzymes in phase one and two detoxification in the liver (Sasaki et al 2005). The clinical significance of this is unknown.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people who are allergic to the Labiatae family of plants. Other cautions are gastritis, enterocolitis and congestive heart failure (Ernst et al 2001).

PREGNANCY USE

Essential oil not recommended in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Although thyme is used as a cooking spice, it is also used medicinally to treat common upper respiratory tract infections, coughs, bronchitis and asthma, dyspepsia and diarrhoea.
- Thyme extract is used as a gargle for pharyngitis or applied topically (5% dilution) as a compress to wounds due to its antimicrobial and astringent activities.
- Thyme has not been significantly investigated in controlled trials, so much information is based on traditional use or evidence of activity.
- Thyme has antispasmodic, antimicrobial, antitussive, astringent and anthelmintic activities as demonstrated in vitro or in animal studies.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

When taken internally, thyme is used to treat bronchitis, symptoms of the common cold, diarrhoea and dyspepsia. It is also used as an antiseptic gargle for sore throats and can be diluted and applied externally to minor wounds.

When will it start to work?

The lack of human studies for this herb make it difficult to determine when effects will start to occur.

Are there any safety issues?

Thyme should not be used by people allergic to the Labiatae family of plants or in pregnancy, and used cautiously in gastritis, enterocolitis and congestive heart failure.

REFERENCES

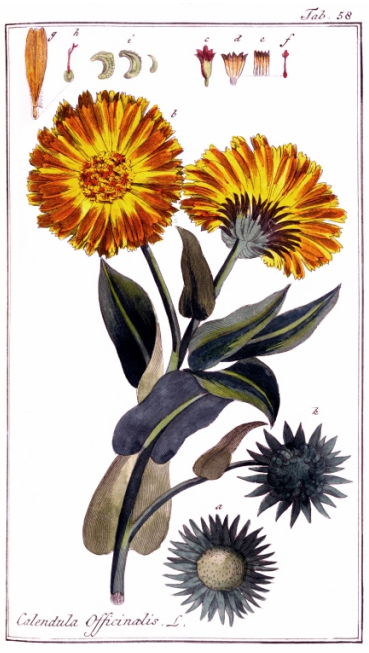
Bennis S et al. Surface alteration of Saccharomyces cerevisiae induced by thymol and eugenol. Lett Appl Microbiol 38.6 (2004): 454-8.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Duke JA. Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. www.ars-grin.gov/duke (accessed 09-06-2003).

Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.
Ernst E et al. Acute bronchitis: effectiveness of Sinupret. Comparative study with common expectorants in 3,187 patients. Fortschr Med 115.11 (1997): 52-3.
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.
Friedman M, Henika PR, Mandrell RE. Bactericidal activities of plant essential oils and some of their isolated constituents against Campylobacter jejuni, Escherichia coli, Listeria monocytogenes, and Salmonella enterica. J Food Prot 65.10 (2002): 1545-60.
Kalemba D, Kunicka A. Antibacterial and antifungal properties of essential oils. Curr Med Chem 10.10 (2003): 813-29.
Lee S et al. Identification of volatile components in basil (Ocimum basilicum L.) and thyme leaves (Thymus vulgaris L.) and their antioxidant properties. Food Chem 91 (2005): 131-7.
Lorenzi S et al. Allergic contact dermatitis due to thymol. Contact Dermatitis 33.6 (1995): 439-40.
Newell CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London: The Pharmaceutical Press, 1996.
Sasaki K et al. Thyme (Thymus vulgaris L.) leaves and its constituents increase the activities of xenobiotic-metabolizing enzymes in mouse liver. J Med Food 8.2 (2005): 184-9.
Tabak M et al. In vitro inhibition of Helicobacter pylori by extracts of thyme. J Appl Bacteriol 80.6 (1996): 667-72.
World Health Organization Department of Essential Drugs and Medicines Policy (EDM). Essential drugs and medicines policy: Herba Thymi. Geneva: WHO, 2003; 259-66.

Tribulus



Historical note Widely distributed in the Mediterranean region, Middle East and southern Africa, tribulus is an important plant used in traditional Ayurvedic, Arabic and Chinese medicine. Different parts of the tribulus plant are used to treat a variety of conditions, such as cough, colicky spasms, diarrhoea, cardiovascular disease, various kidney disorders, including kidney stones, and as an insect repellent.

COMMON NAME
Tribulus

OTHER NAMES
Al-gutub, cats-head, devil's-thorn, devil's-weed, goathead, puncture vine, qutiba

BOTANICAL NAME/FAMILY
Tribulus terrestris (family Zygophyllaceae)

PLANT PARTS USED
Leaf

CHEMICAL COMPONENTS
Different parts of the plant contain different constituents in varying ratios. Overall, the steroidal saponin content is considered the most important and includes constituents such as protodioscin, diosgenin, yamogenin, epismilagenin, tigogenin, neotigogenin, gitogenin and neogitogenin (Miles et al 1994). Two additional steroidal saponins, terrestrinins A (1) and B (2), have recently been isolated in 80% ethanol from the fruit (Huang et al 2003). The significance of this has not yet been determined. Beta-sitosterol, vitamin C, potassium and calcium are also found in the herb (Li et al 1998). Two major alkaloids have been identified: harmane and norharmane (Bourke et al 1992).

Of the steroidal saponins, protodioscin is considered the chief constituent responsible for the plant's effects on libido and sexual functioning. Preliminary observations suggest that *Tribulus terrestris* grown in different soils does not consistently produce this constituent and considerable variations have been identified in commercial products (Ganzera et al 2001).

Steroidal saponins consist of a furostanol- or spirostanol-based aglycone and an oligosaccharide attached to a steroid nucleus. Steroidal saponins are very common in

the plant kingdom and are natural components in many foods, such as asparagus, garlic and oats.

MAIN ACTIONS

Tribulus has not undergone significant clinical investigation; therefore, evidence of activity primarily derives from animal and in vitro studies. Additionally, some studies have investigated the pharmacological effects of the isolated saponin content.

INCREASES LIBIDO AND ENHANCES SEXUAL FUNCTION

The exact mechanism by which tribulus influences sexual behaviour is not known, but increasing androgenic status and NO release appear to be chiefly responsible (Gauthaman et al 2002). More specifically, some reports have suggested increases in dehydroepiandrosterone (DHEA) and testosterone are possible (Adimoelja 2000, Gauthaman et al 2002).

The constituent protodioscin is considered the most important in this regard and is converted to DHEA. Additionally, ex vivo tests have observed pro-erectile effects with protodioscin due to increased release of NO from the endothelium and nitronergic nerve endings (Adaikan et al 2000).

DIURETIC

A large oral dose of 5 g/kg tribulus was shown to have greater diuretic activity than frusemide 120 mg/kg in a recent animal study (Al Ali et al 2003).

KIDNEY STONE PREVENTION

With regard to kidney stones, tribulus has been found to decrease the amount of urinary oxalate in rats (Sangeeta et al 1994) and produce significant dose-dependent protection against experimentally induced uroliths in animal studies (Anand et al 1994, Sangeeta et al 1994). A recent in vitro study using human urine suggests that the diuretic properties of tribulus may be the most crucial mechanism for preventing urinary stone formation (Joshi et al 2005).

OTHER ACTIONS

A Chinese report of successful treatment of angina pectoris with the saponin content of tribulus suggests that the preparation dilates coronary arteries and improves coronary circulation (Wang et al 1990).

In another study 10 mg/kg/day of the aqueous extract of the fruit has shown antihypertensive effects in an animal trial when compared to control. The authors concluded that effects are possibly due to inhibition of ACE activity (Sharifi et al 2003).

Experiments with healthy mice have found *Tribulus terrestris* significantly inhibits gluconeogenesis and influences glycometabolism and reduces triglyceride and total cholesterol levels (Li et al 2001).

A dose-dependent antispasmodic activity causing a significant decrease in peristaltic movements has been demonstrated with the isolated saponin content of tribulus (Arcasoy et al 1998).

More recently, an in vitro test has also identified COX-2 inhibition activity (Hong et al 2002), suggesting possible anti-inflammatory actions.

Two isolated constituents tribulosin and beta-sitosterol-d-glucoside have shown anthelmintic activity in vitro against *Caenorhabditis elegans* (Deepak et al 2002).

Of eight steroid saponins tested, two showed potent antifungal activity against *Candida albicans*, with one, TTS-12, demonstrating its ability to decrease virulence and destroy the cell membrane (Zhang et al 2005).

CLINICAL USE

APHRODISIAC

The observed pharmacological effects on androgen status provide a theoretical basis for this activity, but little clinical testing has been conducted.

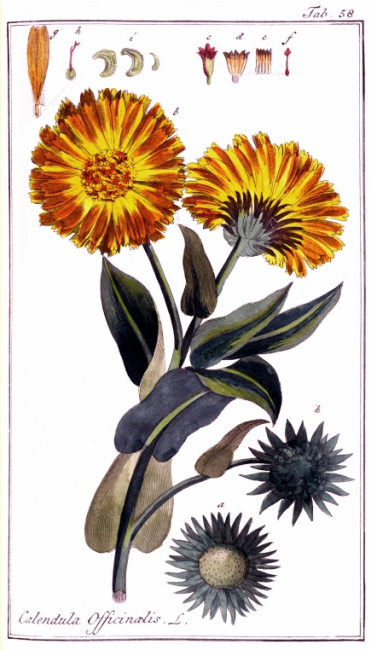
Results from a 2002 animal study have produced positive results suggestive of aphrodisiac activity (Gauthaman et al 2002). The study compared the effects of subcutaneous testosterone, an orally administered tribulus extract containing protodioscin (45% dry weight) or placebo over 8 weeks in castrated rodents. Both testosterone and tribulus treatment significantly improved sexual behaviour compared with controls, although testosterone was the more effective treatment.

A follow-up study by the same research team added further data (Gauthaman et al 2003). In this study rats were treated with 2.5, 5 and 10 mg/kg once daily for 8 weeks. The results showed a considerable increase in sexual behaviour and slight weight gain compared to controls. Interestingly, the results were more pronounced at the lower dose range.

Despite positive data from animal studies, a recent small controlled clinical trial of tribulus in young men aged between 20 and 36 years showed no statistical increase in testosterone levels in the treated group (Neychev & Mitev 2005). Men were divided into two treatment groups (each $n = 7$) and one control group ($n = 7$). One group was given 10 mg/kg and the other 20 mg/kg per day divided into three even doses for 4 weeks. There was no significant change in testosterone, androstenedione or luteinising hormone.

ERGOGENIC AID

Tribulus has been used as an ergogenic aid to improve physical performance in athletes. Once again, the observed pharmacological effects on androgen status provide a theoretical basis for this activity. A small, randomised, placebo-controlled study found that treatment with tribulus (3.21 mg/kg body weight daily) had no effects on body composition and exercise performance in resistance-trained men after 8 weeks (Antonio et al 2000). The study has been criticised by some athletes, as the dose of tribulus tested was very low and not indicative of the doses used in real life.



OTHER USES

Traditionally, the acidic fruits are thought to be cooling and are used for painful micturition, urinary disorders, kidney stone prevention and impotence, whereas the leaves are thought to possess tonic, diuretic and anti-inflammatory properties and are used to increase menstrual flow. Interestingly, preliminary research into the pharmacological actions of tribulus or its constituents provides some support for several of these uses.

DOSAGE RANGE

In Australia, preparations containing both the fruit and the root are available that are standardised to saponin content. As no clinical studies are available, the manufacturers' recommended dose is included here, which is 2–30 g/day.

- Leaf: 750–1500 mg/day of extract standardised to contain 45% protodioscin.

TOXICITY

Although toxicity levels in humans are not known, extensive grazing on tribulus by sheep produces a syndrome known as 'staggers', which is characterised by nervous and muscular locomotor disturbances (Bourke 1984). Outbreaks are repeatedly associated with drought periods during which sheep graze on large areas of *Tribulus terrestris* for many months at a time (Bourke 1995, Glastonbury et al 1984). Investigation with isolated harmane and norharmane found naturally in tribulus have found these constituents to be responsible for the 'staggers' syndrome (Bourke et al 1992).

Hepatogenous photosensitivity has also been reported among sheep grazing on *Tribulus terrestris* for long periods (Bourke 1984, Glastonbury et al 1984, McDonough et al 1994, Miles et al 1994, Tapia et al 1994, Wilkins et al 1996). A small animal study examined the clinical, laboratory and pathological findings of this disease in sheep and concluded that tribulus was responsible for hepatogenous photosensitivity (Aslani et al 2003). Laboratory and pathology tests found significantly increased white blood cells, bilirubin, total serum protein and plasma fibrinogen, and histological

findings showed crystalloid materials in the bile ducts with hepatocyte degeneration. A year later the same research team found very similar results in goats (Aslani et al 2004).

ADVERSE REACTIONS

Gastrointestinal disturbance may occur in sensitive individuals due to the herb's saponin content.

SIGNIFICANT INTERACTIONS

Controlled studies are not available and currently no interactions are known.

CONTRAINDICATIONS AND PRECAUTIONS

People with androgen-sensitive tumours should avoid use.

PREGNANCY USE

Not to be used in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Tribulus has been used traditionally in various parts of the world to treat colicky spasms, diarrhoea, cardiovascular disease, various kidney disorders, including kidney stones, and as an insect repellent.
- Tribulus has not undergone significant clinical testing, so much information is speculative and based on animal and test tube studies.
- Popular as an aphrodisiac, some research suggests that it increases levels of DHEA, testosterone and NO release, providing a theoretical basis for this activity. Until controlled studies are available, it is uncertain whether these effects are clinically significant.
- Tribulus is also popular amongst athletes as an ergogenic aid, although large controlled studies of efficacy are lacking.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Preliminary research suggests that this herb increases androgen levels and improves sexual function, but human studies are not available to confirm these effects.

When will it start to work?

This is unknown.

Are there any safety issues?

Pregnant and lactating women and people with androgen-sensitive tumours should avoid use.

REFERENCES

Adaikan PG et al. Proerectile pharmacological effects of Tribulus terrestris extract on the rabbit corpus cavernosum. Ann Acad Med Singapore 29.1 (2000): 22-6.

Adimoelja A. Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions. Int J Androl 23 (Suppl 2) (2000): 82-4.

Al Ali M et al. Tribulus terrestris: preliminary study of its diuretic and contractile effects and comparison with Zea mays. J Ethnopharmacol 85.2-3 (2003): 257-60.

Anand R et al. Activity of certain fractions of Tribulus terrestris fruits against experimentally induced urolithiasis in rats. Indian J Exp Biol 32.8 (1994): 548-52.

Antonio J et al. The effects of Tribulus terrestris on body composition and exercise performance in resistance-trained males. Int J Sport Nutr Exerc Metab 10.2 (2000): 208-15.

Arcasoy HB et al. Effect of Tribulus terrestris L. saponin mixture on some smooth muscle preparations: a preliminary study. Boll Chim Farm 137.11 (1998): 473-5.

Aslani MR et al. Experimental Tribulus terrestris poisoning in sheep: clinical, laboratory and pathological findings. Vet Res Commun 27.1 (2003): 53-62.

Aslani MR et al. Experimental Tribulus terrestris poisoning in goats. Small Ruminant Res 51 (2004): 261-7.

Bourke CA. Staggers in sheep associated with the ingestion of Tribulus terrestris. Aust Vet J 61.11 (1984): 360-3.

Bourke CA. The clinical differentiation of nervous and muscular locomotor disorders of sheep in Australia. Aust Vet J 72.6 (1995): 228-34.

Bourke CA, Stevens GR, Carrigan MJ. Locomotor effects in sheep of alkaloids identified in Australian Tribulus terrestris. Aust Vet J 69.7 (1992): 163-5.

Deepak M et al. Tribulosin and beta-sitosterol-D-glucoside, the anthelmintic principles of Tribulus terrestris. Phytomedicine 9.8 (2002): 753-6.

Ganzera M, Bedir E, Khan IA. Determination of steroidal saponins in Tribulus terrestris by reversed-phase high-performance liquid chromatography and evaporative light scattering detection. J Pharm Sci 90.11 (2001): 1752-8.

Gauthaman K et al. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci 71.12 (2002): 1385-96.

Gauthaman K et al. Sexual effects of puncturevine (Tribulus terrestris) extract (protodioscin): an evaluation using a rat model. J Altern Complement Med 9.2 (2003): 257-65.

Glastonbury JR et al. A syndrome of hepatogenous photosensitisation, resembling geeldikkop, in sheep grazing Tribulus terrestris. Aust Vet J 61.10 (1984): 314-16.

Hong CH et al. Evaluation of natural products on inhibition of inducible cyclooxygenase (COX-2) and nitric oxide synthase (iNOS) in cultured mouse macrophage cells. J Ethnopharmacol 83.1-2 (2002): 153-9.

Huang JW et al. Terrestrinins A and B, two new steroid saponins from Tribulus terrestris. J Asian Nat Prod Res 5.4 (2003): 285-90.

Joshi VS et al. Inhibition of the growth of urinary calcium hydrogen phosphate dihydrate crystals with aqueous extracts of Tribulus terrestris and Bergenia ligulata. Urol Res 33.2 (2005): 80-6.

Li JX et al. Tribulusamide A and B, new hepatoprotective lignanamides from the fruits of Tribulus terrestris: indications of cytoprotective activity in murine hepatocyte culture. Planta Med 64.7 (1998): 628-31.

Li M et al. Effect of the decoction of Tribulus terrestris on mice gluconegenesis. Zhong Yao Cai 24.8 (2001): 586-8.

McDonough SP et al. Hepatogenous photosensitization of sheep in California associated with ingestion of Tribulus terrestris (puncture vine). J Vet Diagn Invest 6.3 (1994): 392-5.

Miles CO et al. Photosensitivity in South Africa. VII. Chemical composition of biliary crystals from a sheep with experimentally induced geeldikkop. Onderstepoort J Vet Res 61.3 (1994): 215-22.

Neychev VK, Mitev VI. The aphrodisiac herb Tribulus terrestris does not influence the androgen production in young men. J Ethnopharmacol 101.1-3 (2005): 319-23.

Sangeeta D et al. Effect of Tribulus terrestris on oxalate metabolism in rats. J Ethnopharmacol 44.2 (1994): 61-6.
Sharifi AM, Darabi R, Akbarloo N. Study of antihypertensive mechanism of Tribulus terrestris in 2K1C hypertensive rats: role of tissue ACE activity. Life Sci 73.23 (2003): 2963-71.
Tapia MO, Giordano MA, Gueper HG. An outbreak of hepatogenous photosensitization in sheep grazing Tribulus terrestris in Argentina. Vet Hum Toxicol 36.4 (1994): 311-13.
Wang B, Ma L, Liu T. 406 cases of angina pectoris in coronary heart disease treated with saponin of Tribulus terrestris. Zhong Xi Yi Jie He Za Zhi 10.2 (1990): 68, 85-7.
Wilkins AL et al. Photosensitivity in South Africa. IX. Structure elucidation of a beta-glucosidase-treated saponin from Tribulus terrestris, and the identification of saponin chemotypes of South African T. terrestris. Onderstepoort J Vet Res 63.4 (1996): 327-34.
Zhang JD et al. Antifungal activities and action mechanisms of compounds from Tribulus terrestris L. J Ethnopharmacol 103.1 (2005): 76-84.

Turmeric

Historical note Turmeric is a perennial herb, yielding a rhizome that produces a yellow powder that gives curry its characteristic yellow colour and is used to colour French mustard and the robes of Hindu priests. Turmeric was probably first cultivated as a dye, and then as a condiment and cosmetic. It is often used as an inexpensive substitute for saffron in cooking and in the 13th century Marco Polo marvelled at its similarities to saffron. Both Indian Ayurvedic and Chinese medicines use turmeric for the treatment of inflammatory and digestive disorders and turmeric has also been used in tooth powder or paste. Research has focused on turmeric's antioxidant, hepatoprotective, anti-inflammatory, anticarcinogenic and antimicrobial properties, in addition to its use in cardio-vascular disease and gastrointestinal disorders (Anon 2001).

COMMON NAME
Turmeric

OTHER NAMES
Chiang huang, curcuma, curcumae longae rhizoma, curcuma rhizome, e zhu, haridra, Indian saffron, jiang huang, jiang huang curcumae rhizoma, turmeric rhizome, turmeric root, yellow root, yu jin, zedoary

BOTANICAL NAME/FAMILY
Curcuma longa (family Zingiberaceae [ginger])

PLANT PART USED
Dried secondary rhizome (containing not less than 3% curcuminoids calculated as curcumin and not less than 3% volatile oil, calculated on dry-weight basis).

CHEMICAL COMPONENTS
Turmeric rhizome contains 5% phenolic curcuminoids (diarylheptanoids), which give turmeric the yellow colour. The most significant curcuminoid is curcumin (diferuloymethane).

It also contains up to 5% essential oil including sesquiterpene (e.g. Zingerberene), sesquiterpene alcohols and ketones, and monoterpenes.

Turmeric also contains immune stimulating polysaccharides, including acid glucans known as ukonan A, B and C (Evans 2002).

MAIN ACTIONS

Most research has focused on a series of curcumin constituents found in the herb. Many of the animal studies; however, involve parenteral administration and oral curcumin or turmeric is likely to be far less active because curcumin is poorly absorbed by the gastrointestinal tract and only trace amounts appear in the blood after oral intake (Ammon & Wahl 1991). Curcumin may, however, have significant activity in the gastrointestinal tract, and systemic effects may take place as a consequence of local gastrointestinal effects or be associated with metabolites of the curcuminoids.

ANTIOXIDANT

Studies have shown that turmeric, as well as curcumin, has significant antioxidant activity (Shalini & Srinivas 1987, Soudamini et al 1992). Turmeric not only exerts direct free radical scavenging activity, it also appears to enhance the antioxidant activity of endogenous antioxidants, such as glutathione peroxidase, catalase and quinine reductase. Curcumin has been shown to induce phase II detoxifying enzymes (glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and catalase) (Iqbal et al 2003). Additionally, its antioxidant effects are 10-fold more potent than ascorbic acid or resveratrol (Song et al 2001). In addition to curcumin, turmeric contains the antioxidants protocatechuic acid and ferulic acid and exhibits significant protection to DNA against oxidative damage in vitro (Kumar et al 2006).

Turmeric's antioxidant activity may mediate damage produced by myocardial ischaemia and diabetes. Turmeric has been shown to restore myocardial antioxidant status, inhibit lipid peroxidation and protect against ischaemia–reperfusion induced myocardial injuries in an animal model with enhancement of functional recovery (Mohanty et al 2004). Curcumin has also been found to prevent protein glycosylation and lipid peroxidation caused by high glucose levels in vitro (Jain et al 2006) and to improve diabetic nephropathy (Srinivasan 2005). Turmeric has also been shown to suppress cataract development and collagen cross-linking, promote wound healing, and lower blood lipids and glucose levels (Jain et al 2006).

NF-KAPPA-B INHIBITION

The many and varied effects of curcumin may be partly associated with the inhibition of transcription factor nuclear factor-kappa beta (NF-kappa-B) and induction of heat shock proteins. NF-kappa-B is a transcription factor pivotal in the regulation of inflammatory genes and is also closely associated with the heat shock response, which is a cellular defence mechanism that confers broad protection against various cytotoxic stimuli. Inhibition of NF-kappa-B may reduce inflammation and protect cells against damage (Chang 2001) and curcumin has been found to attenuate experimen-

tal colitis in animal models through a mechanism correlated with the inhibition of NF-kappa-B (Salh et al 2003). The clinical significance of this is unclear.

ANTI-INFLAMMATORY

There have been a large number of studies examining the anti-inflammatory effects of curcumin. Turmeric is a dual inhibitor of the arachidonic acid cascade. Curcumin has been shown to exert anti-inflammatory effects via phospholipase, lipo-oxygenase, COX-2, leukotrienes, thromboxane, PGs, NO, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, IFN-inducible protein, TNF and IL-12 (Chainani-Wu 2003, Lantz et al 2005).

The anti-inflammatory effect of curcumin was tested in adjuvant-induced chronic inflammation rats which found that curcumin significantly reduced C-reactive protein, TNF-alpha, IL-1 and NO, with no significant changes observed in PGE_2 and leukotriene B4 levels or lymphocyte proliferation (Banerjee et al 2003). Curcumin has also been shown to inhibit inflammation in experimental pancreatitis via inhibition of NF-kappa-B and activator protein-1 in two rat models (Gukovsky et al 2003).

GASTROINTESTINAL EFFECTS

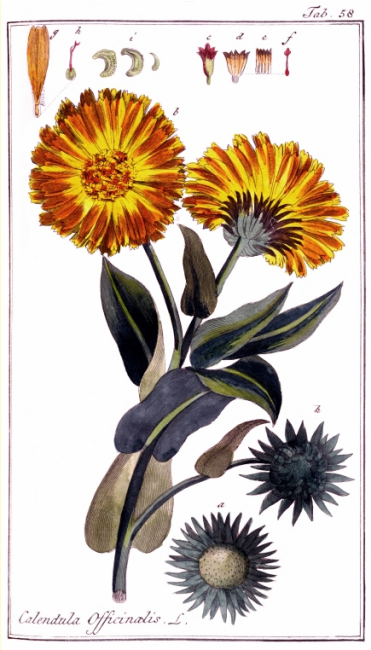
Hepatoprotective Curcumin prevents carbon tetrachloride-induced liver injury both in vivo and in vitro (Deshpande et al 1998, Kang et al 2002), reverses aflatoxin-induced liver damage in experimental animals (Soni et al 1992) and effectively suppresses the hepatic microvascular inflammatory response to lipopolysaccharides in vivo (Lukita-Atmadja et al 2002). An ethanol soluble fraction of turmeric was shown to contain three antioxidant compounds, curcumin, demethoxycurcumin and bisdemethoxycurcumin, which exert similar hepatoprotective activity to silybin and silychristin in vitro (Song et al 2001).

Several different mechanisms may contribute to turmeric's hepatoprotective activity. Curcumin has been shown to prevent lipoperoxidation of subcellular membranes in a dosage-dependent manner, due to an antioxidant mechanism (Quiles et al 1998) and turmeric may also protect the liver via inhibition of NF-kappa-B (see above), which has been implicated in the pathogenesis of alcoholic liver disease. Curcumin also blocked endotoxin-mediated activation of NF-kappa-B and suppressed the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells (Nanji et al 2003).

Cholagogue and hypolipidaemic Turmeric extract or curcumin extract has shown dose-dependent hypolipidaemic activity in vivo (Asai & Miyazawa 2001, Babu & Srinivasan 1997, Keshavarz 1976, Ramirez-Tortosa et al 1999, Soudamini et al 1992). One in vivo study suggests that curcumin may stimulate the conversion of

cholesterol into bile acids, and therefore, increase the excretion of cholesterol (Srinivasan & Sambaiah 1991). A further study demonstrated that supplementation with turmeric reduces fatty streak development and oxidative stress (Quiles et al 2002). Oral curcumin has also been shown to stimulate contraction of the gall bladder and promote the flow of bile in healthy subjects (Rasyid & Lelo 1999).

Antispasmodic Curcuminoids exhibit smooth muscle relaxant activity possibly mediated through calcium-channel blockade, although additional mechanisms cannot be ruled out (Gilani et al 2005). Curcuminoids produced antispasmodic effects on isolated guinea pig ileum and rat uterus by receptor-dependent and independent mechanisms (Itthipanichpong et al 2003).



CANCER

Curcumin has been studied for its wide-ranging effects on tumorigenesis, angiogenesis, apoptosis and signal transduction pathways (Gururaj et al 2002, Mohan et al 2000, Thaloor et al 1998). It is known to inhibit oncogenesis during both the promotion and progression periods in a variety of cancers (Anto et al 1996, Kuttan et al 1985, Menon et al 1999, Ruby et al 1995). Recently, curcumin was found to possess chemopreventive effects against skin cancer, stomach cancer, colon cancer and oral cancer in mice.

Chemoprevention Chemoprevention refers to reversing, suppressing or preventing the process of carcinogenesis. Carcinogenesis results from the accumulation of multiple sequential mutations and alterations in nuclear and cytoplasmic molecules, culminating in invasive neoplasms. These events have traditionally been separated into three phases: initiation, promotion and progression. Typically, initiation is rapid, whereas promotion and progression can take many years. Ultimately, chemoprevention aims at preventing the growth and survival of cells already committed to becoming malignant (Gescher et al 1998, 2001).

Curcumin has been found to effectively block carcinogen-induced skin (Azuine & Bhide 1992), colon (Rao et al 1995, 1999) and liver (Chuang et al 2000) carcinogenesis in animals. It has been suggested that the chemoprotective activity of curcumin occurs via changes in enzymes involved in both carcinogen bioactivation and oestrogen metabolism. This is supported by the findings that curcumin treatment produced changes in CYP1A, CYP3A and GST in mice (Valentine et al 2006) and alleviated the CCl4-induced inactivation of CYPs 1A, 2B, 2C and 3A isozymes in rats, possibly through its antioxidant properties, without inducing hepatic CYPs (Sugiyama et al 2006).

Oral curcumin inhibited chemically induced skin carcinogenesis in mice (Huang et al 1992) and curcumin prevented radiation-induced mammary and pituitary tumors

in rats (Inano & Onoda 2002). Curcumin and genistein (from soybeans) inhibited the growth of oestrogen-positive human breast MCF-7 cells induced individually or by a mixture of the pesticides endosulfane, DDT and chlordane, or 17-beta oestradiol (Verma et al 1997).

Apoptosis Apoptosis (programmed cell death) plays a crucial role in regulating cell numbers by eliminating damaged or cancerous cells. Curcumin induced apoptosis in vitro (Kim et al 2001, Kuo et al 1996) and may act via reactive oxygen species and other mechanisms. Curcumin has been demonstrated to induce apoptosis in human basal cell carcinoma cells associated with the p53 signalling pathway, which controls intracellular redox status, levels of oxidation-damaged DNA and oxidative stress-induced apoptosis (Jee et al 1998). Curcumin has also been found to induce apoptosis in human mutant p53 melanoma cell lines and block the NF-kappa-B cell survival pathway and suppress the apoptotic inhibitor known as XIAP. Because melanoma cells with mutant p53 are strongly resistant to conventional chemotherapy, curcumin may overcome the chemoresistance of these cells and provide potential new avenues for treatment (Bush et al 2001).

Curcumin has also been found to inhibit prostate cancer cell growth in mice (Dorai et al 2001) and decrease proliferation and induce apoptosis in androgen-dependent and androgen-independent prostate cancer cells in vitro. This was found to be mediated through modulation of apoptosis suppressor proteins and interference with growth factor receptor signalling pathways (Dorai et al 2000). In a further study with rats, however, curcumin did not prevent prostate carcinogenesis (Imaida et al 2001).

Antiproliferative Reduction in proliferation and/or increased apoptosis will lead to tumour regression; however, a more potent effect will be achieved if the two mechanisms occur simultaneously. Curcumin has been shown to do this. The inhibition of cell proliferation is partly related to inhibition of various kinases, such as protein kinase and phosphorylase kinase (Reddy and Aggarwal 1994), and inhibition of several oncogenes and transcription factors. For example, turmeric inhibited epidermal growth factor receptor (EGF-R) signalling via multiple mechanisms including downregulation of the EGF-R protein, inhibition of intrinsic EGF-R tyrosine kinase activity and inhibition of ligand-induced activation of the EGF-R (Dorai et al 2000). These mechanisms may be particularly important in preventing prostate cancer cells from progressing to a hormone refractory state (Dorai et al 2000). Curcumin has also been found to suppress the growth of multiple breast cancer cell lines and deplete p185neu, the protein product of the HER2/neu proto-oncogene that is thought to be important in human carcinogenesis (Hong et al 1999).

Antimetastatic Curcumin demonstrated the ability to reduce lung metastases from melanoma cells in mice. The activity of curcumin is varied.

- In cell adhesion assays, curcumin-treated cells showed a dose-dependent reduction in their binding to four extracellular matrix proteins (binding to proteins is associated with the spreading of the cancer).
- Curcumin-treated cells showed a marked reduction in the expression of integrin receptors (integrins functionally connect the cell interior with the extracellular matrix, another process necessary for metastases).
- Curcumin also enhanced the expression of antimetastatic proteins, tissue inhibitor metalloproteinase, non-metastatic gene 23 and E-cadherin (a cell adhesion factor) (Ray et al 2003).

Chemotherapy Curcumin enhanced the cytotoxicity of chemotherapeutic agents in prostate cancer cells in vitro by inducing the expression of certain androgen receptor and transcription factors and suppressing NF-kappa-B activation (Hour et al 2002). Curcumin also enhanced the antitumour effect of cisplatin against fibrosarcoma (Navis et al 1999).

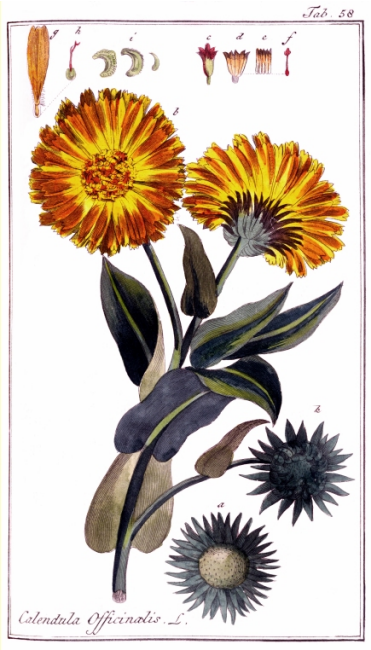
Curcumin, however, was found to significantly inhibit cyclophosphamide-induced tumour regression in an in vivo model of human breast cancer. It is suspected that this occurred as a result of inhibition of free radical generation and blockade of JNK function. As such, curcumin intake should be limited in people undergoing treatment for breast cancer with cyclophosphamide until further investigation can clarify the significance of these findings (Somasundaram et al 2002).

Immunomodulation Curcumin administration was found to significantly increase the total white blood cell count and circulating antibodies in mice. A significant increase in macrophage phagocytic activity was also observed in curcumin-treated animals (Antony et al 1999). However, curcumin has also been demonstrated to have some immunosuppressive activity. Curcumin inhibits PAR2- and PAR4-mediated human mast cell activation by block of ERK pathway (Baek et al 2003).

An in vivo study using a cardiac transplant model found that curcumin also significantly reduced expression of IL-2, IFN-gamma and granzyme B (a serine protease associated with the activity of killer T-lymphocytes and NK cells) and increased mean survival time. Curcumin was further shown to work synergistically with the anti-rejection drug cyclosporine (Chueh et al 2003).

Curcumin also modulates other interleukins and has been shown in vitro to be a potent inhibitor of the production of the pro-inflammatory cytokine IL-8, thereby reducing tumour growth and carcinoma cell viability. Curcumin not only inhibited IL-8 production but also inhibited signal transduction through IL-8 receptors (Hidaka et al

2002) and to inhibit cell proliferation, cell-mediated cytotoxicity and cytokine production most likely by inhibiting NF-kappa-B target genes (Gao et al 2004).



CARDIOVASCULAR EFFECTS

Antiplatelet Curcumin has been shown to inhibit platelet aggregation in vivo (Srivastava et al 1985, 1986) and in vitro (Srivastava 1989, 1995). The anticoagulant effect of curcumin is weaker than that of aspirin, which is four-fold more potent than curcumin in treatment of collagen- and noradrenalin-induced thrombosis. Curcumin 100 mg/kg and aspirin 25 mg/kg resulted in 60% protection from thrombosis (Srivastava et al 1985).

Anti-atherogenic A hydro-ethanolic extract of turmeric was found to decrease LDL oxidation, have a vitamin E-sparing effect and lower the oxidation of erythrocyte and liver membranes in rabbits fed a diet high in saturated fat and cholesterol (Mesa et al 2003, Ramirez-Tortosa et al 1999). The atherosclerosprotective potential of turmeric was further demonstrated by an animal study that found turmeric lowered blood pressure and reduced the atherogenic properties of cholesterol (Zahid Ashraf et al 2005).

Dietary curcumin has also been shown to significantly lower blood cholesterol in diabetic animals. Cholesterol decrease was exclusively from the LDL-VLDL fraction. Significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin in diabetic rats (Babu & Srinivasan 1997). In a parallel study in which diabetic animals were maintained on a high cholesterol diet, curcumin lowered cholesterol and phospholipid and countered the elevated liver and renal cholesterol and triglyceride levels seen in the diabetic animals (Babu & Srinivasan 1997).

WOUND HEALING

Wound healing is a highly ordered process, requiring complex and coordinated interactions involving peptide growth factors, of which transforming growth factor-beta (TGF-beta) is one of the most important. Nitric oxide is also an important factor in healing, and its production is regulated by iNOS. Topical application of curcumin accelerated wound healing in normal and diabetic rats. The wound healing is partly associated with the regulation of the growth factor TGF-beta-1 and iNOS (Mani et al 2002). Curcumin's wound healing ability has been confirmed in several other animal studies (Sidhu et al 1998, 1999). Wounds of animals treated with curcumin showed earlier re-epithelialisation, improved neovascularisation, increased migration of various cells including dermal myofibroblasts, fibroblasts, and macrophages into the wound bed, and a higher collagen content (Sidhu et al 1999). It appears to be effective when used orally or as a local application.

Curcumin has also demonstrated powerful inhibition against hydrogen peroxide damage in human keratinocytes and fibroblasts (Phan et al 2001) and pretreatment with curcumin significantly enhanced the rate of wound contraction, decreased mean wound healing time, increased synthesis of collagen, hexosamine, DNA and NO, and improved fibroblast and vascular densities in full thickness wounds in mice exposed to whole-body [gamma]-radiation (Jagetia & Rajanikant 2004).

ANTIMICROBIAL

Turmeric is used as an antimicrobial for preserving food (Jayaprakasha et al 2005) and has been found to have antifungal activity, as well as inhibiting aspergillus growth and aflatoxin production in feeds (Gowda et al 2004).

Curcumin has also been found to have dose-dependent, antiprotozoan activity against *Giardia lamblia* with inhibition of parasite growth and adherent capacity, induction of morphological alterations and apoptosis-like changes in vitro (Perez-Arriaga et al 2006). Curcumin has also shown in vitro and in vivo activity against malaria, with inhibition of growth of chloroquine-resistant *Plasmodium falciparum* in vitro and enhancement of survival in mice infected with *P. berghei* (Reddy et al 2005).

PSORIASIS

Topical curcumin reduced the severity of active, untreated psoriasis as assessed by clinical, histological and immunohistochemical criteria in an observational study of 10 patients. Curcumin was also found to decrease phosphorylase kinase, which is involved in signalling pathways, including those involved with cell migration and proliferation (Heng et al 2000). Topical administration of curcumin also induced normal skin formation in the modified mouse tail test (Bosman 1994). The effects are thought to be due to immune-modulating, anti-inflammatory and cyclo-oxygenase inhibitory actions. The downregulation of pro-inflammatory cytokines supports the view that turmeric antioxidants may exert a favourable effect on psoriasis-linked inflammation. Moreover, because IL-6 and IL-8 are growth factors for keratinocytes, their inhibition by those antioxidants may reduce psoriasis-related keratinocyte hyperproliferation (Miquel et al 2002).

OTHER ACTIONS

Curcumin's anti-inflammatory and antioxidant actions may be useful in preventing neurodegenerative diseases, such as Alzheimer's dementia and Parkinson's disease, and curcumin has been found to target multiple pathogenic cascades in preclinical models (transgenic and amyloid infusion models) of AD (Cole et al 2005). Curcumin has also been found to dose-dependently inhibit neuroglial proliferation, with low

doses being as effective as higher doses given a longer period of treatment (Ambegaokar et al 2003).

Curcumin had anti-asthmatic activity in animal models of induced asthma. Curcumin (20 mg/kg body weight) treatment significantly inhibited chemical (ovalbumin)-induced airway constriction and airway hyperreactivity. The results demonstrate that curcumin is effective in improving the impaired airways features in ovalbumin-sensitised guinea pigs (Ram et al 2003).

Curcumin has been found to have inhibitory effects on P-glycoprotein in numerous test tube studies (Anuchapreeda et al 2002, Limtrakul et al 2004, Nabekura et al 2005). The clinical significance of this observation has yet to be determined.

CLINICAL USE

In practice turmeric and the various curcuminoids are used in many forms and administered via various routes. This review will focus mostly on those methods of use that are commonly used and preparations that are available OTC, such as oral dose forms and topical applications.

CANCER

Epidemiological data suggest that curcumin reduces the rate of colorectal cancer (Hergenhahn et al 2002) and curcumin has wide-ranging chemopreventive activity in preclinical carcinogenic models (Plummer et al 2001), most notably for gastrointestinal cancers (Ireson et al 2001). To date, however, there are no controlled trials to attest to turmeric's efficacy in cancer treatment or prevention.

In a phase 1 study, curcumin taken orally for 3 months at a starting dose of 500 mg/day was found to produce histologic improvement in cases of bladder cancer, oral leucoplakia, intestinal metaplasia of the stomach, cervical intraepithelial neoplasm and Bowen's disease (Cheng et al 2001).

An ethanol extract of turmeric, as well as an ointment of curcumin, were found to produce remarkable symptomatic relief in patients with external cancerous lesions (Kuttan et al 1987) and there are clinical reports to suggest that curcumin could be safe and effective in the treatment of idiopathic inflammatory orbital pseudotumours (Lal et al 2000).

DYSPEPSIA/PEPTIC ULCERS

A randomised, controlled, double-blind prospective multicentre pilot study compared the effects of dried extracts of greater celandine and turmeric with placebo in 76 patients with colicky abdominal pain in the right upper quadrant due to biliary dyskinesia. Abdominal pain was reduced more quickly with active treatment;

however, other symptoms such as fullness, nausea and vomiting did not respond (Niederau & Gopfert 1999). Another randomised, placebo-controlled, double-blind study that investigated the efficacy of turmeric for treatment of dyspepsia and flatulence in 116 adult patients with acidic dyspepsia, flatulent dyspepsia or atonic dyspepsia found that 87% of patients receiving turmeric responded compared to 53% receiving placebo (Thamlikitkul et al 1989).

In a study of 24 patients with duodenal or gastric ulcers varying between 0.5 and 1.5 cm in diameter, 300 mg of turmeric given five times daily, 30–60 minutes before meals, at 1600 hours and at bedtime successfully healed 48% of ulcers after 4 weeks and 76% after 12 weeks. Of 20 patients who had erosion gastritis and dyspepsia, the same treatment produced a satisfactory reduction in abdominal pain and discomfort after the first and second week (Prucksunand et al 2001). Turmeric has also been positively compared to a liquid antacid for the treatment of gastric ulcer in a controlled clinical trial (Kositchaiwat et al 1993).

HYPERLIPIDAEMIA

Turmeric may be associated with a decrease in the risk of cardiovascular disease and an intake of 200 mg of a hydro-ethanolic extract of turmeric may decrease total blood lipid peroxides and HDL- and LDL-lipid peroxidation, as well as normalise plasma fibrinogen levels and apolipoprotein B/apolipoprotein A ratio (Miquel et al 2002).

In an open trial, 10 healthy volunteers received 500 mg/day of curcumin for 7 days. A significant decrease in the level of serum lipid peroxides (33%), increase in HDL-cholesterol (29%), and a decrease in total serum cholesterol (11.63%) were noted. It also reduced serum lipid peroxides (Soni & Kuttan 1992). In a subsequent study, a 45-day intake (by healthy individuals 27–67 years of age) of a turmeric hydro-alcoholic extract at a daily dose equivalent to 20 mg of curcumin resulted in a significant decrease in serum lipid peroxides (Ramirez-Bosca et al 1995). A daily intake of turmeric equivalent to 20 mg of the phenolic antioxidant curcumin for 60 days also decreased peroxidation of both HDL and LDL in 30 healthy volunteers ranging in age from 40 to 90 years. The effect was quite striking in the persons with high baseline values of peroxidised compounds in these lipoproteins, although no apparent change took place in the persons having low baseline values (Ramirez et al 1997).

ARTHRITIS

In a randomised, controlled double-blind study, curcumin 1200 mg/day was compared with phenylbutazone in subjects with RA. Curcumin was found to be effective

in improving morning stiffness, walking time and joint swelling; however, the effects of phenylbutazone were stronger (Deodhar et al 1980).

Curcumin combined with boswellia, withania and zinc produced a significant drop in pain and disability in OA of the knee in a randomised, double-blind, placebo-controlled crossover study of 42 patients (Kulkarni et al 1991); however, the contribution of cucurmin to these results is unknown.

OTHER USES

CHRONIC ANTERIOR UVEITIS

An open study of 32 patients found that orally administered curcumin improved symptoms and reduced recurrences of chronic anterior uveitis (a condition often associated with other autoimmune disorders) with an efficacy comparable to corticosteroid therapy, yet without significant side-effects (Lal et al 1999).

ORAL SUBMUCOUS FIBROSIS

Turmeric extract 3 g, oil 600 mg and oleoresin 600 mg effectively relieved symptoms and reduced the number of micronuclei (a sign of damage to the DNA and chromosomal integrity) in circulating lymphocytes and oral mucosal cells in patients with oral submucous fibrosis, a debilitating disease of the oral cavity mainly caused by chewing betel nut or tobacco (Hastak et al 1997).

DOSAGE RANGE

INTERNAL USE

- Powdered turmeric: 1.5–3 g/day in water or cooking.
- Liquid extract (1:1) in 45% ethanol: 5–15 mL/day.
- Powdered extract standardised to 95% curcumin: 100–300 mg/day. Higher doses used for arthritis and cancer.

EXTERNAL USE

- Turmeric powder of standardised powdered extract applied as a paste or poultice — half cup of turmeric combined with 1 teaspoon of carbonate of soda and then mixed with hot water to make a paste; spread on gauze and apply to affected area.

ADVERSE REACTIONS

The safety of curcumin is demonstrated by the fact that it has been consumed for centuries at levels of up to 10 mg/day by people in certain countries (Ammon & Wahl 1991). Curcumin was not toxic to humans in doses up to 8000 mg/day when taken by mouth for 3 months (Cheng et al 2001). Multiple other human trials have also found it to be safe with no alteration of liver or renal function tests (Chainani-Wu

2003, Prucksunand et al 2001, Ramirez-Bosca et al 1995, Ramirez et al 1997, Sharma et al 2001).

Large doses of turmeric powder may cause gastrointestinal irritation in some persons (Bhavani at al 1980) and very high dosages have been shown to reduce fertility in male rats (human equivalent doses would be 35 g turmeric/70 kg adult) (Meenakshi & Ashok 2001). Normal therapeutic dosages of turmeric are not expected to affect fertility. Contact dermatitis has been reported (Hata et al 1997), as has a single case of anaphylaxis (Robinson 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available so interactions are based on evidence of activity and are largely theoretical and speculative.

ANTIPLATELET DRUGS

Turmeric has a theoretical interaction with antiplatelet drugs; antiplatelet properties have been demonstrated for curcumin, therefore it may produce an additive effect. The clinical significance of this interaction is unclear and likely to be dose-dependent.

ANTICOAGULANTS

Theoretically, high-dose turmeric preparations may increase the risk of bleeding when used together with anticoagulant drugs — caution is advised.

CYCLOPHOSPHAMIDE

Animal studies suggest curcumin may reduce drug efficacy — avoid.

CONTRAINDICATIONS AND PRECAUTIONS

Turmeric is contraindicated in bile duct obstruction (Blumenthal et al 2000) and high doses are probably best avoided in males and females wanting to conceive.

Curcumin is also contraindicated in breast cancer patients treated with cyclophosphamide until the significance of an in vivo model of breast cancer, which found that curcumin reduced the tumour regression effects of chemotherapy, is clarified (Somasundaram et al 2002).

Due to antiplatelet activity and possible increased risk of bleeding, use of concentrated extracts should be suspended 1 week prior to major surgery; however, usual dietary intakes are likely to be safe.

PREGNANCY AND LACTATION USE

When used as a spice this herb is most likely to be safe; however, the safety of therapeutic doses has not been established. Turmeric has been demonstrated not to be mutagenic in vitro (Nagabhushan 1986) or to be teratrogenic in mice (Garg 1974,

Vijayalaxmi 1980). Constituents and/or metabolites of turmeric and curcumin were transferred to suckling pups, but no ill effect on the offspring was reported.

PRACTICE POINTS/PATIENT COUNSELLING

- In Ayurvedic medicine, turmeric is used to strengthen the overall energy of the body, relieve gas, dispel worms, improve digestion, regulate menstruation, dissolve gallstones, relieve arthritis and purify the blood (Blumenthal et al 2000).
- In TCM, turmeric is used for bruises, sores, ringworm, chest pain, toothache and jaundice. Turmeric was also recommended for abdominal pain, mass formation in the abdomen and amenorrhoea (Blumenthal et al 2000).
- Turmeric is commonly used in foods and is likely to be a safe and healthy addition to the diet.
- Turmeric has been shown to have antioxidant, anti-inflammatory and anti-atherosclerotic activity; however, further clinical evidence is needed before it can be recommended to treat specific conditions.
- Clinical evidence suggests that turmeric may provide benefit for people with dyspepsia, peptic ulcer, hyperlipidaemia, and arthritis and there is emerging evidence to suggest that turmeric may help prevent a number of cancers as well as being useful as an adjuvant in cancer treatment.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

In countries where people use turmeric extensively in cooking (generally in curries), the intake seems to be associated with a lower level of certain chronic conditions, possibly including cancer, gastrointestinal diseases and arthritis. There have been some encouraging studies supporting this.

When will it start to work?

In some studies the effect began to be noticed after 2 weeks. However, as most of the conditions where turmeric may be beneficial are chronic in nature, treatment with turmeric should be considered long term.

Are there any safety issues?

Turmeric is considered very safe at normal dietary or therapeutic dosages with turmeric extracts. High doses are generally not recommended during pregnancy or for those wanting to conceive.

REFERENCES

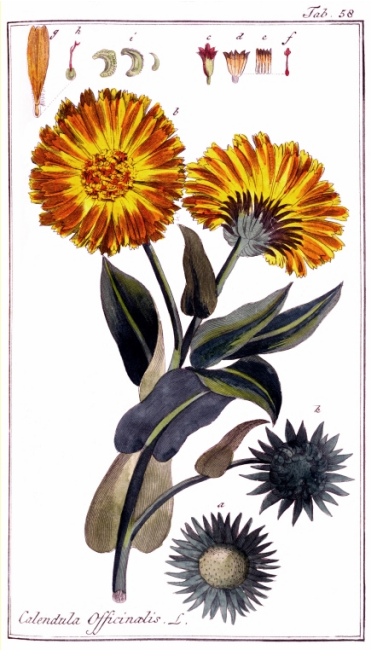
Ambegaokar SS et al. Curcumin inhibits dose-dependently and time-dependently neuroglial cell proliferation and growth. Neuroendocrinol Lett 24.6 (2003): 469-73.

Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Med 57.1 (1991): 1-7.

Anon. Curcuma longa (turmeric). Altern Med Rev 6 (Suppl) (2001): S62-6.

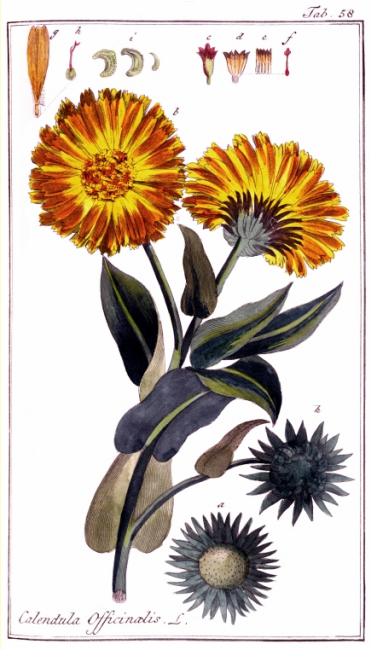
Anto RJ et al. Antimutagenic and anticarcinogenic activity of natural and synthetic curcuminoids. Mutat Res 370.2 (1996): 127-31.
Antony S, Kuttan R, Kuttan G. Immunomodulatory activity of curcumin. Immunol Invest 28.5-6 (1999): 291-303.
Anuchapreeda S et al. Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells. Biochem Pharmacol 64.4 (2002): 573-82.
Asai A, Miyazawa T. Dietary curcuminoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. J Nut. 131.11 (2001): 2932-5.
Azuine MA, Bhide SV. Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. Nutr Cancer 17.1 (1992): 77-83.
Babu PS, Srinivasan K. Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats. Mol Cell Biochem 166.1-2 (1997): 169-75.
Baek O-S et al. Curcumin inhibits protease-activated receptor-2 and -4-mediated mast cell activation. Clin Chim Acta 338.1-2 (2003): 135-41.
Banerjee M et al. Modulation of inflammatory mediators by ibuprofen and curcumin treatment during chronic inflammation in rat. Immunopharm Immunotoxicol 25.2 (2003): 213-24.
Bhavani Shankar TN, Shantha NV, Ramesh HP. Toxicity studies on turmeric (Curcuma longa): Acute toxicity studies in rats, guinea pigs and monkeys. Indian J Exp Biol 18.1 (1980): 73-75.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Bosman B. Testing of lipoxygenase inhibitors, cyclooxygenase inhibitors, drugs with immunomodulating properties and some reference antipsoriatic drugs in the modified mouse tail test, an animal model of psoriasis. Skin Pharmacol 7.6 (1994): 324-34.
Bush JA, Cheung K-J, Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. Exp Cell Res 271.2 (2001): 305-14.
Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma longa). J Altern Complement Med 9.1 (2003): 161-8.
Chang D-M. Curcumin: A heat shock response inducer and potential cytoprotector. Crit Care Med 29.11 (2001): 2231-32.
Cheng AL et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 21.4B (2001b): 2895-900.
Chuang SE et al. Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis. Carcinogenesis 21.2 (2000): 331-5.
Chueh S-CJ et al. Curcumin enhances the immunosuppressive activity of cyclosporine in rat cardiac allografts and in mixed lymphocyte reactions. Transplant Proc 35.4 (2003): 1603-5.
Cole GM et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiol Aging Suppl, 2005.
Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). Indian J Med Res 71 (1980): 632-4.
Deshpande UR et al. Protective effect of turmeric (Curcuma longa L.) extract on carbon tetrachloride-induced liver damage in rats. Indian J Exp Biol 36.6 (1998): 573-7.
Dorai T et al. Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits tyrosine kinase activity of epidermal growth factor receptor and depletes the protein. Mol Urol 4.1 (2000): 1-6.
Dorai T et al. Therapeutic potential of curcumin in human prostate cancerIIICurcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. Prostate 47.4 (2001): 293-303.
Evans W. Trease and Evans: Pharmacognosy, 15th edn, Edinburgh: WS Saunders, 2002.
Gao X et al. Immunomodulatory activity of curcumin: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production in vitro. Biochem Pharmacol 68.1 (2004): 51-61.

Garg SK. Effect of Curcuma longa (rhizomes) on fertility in experimental animals. Planta Med 26.3 (1974): 225-7.
Gescher A et al. Suppression of tumour development by substances derived from the diet: mechanisms and clinical implications. Br J Clin Pharmacol 45.1 (1998): 1-12.
Gescher A et al. Cancer chemoprevention by dietary constituents: a tale of failure and promise. Lancet Oncol 2 (2001): 371-9.
Gilani AH et al. Pharmacological basis for the use of turmeric in gastrointestinal and respiratory disorders. Life Sci 76.26 (2005): 3089-105.
Gowda NKS et al. Effect of some chemical and herbal compounds on growth of Aspergillus parasiticus and aflatoxin production. Animal Feed Sci Technol 116.3-4 (2004): 281-91.
Gukovsky I et al. Curcumin ameliorates ethanol and nonethanol experimental pancreatitis. Am J Physiol Gastrointest Liver Physiol 284.147-1 (2003): G85-95.
Gururaj A et al. Molecular mechanisms of anti-angiogenic effect of curcumin. Biochem Biophys Res Commun 297.4 (2002): 934-42.
Hastak K et al. Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis. Cancer Lett 116.2 (1997): 265-9.
Hata M et al. Allergic contact dermatitis from curcumin (turmeric). Contact Dermatitis 36.2 (1997): 107-8.
Heng MCY et al. Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br J Dermatol 143.5 (2000): 937-49.
Hergenhahn M et al. The chemopreventive compound curcumin is an efficient inhibitor of Epstein-Barr virus BZLF1 transcription in Raji DR-LUC cells. Mol Carcinogen 33.3 (2002): 137-45.
Hidaka H et al. Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface: impact on human pancreatic carcinoma cell growth by autocrine regulation. Cancer 95.6 (2002): 1206-14.
Hong RL, Spohn WH, Hung MC. Curcumin inhibits tyrosine kinase activity of p185neu and also depletes p185neu. Clin Cancer Res 5.7 (1999): 1884-91.
Hour T-C et al. Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21WAF1/CIP1 and C/EBPbeta expressions and suppressing NF-kappaB activation. Prostate 51.3 (2002): 211-18.
Huang M-T et al. Inhibitory effects of curcumin on tumor initiation by benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene. Carcinogenesis 13.11 (1992): 2183-6.
Imaida K et al. Lack of chemopreventive effects of lycopene and curcumin on experimental rat prostate carcinogenesis. Carcinogenesis 22 (2001): 467-72.
Inano H, Onoda M. Radioprotective action of curcumin extracted from Curcuma longa LINN: inhibitory effect on formation of urinary 8-hydroxy-2'-deoxyguanosine, tumorigenesis, but not mortality, induced by gamma-ray irradiation. Int J Radiat Oncol Biol Phys 53 (2002): 735-43.
Iqbal M et al. Dietary supplementation of curcumin enhances antioxidant and phase II metabolizing enzymes in ddY male mice: possible role in protection against chemical carcinogenesis and toxicity. Pharmacol Toxicol 92.1 (2003): 33-8.
Ireson C et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res 61.3 (2001): 1058-64.
Ireson CR et al. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Biomarkers Prev 11.1 (2002): 105-11.
Itthipanichpong C et al. Antispasmodic effects of curcuminoids on isolated guinea-pig ileum and rat uterus. J Med Assoc Thai 86 (Suppl 2) (2003): S299-309.
Jagetia GC, Rajanikant GK. Role of curcumin, a naturally occurring phenolic compound of turmeric, in accelerating the repair of excision wound, in mice whole-body exposed to various doses of [gamma]-radiation. J Surg Res 120.1 (2004): 127-38.



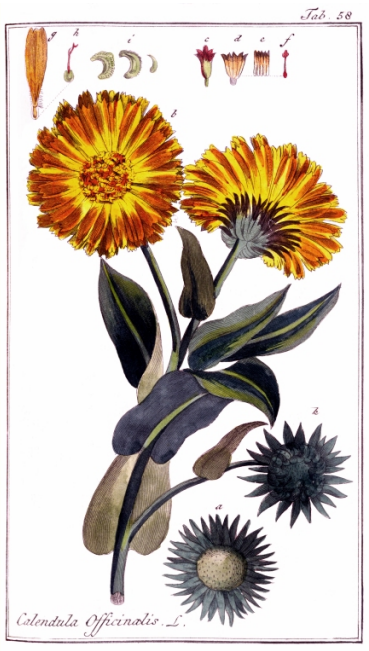
Jain SK et al. Effect of curcumin on protein glycosylation, lipid peroxidation, and oxygen radical generation in human red blood cells exposed to high glucose levels. Free Radical Biol Med 41.1 (2006): 92-6.
Jayaprakasha GK et al. Chemistry and biological activities of C. longa. Trends Food Sci Technol 16.12 (2005): 533-48.
Jee S-H et al. Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. J Invest Dermatol 111.4 (1998): 656-61.
Kang H-C et al. Curcumin inhibits collagen synthesis and hepatic stellate cell activation in-vivo and in-vitro. J Pharm Pharmacol 54.1 (2002): 119-26.
Keshavarz K. The influence of turmeric and curcumin on cholesterol concentration of eggs and tissues. Poultry Sci 55.3 (1976): 1077-83.
Kim MS, Kang HJ, Moon A. Inhibition of invasion and induction of apoptosis by curcumin in H-ras-transformed MCF10A human breast epithelial cells. Arch Pharm Res 24.4 (2001): 349-54.
Kositchaiwat C, Kositchaiwat S, Havanondha J. Curcuma longa Linn. in the treatment of gastric ulcer comparison to liquid antacid: a controlled clinical trial. J Med Assoc Thai 76.11 (1993): 601-5.
Kulkarni RR et al. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. J Ethnopharmacol 33.1-2 (1991): 91-5.
Kumar GS et al. Free and bound phenolic antioxidants in amla (Emblica officinalis) and turmeric (Curcuma longa). J Food Comp Anal 19.5 (2006): 446-52.
Kuo M-L, Huang T-S, Lin J-K. Curcumin, an antioxidant and anti-tumor promoter, induces apoptosis in human leukemia cells. Biochem Biophys Acta Mol Basis Dis 1317.2 (1996): 95-100.
Kuttan R et al. Potential anticancer activity of turmeric (Curcuma longa). Cancer Lett 29.2 (1985): 197-202.
Kuttan R et al. Turmeric and curcumin as topical agents in cancer therapy. Tumori 73.1 (1987): 29-31.
Lal B et al. Efficacy of curcumin in the management of chronic anterior uveitis. Phytother Res 13.4 (1999): 318-22.
Lal B et al. Role of curcumin in idiopathic inflammatory orbital pseudotumours. Phytother Res 14.6 (2000): 443-7.
Lantz RC et al. The effect of turmeric extracts on inflammatory mediator production. Phytomedicine 12.6-7 (2005): 445-52.
Limtrakul P, Anuchapreeda S, Buddhasukh D. Modulation of human multidrug-resistance MDR-1 gene by natural curcuminoids. BMC Cancer 4 (2004): 13.
Lukita-Atmadja W et al. Effect of curcuminoids as anti-inflammatory agents on the hepatic microvascular response to endotoxin. Shock 17.5 (2002): 399-403.
Mani H et al. Curcumin differentially regulates TGF-beta1, its receptors and nitric oxide synthase during impaired wound healing. Biofactors 16.1-2 (2002): 29-43.
Meenakshi B, Ashok Antifertility effects of various extracts of Curcuma longa in male albino rats. Indian Drugs 38.2 (2001): 79-81.
Menon LG, Kuttan R, Kuttan, G. Anti-metastatic activity of curcumin and catechin. Cancer Lett 141.1-2 (1999): 159-65.
Mesa MD et al. Oral administration of a turmeric extract inhibits erythrocyte and liver microsome membrane oxidation in rabbits fed with an atherogenic diet. Nutrition 19.9 (2003): 800-4.
Miquel J et al. The curcuma antioxidants: Pharmacological effects and prospects for future clinical use: A review. Arch Gerontol Geriatr 34.1 (2002): 37-46.
Mohan R et al. Curcuminoids inhibit the angiogenic response stimulated by fibroblast growth factor-2, including expression of matrix metalloproteinase gelatinase B. J Biol Chem 275.14 (2000): 10405-12.
Mohanty I et al. Protective effects of Curcuma longa on ischemia-reperfusion induced myocardial injuries and their mechanisms. Life Sci 75.14 (2004): 1701-11.
Nabekura T et al. Effects of dietary chemopreventive phytochemicals on P-glycoprotein function. Biochem Biophys Res Commun 327.3 (2005): 866-70.
Nagabhushan Mand Bhide SV. Nonmutagenicity of curcumin and its antimutagenic action versus chili and capsaicin. Nutr Cancer 8.3 (1986): 201-10.

Nanji AA et al. Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappaB-dependent genes. Am J Physiol Gastrointest Liver Physiol 284.2 47-2 (2003): G321-7.
Navis I, Sriganth P, Premalatha B. Dietary curcumin with cisplatin administration modulates tumour marker indices in experimental fibrosarcoma. Pharmacol Res 39.3 (1999): 175-9.
Niederau C, Gopfert E. [The effect of chelidonium- and turmeric root extract on upper abdominal pain due to functional disorders of the biliary system: Results from a placebo-controlled double-blind study]. Med Klin 94.8 (1999): 425-30.
Perez-Arriaga L et al. Cytotoxic effect of curcumin on Giardia lamblia trophozoites. Acta Tropica 98.2 (2006): 152-61.
Phan T-T et al. Protective effects of curcumin against oxidative damage on skin cells in vitro: Its implication for wound healing. J Trauma-Injury Infect Crit Care 51.5 (2001): 927-31.
Plummer SM et al. Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. Cancer Epidemiol Biomarkers Prev 10.12 (2001): 1295-9.
Polasa K et al. Effect of turmeric on urinary mutagens in smokers. Mutagenesis 7.2 (1992): 107-9.
Prucksunand C et al. Phase II clinical trial on effect of the long turmeric (Curcuma longa Linn) on healing of peptic ulcer. Southeast Asian J Trop Med Public Health 32.1 (2001): 208-15.
Quiles JL et al. An ethanolic-aqueous extract of Curcuma longa decreases the susceptibility of liver microsomes and mitochondria to lipid peroxidation in atherosclerotic rabbits. Biofactors 8.1-2 (1998): 51-7.
Quiles JL et al. Curcuma longa extract supplementation reduces oxidative stress and attenuates aortic fatty streak development in rabbits. Arterioscler Thromb Vasc Biol 22.7 (2002): 1225-31.
Ram A, Das M, Ghosh B. Curcumin attenuates allergen-induced airway hyperresponsiveness in sensitized guinea pigs. Biol Pharm Bull 26.7 (2003): 1021-4.
Ramirez BA et al. Effects of the antioxidant turmeric on lipoprotein peroxides: Implications for the prevention of atherosclerosis. Age 20.3 (1997): 165-8.
Ramirez-Bosca A et al. Antioxidant Curcuma extracts decrease the blood lipid peroxide levels of human subjects. Age 18.4 (1995): 167-9.
Ramirez-Tortosa MC et al. Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. Atherosclerosis 147.2 (1999): 371-8.
Rao CV et al. Chemoprevention of colon carcinogenesis by phenylethyl-3-methylcaffeate. Cancer Res 55.11 (1995a): 2310-15.
Rao CV et al. Chemoprevention of colon cancer by dietary curcumin. Ann NY Acad Sci 768 (1995b): 201-4.
Rao CV et al. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res 55.2 (1995c): 259-66.
Rao CV et al. Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. Carcinogenesis 20.4 (1999): 641-4.
Rasyid A, Lelo A. The effect of curcumin and placebo on human gall-bladder function: An ultrasound study. Aliment Pharmacol Ther 13.2 (1999): 245-9.
Ray S et al. Curcumin exhibits antimetastatic properties by modulating integrin receptors, collagenase activity, and expression of Nm23 and E-cadherin. J Environ Pathol Toxicol Oncol 22.1 (2003): 49-58.
Reddy S, Aggarwal BB. Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase. FEBS Lett 341.1 (1994): 19-22.
Reddy RC et al. Curcumin for malaria therapy. Biochem Biophys Res Commun 326.2 (2005): 472-4.
Robinson DM. Anaphylaxis to turmeric. J Allergy Clin 111.1 (Suppl 2) (2003): S100.
Ruby AJ et al. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett 94.1 (1995): 79-83.
Salh B et al. Curcumin attenuates DNB-induced murine colitis. Am J Physiol Gastrointest Liver Physiol 285.1 (2003): G235-43.
Shalini VK, Srinivas L. Lipid peroxide induced DNA damage: protection by turmeric (Curcuma longa). Mol Cell Biochem 77.1 (1987): 3-10.



Sharma RA et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res 7.7 (2001): 1894-900.
Sidhu GS et al. Enhancement of wound healing by curcumin in animals. Wound Repair Regen 6.2 (1998): 167-77.
Sidhu GS et al. Curcumin enhances wound healing in streptozotocin induced diabetic rats and genetically diabetic mice. Wound Repair Regen 7.5 (1999): 362-74.
Somasundaram S et al. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. Cancer Res 62.13 (2002): 3868-75.
Song E-K et al. Diarylheptanoids with free radical scavenging and hepatoprotective activity in vitro from Curcuma longa. Planta Med 67.9 (2001): 876-7.
Soni KB, Kuttan R. Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers. Indian J Physiol Pharmacol 36.4 (1992): 273-5.
Soni KB, Rajan A, Kuttan R. Reversal of aflatoxin induced liver damage by turmeric and curcumin. Cancer Lett 66.2 (1992): 115-21.
Soudamini KK et al. Inhibition of lipid peroxidation and cholesterol levels in mice by curcumin. Indian J Physiol Pharmacol 36.4 (1992): 239-43.
Srinivasan K. Spices as influencers of body metabolism: an overview of three decades of research. Food Res Int 38.1 (2005): 77-86.
Srinivasan K, Sambaiah K. The effect of spices on cholesterol 7 alpha-hydroxylase activity and on serum and hepatic cholesterol levels in the rat. Int J Vitamin Nutr Res 61.4 (1991): 364-9.
Srivastava KC. Extracts from two frequently consumed spices – cumin (Cuminum cyminum) and turmeric (Curcuma longa) – inhibit platelet aggregation and alter eicosanoid biosynthesis in human blood platelets. Prostaglandins Leukot Essent Fatty Acids 37.1 (1989): 57-64.
Srivastava R et al. Anti-thrombotic effect of curcumin. Thromb Res 40.3 (1985): 413-17.
Srivastava R et al. Effect of curcumin on platelet aggregation and vascular prostacyclin synthesis. Arzneimittel-Forschung 36.4 (1986): 715-17.
Srivastava KC et al. Curcumin, a major component of food spice turmeric (Curcuma longa), inhibits aggregation and alters eicosanoid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids 52.4 (1995): 223-27.
Sugiyama T et al. Selective protection of curcumin against carbon tetrachloride-induced inactivation of hepatic cytochrome P450 isozymes in rats. Life Sci 78.19 (2006): 2188-93.
Thaloor D et al. Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by curcumin. Cell Growth Differ 9.4 (1998): 305-12.
Thamlikitkul V et al. Randomized double blind study of Curcuma domestica Val for dyspepsia. J Med Assoc Thai 72.11 (1989): 613-20.
Valentine SP et al. Curcumin modulates drug metabolizing enzymes in the female Swiss Webster mouse. Life Sci 78.20 (2006): 2391-8.
Verma SP, Salamone E, Goldin B. Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides. Biochem Biophys Res Commun 233.3 (1997): 692-6.
Vijayalaxmi. Genetic effects of turmeric and curcumin in mice and rats. Mutat Res 79.2 (1980): 125-32.
Zahid Ashraf M et al. Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. Life Sci 77.8 (2005): 837-57.

Tyrosine



Historical note Tyrosine has been used by the military in the USA and the Netherlands to counter the stressful effects of cold, prolonged and excessive physical activity. It also appears to improve cognition and performance in soldiers under psychologically stressful conditions and has been scientifically shown to improve physical and mental endurance (Deijen et al 1999).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Tyrosine is a conditionally essential amino acid. It can be taken in through the diet or synthesised in the body from phenylalanine, except in phenyketonurics. L-Tyrosine is absorbed in the small intestine by active transport and transported to the liver where it is involved in a number of biochemical reactions, such as protein synthesis and oxidative catabolic reactions. L-Tyrosine that is not metabolised in the liver is distributed via systemic circulation to various tissues in the body where it is involved in the synthesis of a number of catecholamines and hormones (Hendler & Rorvick 2001).

There is some question as to tyrosine's ability to cross the blood–brain barrier and this may explain some of the negative results demonstrated in clinical trials. A rat study has demonstrated that combining the essential fatty acid, alpha-linolenic acid, with L-tyrosine, via a special bond, produces an active biological molecule with potent dopaminergic activity, suggesting that the alpha-linolenic acid may play a dual role as a carrier for tyrosine and a membrane- and receptor-improving agent (Yehuda 2002).

CHEMICAL COMPONENTS

L-Tyrosine is the form generally used. Tyrosine is also known as beta-(para-hydroxyphenyl) alanine, alpha-amino-para-hydroxyhydrocinnamic acid and *(S)*-alpha-amino-4-hydroxybenzenepropanoic acid.

FOOD SOURCES

Good dietary sources include soy products, chicken, fish, almonds, avocados, bananas, dairy products, meat, eggs, nuts, beans, oats, wheat, lima beans, pumpkin seeds, sesame seeds and fermented foods such as yoghurt and miso.

DEFICIENCY SIGNS AND SYMPTOMS

The following have been associated with low levels of tyrosine:

- depression

- low blood pressure
- low body temperature
- restless legs syndrome
- hypothyroidism.

MAIN ACTIONS

NEUROTRANSMITTER AND HORMONE PRODUCTION

Many of the pharmacological actions of tyrosine relate to its role as a precursor for a number of neurotransmitters and hormones.

Elevating tyrosine concentrations in brain catecholamine neurons (particularly dopamine and noradrenaline neurons) can stimulate neurotransmitter production in actively firing neurones but not in those that are quiescent or firing slowly (Fernstrom 2000).

It plays an essential role in the body as a precursor to the catecholamine neurotransmitters as illustrated below.

Phenylalanine → **Tyrosine** → L-Dopa → Dopamine → Noradrenaline → Adrenaline

Folate, vitamins B3, B6, B12 and C, iron, copper and other nutrients are required for the metabolism of tyrosine to catecholamines.

Thyroid hormones As tyrosine is a precursor for the synthesis of thyroid hormones it is involved in the regulation of basal metabolic rate, oxygen use, cellular metabolism, growth and development (Tortora & Grabowski 1996).

Tyrosine undergoes iodination to form T_1 (mono-iodotyrosine), a second iodination produces T_2 (di-iodotyrosine) and these combine to produce the active thyroid hormones known as T_3 (tri-iodothyronine) and T_4 (tetra-iodothyronine or thyroxine) (Tortora & Grabowski 1996).

Tyrosine is also involved in the production of other compounds such as melanin, and some types of oestrogen (Hass 1992, Tortora & Grabowski 1996).

ANTIOXIDANT

Because tyrosine binds unstable molecules that can potentially cause damage to the cells and tissues, it is considered an antioxidant (Haas 1992).

CLINICAL USE

PHENYLKETONURIA

Phenylketonuria (PKU) is treated by restricting dietary intake of natural protein and substituting a protein source that lacks phenylalanine but is fortified with tyrosine. This recommendation is because people with PKU are unable to metabolise

phenylalanine, the precursor to tyrosine. Unfortunately, tyrosine supplementation has not been shown to consistently improve neuropsychologic function in PKU, which is possibly because increases in plasma tyrosine levels are not sustained and brain influx often remains suboptimal despite tyrosine supplementation (Kalsner et al 2001). In practice, plasma tyrosine levels are monitored and controlled (normal: 45 micromol/L) before tyrosine supplementation is considered (Poustie & Rutherford 2000, van Spronsen et al 2001).

ENHANCED COGNITION

Therapeutically, tyrosine supplements are used to enhance levels of its derivatives and, therefore, improve cognitive function.

One randomised, placebo-controlled study investigated the effects of L-tyrosine (150 mg/kg) on cognitive performance following one night's sleep loss. Supplementation was found to significantly reduce performance decline, with cognitive improvements lasting approximately 3 hours (Neri et al 1995).

RCTs comparing the effects of a balanced amino acid drink with one lacking in tyrosine and phenylalanine demonstrated that tyrosine-depleted individuals experienced impaired spatial recognition memory and spatial working memory and an increase in plasma prolactin levels (Harmer et al 2001, McTavish et al 2005), indicating a decrease in dopamine neurotransmission within the hypothalamus. Although ratings of depression and other aspects of cognitive function were unaffected, subjective feedback indicated that the participants felt better on the balanced drink (Harmer et al 2001).

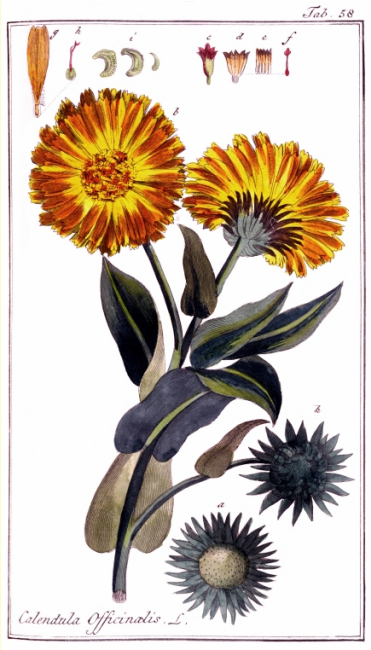
Changes in tyrosine transport may also influence cognitive functioning in schizophrenia via the dopamine system (Wiesel et al 2005).

DEPRESSION

As tyrosine is a precursor to both dopamine and noradrenalin, researchers have suggested that tyrosine depletion may play a role in the pathogenesis of depression. To date studies testing this hypothesis have produced mixed results. One study found that tyrosine- and phenylalanine-depleted individuals became less content and more apathetic than those given a balanced amino acid mixture (McLean et al 2004). However, a separate study in individuals with a past history of recurrent depression found that tyrosine depletion did not alter objective or subjective measures of mood (McTavish et al 2005), although plasma prolactin levels did increase and performance on a spatial recognition memory task was impaired (McTavish et al 2005).

Tyrosine appears to be most effective in treating depression associated with a lack of dopamine. One study involving patients with signs of dopamine-dependent

depression (DDD) found that treatment with oral tyrosine (3200 mg/day) caused an immediate improvement in mood, as judged by clinical impression and objective test scores (Montgomery–Asperg Depression Rating Scale) and sleep parameters from day 1 of treatment. Considered ineffective in other types of depression, supplementation with tyrosine should be limited to DDD (Mouret et al 1988a).



REWARD DEFICIENCY SYNDROME

Tyrosine depletion appears to affect reward-based processing (McLean et al 2004) and tests involving reward/punishment processing are affected by dopamine depletion (Roiser et al 2005). A lack of D_2 receptors and/or dopamine depletion states have been implicated in a number of conditions or destructive behaviours thought to be caused by poorly functioning biochemical reward systems.

Individuals tend to be at risk of multiple addictive, impulsive and compulsive behavioural problems, such as severe alcoholism, cocaine, heroin, marijuana and nicotine addiction, pathological gambling, sex addiction, chronic violence, post-traumatic stress disorder, risk taking behaviours and antisocial behaviour. As such, the use of tyrosine as a precursor to dopamine has a theoretical basis for use in this condition (Blum et al 2000).

Reward deficiency syndrome has also been proposed as a possible mechanism explaining the tendency to drug and alcohol addiction in schizophrenics (Green et al 1999).

To date, no large controlled studies are available to determine the clinical effects of tyrosine supplementation in this condition.

Drug withdrawal Tyrosine has been used to aid in the withdrawal of cocaine, caffeine and nicotine. Anecdotal reports suggest it is successful; however, large controlled studies are not available to determine clinical significance.

L-tyrosine supplementation has been considered because chronic cocaine use is believed to cause catecholamine depletion and cocaine withdrawal has been associated with major depression. To date, results from trials using tyrosine as a stand-alone treatment during cocaine withdrawal have produced disappointing results (Chadwick et al 1990, Galloway et al 1996). Although untested as yet, the effects of tyrosine may be of most assistance where a deficiency of dopamine D_2 receptors is suspected, such as in reward deficiency syndrome.

STRESS ADAPTATION

Physical and emotional stress can impair performance and memory. In order to reduce the adverse effects of stress on these functions, improvements in stress adaptation are sought, such as with the use of supplements such as tyrosine. Several

clinical studies have explored the effects of tyrosine in volunteers exposed to stressful situations, generally producing positive results on some parameters. (See 'Clinical note: allostatic responses to stress' in the Siberian ginseng monograph for more information about stress adaptation.)

Tyrosine supplementation was found to reduce the effects of stress and fatigue on cognitive task performance in a study conducted with a group of 21 cadets during a demanding military combat training course. Subjects received a protein-rich drink containing (2 g) tyrosine five times daily or a carbohydrate-rich drink with the same amount of calories (255 kcal). Assessments on day 6 of the course showed that the tyrosine group performed better on a memory and a tracking task than the control group and further experienced a decrease in systolic blood pressure; however, no effects on mood were observed (Deijen et al 1999).

Other studies indicate that high-dose tyrosine (150 mg/kg) may also improve some aspects of performance and help sustain working memory when multi-tasking in stressful situations. One placebo-controlled trial involving 20 people found that administration of tyrosine significantly enhanced accuracy and working memory during the multiple task battery 1 hour after ingestion. However, tyrosine did not significantly alter performance on the arithmetic, visual, or auditory tasks during the multiple task, or modify any performance measures during the simple task battery (Thomas et al 1999).

Cold stress Similar results were obtained in another controlled trial that investigated the effects of tyrosine (150 mg/kg) on memory tasks in cold (4°C) conditions. Two hours after ingesting L-tyrosine, matching accuracy significantly improved in the cold and was at the same level as administration of either tyrosine or placebo at a comfortable 22°C (Shurtleff et al 1994).

Other beneficial effects have been obtained with tyrosine supplementation in volunteers exposed to cold stress. A double-blind, placebo-controlled, crossover study found that tyrosine (100 mg/kg) could protect humans from some of the adverse consequences of a 4.5 hour exposure to cold and hypoxia. Tyrosine significantly decreased symptoms, adverse moods and performance impairment in subjects who exhibited average or greater responses to these environmental conditions (Banderet & Lieberman 1989).

OTHER USES

PREMENSTRUAL SYNDROME

Although tyrosine is used to reduce symptoms of irritability, depression, and fatigue associated with PMS, this is largely based on theoretical considerations and the

observation that a significant reduction in tyrosine levels occurs during the premenstrual period according to one study (Menkes et al 1994).

This study further found that tryptophan depletion caused a significant aggravation of premenstrual symptoms, particularly irritability, and symptom magnitude was correlated with reduction in tryptophan relative to other amino acids.

LOW LIBIDO

Although no controlled studies are available, tyrosine is sometimes used for this indication as it indirectly increases testosterone and dopamine levels, both factors important in libido.

PARKINSON'S DISEASE

Administration of tyrosine has been shown to increase dopamine production in the CNS of patients with Parkinson's disease (Growdon et al 1982).

WEIGHT LOSS

Tyrosine is thought to potentially suppress appetite and stimulate brown adipose tissue due to its enhancement of noradrenaline synthesis. Additionally, as a precursor for thyroid hormones it may also increase the basal metabolic rate.

CHRONIC FATIGUE SYNDROME

Low tyrosine levels have been identified in subjects with chronic fatigue syndrome, suggesting a possible role for supplementation in this condition (Georgiades et al 2003).

NARCOLEPSY

Abnormalities of the dopaminergic system are thought to be part of the underlying aetiology of this disorder, therefore tyrosine is used on the theoretical basis that an increase in dopamine levels will produce an improvement (Roufs 1990).

A randomised, double-blind placebo-controlled study of L-tyrosine (9 g/day for 4 weeks) has been conducted in 10 subjects with narcolepsy and cataplexy that tests this theory. While receiving tyrosine, subjects reported feeling less tired, less drowsy and more alert; however, ratings of daytime drowsiness, cataplexy, sleep paralysis, night-time sleep, overall clinical response, and measurements of multiple sleep latency and tests of speed and attention did not detect a significant difference with placebo (Elwes et al 1989). An earlier trial of longer duration, however, reported that within 6 months all eight participants were free from daytime sleep attacks and cataplexy (Mouret et al 1988b).

DOSAGE RANGE

- As tyrosine is considered to be a non-essential amino acid there is no specific recommended daily intake. The typical dose in clinical trials appears to be 100–150 mg/kg.
- Depression, PMS and chronic fatigue: 500–1000 mg before meals three times daily.
- Stress: 1500 mg/day in divided doses.
- Decreased libido, Parkinson's disease, drug detoxification, and weight loss: 1–2 g/day in divided doses.
- Natural stimulant: 500–1000 mg on an empty stomach first thing in the morning.
- Alertness following sleep deprivation: 150 mg/kg/day.
- As individual sensitivity to tyrosine can vary, it is recommended to start at 100 mg/day and gradually increase dose (Cass & Holford 2001).

ADVERSE REACTIONS

Migraine headache, mild gastric upset, nausea, headache, fatigue, heartburn, arthralgia, insomnia and nervousness (Hendler & Rorvik 2001).

High blood pressure may occur in susceptive individuals — hypertensive patients taking tyrosine should be monitored closely.

SIGNIFICANT INTERACTIONS

AMPHETAMINE, EPHEDRINE, PHENYLPROPANOLAMINE

L-tyrosine (200 and 400 mg/kg) has been shown to increase the side-effect of anorexia caused by phenylpropanolamine, ephedrine and amphetamine in a dose-dependent manner in rats (Hull & Maher 1990) — observe patients using this combination.

ANTIDEPRESSANT DRUGS

Monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants or selective serotonin reuptake inhibitor drugs (SSRIs) Theoretically, concurrent use may result in elevated blood pressure and/or enhanced antidepressant effects. In the case of MAOIs some tyrosine may be metabolised to tyramine and concurrent use with MAOIs may lead to hypertensive crisis.

Tyrosine should be avoided unless under medical supervision.

CNS STIMULANTS

Tyrosine is a precursor to a number of neurotransmitters so additive effects may occur — caution.

LEVODOPA

L-dopa competes with tyrosine for uptake, therefore concurrent use may decrease uptake of both substances, thereby reducing efficacy (Riederer 1980, DiPirro et al 1999, Awad 1984) — avoid unless under medical supervision.

MORPHINE SULFATE

L-tyrosine potentiates morphine-induced analgesia 154% in mice (Hull et al 1994). Observe patients taking tyrosine and morphine sulfate concurrently — potential beneficial interaction.

THYROID HORMONE MEDICATION

Additive effects possible because tyrosine is a precursor to thyroid hormones — observe patients taking tyrosine concurrently with thyroid hormone medication.

CONTRAINDICATIONS AND PRECAUTIONS

- Malignant melanoma: a theoretical concern exists that tyrosine supplementation may promote the division of cancer cells (McArdle et al 2001). Tyrosine is contraindicated until safety is established.
- Manic conditions: due to the theoretical possibility that tyrosine may significantly increase neurotransmitter synthesis, close medical supervision is required (Cass & Holford 2001).
- Hyperthyroidism and Graves' disease: theoretically tyrosine may aggravate these conditions as it is a precursor to thyroxine (van Spronsen et al 2001).
- Alkaptonuria and tyrosinaemia (inborn errors of tyrosine metabolism).
- Hypertension: use tyrosine with caution at high dose.

PREGNANCY USE

Not recommended during pregnancy (Cass & Holford 2001).

PRACTICE POINTS/PATIENT COUNSELLING

- Tyrosine is a conditionally essential amino acid that is ingested from the diet or produced from phenylalanine in the body.
- Many of the pharmacological actions of tyrosine relate to its role as a precursor to a number of neurotransmitters and thyroid hormones.
- Protein sources enriched with tyrosine but lacking in phenylalanine are used in PKU.
- Tyrosine supplements are used to improve cognitive function, in the management of depression or reward deficiency syndrome associated with noradrenaline or dopamine depletion, and to enhance stress adaptation systems.

- Due to its effects on neurotransmitters, it may elevate blood pressure in susceptible people when taken in high doses, and increase the effects of amphetamines, ephedrine, phenylpropanolamine, thyroxine and pharmaceutical antidepressants.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Tyrosine supplementation appears to increase the levels of important brain chemicals and thyroid hormones. As such, it may elevate mood and alertness, and enhance the body's ability to deal with stress.

When will it start to work?

Although some research suggests that effects begin within 1–2 hours, it may take up to 1 week for maximal effects to be seen.

Are there any safety issues?

Theoretically, tyrosine may increase blood pressure in susceptible individuals and also interact with a number of medicines such as pharmaceutical antidepressants and thyroid treatment. It is also not recommended in pregnancy.

REFERENCES

Amodia D, Stewart P. A historically controlled trial of tyrosine for cocaine dependence. J Psychoactive Drugs 28(3) (1996): 305-9.

Awad AG. Diet and drug interactions in the treatment of mental illness: a review. Can J Psychiatry 29 (1984): 609-13.

Balch JF, Balch PA. Prescriptions for Nutritional Healing, 2nd edn. Garden City Park, NY: Avery Publishing; 1997: 42.

Banderet LE, Lieberman HR. Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. Brain Res Bull 22(4) (1989): 759-62.

Berman RM et al. Transient depressive relapse induced by catecholamine depletion: potential phenotypic vulnerability marker? Arch Gen Psychiatry 56(5) (1999): 395-403.

Blum K et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 32 (Suppl i-iv) (2000): 1-112.

Brunello N et al. A double-blind amino acids, L-tryptophan and L-tyrosine, and placebo study with cocaine-dependent subjects in an inpatient chemical dependency treatment center. Am J Drug Alcohol Abuse 16(3-4) (1990): 275-86.

Cass H, Holford P. Natural Highs. Piatkus, 2001: 100.

Chadwick MJ, Gregory DL, Wendling G. A double-blind amino acids, L-tryptophan and L-tyrosine, and placebo study with cocaine-dependent subjects in an inpatient chemical dependency treatment center. Am J Drug Alcohol Abuse 16(3-4) (1990): 275-86.

Deijen JB et al. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull 48(2) (1999): 203-9.

DiPiro JT et al (eds). Pharmacotherapy: A Pathophysiologic Approach, 4th edn. Stamford: Appleton & Lang, 1999.

Dollins AB et al. L-tyrosine ameliorates some effects of lower body negative pressure stress. Physiol Behav 57(2) (1995): 223-30.

Elwes RD et al. Treatment of narcolepsy with L-tyrosine: double-blind placebo-controlled trial. Lancet 2(8671) (1989): 1067-9.

Fernstrom JD. Can nutrient supplements modify brain function? Am J Clin Nutr 71(6) (2000): 1669-72S.
Galloway GP et al. A historically controlled trial of tyrosine for cocaine dependence. J Psychoactive Drugs 28(3) (1996): 305-9.
Gelenberg AJ et al. Tyrosine for depression: a double-blind trial. J Affect Disord 19(2) (1990): 125-32.
Georgiades E et al. Chronic fatigue syndrome: new evidence for a central fatigue disorder. Clin Sci (Lond) 105(2) (2003): 213-18.
Green AI et al. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry 6(6) (1999): 287-96.
Growdon JH et al. Effects of oral L-tyrosine administration on CSF tyrosine and homovanillic acid levels in patients with Parkinson's disease. Life Sci 30 (1982): 827–32.
Haas EM. Staying Healthy with Nutrition. Berkeley, CA: Celestial Arts, 1992: 51.
Harmer CJ et al. Tyrosine depletion attenuates dopamine function in healthy volunteers. Psychopharmacology (Berl). 154(1) (2001): 105-11.
Harvie MN et al. Acceptability and tolerance of a low tyrosine and phenylalanine diet in patients with advanced cancer: a pilot study. J Hum Nutr Diet 15(3) (2002): 193-202.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Hull KM, Maher TJ. L-Tyrosine potentiates the anorexia induced by mixed-acting sympathomimetic drugs in hyperphagic rats. J Pharmacol Exp Ther. 255(2) (1990): 403-9.
Hull KM, Tolland DE, Maher TJ. L-tyrosine potentiation of opioid-induced analgesia utilizing the hot-plate test. J Pharmacol Exp Ther. 269(3) (1994): 1190-5.
Kalsner LR et al. Tyrosine supplementation in phenylketonuria: diurnal blood tyrosine levels and presumptive brain influx of tyrosine and other large neutral amino acids. J Pediatr 139(3) (2001): 421-7.
Martignoni E et al. Peripheral markers of oxidative stress in Parkinson's disease. The role of L-DOPA. Free Radic Biol Med 27(3-4) (1999): 428-37.
McArdle L et al. Protein tyrosine phosphatase genes downregulated in melanoma. J Invest Dermatol 117(5) (2001): 1255-60.
McLean A et al. The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. Psychopharmacology (Berl) 171(3) (2004): 286-97.
McTavish SF et al. Lack of effect of tyrosine depletion on mood in recovered depressed women. Neuropsychopharmacology 30(4) (2005): 786-91.
Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome J Affect Disord 32(1) (1994): 37-44.
Mindell E, Hopkins V. Prescription Alternatives. New Canaan, CT: Keats Publishing, 1998: 398.
Mouret J et al. L-tyrosine cures, immediate and long term, dopamine-dependent depressions. Clinical and polygraphic studies. C R Acad Sci III 306(3) (1988a): 93-8 [in French].
Mouret J et al. Treatment of narcolepsy with L-tyrosine. Lancet 2(8626-8627) (1988b): 1458-9.
Neri DF et al. The effects of tyrosine on cognitive performance during extended wakefulness. Aviat Space Environ Med 66(4) (1995): 313-19.
Poustie VJ, Rutherford P. Tyrosine supplementation for phenylketonuria. Cochrane Database Syst Rev 2 (2000): CD001507.
Riederer P. L-Dopa competes with tyrosine and tryptophan for human brain uptake. Nutr Metab 24(6) (1980): 417-23.
Roiser JP et al. The subjective and cognitive effects of acute phenylalanine and tyrosine depletion in patients recovered from depression. Neuropsychopharmacology 30(4) (2005): 775-85.
Roufs JB. L-tyrosine in the treatment of narcolepsy. Med Hypotheses 33(4) (1990): 269-73.
Scarna A et al. Effects of a branched-chain amino acid drink in mania. Br J Psychiatry 182 (2003): 210-13.
Shealy CN. The Illustrated Encyclopedia of Healing Remedies. Shaftesbury, UK: Element, 1998: 269.
Shurtleff D et al. Tyrosine reverses a cold-induced working memory deficit in humans. Pharmacol Biochem Behav 47(4) (1994): 935-41.

Thomas JR et al. Tyrosine improves working memory in a multitasking environment. Pharmacol Biochem Behav 64(3) (1999): 495-500.
Tortora GJ, Grabowski SR. Principles of Anatomy and Physiology. Harper Collins, 1996: 128, 522.
van Spronsen FJ, van Rijn M, Bekhof J. Phenylketonuria: tyrosine supplementation in phenylalanine restricted diets. Am J Clin Nutr 73 (2001): 153-7.
Versiani M, Racagni G. The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. Eur Neuropsychopharmacol 12(5) (2002): 461-75.
Werbach MR. Nutritional Influences on Illness. New Canaan, CT: Keats Publishing, 1987: 162.
Wiesel FA et al. Kinetics of tyrosine transport and cognitive functioning in schizophrenia. Schizophrenia Res 74(1) (2005): 81-9.
Yehuda S. Possible anti-Parkinson properties of N-([alpha]-linolenoyl) tyrosine: A new molecule. Pharmacol Biochem Behav 72(1-2) (2002): 7-11.

Valerian

Historical note The sedative effects of valerian have been recognised for over 2000 years, having been used by Hippocrates and Dioscorides in ancient Greece. Over the past 500 years, it was widely used in Europe as a calmative for nervousness or hysteria and also to treat dyspepsia and flatulence. Legend has it that the Pied Piper put valerian in his pockets to attract the rats out of Hannover. Valerian was widely used by the Eclectic physicians and listed in the United States Formulary until 1946.

COMMON NAME
Valerian

OTHER NAMES
All-heal, amantilla, balderbrackenwurzel, baldrian, baldrianwurzel, fragrant valerian, heliotrope, herbe aux chats, katzenwurzel, phu germanicum, phu parvum, valeriana, wild valerian

BOTANICAL NAME/FAMILY
Valeriana officinalis (family Valerianaceae)

PLANT PART USED
Rhizome

CHEMICAL COMPONENTS
Valtrates, didrovaltrates, isovaltrates, monoterpenes, sesquiterpenes, caffeic, gamma-amino butyric and chlorogenic acids, beta-sitosterol, methyl 2-pyrrolketone, choline, tannins, gum, alkaloids, a resin. Essential oils (0.5–2%) in the plant contain the compounds bornyl acetate and the sesquiterpene derivatives valerenic acid, valeranone and valerenal.

The chemical composition of valerian varies greatly depending on such factors as age of plant and growing conditions. Processing and storage of the herb also affects its constituents, such as the iridoid esters, which are chemically unstable.

MAIN ACTIONS

ANXIOLYTIC AND HYPNOTIC
Extensive pharmacological research has been conducted; however, identifying the main active constituents in valerian and their mode of action remains unclear and

several neurobiological mechanisms are believed to be at work. In vitro tests so far have demonstrated that valerian stimulates the release of GABA, inhibits GABA reuptake and may have an effect at GABA receptors (Ortiz et al 1999, Santos et al 1994). There is also evidence of agonist effects at the human A_1 adenosine receptor (Schumacher et al 2002).

One clinical study using both kava kava and valerian treatment has observed anxiolytic effects; however, it is uncertain what role valerian played in producing the effect (Wheatley 2001).

Both in vivo and numerous clinical studies confirm sedative activity (Ammer & Melnizky 1999, Balderer & Borbely 1985, Della et al 1981, Donath et al 2000, Dorn 2000, Leathwood & Chauffard 1985, Gerhard et al 1996, Gessner & Klasser 1984, Leuschner et al 1993, Lindahl & Lindwall 1989, Schulz et al 1994, Wheatley 2001).

ANTISPASMODIC

Both in vitro and in vivo studies provide evidence of antispasmodic activity on smooth muscle (Hazelhoff et al 1982).

OTHER ACTIONS

A pharmacokinetic study with healthy adults found that typical doses of valerian are unlikely to produce clinically significant effects on the CYP2D6 or CYP3A4 pathways of metabolism (Donovan et al 2004). These results were confirmed in another human pharmacokinetic study that found no evidence that valerian affects CYP3A4/5, CYP1A2, CYP2E1, and CYP2D6 activity (Gurley et al 2005).

CLINICAL USE

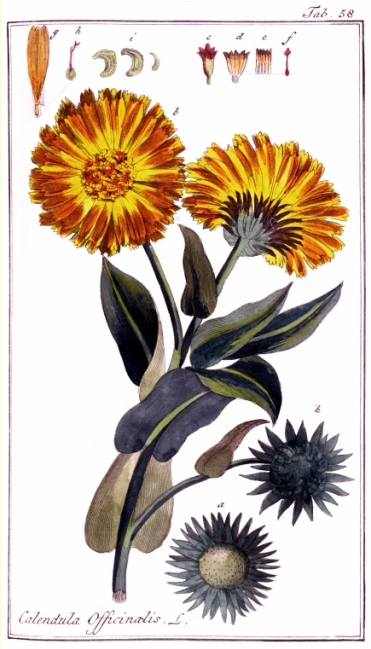
In practice, valerian is rarely used as a stand-alone treatment and is often combined with other sedative or relaxant herbs, such as chamomile, passionflower, skullcap, lemon balm and hops.

INSOMNIA

Numerous RCTs have investigated the effects of valerian as a treatment for insomnia. Although not all results are positive, results from several well conducted placebo-controlled studies suggest that valerian decreases sleep latency and increases sleep quality in poor sleepers. Preliminary evidence suggests that ongoing use may be more effective than single dose use and effects on sleep progress over several weeks.

A number of different valerian products have been studied (e.g. Baldosedron, Baldrien-Dispert, Euvegal, Harmonicum Much, Seda-Kneipp, Sedonium, Valdispert, Valverde and Valerina Nutt). The LI 156 valerian extract is one of the most studied.

A systematic review by Stevinson and Ernst (2000) identified 19 studies involving valerian treatment that were published prior to May 1999. Of these, nine were



chosen for inclusion because they were randomised, measured sleep parameters and tested single ingredient valerian products. Three studies considered the cumulative effects of long-term use of valerian whereas six investigated the effects of single-dose treatment. Two of the three studies investigating repeated administration of valerian found that effects were established by 2 weeks. The most rigorous placebo-controlled study showed that valerian LI 156 (600 mg) produced improvement on nearly all measures between weeks 2 and 4 (Vorbach et al 1996 as reported by Stevinson & Ernst 2000). The 4-week study involved 121 volunteers and assessed clinical effectiveness using four validated rating scales. At the end of the study, valerian was rated better than placebo on the Clinical Global Impression Scale, and at conclusion of the study (day 28) 66% of patients rated valerian effective, compared to 26% with placebo. Of the six studies investigating acute effects, valerian produced positive results in three whereas in the other three it was no better than placebo.

Interpretation of study results is difficult because of varying research methodologies. For example, some studies used surveys whereas others used EEG readings, some were conducted at home and others off site in hospitals or sleep laboratories, and pre-bedtime variables (e.g. caffeine consumption) were not fully controlled. Additionally, some studies used healthy volunteers with no sleep disturbances with little scope to observe further improvements. Since then, several other studies have been published.

Donath et al reported positive effects on sleep structure and sleep perception in subjects with insomnia after taking valerian for 14 days under double-blind crossover conditions, whereas single doses of valerian had no effect on sleep structure or subjective sleep assessment (Donath et al 2000).

More recently, a placebo-controlled, three-way crossover study using standardised sleep EEG and psychometric tests evaluated the clinical efficacy of a valerian preparation (LI 156) (Diaper & Hindmarch 2004). The 16 adults with sleep disturbances had a mean age of 56 years. Participants slept overnight in a sleep laboratory, following a dose of valerian 300 or 600 mg, or placebo at 9 pm and test periods were separated by 6 days of washout. Results showed no significant effect between valerian 300 and 600 mg or placebo on any EEG parameter or psychometric measure.

In Queensland, a series of n = 1 tests were carried out to investigate the effectiveness of valerian versus placebo for the management of chronic insomnia in general practice (Coxeter et al 2003). Of the 24 volunteers who had sufficient data for inclusion in the n-of-1 analysis, the response to valerian was poor or modest for all 24 (100%) for 'total sleep time' and for 23 (96%) for 'number of night awakenings' and

'morning refreshment'. Valerian was not shown to be appreciably better than placebo in promoting sleep or sleep-related factors for any individual patient or for all patients as a group. Each valerian tablet contained 225 mg *V. officinalis* root and rhizome extract equivalent to 1000 mg dry root and rhizome (Mediherb, Warwick, Australia; contents standardised to 2.94 mg total valerenic acids, 0.46 mg Valerenal and 1.23 mg Valtrates). Tablets were dispensed as per approved dosage recommendations: two tablets at night taken 30 minutes before bed.

Comparisons with benzodiazepines Two randomised studies have compared valerian with benzodiazepine drugs. One double-blind trial found that subjects treated with either 600 mg valerian or 10 mg oxazepam experienced significantly improved sleep, with no statistically significant differences detected between the treatments (Dorn 2000). Another study comparing the immediate sedative effects and residual effects of a valerian and hops preparation, a sole valerian preparation, flunitrazepam and placebo found that subjective perceptions of sleep quality were improved in all treatment groups; however, only flunitrazepam treatment impaired performance the morning after as assessed both objectively and subjectively (Gerhard et al 1996). Furthermore, 50% of subjects receiving flunitrazepam reported mild side-effects compared with only 10% from the other groups.

A 2002 double-blind randomised trial compared the effects of valerian extract LI 156 (Sedonium) 600 mg/day to 10 mg oxazepam over 6 weeks in 202 patients with non-organic insomnia (Ziegler et al 2002). The multicentre trial took place at 24 study centres in Germany and found that valerian treatment was at least as efficacious as oxazepam, with both treatments improving sleep quality. Subjectively, 83% of patients receiving valerian rated it as 'very good' compared with 73% receiving oxazepam.

Children The efficacy and tolerability of a valerian and lemon balm combination (Euvegal® forte) was tested in a large, open, multicentre study of 918 children (aged under 12 years) with restlessness and nervous sleep disturbance (dyssomnia) (Muller & Klement 2006). Both investigators and parent's ratings revealed a reduction in the severity of symptoms for most patients. The study reported that 81% of children with dyssomnia experienced an improvement and 70% of children with restlessness improved. Treatment was generally rated as good or very good and considered well tolerated. Each Euvegal® forte tablet consisted of 160 mg valerian root dry extract (*Valeriana officinalis* L.) with a drug-extract ratio of 4–5:1 (extraction solvent ethanol 62% v/v) and 80 mg lemon balm leaf dry extract (*Melissa officinalis*) with a drug-extract ratio of 4–6:1 (extraction solvent ethanol 30% v/v). The standard dosage of

Euvegal® forte (4 tablets daily) was used by 75% of patients and chosen by the investigator.

ANXIETY AND PSYCHOLOGICAL STRESS STATES

Less investigation has taken place to determine the role of valerian as a treatment for anxiety states. The few studies published thus far have produced encouraging results, but are hampered by methodological problems and well conducted trials are still required.

A randomised study found that low-dose valerian (100 mg) reduced situational anxiety without causing sedation (Kohnen & Oswald 1988). Positive results were also obtained in a smaller open study of 24 patients suffering from stress-induced insomnia who found treatment (valerian 600 mg/day for 6 weeks) significantly reduced symptoms of stress and insomnia (Wheatley 2001). Another randomised trial compared the effects of a preparation of valepotriates (mean daily dose 81.3 mg) with diazepam (mean daily dose 6.5 mg) and placebo in 36 outpatients with GAD under double-blind conditions (Andreatini et al 2002). After 4 weeks' treatment, all groups had significant reductions in Hamilton anxiety (HAM-A) scale scores; however, only those receiving valepotriates or diazepam showed a significant reduction in the psychic factor of HAM-A.

Kava kava is a herbal medicine also used in the treatment of anxiety and found to be effective in clinical studies (Pittler & Ernst 2002). A study that compared the effects of kava kava to valerian and placebo in a standardised mental stress test found that both herbal treatments reduced systolic blood pressure, prevented a stress-induced rise in heart rate and decreased self-reported feelings of stress (Cropley et al 2002).

MUSCLE SPASM AND CRAMPING

Valerian preparations have long been used to treat a wide variety of gastrointestinal disorders associated with spasms such as diarrhoea, colic and irritable bowel. It has also been used to relieve cramping in dysmenorrhoea. Although no controlled studies are available to confirm clinical effectiveness in these conditions, valerian is likely to exert some degree of antispasmodic activity based on its pharmacological actions.

OTHER USES

FIBROMYALGIA

One randomised study, which was investigator blinded, tested the effects of whirl baths with plain water or with water containing pine oil or valerian on pain, disturbed sleep and tender point count in 30 outpatients with generalised fibromyalgia. Valerian significantly improved wellbeing and sleep together with decreasing tender point count, whereas baths with pine oil worsened pain and plain water baths

reduced pain but had no effect on wellbeing and sleeplessness (Ammer & Melnizky 1999).

BENZODIAZEPINE WITHDRAWAL

Although no clinical studies are available, the herb is also used in practice to reduce dependency on benzodiazepine drugs. Valerian is prescribed together with other herbal medicines and psychological counselling while the benzodiazepine dose is slowly reduced.

DOSAGE RANGE

- Infusion of dried root: 3–9 g/day.
- Liquid extract (1:2): 2–6 mL/day.
- Tincture (1:5): 5–15 mL/day.
- When used for insomnia, valerian should be taken approximately 1 hour prior to bedtime.

ACCORDING TO CLINICAL STUDIES

- Anxiety: 100 mg–600 mg/day of the dried root or valepotriates (mean daily dose 81.3 mg).
- Insomnia: doses above 600 mg/day taken 1 hour before bedtime.

TOXICITY

According to one case report, a dose of valerian taken at approximately 20-fold the recommended therapeutic dose appears to be benign (Willey et al 1995).

ADVERSE REACTIONS

As with numerous pharmaceutical sedatives, next morning somnolence is a possible side-effect of therapy; however, evidence from two human studies suggests this is not associated with valerian use (Gerhard et al 1996, Kuhlmann et al 1999).

Vivid dreams were reported in one study; however, this is considered rare by clinicians (Wheatley 2001).

Paradoxical effects have been observed in clinical practice; however, this also appears to be rare (Mills & Bone 2000).

Occasionally, headache and gastrointestinal symptoms have been reported (Ernst 2001).

SIGNIFICANT INTERACTIONS

PHARMACEUTICAL SEDATIVES

Theoretically, potentiation effects may occur at high doses; however, this has not been tested under clinical conditions — observe patients taking valerian concurrently with pharmaceutical sedatives.

ALCOHOL

RCTs have shown no potentiation effects with alcohol use (Ernst 2001).

CONTRAINDICATIONS AND PRECAUTIONS

No known contraindications. Care should be taken when driving a car or operating heavy machinery when high doses are used.

PREGNANCY USE

No restrictions are known; however, safety has not been well established in pregnancy. No significant negative effects have been reported in toxicological tests with animals and none reported in clinical studies (Upton 1999).

PRACTICE POINTS/PATIENT COUNSELLING

- There is good scientific evidence to support the use of valerian as a treatment for insomnia; however, it appears that ongoing use may be more effective than single-dose use and effects on sleep progress over several weeks.
- It appears to be best suited to reducing sleep latency (i.e. time taken until falling asleep) and improves subjective assessments of sleep.
- There is no evidence of next-day somnolence or significant adverse effects.
- Valerian also relieves symptoms of stress and anxiety, with several studies observing effects similar to benzodiazepines; however, further research is required.
- Due to its pungent odour, solid-dose forms may be preferable.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Valerian is classified as a mild, sedative herbal medicine. It can reduce the time it takes to fall asleep at night and may also relieve stress and anxiety during the day. When added to a bath, it may increase relaxation, wellbeing and reduce some forms of pain.

When will it start to work?

For some, it works within an hour of the first dose; however, research suggests it works best after several weeks of regular use.

Are there any safety issues?

From the available evidence, next-day drowsiness is uncommon and physical addiction highly unlikely. Taking high doses during the day may increase drowsiness, so care is needed when driving a car or operating heavy machinery.

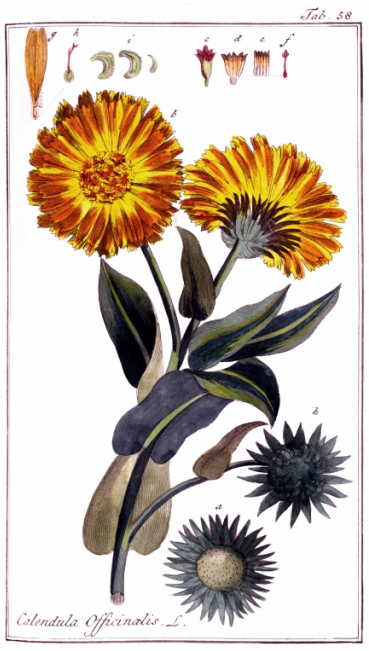
REFERENCES

Ammer K, Melnizky P. Medicinal baths for treatment of generalized fibromyalgia. Forsch Komplementarmed 6.2 (1999): 80-5.

Andreatini R et al. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother Res 16.7 (2002): 650-4.
Balderer G, Borbely AA. Effect of valerian on human sleep. Psychopharmacology (Berl) 87.4 (1985): 406-9.
Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Coxeter PD et al. Valerian does not appear to reduce symptoms for patients with chronic insomnia in general practice using a series of randomised n-of-1 trials. Complement Ther Med 11.4 (2003): 215-22.
Cropley M et al. Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. Phytother Res 16.1 (2002): 23-7.
Della Loggia R, Tubaro A, Redaelli C. Evaluation of the activity on the mouse CNS of several plant extracts and a combination of them. Riv Neurol 51.5 (1981): 297-310.
Diaper A, Hindmarch I. A double-blind, placebo-controlled investigation of the effects of two doses of a valerian preparation on the sleep, cognitive and psychomotor function of sleep-disturbed older adults. Phytother Res 18.10 (2004): 831-6.
Donath F et al Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. Pharmacopsychiatry 33.2 (2000): 47-53.
Donovan JL et al. Multiple night-time doses of valerian (Valeriana officinalis) had minimal effects on CYP3A4 activity and no effect on CYP2D6 activity in healthy volunteers. Drug Metab Dispos 32.12 (2004): 1333-6.
Dorn M. Efficacy and tolerability of Baldrian versus oxazepam in non-organic and non-psychiatric insomniacs: a randomized, double-blind, clinical, comparative study. Forsch Komplementarmed Klass Naturheilkd 7.2 (2000): 79-84.
Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.
Gerhard U et al. Acute sedative effect of a herbal relaxation tablet as compared to that of bromazepam. Schweiz Rundsch Med Prax 80.52 (1991): 1481-6.
Gerhard U et al. Vigilance-decreasing effects of 2 plant-derived sedatives. Schweiz Rundsch Med Prax 85.15 (1996): 473-81.
Gessner B, Klasser M. Studies on the effect of Harmonicum Much on sleep using polygraphic EEG recordings. Z Elektroenzephalog Elektromyogr Verwandte Geb 15.1 (1984): 45-51.
Gurley BJ et al. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 77.5 (2005): 415-26.
Hazelhoff B, Malingre TM, Meijer DK. Antispasmodic effects of valeriana compounds: an in-vivo and in-vitro study on the guinea-pig ileum. Arch Int Pharmacodyn Ther 257.2 (1982): 274-87.
Kohnen R, Oswald WD. The effects of valerian, propranolol, and their combination on activation, performance, and mood of healthy volunteers under social stress conditions. Pharmacopsychiatry 21.6 (1988): 447-8.
Kuhlmann J et al. The influence of valerian treatment on reaction time, alertness and concentration in volunteers. Pharmacopsychiatry 32.6 (1999): 235-41.
Leathwood PD, Chauffard F. Quantifying the effects of mild sedatives. J Psychiatr Res 17.2 (1982): 115-22.
Leathwood PD, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. Planta Med 2 (1985): 144-8.
Leathwood PD et al. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. Pharmacol Biochem Behav 17.1 (1982): 65-71.
Leuschner J, Muller J, Rudmann M. Characterisation of the central nervous depressant activity of a commercially available valerian root extract. Arzneimittelforschung 43.6 (1993): 638-41.
Lindahl O, Lindwall L. Double blind study of a valerian preparation. Pharmacol Biochem Behav 32.4 (1989): 1065-6.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Muller SF, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. Phytomedicine 13.6 (2006): 383-7.

Ortiz JG, Nieves-Natal J, Chavez P. Effects of Valeriana officinalis extracts on [3H]flunitrazepam binding, synaptosomal [3H]GABA uptake, and hippocampal [3H]GABA release. Neurochem Res 24.11 (1999): 1373-8.
Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev 2 (2002): CD003383.
Santos MS et al. Synaptosomal GABA release as influenced by valerian root extract: involvement of the GABA carrier. Arch Int Pharmacodyn Ther 327.2 (1994): 220-31.
Schulz H, Stolz C, Muller J. The effect of valerian extract on sleep polygraphy in poor sleepers: a pilot study. Pharmacopsychiatry 27.4 (1994): 147-51.
Schumacher B et al. Lignans isolated from valerian: identification and characterization of a new olivil derivative with partial agonistic activity at (A)1 adenosine receptors. J Nat Prod 65.10 (2002): 1479-85.
Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. Sleep Med 1.2 (2000): 91-9.
Upton R (ed). Valerian root. Santa Cruz: American Herbal Pharmacopoeia, 1999.
Wheatley D. Kava and valerian in the treatment of stress-induced insomnia. Phytother Res 15.6 (2001): 549-51.
Willey LB et al. Valerian overdose: a case report. Vet Hum Toxicol 37.4 (1995): 364-5.
Ziegler G et al. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia: a randomized, double-blind, comparative clinical study. Eur J Med Res 7.11 (2002): 480-6.

Vitamin A



Historical note In ancient Egypt and Greece, physicians recommended the liver of an ox to cure night blindness. Although this could be interpreted as applying the liver locally, it could also refer to ingesting some, which would have provided a good source of vitamin A and proven to be a cure for night-blindness caused by deficiency (Shils 2006). Modern day scientific research into vitamin A began in 1913 with its discovery at both Yale and Wisconsin Universities. Researchers at both sites independently noticed that the substance could promote survival and growth of young animals. Since then, each decade has brought important new discoveries about vitamin A. The period from the 1960s to 1980s was particularly fruitful, as several proteins essential for transport and metabolism of vitamin A were isolated and purified. During the 1980s another major discovery was made when a link between childhood mortality and subclinical deficiency was identified. Vitamin A research continues to interest a wide spectrum of researchers and influence public health initiatives.

BACKGROUND AND RELEVANT PHARMACOKINETICS

The term 'vitamin A' refers to a family of fat-soluble dietary compounds that are structurally related to retinol, and share its biological function. Vitamin A is found in foods as itself or as a precursor, which is converted into vitamin A in the body. The precursors, known as carotenes, are found in deep yellow, green and red coloured plants.

Retinyl esters, retinol or carotenoids from the diet or supplements are hydrolysed in the small intestine where they are absorbed as retinol into the mucosal cells (Miller et al 1998). Entering the body within the lipid core of chylomicrons, they are transported through lymph to blood, where it then recycles between plasma and tissues numerous times, before arriving at the liver. The liver performs three key tasks in relation to vitamin A. It is responsible for regulating the secretion of retinol to specific transport proteins known as 'retinol binding proteins', it serves as a major storage organ, and is the major site of vitamin A catabolism. Vitamin A metabolites are excreted mainly through the faeces and urine.

The body has a good capacity for vitamin A storage; however, its ability to rapidly dispose of excess vitamin A is quite limited (Shils 2006). This may explain why vitamin A can accumulate to toxic levels when intake greatly exceeds requirements.

This monograph will focus on preformed vitamin A and retinoic acid only. Further information about the carotenoids can be found in other monographs.

FOOD SOURCES

Preformed vitamin A (retinyl esters) is chiefly found in foods of animal origin, such as liver, red meat and eggs, as well as in fish, milk, butter and cream.

Cooking can destroy up to 40% of the vitamin A content of food (Wahlqvist et al 1997).

DEFICIENCY SIGNS AND SYMPTOMS

- Night blindness, which can progress to complete blindness if left untreated.
- Keratinisation of epithelial surfaces, causing them to dry and harden.
- Poor dental health.
- Compromised immune function.
- Reduced reproductive capabilities.

PRIMARY DEFICIENCY

Primary deficiency is caused by prolonged dietary deprivation. In large areas of the world, vitamin A deficiency is endemic, causing widespread blindness and mortality (Sklan 1987).

SECONDARY DEFICIENCY

Secondary deficiency can develop when absorption, storage or transport is reduced or carotene is not adequately converted to vitamin A. Conditions associated with risk of secondary deficiency include malabsorption syndromes, such as coeliac disease and cystic fibrosis, pancreatic disease, duodenal bypass, congenital partial obstruction of the jejunum, obstruction of the bile ducts, giardiasis, diabetes and kwashiorkor.

MAIN ACTIONS

Vitamin A is an essential nutrient required for life and serves two very different biological functions. First, in the form of retinaldehyde, it constitutes the light-sensitive component of the retina, rhodopsin, and second, in the form of retinoic acid, it activates a large number of transcription factors (McCaffery & Drager 1993).

ANTIOXIDANT

Vitamin A exhibits free radical scavenging properties.

GROWTH AND DEVELOPMENT

Vitamin A is essential for embryonic growth. Deficiency, as well as excess, has been shown to be teratogenic in animal studies, suggesting the same may be true in humans. It is currently unclear whether vitamin A itself or one of its metabolites or

both are responsible for the teratogenic effects seen with high exposure (Miller et al 1998).

Vitamin A is also necessary for healthy bone formation in children.

IMMUNE FUNCTION AND MAINTENANCE OF EPITHELIAL SURFACES

Vitamin A maintains the health of epithelial cells in the body, which form an important barrier to infection, and immune system function. More specifically, studies in animal models and cell lines show that vitamin A and related retinoids play a major role in immunity, including expression of mucins and keratins, lymphopoiesis, production of antibodies, and the function of neutrophils, NK cells, macrophages, T-lymphocytes and B-lymphocytes (Semba 1999). It has also been shown to potentiate antibody responses and lymphocyte proliferation in response to antigens and restore the integrity and function of mucosal surfaces (Semba 1994).

VISION

Vitamin A is involved in ocular health and function in two distinct ways. First, in the form retinaldehyde, it is an essential component of rhodopsin and is necessary for maintaining vision (Wahlqvist et al 1997). Deficiency states initially cause a reversible night-blindness that can progress to complete blindness due to photoreceptor degeneration (McCaffery & Drager 1993). Second, as retinoic acid it maintains normal differentiation of cells in the conjunctiva, cornea and other ocular structures, with deficiency resulting in xerophthalmia (dry eye) and corneal ulceration. In xerophthalmia, the cells lining the cornea lose their ability to produce mucus, and therefore lubrication of the eye becomes compromised. Dirt particles that eventually enter the eye are more easily able to scratch the surface, increasing the risk of infection and, ultimately, blindness.

CHEMOPREVENTION

Studies in cell culture and animal models have documented the capacity for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, cervical, prostate and other sites (Ross 1999). The mechanism of action responsible has not been fully elucidated, but several theories exist. It has been known since early in the 20th century that vitamin A deficiency can induce metaplastic changes to epithelial cells (De Luca et al 1997). Retinoic acid is thought to act as an inhibitor of carcinogenesis by interfering with promotion rather than with initiation, which may be blocked by inhibition of proliferation, stimulation of differentiation or induction of apoptosis (Niles 2000). Other research suggests it may also inhibit the final stage when malignant conversion of a benign tumour to a carcinoma occurs (De Luca et al 1997).

CLINICAL USE

DEFICIENCY: PREVENTION AND TREATMENT

Traditionally, vitamin A supplementation has been used to treat deficiency or prevent deficiency in conditions associated with risk of vitamin A deficiency, such as diabetes, hyperthyroidism, protein deficiency, intestinal infections and infestations and cystic fibrosis.

PAEDIATRICS

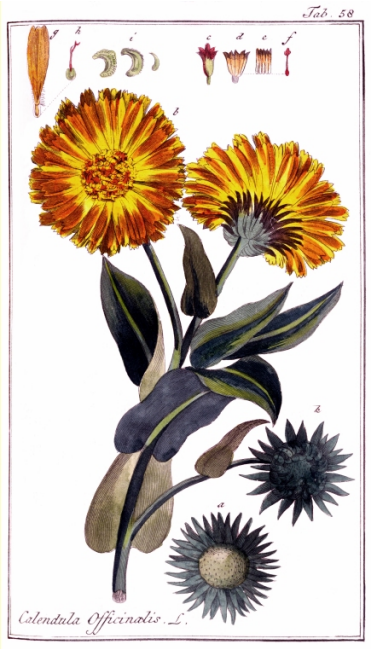
Reducing infection severity Vitamin A deficiency impairs systemic immunity and increases the incidence and severity of infections during childhood, particularly measles and infectious diarrhoea. There is also evidence that infectious diseases, such as measles, will in turn depress serum retinol concentrations, by >30% according to one study (Enwonwu & Phillips 2004). This phenomenon does not just occur in undernourished populations. A study of well-nourished children in the USA with measles identified that 50% had concurrent vitamin A deficiency (Arrieta et al 1992).

It is suspected that infectious diseases influence retinol metabolism through mechanisms that are more complex than simple loss of retinol stores (Enwonwu & Phillips 2004). Impaired synthesis of retinol-binding protein and transthyretin and decreased expression of the receptors for retinoic acid could also be responsible. As such, the use of vitamin A in the treatment of infectious disease is not limited to developing countries, but may also have application in well-nourished populations.

In areas where vitamin A deficiency may be present, the World Health Organization recommends administration of an oral dose of 200 000 IU (or 100 000 IU in infants) of vitamin A per day for 2 days to children with measles (D'Souza & D'Souza 2002a,b). It has also been recommended that prophylactic vitamin A supplements be given to all infants and young children (0–59 months), pregnant women and postpartum women 6 weeks after delivery, in these same areas (Ross 2002).

According to a 2005 Cochrane review, the WHO recommendation of two large doses of vitamin A does successfully lower the risk of death from measles in hospitalised children under the age of 2 years, but not in all children with measles (Huiming et al 2005).

Reducing secondary infections associated with measles A meta-analysis of six clinical trials found a 47% reduction in the incidence of croup in children with measles who were treated with 200 000 IU of vitamin A on 2 consecutive days. One study in the analysis reported a 74% reduction in the incidence of otitis media, but this was not confirmed in others. A statistically significant decrease in the duration of



diarrhoea, pneumonia, hospital stay and fever was also observed (D'Souza & D'Souza 2002a).

Reducing childhood mortality It has been estimated that a 23% reduction in young child mortality is possible with improvements in vitamin A status. This is most marked for deaths due to acute gastroenteritis and measles, but not acute respiratory infections or malaria (Ramakrishnan & Martorell 1998) and is particularly the case for older preschool children, whereas the effect on infants is less clear.

Very low birth weight infants Supplementing VLBW infants with intramuscularly administered vitamin A is associated with a reduction in death or oxygen requirement at 1 month of age (Darlow & Graham 2002).

Reducing the risk of HIV transmission from mother to infant The dominant mode of acquisition of HIV infection for children is mother-to-child transmission. Currently this results in more than 2000 new paediatric HIV infections each day worldwide. A 2005 Cochrane review analysed results from four trials, which enrolled 3,033 HIV-infected pregnant women, and found no evidence to support the use of vitamin A supplementation for this indication (Wiysonge et al 2005). One benefit that was identified for vitamin A supplementation was an improvement in infant birth weight.

CANCER PREVENTION

Most forms of cancer arise from cells that are influenced by vitamin A (Wardlaw et al 1997). Combined with its antioxidant and immunomodulatory activities, vitamin A has been considered as a potential chemopreventive agent. Research thus far using cell cultures and animal models has identified the ability for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, prostate, and other sites (Krinsky 2002). A look at the literature shows that impressive treatment results have mainly been obtained for synthetic retinoids and the relationship between natural vitamin A ingestion and cancer is less clear in humans.

Lung cancer A number of epidemiological studies have identified an inverse association between risk of lung cancer and serum carotenoid levels, but intervention studies have produced conflicting results. In general, vitamin A is supplied together with carotenoids making it difficult to determine the role of vitamin A as a stand alone agent. (See Beta-carotene monograph for further discussion.)

DERMATOLOGY

Numerous clinical studies have shown beneficial effects of vitamin A or its derivatives on skin diseases such as acne, psoriasis, ichthyoses, keratodermas, skin cancers, lichen planus and UV-induced skin damage and photo-ageing (Futoryan & Gilchrest 1994).

Currently, most research has been conducted with synthetic retinoid derivatives and is not representative of the effects of natural vitamin A.

OPHTHALMOLOGICAL DISEASES

Retinitis pigmentosa One randomised, double-blind trial found that people receiving 15 000 IU/day of vitamin A experienced a slowed rate of retinal function decline (Berson et al 1993). The mechanism responsible is poorly understood, but it is possible that vitamin A transport or the retention capacity of the retina is abnormal in retinitis pigmentosa or defects in the pigment epithelium involving vitamin-associated proteins occurs (Sharma & Ehinger 1999).

Clinical note — Retinitis pigmentosa
Retinitis pigmentosa describes a group of hereditary retinal dystrophies, characterised by the early onset of night-blindness followed by a progressive loss of the visual field. The underlying pathology is a defect that alters the function of the rod photoreceptor cell and subsequent degeneration of these cells (van Soest et al 1999).

Xerophthalmia Xerophthalmia is responsible for at least half of all cases of measles-associated blindness and is the cause of at least half a million cases of paediatric blindness worldwide (Sommer 1998). This condition is associated with vitamin A deficiency and protein malnutrition.

REDUCING MORBIDITY AND MORTALITY OF PREGNANT WOMEN

Vitamin A supplements have been recommended in pregnancy to improve outcomes, including maternal mortality and morbidity. There is a Cochrane review of five trials involving 23,426 women that investigated the effects of vitamin A supplementation during pregnancy, alone or in combination with other supplements (Van et al 2002). Trials were heterogeneous and difficult to pool; however, two trials from Nepal and Indonesia suggested beneficial effects of vitamin A supplementation. In addition, daily or weekly vitamin A supplementation reduced night-blindness in pregnant women living in high-risk areas.

OTHER USES

Vitamin A has also been used in the treatment of menorrhagia and PMS, to prevent glaucoma and cataract, Crohn's disease, asthma, sinusitis and rhinitis.

DOSAGE RANGE

- Vitamin A activity is expressed as a unit called microgram retinol equivalents (RE) (Miller et al 1998): 1 μg RE = 1 μg all-trans retinol or 6 μg all-trans betacarotene or

3.33 international units (IU) of vitamin A or 1 μg RE is equivalent in activity to 1.78 μg of retinyl palmitate and 10 IU activity from beta-carotene.

AUSTRALIAN RDI (IN MICROGRAMS RE)

Children

1–3 years: 300 μg/day.
4–8 years: 400 μg/day.
9–13 years: 600 μg/day.
Girls 14–18 years: 700 μg/day.
Boys 14–18 years: 900 μg/day.

Adults

Females: 700 μg/day.
Males: 900 μg/day.
Upper level of intake: 3000 μg/day.

Pregnancy

<18 years: 700 μg/day.
>18 years: 800 μg/day.

Lactation : 1100 μg/day.

- Deficiency without corneal changes: 10 000–15 000 IU/day for 1–2 weeks, until clinical improvement is apparent.
- General treatment doses: 10 000–50 000 IU/day have been used short term.

ACCORDING TO CLINICAL STUDIES

- Reducing secondary infection in children with measles: 200 000 IU of vitamin A on two consecutive days when vitamin A deficiency may be present.
- Retinitis pigmentosa: 15 000 IU/day.

TOXICITY

Cumulative toxicity is possible when doses greater than 100 000 IU are ingested long term. Acute toxicity is very difficult to induce in adults, as doses above 2 000 000 IU are required (Hendler et al 2001).

Early signs of toxicity include dry rough skin, cracked lips, coarse hair, sparse hair, alopecia of eyebrows, diplopia, dryness of the mucous membranes, desquamation, bone and joint pain, fatigue and malaise, nausea and vomiting, and psychological changes mimicking depression and schizophrenia.

Later signs include irritability, increased intracranial pressure and headache, dizziness, liver cirrhosis, fibrosis and cirrhosis, vomiting, haemorrhage and coma (Miller et al 1998).

People with chronic renal disease typically have elevated plasma retinol levels and therefore may be at greater risk of toxicity if supplementation is used.

It is important to note that beta-carotene is not associated with teratogenic effects or vitamin A toxicity and is considered a far safer nutrient.

Clinical note — Vitamin A toxicity in two young children

In 2001, a report of two children admitted to hospital with symptoms of vitamin A toxicity was published in the *Medical Journal of Australia*. One case involved a 2-year-old girl with anorexia, lethargy and leg pain, an erythematous rash over her back and elbows and irritability. All symptoms resolved over 2 weeks following withdrawal of the supplement. The second case involved a child who had previously been prescribed oral etretinate by a dermatologist (for an unspecified period of time), which was ceased 3 months prior to vitamin A supplementation. In both cases, the dose of vitamin A taken was in excess of that provided by standard OTC products (Coghlan & Cranswick 2001).

ADVERSE REACTIONS

In general, doses of vitamin A that do not exceed physiological requirements have no adverse effects.

SIGNIFICANT INTERACTIONS

CHOLESTYRAMINE

Reduces vitamin A absorption — increase dietary intake of vitamin A rich foods or consider supplementation with long-term use.

HMG-COA REDUCTASE INHIBITOR DRUGS (STATINS)

These drugs increase the serum levels of vitamin A, the clinical significance of which is unclear — observe patients taking this combination (Muggeo et al 1995).

ISOTRETINOIN

Toxicity may be increased — avoid this combination.

MINOCYCLINE

Long-term vitamin A use with this drug increases the risk of pseudotumour cerebri — use with caution.

ORAL CONTRACEPTIVES

Increased vitamin A levels occur in OCP users due to longer storage in the liver (Tyrer 1984) — use caution with large doses of retinol.

ORLISTAT
Reduces vitamin A levels — increase dietary intake of vitamin A rich foods or consider supplementation with long-term use.

CONTRAINDICATIONS AND PRECAUTIONS

Doses greater than 10 000 IU/day long term should be given with caution.

People with liver or renal disease or alcoholism should use vitamin A supplements with caution.

PREGNANCY USE

In the USA sources state that doses up to 10 000 IU/day are safe in pregnancy, but Australian authorities recommend that supplements containing ≥2500 IU of vitamin A per dose must have pregnancy warning statements on their labels.

It is important to note that beta-carotene, found naturally in plants, is not associated with teratogenic effects or vitamin A toxicity.

The teratogenicity of 13-cis-retinoic acid, a synthetic derivative of vitamin A available in Australia as Roaccutane, is well established and that substance is contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin A is a fat-soluble antioxidant that is chiefly stored in the liver.
- It is involved in maintaining vision, healthy immune function, necessary for growth and development, reproductive capability and healthy epithelial cell function.
- It is used to treat and prevent deficiency states, and there is clinical evidence that supplementation reduces the incidence and severity of infections during childhood, particularly measles and infectious diarrhoea, reduces the incidence of croup and otitis media in children with measles, and may be useful in retinitis pigmentosa.
- Vitamin A deficiency is widespread in some countries, increasing the risk of childhood infectious disease, mortality and deficiency-associated blindness.
- Excessive vitamin A supplementation can induce a toxicity state that can have serious, sometimes irreversible consequences.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin A is essential for health and is involved in many different biochemical processes in the body. Some research has suggested that it reduces the incidence and severity of some infectious diseases in children. Vitamin A or its synthetic derivatives have also been used in many skin conditions such as acne, psoriasis, UV-induced skin damage and photo-ageing and the treatment of some cancers.

When will it start to work?

This will depend on the form of vitamin A being used and the indication it is being used to treat.

Are there any safety issues?

Taking high doses of vitamin A long term can cause side-effects and is contraindicated in pregnancy.

REFERENCES

Albanes D et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 88.21 (1996): 1560-70.

Arrieta AC et al. Vitamin A levels in children with measles in Long Beach, California. J Pediatr 121.1 (1992): 75-8.

Berson EL et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol 111.6 (1993): 761-72.

Chainani-Wu N. Diet and oral, pharyngeal, and esophageal cancer. Nutr Cancer 44.2 (2002): 104-26.

Clarke R, Armitage J. Antioxidant vitamins and risk of cardiovascular disease. Review of large-scale randomised trials. Cardiovasc Drugs Ther 16.5 (2002): 411-15.

Coghlan D, Cranswick NE. Complementary medicine and vitamin A toxicity in children. Med J Aust 175.4 (2001): 223-24.

Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. Cochrane Database Syst Rev 4 (2002): CD000501.

De Luca L et al. The role of vitamin in differentiation and skin carcinogenesis. J Nutr Biochem 8 (1997): 426-37.

D'Souza RM, D'Souza R. Vitamin A for preventing secondary infections in children with measles: a systematic review. J Trop Pediatr 48.2 (2002a): 72-7.

D'Souza RM, D'Souza R. Vitamin A for treating measles in children. Cochrane Database Syst Rev 1 (2002b): CD001479.

Enwonwu CO, Phillips RS. Increased retinol requirement in acute measles infection in children: an hypothesis on role of hypercortisolemia. Nutr Res 24.3 (2004): 223-7.

Futoryan T, Gilchrest BA. Retinoids and the skin. Nutr Rev 52.9 (1994): 299-310.

Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.

Hennekens CH et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 334.18 (1996): 1145-9.

Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. Cochrane Database Syst Rev 4 (2005): CD001479.

Ito Y et al. Serum carotenoids and mortality from lung cancer: a case-control study nested in the Japan Collaborative Cohort (JACC) study. Cancer Sci 94.1 (2003): 57-63.

Krinsky NI. Vitamin A. Oregon: Linus Pauling Institute, 2002.

McCaffery P, Drager UC. Retinoic acid synthesis in the developing retina. Adv Exp Med Biol 328 (1993): 181-90.

Miller RK et al. Periconceptional vitamin A use: how much is teratogenic? Reprod Toxicol 12.1 (1998): 75-88.

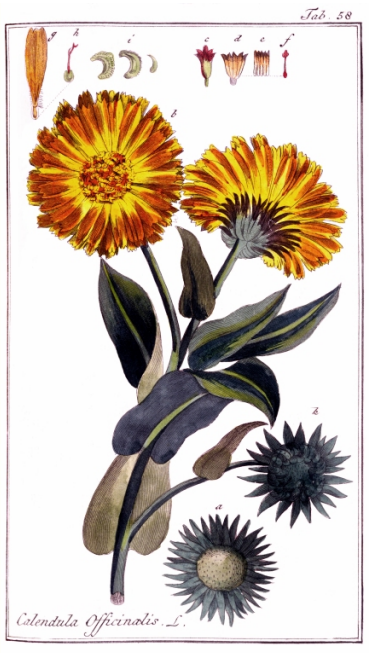
Muggeo M et al. Serum retinol levels throughout 2 years of cholesterol-lowering therapy. Metabolism 44.3 (1995): 398-403.

Niles RM. Recent advances in the use of vitamin A (retinoids) in the prevention and treatment of cancer. Nutrition 16.11-12 (2000): 1084-9.

Ramakrishnan U, Martorell R. The role of vitamin A in reducing child mortality and morbidity and improving growth. Salud Publica Mex 40.2 (1998): 189-98.

Ross AC. Vitamin A and retinoids. In: Shils M et al (eds). Modern Nutrition in Health and Disease, 9th edn. Baltimore: Williams & Wilkins, 1999: 305-27.
Ross DA. Recommendations for vitamin A supplementation. J Nutr 132.9 (Suppl) (2002): 2902-6S.
Semba RD. Vitamin A and immunity to viral, bacterial and protozoan infections. Proc Nutr Soc 58.3 (1999): 719-27.
Semba RD. Vitamin A, immunity, and infection. Clin Infect Dis 19.3 (1994): 489-99.
Sharma RK, Ehinger B. Management of hereditary retinal degenerations: present status and future directions. Surv Ophthalmol 43.5 (1999): 427-44.
Shils M et al (eds). Modern Nutrition in Health and Disease. Baltimore: Lippincott Williams & Wilkins, 2006. Available at: Clinicians Health Channel gateway.ut.ovid.com (accessed 21-06-06).
Sklan D. Vitamin A in human nutrition. Prog Food Nutr Sci 11.1 (1987): 39-55.
Sommer A. Xerophthalmia and vitamin A status. Prog Retin Eye Res 17.1 (1998): 9-31.
Tyrer LB. Nutrition and the pill. J Reprod Med 29.7 Suppl (1984): 547-50.
Van DE et al. Vitamin A supplementation during pregnancy. Cochrane Database Syst Rev 4 (2002): CD001996.
van Soest S et al. Retinitis pigmentosa: defined from a molecular point of view. Surv Ophthalmol 43.4 (1999): 321-34.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wardlaw G et al. Contemporary Nutrition, 3rd edn. Dubuque: Brown and Benchmark, 1997.
Wiysonge CS et al. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev 4 (2005): CD003648.

Vitamin B1



Historical note The Chinese medical book 'Neiching' describes beriberi in 2697 BC, but it was not known for a long time that vitamin B1 deficiency was responsible. In 1926, two Dutch chemists isolated anti-beriberi factor from rice bran extracts and in the 1930s its structure was determined.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B1 is a water-soluble compound required by all tissues. It is also known as thiamine, anti-beriberi factor, antineuritic factor and its active coenzyme form: thiamine diphosphate. Thiamine's phosphate ester functions as a coenzyme in carbohydrate metabolism and nerve conduction. The free form is found in plasma, but intracellularly it is phosphorylated to one of three forms: thiamine-monophosphate (TMP), thiamine diphosphate (TDP) or thiamine triphosphate (TTP), with the majority as TDP, which is the most active form. The ability of thiamine to shift between these different levels of phosphorylation makes it a key nutrient in energy pathways.

There are two sources of thiamine: dietary and a bacterial source whereby it is synthesised by the normal intestinal microflora. Thiamine is absorbed from the small intestine by a saturable rate-limiting transport mechanism. The absorption of thiamine in the gastrointestinal tract can be impaired by the presence of naturally occurring thiaminases that are found in raw fish or polyhydroxyphenols found in certain food and beverages; for example, coffee, tea, blueberries, red cabbage and brussel sprouts (Groff & Gropper 2000).

It is transported by the portal circulation to the liver where it is metabolised, then excreted mainly through the kidneys. Thiamine is found in high concentrations in skeletal muscle, heart, liver, kidneys and brain and its half-life is approximately 15 days (Singleton & Martin 2001).

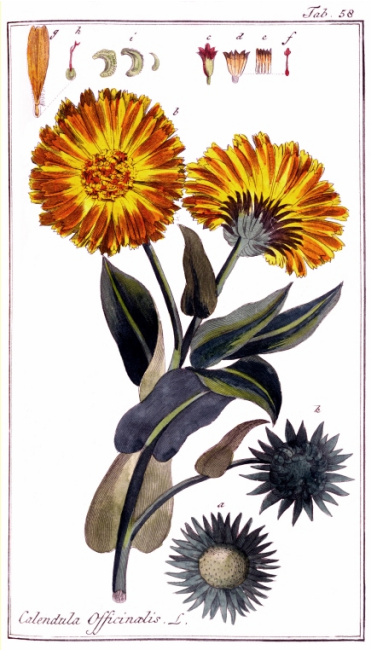
CHEMICAL COMPONENTS

Thiamine (vitamin B1) is a water-soluble substance, consisting of thiazole and pyrimidine rings joined by a methylene bridge.

FOOD SOURCES

Brewer's yeast, lean meat and legumes are considered the richest sources of thiamine. Other sources include cereals, grains, pasta, wheatgerm, soy milk, seeds and peanuts.

It is possible to lose up to 85% of the thiamine content in meat through cooking and canning, and up to 60% from cooking vegetables (Tanphaichitr 1999). There is also loss through refining of grains and in some countries the fortification of wheat flour with B vitamins is mandatory to compensate for this loss.



DEFICIENCY SIGNS AND SYMPTOMS

The body only stores a small amount of thiamine and signs of deficiency tend to develop within 15–18 days of restricted intake.

Beriberi is the classic thiamine deficiency state. General early deficiency signs and symptoms include fatigue, irritability, poor memory, sleep disturbances, chest wall pain, anorexia, abdominal discomfort and constipation.

There are three forms of beriberi: dry, wet and cerebral, also known as Wernicke-Korsakoff syndrome. Dry beriberi is associated with peripheral neurological changes whereas cerebral beriberi involves alterations to ocular function, cognitive function and produces ataxia, which can also be fatal. In addition to neurological changes, wet beriberi is associated with cardiovascular changes characterised by peripheral vasodilation, sodium and water retention, increased cardiac output and myocardial failure, which can advance to become fatal in severe cases. Although alcoholism is the major cause of Wernicke-Korsakoff syndrome, it has also been reported in several other conditions such as hyperemesis gravidarum and hyperemesis due to gastroplasty (Gardian et al 1999, Ogershok et al 2002, Seehra et al 1996, Spruill & Kuller 2002, Tan & Ho 2001, Togay-Isikay et al 2001, Toth & Voll 2001).

PRIMARY DEFICIENCY

Primary deficiency is caused by inadequate dietary intake of thiamine, particularly in people subsisting mainly on highly polished rice (de Montmollin et al 2002) or unfortified grain products. Insufficient intake may also occur in anorexia and in people receiving TPN without supplemental thiamine.

SECONDARY DEFICIENCY

Secondary deficiency is caused by an increased requirement, as in hyperthyroidism, pregnancy, lactation, fever, acute infection, increased carbohydrate intake, folate deficiency, malabsorption states, hyperemesis, prolonged diarrhoea, strenuous physical exertion, breast feeding, adolescent growth, and states of impaired utilisation such as severe liver disease, alcoholism and people taking loop diuretics long term. Additionally, pyruvate dehydrogenase deficiency can result in deficiency (Beers & Berkow 2003, Wahlqvist et al 1997, Wardlaw et al 1997).

Clinical note — Thiamine deficiency is not uncommon
Several observational studies have reported that thiamine deficiency is not uncommon in the elderly. A study of 118 aged hospital patients identified a moderate deficiency incidence of 40% (Pepersack et al 1999). Similar results were obtained in another survey where marginal thiamine deficiency had an incidence of 31% and frank deficiency of 17% (O'Keeffe et al 1994). Besides inducing deficiency signs and symptoms, preliminary research suggests that inadequate intake could increase susceptibility to neurodegeneration, particularly in aged organisms (Pitkin & Savage 2004).

MAIN ACTIONS

COENZYME

Carbohydrate and branched chain amino acid metabolism Thiamine serves as a cofactor for several enzymes involved in carbohydrate catabolism, including pyruvate dehydrogenase, transketolase, and alpha-ketoglutarate, and for the branched-chain alpha-keto acid dehydrogenase complex that is involved in amino acid catabolism (Singleton & Martin 2001). Some of these enzymes are also important in brain oxidative metabolism (Molina et al 2002).

Neurotransmitter biosynthesis Thiamine is involved in the biosynthesis of a number of cell constituents, including the neurotransmitters acetylcholine and GABA.

DNA Thiamine is involved in the synthesis of precursors of DNA, therefore thiamine use is increased in tumours.

NEUROPSYCHOLOGICAL ACTIONS

Besides its involvement in neurotransmitter biosynthesis, thiamine is required for neurotransmission, nerve conduction and muscle action. In the form of TTP, it concentrates in nerve and muscle cells and activates membrane ion channels. As such, thiamine deficiency is associated with neurological changes and suspected of contributing to the development of alcoholic peripheral neuropathy (D'Amour et al 1991).

CLINICAL USE

Many of the clinical uses of thiamine supplements are conditions thought to arise from a marginal deficiency, but some indications are based on the concept of high-dose supplements acting as therapeutic agents. In practice, vitamin B1 is usually recommended in combination with other B group vitamins.

DEFICIENCY: TREATMENT AND PREVENTION

Thiamine supplements are traditionally used to treat or prevent thiamine deficiency states in people at risk (see Secondary Deficiency).

Hyperemesis Although thiamine supplementation will not reduce the symptoms of hyperemesis, it may be necessary in cases of hyperemesis gravidarum and hyperemesis due to gastroplasty in order to avoid deficiency states and the development of Wernicke's encephalopathy, which has been reported in these situations, although noted to be a rare consequence. It may be precipitated in part by intravenous fluids containing dextrose, and is more commonly seen when the patient's liver transaminases are elevated, which may contribute to the encephalopathy (Gardian et al 1999, Seehra et al 1996, Spruill & Kuller 2002, Tan & Ho 2001, Togay-Isikay et al 2001, Toth & Voll 2001, Welsh 2005).

Alcoholism In alcoholism, a state of decreased intake, absorption, utilisation and increased requirement for thiamine occurs, suggesting a need to increase intakes to avoid deficiency states (D'Amour et al 1991). In cases of Wernicke's encephalopathy, monitoring of thiamine status and prophylactic intravenous treatment will inhibit the progression to Korsakoff's psychosis (Thomson & Marshall 2005). Ongoing research has revealed that the cerebellar neurotoxicity associated with excess alcohol is more likely to be predominantly mediated by thiamine deficiency rather than direct ethanol cytotoxicity as previously believed (Mulholland et al 2005).

Total parenteral nutrition Several case reports show patients who have received TPN without proper replacement of thiamine are at risk of developing deficiency signs and Wernicke's encephalopathy (Hahn et al 1998, van Noort et al 1987, Vortmeyer et al 1992, Zak et al 1991).

ACUTE ALCOHOL WITHDRAWAL

Several guidelines for the support of alcohol withdrawal recommend a dose of 100 mg thiamine administered intravenously or intramuscularly before routine administration of dextrose-containing solutions (Adinoff et al 1988, Erstad & Cotugno 1995).

ALZHEIMER'S DEMENTIA

Thiamine status has been investigated and found, amongst other nutrients, to have an inverse relationship with cognitive function in the elderly (Nourhashemi et al 2000). More specifically, AD has been associated with reduced plasma levels of thiamine, according to several clinical studies (Gold et al 1995, 1998, Molina et al 2002). One study analysed cerebral cortex samples from autopsied patients with AD

and found slight reductions in thiamine diphosphate levels compared with matched controls (Mastrogiacoma et al 1996).

Proposed mechanisms for the relationship between thiamine and AD are varied, ranging from its role as an antioxidant and its critical contribution to the Krebs cycle to its involvement in the production of acetylcholine, disturbances of which have all been implicated in the pathology of AD (Bubber et al 2004, Butterfield et al 2002, Kruse et al 2004).

Investigation with high-dose thiamine supplementation in this population has produced mixed results (Blass et al 1988, Meador et al 1993, Mimori et al 1996). One double-blind, placebo-controlled crossover study showed that a dose of 3000 mg thiamine/day produced higher global cognitive ratings as assessed by the Mini-Mental State Examination compared with a niacinamide placebo. However, there were no changes to clinical state and behavioural ratings (Blass et al 1988). Another clinical study of unknown design found positive results with a dose ranging between 3 and 8 g/day of thiamine (Meador et al 1993) whereas a long-term study using high-dose supplementation produced negative results (Mimori et al 1996).

Although promising overall, a 2001 Cochrane review stated that it is still not possible to draw any conclusions about the effectiveness of thiamine supplementation in AD (Rodriguez-Martin et al 2001). In practice, it is often used as part of a broad-spectrum approach with other B-group vitamins in age-related cognitive decline; however, further research is required to determine whether this method produces more consistent results.

CONGESTIVE HEART FAILURE

A 2001 review concluded that there was insufficient evidence from large trials to confirm thiamine as a corrective treatment in congestive heart failure (CHF); however, prophylactic supplementation was worthwhile considering the high prevalence of deficiency in this population (Blanc & Boussuges 2001). The largest and most recent trial since then was published in 2006 and confirmed that the incidence of deficiency is notable in this population (Hanninen et al 2006). It is suspected that patients with existing heart failure are at increased risk of thiamine deficiency because of diuretic-induced depletion, advanced age, malnutrition or periods of hospitalisation.

A number of small interventional studies have assessed the effect of thiamine supplementation in patients with CHF with promising results. In one pilot study six patients treated with IV thiamine, such that their thiamine status returned to normal, resulted in increased left ventricular ejection fraction (LVEF) in four of five of patients studied by ECG (Seligman et al 1991). A randomised, placebo-controlled, double-blind study of 30 patients compared the effects of IV thiamine (200 mg/day) to

placebo over 1 week followed by oral thiamine (200 mg/day) taken for 6 weeks. In the 27 patients completing the full 7-week intervention, LVEF rose by 22%. Other positive results have been reported from similar studies (Hanninen et al 2006).

DYSMENORRHOEA

A Cochrane review of herbal and dietary therapies for primary and secondary dysmenorrhoea concluded that thiamine is an effective treatment when taken at 100 mg/day, although this conclusion is tempered slightly by its basis on only one large RCT (Wilson & Murphy 2001). That trial was a randomised, double-blind, placebo-controlled crossover design conducted over 5 months in 556 women and procured a positive improvement in >90% of the treatment cycle versus <1% in the placebo phase. The improvements observed during treatment appeared to have lasting effects, even after cessation of supplementation, for up to 3 months (Gokhale 1996). Due to the dramatic 'success' of this study, it has attracted skepticism regarding its methodology; certainly a question is why, with such positive results, an attempt to replicate the findings has not been undertaken in over 9 years (Fugh-Berman & Kronenberg 2003).

Clinical note — No protection against insect bites

One claim that has been around for many years is that high oral doses of certain B vitamins could act as a deterrent to insects such as mosquitoes. Principally the myth has centred around thiamine. A recent review of prophylaxis against insect bites found that neither topical application nor oral dosing of thiamine is an effective preventative strategy (Rudin 2005).

OTHER USES

CATARACTS

A case-controlled study of 72 patients found that thiamine supplementation reduced the incidence of cortical, nuclear and mixed cataract (Leske et al 1991).

COMA

A general approach to patients presenting to hospital with coma is to ensure adequate oxygenation, blood flow and treatment with hypertonic glucose and thiamine (Alguire 1990, Buylaert 2000).

EPILEPSY

A randomised, placebo-controlled study involving 72 patients with epilepsy who had received long-term phenytoin treatment alone or in combination with phenobarbital found that administration of thiamine (50 mg/day) over 6 months improved

neuropsychological functions in both verbal and non-verbal IQ testing (Botez et al 1993). This study also found both folate supplementation and placebo ineffective.

FATIGUE

B group vitamins are often taken by the public to lessen the impact of 'stress' and provide an energy boost. In one study, thiamine 10 mg/day significantly increased appetite, energy intake, body weight, general wellbeing and decreased fatigue, compared with placebo in a group of 80 randomly chosen women from a population with known marginal deficiency (Smidt et al 1991). Thiamine supplementation also tended to reduce daytime sleep time, improve sleep patterns, and increase activity.

HIV

Several neuropathological reports have described brain lesions characteristic of Wernicke's encephalopathy in patients with AIDS. One study found a 23% prevalence of thiamine deficiency in AIDS patients with no history of alcohol abuse (Butterworth et al 1991).

NEUROGENIC IMPOTENCE

A dose of 25 mg thiamine taken orally resulted in normalisation of erection in a man with a history of chronic alcoholism and erectile dysfunction of 1 year's duration (Tjandra & Janknegt 1997). However, more recent evidence discussing the causes of neurogenic impotence suggests that thiamine deficiency is relatively rare (Finsterer 2005).

MAPLE SYRUP URINE DISEASE

Of four pediatric patients with maple syrup urine disease, three responded to thiamine therapy with a reduction in concentration of plasma and urinary branched-chain amino and ketoacids (Fernhoff et al 1985).

OPTIC NEUROPATHY

Several case reports suggest this condition can be caused by thiamine deficiency and successfully treated with supplementation. One case report of a man developing optic neuropathy as a result of receiving TPN without thiamine for 4 weeks found that supplementation with thiamine reversed the condition (Suzuki et al 1997). Two cases of symmetrical, bilateral optic neuropathy associated with thiamine deficiency were successfully treated with thiamine supplementation (Hoyt & Billson 1979).

DOSAGE RANGE

- Prevention of deficiency (adult Australian RDI): 1.1–1.2 mg/day.
- Treatment of marginal deficiency states: 5–30 mg/day.

- Critical deficiency: 50–100 mg IV or IM for 7–14 days after which oral doses are used (Tanphaichitr 1999).
- Congestive heart failure: 100 mg twice daily IV for 1–2 weeks then 200 mg/day orally .
- Dysmenorrhoea: 100 mg/day orally.
- Support of alcohol withdrawal: 100 mg given IV or IM.
- Fatigue (when marginal deficiency likely): 10 mg/day.

AUSTRALIAN RDI

Females >13 years: 1.1 mg/day.

Males >13 years: 1.2 mg/day.

TOXICITY

Toxicity does not occur with oral thiamine as it is rapidly excreted by the kidneys (Tanphaichitr 1999), although there is some evidence that toxicity can occur with very large doses given parenterally (Jacobs & Wood 2003).

ADVERSE REACTIONS

Thiamine is well tolerated.

SIGNIFICANT INTERACTIONS

ANTIBIOTICS

Antibiotics can reduce the endogenous production of B-group vitamins by gastrointestinal flora, theoretically resulting in lowered B vitamin levels. The clinical significance of this is unclear — increase intake of vitamin B1 rich foods or consider supplementation.

IRON

Iron precipitates thiamine, thereby reducing its absorption — separate doses by 2 hours.

LOOP DIURETICS

Chronic use may result in lowered levels of vitamin B1 — increase intake of vitamin B1-rich foods or consider long-term supplementation.

OTHER B VITAMINS

Thiamine deficiency commonly occurs in conjunction with poor B2 and B6 status (Jacobs & Wood 2003).

SULFITES

Concomitant intake may inactivate thiamine, which has been reported in TPN solutions (Bowman & Nguyen 1983).

TANNINS
Tannins precipitate thiamine, thereby reducing its absorption — separate doses by 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS

CANCER
There is some evidence of thiamine being associated with nucleic acid ribose synthesis of tumour cells in its biologically activated form (Boros 2000). As such, thiamine may theoretically increase tumour formation. To date, the clinical relevance of this finding has not been explored.

PREGNANCY USE
Safe during pregnancy and lactation.

PRACTICE POINTS/PATIENT COUNSELLING
- Thiamine is necessary for healthy functioning and is involved in carbohydrate and protein metabolism, the production of DNA, several neurotransmitters and nerve and muscle function.
- Supplements are used to treat deficiency or prevent secondary deficiency in people at risk (e.g. alcoholism, malabsorption syndromes, hyperemesis, chronic diarrhoea, hyperthyroidism, pregnancy, lactation, fever, acute infection, folate deficiency, strenuous physical exertion, breast feeding, adolescent growth, severe liver disease and chronic use of loop diuretics).

  There is a higher incidence of deficiency in people with CHF; however, it is not known whether correction of the deficiency will improve disease symptoms.
- High-dose thiamine supplements relieve symptoms of dysmenorrhoea according to one large RCT.
- Additionally, some early research has found an association between Alzheimer's dementia and low plasma thiamine levels with supplementation producing some benefits; however, further investigation is still required.
- Oral supplements are non-toxic, but should be used with caution in patients with cancer.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this vitamin do for me?

Thiamine is necessary for healthy functioning and is involved in carbohydrate and protein metabolism, the production of DNA, several brain chemicals and nerve and muscle function. Supplements are taken to avoid deficiency states that can occur, for instance, in alcoholism, extreme vomiting, chronic diarrhoea or malabsorption

syndromes. In high doses, it may relieve symptoms of painful menstruation and may be a useful adjunct in CHF.

When will it start to work?

Thiamine supplements can have dramatic effects on deficiency states within 24 hours. The response time for other conditions, such as dysmenorrhoea and CHF, also appear to be reasonably fast. Within two menstrual cycles, supplementation produced marked reductions in dysmenorrhoea, and CHF patients treated for only 7 weeks showed positive responses.

Are there any safety issues?

Taken orally, thiamine is considered non-toxic. People with cancer should consult with their physician before taking high-dose thiamine supplements.

REFERENCES

Adinoff B et al. Acute ethanol poisoning and the ethanol withdrawal syndrome. Med Toxicol Adverse Drug Exp 3.3 (1988): 172-96.

Alguire PC. Rapid evaluation of comatose patients. Postgrad Med 87.6 (1990): 223-8, 233.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc, 2003.

Blanc P, Boussuges A. Is thiamin supplementation necessary in patients with cardiac insufficiency? [Abstract]. Ann Cardiol Angeiol 50.3 (2001): 160-8.

Blass JP et al. Thiamin and Alzheimer's disease: A pilot study. Arch Neurol 45.8 (1988): 833-5.

Boros LG. Population thiamin status and varying cancer rates between western, Asian and African countries. Anticancer Res 20.3B (2000): 2245-8.

Botez MI et al. Thiamin and folate treatment of chronic epileptic patients: a controlled study with the Wechsler IQ scale. Epilepsy Res 16.2 (1993): 157-63.

Bowman BB, Nguyen P. Stability of thiamin in parenteral nutrition solutions. J Parenter Enteral Nutr 7.6 (1983): 567-8.

Bubber P et al. Tricarboxylic acid cycle enzymes following thiamin deficiency. Neurochem Int 45.7 (2004): 1021-8.

Butterfield DA et al. Nutritional approaches to combat oxidative stress in Alzheimer's disease. J Nutr Biochem 13.8 (2002): 444-61.

Butterworth RF et al. Thiamin deficiency and Wernicke's encephalopathy in AIDS. Metab Brain Dis 6.4 (1991): 207-12.

Buylaert WA. Coma induced by intoxication. Acta Neurol Belg 100.4 (2000): 221-4.

D'Amour ML et al. Abnormalities of peripheral nerve conduction in relation to thiamin status in alcoholic patients. Can J Neurol Sci 18.2 (1991): 126-8.

de Montmollin D et al. Outbreak of beri-beri in a prison in West Africa. Trop Doct 32.4 (2002): 234-6.

Erstad BL, Cotugno CL. Management of alcohol withdrawal. Am J Health Syst Pharm 52.7 (1995): 697-709.

Fernhoff PM et al. Thiamin response in maple syrup urine disease. Pediatr Res 19.10 (1985): 1011-16.

Finsterer J. Mitochondrial neuropathy. Clin Neurol Neurosurg 107.3 (2005): 181-6.

Fugh-Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. Reprod Toxicol 17.2 (2003): 137-52.

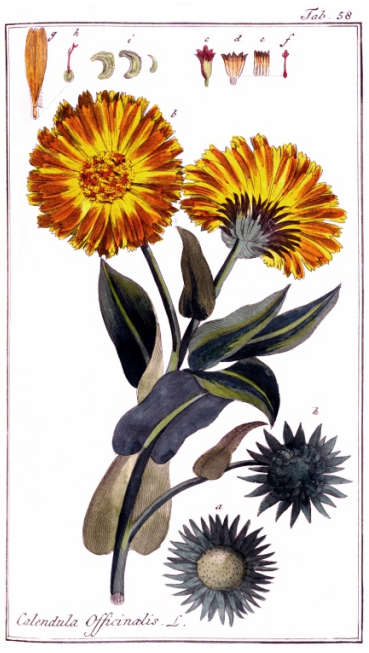
Gardian G et al. Wernicke's encephalopathy induced by hyperemesis gravidarum. Acta Neurol Scand 99.3 (1999): 196-8.

Gokhale LB. Curative treatment of primary (spasmodic) dysmenorrhoea. Indian J Med Res 103 (1996): 227–31.

Gold M et al. Plasma and red blood cell thiamin deficiency in patients with dementia of the Alzheimer's type. Arch Neurol 52.11 (1995): 1081-6.
Gold M et al. Plasma thiamine deficiency associated with Alzheimer's disease but not Parkinson's disease. Metab Brain Dis 13.1 (1998): 43-53.
Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism. Belmont, CA: Wadsworth, 2000.
Hahn JS et al. Wernicke encephalopathy and beriberi during total parenteral nutrition attributable to multivitamin infusion shortage. Pediatrics 101.1 (1998): E10.
Hanninen SA et al. The prevalence of thiamin deficiency in hospitalized patients with congestive heart failure. J Am Coll Cardiol 47 (2006): 354-61.
Hoyt CS, Billson FA. Optic neuropathy in ketogenic diet. Br J Ophthalmol 63.3 (1979): 191-4.
Jacobs P, Wood L. Hematology of malnutrition. II: Vitamin B_1. Disease-a-Month 49.11 (2003): 646-52
Kruse M et al. Increased brain endothelial nitric oxide synthase expression in thiamin deficiency: relationship to selective vulnerability. Neurochem Int 45.1 (2004): 49-56.
Leske MC et al. The Lens Opacities Case-Control Study: Risk factors for cataract. Arch Ophthalmol 109.2 (1991): 244-51.
Mastrogiacoma F et al. Brain thiamin, its phosphate esters, and its metabolizing enzymes in Alzheimer's disease. Ann Neurol 39.5 (1996): 585-91.
Meador K et al. Preliminary findings of high-dose thiamin in dementia of Alzheimer's type. J Geriatr Psychiatry Neurol 6.4 (1993): 222-9.
Mimori H et al. Thiamin therapy in Alzheimer's disease. Metab Brain Dis 11 (1996): 89–94.
Molina JA et al. Cerebrospinal fluid levels of thiamin in patients with Alzheimer's disease. J Neural Transm 109.7-8 (2002): 1035-44.
Mulholland PJ et al. Thiamine deficiency in the pathogenesis of chronic ethanol-associated cerebellar damage in vitro. Neuroscience 135.4 (2005): 1129-39.
Nourhashemi S et al. Alzheimer disease: protective factors. Am J Clin Nutr 71 (2000): 643-9s.
O'Keeffe ST et al. Thiamine deficiency in hospitalized elderly patients. Gerontology 40.1 (1994): 18-24.
Ogershok PR et al. Wernicke encephalopathy in nonalcoholic patients. Am J Med Sci 323.2 (2002): 107-11.
Pepersack T et al. Clin relevance of thiamin status amongst hospitalized elderly patients. Gerontology 45.2 (1999): 96-101.
Pitkin SR, Savage LM. Age-related vulnerability to diencephalic amnesia produced by thiamin deficiency: the role of time of insult. Behav Brain Res 148.1-2 (2004): 93-105.
Rodriguez-Martin JL et al. Thiamin for Alzheimer's disease. Cochrane Database Syst Rev 2 (2001): CD001498.
Rudin W. Protection against insect bites. Ther Umsch 62.11 (2005): 713-18.
Seehra H et al. Wernicke's encephalopathy after vertical banded gastroplasty for morbid obesity. BMJ 312.7028 (1996): 434.
Seligmann H et al. Thiamin deficiency in patients with congestive heart failure receiving long-term furosemide therapy: A pilot study. Am J Med 91 (1991): 151-5.
Singleton CK, Martin PR. Molecular mechanisms of thiamin utilization. Curr Mol Med 1.2 (2001): 197-207.
Smidt LJ et al. Influence of thiamin supplementation on the health and general well-being of an elderly Irish population with marginal thiamin deficiency. J Gerontol 46.1 (1991): M16-22.
Spruill SC, Kuller JA. Hyperemesis gravidarum complicated by Wernicke's encephalopathy. Obstet Gynecol 99.5 (2002): 875-7.
Suzuki S et al. Optic neuropathy from thiamin deficiency. Intern Med 36.7 (1997): 532.
Tan JH, Ho KH. Wernicke's encephalopathy in patients with hyperemesis gravidarum. Singapore Med J 42.3 (2001): 124-5.
Tanphaichitr V. Thiamin. In: Shils M et al (eds). Modern Nutrition in Health and Disease. Baltimore: Lippincott Williams & Wilkins, 1999.
Thomson AD, Marshall EJ. The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff's psychosis. Alcohol Alcohol 41(2) (2005): 151-8.

Tjandra BS, Janknegt RA. Neurogenic impotence and lower urinary tract symptoms due to vitamin B1 deficiency in chronic alcoholism. J Urol 157.3 (1997): 954-5.
Toth C, Voll C. Wernicke's encephalopathy following gastroplasty for morbid obesity. Can J Neurol Sci 28.1 (2001): 89-92.
van Noort BA et al. Optic neuropathy from thiamine deficiency in a patient with ulcerative colitis. Doc Ophthalmol 67.1-2 (1987): 45-51.
Vortmeyer AO et al. Haemorrhagic thiamine deficient encephalopathy following prolonged parenteral nutrition. J Neurol Neurosurg Psychiatry 55.9 (1992): 826-9.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wardlaw G et al. Contemporary Nutrition, 3rd edn. Brown and Benchmark, 1997.
Togay-Isikay C et al. Wernicke's encephalopathy due to hyperemesis gravidarum: an under-recognised condition. Aust NZ J Obstet Gynaecol 41.4 (2001): 453-6.
Welsh A. Hyperemesis, gastrointestinal and liver disorders in pregnancy. Curr Obstet Gynaecol 15.2 (2005): 123-31.
Wilson ML, Murphy PA. Herbal and dietary therapies for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 3 (2001): CD002124.
Zak J III et al. Dry beriberi: unusual complication of prolonged parenteral nutrition. J Parenter Enteral Nutr 15.2 (1991): 200-1.

Vitamin B2 — Riboflavin



BACKGROUND AND RELEVANT PHARMACOKINETICS

Riboflavin is a water soluble B group vitamin that is sensitive to light and alkali conditions. Once absorbed, it is converted into its active form. Riboflavin works as a component of two primary coenzymes, flavin adenine dinucleotide (PAD) and flavin mononucleotide (FMN), belonging to the class known as the flavin coenzymes, all active in redox reactions involving hydrogen transfer and consequently important for the body's production of ATP. Although some organs (such as the liver) have relatively high concentrations of flavin coenzymes, the flavin seems to be present as coenzyme moieties of flavin holoenzymes, which are fully functional.

There are two sources of riboflavin: dietary and bacterial whereby the vitamin is produced by the normal gastrointestinal microflora. The amount of bacterially synthesised riboflavin depends on the type of diet consumed, with higher synthesis resulting from intake of vegetable-based diets compared with meat-based diets (Said 2004). Direct dietary sources are discussed later.

Riboflavin uptake occurs mainly in the proximal part of the small intestine and involves a specialised, Na^+-independent carrier-mediated system. Adaptive changes alter the number and/or activity of carriers and uptake is saturable when large pharmacological doses of riboflavin are ingested. There is evidence that bioavailability is optimal once 25 mg has been reached and doses in excess of this show reduced or unaltered absorption efficacy (Groff & Gropper 2004). The absorption of B2 is enhanced when it is consumed in flesh foods and impeded by the presence of divalent metals (e.g. zinc, iron, copper and manganese).

FOOD SOURCES

The main food sources are organ meats, yeast products (including Vegemite), almonds, wheatgerm, wild rice and mushrooms. It is also found to a lesser extent in dairy products and vegetables. Maximum loss during cooking is 75% (Wahlqvist 1997).

DEFICIENCY SIGNS AND SYMPTOMS

PRIMARY DEFICIENCY

Primary deficiency is associated with inadequate dietary intake such as poor consumption of milk and other animal products. Primary deficiency is reported to be more common in the elderly and adolescent girls.

SECONDARY DEFICIENCY

Secondary deficiencies can develop in chronic diarrhoea, liver disease, chronic alcoholism, adrenal or thyroid hormone insufficiency and postoperative situations in which TPN solutions lack riboflavin. In most cases, riboflavin deficiency is accompanied by other vitamin deficiencies such as vitamin B6, niacin and folic acid. Drugs that impair riboflavin absorption or utilisation by inhibiting the conversion of the vitamin to the active coenzymes include tricyclic, antidepressants, chemotherapy drugs and psychotropic agents. There is also evidence suggesting an apparent increase in riboflavin requirements with increased physical exercise.

SIGNS AND SYMPTOMS OF DEFICIENCY

The body's 'storage capacity' is sufficient to provide riboflavin for 2–6 weeks when nutritional status is normal, but during protein deficiency the stores are significantly reduced.

Initial symptoms of riboflavin deficiency are often non-specific and include: weakness, fatigue, mouth pain and personality changes. Isolated riboflavin deficiency seldom occurs and is usually associated with a deficiency of other B group vitamins.

Other signs and symptoms are:

- angular stomatitis, cracked lips, cold sores and cheilosis
- glossitis, magenta tongue (Lo 1984)
- failure to grow in children
- ocular and visual disturbances with symptoms such as burning, itching and sensitivity to light and conjunctivitis
- scaly and greasy dermatitis affecting the nasolabial folds, ears, eye lids, scrotum and labia majora (Lo 1984)
- desquamative dermatitis
- hair loss
- poor wound healing.

Of interest, a study of 154 pregnant women at increased risk of pre-eclampsia found that those who were riboflavin deficient were 4.7-fold more likely to develop the condition than those with adequate levels (Wacker et al 2000).

MAIN ACTIONS

Riboflavin is involved in many different biological processes and is essential for maintaining good health. It is involved in ATP production, is essential for immune function, tissue repair processes and general growth (it is required for the healthy growth of skin, nails and hair) and plays a key role in fatty acid oxidation and the metabolism of several other B vitamins.

Riboflavin has important antioxidant activity in itself but also as part of the FAD-dependent enzyme glutathione reductase. It also activates vitamin B6 and folate.

CLINICAL USE

A number of clinical trials have been conducted whereby patients presenting with one condition have subsequently been found to have riboflavin deficiency. Treating the deficiency in these cases has, in some situations, been shown to improve the initial presenting condition.

WOUND HEALING

Riboflavin deficiency lengthens the time to epithelialisation of wounds, slows the rate of wound contraction and reduces the tensile strength of incision wounds in vivo. Total collagen content is also significantly decreased, suggesting riboflavin deficiency will slow down wound healing rate (Lakshmi et al 1989).

MIGRAINE HEADACHES: PROPHYLAXIS

Clinical note

Numerous theories exist to explain the underlying pathology of migraine headache. One theory proposes a deficit of mitochondrial energy metabolism, as patients with migraine show decreased brain mitochondrial energy reserve between attacks. Considering nutrients such as riboflavin and coenzyme Q10 can enhance mitochondrial energy efficiency, they have been tested for prophylactic activity in migraine (Schoenen et al 1994). Recent studies in experimental models add to our knowledge of the actions of riboflavin in migraine, with confirmation that it produces antinociception and anti-inflammatory effects. The analgesic activity observed is independent of opioid mechanisms (Granados-Soto et al 2004).

Three clinical studies of varying design have found that treatment with high-dose riboflavin (400 mg) can reduce the frequency of migraine headache; however, one double-blind study that used it in combination with magnesium and feverfew failed to show beneficial effects over low-dose riboflavin (25 mg).

The first was an open pilot study testing the effects of 400 mg riboflavin over 3 months in 49 patients. Active treatment produced positive results, with 59% of the treatment group experiencing a reduction in migraine frequency by at least 50% (Schoenen et al 1994). Based on these results, a second study with 55 subjects was conducted using a randomised, placebo-controlled design, with similar positive findings (Schoenen et al 1998). In 2004 an open-label study retested the same high dose of B2 over 6 months and once again showed a significant reduction in headache frequency from 4 days/month at baseline to 2 days/month after 3 and 6 months of

treatment ($P < 0.05$). Use of abortive drugs reduced from 7 units/month to 4.5 units/month; however, the duration and intensity of each episode did not change significantly (Boenke et al 2004).

Alternatively, a randomised, double-blind, controlled study using a combination of vitamin B2 (400 mg), magnesium (300 mg) and feverfew (100 mg) failed to show benefits over riboflavin 25 mg. Both groups showed a comparable significant reduction in number of migraines, migraine days, and migraine index; however, neither successfully reduced frequency by greater than 50%, which was the primary outcome (Maizels et al 2004). Interestingly, the response obtained was greater than the placebo response reported in other migraine prophylaxis trials.

Comparative trial A clinical trial comparing riboflavin supplementation with standard beta-adrenergic antagonists found that both treatments significantly improved the clinical symptoms of migraine headache (Sandor et al 2000). Analysis of their effects on cortical potentials showed that the two treatments achieve these results by working through different mechanisms.

AGE-RELATED CATARACT PREVENTION

Clinical note

Age-related cataract is an important public health problem because approximately 50% of the 30–50 million cases of blindness worldwide result from leaving the condition untreated (Jacques 1999). The mechanisms that bring about a loss in transparency include oxidation, osmotic stress, and chemical adduct formation (Bunce et al 1990). Besides traditional risk factors such as diabetes, nutrient deficiency is also being considered, particularly those with antioxidant properties.

Cataract was shown to be associated with riboflavin deficiency in animals in the 1930s and subsequently with deficiencies of amino acids, vitamins and some minerals (Wynn & Wynn 1996). This has been confirmed in human studies whereby lens opacities have been associated with lower levels of riboflavin, vitamins A, C and E, iron, and protein status (Leske et al 1995, Mares-Perlman et al 1995).

Glutathione reductase is a key enzyme involved in lens protection. Riboflavin levels indirectly influence glutathione reductase activity, increasing the lens's ability to deal with free radical formation (Head 2001). One study documented severe glutathione reductase deficiency in 23% of human lens-epithelium specimens, possibly reflecting a dietary deficiency of riboflavin (Straatsma et al 1991). Another study identified that a significant number of people with cataracts have inactive epithelial glutathione reductase (Horwitz et al 1987).

A large cross-sectional survey of 2873 volunteers aged 49–97 years detected a link between dietary vitamin supplement and a lower incidence of both nuclear and cortical cataract. Vitamin A, niacin, riboflavin, thiamine, folate and vitamin B12 all appeared to be protective, either in isolation or as constituents of multivitamin preparations (Kuzniarz et al 2001).

A recent sample of 408 women from the Nurses' Health Study aged 52–74 years at baseline participated in a 5-year study that assessed nutrient intake and the degree of nuclear density (opacification). Findings revealed that the geometric mean 5-year change in nuclear density was inversely associated with the intake of riboflavin ($P = 0.03$) and thiamin ($P = 0.04$), and most significantly with the duration of vitamin E supplement use ($P = 0.006$) (Jacques et al 2005).

The evidence currently suggests that higher intakes of riboflavin are protective against the progression of age-related lens opacification.

SICKLE CELL ANAEMIA

Riboflavin supplementation (5 mg twice daily for 8 weeks) in patients with sickle cell anaemia resulted in improved haematological measurements compared with controls, suggesting that riboflavin enhances erythropoiesis (Ajayi et al 1993).

RHEUMATOID ARTHRITIS

One study has suggested that patients with higher pain scores and active disease are at significantly greater risk of riboflavin deficiency than those with inactive disease (Mulherin et al 1996). In this study of 91 patients, pain score, articular index, C-reactive protein, and erythrocyte sedimentation rate were all increased in those patients exhibiting riboflavin deficiency (all $P < 0.02$). It is unclear whether riboflavin deficiency influences pain threshold or is a result of the disease.

OTHER USES

Riboflavin is also used to treat carpal tunnel syndrome and acne, although only case reports are available (Folkers et al 1984).

DOSAGE RANGE

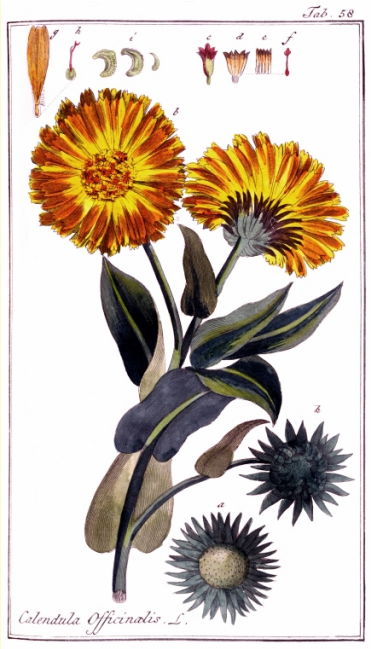
- Migraine prevention: 400 mg/day taken for at least 3 months.
- Treating deficiency states: 10 mg/day.
- Intake of vitamin B2 causes a characteristic bright yellow-orange discolouration to urine.

AUSTRALIAN RDI

<70 years

- Women: 1.1 mg/day

- Men: 1.3 mg/day
  >70 years
- Women: 1.3 mg/day
- Men: 1.6 mg/day



TOXICITY
Riboflavin is considered an extremely safe supplement. Even at the high doses (400 mg) used in some of the trials, riboflavin remains non-toxic.

ADVERSE REACTIONS
General side-effects noted in trials using high doses were reasonably uncommon, but included diarrhoea and polyuria (Bianchi et al 2004). One case of anaphylaxis has been reported (Ou et al 2001).

SIGNIFICANT INTERACTIONS
Certain medicines can increase the body's requirements of riboflavin.

ANTIBIOTICS
Antibiotic drugs can reduce endogenous production of B group vitamins — increase intake of vitamin B2.

ORAL CONTRACEPTIVE PILL
The OCP may increase demand for vitamin B2 (Pelton et al 2000) — consider increasing intake with long-term use.

TRICYCLIC ANTIDEPRESSANTS
Reduces the absorption of riboflavin — may increase riboflavin requirements (Pelton et al 2000).

AMITRYPTYLINE
Increases the renal excretion of riboflavin (Bianchi et al 2004) — consider increased dietary intake with long-term use.

CONTRAINDICATIONS AND PRECAUTIONS
None known.

PREGNANCY USE
Considered safe.

PRACTICE POINTS/PATIENT COUNSELLING
- Vitamin B2 deficiency signs include poor wound healing, hair loss, greasy dermatitis, ocular disturbances, failure to grow in children, angular stomatitis, cold sores, cracked lips and magenta tongue.

- Besides inadequate intake, deficiency can also result from chronic diarrhoea, liver disease and chronic alcoholism.
- There is some evidence suggesting high-dose supplements (400 mg daily) significantly reduce the frequency of migraine headache.
- Preliminary evidence suggests that regular supplementation with a multivitamin may also reduce the risk of developing cataracts.
- Supplementation results in a characteristic yellow-orange discolouration to urine.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin B2 is essential for health and is involved in many different biochemical processes in the body. Research has suggested that when taken in high doses, it can significantly reduce the incidence of migraine headaches.

When will it start to work?

Deficiency is reversed rapidly with supplementation. If using riboflavin to prevent migraine headaches, 3–4 months' treatment is required to see significant effects.

Are there any safety issues?

The vitamin is considered a safe nutrient.

REFERENCES

Ajayi OA et al. Clinical trial of riboflavin in sickle cell disease. East Afr Med J 70.7 (1993): 418-21.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Bianchi A et al. Role of magnesium, coenzyme q10, riboflavin, and vitamin B12 in migraine prophylaxis. Vitamins Hormones 69 (2004): 297-312.

Bunce GE et al. Nutritional factors in cataract. Annu Rev Nutr 10 (1990): 233-54.

Folkers K et al. Enzymology of the response of the carpal tunnel syndrome to riboflavin and to combined riboflavin and pyridoxine. Proc Natl Acad Sci USA 81.22 (1984): 7076-8.

Granados-Soto V et al. Riboflavin reduces hyperalgesia and inflammation but not tactile allodynia in the rat. Eur J Pharmacol 492.1 (2004): 35-40.

Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism. Belmont, CA: Wadsworth, 2004.

Head KA. Natural therapies for ocular disorders, part two: cataracts and glaucoma. Altern Med Rev 6.2 (2001): 141-66.

Horwitz J et al. Glutathione reductase in human lens epithelium: FAD-induced in vitro activation. Curr Eye Res 6.10 (1987): 1249-56.

Jacques PF. The potential preventive effects of vitamins for cataract and age-related macular degeneration. Int J Vitam Nutr Res 69.3 (1999): 198-205.

Kuzniarz M et al. Use of vitamin supplements and cataract: the Blue Mountains Eye Study. Am J Ophthalmol 132.1 (2001): 19-26.

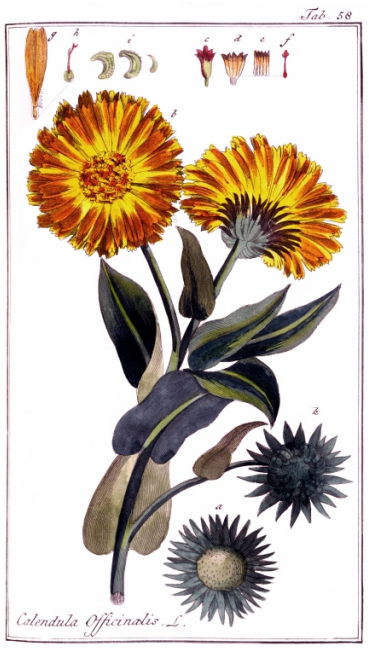
Lakshmi R et al. Skin wound healing in riboflavin deficiency. Biochem Med Metab Biol 42.3 (1989): 185-91.

Leske MC et al. Biochemical factors in the lens opacities: Case-control study (The Lens Opacities Case-Control Study Group). Arch Ophthalmol 113.9 (1995): 1113-19.

Lo CS. Riboflavin status of adolescents in southern China: Average intake of riboflavin and clinical findings. Med J Aust 141.10 (1984): 635-7.

Maizels M et al. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. Headache 44.9 (2004): 885-90.
Mares-Perlman JA et al. Diet and nuclear lens opacities. Am J Epidemiol 141.4 (1995): 322-34.
Mulherin DM et al. Glutathione reductase activity, riboflavin status, and disease activity in rheumatoid arthritis. Ann Rheum Dis 55.11 (1996): 837-40.
Ou LS et al. Anaphylaxis to riboflavin (vitamin B2). Ann Allergy Asthma Immunol 87.5 (2001): 430-3.
Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.
Said HM. Recent advances in carrier-mediated intestinal absorption of water-soluble vitamins. Annu Rev Physiol 66 (2004): 419-46.
Sandor PS et al. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 40.1 (2000): 30-5.
Schoenen J et al. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. Cephalalgia 14.5 (1994): 328-9.
Schoenen J et al. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 50.2 (1998): 466-70.
Straatsma BR et al. Lens capsule and epithelium in age-related cataract. Am J Ophthalmol 112.3 (1991): 283-96.
Wacker J et al. Riboflavin deficiency and preeclampsia. Obstet Gynecol 96.1 (2000): 38-44.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wynn M, Wynn A. Can improved diet contribute to the prevention of cataract? Nutr Health 11.2 (1996): 87-104.

Vitamin B3 — Niacin



Historical note The term 'niacin' is used interchangeably with nicotinic acid, and is also used collectively to include nicotinamide or niacinamide (the amide form of nicotinic acid). Niacin originally derived its name from its discovery as an oxidation by-product of nicotine and has been used generically since the 1940s to label foods and avoid association with nicotine, the alkaloid from tobacco. Nicotinic acid was the first hypolipidaemic agent shown to decrease the incidence of secondary myocardial infarction and reduce total mortality in these patients (Wilson et al 1991).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B3 (niacin) is a water-soluble vitamin of the B complex family. Both nicotinic acid and nicotinamide are absorbed in the stomach and small intestine by passive diffusion at high doses, or sodium-dependent facilitated diffusion at low doses, and excreted in the urine. Recent studies suggest that regulation of niacin uptake may be regulated by an acidic pH-dependent carrier-mediated system and PTK-mediated pathway (Nabokina et al 2005). The immediate-release form of nicotinic acid reaches peak concentration at 45 minutes and the extended release form in 4–5 hours. While nicotinamide can be directly converted to nicotinic acid, nicotinic acid must undergo a number of metabolic steps to produce NAD(+) before being converted to nicotinamide (Hendler & Rorvik 2001, Wilson et al 1991). The body's niacin requirement is also met by the biosynthesis of niacin from tryptophan, an amino acid. It has been estimated that each 60 mg excess of tryptophan (after protein synthesis) is converted to approximately 1 mg of niacin. In the absence of sufficient levels of B3 the body will preferentially convert tryptophan to B3. Niacin is widely distributed throughout the body and concentrates in the liver, spleen and adipose tissue. It is finally excreted by the kidneys.

COMMON FORMS AVAILABLE

The term niacin is used to refer to both nicotinic acid (niacin) and nicotinamide (niacinamide). Niacin is also referred to as vitamin B3.

The immediate-release form, which requires more regular dosing, is associated with significant vasodilation ('flushing'), whereas the sustained-release form is associated with an increased risk of adverse events. Extended-release forms of niacin

allow once-daily dosing and avoid much of the flushing and hepatotoxicity of the immediate- and sustained-release preparations (Sadovsky 2002).

FOOD SOURCES

Organ and muscle meats, lamb's liver, beef, poultry, fish, yeast, legumes, peanuts, Vegemite, yeast, wheat bran and fruit all contain vitamin B3. Trace amounts are found in vegetables and eggs and although milk contains only small amounts of B3, it is a good source of tryptophan, which can be converted to B3 in the body. In cereals such as corn and wheat it is present in a bound form, such as glycoside niacytin, which is unavailable to the body and has negligible nutritional value. Soaking corn in an alkaline solution such as lime helps to increase B3 bioavailability.

Maximum loss in cooking is 75% (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

Pellagra is a deficiency syndrome of vitamin B3, due to inadequate conversion of tryptophan to niacin or a lack of dietary niacin or tryptophan. The main symptoms are often referred to as 'the four Ds' (Jacobs & Wood 2003).

- Diarrhoea.
- Dermatitis — primarily on sun-exposed areas such as the face, hands, feet and arms. The rash starts as red, itchy areas that develop vesicles, blisters, scales and fissures. At the final stage, the skin becomes thickened, lichenified and hyperpigmented (Hendler & Rorvik 2001).
- Dementia — may include aggressiveness and cloudy thinking (Llancapi et al 1998).
- Death — if left untreated, vitamin B3 deficiency can be fatal.

Vitamin B3 deficiency may be found in conjunction with other deficiencies and may be associated with peripheral neuropathy. Early signs include anorexia, weakness, anaemia, glossitis, redness on sun-exposed areas and photosensitivity.

PRIMARY DEFICIENCY

This usually occurs in areas where maize (Indian corn) forms a major part of the diet. Bound niacin, found in maize, is not assimilated in the intestinal tract unless it has been previously treated with alkali, as in the preparation of tortillas. Corn protein is also deficient in tryptophan. Amino acid imbalance may also contribute to deficiency, since pellagra is common in India among people who eat millet with a high leucine content.

In the West, vitamin B3 deficiency is mostly associated with conditions that affect the person's nutritional intake such as alcoholism, mental illness or homelessness. It may also occur in anorexia nervosa, where dietary niacin and tryptophan are deficient (Prousky 2003).

SECONDARY DEFICIENCY

This may develop in conditions associated with diarrhoea, cirrhosis or malabsorption, as well as after extensive postoperative use of parenteral nutrition lacking adequate niacin. Pellagra may occur during prolonged isoniazid therapy (the drug replaces niacinamide in NAD), in malignant carcinoid tumour (tryptophan is diverted to form 5-hydroxytryptamine), and in Hartnup disease, an autosomal recessive disorder in which there is defective conversion of tryptophan to niacin (Beers & Berkow 2003). It has also been observed in Crohn's disease, most likely due to malnutrition and intestinal malabsorption (Abu-Qurshin et al 1997).

MAIN ACTIONS

Vitamin B3 is involved in a wide range of biological functions, such as energy production, fatty acid synthesis, cholesterol and steroid synthesis, signal transduction, regulation of gene expression and maintenance of genome integrity. Other functions of vitamin B3 include the regulation of blood sugar, antioxidant mechanisms, and detoxification reactions (IMG 2006).

Niacin is a dietary precursor for the coenzymes NAD(+) (nicotinamide adenine dinucleotide) and NADP, which are involved in a number of metabolic functions such as DNA synthesis (Hageman & Stierum 2001), glycolysis, fatty acid synthesis and cellular respiration (Kobayashi & Shimizu 1999). Like chromium, B3 is an important component of glucose tolerance factor.

LIPID-LOWERING

Large doses of niacin (nicotinic acid) reduce total cholesterol, LDL-cholesterol, triglycerides and lipoprotein (a) levels and also markedly raise HDL-cholesterol levels (Illingworth et al 1994). The beneficial effects of niacin in reducing triglycerides and lipoproteins that contain apolipoprotein-B (such as VLDL and LDL) are thought to be mediated by inhibiting fatty acid mobilisation from adipose tissue triglyceride stores and increasing intracellular apolipoprotein-B degradation resulting in decreased secretion of VLDL and LDL particles (Ganji et al 2003). The cardioprotective properties of HDL-cholesterol appear to be due to its involvement in processes such as reverse cholesterol transport and inhibition of LDL-cholesterol oxidation (Ganji et al 2003, Kwiterovich 2000).

IMPAIRS GLUCOSE REGULATION

Although niacin is an important part of glucose tolerance factor, in high doses it may impair glucose regulation, resulting in insulin resistance, increased insulin secretion and increased fasting blood glucose in patients with type 2 diabetes, although some authors suggest that niacin is both safe and effective in diabetes (Meyers et al 2004).

Interestingly, nicotinamide has also been shown to cause insulin resistance, resulting in increased insulin secretion in healthy subjects with a family history of type 1 diabetes (Greenbaum et al 1996).

Modest increases in fasting blood glucose levels have been noted in a number of clinical trials (Elam et al 2000, Goldberg 1998, Rindone & Achacoso 1996), although other trials have found that changes in fasting blood glucose reverted to normal at 4 months (Grundy et al 2002) and 8 months (Zhao et al 2004).

In practice, this effect on glucose regulation may not be clinically significant (Gardner et al 1997, Guyton 2004, Meyers et al 2004, Zhao et al 2004) and the potential benefits of improved lipid control in diabetic patients for whom other lipid-lowering medications provide inadequate control may outweigh any concerns. Nevertheless hypoglycaemic medications may need to be monitored and adjusted if necessary (Fonseca 2003).

ANTIOXIDANT

Niacinamide has been shown in vitro to have an antioxidant activity comparable to that of ascorbic acid (Hageman & Stierum 2001).

PROTECTS BETA-CELLS IN THE PANCREAS

Nicotinamide has been shown to protect beta-cells from inflammatory insults and to improve residual beta-cell function in patients after onset of type 1 diabetes (Lampeter et al 1998). It may also prevent damage to beta-cells by the immune system due to its antioxidant effects (Anderson 1994).

CHONDROPROTECTION

The generation of IL-1 in the synovium and subsequent induction of NO synthase is crucial to the pathogenesis of OA. The ability of niacinamide to suppress cytokine-mediated induction of NO synthase in a number of types of cells (McCarty & Russell 1999) provides a theoretical basis for its use as a chondroprotective agent.

CHEMOPROTECTION

The dietary status of niacin has the potential to affect DNA repair, genomic stability, and the immune system thus influencing cancer risk (Kirkland 2003), and increased demand may occur in many malignancies, including primary hepatoma (Jacobs & Wood 2003).

In vitro studies have shown that NAD(+) is important for PARP-1 activity, an enzyme that is thought to be important for genomic stability. In vitro and animal studies have indicated that niacin deficiency increases genomic instability and may increase the risk for certain tumours. While NAD(+) is niacin dependent, high doses

of nicotinamide inhibit PARP-1 in vitro, hence the effects may be dose dependent (Hageman & Stierum 2001). Niacin as a precursor for NAD(+) also inhibits DNA strand breakage in vitro and stimulates repair (Weitberg & Corvese 1990).

CLINICAL USE

DEFICIENCY

Severe deficiencies of niacin and tryptophan, a precursor from which the body can synthesise niacin, are the principal causes of pellagra.

ANOREXIA NERVOSA

The most common features of pellagra in patients with anorexia nervosa include erythema on sun-exposed areas, glossitis and stomatitis. A trial of supplementation with 150–500 mg for 24–48 hours will quickly determine if symptoms are due to pellagra (Prousky 2003).

HIV AND TRYPTOPHAN DEPLETION

A pellagra-like state can develop in malnourished patients with HIV and this may be due to impaired niacin status (Monteiro et al 2004) and result in tryptophan depletion. As tryptophan is preferentially converted to vitamin B3 (if B3 is depleted), a trial was conducted using high-dose niacin for 2 months in HIV patients and it was found that the high-dose niacin increased plasma tryptophan levels by 40% (Murray et al 2001).

An open, prospective trial has also concluded that extended-release niacin therapy is safe and effective for the treatment of dyslipidaemia associated with antiretroviral therapy; 2000 mg/day was given to 14 subjects for 14 weeks and resulted in significant reductions in serum levels of triglycerides, total cholesterol, and non-HDL-cholesterol (Gerber et al 2004).

DEPRESSION

As tryptophan is a precursor to serotonin, the preferential conversion of tryptophan to B3 in deficiency states may theoretically result in serotonin depletion. If sufficiently severe, this could produce symptoms of depression.

HYPERCHOLESTEROLAEMIA AND HYPERTRIGLYCERIDAEMIA

Niacin has been used for the treatment of hypercholesterolaemia and hypertriglyceridaemia since the 1950s. Large doses of niacin reduce total cholesterol, LDL-cholesterol, triglycerides and lipoprotein (a) levels and also markedly raise HDL-cholesterol C levels (Illingworth et al 1994). Considering these factors are also predictive of cardiovascular events, niacin is used to reduce overall risk of cardiovascular disease (Canner et al 1986). According to a recent meta-analysis effects on LDL-

cholesterol and triglycerides appear to be more significant in females especially at doses >1500 mg/day (Goldberg 2004).

Extended-release niacin (nicotinic acid) has been evaluated in at least four randomised, placebo-controlled trials, with the most efficacious results occurring at doses of 1500–2000 mg/day (Goldberg 1998, Grundy 2002, Guyton et al 2000, Morgan et al 2003). Results were dose- and time-dependent, with trials ranging in length from 4 to 16 weeks. At the 1500 and 2000 mg doses, reductions were noted in total cholesterol (–7 to –12.1%); total cholesterol to HDL-C ratio (–17 to –22%); LDL-cholesterol (0 to –7%); triglycerides (–16 to –36%); and lipoprotein (a) (–7 to –23.6%). One trial noted a particular decrease in the smaller, more atherogenic, dense LDL particles and an increase in the larger cardioprotective HDL particles (Morgan et al 2003). HDL-cholesterol increased by 21–25.8% and apolipoprotein A-I levels were reported in one study to be increased 9–11% (Guyton et al 2000). The main side-effects reported included flushing, a 5% increase in fasting blood glucose, pruritis and rash (Goldberg 1998).

A 2002 review suggests that niacin is the 'only agent currently available that favourably affects all components of the lipid profile to a significant degree' and has the greatest effect on HDL levels (Pieper 2002).

Niacin may also be combined with chromium (Bolkent et al 2004, Shara et al 2005, Yanardag et al 2005) or phytosterols (Yeganeh et al 2005) for synergistic effects.

Clinical note — Major lipids affecting cardiovascular disease risk

Cardiovascular risk is predicted by a number of factors; however, the major lipids involved are LDL-cholesterol lipoprotein (a), triglycerides and HDL-cholesterol. Furthermore, LDL particle size and number are associated with different levels of atherogenicity.

A reduction in HDL-cholesterol and an increase in triglycerides and LDL-cholesterol has been associated with an increased risk of cardiovascular disease, whereas high HDL-cholesterol is protective against atherosclerosis and is inversely related to risk of early coronary heart disease (Packard et al 2002). Its cardioprotective properties appear to be due to its involvement in processes such as reverse cholesterol transport and inhibition of LDL-cholesterol oxidation (Kwiterovich 2000). The potential for regression of atherosclerosis has been suggested due to the ability of niacin to affect reverse cholesterol transport out of vessel walls (Rubic et al 2004).

Furthermore, the LDL phenotype B, characterised by small, dense LDL particles, is associated with increased atherogenicity than phenotype A and niacin increases LDL

particle size from small LDL to the less atherogenic, large LDL subclasses (Morgan et al 2004). The frequency of the LDL phenotype B increases as HDL's decrease and triglycerides increase.

Lipoprotein (a) has been identified as an independent risk factor for premature coronary artery disease and aggravates the atherogenic effect of diabetes mellitus (Wassef 1999).

A 2002 review highlights the ability of niacin to effectively lower triglycerides, raise HDL-cholesterol, and shift LDL particles to the less atherogenic phenotype A, all important factors that reduce the risk of cardiovascular disease (Ito 2002).

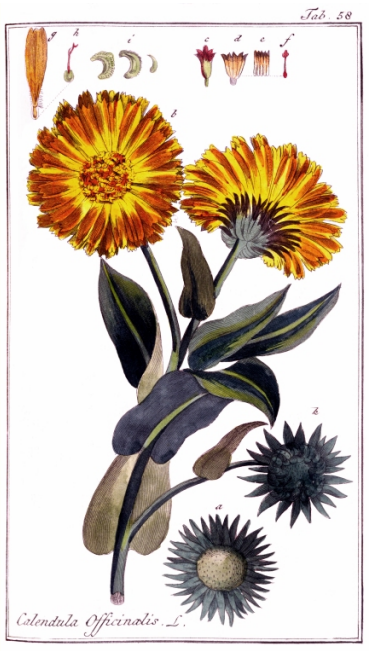
Combined therapy: statins and niacin Although monotherapy with statin drugs (HMG-CoA reductase inhibitors) cause significant reductions in LDL-cholesterol, they provide only modest improvements in triglycerides and HDL-cholesterol. Niacin, on the other hand, provides significant reduction of triglycerides and enhancement of HDL-cholesterol levels, although reductions in LDL-cholesterol are less significant. As a result, combinations of these lipid-modifying agents will better address lipid abnormalities and improve clinical outcomes (Ito 2002, Levy & Pearson 2005).

In practice, the concurrent use of niacin with a statin has demonstrated improved outcomes in patients for whom monotherapy was unable to achieve adequate lipid control (Gardner et al 1997, Guyton & Capuzzi 1998). The combination may also slow the progression of atherosclerosis in individuals with known coronary heart disease and moderately low HDL-cholesterol (Taylor et al 2004).

Numerous studies exist to support the safe and effective use of extended-release niacin with lovastatin (Armstrong et al 2004, Bays et al 2003, Rubenfire 2004), simvastatin (Kaur et al 2004, Zhao et al 2004), pravastatin (Gardner et al 1997), and rosuvastatin (Capuzzi et al 2003).

Lovastatin plus extended-release niacin is comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, more effective in increasing HDL-cholesterol and provides greater global improvements in non-HDL-cholesterol, triglycerides, and lipoprotein-a (Bays et al 2003). The combination is associated with good compliance and safety (Rubenfire 2004) and may also be less costly than simvastatin (Armstrong et al 2004).

In a clinical trial of diabetic patients, the addition of niacin 500 mg three times daily to pravastatin 20 mg resulted in a significant lowering of LDL-cholesterol compared with pravastatin monotherapy. Furthermore, improvements in lipid profile were gained without compromising glycaemic control (Gardner et al 1997). In a separate trial of simvastatin plus niacin among people with diabetes, glycaemic



control initially declined mildly but returned to pretreatment levels at 8 months and remained stable for the remainder of the study (Zhao et al 2004).

As early studies indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of the sustained-release form of niacin in combination with statins is controversial. Although current trials tend to focus on the safer extended-release form, liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998).

Low-dose niacin therapy (50 mg twice daily) in combination with statins for 3 months may also significantly increase HDL-cholesterol, while avoiding the side-effects commonly associated with higher doses (Wink et al 2002).

DIABETES

In people with diabetes the extended-release niacin may be useful in treating diabetic dyslipidaemia (Pan et al 2002); however, research has indicated the possibility of impaired glucose regulation in patients with type 2 diabetes. In practice this may not be clinically significant (Gardner et al 1997, Guyton 2004, Meyers et al 2004, Zhao et al 2004) and the potential benefits of improved lipid control in diabetic patients for whom other lipid-lowering medications provide inadequate control may outweigh any concerns. Nevertheless, hypoglycaemic medications may need to be monitored and adjusted if necessary (Fonseca 2003).

OTHER USES

SYNDROME X

Syndrome X, also known as metabolic syndrome or insulin resistance syndrome, is a highly prevalent condition that significantly increases the risk of coronary heart disease and is associated with elevated triglycerides, low HDL-cholesterol, and LDL-cholesterol. As niacin raises HDL-cholesterol, lowers triglycerides and increases LDL-cholesterol particle size, it may be considered a useful therapeutic option for the treatment of dyslipidaemia in such cases (Ito 2004). The potential for niacin to induce insulin resistance, however, may affect its use in practice.

PREVENTING DIABETES

Nicotinamide has been proposed as a useful therapeutic agent for the prevention of type 1 diabetes and also as an adjunct to intensive insulin therapy (Pocoit et al 1996). Interestingly, nicotinamide has also been shown to cause insulin resistance resulting in increased insulin secretion in healthy subjects with a family history of type 1 diabetes (Greenbaum et al 1996). A concern therefore exists that monitoring such people for signs of development of the disease may be complicated by the use of nicotinamide.

Protects beta-cells Type 1 diabetes is characterised by progressive beta-cell destruction, which leads to complete insulin deficiency; at the time of diagnosis 80–90% of beta cells have been destroyed (Virtanen & Aro 1994). Nicotinamide has been shown to protect beta-cells from inflammatory insults and to improve residual beta-cell function in patients after onset of type 1 diabetes (Gale 1996, Lampeter et al 1998).

One RCT using 25 mg/kg versus 50 mg/kg nicotinamide in early onset type 1 diabetes (<4 weeks) found that both doses were likely to be effective in reducing beta-cell dysfunction. As a higher dose may cause insulin resistance, the lower dose is probably preferable (Visalli et al 1999).

Alternatively, another RCT that used slow-release nicotinamide failed to detect a reduction in diabetes incidence after 3 years (Lampeter et al 1998).

OSTEOARTHRITIS

As the generation of IL-1 in the synovium and subsequent induction of NO synthase is crucial to the pathogenesis of OA, the ability of niacinamide to suppress cytokine-mediated induction of NO synthase in a number of types of cells (McCarty & Russell 1999) provides a theoretical basis for its use in the prevention of this condition.

Positive results obtained by a randomised, double-blind placebo-controlled trial support this theory. In the study, 72 patients with OA were treated over 12 weeks with niacinamide or placebo, with active treatment improving the global impact of OA, improving joint flexibility, reducing inflammation and allowing for reduction in standard anti-inflammatory medications (Jonas et al 1996).

CANCER PREVENTION

Because niacin is required for genomic stability and a deficiency is associated with an increased risk of certain tumours, it has been suggested that niacin may reduce the risk of various cancers (Hageman & Stierum 2001).

MIGRAINE

A systematic review concluded that niacin may have beneficial effects on migraine and tension-type headaches (Prousky & Seely 2005). The effects may be mediated by vasodilation, improved mitochondrial energy metabolism, or the correction of low plasma levels of serotonin, which have been implicated in migraine pathogenesis. Niacin may act as a negative feedback regulator to shunt tryptophan into the serotonin pathway, thus increasing plasma serotonin levels (Velling et al 2003).

ALZHEIMER'S DEMENTIA

Dementia can be caused by severe niacin deficiency and a prospective study of 6158 people aged >65 years found that dietary niacin intake (as determined by a food frequency questionnaire) had a protective effect on the development of AD and cognitive decline (Morris et al 2004).

OTHER CONDITIONS

Although substantial evidence is so far lacking, niacin is also being investigated for the treatment of intermittent claudication, Raynaud's syndrome and hypothyroidism.

Clinical note — Patients with schizophrenia rarely experience skin-flushing side-effect

The relative absence of skin flushing in response to niacin supplementation by patients with schizophrenia (80% vs 20%) has been attributed to a reduced pharmacological sensitivity rather than an inadequate cutaneous vasodilatory response. As the skin flush response is PG-mediated, schizophrenia may be associated with essential fatty acid deficiency or abnormalities in enzymes, receptors or signal transduction mechanisms that affect the synthesis, release or response to vasodilatory PG (Messamore 2003, Messamore et al 2003, Tavares et al 2003). Diminished sensitivity to niacin skin tests in early psychosis may predict the severity of symptoms (Smesny et al 2003, 2005).

DOSAGE RANGE

AUSTRALIAN ADI

- Women: 11 mg/day
- Men: 12 mg/day

Administration with food maximises bioavailability and minimises GI intolerance.

HIGH BLOOD CHOLESTEROL AND TRIGLYCERIDE LEVELS

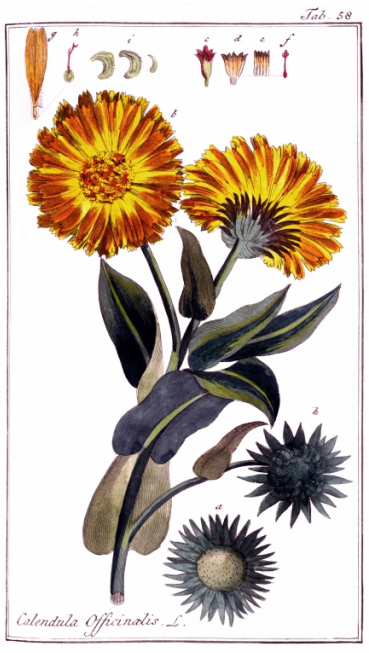
- 1500–2000 mg pure crystalline niacin (nicotinic acid) daily — this level should be reached gradually over a period of 4–6 weeks.
- 1500–2000 mg taken once daily for extended-release preparations (best taken at night).
- Inositol hexaniacinate is often associated with less flushing (Rakel 2003).

Clinical note — Differences between major forms of niacin supplements

Three main forms of niacin supplements are produced, each with their own set of safety issues. Immediate-release niacin is associated with increased incidence of flushing and other adverse reactions, whereas sustained-release forms have been

associated with potential liver damage (Henkin et al 1990, McKenney 2004). In comparison, extended-release niacin has been found to have similar efficacy to immediate-release forms but results in minimal flushing, myopathy or hepatotoxicity (Guyton 2004, McKenney 2004, Pieper 2002, Yim & Chong 2003).

No-flush preparations of OTC niacin contain no free nicotinic acid and are unlikely to be effective in treating dyslipidaemia (Meyers et al 2003).



ADVERSE REACTIONS

Flushing is a common side-effect of niacin therapy and may lead to discontinuation of therapy in some individuals (Rubenfire 2004). Night-time administration of extended-release niacin appears to reduce this effect, as does concurrent administration of aspirin (Mills et al 2003, White Robinson et al 2000).

Niacin has been associated with palpitations, worsening of diabetes control, exacerbation of peptic ulcer disease, gout, hepatitis (Crouse 1996), chills, generalised pruritus, gastrointestinal upset, and cutaneous tingling (Mills et al 2003).

However, reports of hepatotoxicity resulting from sustained-release niacin supplementation appear to be idiosyncratic, as there is no evidence to suggest intrinsic hepatotoxic activity; this also appears to be the case for statins (Parra & Reddy 2003).

SIGNIFICANT INTERACTIONS

STATIN DRUGS (HMG-CoA REDUCTASE INHIBITORS)

The combined use of niacin and statins, including atorvastatin (lipitor), fluvastatin (lescol), lovastatin (mevacor), pravastatin (pravachol), simvastatin (zocor), has been found to provide added therapeutic effects and reduce requirements for statin medications (Gardner et al 1996, 1997, Jacobson et al 1994, Yim & Chong 2003). A review of the combination of once daily, extended-release niacin and lovastatin therapy found that the addition of niacin may enhance or improve the lipid profile of those who require a further decrease of triglycerides, LDL-cholesterol and/or increase of HDL-cholesterol, even after stable statin therapy. The combination has been found to be safe with no increase in adverse reactions (Yim & Chong 2003) — beneficial interaction possible.

As early studies using the sustained-release form of niacin in combination with lovastatin indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of this form is controversial. Liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998) — use sustained-release niacin with caution.

HYPOLIPIDAEMIC AGENTS

Several clinical studies confirm the lipid-lowering effects of vitamin B3. Although a beneficial interaction has been shown in clinical trials with statin drugs, similar additive effects are theoretically possible with other hypolipidaemic drugs — beneficial interaction possible.

DIABETES MEDICATIONS

Niacin may affect glycaemic control and increase fasting blood glucose levels, therefore medication doses may need to be reviewed — exercise caution and monitor drug requirements when prescribing diabetes medications concurrently with niacin.

ANTIRETROVIRAL THERAPY

Extended-realease niacin may improve the dyslipidaemia associated with antiretroviral therapy and is considered a safe and effective therapeutic option (Gerber et al 2004) — beneficial interaction possible.

ISONIAZID

Prolonged isoniazid therapy (the drug replaces niacinamide in NAD) may induce pellagra (Beers and Berkow 2003). Increased vitamin B3 intake may be required with long-term therapy — beneficial interaction possible.

ORAL CONTRACEPTIVE PILL

Use of the OCP may reduce vitamin B3 levels (Lininger 1999). Increased vitamin B3 intake may be required with long-term therapy — beneficial interaction possible.

TAMOXIFEN

The addition of niacin, riboflavin, and CoQ10 to tamoxifen therapy may improve mitochondrial antioxidant status and antitumour activity (Perumal et al 2005). The exact role of niacin is unclear; however, the addition of antioxidants to tamoxifen therapy may prove advantageous — beneficial interaction possible.

IMIPRAMINE

A combination of imipramine with L-tryptophan 6 g/day and niacinamide 1500 mg/day has been shown to be more effective for people with bipolar disorder than imipramine alone (Chouinard et al 1979) — beneficial interaction possible.

CONTRAINDICATIONS AND PRECAUTIONS

Gout — excess supplementation can lead to increased production or crystallisation of uric acid (Rakel 2003).

Supplemental vitamin B3 should be used with caution in conditions involving insulin resistance, although the potential benefits may outweigh the slight increase in blood glucose. In such cases, medication requirements may need to be revised.

As early studies indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of the sustained-release form of niacin in combination with statins is controversial. Liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998).

PREGNANCY USE

Nicotinic acid is classified as a category B2 medicine in pregnancy by the Australian Drug Evaluation Committee. (This means that it has been taken by a limited number of pregnant women and women of childbearing age without an increase in malformations or other direct or indirect harmful effects on the human fetus having been observed.)

PRACTICE POINTS/PATIENT COUNSELLING

- The term niacin is used interchangeably with nicotinic acid, and is also used collectively to include nicotinamide or niacinamide (the amide form of nicotinic acid).
- In practice, nicotinic acid decreases the incidence of secondary myocardial infarction and reduces total mortality incidence in these patients.
- Large doses of niacin reduce total cholesterol, LDL-cholesterol, triglycerides and lipoprotein-a levels and also markedly raise HDL-cholesterol levels.
- The extended-release form appears to have a better safety profile with reduced incidence of flushing.
- In high doses it can impair glucose regulation, resulting in insulin resistance, increased insulin secretion and increased fasting blood glucose in patients with type 2 diabetes, so care is advised when using the supplement in this group of patients. Alternatively, nicotinamide protects beta-cells from inflator damage and may improve residual beta-cell function in patients after onset of type 1 diabetes.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Niacin in high doses will favourably alter lipid levels and reduce the risk of cardiovascular disease, risk of heart attack and risk of death post-heart attack. It may also be useful in diabetes when used under professional supervision.

When will it start to work?

Beneficial effects on lipid levels have been seen within 4 weeks; however, several months of use may be required for optimal effects.

Are there any safety issues?

There are several different forms of niacin supplements produced; however, the extended-release form appears to have a better safety profile than the others and a reduced risk of flushing.

REFERENCES

Abu-Qurshin R et al. Crohn's disease associated with pellagra and increased excretion of 5-hydroxyindolacetic acid. Am J Med Sci 313(2) (1997): 111-13.

Anderson H. Nicotinamide prevents interleukin-1 effects on accumulated insulin release and nitric oxide production in rat islets of Langerhans. Diabetes 43 (1994): 770-7.

Armstrong EP et al. Cost-effectiveness analysis of simvastatin and lovastatin/extended-release niacin to achieve LDL and HDL goal using NHANES data. J Manag Care Pharm 10(3) (2004): 251-8.

Bays HE et al. Comparison of Once-Daily, niacin Extended-Release/lovastatin with standard doses of atorvastatin and simvastatin (the advicor versus other Cholesterol-Modulating agents trial evaluation [ADVOCATE]). Am J Cardiol 91(6)(2003): 667-72.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Bolkent S et al. Beneficial effects of combined treatment with niacin and chromium on the liver of hyperlipemic rats. Biol Trace Elem Res 101(3) (2004): 219-29.

Canner BL et al. Mortality in Coronary Drug Project patients during a nine year post-treatment period. Am Coll Cardiol 8 (1986): 1245-55.

Capuzzi DM et al. Beneficial effects of rosuvastatin alone and in combination with extended-release niacin in patients with a combined hyperlipidemia and low high-density lipoprotein cholesterol levels. Am J Cardiol 91(11) (2003): 1304-10.

Chouinard G et al. Tryptophan, niacinamide, imipramine and their combination in depression. Acta Psychiatr Scand 59 (1979): 395-414.

Crouse JR 3rd. New developments in the use of niacin for treatment of hyperlipidemia: new considerations in the use of an old drug. Coron Artery Dis 7(4) (1996): 321-6.

Elam MB et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA 284(10) (2000): 1263-70.

Fonseca V. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. Diabetes Care 26(1) (2003): 258.

Gale EA. Theory and practice of nicotinamide trials in pre-type 1 diabetes. J Pediatr Endocrinol Metab 9.3 (1996): 375-9.

Ganji SH et al. Niacin and cholesterol; role in cardiovascular disease (Review). J Nutr Biochem 14(6) (2003): 298-305.

Gardner SF et al. Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin. Pharmacotherapy 16 (1996): 419-23.

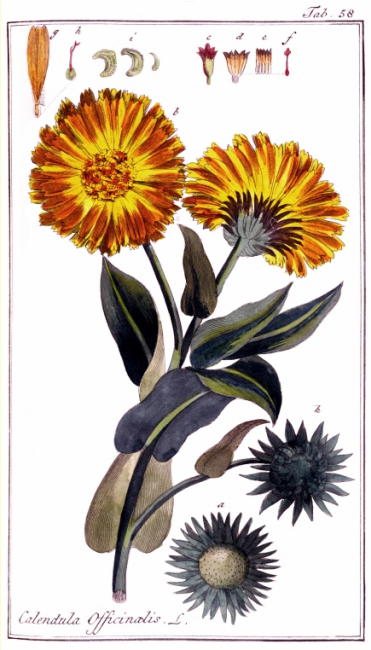
Gardner SF et al. Combination of low-dose niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control. Ann Pharmacother 31(6) (1997): 677-82.

Gerber M et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. Clin Infect Dis 39(3) (2004): 419-25.

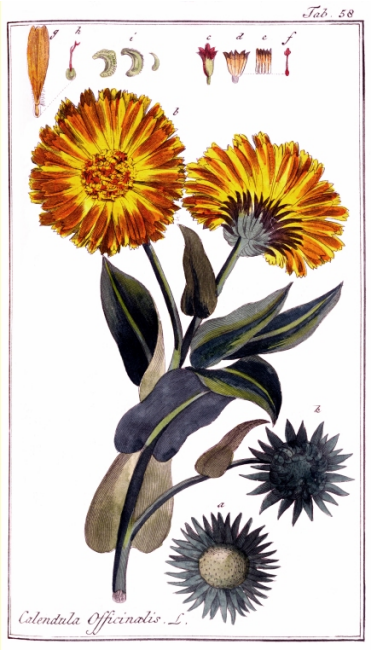
Goldberg AC. Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. Am J Cardiol 82(12A) (1998): 35-8U.

Goldberg AC. A meta-analysis of randomized controlled studies on the effects of Extended-Release niacin in women. Am J Cardiol 94(1) (2004): 121-4.

Greenbaum CJ et al. Nicotinamide's effects on glucose metabolism in subjects at risk for IDDM. Diabetes 45(11) (1996): 1631-4.
Grundy SM et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (Original Investigation). Arch Intern Med 162(14) (2002): 1568–9.
Guyton JR. Extended-release niacin for modifying the lipoprotein profile. Expert Opin Pharmacother 5(6) (2004): 1385-98.
Guyton JR, Capuzzi DM. Treatment of hyperlipidemia with combined niacin-statin regimens. Am J Cardiol 82(12A) (1998): 82-4U.
Guyton JR et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol: Niaspan-Gemfibrozil Study Group. Arch Intern Med 160(8) (2000): 1177-84.
Hageman GJ, Stierum RH. Niacin, poly(ADP-ribose) polymerase-1 and genomic stability. Mutat Res 475(1-2) (2001): 45-56.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Henkin Y et al. Rechallenge with crystalline niacin after drug induced hepatitis from sustained-release niacin. JAMA 264 (1990): 241-3.
Illingworth DR et al. Comparative effects of lovastatin and niacin in primary hypercholesterolaemia. Arch Intern Med 154 (1994): 1586-95.
Integrative Medicine Gateway (IMG). Unity Health 2001-06. Available at: www.imgateway.net (accessed 03-06).
Ito MK. Niacin-based therapy for dyslipidemia: past evidence and future advances. Am J Manag Care 8 (12 Suppl) (2002): S315-22.
Ito MK. The metabolic syndrome; pathophysiology, clinical relevance, and use of niacin. Ann Pharmacother 38(2) (2004): 277-85.
Jacobs P, Wood L. Vitamin B3. Disease-a-Month 49(11) (2003): 658-63.
Jacobson TA et al. Fluvastatin with and without niacin for hypercholesterolaemia. Am J Cardiol 74 (1994): 149-54.
Jonas WB et al. The effect of niacinamide on osteoarthritis: a pilot study. Inflamm Res 45.7 (1996): 330-4.
Kaur K et al. An open-label comparison of the effects of simvastatin and niacin alone and combined on the lipid profile and lipoprotein (a) level in an Indian population with dyslipidemia. Curr Ther Res 65(6) (2004): 455-69.
Kirkland J. Niacin and carcinogenesis. Nutr Cancer 46(2) (2003): 110-18.
Kobayashi M, Shimizu S. Nicotinic acid and nicotinamide. Nippon Rinsho 57(10) (1999): 2211-17.
Kwiterovich PO Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. Am J Cardiol 86 (12A) (2000): 5-10L.
Lampeter EF et al. The Deutsche Nicotinamide Intervention Study: an attempt to prevent type 1 diabetes. DENIS Group. Diabetes 47.6 (1998): 980-4.
Levy DR, Pearson TA. Combination niacin and statin therapy in primary and secondary prevention of cardiovascular disease. Clin Cardiol 28(7) (2005): 317-20.
Lininger SW (ed). A-Z Guide to Drug-Herb-Vitamin Interactions. Healthnotes USA, 1999.
Llancapi P et al. Pellagra: diagnosis still valid. Rev Med Chil 126(4) (1998): 435-8 [in Spanish].
McCarty MF, Russell AL. Niacinamide therapy for osteoarthritis: does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? Med Hypotheses 53.4 (1999): 350-60.
McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. Arch Intern Med 164(7) (2004): 697-705.
Messamore E. Relationship between the niacin skin flush response and essential fatty acids in schizophrenia. Prostaglandins Leukot Essent Fatty Acids 69(6) (2003): 413-19.
Messamore E et al. The niacin skin flush abnormality in schizophrenia: a quantitative dose-response study. Schizophrenia Res 62(3) (2003): 251-8.

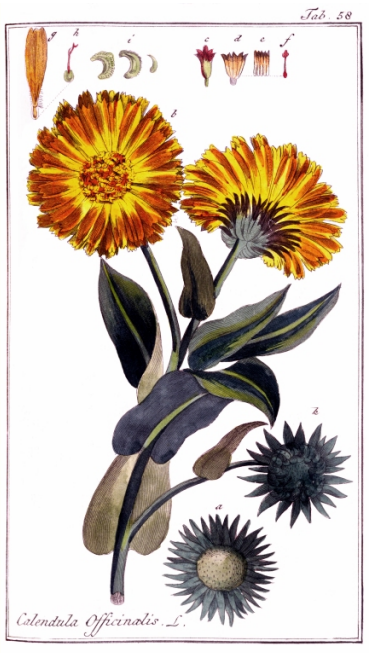


Meyers C et al. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. Ann Intern Med 139(12) (2003): 996-1002.
Meyers C et al. Niacin therapy in atherosclerosis. Curr Opin Lipidol 15(6) (2004): 659-65.
Mills E et al. The safety of over-the-counter niacin: A randomized placebo-controlled trial ISRCTN18054903. BMC Clin Pharmacol 3(1) (2003): 4.
Monteiro JP et al. Niacin metabolite excretion in alcoholic pellagra and AIDS patients with and without diarrhea. Nutrition 20(9) (2004): 778-82.
Morgan JM et al. Effects of extended-release niacin on lipoprotein subclass distribution. Am J Cardiol 91(12) (2003): 1432-3.
Morgan JM et al. The effects of niacin on lipoprotein subclass distribution. Prev Cardiol 7(4) (2004): 182-7.
Morris MC et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry 75(8) (2004): 1093-9.
Murray MF et al. Increased plasma tryptophan in HIV-infected patients treated with pharmacologic doses of nicotinamide. Nutrition 17(7-8) (2001): 654-6.
Nabokina SM et al. Mechanism and regulation of human intestinal niacin uptake. Am J Physiol Cell Physiol 289(1) (2005): C97-103.
Packard C et al. Future Forum Editorial Board: High density lipoprotein: guardian of the vascular system? Int J Clin Pract 56(10) (2002): 761-71.
Pan J et al. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. Metabolism 51(9) (2002): 1120-7.
Parra JL, Reddy KR. Hepatotoxicity of hypolipidemic drugs. Clin Liver Dis 7(2) (2003): 415-33.
Perumal SS et al. Augmented efficacy of tamoxifen in rat breast tumorigenesis when gavaged along with riboflavin, niacin, and CoQ10: Effects on lipid peroxidation and antioxidants in mitochondria. Chemico-Biol Interact 152(1) (2005): 49-58.
Pieper JA. Understanding niacin formulations. Am J Manag Care 8 (12 Suppl) (2002): S308-14.
Pocoit F et al. Nicotinamide: Biological actions and therapeutic potential in diabetes prevention. Diabetologia 36 (1996): 574-6.
Prousky JE. Pellagra may be a rare secondary complication of anorexia nervosa: a systematic review of the literature. Altern Med Rev 8(2) (2003): 180-5.
Prousky J, Seely D. The treatment of migraines and tension-type headaches with intravenous and oral niacin (nicotinic acid): Systematic review of the literature. Nutr J 4 (2005): 3.
Rakel D. Integrative Medicine. Philadelphia: Saunders, 2003; 592.
Rindone JP, Achacoso S. Effect of low-dose niacin on glucose control in patients with non-insulin-dependent diabetes mellitus and hyperlipidemia. Am J Ther 3(9) (1996): 637-9.
Rubenfire M. Safety and compliance with once-daily niacin extended-release/lovastatin as initial therapy in the Impact of Medical Subspecialty on Patient Compliance to Treatment (IMPACT) study. Am J Cardiol 94(3) (2004): 306-11.
Rubic T et al. Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. Biochem Pharmacol 67(3) (2004): 411-19.
Sadovsky R. Extended-release niacin for type 2 diabetes dyslipidemia. Am Fam Physician 66(10) (2002): 1982.
Shara M et al. Safety and toxicological evaluation of a novel niacin-bound chromium (III) complex. J Inorganic Biochem 99(11) (2005): 2161-83.
Smesny S et al. Potential use of the topical niacin skin test in early psychosis: a combined approach using optical reflection spectroscopy and a descriptive rating scale. J Psychiatric Res 37(3) (2003): 237-47.
Smesny S et al. Impaired niacin sensitivity in acute first-episode but not in multi-episode schizophrenia. Prostaglandins Leukot Essent Fatty Acids 72(6) (2005): 393-402.
Tavares H et al. Increased phospholipase A2 activity in schizophrenia with absent response to niacin. Schizophrenia Res 61(1) (2003): 1-6.



Taylor AJ et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 110(23) (2004): 3512-7.
Velling DA et al. Sustained-release niacin for prevention of migraine headache. Mayo Clin Proc 78(6) (2003): 770-1.
Virtanen SM, Aro A. Dietary factors in the aetiology of diabetes. Ann Med 26(6) (1994): 469-78.
Visalli N et al. A multi-centre randomized trial of two different doses of nicotinamide in patients with recent-onset type 1 diabetes (the IMDIAB VI). Diabetes Metab Res Rev 15(3) (1999): 181-5.
Wahlqvist ML (ed.). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Wassef GN. Lipoprotein (a) in android obesity and NIDDM: a new member in 'the metabolic syndrome'. Biomed Pharmacother 53(10) (1999): 462-5.
Weitberg AB, Corvese D. Niacin prevents DNA strand breakage by adenosine deaminase inhibitors. Biochem Biophys Res Commun 167(2) (1990): 514-19.
White Robinson A et al. The antilipidemic effects of plain and extended-release niacin. Prev Cardiol 3(3) (2000): 131-5.
Wilson JD et al. Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991.
Wink J et al. Effect of very-low-dose niacin on high-density lipoprotein in patients undergoing long-term statin therapy. Am Heart J 143(3) (2002): 514-18.
Yanardag R et al. Effects of a combination of niacin and chromium(III)-chloride on the skin and lungs of hyperlipemic rats. Biol Trace Elem Res 103(3) (2005): 249-60.
Yeganeh B et al. Combination of dietary phytosterols plus niacin or fenofibrate; effects on lipid profile and atherosclerosis in apo E-KO mice. J Nutr Biochem 16(4) (2005): 222-8.
Yim B, Chong P. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. Ann Pharmacother 37(1) (2003): 106-15.
Zhao XQ et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). Am J Cardiol 93(3) (2004): 307-12.

Vitamin B5 — Pantothenic acid



BACKGROUND AND RELEVANT PHARMACOKINETICS

The Greek word *pantos* means 'everywhere'. As the name pantothenic acid implies, it is widely distributed and present in nearly all plant and animal foods. It is sensitive to heat and both acid and alkali and considerable amounts are lost through the milling of cereal grains. The intestine is exposed to two sources of pantothenic acid: dietary and bacterial. Current research suggests that bacterial synthesis may be more dominant and important in ruminant species (Bates 1998). Approximately 50% of pantothenic acid is absorbed in the jejunum, an amount that decreases when doses 10-fold greater than the RDI are taken (Groff & Gropper 2000).

The organ with the highest concentration of pantothenate is the liver, followed by the adrenal cortex, which reflects the large requirements of these tissues and is indicative of the biochemical role of its coenzyme derivatives. There are contrasting opinions about whether a genuine storage capacity exists for this vitamin; however, if there is any at all, the consensus is that pantothenic acid is 'stored' in very limited amounts and in those tissues with the greatest requirements (Groff & Gropper 2000).

Study of placental tissue demonstrates that biotin uses the same transport mechanisms as pantothenic acid, which may indicate competition between these two nutrients in other tissues (Bates 1998).

CHEMICAL COMPONENTS

Pantothenic acid is an amide and consists of B-alanine and pantoic acid joined by a peptide bond. In supplements, it is often found as calcium pantothenate.

FOOD SOURCES

The most concentrated sources are meats (especially liver), egg yolk, broad beans and legumes, but it is also found in many other foods such as whole grains, milk, peanuts, broccoli, avocado, mushroom and apricots. Up to 50% can be lost through cooking (Wahlqvist et al 1997).

Approximately 85% occurs in food as a component of coenzyme A (CoA), which is hydrolysed to pantothenic acid or pantethine during digestion.

DEFICIENCY SIGNS AND SYMPTOMS

Because it is so rare, most information regarding the signs and symptoms of pantothenic acid deficiency comes from experimental research in animals or cases of severe malnutrition. The deficiency picture appears to be generalised and species

specific (Bates 1998). Preliminary studies in humans using competitive analogues of pantothenic acid have produced the following symptoms:

- 'burning feet syndrome': this affects the lower legs and is characterised by sensation of heat
- cardiac instability
- gastrointestinal disturbance
- dizziness, paraesthesia and depression
- loss of immune (antibody) function
- insensitivity to adrenocorticotrophic hormone
- increased sensitivity to insulin
- vomiting
- fatigue
- weakness.

Some conditions that have been associated with increased requirements are:

- alcoholism (due to typically low intakes of vitamin B complex)
- diabetes mellitus (as a result of increased excretion)
- inflammatory bowel diseases (due to decreased vitamin absorption).

MAIN ACTIONS

Pantothenic acid is involved in myriad important chemical reactions in the body as a result of its involvement in CoA synthesis.

COENZYME FUNCTION

CoA and the Krebs cycle Pantothenic acid is required for CoA synthesis and cellular respiration. It also plays a pivotal role in the oxidation of fatty acids and acetylation of other molecules, so as to enable transportation. Together with thiamine, riboflavin and niacin, it is involved in the oxidative decarboxylation of pyruvate and alpha-ketoglutarate in the Krebs cycle and, ultimately, is important for energy storage as well as release.

Acyl carrier protein Pantothenic acid is the prosthetic group for acyl carrier protein and, therefore, is involved in the synthesis of fatty acids.

Indirect antioxidant effects New in vitro research supports an indirect antioxidant role for pantothenic acid through its ability to increase cellular ATP, which in turn creates increased levels of free glutathione and enhanced protection of cells against peroxidative damage (Slyshenkov et al 2004).

Other functions It is involved in the synthesis of amino acids, sterols (e.g. cholesterol) and vitamin D. It is necessary for production of the neurotransmitter acetylcholine and the formation of red cells. Vitamin B5 plays an important role in

adrenal function and, as CoA, is needed for proper adrenal cortex function and the synthesis of steroid hormones.

Clinical Note — Could pantothenic acid be an anti-ageing nutrient?
A contemporary theory of ageing implicates mitochondrial functional decline or 'oxidative decay' of the mitochondria as a major contributor. In light of this hypothesis, nutrients that possess a critical role in the mitochondria are being re-examined to determine their ability to prevent ageing in humans. The focus has been on pantothenic acid, biotin, lipoic acid, iron and zinc because deficiencies of these micronutrients have been implicated in increased mitochondrial oxidation (Ames et al 2005, Atamna 2004). In addition, those with antioxidant capabilities are of particular interest, such as pantothenic acid, lipoic acid and zinc.

Due to the numerous nutrients implicated in mitochondrial health and disease, a broad-based multivitamin should be considered instead of a single nutrient supplement for those populations at increased risk of poor nutrition such as the elderly, young, poor and obese (Ames et al 2005).

LIPID-LOWERING

Pantethine, a metabolite of pantothenic acid, has been investigated in several clinical studies and found to exert significant lipid-lowering activity (Coronel et al 1991, Donati et al 1986, Gaddi et al 1984).

The mechanism of action relates to reduced insulin resistance and activation of lipolysis in serum and adipose tissue, according to in vivo research (Naruta & Buko 2001). Additionally, inhibition of HMG-CoA reductase, as well as more distal enzymes in the cholesterol synthetic pathway, are likely to be responsible (McCarty 2001). More recently, an in vitro study demonstrated that pantethine produced a 50% inhibition of fatty acid synthesis and an 80% inhibition of cholesterol synthesis (McRae 2005).

ENHANCES WOUND HEALING

Both oral supplements and topical applications have been shown to accelerate closure of wounds and increase strength of scar tissue in vivo (Plesofsky 2002, Vaxman et al 1990). Both in vitro and in vivo studies reveal that topical dexpanthenol induces activation of fibroblast proliferation, which contributes to accelerated re-epithelisation in wound healing (Ebner et al 2002).

CLINICAL USE

Although pantothenic acid has been investigated in some studies, most investigation has occurred with several of its derivatives, chiefly an alcoholic analogue of

pantothenic acid called dexpanthenol (available commercially as Bepanthen) and pantethine.

DEFICIENCY STATES: PREVENTION AND TREATMENT

Traditionally, pantothenic acid is recommended together with other vitamin B complex nutrients to treat general deficiency or prevent deficiency in conditions associated with deficiency such as alcoholism, diabetes mellitus and malabsorption syndromes.

ENHANCE WOUND HEALING

Pantothenic acid has been both used as an oral supplement and applied topically in a cream base to enhance wound healing and it has been shown to accelerate closure of wounds and increase strength of scar tissue in experimental animals (Plesofsky 2002, Vaxman et al 1990). Although these results are encouraging, there has been little investigation in humans. One double-blind study testing the effects of vitamin C (1000 mg) and pantothenic acid (200 mg) supplements over a 21-day period showed no significant alteration to wound healing with this treatment regimen (Vaxman et al 1995).

Topical use Bepanthen is a well-known dermatological preparation containing dexpanthenol, an alcoholic analogue of pantothenic acid. It has been investigated in numerous studies and found to act like a moisturiser, activate fibroblast proliferation, accelerate re-epithelialisation in wound healing, have anti-inflammatory activity against UV-induced erythema and reduce itch (Ebner et al 2002). Under double-blind study conditions, epidermal wounds treated with dexpanthenol emulsion showed a reduction in erythema, and more elastic and solid tissue regeneration. Another randomised, prospective, double-blind, placebo-controlled study published in 2003 investigated the efficacy of topical dexpanthenol as a skin protectant against irritation. The study involved 25 healthy volunteers who were treated with a topical preparation containing 5% dexpanthenol or placebo and then exposed to sodium lauryl sulphate 2% twice daily over 26 days. Treatment with topical dexpanthenol provided protection against skin irritation whereas a statistically significant deterioration was observed in the placebo group (Biro et al 2003).

Although commonly used in radiotherapy departments to ameliorate acute radiotherapy skin reactions, a prospective study of 86 patients undergoing radiotherapy showed that topical use of Bepanthen did not improve skin reactions under these conditions (Lokkevik et al 1996). Similarly, negative results were also obtained in an animal study by Dorr et al (2005).

Nasal spray A RCT of 48 outpatients diagnosed with rhinitis sicca anterior found that dexpanthenol nasal spray is an effective symptomatic treatment for this condition (Kehrl & Sonnemann 1998). Two years later, another RCT compared the effects of xylometazoline-dexpanthenol nasal spray versus xylometazoline nasal spray over a 2-week period in 61 patients with rhinitis after nasal surgery (Kehrl & Sonnemann 2000) and showed that the combination of xylometazoline-dexpanthenol nasal spray was significantly superior to the other treatment and well tolerated.

More recent studies support this emerging trend and point towards a reduction in ciliary and cytotoxic effects from the nasal decongestants when 5% dexpanthenol is concurrently administered (Klocker et al 2003).

ELEVATED CHOLESTEROL AND TRIGLYCERIDE LEVELS

Pantethine, a metabolite of pantothenic acid, has been investigated in several clinical studies and found to exert significant lipid-lowering activity (Coronel et al 1991, Donati et al 1986, Gaddi et al 1984).

One double-blind study of 29 patients found that 300 mg of pantethine taken three times daily resulted in significant reductions to plasma total cholesterol, LDL-cholesterol, triglycerides and an increase in HDL-C levels (Gaddi et al 1984).

A 2005 review analysed results from 28 clinical trials encompassing a pooled population of 646 hyperlipidaemic patients supplemented with a mean dose of 900 mg pantethine over an average trial length of 12.7 weeks. The results of these studies suggest a response to pantethine that is time dependent, with reductions in LDL-cholesterol and triacylglycerols progressively increasing between month 1 and 9. The most impressive results were observed at 9 months, with a reduction of total cholesterol by 20.5%, LDL-cholesterol by 27.6% and triacylglycerols by 36.5% from baseline. Although minor increases were observed in HDL levels in the early stages of most trials, longer term studies suggested this is not sustained.

Of the trials studied, 22 were conducted in Italy and all were conducted between 1981 and 1991. The authors point out that no further clinical trials were published and concluded that evidence to date has yielded positive and promising results and further research is warranted.

OTHER USES

Pantothenic acid has been used for many other indications, but controlled studies to determine whether treatment is effective are lacking.

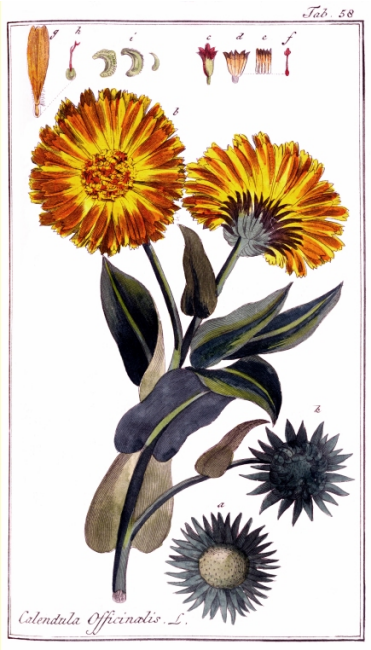
STRESS
As vitamin B5 is essential for adrenal cortex function and the synthesis of steroid hormones, it is often used together with other B vitamins during times of 'stress' in order to improve the body's response and restore nutrient levels. Interestingly there were a large number of experiments conducted in the 1950s, attempting to elicit the impact of pantothenic acid deficiency on adrenal function and stress response in animals; however, little research has been done since. A small study demonstrated that injections of pantothenic acid in B5-deficient rats were corrective of the deficiency picture and had a steroidogenous effect.

INFLAMMATORY CONDITIONS
Pantothenic acid has been used as adjunctive treatment in inflammatory conditions, such as asthma and dermatitis, under the basis of improving adrenal cortex output of hormones with anti-inflammatory activity.

ERGOGENIC AID
Based on this vitamin's role in carbohydrate metabolism, it has been used to increase stamina and athletic performance.

REDUCING DRUG TOXICITY
Preliminary research in animal models shows that pantothenic acid reduces the toxicity effects of kanamycin and carbon tetrachloride, and when combined with carnitine, protects against valproate toxicity (Moiseenok et al 1984, Nagiel-Ostaszewski & Lau-Cam 1990, Thurston & Hauhart 1992).

FEMALE ALOPECIA
According to a study of 46 women with symptoms of diffuse alopecia, calcium pantothenate (200 mg/day) over 4–5 months does not cause a significant improvement in this condition (Brzezinska-Wcislo 2001).



DOSAGE RANGE

AUSTRALIAN ADI
- Women: 4 mg/day
- Men: 6 mg/day

ACCORDING TO CLINICAL STUDIES
- Wound healing: dexpanthenol cream 5% applied to affected areas up to two times daily.
- Lipid-lowering: pantethine 300 mg three times daily.

TOXICITY
No toxicity level known.

ADVERSE REACTIONS
Pantothenic acid is well tolerated, but contact dermatitis has been reported for topical dexpanthenol.

SIGNIFICANT INTERACTIONS
ANTIBIOTICS
Antibiotics will reduce endogenous production of vitamin B5 by gastrointestinal flora — increase vitamin B5 rich foods or consider supplementation.

ORAL CONTRACEPTIVES
Taking the OCP may increase the requirement for pantothenic acid — increase vitamin B5 rich foods or consider supplementation (Plesofsky 2002).

CONTRAINDICATIONS AND PRECAUTIONS
None known

PREGNANCY USE
Considered safe when ingested at usual dietary doses.

PRACTICE POINTS/PATIENT COUNSELLING
- Deficiency is extremely rare as pantothenic acid is widely distributed and present in nearly all plant and animal foods. Those at risk of reduced vitamin status are alcoholics, diabetics and people with malabsorption syndromes.
- Pantethine reduces total cholesterol levels significantly, according to controlled studies in both healthy and diabetic people.
- Dexpanthenol cream acts like a moisturiser, activates fibroblast proliferation, accelerates re-epithelialisation in wound healing, has anti-inflammatory activity against UV-induced erythema and reduces itch. When used in a nasal spray, it reduces symptoms of rhinitis.
- Vitamin B5 supplements are commonly used together with other B vitamins during times of 'stress' in order to improve the body's response and restore nutrient levels.
- It has also been used as adjunctive treatment for inflammatory conditions such as dermatitis and asthma, as an ergogenic aid, to treat alopecia and restore colour to greying hair, although no controlled studies are available to determine effectiveness in these conditions.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

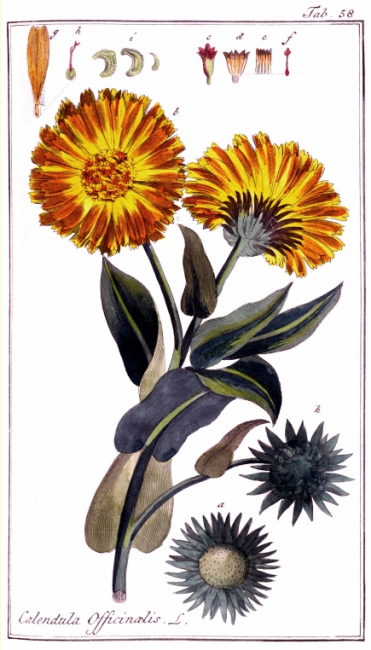
Vitamin B5 is essential for health and is used for many different conditions, for example, it is often used as part of a vitamin B complex supplement to aid the body during times of 'stress'. For many uses, research is not available to determine whether it is effective. Research generally supports its use in wound healing and in the form of pantethine, to reduce cholesterol levels.

When will it start to work?

Pantethine reduces cholesterol levels within 2 months; however, optimal results are achieved with 9 months of supplementation. Xylometazoline-dexpanthenol nasal spray reduces symptoms of rhinitis within 2 weeks. It is not known how quickly the vitamin starts to work in most other conditions.

Are there any safety issues?

Pantothenic acid and pantethine are considered safe substances and generally well tolerated.



REFERENCES

Ames BN et al. Mineral and vitamin deficiencies can accelerate the mitochondrial decay of aging. Mol Aspects Med 26(4-5) (2005): 363-78.

Atamna H. Heme, iron, and the mitochondrial decay of ageing. Age Res Rev 3(3) (2004): 303-18.

Bates CJ. Pantothenic acid. In: Physiology, Dietary Sources and Requirements, Encyclopedia of Human Nutrition. St Louis: Elsevier 1998, 1511-15.

Biro K et al. Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. Contact Dermatitis 49(2) (2003): 80-4.

Brzezinska-Wcislo L. Evaluation of vitamin B6 and calcium pantothenate effectiveness on hair growth from clinical and trichographic aspects for treatment of diffuse alopecia in women. Wiad Lek 54.1-2 (2001): 11-18.

Coronel F et al. Treatment of hyperlipemia in diabetic patients on dialysis with a physiological substance. Am J Nephrol 11.1 (1991): 32-6.

Donati C et al. Pantethine improves the lipid abnormalities of chronic hemodialysis patients: results of a multicenter clinical trial. Clin Nephrol 25.2 (1986): 70-4.

Dorr W et al. Effects of dexpanthenol with or without Aloe vera extract on radiation-induced oral mucositis: preclinical studies. Int J Radiat Biol 81(3) (2005): 43-50.

Ebner F et al. Topical use of dexpanthenol in skin disorders. Am J Clin Dermatol 3.6 (2002): 427-33.

Gaddi A et al. Controlled evaluation of pantethine, a natural hypolipidemic compound, in patients with different forms of hyperlipoproteinemia. Atherosclerosis 50.1 (1984): 73-83.

Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism, 3rd edn. Belmont, CA: Wadsworth, 2000.

Kehrl W, Sonnemann U. Dexpanthenol nasal spray as an effective therapeutic principle for treatment of rhinitis sicca anterior. Laryngorhinootologie 77.9 (1998): 506-12.

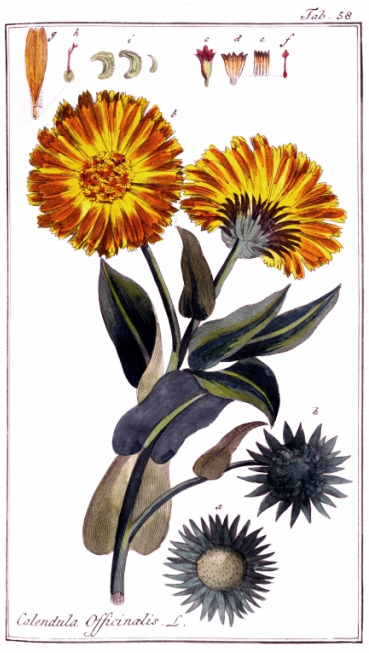
Kehrl W, Sonnemann U. Improving wound healing after nose surgery by combined administration of xylometazoline and dexpanthenol. Laryngorhinootologie 79.3 (2000): 151-4.

Klocker N et al. The protective effect of dexpanthenol in nasal sprays. First results of cytotoxic and ciliary-toxic studies in vitro. Laryngorhinootologie 82(3) (2003): 177-82.

Lokkevik E et al. Skin treatment with bepanthen cream versus no cream during radiotherapy: a randomized controlled trial. Acta Oncol 35.8 (1996): 1021-6.

McCarty MF. Inhibition of acetyl-CoA carboxylase by cystamine may mediate the hypotriglyceridemic activity of pantethine. Med Hypotheses 56.3 (2001): 314-17.
McRae MP. Treatment of hyperlipoproteinemia with pantethine: A review and analysis of efficacy and tolerability. Nutr Res 25(4) (2005): 319-33.
Moiseenok AG et al. Antitoxic properties of pantothenic acid derivatives, precursors of coenzyme A biosynthesis, with regard to kanamycin. Antibiotiki 29.11 (1984): 851-5.
Nagiel-Ostaszewski I, Lau-Cam CA. Protection by pantethine, pantothenic acid and cystamine against carbon tetrachloride-induced hepatotoxicity in the rat. Res Commun Chem Pathol Pharmacol 67.2 (1990): 289-92.
Naruta E, Buko V. Hypolipidemic effect of pantothenic acid derivatives in mice with hypothalamic obesity induced by aurothioglucose. Exp Toxicol Pathol 53.5 (2001): 393-8.
Plesofsky N. Pantothenic Acid. Oregon: Linus Pauling Institute, 2002.
Slyshenkov VS et al. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. FEBS Lett 569(1-3) (2004): 169-72.
Thurston JH, Hauhart RE. Amelioration of adverse effects of valproic acid on ketogenesis and liver coenzyme A metabolism by cotreatment with pantothenate and carnitine in developing mice: possible clinical significance. Pediatr Res 31.4 (1992): 419-23.
Vaxman F et al. Improvement in the healing of colonic anastomoses by vitamin B5 and C supplements: Experimental study in the rabbit. Ann Chir 44.7 (1990): 512-20.
Vaxman F et al. Effect of pantothenic acid and ascorbic acid supplementation on human skin wound healing process. A double-blind, prospective and randomized trial. Eur Surg Res 27(3) (1995): 158-66.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.

Vitamin B6



BACKGROUND AND RELEVANT PHARMACOKINETICS

Absorption of vitamin B6, also known as pyridoxine, takes place in the jejunum by a passive, non-saturable process. It is transported in the plasma and red blood cells to the liver, where it is converted to pyridoxal 5′-phosphate, and is then available to other tissues. It is mainly stored in muscle tissue, and ultimately metabolised and excreted via the kidneys.

CHEMICAL COMPONENTS

Vitamin B6 is a water-soluble vitamin and has six forms, of which pyridoxine hydrochloride is the main form found in supplements and used to fortify foods.

FOOD SOURCES

Vitamin B6 is widely distributed in animal and plant foods. The best food sources are fish, organ meats, legumes, wheatgerm, eggs, nuts, potatoes and bananas. Per milligram, Vegemite is one of the richest sources.

Up to 40% can be lost through cooking (Wahlqvist et al 1997).

DEFICIENCY SIGNS AND SYMPTOMS

Clinical signs and symptoms are non-specific because this vitamin is necessary for the proper functioning of over 60 enzymes (Pelton et al 1999, Wahlqvist et al 1997). Chiefly, dermatological, circulatory and neurological changes develop with vitamin B6 deficiency.

- Dermatitis (similar to that seen in pellagra).
- Angular stomatitis and glossitis and cheilosis.
- Sideroblastic anaemia.
- Impaired antibody production.
- Renal calculi.
- Elevated homocysteine levels (Lakshmi & Ramalakshmi 1998).
- CNS effects such as irritability, confusion, lethargy, clinical depression, elevated seizure activity (particularly in children), abnormal brain wave patterns and nerve conduction.
- Birth defects such as cleft palate (associated with elevated homocysteine) (Weingaertner et al 2005)

Pyridoxine deficiency has also been associated with premature coronary artery disease and with impaired oxidative defence mechanisms (Miner et al 2001).

PRIMARY DEFICIENCY
Primary deficiency is rare because this vitamin is widely available in many foods.

SECONDARY DEFICIENCY
This may result from malabsorption syndromes, cancer, liver cirrhosis and alcoholism, hyperthyroidism, congestive heart failure or medicine use, such as OCP, isoniazid, hydralazine, penicillamine, theophylline or MAO inhibitors (Beers & Berkow 2003, Bratman & Kroll 2000, Wardlaw et al 1997).

Clinical note — Marginal B6 deficiency
Although frank deficiency is rare, marginal deficiency appears to be common. One study found that 100% of 174 university students tested had some degree of vitamin B6 deficiency (Shizukuishi et al 1981). A larger survey of 11,658 adults found that 71% of males and 90% of females did not meet the RDI requirements for B6 (Kant & Block 1990).

MAIN ACTIONS

COENZYME
Vitamin B6 is an important coenzyme in the biosynthesis of the neurotransmitters GABA, dopamine and serotonin (Gerster 1996). It is also involved in protein metabolism, haemoglobin synthesis, gluconeogenesis, lipid metabolism, niacin formation, immune system processes, nucleic acid synthesis and hormone modulation (Bratman & Kroll 2000, Wardlaw et al 1997).

Homocysteine Homocysteine is formed from the essential amino acid methionine and about 50% is then remethylated to methionine via steps that require folic acid and vitamin B12. Vitamin B6 is required for another metabolic pathway and is a cofactor for cystathionine beta-synthase, which mediates the transformation of homocysteine to cystathionine (Wilcken & Wilcken 1998).

Serotonin Pyridoxine is required for the synthesis of many neurotransmitters, including serotonin. It is a cofactor for the enzyme 5-hydroxytryptophan decarboxylase, which is involved in one of the steps that converts tryptophan to serotonin (Pelton et al 1999). As such, deficiency states are associated with alterations to mood and other psychological disturbances.

CLINICAL USE

Vitamin B6 supplementation is used to treat a large variety of conditions and is mostly prescribed in combination with other B group vitamins.

DEFICIENCY
Vitamin B6 is traditionally used to treat vitamin B6 deficiency states.

PREMENSTRUAL SYNDROME

Vitamin B6 supplementation is used in doses beyond RDI levels for the treatment of PMS. A 1999 systematic review of nine clinical trials involving 940 patients with PMS support this use, finding that doses up to 100 mg/day are likely to be of benefit in treating symptoms and PMS-related depression (Wyatt et al 1999).

Comparative study One randomised double-blind study compared the effects of pyridoxine (300 mg/day), alprazolam (0.75 mg/day), fluoxetine (10 mg/day) or propranolol (20 mg/day) in four groups of 30 women with severe PMS (Diegoli et al 1998). In this study, fluoxetine produced the best results (a mean reduction of 65.4% in symptoms) followed by propanolol (58.7%), alprazolam (55.6%), pyridoxine (45.3%) and placebo (39.4–46.1%). Symptoms responding well to pyridoxine were tachycardia, insomnia, acne and nausea (Diegoli et al 1998).

MORNING SICKNESS

A 2000 Cochrane review of 23 randomised trials investigating all treatments for morning sickness concluded that pyridoxine significantly reduces the severity of morning sickness (Jewell & Young 2002).

HEART DISEASE

Elevated homocysteine levels Elevated fasting plasma concentrations of homocysteine have a high prevalence in subjects with cardiovascular disease and have also been associated with an increased risk of atherothrombosis in most, but not all, prospective studies (van Guldener & Stehouwer 2001). Clinical studies have found that supplementation with vitamin B6 significantly reduces plasma homocysteine concentrations (Lakshmi & Ramalakshmi 1998). In practice, pyridoxine is typically recommended together with folic acid and vitamin B12.

Improving outcomes after heart transplantation Cardiac transplantation represents a potentially life-saving procedure for patients with end-stage cardiac disease. Short-term survival is improving because of improved immunosuppression, but long-term survival remains limited by an aggressive form of atherosclerosis known as transplant coronary artery disease (Miner et al 2001).

Hyperhomocysteinaemia is one of several factors implicated in the development of this state as it is common in cardiac transplant recipients. As such, tests with B group vitamins have started. A randomised, double-blind placebo-controlled study showed that pyridoxine supplementation (100 mg/day) taken for 10 weeks improved endothelial function as assessed by flow-mediated dilatation in cardiac transplant recipients (Miner et al 2001). Interestingly, homocysteine levels remained unchanged with treatment, suggesting other mechanisms are responsible.

CARPAL TUNNEL SYNDROME

It has been suspected that vitamin B6 deficiency may play a role in the development of carpal tunnel syndrome (CTS) as several studies have found that patients with CTS and pyridoxine deficiency respond to supplementation (Ellis et al 1991). Although these observations are encouraging, a 2002 review found no benefit with pyridoxine treatment in CTS (Gerritsen et al 2002).

AUTISM

High-dose pyridoxine and magnesium supplementation is a popular nutritional treatment in autism, although current evidence is contradictory. A critical analysis of 12 published studies concluded that evidence generally supports the efficacy of vitamin treatment; however, there were methodological shortcomings inherent in many of the studies (Pfeiffer et al 1995). In contrast, a small, 10-week, double-blind placebo-controlled trial found that an average dose of 638.9 mg pyridoxine and 216.3 mg magnesium oxide was ineffective in ameliorating autistic behaviours (Findling et al 1997).

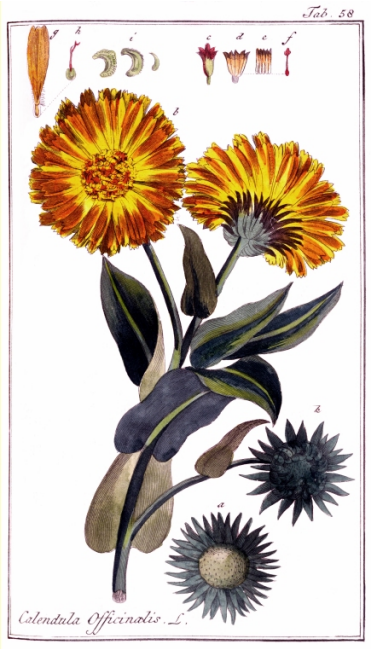
REDUCING THE INCIDENCE OF REPEATED CONVULSIONS DURING A FEBRILE EPISODE

Two randomised trials have been conducted in children, producing conflicting results. One study of 65 children who had been admitted to hospital with febrile convulsions showed that a dose of 2–10 mg/kg pyridoxal phosphate daily (PO or IV) produced a 100% success rate, whereas 43% in the control group experienced repeated convulsions (Kamiishi et al 1996). A second randomised trial found that a lower dose of 20 mg twice daily did not alter the incidence of febrile convulsions compared with placebo (McKiernan et al 1981).

SYMPTOMATIC TREATMENT FOR 'STRESS'

The term 'stress', as used by the public, is a subjective one and often described in different ways. One theoretical model that has been developed to predict psychological 'stress' includes measures of life stressors, social support and coping style. Using this model, pyridoxine deficiency has been identified as a significant predictor of increased overall psychological stress during bereavement. More specifically, pyridoxine deficiency is significantly associated with increases in depression, fatigue and confused mood levels, but not with those of anxiety, anger or vigour (Baldewicz et al 1998).

One explanation is that pyridoxine is involved in neurotransmitter biosynthesis, such as GABA and serotonin, and therefore deficiency states are associated with



mood disturbances that are improved with consequent supplementation (McCarty 2000).

RHEUMATOID ARTHRITIS

As inflammation reduces vitamin B6 levels (Chiang et al 2005a), a placebo-controlled clinical trial of 36 adults with RA were given 50 mg of pyridoxine hydrocholoride for 30 days. Inflammation did not reduce, but the plasma levels of vitamin B6 did increase (Chiang et al 2005a), suggesting that inflammation may reduce levels of vitamin B6 but low levels may not cause inflammation.

OTHER USES

Vitamin B6 supplements have also been used to prevent diabetic retinopathy, kidney stones and to treat symptoms of tardive dyskinesia, vertigo, allergy to monosodium glutamate, asthma, schizophrenia and photosensitivity. Supplements have also been used as an adjunct to the OCP, to relieve mood disturbances and restore vitamin status.

DREAM STATES

Many have suspected that pyridoxine supplements taken at night are able to influence dream states and sleep, causing disruption in some people. The results of a 2002 double-blind, placebo-controlled crossover study support this observation (Ebben et al 2002). Pyridoxine supplementation (250 mg) taken before bedtime was shown to significantly influence dream-salience scores (a composite score containing measures on vividness, bizarreness, emotionality and colour) starting on the first night of treatment.

DOSAGE RANGE

- Prevention of deficiency: Australian RDI for adults and children >8 years: 1–1.7 mg/day.
- Treatment of deficiency: 5–25 mg/day.
- Morning sickness: 30–75 mg/day, sometimes taken as 25 mg three times daily.
- Symptoms of PMS: 100–500 mg/day.
- Elevated homocysteine levels: 100 mg/day.
- Carpal tunnel syndrome: 100–200 mg/day.

TOXICITY

Symptoms of toxicity include paraesthesia, hyperaesthesia, bone pain, muscle weakness, numbness and fasciculation, most marked at the extremities (Dalton & Dalton 1987, Diegoli et al 1998).

The dose and time frame at which toxicity occurs varies significantly between individuals. Studies involving large population groups using 100–150 mg/day have shown minimal or no toxicity in 5- to 10-year studies, whereas women self-medicating for PMS taking 117 ± 92 mg for 2.9 ± 1.9 years have reported increased incidence in peripheral neuropathy in others (Bernstein 1990, Dalton & Dalton 1987).

ADVERSE REACTIONS

Pyridoxine is considered non-toxic, although nausea and vomiting, headache, paraesthesia, sleepiness and low serum folic acid levels have been reported.

Supplements taken at night-time may result in more vivid dreams and, for some individuals, disrupted sleep (Ebben et al 2002).

SIGNIFICANT INTERACTIONS

AMIODARONE

Pyridoxine may increase the risk of drug-induced photosensitivity — caution with patients taking pyridoxine and amiodarone concurrently.

ANTIBIOTICS

Destruction of gastrointestinal flora can decrease endogenous production of vitamin B6 — increase intake of vitamin B6 rich foods or consider supplementation with long-term drug treatment.

HYDRALAZINE

Hydralazine may induce B6 deficiency according to a clinical study — increased intake may be required with long-term drug therapy.

ISONIAZID

Isoniazid increases vitamin B6 requirements — increase intake of vitamin B6 rich foods or consider supplementation with long-term drug treatment.

L-DOPA (WITHOUT CARBIDOPA)

Pyridoxine may reduce drug efficacy — monitor for drug effectiveness and observe.

ORAL CONTRACEPTIVES

Oral contraceptives increase vitamin B6 requirements — increase intake of vitamin B6 rich foods or consider supplementation with long-term drug treatment.

PENICILLAMINE

This drug increases vitamin B6 requirements — increase intake of vitamin B6 rich foods or consider supplementation.

PHENOBARBITAL, PHENYTOIN
Vitamin B6 supplements may lower plasma levels and efficacy of these drugs — monitor for drug effectiveness, and exercise caution when these drugs are being taken concurrently.

THEOPHYLLINE
May induce pyridoxine deficiency — increased intake may be required with long term drug therapy.

CONTRAINDICATIONS AND PRECAUTIONS
Monitor long-term use of high-dose pyridoxine supplements (>100 mg although this level varies between individuals).

PREGNANCY USE
Pyridoxine supplements are commonly used during pregnancy to reduce symptoms of morning sickness, suggesting safety when used in appropriate doses.

PRACTICE POINTS/PATIENT COUNSELLING
- Vitamin B6 is available in many foods, however suboptimal, but several surveys suggest that inadequate intakes are common.
- Deficiency can manifest with psychological symptoms of depression, irritability and confusion and physical symptoms of lethargy, dermatitis, angular stomatitis, glossitis and impaired immunity.
- Overall, clinical research supports the use of vitamin B6 supplements in relieving mild to moderate symptoms of PMS (particularly breast tenderness and mood disturbance), nausea in pregnancy and as a treatment for hyperhomocysteinaemia.
- There is conflicting evidence as to whether vitamin B6 supplements improve symptoms of carpel tunnel syndrome, autism (together with magnesium) and prevent febrile convulsions in children.
- Pyridoxine should not be used in high doses long term, as this can induce toxicity.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS
What will this vitamin do for me?
Vitamin B6 is essential for the body's normal functioning. It has been used to treat many different conditions; however, scientific evidence generally supports its use in only a few conditions (e.g. morning sickness, mild to moderate PMS and elevated homocysteine levels).

When will it start to work?

This will depend on the indication being treated. In regard to PMS symptoms, 2–3 cycles may be required, whereas effects can be seen within 2–3 days for morning sickness.

Are there any safety issues?

High doses should not be taken long term, as this can cause toxicity.

REFERENCES

Baldewicz T et al. Plasma pyridoxine deficiency is related to increased psychological distress in recently bereaved homosexual men. Psychosom Med 60.3 (1998): 297-308.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Bernstein AL. Vitamin B6 in clinical neurology. Ann NY Acad Sci 585 (1990): 250-60.

Bratman S, Kroll D. Natural Health Bible. Rocklin, CA: Prima Health, 2000.

Chiang EP et al. Inflammation causes tissue-specific depletion of vitamin B6. Arthritis Res Ther 7.6 (2005a): R1254-62

Chiang EP et al. Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis. Arthritis Res Ther 7.6 (2005b): R1404-11.

Dalton K, Dalton MJ. Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurol Scand 76.1 (1987): 8-11.

Diegoli MS et al. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet 62.1 (1998): 63-7.

Ebben M et al. Effects of pyridoxine on dreaming: a preliminary study. Percept Mot Skills 94.1 (2002): 135-40.

Ellis JM et al. A deficiency of vitamin B6 is a plausible molecular basis of the retinopathy of patients with diabetes mellitus. Biochem Biophys Res Commun 179.1 (1991): 615-19.

Findling RL et al. High-dose pyridoxine and magnesium administration in children with autistic disorder: an absence of salutary effects in a double-blind, placebo-controlled study. J Autism Dev Disord 27.4 (1997): 467-78.

Gerritsen AA et al. Conservative treatment options for carpal tunnel syndrome: a systematic review of randomised controlled trials. J Neurol 249.3 (2002): 272-80.

Gerster H. The importance of vitamin B6 for development of the infant: Human medical and animal experiment studies. Ernahrungswiss 35.4 (1996): 309-17.

Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 1 (2002): CD000145.

Kamiishi A et al. A clinical study of the effectiveness of vitamin B6 for the prevention of repeated convulsions during one febrile episode. Brain Dev 18 (1996): 471-8.

Kant AK, Block G. Dietary vitamin B-6 intake and food sources in the US population: NHANES II, 1976-1980. Am J Clin Nutr 52.4 (1990): 707-16.

Lakshmi AV, Ramalakshmi BA. Effect of pyridoxine or riboflavin supplementation on plasma homocysteine levels in women with oral lesions. Natl Med J India 11.4 (1998); as cited by Court S. A controlled trial of pyridoxine supplementation in children with febrile convulsions. Clin Pediatr 20.3 (1981): 208-11.

McCarty MF. High-dose pyridoxine as an 'anti-stress' strategy. Med Hypotheses 54(5) (2000): 803-07.

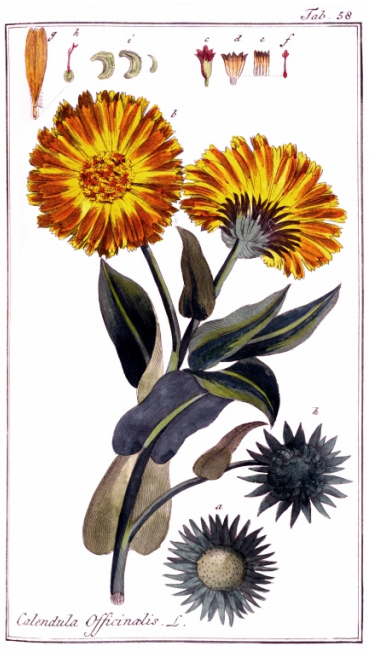
McKiernan J et al. A controlled trial of pyridoxine supplementation in children with febrile convulsions. Clin Pediatr (Phila) 20(3) (1981): 208-11.

Miner SE et al. Pyridoxine improves endothelial function in cardiac transplant recipients. J Heart Lung Transplant 20.9 (2001): 964-9.

Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.

Pfeiffer SI et al. Efficacy of vitamin B6 and magnesium in the treatment of autism: a methodology review and summary of outcomes. J Autism Dev Disord 25.5 (1995): 481-93.
Shizukuishi S et al. Distribution of vitamin B6 deficiency in university students. J Nutr Sci Vitaminol (Tokyo) 27.3 (1981): 193-7.
van Guldener C, Stehouwer CD. Homocysteine-lowering treatment: an overview. Expert Opin Pharmacother 2.9 (2001): 1449-60.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wardlaw G et al. Contemporary Nutrition, 3rd edn. Brown and Benchmark, 1997.
Weingaertner J et al. Initial findings on teratological and developmental relationships and differences between neural tube defects and facial clefting: First experimental results. J Cranio-Maxillofacial Surg 33.5 (2005): 297-300.
Wilcken DE, Wilcken B. B vitamins and homocysteine in cardiovascular disease and aging. Ann NY Acad Sci 854 (1998): 361-70.
Wyatt KM et al. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. BMJ 318.7195 (1999): 1375-81.

Vitamin B12



BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B12 (cobalamin) is a water-soluble vitamin obtained mostly from animal protein products in the diet. In the stomach gastric acid is required to liberate protein-bound cobalamin, which is then immediately bound to R-binders (glycoproteins) that protect it from being denatured. When the contents of the stomach reach the duodenum the R-binders are partially digested by pancreatic proteases, releasing them to bind to intrinsic factor (a glycoprotein), which is secreted by the parietal cells of the gastric mucosa. This complex is then absorbed in the terminal ileum and transported to cells, where it carries out its metabolic function, or to the liver, where it is stored until required (FAO/WHO 2002, Oh & Brown 2003). An alternative method of absorption, which is independent of intrinsic factor, also appears to exist and accounts for the absorption of approximately 1% of large oral doses (> 300 μg) of B12 (Elia 1998). Absorption via intrinsic factor is limited to about 1.5–2.0 μg/meal owing to limited receptor capacity (FAO/WHO 2002).

CHEMICAL COMPONENTS

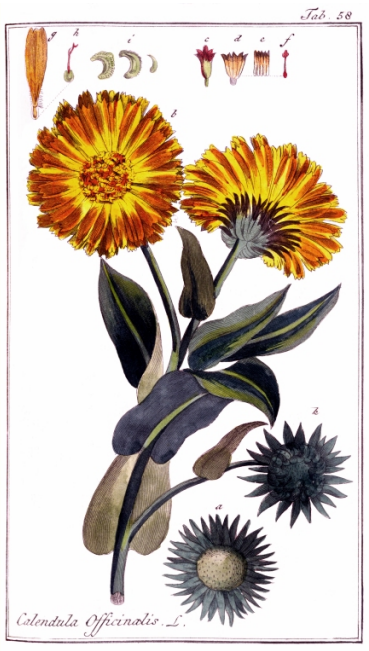
Vitamin B12 is the largest of the B vitamins and is a complex structure containing a central cobalt atom. There are five forms of B12: cyanocobalamin (a synthetic form that has a cyanide attached to the cobalt), hydroxycobalamin (hydroxyl group attached to the cobalt; it is produced for parenteral administration), aquacobalamin (water group bound to the cobalt) and the coenzymatically active forms (methylcobalamin and 5-deoxyadenosylcobalamin), in which a methyl group or a 5-deoxyadenosyl group is bound to the cobalt atom (FAO/WHO 2002, Freeman et al 1999).

FOOD SOURCES

Lambs liver, sardines, oysters, egg yolk, fish, beef, kidney, cheese and milk. Up to 10% is lost in cooking (Wahlqvist 2002).

Plants do not contain B12 because they have no cobalamin-dependent enzymes (Croft et al 2005). Most microorganisms, including bacteria and algae, synthesise B12, which then makes its way into the food chain (FAO/WHO 2002). Human intestinal bacteria also synthesise B12, but this is not absorbed to any considerable extent (Wahlqvist 2002). Vegans living in situations with more stringent hygiene are therefore more likely to develop deficiencies.

Clinical note — Nori: a source for vegetarians
Rat studies have demonstrated improvements in B12 status following the ingestion of nori (seaweed). Nori is said to contain as much B12 as liver (Croft et al 2005) approximately 55–59 μg/100 g dry weight. Five different biologically active vitamin B12 compounds have been identified in nori: cyanocobalamin, hydroxycobalamin, sulfitocobalamin, adenosylcobalamin and methylcobalamin (Takenaka et al 2001); the source of B12 appears to be bacteria (Croft et al 2005).



DEFICIENCY SIGNS AND SYMPTOMS

Vitamin B12 deficiencies manifest primarily as haematological and neurological disturbances, and are estimated to affect 10–15% of individuals over the age of 60 years (Baik & Russell 1999):

- Haemotological: macrocytic (megaloblastic) anaemia, pancytopenia (leukopenia, thrombocytopenia); symptoms may include lethargy, dyspnoea, anorexia, weight loss and pallor (Wahlqvist 2002).
- Neurological disturbances: paraesthesias, optic neuropathy (reversible), peripheral neuropathy and demyelination of the corticospinal tract and dorsal columns (subacute combined systems disease).
- Psychological disturbances: impaired memory, irritability, depression, personality change, dementia and psychosis (Lee 1999, Lindenbaum et al 1988).
- Various gastrointestinal symptoms can also develop, such as loss of appetite, intermittent constipation and diarrhoea, glossitis and abdominal pain.
- Folic acid supplementation may mask an underlying B12 deficiency, leading to the progression of neurological symptoms.

PRIMARY DEFICIENCY

People at risk are those living in India, Central and South America, and selected areas in Africa (Stabler & Allen 2004), strict vegetarians and vegans, breastfed infants of vegetarian mothers with low B12 stores, elderly patients with 'tea and toast diets' and chronic alcoholics. As vitamin B12 is stored to a considerable extent, even after complete depletion of food-ingested cobalamin, clinically relevant deficiencies will usually only develop after 5–10 years (Schenk et al 1999). This time frame increases to an average of approximately 18 years in strict vegetarians when intrinsic factor secretion is intact (Babior 1996). In this case, some enterohepatic recycling of cobalamin should occur in the distal ileum (Howden 2000).

SECONDARY DEFICIENCY

Vitamin B12 deficiency is more likely to result from inadequate absorption, defects in vitamin B12 metabolism or gastrointestinal disorders than a lack of dietary intake.

- Pernicious anaemia: an autoimmune condition affecting gastric parietal cells that produce intrinsic factor; common cause of megaloblastic anaemia, especially in persons of European or African descent (Stabler & Allen 2004).
- Methylmalonic acidaemia: inherited defect in B12 metabolism.
- Congenital absence of transcobalamin II.
- Medications that reduce gastric acidity (e.g. H_2 blockers and PPI).
- Atrophic gastritis/gastric atrophy: probably due to a decrease in acid output and intrinsic factor production (Schenk et al 1999). Gastric atrophy is more common in the elderly.
- Intestinal resection of the part of the ileum where absorption takes place or gastric resection, which affects the parietal cells and in turn production of intrinsic factor.
- Achlorhydria (Termanini et al 1998).
- Pancreatic insufficiency: the cobalamin-R-protein complex is split by pancreatic enzymes in the duodenum (Festen et al 1991).
- Ileal dysfunction (Howden 2000): may affect absorption at this site.
- Crohn's disease, irritable bowel disease, coeliac disease: reduced absorption.
- Bacteria and parasites in the intestine may also compete for B12.
- Radiotherapy for rectal cancer: causes a rapid and persistent decrease in B12 status as reflected by reduced serum B12 combined with increased serum methylmalonic acid (MMA) (Gronlie Guren et al 2004).

The elderly deserve a separate mention as a population at risk of deficiency because of both primary and secondary causes, such as poor dietary intakes, failure to separate vitamin B12 from food protein, inadequate absorption, utilisation and storage, as well as drug–food interactions leading to malabsorption and metabolic inactivation (Bradford & Taylor 1999, Dharmarajan et al 2003). Subtle signs of deficiency may include lethargy, weight loss and dementia (Dharmarajan et al 2003).

Clinical note — Testing for vitamin B12 deficiency

Numerous studies have indicated that serum B12 levels are an inadequate guide to B12 status (Briddon 2003, Carmel 1988, Kapadia 2000, Karnaze & Carmel 1990, Termanini et al 1998). The use of this test has led to poorly defined reference intervals for serum B12 (Briddon 2003), potentially delaying the diagnosis and allowing the progression of B12 deficiency. Approximately 50% of patients with subclinical disease have normal serum B12 levels and older patients present with neurological and psychiatric symptoms without haemotological findings. In ad-

dition, use of the OCP may also affect test results (Bor 2004). As a result, this method of testing has lost favour as an adequate measure of B12 status. A combination of two tests appears to be more conclusive. Elevated levels of total homocysteine in serum and plasma reflects deficiencies of either folate or B12. MMA is a more specific marker of cobalamin function, but renal insufficiency may affect the results of this test. Therefore, a combination of the two is probably the clearest indicator (Bjorke Monsen & Ueland 2003, FAO/WHO 2002, Kapadia 2000). Preliminary evidence also suggests that overnight fasting urinary MMA concentrations correlate strongly with serum MMA; however, further investigations are required to confirm the application of this test in various populations (Kwok et al 2004). While the use of such markers may improve the assessment of B12 deficiency, establishing the cause of deficiency should also be part of the diagnostic approach (Schneede & Ueland 2005).

Elevated levels of serum cobalamin may be a sign of a serious, even life-threatening, disease such as chronic myelogeneous leukaemia, promyelocytic leukaemia, polycythaemia vera, hypereosinophilic syndrome, acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver disease. Elevated B12 levels, therefore, warrant a full diagnostic work up to assess the presence of disease (Ermens et al 2003).

MAIN ACTIONS

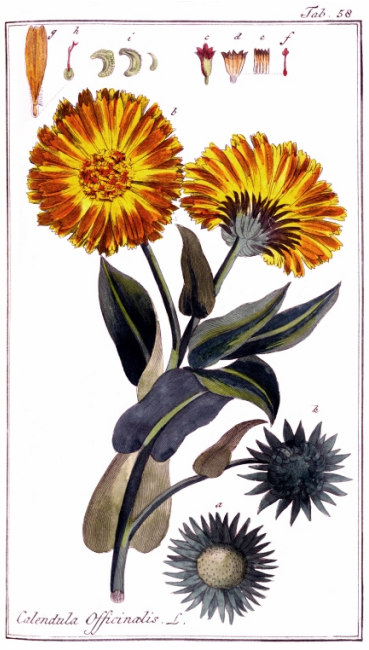
IMPORTANT COFACTOR

Vitamin B12 is essential for the normal function of all cells. It affects cell growth and replication, the metabolism of carbohydrates, lipids and protein and is involved in fatty acid and nucleic acid synthesis. It is also involved in the production of red blood cells in bone marrow, and activates folacin coenzymes for red blood cell production.

Homocysteine reduction Methylcobalamin aids in the conversion of homocysteine to methionine by the action of methionine synthase, transferring a methyl group from methylfolate (folic acid).

After conversion from homocysteine, methionine is then converted to *S*-adenosyl-L-methionine (SAMe), important for methylation reactions and protein synthesis. An increase in homocysteine levels and decrease in SAMe levels has been implicated in depression and may also contribute to the neurological symptoms seen in pernicious anaemia (IMG 2003).

Nervous system Vitamin B12 is involved in the synthesis of protein structures in the myelin sheath and nerve cells. As methylation is required for the production of myelin basic protein, a reduction in B12 and SAMe will result in demyelination of



peripheral nerves and the spinal column (subacute combined degeneration) (FAO/WHO 2002).

Immune system Vitamin B12 acts as an immunomodulator for cellular immunity (Tamura et al 1999).

CLINICAL USE

Vitamin B12 supplementation is administered using various routes such as intravenous and oral doses. This review will focus on oral supplementation as this is the form generally used by the public and available OTC.

DEFICIENCY: TREATMENT AND PREVENTION

Traditionally, vitamin B12 supplementation has been used to treat deficiency or prevent deficiency in conditions such as pernicious anaemia and atrophic gastritis, but special consideration should be given to the elderly who are at high risk.

Pernicious anaemia Pernicious anaemia is caused by a deficiency of intrinsic factor leading to malabsorption of vitamin B12. Signs and symptoms include pallor, glossitis, weakness and neurological symptoms including paraesthesias of the hands and feet, decreased deep-tendon reflexes and loss of sensory perception and motor controls (neurological symptoms may be irreversible). In more progressed conditions confusion, memory loss, moodiness, psychosis and delusional behaviour may be present. Achlorhydria and gastric mucosal atrophy may also occur, further complicating the condition.

Uncomplicated pernicious anaemia is characterised by mild or moderate megaloblastic anaemia without leukopenia, thrombocytopenia or neurologic symptoms. In more advanced cases urgent parenteral administration of vitamin B12 and folic acid (typically 100 μg of cyanocobalamin and 1–5 mg of folic acid) is given intramuscularly, as well as blood transfusions.

Elderly Vitamin B12 deficiency is common in the elderly, with estimates as high as 43% (Wolters et al 2004). Poor vitamin B12 status has been associated with vascular disease, depression, impaired cognitive performance and dementia. Elderly patients (>60 years) should be monitored for evidence of B12 deficiency (a minimum threshold of 220–258 pmol/L (300–350 pg/mL) is desirable in the elderly) and general supplementation with vitamin B12 (>50 μg/day) should be considered (Wolters et al 2004). Significantly higher doses may be required to correct deficiency. A randomised, parallel-group, double-blind, dose-finding trial found that the lowest dose of oral cyanocobalamin required to normalise mild vitamin B12 deficiency in the elderly is 647–1032 μg/day, more than 200-fold the recommended dietary allowance (Eussen et al 2005).

Clinical note — Oral forms are effective

Vitamin B12 is often given parenterally as an intramuscular injection, based on the understanding that oral doses will not be efficacious in cases of malabsorption.

There is now considerable evidence that oral vitamin B12 therapy is comparable in efficacy to parenteral therapy, even when intrinsic factor is not present or in other diseases affecting absorption (Andres et al 2005a, b, Bolaman et al 2003, Delpre et al 1999, Kuzminski et al 1998, Lederle 1991, Nyholm 2003, Oh & Brown 2003, Roth & Orija 2004; Vidal-Alaball et al 2005). A recent Cochrane review suggests 2000 μg/day of oral vitamin B12 or 1000 μg initially daily then weekly and monthly may be as effective as intramuscular injections in obtaining short term haematological and neurological responses in vitamin B12-deficient patients (Vidal-Alaball et al 2005). As rare cases of anaphylaxis may occur with parenteral administration, oral therapy is also considered a safer option with improved cost and compliance (Bilwani et al 2005, Bolaman et al 2003). At doses of 500 μg/day correction of serum B12 levels is likely to occur within 1 week to 1 month, with correction of haematological abnormalities after at least 3 months (Andres et al 2005b).

HYPERHOMOCYSTEINAEMIA

Together with folic acid and vitamin B6, vitamin B12 has been shown to reduce high plasma levels of homocysteine, which has been proposed as an independent risk factor for cardiovascular disease (including atherosclerosis and coronary artery disease), cerebrovascular disease, peripheral vascular disease and venous thromboembolism (Clarke et al 1991, den Heijer et al 1996, Hung et al 2003, Lobo et al 1999, Malinow et al 1989, Selhub et al 1995), exudative ARMD, noise-induced hearing loss, cognitive dysfunction, and adverse pregnancy outcomes (Bjorke Monsen & Ueland 2003, Gok et al 2004, Nowak et al 2005).

As a result, vitamin B12 is often recommended in combination with folic acid and vitamin B6 in conditions for which homocysteine is implicated as a possible causative factor.

Cardiovascular protection In practice, the relative safety and affordability of combined vitamin B supplementation (B12, folic acid and B6) make it an attractive recommendation in people with familial hyperhomocysteinaemia or cardiovascular disease. Whether lowering total homocysteine improves cardiovascular mortality and morbidity, however, is questionable (Toole et al 2004). Current evidence suggests that lowering total homocysteine by 3.7 micromol/L (using folic acid 2 mg, vitamin B12 0.5 mg, and vitamin B6 25 mg) does not significantly reduce blood concen-

trations of the biomarkers of inflammation, endothelial dysfunction, or hypercoagulability in patients with recent transient ischaemic attack or stroke (Dusitanond et al 2005). This may reflect an inability of these markers to truly reflect morbidity and mortality rates or a lack of effect for homocysteine-lowering therapy.

The consistent findings of an association between elevated plasma total homocysteine levels and vascular risk suggests that longer trials in different populations with elevated total homocysteine may be necessary to understand whether the association is a cause or consequence of disease (Toole et al 2004).

Renal transplant recipients Although studies investigating the effects of vitamin B12 as a stand-alone treatment in this condition are not available, several clinical studies have produced supporting evidence for the use of combination vitamin B treatment (vitamin B12, folic acid and B6).

A RCT involving 56 renal transplant patients found that vitamin supplementation with folic acid (5 mg/day), vitamin B6 (50 mg/day) and vitamin B12 (400 μg/day) for 6 months reduced the progression of atherosclerosis. Patients taking the vitamin combination experienced a significant decrease in homocysteine levels and carotid intima-media thickness, which is reflective of early atherosclerosis (Marcucci et al 2003).

Parenteral B12 therapy has also been trialled in patients with end-stage renal disease in whom hyperhomocysteinaemia is common (Hoffer et al 2005a, b, Hyndman et al 2003).

Restenosis after percutaneous coronary intervention A RCT found that vitamin B12 (cyanocobalamin, 400 μg/day), folic acid (1 mg/day) and vitamin B6 (pyridoxine hydrochloride, 10 mg/day) taken for 6 months significantly decreased the incidence of major adverse events including restenosis after percutaneous coronary intervention (Schnyder et al 2002).

Neural tube defects Postpartum analysis of serum B12 levels has shown an increased risk of NTD in women with low B12 status (Groenen et al 2004, Ray & Blom 2003, Suarez et al 2003). As a result some authors have called for combined fortification of food with folic acid and vitamin B12 because there are concerns about masking B12 deficiency (Czernichow et al 2005).

Noise-induced hearing loss Homocysteine levels are significantly higher in subjects with noise-induced hearing loss as compared to healthy controls (Gok et al 2004) and elevated plasma B12 levels appear to play a protective role (Quaranta et al 2004).

Recurrent abortion There appears to be a correlation between low serum B12 levels, increased homocysteine levels and early or very early recurrent abortion in

some women (Reznikoff-Etievant et al 2002, Zetterberg et al 2002). One small study of five women with a history of very early recurrent abortion found that vitamin B12 supplementation resulted in four normal pregnancies (Reznikoff-Etievant et al 2002).

DEPRESSION

Elevation of homocysteine and low levels of vitamin B12 and folate are commonly seen in depression (Coppen & Bolander-Gouaille 2005). Observational studies have found as many as 30% of patients hospitalised for depression to be deficient in vitamin B12 (Hutto 1997). A recent cross-sectional study of 700 community-living, physically disabled women over the age of 65 years found that vitamin B12 deficient women were twice as likely to be severely depressed as non-deficient women (Penninx et al 2000). Considering symptoms of vitamin B12 deficiency can manifest as psychological disturbances such as depression, deficiency should be investigated in this population.

AIDS AND HIV

Low vitamin B12 levels are often observed in patients infected with HIV type 1 (HIV-1) (Remacha & Cadafalch 1999, Remacha et al 1993). One study identified deficiency in 10–35% of all patients seropositive for HIV, presumably as a result of decreased intake, intestinal malabsorption and/or abnormalities in plasma binding proteins or antagonism by the drug azidothymidine. Importantly, as serum cobalamin levels declined, progression to AIDS increased and neurological symptoms worsened.

COGNITIVE IMPAIRMENT

Women in the highest quartile of plasma vitamin B12 levels during mid-life score significantly higher on cognitive function tests in later years and are cognitively equivalent to those 4 years younger (Kang & Grodstein 2005). Supplementation with vitamin B12 significantly reverses impaired mental function in individuals with pre-existing low levels (Healton et al 1991, Miller 2003, Refsum & Smith 2003, Tripathi et al 2001, Weir & Scott 1999). A complete recovery was observed in 61% of people with mental impairment due to low levels of vitamin B12, according to one study (Healton et al 1991). It is unclear whether vitamin B12 (and folate) deficiency exacerbates a pre-existing but undiagnosed pathological condition or whether it may cause cognitive decline even in normal subjects (Moretti et al 2004).

Prevention of cognitive impairment when associated with elevated homocysteine Hyperhomocysteinaemia has been shown to be an independent risk factor for cognitive dysfunction, as both indirect and direct vascular damage can be caused by homocysteine. It has also been implicated in vascular dementia, with an increased risk of multiple brain infarcts and dementia as homocysteine levels rise. As a

result, the homocysteine-lowering action of vitamin B12 provides a theoretical basis for its use in these cases.

One study of 370 non-demented 75-year-olds found a twofold increased risk of developing Alzheimer's dementia in subjects with low serum levels of vitamin B12 and folate over a 3-year period (Wang et al 2001).

DIABETIC NEUROPATHY

According to a recent review of seven RCTs, vitamin B12 supplementation may improve pain and paraesthaesia in patients with diabetic neuropathy (Sun et al 2005). The studies cited, however, are generally of low quality and more research is required to confirm these results and determine whether positive effects are due to the correction of deficiency or alteration of abnormal metabolism.

SLEEP DISORDERS

A preliminary study investigated the effects of randomly assigned methyl- and cyanocobalamin on circadian rhythms, wellbeing, alertness and concentration after 14 days in 20 healthy subjects (Mayer et al 1996).

Methylcobalamin supplementation led to a significant decrease in daytime melatonin levels, improved sleep quality, shorter sleep cycles, increased feelings of alertness, better concentration, and a feeling of waking up refreshed in the morning. It appeared that methylcobalamin was significantly more effective than cobalamin.

TINNITUS

A group of 113 army personnel (mean age 39 years) exposed to military noise was studied, of which 57 had chronic tinnitus and noise-induced hearing loss (Shemesh et al 1993). Of this subset, 47% also had vitamin B12 deficiency. Treatment with vitamin B12 supplementation produced some improvement in tinnitus and associated symptoms.

OTHER USES

Human trials have shown vitamin B12 levels to be low in people with recurrent aphthous stomatitis, suggesting a possible aetiological factor (Piskin et al 2002).

MYOCARDIAL INFARCTION

Rat studies have suggested that hyperhomocysteinaemia aggravates myocardial infarction via oxidative stress mechanisms and that lowering homocysteine levels with folic acid and vitamin B12 may therefore reduce the risk of myocardial infarction (Hagar 2002). Studies in humans are less clear.

ERYTHEMA NODOSUM

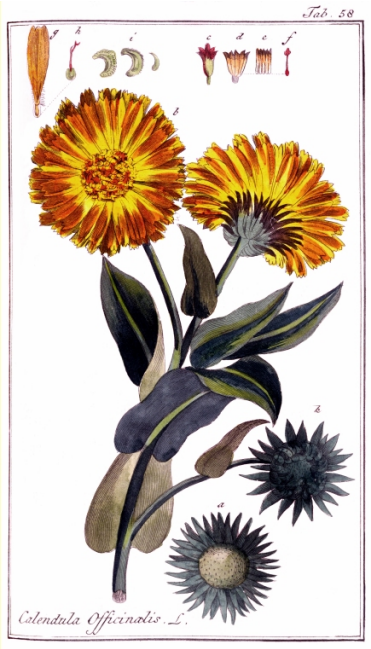
A case report exists of a 38-year-old female diagnosed with erythema nodosum and B12 deficiency whose symptoms resolved completely without re-occurrence following vitamin B12 therapy (Volkov et al 2005). Testing for deficiency may be advised in such cases.

ATOPIC DERMATITIS

A novel use for B12 in a topical cream for atopic dermatitis has recently been tested. A prospective, randomised, placebo-controlled phase III multicentre trial involving 49 patients was conducted. Subjects applied the B12 cream twice daily to one side of the body and a placebo cream to the contralateral side, according to the randomisation scheme, for 8 weeks. The B12 cream was reported to significantly improve the extent and severity of atopic dermatitis and was considered safe and very well tolerated (Stucker et al 2004).

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) and vitamin B12 deficiency share common inflammatory and neurodegenerative characteristics and low or decreased levels of vitamin B12 have been demonstrated in MS patients and may correlate with early onset (<18 years) (Miller et al 2005). Considering vitamin B12 is a cofactor, and myelin formation has important immunomodulatory and neurotrophic effects (Loder et al 2002, Miller et al 2005, Sandyk & Awerbuch 1993), a theoretical basis exists for its use in MS.



DOSAGE RANGE

AUSTRALIAN RDI

- Adult >13 years: 2.4 μg/day.
- Pregnancy: 2.6 μg/day.
- Lactation: 2.8 μg/day.

Requirements may be higher for elderly people with impaired digestion or absorption.

- Sublingual cyanocobalamin: 1000–2000 μg/day taken 30 minutes before breakfast.
- Pernicious anaemia: generally, vitamin B12 1000 μg IM 2–4 times weekly is given until haematological abnormalities are corrected, and then it is given once monthly. Alternatively, oral B12 can be given in very large doses (0.5–2 mg/day). Correction of haematological abnormalities usually occurs within 6 weeks of treatment, but neural improvement may take up to 18 months.
- Homocysteine lowering: vitamin B12 6–400 μg/day (typical dose 250 μg/day) in conjunction with folic acid 20 μg–2.5 mg/day and vitamin B6 200 μg–25 mg/day (Anon 2003).

ADVERSE REACTIONS

Although adverse effects have been reported to parenteral cobalamin, oral supplements appear to be well tolerated (Hillman 1996, Branco-Ferreira et al 1997).

SIGNIFICANT INTERACTIONS

METFORMIN

Long-term use can cause B12 deficiency — increased B12 intake may be required.

PHENOBARBITAL AND PHENYTOIN

One clinical study reports that combined long-term use of phenobarbital and phenytoin resulted in significantly increased serum levels of vitamin B12 (Dastur & Dave 1987) — observe patients taking this combination.

CARBAMAZEPINE

In studies with children, long-term carbamazepine use led to a decrease in vitamin B12 levels (Karabiber et al 2003) — observe for signs and symptoms of B12 deficiency. Increased intake may be required with long-term therapy.

TETRACYCLINE ANTIBIOTICS

B complexes containing B12 may significantly reduce the bioavailability of tetracycline hydrochloride (Omray 1981) — separate doses by at least 2 hours.

ORAL CONTRACEPTIVE PILL

Users of the OCP showed significantly lower concentrations of cobalamin than controls in a 2003 clinical study (Sutterlin et al 2003). However, it would appear that this may be due to an effect on B12 binding proteins in serum affecting test results, because total homocysteine and methylmalonic acid markers were unchanged and no symptoms of deficiency were present (Bor 2004) — observe for signs and symptoms of B12 deficiency and conduct testing if deficiency is suspected.

GASTRIC ACID INHIBITORS: PPI AND H_2 RECEPTOR ANTAGONISTS

Gastric acid is required to liberate protein-bound cobalamin. Therefore, vitamin B12 concentration may be decreased when gastric acid is markedly suppressed for prolonged periods (Laine et al 2000, Schenk et al 1999, Termanini et al 1998). Studies have shown that omeprazole therapy acutely decreases cyanocobalamin absorption in a dose-dependent manner (Marcuard et al 1994, Saltzman et al 1994) and deficiency may occur with long-term use (Valuck and Ruscin 2004). It should be noted that vitamin B12 supplements do not suffer the same fate, as they are not bound to protein — observe for signs and symptoms of B12 deficiency; vitamin B12 supplements may be required with long-term therapy.

HYDROCHLOROTHIAZIDE

There are a number of medications that have the ability to increase homocysteine levels, such as hydrochlorothiazide (Westphal et al 2003), therefore concurrent use of vitamin B12 (with folic acid) may be a useful adjunct — potential beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

- Parenteral cyanocobalamin given for vitamin B12 deficiency caused by malabsorption should be given intramuscularly or by the deep subcutaneous route but never intravenously.
- Folic acid supplementation may mask a B12 deficiency.
- Treatment with cyanocobalamin should be avoided in cases of altered cobalamin metabolism or deficiency associated with chronic cyanide intoxication (Freeman et al 1999).

PREGNANCY USE

Vitamin B12 is considered safe in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin B12 (cobalamin) is a water-soluble vitamin obtained mostly from animal protein products in the diet.
- There is considerable evidence that oral vitamin B12 therapy is comparable in efficacy to parenteral therapy even when intrinsic factor is not present or in other diseases affecting absorption.
- As numerous studies have indicated that serum B12 levels are an inadequate guide to B12 status, a combination of total homocysteine and methylmalonic acid is probably the clearest indicator.
- Vitamin B12 deficiencies manifest primarily as haematological and neurological disturbances and is estimated to affect 10–15% of individuals over the age of 60 years.
- Traditionally, supplementation is recommended to treat deficiency states or prevent them in people at risk such as in pernicious anaemia or atrophic gastritis.
- When administered together with folic acid and vitamin B6 (pyridoxine), it is used to reduce homocysteine levels. In this way, vitamin B12 is sometimes recommended in conditions where homocysteine is implicated as a possible causative factor.
- Some evidence has shown supplementation can be useful in HIV and AIDS, depression, tinnitus and cognitive impairment when low vitamin B12 levels are also

present. Preliminary evidence also suggests a possible role for supplementation in diabetic retinopathy and sleep disturbances.
- There are several commonly prescribed pharmaceutical medicines that can reduce vitamin B12 absorption when used long term.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin B12 is essential for healthy growth, development and health maintenance. It will reverse signs and symptoms of deficiency and can alleviate symptoms of tinnitus, poor memory, depression and HIV and AIDS when low vitamin B12 levels are also present. There is also some research suggesting some positive effects in diabetic retinopathy and sleep disturbances.

When will it start to work?

In cases of pernicious anaemia, the classical deficiency state, correction of blood abnormalities occurs within 6 weeks; however, correction of nervous system changes is slower and may take up to 18 months.

Are there any safety issues?

Vitamin B12 is considered a very safe nutrient.

REFERENCES

Andres E et al. Food-cobalamin malabsorption in elderly patients: Clinical manifestations and treatment. Am J Med 118(10) (2005a): 1154-9.

Andres E et al. Usefulness of oral vitamin B12 therapy in vitamin B12 deficiency related to food-cobalamin malabsorption: Short and long-term outcome. Eur J Intern Med 16(3) (2005b): 218.

Anon. Three B's, or not three B's? [vitamin B6, B12, and folic acid evaluated as a protection against heart disease]. Harvard Heart Lett 13.10.

Babior BM. Metabolic aspects of folic acid and cobalamin. In: Beutler E, et al (eds). Williams Haematology, 5th edn. New York: McGraw-Hill, 1996: 380-93.

Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annu Rev Nutr 19 (1999): 357-77.

Bhatt HR et al. Can faulty vitamin B-12 (cobalamin) metabolism produce diabetic neuropathy? Lancet 2(8349) (1983): 572; as cited in Micromedex. Thomson 2003. Available at: www.micromedex.com

Bilwani F et al. Anaphylactic reaction after intramuscular injection of cyanocobalamin (vitamin B12): a case report. J Pak Med Assoc 55(5) (2005): 217-19.

Bjorke Monsen AL, Ueland PM. Homocysteine and methylmalonic acid in diagnosis and risk assessment from infancy to adolescence. Am J Clin Nutr 78(1) (2003): 7-21.

Bolaman Z et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. Clin Ther 25(12) (2003): 3124-34.

Bor MV. Do we have any good reason to suggest restricting the use of oral contraceptives in women with pre-existing vitamin B12 deficiency? Eur J Obstet Gynecol Reprod Biol 115(2) (2004): 240-1.

Bradford GS, Taylor CT. Omeprazole and vitamin B12 deficiency. Ann Pharmacother 33(5) (1999): 641-3.

Branco-Ferreira M et al. Anaphylactic reaction to hydroxycobalamin. Allergy 52 (1997): 118-19.

Briddon A. Homocysteine in the context of cobalamin metabolism and deficiency states. Amino Acids 24(1-2) (2003): 1-12.

Carmel R. Pernicious anemia: The expected findings of very low serum cobalamin levels, anemia, and macrocytosis are often lacking. Arch Intern Med 148(8) (1988): 1712-14.

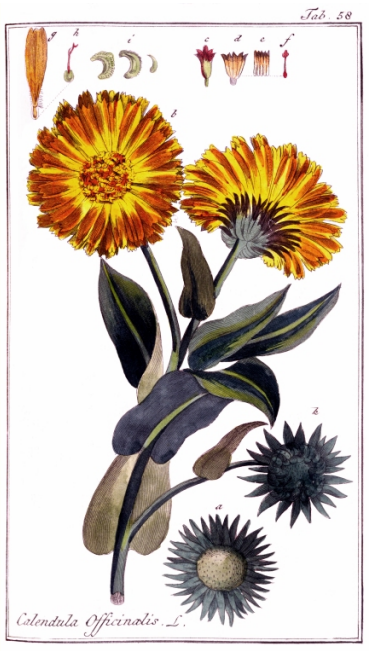
Clarke R et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 324 (1991): 1149-55.
Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol 19(1) (2005): 59-65.
Croft MT et al. Algae acquire vitamin B12 through a symbiotic relationship with bacteria. Nature 438(7064) (2005): 90-3.
Czernichow S et al. Case for folic acid and vitamin B12 fortification in Europe. Semin Vasc Med 5(2) (2005): 156-62.
Dastur DK, Dave UP. Effect of prolonged anticonvulsant medication in epileptic patients: serum lipids, vitamins B6, B12, and folic acid, proteins, and fine structure of liver. Epilepsia 28(2) (1987): 147-59.
Delpre G et al. Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation. Lancet 354(9180) (1999): 740.
den Heijer M et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 334 (1996): 759-62.
Dharmarajan TS, Adiga GU, Norkus EP. Vitamin B12 deficiency. Recognizing subtle symptoms in older adults. Geriatrics 58(3) (2003): 30-4, 37-8.
Dusitanond P et al. Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: a randomized substudy of the VITATOPS trial. Stroke 36(1) (2005): 144-6.
Elia M. Oral or parenteral therapy for B12 deficiency. Lancet 352 (1998): 1721-2.
Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. Clin Biochem 36(8) (2003): 585-90.
Eussen SJ et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Arch Intern Med 165(10) (2005): 1167-72.
Festen HP. Intrinsic factor secretion and cobalamin absorption: Physiology and pathophysiology in the gastrointestinal tract. Scand J Gastroenterol Suppl 188 (1991): 1-7.
Food and Agriculture Organization/World Health Organization. Vitamin B12: Report of a joint FAO/WHO expert consultation. Rome, 2002.
Freeman AG et al. Sublingual cobalamin for pernicious anaemia. Lancet 354(9195) (1999): 2080.
Gok U et al. Comparative analysis of serum homocysteine, folic acid and Vitamin B12 levels in patients with noise-induced hearing loss. Auris Nasus Larynx 31(1) (2004): 19-22.
Groenen PMW et al. Marginal maternal vitamin B12 status increases the risk of offspring with spina bifida. Am J Obstet Gynecol 191(1) (2004): 11-17.
Gronlie Guren M et al. Biochemical signs of impaired cobalamin status during and after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys60(3) (2004): 807-13.
Hagar HH. Folic acid and vitamin B(12) supplementation attenuates isoprenaline-induced myocardial infarction in experimental hyperhomocysteinemic rats. Pharmacol Res 46(3) (2002): 213-19.
Healton EB et al. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore) 70(4) (1991): 229-45.
Hillman RS. Hematopoietic agents: growth factors, minerals, and vitamins. In: Hardman JG et al (eds). The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996: 1311-40.
Hoffer LJ et al. Comparative effects of hydroxycobalamin and cyanocobalamin on plasma homocysteine concentrations in end-stage renal disease. Metabolism 54(10) (2005a): 1362-7.
Hoffer LJ et al. Cobalamin dose regimen for maximum homocysteine reduction in end-stage renal disease. Metabolism 54(6) (2005b): 835-40.
Howden C. Vitamin B12 levels during prolonged treatment with proton pump inhibitors. J Clin Gastroenterol 30(1) (2000): 29-33.
Hung J et al. Folate and vitamin B-12 and risk of fatal cardiovascular disease: cohort study from Busselton, Western Australia. BMJ 326(7381) (2003): 131.
Hutto BR. Folate and cobalamin in psychiatric illness. Compr Psychiatry 38(6) (1997): 305-14.

Hyndman ME et al. Vitamin B12 decreases, but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and possible explanation of hyperhomocysteinemia in end-stage renal disease. Metabolism 52(2) (2003): 168-72.
Integrative Medicine Gateway (IMG). Unity Health 2001-06. Available at: www.imgateway.net (accessed 2003).
Kang JH, Grodstein F. Mid-life plasma folate and vitamin B12 levels and cognitive function in older women. Alzheimer Dementia 1(1) (Suppl 1) (2005): 28.
Kapadia C. Cobalamin [Vitamin B12] Deficiency; Is it a problem for our aging population and is the problem compounded by drugs that inhibit gastric acid secretion? J Clin Gastroenterol 30(1) (2000): 4-6.
Karabiber H et al. Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B12, and folic acid. Brain Dev 25(2) (2003): 113-15.
Karnaze DS, Carmel R. Neurologic and evoked potential abnormalities in subtle cobalamin deficiency states, including deficiency without anemia and with normal absorption of free cobalamin. Arch Neurol 47(9) (1990): 1008-12.
Kuzminski AM et al. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 92 (1998): 1191-8.
Kwok T et al. Use of fasting urinary methylmalonic acid to screen for metabolic vitamin B12 deficiency in older persons. Nutrition 20(9) (2004): 764-8.
Laine L et al. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther 14(6) (2000): 651-8.
Lederle F. Oral cobalamin for pernicious anaemia. Medicine's best kept secret? JAMA 265 (1991): 94-5.
Lee GR. Pernicious anemia and other causes of vitamin B12 (cobalamin) deficiency. In: Lee GR et al (eds). Wintrobe's Clinical Hematology, 10th edn. Baltimore: Williams & Wilkins, 1999: 941-64.
Lindenbaum J et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 318 (1988): 1720-8.
Lobo A et al. Reduction of homocysteine levels in coronary artery disease by low-dose folic acid combined with levels of vitamins B6 and B12. Am J Cardiol 83 (1999): 821-5.
Loder C et al. Treatment of multiple sclerosis with lofepramine, L-phenylalanine and vitamin B(12): mechanism of action and clinical importance: roles of the locus coeruleus and central noradrenergic systems. Med Hypotheses 59(5) (2002): 594-602.
Malinow MR et al. Prevalence of hyperhomocyst(e)inemia in patients with peripheral arterial occlusive disease. Circulation 79 (1989): 1180-8.
Marcuard SP et al. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12). Ann Intern Med 120(3) (1994): 211-15.
Marcucci R et al. Vitamin supplementation reduces the progression of atherosclerosis in hyperhomocysteinemic renal-transplant recipients. Transplantation 75(9) (2003): 1551-5.
Mayer G et al. Effects of vitamin B12 on performance and circadian rhythm in normal subjects. Neuropsychopharmacology 15(5) (1996): 456-64.
Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. Altern Med Rev 8(1) (2003): 7-19.
Miller A et al. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. J Neurol Sci 233(1-2) (2005): 93-7.
Moretti R et al. Vitamin B12 and folate depletion in cognition: a review. Neurol India 52(3) (2004): 310-18.
Nowak M et al. Homocysteine, vitamin B12, and folic acid in age-related macular degeneration. Eur J Ophthalmol 15(6) (2005): 764-7.
Nyholm E et al. Oral vitamin B12 can change our practice. Postgrad Med J 79(930) (2003): 218(3).
Oh RC, Brown DL. Vitamin B12 deficiency. Am Fam Physician 67(5) (2003): 979.
Omray A. Evaluation of pharmacokinetic parametres of tetracycline hydrochloride upon oral administration with vitamin C and B complex. Hindustan Antibiot Bull 23(VI) (1981): 33-7.
Penninx BW et al. Vitamin B (12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry 157(5) (2000): 715-21.

Piskin S et al. Serum iron, ferritin, folic acid, and vitamin B12 levels in recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol 16(1) (2002): 66-7.
Quaranta A et al. The effects of 'supra-physiological' vitamin B12 administration on temporary threshold shift. Int J Audiol 43(3) (2004): 162-5.
Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. Q J Med 96(4) (2003): 289-95.
Refsum H, Smith AD. Low vitamin B-12 status in confirmed Alzheimer's disease as revealed by serum holotranscobalamin. J Neurol Neurosurg Psychiatry 74(7) (2003): 959-61.
Remacha AF, Cadafalch J. Cobalamin deficiency in patients infected with the human immunodeficiency virus. Semin Hematol 36(1) (1999): 75-87.
Remacha AF et al. Vitamin B12 transport proteins in patients with HIV-1 infection and AIDS. Haematologica 78(2) (1993): 84-8.
Reznikoff-Etievant MF et al. Low vitamin B(12) level as a risk factor for very early recurrent abortion. Eur J Obstet Gynecol Reprod Biol 104(2) (2002): 156-9.
Roth M, Orija I. Oral vitamin B12 therapy in vitamin B12 deficiency. Am J Med 116(5) (2004): 358.
Saltzman JR et al. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B12 absorption. J Am Coll Nutr 13(6) (1994): 584-91.
Sandyk R, Awerbuch GI. Vitamin B12 and its relationship to age of onset of multiple sclerosis. Int J Neurosci 71(1-4) (1993): 93-9.
Schenk BE et al. Atrophic gastritis during long-term omeprazole therapy affects serum vitamin B12 levels. Aliment Pharmacol Ther 13(10) (1999): 1343-6.
Schneede J, Ueland PM. Novel and established markers of cobalamin deficiency: complementary or exclusive diagnostic strategies. Semin Vasc Med 5(2): (2005) 140-55.
Schnyder G et al. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. JAMA 288(8) (2002): 973-9.
Selhub J et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 332 (1995): 286-91.
Shemesh Z et al. Vitamin B12 deficiency in patients with chronic tinnitus and noise-induced hearing loss. Am J Otolaryngol 14(2) (1993): 94-9.
Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr 24 (2004): 299-326.
Stucker M et al. Topical vitamin B12: a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. Br J Dermatol 150(5) (2004): 977-83.
Suarez L et al. Maternal serum B12 levels and risk for neural tube defects in a Texas-Mexico border population. Ann Epidemiol 13(2) (2003): 81-8.
Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurol Taiwan 14(2) (2005): 48-54.
Sutterlin MW et al. Serum folate and Vitamin B12 levels in women using modern oral contraceptives (OC) containing 20 µg ethinyl estradiol. Eur J Obstet Gynecol Reprod Biol 107(1) (2003): 57-61.
Takenaka S et al. Feeding dried purple laver (nori) to vitamin B12-deficient rats significantly improves vitamin B12 status. Br J Nutr 852 (2001): 699-70.
Tamura J et al. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunol. 116(1) (1999): 28-32.
Termanini B et al. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. Am J Med 104(5) (1998): 422-30.
Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 291(5) (2004): 565-75.

Tripathi M et al. Serum cobalamin levels in dementias. Neurol India 49(3) (2001): 284-6.
Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. J Clin Epidemiol 57(4) (2004): 422-8.
Vidal-Alaball J et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev 3 (2005): CD004655.
Volkov I, Rudoy I, Press Y. Successful treatment of chronic erythema nodosum with vitamin B12. J Am Board Fam Pract 18(6) (2005): 567-9.
Wahlqvist ML (ed.). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002: 260.
Wang HX et al. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology 56(9) (2001): 1188-94.
Weir GD, Scott MJ. Brain function in the elderly: role of vitamin B12 and folate. Br Med Bull 55(3) (1999): 669(14).
Westphal S et al. Antihypertensive treatment and homocysteine concentrations. Metabolism 52(3) (2003): 261-3.
Wolters M, Strohle A, Hahn A. Cobalamin: a critical vitamin in the elderly. Prev Med 39(6) (2004): 1256-66.
Yoshioka K, Tanaka K. Effect of methylcobalamin on diabetic autonomic neuropathy as assessed by power spectral analysis of heart rate variations. Horm Metab Res 27.1 (1995): 43-4.
Zetterberg H et al. The transcobalamin codon 259 polymorphism influences the risk of human spontaneous abortion. Hum Reprod 17(12) (2002): 3033-6.

Vitamin C



Historical note Vitamin C deficiency has been known for many centuries as scurvy, a potentially fatal condition, dreaded by seamen and explorers from the 15th century, who were often forced to subsist for months on diets of dried beef and biscuits. It was also described by the European crusaders during their numerous sieges. In the mid 1700s Lind was the first doctor to conduct systematic clinical trials of potential cures for scurvy, identifying oranges and lemons as successful treatments (Bartholomew 1753). However, it was not until 1928 that vitamin C (then known as antiscorbutic factor) was isolated and the mid 1930s that it was able to be mass produced.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin C is an essential nutrient for humans and required from the diet on a regular basis, as we are one of few species of animals that cannot synthesise it. This is because humans lack the enzyme L-gluconolactone oxidase, which is required for the conversion of glucose into vitamin C (Braunwald et al 2003). It is easily absorbed from the gastrointestinal tract through an active transport process, as well as through passive diffusion. The degree of absorption depends on the dose ingested, and decreases as the dose increases. In other words, transport systems for vitamin C are dose-dependent and saturable. Because of this, vitamin C is best absorbed when it is ingested in small doses at regular intervals. Pectin and zinc are also able to impair oral absorption. These limitations are bypassed with the use of intravenously administered vitamin C, which can achieve much higher plasma levels than the oral route. Vitamin C concentrates in many tissues, with the highest concentrations in the adrenal and pituitary glands. It is metabolised in the liver and kidneys, and excreted in the urine. The biological half-life of vitamin C is 8–40 days (NHMRC 2006).

CHEMICAL COMPONENTS

Vitamin C exists as both its reduced form (L-ascorbic acid) and oxidised form (L-dehydroascorbic acid). The two forms interchange in the body in a reversible equilibrium.

Clinical note — Differences between major forms of vitamin C supplement

Here is a brief summary of the most common forms found in OTC supplements.

Ascorbic acid: The major dietary form of vitamin C.

Mineral ascorbates (also known as non-acid vitamin C): These are buffered forms of vitamin C and believed to be less irritating to the stomach than ascorbic acid. Sodium ascorbate and calcium ascorbate are the most common forms. When mineral salts are taken, both the ascorbic acid and the mineral are absorbed. For example, sodium ascorbate generally provides 131 mg of sodium per 1000 mg of ascorbic acid, and calcium ascorbate provides 114 mg of calcium per 1000 mg of ascorbic acid.

Vitamin C with bioflavonoids: Many bioflavonoids are antioxidant substances, and added to some vitamin C preparations in the belief that this increases the bioavailability or efficacy of vitamin C. Typically, the bioflavonoids are sourced from citrus fruits.

Ascorbyl palmitate: A fat-soluble form of vitamin C formed by esterification with palmitic acid and most often used in topical creams.

FOOD SOURCES

Vitamin C is found in many different fruits and vegetables. The most concentrated food sources are blackcurrants, sweet green and red peppers, hot red peppers, green chilli peppers, oranges and its fresh juice, and strawberries. Other good sources are watermelon, papaya, citrus fruits, cantaloupe, mango, cabbage, cauliflower, broccoli and tomato juice. In practice, vegetables may be a more important source of vitamin C than fruits because the vegetable supply often extends for longer periods during the year.

The vitamin C content of food is strongly influenced by many factors, such as season, transportation, shelf life, storage conditions and storage time, cooking techniques and chlorination of water (FAO/WHO 2002). Cutting or bruising food sources will reduce its vitamin C content; however, blanching or storing at low pH will preserve it.

Up to 100% of the vitamin C content of food can be destroyed during cooking and storing because the vitamin is sensitive to light, heat, oxygen and alkali (Wahlqvist et al 2002). Additionally, using too much water during cooking can leach it from the food and further reduce the vitamin C content.

DEFICIENCY SIGNS AND SYMPTOMS

In adults, scurvy remains latent for 3–6 months after reducing dietary intake to less than 10 mg/day (Beers & Berkow 2003). It manifests when the body pools fall below 300–400 mg (NHMRC 2006). Many of the features of frank vitamin C deficiency (scurvy) result from a defect in collagen synthesis.

Early symptoms:

- weakness
- fatigue and listlessness
- muscular weakness
- petechial haemorrhages and ecchymoses (bruising)
- swollen gums
- poor wound healing and the breakdown of recently healed wounds
- poor appetite and weight loss
- emotional changes such as irritability and depression
- vague myalgias and arthralgias
- congested hair follicles.

Symptoms of more severe deficiency:

- fever
- drying of the skin and mucous membranes
- susceptibility to infection
- bleeding gums and loosening of teeth
- oedema of the lower extremities
- anaemia
- joint swelling and tenderness, due to bleeding around or into the joint
- oliguria
- pain in the extremities
- haemorrhage
- convulsions
- shock
- eventually death if left untreated.

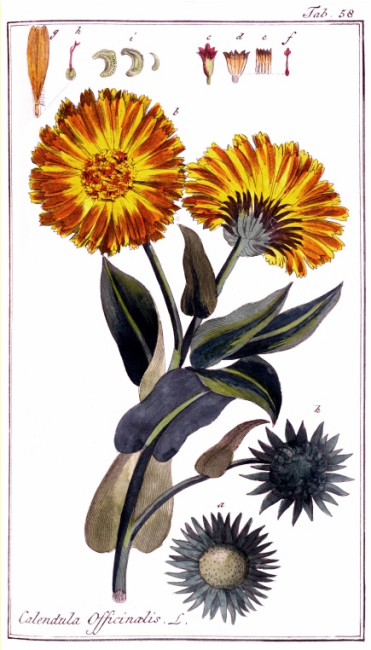
Although frank deficiency is uncommon in Westernised countries, marginal deficiency states are not uncommon.

PRIMARY DEFICIENCY

This occurs if there is an inadequate dietary intake, which is often caused by a combination of poor cooking and eating habits. It occurs in areas of urban poverty, famine and war, in young children fed exclusively on cow's milk for a prolonged period, the institutionalised or isolated elderly, and chronic alcoholics (Pimentel 2003, Richardson et al 2002). One Australian hospital identified 73% of all new admissions with hypovitaminosis C and 30% as having levels suggestive of scurvy (Richardson et al 2002).

SECONDARY DEFICIENCY

Factors that increase nutritional requirements include cigarette smoking, pregnancy, lactation, thyrotoxicosis, acute and chronic inflammatory diseases, major surgery and burns, infection and diabetes (Beers & Berkow 2003, FAO/WHO 2002, Hendler et al 2001, Wahlqvist et al 2002). Decreased vitamin C absorption in achlorhydria and increased excretion in chronic diarrhoea also increase the risk of deficiency, particularly when combined with poor dietary intake.



MAIN ACTIONS

Vitamin C is an electron donor (reducing agent or antioxidant), and most of its biochemical and molecular functions can be accounted for by this function. It is involved in many biochemical processes in the body such as:

- energy release from fatty acids
- metabolism of cholesterol
- reduction of nitrosamine formation in the stomach
- formation of thyroid hormone
- carnitine biosynthesis
- modulation of iron and copper absorption
- corticosteroid biosynthesis
- protection of folic acid reductase, which converts folic acid to folinic acid
- collagen biosynthesis
- tyrosine biosynthesis and catabolism
- neurotransmitter biosynthesis.

The main actions of vitamin C are summarised below.

ANTIOXIDANT

Vitamin C is one of the most important water-soluble antioxidant substances in the body. It scavenges free radical oxygen and nitrogen species such as superoxide, hydroxyl, peroxyl and nitroxide radicals and non-radical reactive species such as singlet oxygen, peroxynitrite and hypochlorite (FAO/WHO 2002, Hendler et al 2001). Besides having a direct antioxidant function, it also indirectly increases free radical scavenging by regenerating vitamin E (Vatassery 1987) and maintaining glutathione in reduced form.

MAINTENANCE OF CONNECTIVE TISSUE

Vitamin C maintains the body's connective tissue and is essential for the formation of collagen, the major fibrous element of blood vessels, skin, tendon, cartilage and teeth (Morton et al 2001). If collagen is produced in the absence of vitamin C, it is unstable and cannot form the triple helix required for normal tissue structure. Vitamin C is

involved in the biosynthesis of other substances important for connective tissue such as elastin, proteoglycans, bone matrix, fibronectin and elastin-associated fibrillin (Hall & Greendale 1998).

These effects have been harnessed by the dermatological and cosmetic industries and are the rationale for producing topically applied products containing vitamin C.

BRAIN AND NERVE FUNCTION

Ascorbate is involved in neurotransmitter synthesis. It is a cofactor required for the biosynthesis of noradrenaline from dopamine and hydroxylation of tryptophan to produce serotonin (Bornstein et al 2003, FAO/WHO 2002).

IMMUNOSTIMULANT

Both in vivo and in vitro studies provide evidence of immunostimulant effects, generally at doses beyond RDI levels. Vitamin C favourably modulates lymphocytes and phagocytes, regulates NK cells and can influence antibody and cytokine synthesis under certain situations (Hendler et al 2001). In high doses, it is a potent immunomodulator and is preferentially cytotoxic to neoplastic cells. Vitamin C enhances the activity of NK cells in vivo and also both B- and T-cell activity (Drisko et al 2003).

ANTIHISTAMINE

An inverse association has been identified between blood histamine levels and vitamin C status in humans (Johnston et al 1996). In that study, increasing vitamin C status with supplements (up to 250 mg/day) over 3 weeks was shown to decrease histamine levels. It is unclear whether single high-dose supplementation also affects histamine levels, as two studies using 2 g doses have produced conflicting results (Bucca et al 1990, Johnston et al 1992).

ANTICANCER

A growing body of cell culture and in vivo research has suggested that vitamin C may be preferentially toxic to tumour cells (Tamayo & Richardson 2003). The effect is thought to be dose-dependent and mediated via several mechanisms, such as immunomodulation, inhibition of cell division and growth (mainly through antioxidant activity) and induction of apoptosis. In vitro studies have identified that concentrations above 1000 micromol/L are required for these effects to occur, a level that may be achieved clinically with intravenous administration but not through oral administration (Padayatty et al 2006). Much investigation has been undertaken to understand how the preferential activity occurs; however, the mechanisms are still largely unknown. For example, studies with radioactive-labelled vitamin C have found

that tumour cells accumulate more vitamin C than healthy cells, whereas other studies have reported no differences in intracellular concentrations (Prasad et al 2002). There is also some preliminary evidence of synergistic cytotoxic effects with some pharmaceutical anticancer agents and decreased drug toxicity (Giri et al 1998).

Ascorbyl stearate is a lipophilic, vitamin C derivative that has also demonstrated antitumorigenic properties in vitro (Fang et al 2006).

OTHER ACTIONS

High oral doses (4–12 g/day in divided doses) can acidify urine.

CLINICAL USE

Vitamin C is an important biological antioxidant and has been a popular nutritional supplement for decades. It is administered as intramuscular or intravenous injections and used topically and orally. This review will chiefly focus on oral and topical use, as these are the forms of vitamin C most commonly used by the public.

As with many nutrients, studies associating dietary vitamin intake and disease risk are difficult to interpret, as separating the effects of the individual vitamin from the effects of other components in the diet is problematic. Where possible, an effort has been made to include information that will help in the interpretation of this type of data.

DEFICIENCY: PREVENTION AND TREATMENT

Traditionally, vitamin C supplements are used to both treat and prevent deficiency. Treatment may include 250 mg vitamin C daily and encouragement to eat fresh fruits and vegetables on a regular basis (Kumar et al 2002), or 100 mg taken 3–5 times daily until 4000 mg has been reached (Braunwald et al 2003). Some deficiency symptoms start to respond within 24 hours, although most take several weeks to months for complete resolution.

IRON DEFICIENCY ANAEMIA

Vitamin C facilitates iron absorption by forming soluble complexes and may be used with an iron supplement and nutritious diet in the treatment of iron deficiency anaemia. It is also recommended for women with menorrhagia in order to reduce the risk of iron deficiency.

UPPER RESPIRATORY TRACT INFECTIONS

Vitamin C is widely used to both prevent and treat common URTI, such as the common cold and influenza, largely based on its immune system effects, ability to reduce histamine levels and the observations that the gastrointestinal absorption of vitamin C increases in the common cold, suggesting an increased demand for this

nutrient, and that vitamin C concentrations in the plasma and leukocytes rapidly decline during infection (Wilson et al 1976, Wintergerst et al 2006). Although extremely popular, its usefulness in these conditions is widely debated.

A 2004 Cochrane review of 29 placebo-controlled studies involving 11,077 participants found that regular ingestion of vitamin C in doses of 200 mg did not reduce the incidence of the common cold in the normal population; however, a subgroup of six trials that involved a total of 642 marathon runners, skiers, and soldiers on subarctic exercises did find significant protective effects (Douglas et al 2004). Data from 9676 respiratory episodes suggested that regular vitamin C supplementation was consistently associated with a small reduction in the duration and severity of common cold symptoms; however, the magnitude of the effect was described as small. When high doses of vitamin C have been started after the onset of cold symptoms, there has been no consistent effect on either the duration or the severity of symptoms. Equivocal results were obtained in one large trial that used a dose of 8 g at the onset of symptoms whereas two trials using supplementation for 5 days did report a benefit.

Since then, a long-term study reported that use of 500 mg/day vitamin C significantly reduced the risk of the common cold (relative risk 0.34), although no reduction in severity or duration was seen (Sasazuki et al 2006). The double-blind RCT was conducted over 5 years and due to protocol amendment, these results should be viewed conservatively.

There are a number of factors that may be contributing to the inconsistent results obtained to date, such as the variable characteristics of the subjects studied, type of infecting virus, lack of control for dietary vitamin C intake and differences in outcomes' measures.

Clearly, further investigation is required to clarify many issues surrounding the use of vitamin C supplements for URTI. In practice, naturopaths often recommend mega doses of vitamin C (taken in small frequent amounts), which are well beyond the doses investigated so far, and often report good results. Although anecdotal, it is interesting to note that little research has investigated this method of use.

DERMATOLOGICAL USES

Vitamin C is used as an oral supplement or topical application in a number of dermatological conditions.

Wound healing Vitamin C is important for effective wound healing, as deficiency contributes to fragile granulation tissue and therefore impairs the wound-healing process (Russell 2001).

In vitro studies with skin graft samples have demonstrated that vitamin C extends cellular viability, promotes formation of epidermal barrier and promotes engraftment (Boyce et al 2002). In this way, vitamin C is used to enhance wound healing before surgery has commenced.

Numerous case reports of surgical and dental patients generally suggest a use for vitamin C supplementation in doses beyond RDI as a means of enhancing the rate of wound healing (Ringsdorf & Cheraskin 1982). One early double-blind study found that vitamin C (500 mg twice daily) resulted in a significant mean reduction in pressure sore area of 84% after 1 month compared with 43% in the placebo group (Taylor et al 1974). The mean rates of healing were 2.47 cm^2 for vitamin C and 1.45 cm^2 for placebo.

Photo-aged skin Two double-blind studies investigating the effects of topical preparations of vitamin C on photo-damaged skin have demonstrated good results after 3 months' use (Fitzpatrick & Rostan 2002, Humbert et al 2003). One study tested a topical application of 5% vitamin C in a cream base, whereas the other used a newly formulated vitamin C complex having 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (lipid soluble) in an anhydrous polysilicone gel base.

Prevention of sunburn One controlled study found oral vitamin C (2000 mg/day) in combination with vitamin E (1000 IU/day) had a protective effect against sunburn after 8 days' treatment in human subjects (Eberlein-Konig et al 1998).

Similar results have been obtained for topical vitamin C preparations in several animal models (Darr et al 1992, 1996, Lin et al 2003) and a small human study (Keller & Fenske 1998). The latter study found that application of an aqueous 10% l-ascorbic acid solution produced a significant reduction in the minimal erythema dose and a less intense erythematous response than controls after UVB radiation.

REDUCTION IN ALL-CAUSE MORTALITY

Several studies have identified an inverse association between plasma ascorbate levels, vitamin C intake and all-cause mortality.

In the Western Electric Company Study, data on diet and other factors were obtained in 1958 and 1959 for a cohort of 1556 employed, middle-aged men and an inverse association between vitamin C and mortality was identified (Pandey et al 1995). The next year, a prospective cohort study conducted with 725 older adults also identified an inverse relationship between vitamin C blood concentrations and total mortality during a 12-year follow-up (Sahyoun et al 1996). Similar results were obtained in the large EPIC-Norfolk study of 19,496 men and women aged 45–79 years (Khaw et al 2001). Plasma ascorbate concentration was inversely related to mortality from all-causes, and from cardiovascular disease and ischaemic heart

disease in both men and women. Risk of mortality in the group with the highest intake was about half that of the low intake group and was independent of age, SBP, serum cholesterol, cigarette smoking, diabetes, or supplement use.

The NHANES II Mortality Study further confirmed the inverse association between plasma ascorbate and risk of dying for all-causes; however, this study identified a gender difference (Loria et al 2000). After adjustments for race, educational level, number of cigarettes smoked at baseline, serum total cholesterol, SBP, BMI, diabetes status, and alcohol consumption, men in the lowest serum ascorbate quartile (serum ascorbate concentrations <28.4 micromol/L) had a 57% higher risk of dying from any cause than did men in the highest quartile (>73.8 micromol/L). Additionally, men in the lowest serum ascorbate quartile had double the risk of dying from cancer than those in the highest quartile after adjustment for age. The dose corresponds to approximately 60 mg/day vitamin C. In contrast, no association was observed between quartiles of serum ascorbate concentration and total mortality or mortality from cardiovascular or cancer among women.

A gender difference was also reported in the NHANES I Epidemiologic Follow-up Study (NHEFS) (Enstrom et al 1992). Vitamin C intakes >50 mg/day plus regular supplement use were associated with reduced mortality compared with intakes <50 mg/day in men, but apparently not in women.

PREVENTION OF CARDIOVASCULAR DISEASE

The association between vitamin C and cardiovascular disease prevention is still unclear, although several themes are emerging as evidence accumulates. In general, laboratory, epidemiological and observational follow-up studies suggest that vitamin C is associated with reduced incidence of cardiovascular disease although not all studies are positive (Houston 2005). Studies have looked at blood levels, dietary intake and supplemental vitamin C and in some studies, vitamin C is co-administered with other nutrients (often vitamin E) making it difficult to assess the contribution of vitamin C alone (Carr & Frei 1999, Khaw et al 2001, Knekt et al 2004, Kushi et al 1996, Lopes et al 1998, MRC/BHF 2002, Ness et al 1996, Nyyssonen et al 1997, Osganian et al 2003). It appears that if a protective effect is observed with supplementation, it is most likely with doses above RDI, long-term use and in populations with a substantial proportion of persons who have low or deficient intakes of vitamin C. Ideally, future human clinical trials will focus on subjects with increased oxidative stress rather than the general population to see whether this variable also influences study outcomes.

Possible mechanisms According to a 2001 review, ascorbic acid is inversely related to several risk factors and indicators of atherosclerotic cardiovascular disease,

including hypertension and elevated concentrations of LDL, acute phase proteins, and haemostatic factors (Price et al 2001). More specifically, vitamin C inhibits oxidative modification of LDL-cholesterol directly through free radical scavenging activity, according to in vitro data, and indirectly by increasing glutathione and vitamin E concentrations within cell membranes. This has been demonstrated against the pro-oxidant combination of homocysteine and iron (Alul et al 2003) and may have implications for other diseases such as Alzheimer's dementia.

More recently, evidence suggests that other mechanisms are also likely to be involved. Vitamin C is linked to endothelial function and glucose metabolism. It improves endothelial dysfunction in smokers, renal transplant recipients, in patients with cardiovascular disease after a fatty meal, or intermittent claudication diabetes and those with hypertension (Kaufmann et al 2000, Ling et al 2002, Silvestro et al 2002, Solzbach et al 1997, Williams et al 2001), but not in healthy elderly people (Singh et al 2002). It is also required for collagen synthesis and metabolism, and has been shown to reduce arterial stiffness and platelet aggregation in healthy male volunteers, smokers and non-smokers, and diabetics (Schindler et al 2002, Wilkinson et al 1999). These effects are often observed in doses several times higher than current RDI levels. In vivo studies further indicate that vitamin C decreases carotid wall thickness, downregulates iNOS expression, normalises gene expression of antioxidant enzymes and inhibits plaque maturation (Kaliora et al 2006).

Clinical studies involving vitamin C supplementation In the recent pooled analysis from the Pooling Project of Cohort Studies on Diet and Coronary Disease, those subjects with higher supplemental vitamin C intake (median intake of 756 mg/day) had a 24% reduced risk of coronary heart disease than those in the lowest quintile, whereas dietary vitamin C had no significant protective effect (Knekt et al 2004). The lower risk was independent of non-dietary risk factors and related to dose.

The researchers also adjusted for many relevant constituents of foods (e.g. dietary fibre and saturated fat) and found this adjustment had no effect on the association.

Effects on blood pressure Although epidemiological evidence and prospective clinical trials point strongly to a role of vitamin C in reducing blood pressure in hypertensive and normotensive subjects, controlled studies have been inconsistent (Houston 2005). Interpretation of these results is difficult as some studies lack a control group, have no baseline readings, use variable vitamin C doses and population characteristics and do not report serum vitamin C or oxidative stress status. Overall, it appears that doses between 100 and 1000 mg of vitamin C daily are

required for a reduction in blood pressure, with greater reduction in SBP than DBP and greater response in people with higher initial value.

A 1997 review of epidemiological studies showed some inverse associations between SBP, DBP or both, and vitamin C plasma concentration or intake (Ness et al 1997). Three more recent studies have supported this finding (Bates et al 1998, Block 2002, Block et al 2001). Over the past 10 years, four intervention studies investigated the effects of vitamin C supplementation, with three producing positive results (Duffy et al 1999, Fotherby et al 2000, Galley et al 1997, Ghosh et al 1994). The doses used were typically 250 mg twice daily for a period of 6–8 weeks, although effects have been reported after 4 weeks' treatment.

The negative study by Ghosh et al showed a significant reduction in both SBP and DBP with ascorbic acid. This became non-significant when compared with the placebo responses, although the placebo and ascorbic acid groups were not evenly matched for baseline plasma ascorbate concentration.

Additionally, plasma ascorbate concentrations have been shown to be inversely correlated to pulse rate in one cross-sectional study involving 500 subjects (Bates et al 1998).

Nitrate tolerance Preliminary studies seem to support the role of vitamin C in attenuating the development of nitrate tolerance. Three human studies have found that vitamin C administration prevents the development of nitrate tolerance (Bassenge et al 1998, Watanabe et al 1998a,b). Although the mechanism responsible is not yet known, results from a double-blind study using an acute dose of 2 g have suggested that vitamin C is likely to protect NO from inactivation by oxygen free radicals (Wilkinson et al 1999), which could in part explain its observed effects.

Myocardial infarction (MI) Two prospective studies in men have suggested that ascorbic acid deficiency (Nyyssonen et al 1997) and marginal deficiency (Gey et al 1993) predict subsequent MI independent of classical risk factors.

The first, a 5-year prospective population study of 1605 middle-aged Finnish men, free of coronary disease at baseline, found that a significantly higher percentage (13.2%) of the 91 men with baseline plasma vitamin C concentrations less than 11.4 micromol/L (2.0 mg/L) experienced MI compared with men with higher plasma vitamin C levels (Nyyssonen et al 1997). These results are particularly impressive because low plasma ascorbate was the strongest risk factor of all the measured factors. The second, a 12-year follow-up study, revealed a significantly increased relative risk of ischaemic heart disease and stroke at initially low plasma levels of vitamin C (<22.7 micromol/L), independently of vitamin E and of the classical cardiovascular risk factors (Gey et al 1993).

In contrast, one smaller study involving 180 male patients with a first acute MI, but no recent angina, failed to detect an association between low plasma concentration of vitamin C and the risk of acute myocardial infarction (Riemersma et al 2000).

There is a large body of evidence that reactive oxygen species produced during myocardial ischaemia and reperfusion play a crucial role in myocardial damage and endothelial dysfunction. As a result, there has been some investigation to determine whether antioxidant supplementation (chiefly vitamins C and E) may improve the clinical outcome of patients with acute AMI and limit the size of the infarct.

According to a large randomised, double-blind, multicentre trial of 800 patients (mean age 62 years) with acute AMI and receiving standard care, co-treatment with vitamin C (1000 mg/12 h infusion) followed by 1200 mg/day orally and vitamin E (600 mg/day) for 30 days resulted in significantly less frequent incidence of re-infarction and other post-MI complications compared to placebo (14% vs 19% respectively) (Jaxa-Chamiec et al 2005). Another randomised, double-blind, placebo-controlled study of 37 patients with acute MI investigated the effects of starting supplementation with vitamins C and E (600 mg/day each) on the first day of symptoms and for a further 14 days (Bednarz et al 2003). Active treatment resulted in significantly lower exercise-induced QT interval dispersion compared to placebo, although baseline QTd was similar in both groups. A prospective, randomised study of 61 patients further suggests that oral vitamin C administration (1 g/day) could be beneficial for patients at higher thrombotic risk post-MI, such as those with diabetes (Morel et al 2003).

CANCER: PREVENTION AND TREATMENT

Several consensus conferences have evaluated the biological effect of vitamin C, and more than 500 published articles have examined the association of vitamin C and cancer.

Prevention Epidemiological evidence of a protective effect of dietary vitamin C for non-hormone-dependent cancers is strong (Block 1991a,b). The majority of studies in which a dietary vitamin C intake was calculated have identified a statistically significant protective effect, with high intake conferring approximately a twofold protective effect compared with low intake. In general, most have shown that higher intakes of vitamin C are associated with decreased incidence of cancers of the mouth, throat and vocal chords, oesophagus and stomach, pancreas, colon, rectum, renal cell and lung (Cohen & Bhagavan 1995, FAO/WHO 2002, Jenab et al 2006, Negri et al 2000, You et al 2000). More recently, a case control study of men in New York found

that a higher intake of vitamin C was associated with reduced risk of prostate cancer (McCann et al 2005).

Two other large studies have identified inverse associations between dietary vitamin C and breast cancer risk (Michels et al 2001, Zhang et al 1999). More specifically, the Nurses' Health Study, which involved 83,234 women, detected a strong inverse association between total vitamin C from foods and breast cancer risk among pre-menopausal women with a positive family history of breast cancer (Zhang et al 1999). Those who consumed an average of 205 mg/day of vitamin C from foods had a 63% lower risk of breast cancer than those who consumed an average of 70 mg/day. A large, Swedish population-based prospective study that comprised 59,036 women identified high dietary intakes of ascorbic acid (mean intake 110 mg/day) as reducing the risk of breast cancer among women who are overweight and/or have a high intake of linoleic acid (Michels et al 2001).

More recently, a case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) identified an inverse risk of gastric cancer in the highest versus lowest quartile of plasma vitamin C (Jenab et al 2006). The inverse association was more pronounced in subjects consuming higher levels of red and processed meats, a factor that may increase endogenous N-nitroso compound production. It has been proposed that vitamin C protects against gastric cancer because it inhibits carcinogenic N-nitroso compound production in the stomach and acts as a free radical scavenger.

Overall, it appears that the effect is dose-dependent, with studies finding significant cancer risk reductions in people consuming at least 80–110 mg of vitamin C daily long term (Carr & Frei 1999).

Clinical studies

Clinical note — Vitamin C for cancer: a historical perspective

The well-known team of Ewan Cameron and Linus Pauling started investigating the effects of high doses of continuous intravenous vitamin C and oral supplements to treat advanced, incurable cancer over three decades ago. The idea of using vitamin C was born out of the recognition that the outcome of every cancer is determined to a significant extent by the individual's inherent resistance, which in turn is influenced by the availability of certain nutritional factors such as ascorbic acid (Cameron 1982). They have published the results of several trials that have shown enhanced QOL for some terminal patients and also improvements in objective markers. As a result, a protocol for the use of vitamin C in the treatment of cancer has been developed at the Vale of Leven Hospital, the chief site of their investigations (Cameron 1991). The protocol emphasises the importance of using

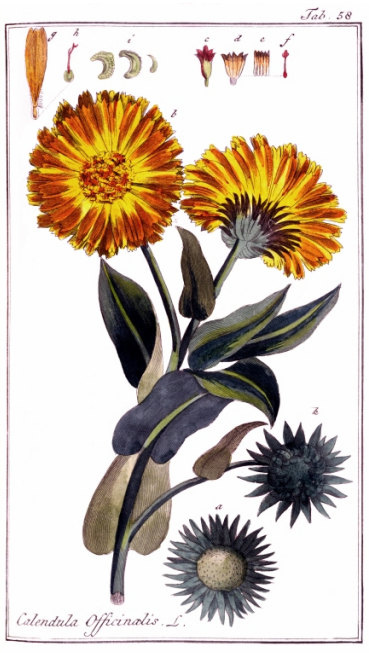
an initial course of intravenous ascorbate followed by a maintenance oral dose. Although their results are encouraging, they have been criticised because randomised double-blind principles were not adopted.

One of the first published studies by Cameron and Pauling (1974) was a Phase I–II study in 50 patients with advanced, untreatable malignancies in which both subjective and objective markers were evaluated. They observed that 27 patients failed to respond to treatment; however, 3 patients experienced stabilisation of disease, tumour regression occurred in 5 patients and tumour haemorrhage and necrosis occurred in 4 patients. Two years later, the same research team published a report that compared the survival rates of 100 terminal cancer patients given supplemental ascorbate as part of their routine management with 1000 patients who were not, and observed the mean survival time to be more than 4.2-fold as great for the ascorbate subjects (>210 days) as for the controls (50 days) (Cameron & Pauling 1976).

In subsequent years, two randomised, placebo-controlled studies investigating the effects of oral vitamin C supplementation (10 g/day) in terminal cancer patients failed to detect a significant difference in outcome (Creagan et al 1979, Moertel et al 1985). These two studies are often cited as evidence disproving the benefits of vitamin C in cancer treatment; however, the different routes of administration investigated in these studies is an important factor central to the discrepant results (Padayatty & Levine 2000), as only intravenous ascorbate can produce millimolar plasma concentrations, which are toxic to many cancer cell lines.

Intravenous vitamin C Intravenous administration of vitamin C achieves much higher plasma and urine concentrations than oral dosing and has been proposed as the only viable means of achieving the high concentrations required to induce the antitumour effects exhibited by the vitamin (Padayatty et al 2004). Currently, there are case studies that suggest this approach can improve patient wellbeing and, in some cases, reduce tumour size and improve survival (Padayatty et al 2006, Riordan et al 2005).

A recent safety study involved 24 late-stage terminal cancer patients who were administered continuous vitamin C infusions of 150–710 mg/kg/day for up to 8 weeks (Riordan et al 2005). This treatment regimen increased plasma ascorbate concentrations to a mean of 1.1 mmol/L and was considered relatively safe. The most common side-effects reported were nausea, oedema and dry mouth or skin, and two 'possible' adverse events occurred. One was a patient with a history of renal calculi who developed a kidney stone after 13 days of treatment and another was a patient



who experienced hypokalaemia after 6 weeks. Interestingly, the majority of patients were vitamin C deficient prior to treatment.

Based on the available evidence of antitumour mechanisms and these case reports, further research into this approach is clearly warranted.

Adjunct to oncology treatments Whether vitamin C improves or hinders responses to standard oncology treatment has been the focus of intense debate for many decades. There are in vitro studies showing that vitamin C can enhance the antitumour activity of cisplatin and doxorubicin (Abdel-Latif et al 2005, Kurbacher et al 1996, Reddy et al 2001, Sarna & Bhola 1993). In vivo evidence shows vitamin C enhances the effectiveness of 5-fluorouracil, doxorubicin, cyclophosphamide and vincristine (Lamson & Brignall 2000, Nagy et al 2003), whereas other studies find no change in drug effect. Although these results are promising, no large randomised studies are available to confirm their significance in humans.

Most recently, vitamin C inactivated the effects of bortezomib, a new proteasome inhibitor approved by the US FDA for the treatment of patients with relapsed multiple myeloma (Zou et al 2006). Interestingly, drug inactivation was not achieved through antioxidative mechanisms.

Evidence from experimental models suggests that vitamin C may also reduce drug toxicity in a dose-dependent manner (Giri et al 1998, Greggi Antunes et al 2000).

Clinical note — The debate continues ... to Vitamin C or not?
One research group based at the University of Colorado has produced evidence that suggests that vitamin C and other antioxidant nutrients may not only protect healthy cells from damage but also improve the antitumour effects of standard treatment (Gottlieb 1999). They are currently conducting further research to identify how cell selectivity occurs but propose that cancer cells may have lost the normal homeostatic regulatory mechanism that stops excessive concentrations of antioxidants from entering the cell. As intracellular levels rise, a series of reactions occurs resulting in growth inhibition and cell death. Another group at Memorial Sloan Kettering Cancer Centre (Gottlieb 1999) argues that tumours already contain higher levels of ascorbic acid than normal cells and have identified a mechanism to explain this observation. As such, they advocate against the use of vitamin C when cytotoxic agents that rely on free radical production are being used (see Chapter 10 for further discussion).

DIABETES

Vitamin C has several actions that provide a basis for its use in diabetes. It has been reported to lower erythrocyte sorbitol concentrations (important for preventing

complications in type 1 diabetes), improve endothelial function (important for slowing atherosclerosis) and reduce blood pressure (Beckman et al 2001, Cunningham 1998). Plasma vitamin C levels seem to play a role in the modulation of insulin activity in aged healthy or diabetic subjects (Paolisso et al 1994) and are inversely related to those of glycosylated haemoglobin. Additionally, free radical production has been reported to be increased in patients with diabetes mellitus as a result of hyperglycaemia, which directly induces oxidative stress (Ceriello et al 1998).

Blood glucose Studies testing the effects of supplemental vitamin C on plasma glucose levels directly are few at this stage. Although one early study demonstrated that an oral dose of 1500 mg vitamin C reduces plasma glucose levels in patients with type 2 diabetes (Sandhya & Das 1981), there are no further published studies that confirm this result.

Endothelial function The results of studies investigating the role of vitamin C on endothelial function in diabetes have attracted recent interest.

A double-blind, placebo-controlled study demonstrated that chronic oral vitamin C supplementation (500 mg/day) in type 2 diabetes significantly lowered arterial blood pressure and improved arterial stiffness compared with placebo (Mullan et al 2002). After 1 month's treatment, SBP fell from 142.1 to 132.3 mmHg, mean pressure from 104.7 to 97.8 mmHg, DBP from 83.9 to 79.5 mmHg and peripheral pulse pressure from 58.2 to 52.7 mmHg, whereas placebo had no effect.

A randomised study of women with a history of gestational diabetes showed that ascorbic acid supplementation resulted in a significant improvement of endothelium-dependent flow-mediated dilatation, with no effect seen for placebo (Lekakis et al 2000).

The mechanism of action appears to involve several steps, such as reduction in LDL oxidation, enhanced endothelial NO synthase activity and NO bioavailability, and reduced insulin resistance, which can cause endothelium-dependent, NO-mediated vasodilation.

Eye health Diabetes mellitus is associated with a number of ocular complications that can eventually lead to blindness. Vitamin C is found in high concentration in the eye and is thought to be important for protection against free radicals. This may have special significance for people with diabetes mellitus, as most studies have found circulating vitamin C levels at least 30% lower than people without the disease (Peponis et al 2002). One study demonstrated that a combination of oral vitamins C (1000 mg/day) and E (400 IU/day) improved tear film stability, tear secretion, and health of the ocular surface in diabetic patients.

Due to the safety, cost effectiveness and generally encouraging results, a strategy of adding 200–600 mg of vitamin C to a healthy diet is worth considering for individuals with type 1 or 2 diabetes.

PREVENTION OF CATARACTS

Numerous observational and prospective clinical studies have been performed to examine the effect of vitamin C alone or in combination with other antioxidants on cataract.

Several epidemiological studies have identified an association between vitamin C and cataract incidence (Ferrigno et al 2005, Jacques & Chylack Jr 1991, Jacques et al 1988, Valero et al 2002); however, studies investigating whether supplementation is protective have produced mixed results (Chasan-Taber et al 1999, Chylack Jr et al 2002, Hammond & Johnson 2002, Jacques et al 1997, 2001, Kuzniarz et al 2001, Seddon et al 1994, Taylor et al 2002).

Results from the Harvard Nurses' Health Study, Physician's Health Study, the Beaver Dam Eye Study and the Australian Blue Mountains study suggests that if protective effects are to be seen, it is most likely if vitamin C is taken long-term (5–10 years or more) and/or used as part of a multivitamin combination (Kuzniarz et al 2001, Mares-Perlman et al 2000, Seddon et al 1994, Taylor et al 2002).

It is suspected that vitamin C protects the lens of the eye from oxygen-related damage over time by both direct free radical scavenging activity and indirect activity. This is achieved primarily by protecting endogenous alpha-tocopherol (the major lipid-soluble antioxidant of retinal membranes) against oxidation induced by UV radiation and by regenerating it (Stoyanovsky et al 1995).

ATOPY AND ASTHMA

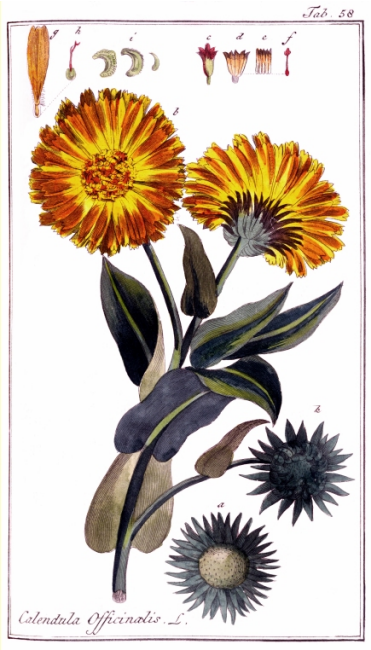
Vitamin C is the major antioxidant present in the extracellular fluid lining of the lung, where it protects against both endogenous free radicals (produced as a by-product of inflammation) and environmental free radicals (such as ozone in air pollution). According to many epidemiological studies, dietary intake of vitamin C-rich foods or serum ascorbate is associated with improved lung function in both asthmatic and normal subjects (Devereux & Seaton 2005).

Despite a theoretical basis for its use in lung diseases such as asthma, its value in this disease is controversial. A 2001 Cochrane review of three studies concluded that current evidence is insufficient to recommend a specific role for vitamin C in the treatment of asthma and that a large-scale RCT is required to clarify its role (Kaur et al 2001). An updated Cochrane review published in 2004 included new data from a

study of 201 adults taking inhaled corticosteroids and came to a similar conclusion, stating that evidence is currently conflicting (Ram et al 2004).

Alternatively, the evidence for its use in exercise-induced asthma appears stronger, as three human studies have produced positive results when vitamin C was used as pretreatment (Cohen et al 1997, Miric & Haxhiu 1991, Schachter & Schlesinger 1982) in doses ranging from 500 mg to 2000 mg.

Clinical note — Do asthmatic lungs need more antioxidant protection?
In 1999, Kelly et al found that people with mild asthma have low levels of antioxidant nutrient vitamins E and C within their lung lining fluid, even though their blood levels may be normal or increased. This observation, together with other factors, indicated that the asthmatic lung is exposed to greater oxidative stress than in non-asthmatics. The researchers suggested that the inflammatory cells in the lungs of asthmatic patients generate more free-radical species than healthy people, adding to the bronchoconstriction, increased mucus secretion and increased airways responsiveness. Considering that oral supplementation in asthma has produced inconsistent results, chief researcher Frank Kelly has discussed whether future studies should focus on other administration forms such as vitamin C inhalers (personal communication, Melbourne, 1998).



BONE MINERAL DENSITY

Although the relationship between calcium, vitamin D and bone mineral density (BMD) is well known, other nutrients such as vitamin C are also critical for bone development, repair and maintenance (Ilich et al 2003).

Data collected from 13,080 adults enrolled in the Third National Health and Nutrition Examination Survey (NHANES III) during 1988–94 have identified an association between dietary and serum ascorbic acid, BMD and bone fracture (Simon & Hudes 2001). Dietary ascorbic acid intake was independently associated with BMD among premenopausal women and postmenopausal women without a history of smoking or oestrogen use. Additionally, fracture risk fell by 49% in postmenopausal women (with a history of smoking and oestrogen use) who had high serum vitamin C levels.

Vitamin C supplementation Two controlled studies have investigated the effects of long-term vitamin C supplementation in postmenopausal women and found that it increases BMD (Hall & Greendale 1998, Morton et al 2001). Both studies identified a positive association with BMD in postmenopausal women with dietary calcium intakes of at least 500 mg or those taking calcium supplements. The effect was especially marked in those women taking calcium supplements and concurrent HRT.

The daily dose taken was generally in excess of the RDI and ranged from 100–5000 mg. More specifically, one study identified that for each 100 mg increment in dietary vitamin C intake there was an associated increase of 0.017 g/cm^2 in BMD (femoral neck and total hip) or for those women with calcium intakes above 500 mg/day, the increment increased to 0.019 g/cm^2 in BMD per 100 mg vitamin C.

A recent Australian study of 533 randomly selected women identified that vitamin C supplements may suppress bone resorption in non-smoking postmenopausal women (Pasco et al 2006).

In contrast to these results, no effect on BMD was observed for dietary or supplemental vitamin C in the Women's Health Initiative Observational Study and Clinical Trial, which involved 11,068 women aged 50–79 years (Wolf et al 2005). However, a significant beneficial interaction was observed between total vitamin C and HRT on total-body, femoral neck, spine and total-hip BMD.

Animal studies have detected an improved healing response in bone fractures with supplemental vitamin C, suggesting a further role in fracture healing (Yilmaz et al 2001).

SPORTS

Vitamin C supplementation is often used by athletes in order to improve recovery, restore immune responses, enhance wound healing, counteract oxidative stress and changes to adrenal hormones and inflammatory responses. It is often taken together with other antioxidant vitamins and minerals, such as vitamin E and zinc. One placebo-controlled study has shown that 20 mg of ascorbic acid twice daily over 14 days has some modest beneficial effects on recovery from unaccustomed exercise (Thompson et al 2001); however, no studies have reported improved performance for vitamin C supplementation.

Prevention of post-endurance exercise infections Athletes often use vitamin C supplements to prevent infections, as strenuous training and physiological stress appears to increase the body's need for vitamin C to a level above the usual RDI (Schwenk & Costley 2002). Additionally, the risk of infection after an intense aerobic training session or competition (such as a marathon) is increased (Jeurissen et al 2003).

A 2004 Cochrane review that analysed results from six trials involving a total of 642 marathon runners, skiers, and soldiers on subarctic exercises found regular vitamin C supplementation significantly reduced the incidence of the common cold, supporting its use in this population (Douglas et al 2004).

Alterations to neurotransmitters and adrenal hormones Several studies have been conducted with ultra-marathon runners to investigate whether vitamin C

supplementation, usually in doses of 1500 mg/day, is able to restore exercise-induced changes to neurotransmitters, adrenal hormones or inflammatory responses (Nieman et al 2000, Peters et al 2001a,b). Overall, it appears that high-dose vitamin C supplements taken at least 7 days prior to racing does have some effect.

One study involving 45 ultra-marathon runners found that doses of 1500 mg vitamin C taken for 7 days before the race, on the day of the race, and for 2 days following completion significantly attenuated exercise-induced elevations in cortisol, adrenaline, IL-10 and IL-1 receptor antagonist levels compared with placebo (Peters et al 2001a); however, the effect was transient.

OTHER USES

Vitamin C is used for numerous indications, although many have not been significantly studied, such as IBS, OA, menopausal hot flushes, cervical dysplasia, prevention of Alzheimer's dementia, allergies, male infertility, treatment of lead toxicity and reducing delayed-onset muscle soreness.

Vitamin C supplements have also been used as part of antioxidant combination therapy in HIV and heroin withdrawal. Preliminary research has shown that some antioxidant combinations reduce oxidative stress (Jaruga et al 2002), induce immunological and virological effects that might be of therapeutic value (Muller et al 2000) and produce a trend towards a reduction in viral load in HIV (Allard et al 1998). High doses of oral ascorbic acid and vitamin E may ameliorate the withdrawal syndrome of heroin addicts after 4 weeks' treatment, according to one study (Evangelou et al 2000).

DOSAGE RANGE

AUSTRALIAN AND NEW ZEALAND RDI

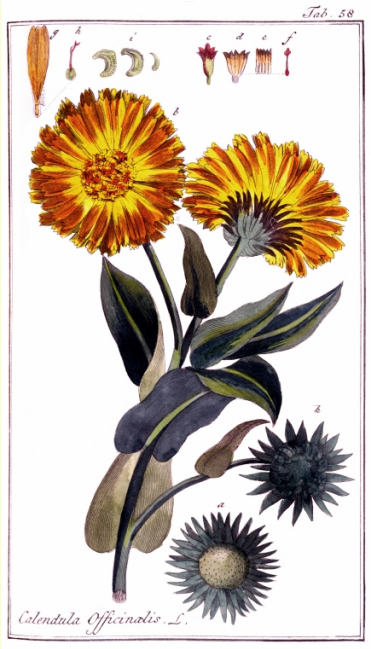
- Children
  - <8 years: 35 mg
  - 9–19 years: 40 mg
- Adults
  - >19 years: 45 mg
- Pregnancy
  - <19 years: 55 mg
  - >19 years: 60 mg
- Lactation
  - <19 years: 80 mg
  - >19 years: 85 mg

DEFICIENCY

- 100 mg taken 3–5 times daily until 4000 mg has been administered, followed by a maintenance dose of 100 mg/day and encouragement to eat a diet with fresh fruit and vegetables.
- In cases of acute infection, CAM practitioners frequently recommend vitamin C in doses of 1000 g (or more) to be taken in divided doses every few hours until loose bowels are experienced, otherwise known as 'bowel tolerance'. The rationale behind this dosage regimen is that body requirements during infection are dramatically increased and high dose vitamin C not only meets these needs but also maximum vitamin C absorption is attained when it is taken in divided doses rather than one large amount.

ACCORDING TO CLINICAL STUDIES

- Asthma: 500–2000 mg prior to exercise.
- Cancer: 10–100 g/day IV.
- Cardiovascular disease prevention: up to 1000 mg/day long term.
- Bone mineral density: 750 mg/day long term.
- Cataract protection: 500 mg/day long term.
- Diabetes: 0.5–3 g/day long term.
- Histamine-lowering effects: 250 mg to 2 g/day for several weeks.
- Respiratory infection: 1–2 g/day.
- Sunburn protection: oral vitamin C (2000 mg/day) in combination with vitamin E (1000 IU/day).
- Urinary acidification: 4–12 g taken in divided doses every 4 hours.



ADVERSE REACTIONS

Adverse effects of oral vitamin C include loose bowels and diarrhoea with high-dose supplements; however, the dose at which this occurs varies between individuals and also varies for each individual at different times.

SIGNIFICANT INTERACTIONS

ALUMINIUM-BASED ANTACIDS

Vitamin C increases the amount of aluminium absorbed — separate doses by at least 2 hours.

ASPIRIN

Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements (observed in animal and human

studies) — increased vitamin C intake may be required with long-term therapy (Basu 1982).

CHITOSAN
According to a preliminary study in rats, taking vitamin C along with chitosan might provide additional benefit in lowering cholesterol — potentially beneficial interaction.

CISPLATIN
Vitamin C enhanced the antitumour activity of cisplatin in several in vitro tests (Abdel-Latif et al 2005, Sarna & Bhola 1993, Reddy et al 2001) and reduced drug toxicity in experimental models (Giri et al 1998, Greggi Antunes et al 2000) — potentially beneficial but difficult to assess.

CORTICOSTEROIDS
Corticosteroids may increase the requirement for vitamin C based on in vitro and in vivo data (Chowdhury & Kapil 1984, Levine & Pollard 1983) — increased intake may be required with long-term drug therapy.

CYANOCOBALAMIN
Vitamin C can reduce absorption of cyanocobalamin — separate doses by at least 2 hours.

CYCLOPHOSPHAMIDE
Vitamin C enhanced the therapeutic drug effect in vivo (Lamson & Brignall 2000) — potentially beneficial but difficult to assess.

DOXORUBICIN
Vitamin C enhanced the therapeutic drug effect and reduced drug toxicity in vivo (Lamson & Brignall 2000) — potentially beneficial but difficult to assess.

ETOPOSIDE
Vitamin C enhanced the antitumor activity of etoposide in vitro (Reddy et al 2001) — potentially beneficial but difficult to assess.

FLUOROURACIL
Vitamin C enhanced the antitumour activity of 5-fluorouracil in vitro and in vivo (Abdel-Latif et al 2005, Nagy et al 2003) — potentially beneficial but difficult to assess.

IRON
Vitamin C increases the absorption of iron — potentially beneficial interaction.

L-DOPA
A case report of co-administration with vitamin C suggests this may reduce drug side effects (Sacks and Simpson 1975) — beneficial interaction.

TAMOXIFEN
Vitamin C enhanced the antitumour activity in vitro (Lamson & Brignall 2000) — potentially beneficial but difficult to assess.

VINCRISTINE
Vitamin C enhanced the drug's effect in vivo (Lamson & Brignall 2000) — potentially beneficial but difficult to assess.

PS-341 (BORTEZOMIB, VELCADE)
This is a proteasome inhibitor approved by the US FDA for the treatment of patients with relapsed multiple myeloma. Vitamin C inactivated drug activity in vitro (Zou et al 2006) — avoid.

Clinical note — Does vitamin C interact with the OCP?
In 1981 a case was reported of a woman who had experienced heavy breakthrough bleeding as a result of stopping vitamin C supplementation while taking the OCP (Morris et al 1981). At the time, it was suspected that vitamin C in high doses increases the bioavailability of oestrogen and raises blood concentrations due to competition for sulfation (resulting in reduced drug metabolism) (Back & Orme 1990). Therefore, ceasing supplement use would have the opposite effect and potentially cause breakthrough bleeding, as reported in this case. Since then, further investigation has been conducted to investigate whether this interaction is clinically significant. In 1993 a placebo-controlled study was conducted with 37 women and found that 1000 mg of vitamin C does not lead to an increased systemic bioavailability of ethinyl oestradiol, and therefore the purported interaction is unlikely to be of any clinical importance (Zamah et al 1993).

CONTRAINDICATIONS AND PRECAUTIONS
In patients who are sensitive to iron overload, vitamin C supplementation may exacerbate iron toxicity by mobilising iron reserves. As such, vitamin C supplementation should be used with caution by people with erythrocyte glucose-6-phosphate dehydrogenase deficiency, haemochromatosis, thalassaemia major or sideroblastic anaemia.

Supplemental vitamin C can affect the results of numerous laboratory tests and should be stopped prior to:

- carbamazepine

- lactate dehydrogenase
- serum AST
- serum bicarbonate
- serum cholesterol
- serum creatinine
- serum creatine kinase
- serum HbA_{1c}
- serum phosphate
- serum triglycerides
- serum urea nitrogen
- stool guiac
- theophylline
- urine 17-hydroxy corticosteroids
- urine 17-ketosteroids
- urine amphetamine
- urine and serum bilirubin
- urine and serum glucose
- urine and serum uric acid.
- urine barbiturate
- urine beta-hydroxybutyrate
- urine iodide
- urine oxalate
- urine paracetamol
- urine protein

Clinical note — Is the kidney stone risk overstated?
Although widely assumed to increase the risk of kidney stones, recent studies suggest high-dose vitamin C supplementation does not significantly increase this risk. In 1994, researchers discovered that vitamin C (in doses as high as 10 g/day) does not increase the amount of oxalate produced in the body (Wandzilak et al 1994). Instead, urine testing used to detect oxalate levels were found to actually be detecting oxalate formed by the conversion of ascorbate during the test procedure. As such, increased urine oxalate as tested by this method does not genuinely represent in vivo oxalate levels when ascorbate is involved. Two prospective studies of over 85,000 women and 45,000 men found that doses ranging from less than 250 mg/day to more than 1500 mg/day taken over 6–14 years did not correlate with occurrence of kidney stones (Curhan et al 1996, 1999). These two large studies

further support the lack of association between vitamin C supplements and kidney stones.

PREGNANCY USE

Vitamin C is safe in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin C is an essential nutrient for humans, as we are one of the few animal species that cannot synthesise it endogenously.
- Although vitamin C is found widely in fruit and vegetables, up to 100% can be destroyed during cooking and storing as it is sensitive to light, heat, oxygen and alkali.
- Although frank deficiency is uncommon in Westernised countries, marginal deficiency states are not uncommon, particularly in young children fed exclusively on cow's milk for a prolonged period, the institutionalised or isolated elderly, chronic alcoholics, the urban poor or cigarette smokers.
- Vitamin C is an antioxidant and is involved in a myriad of biochemical processes in the body, such as neurotransmitter and hormone synthesis, maintenance of connective tissue, immune function and adrenal function.
- Many studies have found a protective effect for dietary vitamin C intake on cardiovascular disease and cancer incidence, emphasising the importance of adequate dietary intake of fresh fruit and vegetables. Positive effects have also been detected for bone density and cataract incidence.
- Oral vitamin C supplements have been investigated in many different conditions. Positive results have been obtained in some of these studies, such as for reducing duration of the common cold, coronary heart disease prevention, prevention of several cardiovascular diseases and bone mineral density. Results in cancer treatment remain controversial for oral supplements.
- New research shows that long-term supplements do not increase the risk of kidney stones and do not interact with oral contraceptives.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin C is necessary for health and wellbeing. Supplements have also been used for a variety of uses and in some cases shown to have benefits.

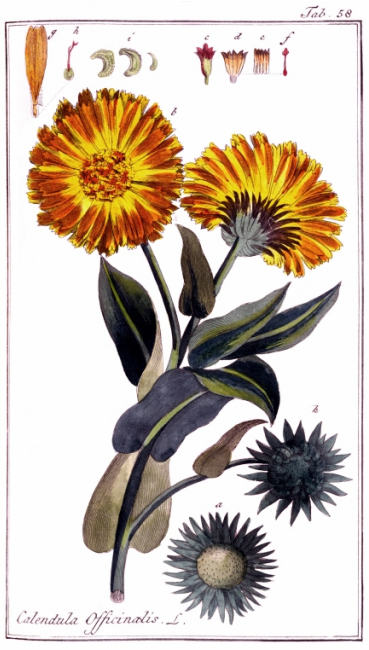
When will it start to work?

Studies have found that dietary or supplemental vitamin C may be required for at least 10 years before protection against heart disease or cancer incidence is detected.

However, other benefits may be experienced more quickly, depending on the dose used and indication.

Are there any safety issues?

Vitamin C is considered very safe, although high doses may induce reversible loose bowels or diarrhoea. Supplements should be taken only under medical supervision by people with erythrocyte glucose-6-phosphate dehydrogenase deficiency, haemochromatosis, thalassaemia or sideroblastic anaemia.



REFERENCES

Abdel-Latif MM et al. Vitamin C enhances chemosensitization of esophageal cancer cells in vitro. J Chemother 17 (2005): 539-49.

Age-Related Eye Disease Study. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 119.10 (2001): 1439-52.

Allard JP et al. Effects of vitamin E and C supplementation on oxidative stress and viral load in HIV-infected subjects. AIDS 12.13 (1998): 1653-9.

Alul RH et al. Vitamin C protects low-density lipoprotein from homocysteine-mediated oxidation. Free Radic Biol Med 34.7 (2003): 881-91.

Audera C et al. Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial. Med J Aust 175.7 (2001): 359-62.

Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 18.6 (1990): 472-84.

Bartholomew M. James Lind's Treatise of the Scurvy (1753). Postgrad Med J 78.925 (2002): 695-6.

Bassenge E et al. Dietary supplement with vitamin C prevents nitrate tolerance. J Clin Invest 102.1 (1998): 67-71.

Basu TK. Vitamin C–aspirin interactions. Int J Vitam Nutr Res Suppl 23 (1982): 83-90.

Bates CJ et al. Does vitamin C reduce blood pressure? Results of a large study of people aged 65 or older. J Hypertens 16.7 (1998): 925-32.

Beckman JA et al. Ascorbate restores endothelium-dependent vasodilation impaired by acute hyperglycemia in humans. Circulation 103.12 (2001): 1618-23.

Bednarz B et al. Antioxidant vitamins decrease exercise-induced QT dispersion after myocardial infarction. Kardiol Pol 58 (2003): 375-9.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Block G et al. Ascorbic acid status and subsequent diastolic and systolic blood pressure. Hypertension 37.2 (2001): 261-7.

Block G. Epidemiologic evidence regarding vitamin C and cancer. Am J Clin Nutr 54.6 (Suppl) (1991a): 1310-14S.

Block G. Vitamin C and cancer prevention: the epidemiologic evidence. Am J Clin Nutr 53.1 (Suppl) (1991b): 270-82S.

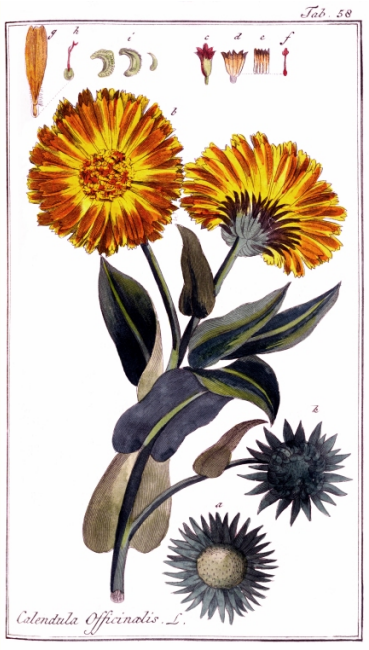
Block G. Ascorbic acid, blood pressure, and the American diet. Ann NY Acad Sci 959 (2002): 180-7.

Bornstein SR et al. Impaired adrenal catecholamine system function in transgenic mice with deficiency of the ascorbic acid transporter (SVCT2). FASEB J 17 (2003): 1928-30.

Boyce ST et al. Vitamin C regulates keratinocyte viability, epidermal barrier, and basement membrane in vitro, and reduces wound contraction after grafting of cultured skin substitutes. J Invest Dermatol 118.4 (2002): 565-72.

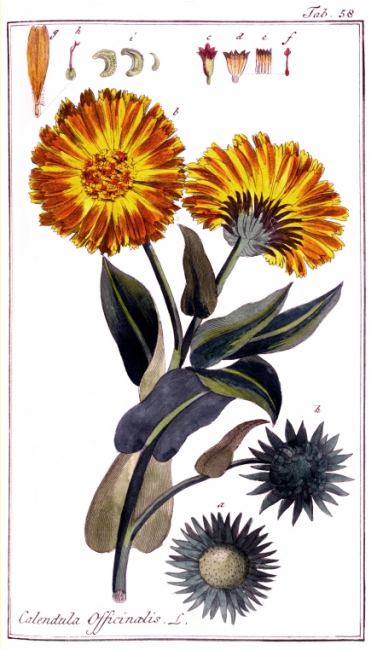
Braunwald E et al (eds). Harrison's Principles of Internal Medicine. New York: McGraw Hill, 2003.

Bucca C et al. Effect of vitamin C on histamine bronchial responsiveness of patients with allergic rhinitis. Ann Allergy 65.4 (1990): 311-14.
Cameron E. Vitamin C and cancer: an overview. Int J Vitam Nutr Res Suppl 23 (1982): 115-27.
Cameron E. Protocol for the use of vitamin C in the treatment of cancer. Med Hypotheses 36.3 (1991): 190-4.
Cameron E, Pauling L. The orthomolecular treatment of cancer. I. The role of ascorbic acid in host resistance. Chem Biol Interact 9.4 (1974): 273-83.
Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 73.10 (1976): 3685-9.
Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 69.6 (1999): 1086-107.
Ceriello A et al. Antioxidant defences are reduced during the oral glucose tolerance test in normal and non-insulin-dependent diabetic subjects. Eur J Clin Invest 28.4 (1998): 329-33.
Chasan-Taber L et al. A prospective study of vitamin supplement intake and cataract extraction among U.S. women. Epidemiology 10.6 (1999): 679-84.
Chowdhury AR, Kapil N. Interaction of dexamethasone and DHEA on testicular ascorbic acid and cholesterol in prepubertal rat. Arch Andriol 12.1 (1984): 65-7; as cited in Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.
Chylack LT Jr et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. Ophthal Epidemiol 9.1 (2002): 49-80.
Cohen M, Bhagavan HN. Ascorbic acid and gastrointestinal cancer. J Am Coll Nutr 14.6 (1995): 565-78.
Cohen HA et al. Blocking effect of vitamin C in exercise-induced asthma. Arch Pediatr Adolesc Med 151.4 (1997): 367-70.
Creagan ET et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: A controlled trial. N Engl J Med 301.13 (1979): 687-90.
Cunningham JJ. The glucose/insulin system and vitamin C: implications in insulin-dependent diabetes mellitus. J Am Coll Nutr 17.2 (1998): 105-8.
Curhan GC et al. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol 155.6 (1996): 1847-51.
Curhan GC et al. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol 10.4 (1999): 840-5.
Darr D et al. Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Dermatol 127.3 (1992): 247-53.
Darr D et al. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. Acta Derm Venereol 76.4 (1996): 264-8.
Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 115 (2005): 1109-17.
Douglas RM et al. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2 (2000): CD000980.
Drisko JA et al. The use of antioxidant therapies during chemotherapy. Gynecol Oncol 88.3 (2003): 434-9.
Duffy SJ et al. Treatment of hypertension with ascorbic acid. Lancet 354.9195 (1999): 2048-9.
Eberlein-Konig B et al. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E). J Am Acad Dermatol 38.1 (1998): 45-8.
Enstrom JE et al. Vitamin C intake and mortality among a sample of the United States population. Epidemiology 3 (1992): 194-202.
Evangelou A et al. Ascorbic acid (vitamin C) effects on withdrawal syndrome of heroin abusers. In Vivo 14.2 (2000): 363-6.
Fang Q et al. Ascorbyl stearate inhibits cell proliferation and tumor growth in human ovarian carcinoma cells by targeting the PI3K/AKT pathway. Anticancer Res 26 (2006): 203-9.



Ferrigno L et al. Associations between plasma levels of vitamins and cataract in the Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract (CTNS): CTNS Report #2. Ophthal Epidemiol 12 (2005): 71-80.
Fitzpatrick RE, Rostan EF. Double-blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. Dermatol Surg 28.3 (2002): 231-6.
Food and Agriculture Organization/World Health Organization. Report of a Joint FAO/WHO Expert Consultation; Bangkok, Thailand. FAO/WHO: Rome, 2002.
Fotherby MD et al. Effect of vitamin C on ambulatory blood pressure and plasma lipids in older persons. J Hypertens 18.4 (2000): 411-15.
Galley HF et al. Combination oral antioxidant supplementation reduces blood pressure. Clin Sci (Lond) 92.4 (1997): 361-5.
Gey KF et al. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: Basel Prospective Study. Clin Invest 71.1 (1993): 3-6.
Ghosh SK et al. A double-blind, placebo-controlled parallel trial of vitamin C treatment in elderly patients with hypertension. Gerontology 40.5 (1994): 268-72.
Giri A et al. Vitamin C mediated protection on cisplatin induced mutagenicity in mice. Mutat Res 421 (1998): 139-48.
Gottlieb N. Cancer treatment and vitamin C: the debate lingers. J Natl Cancer Inst 91 (1999): 2073-5.
Greggi Antunes LM et al. Protective effects of vitamin C against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: a dose-dependent study. Pharmacol Res 41 (2000): 405-11.
Hall SL, Greendale GA. The relation of dietary vitamin C intake to bone mineral density: results from the PEPI study. Calcif Tissue Int 63.3 (1998): 183-9.
Hammond BR Jr, Johnson MA. The Age-Related Eye Disease Study (AREDS). Nutr Rev 60 (2002): 283-8.
Hemila H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberc Lung Dis 3.9 (1999): 756-61.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Houston MC. Nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. Prog Cardiovasc Dis 47 (2005): 396-449.
Humbert PG et al. Topical ascorbic acid on photoaged skin: Clinical, topographical and ultrastructural evaluation: double-blind study vs placebo. Exp Dermatol 12.3 (2003): 237-44.
Ilich JZ et al. Bone and nutrition in elderly women: protein, energy, and calcium as main determinants of bone mineral density. Eur J Clin Nutr 57.4 (2003): 554-65.
Jacques PF, Chylack LT Jr. Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. Am J Clin Nutr 53 (1991): 352-5S.
Jacques PF et al. Nutritional status in persons with and without senile cataract: blood vitamin and mineral levels. Am J Clin Nutr 48 (1988): 152-8.
Jacques PF et al. Long-term vitamin C supplement use and prevalence of early age-related lens opacities. Am J Clin Nutr 66 (1997): 911-16.
Jacques PF et al. Long-term nutrient intake and early age-related nuclear lens opacities. Arch Ophthalmol 119.7 (2001): 1009-19.
Jaruga P et al. Supplementation with antioxidant vitamins prevents oxidative modification of DNA in lymphocytes of HIV-infected patients. Free Radic Biol Med 32.5 (2002): 414-20.
Jaxa-Chamiec T et al. Antioxidant effects of combined vitamins C and E in acute myocardial infarction: The randomized, double-blind, placebo controlled, multicenter pilot Myocardial Infarction and VITamins (MIVIT) trial. Kardiol Pol 62 (2005): 344-50.
Jenab M et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investation into Cancer and Nutrition (EPIC-EURGAST). Carcinogenesis, 2006. [Epub ahead of print.]
Jeurissen A et al. [The effects of physical exercise on the immune system]. Ned Tijdschr Geneeskd 147.28 (2003): 1347-51.
Johnston CS et al. Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. J Am Coll Nutr 11.2 (1992): 172-6.

Johnston CS et al. Vitamin C depletion is associated with alterations in blood histamine and plasma free carnitine in adults. J Am Coll Nutr 15.6 (1996): 586-91.
Kaliora AC et al. Dietary antioxidants in preventing atherogenesis. Atherosclerosis 187 (2006): 1-17.
Kaufmann PA et al. Coronary heart disease in smokers: vitamin C restores coronary microcirculatory function. Circulation 102.11 (2000): 1233-8.
Kaur B et al. Vitamin C supplementation for asthma. Cochrane Database Syst Rev 4 (2001): CD000993.
Keller KL, Fenske NA. Uses of vitamins A, C, and E and related compounds in dermatology: A review. J Am Acad Dermatol 39 (1998): 611-25.
Kelly FJ et al. Altered lung antioxidant status in patients with mild asthma. Lancet 354.9177 (1999): 482-3.
Khaw KT et al. Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. European Prospective Investigation into Cancer and Nutrition. Lancet 357.9257 (2001): 657-63.
Knekt P et al. Antioxidant vitamins and coronary heart disease risk: A pooled analysis of 9 cohorts. Am J Clin Nutr 80 (2004): 1508-20.
Kumar P et al. Clinical Medicine, 5th edn. London: WB Saunders, 2002.
Kurbacher CM et al. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 103 (1996): 183-9.
Kushi LH et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 334 (1996): 1156-62.
Kuzniarz M et al. Use of vitamin supplements and cataract: the Blue Mountains eye study. Am J Ophthalmol 132 (2001): 19-26.
Lamson DW, Brignall MS. Antioxidants and cancer therapy II: quick reference guide. Altern Med Rev 5 (2000): 152-63.
Lekakis JP et al. Short-term oral ascorbic acid improves endothelium-dependent vasodilatation in women with a history of gestational diabetes mellitus. Diabetes Care 23.9 (2000): 1432-4.
Levine MA, Pollard HB. Hydrocortisone inhibition of ascorbic acid transport by Chromaffin cells. FEBS Lett 158.1 (1983): 13408; as cited in Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.
Lin JY et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol 48.6 (2003): 866-74.
Ling L et al. Vitamin C preserves endothelial function in patients with coronary heart disease after a high-fat meal. Clin Cardiol 25.5 (2002): 219-24.
Lopes C et al. [Diet and risk of myocardial infarction: A case-control community-based study]. Acta Med Port 11.4 (1998): 311-17.
Loria CM et al. Vitamin C status and mortality in US adults. Am J Clin Nutr 72 (2000): 139-45.
Mares-Perlman JA et al. Vitamin supplement use and incident cataracts in a population-based study. Arch Ophthalmol 118.11 (2000): 1556-63.
McCann SE et al. Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. Nutr Cancer 53 (2005): 33-41.
Michels KB et al. Dietary antioxidant vitamins, retinol, and breast cancer incidence in a cohort of Swedish women. Int J Cancer 91.4 (2001): 563-7.
Miric M, Haxhiu MA. Effect of vitamin C on exercise-induced bronchoconstriction. Plucne Bolesti 43.1-2 (1991): 94-7.
Moertel CG et al. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: A randomized double-blind comparison. N Engl J Med 312.3 (1985): 137-41.
Morel O et al. Protective effects of vitamin C on endothelium damage and platelet activation during myocardial infarction in patients with sustained generation of circulating microparticles. J Thromb Haemost 1 (2003): 171-7.

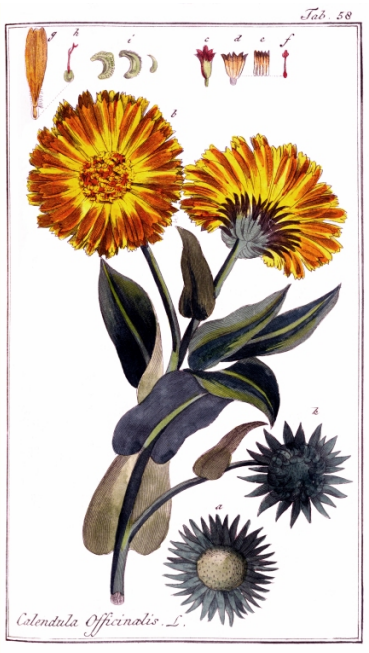


Morris JC et al. Interaction of ethinyl estradiol with ascorbic acid in man. BMJ 283 (1981): 503; as cited in Micromedex. Thomson 2003. Available at: www.micromedex.com
Morton DJ et al. Vitamin C supplement use and bone mineral density in postmenopausal women. J Bone Miner Res 16.1 (2001): 135-40.
MRC/BHF. Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360.9326 (2002): 23-33.
Mullan BA et al. Ascorbic acid reduces blood pressure and arterial stiffness in type 2 diabetes. Hypertension 40.6 (2002): 804-9.
Muller F et al. Virological and immunological effects of antioxidant treatment in patients with HIV infection. Eur J Clin Invest 30.10 (2000): 905-14.
Nagy B et al. Chemosensitizing effect of vitamin C in combination with 5-fluorouracil in vitro. In Vivo 17 (2003): 289-92.
National Health & Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Canberra: NHMRC, 2006.
Negri E et al. Selected micronutrients and oral and pharyngeal cancer. Int J Cancer 86.1 (2000): 122-7.
Ness AR et al. Vitamin C and cardiovascular disease: a systematic review. J Cardiovasc Risk 3.6 (1996): 513-21.
Ness AR et al. Vitamin C and blood pressure: an overview. J Hum Hypertens 11.6 (1997): 343-50.
Nieman DC et al. Vitamin C supplementation does not alter the immune response to 2.5 hours of running. Int J Sport Nutr 7.3 (1997): 173-84.
Nieman DC et al. Influence of vitamin C supplementation on cytokine changes following an ultramarathon. J Interferon Cytokine Res 20.11 (2000): 1029-35.
Nieman DC et al. Influence of vitamin C supplementation on oxidative and immune changes after an ultramarathon. J Appl Physiol 92.5 (2002): 1970-7.
Nyyssonen K et al. Vitamin C deficiency and risk of myocardial infarction: prospective population study of men from eastern Finland. BMJ 314.7081 (1997): 634-8.
Osganian SK et al. Vitamin C and risk of coronary heart disease in women. J Am Coll Cardiol 42.2 (2003): 246-52.
Padayatty SJ, Levine M. Reevaluation of ascorbate in cancer treatment: emerging evidence, open minds and serendipity. J Am Coll Nutr 19.4 (2000): 423-5.
Padayatty SJ et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 140 (2004): 533-7.
Padayatty SJ et al. Intravenously administered vitamin C as cancer therapy: three cases. Can Med Assoc J 174 (2006): 937-42.
Pandey DK et al. Dietary vitamin C and beta-carotene and risk of death in middle-aged men: The Western Electric Study. Am J Epidemiol 142 (1995): 1269-78.
Paolisso G et al. Plasma vitamin C affects glucose homeostasis in healthy subjects and in non-insulin-dependent diabetics. Am J Physiol 266.2 Pt 1 (1994): E261-8.
Pasco JA et al. Antioxidant vitamin supplements and markers of bone turnover in a community sample of nonsmoking women. J Womens Health 15 (2006): 295-300.
Peponis V et al. Protective role of oral antioxidant supplementation in ocular surface of diabetic patients. Br J Ophthalmol 86.12 (2002): 1369-73.
Peters EM et al. Vitamin C supplementation attenuates the increases in circulating cortisol, adrenaline and anti-inflammatory polypeptides following ultramarathon running. Int J Sports Med 22.7 (2001a): 537-43.
Peters EM et al. Attenuation of increase in circulating cortisol and enhancement of the acute phase protein response in vitamin C-supplemented ultramarathoners. Int J Sports Med 22.2 (2001b): 120-6.
Pimentel L. Scurvy: Historical review and current diagnostic approach. Am J Emerg Med 21.4 (2003): 328-32.
Prasad KN et al. Pros and cons of antioxidant use during radiation therapy. Cancer Treat Rev 28 (2002): 79-91.
Price KD et al. Hyperglycemia-induced ascorbic acid deficiency promotes endothelial dysfunction and the development of atherosclerosis. Atherosclerosis 158.1 (2001): 1-12.
Ram FS et al. Vitamin C supplementation for asthma. Cochrane Database Syst Rev 3 (2004): CD000993.

Reddy VG et al. Vitamin C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing P53. Biochem Biophys Res Commun 282 (2001): 409-15.
Richardson TI et al. Will an orange a day keep the doctor away? Postgrad Med J 78.919 (2002): 292-4.
Riemersma RA et al. Vitamin C and the risk of acute myocardial infarction. Am J Clin Nutr 71.5 (2000): 1181-6.
Ringsdorf J, Cheraskin E. Vitamin C and human wound healing. Oral Surg Oral Med Oral Pathol 53 (1982): 231-6.
Riordan HD et al. A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. Puerto Rica Health Sci J 24 (2005): 269-76.
Russell L. The importance of patients' nutritional status in wound healing. Br J Nurs 10.6 (Suppl) (2001): S42-4, S49.
Sacks W, Simpson GM. Ascorbic acid in levodopa therapy (Letter). Lancet 1.7905 (1975): 527; as cited in Micromedex. Thomson 2003. Available at: www.micromedex.com
Sahyoun NR et al. Carotenoids, vitamins C and E, and mortality in an elderly population. Am J Epidemiol 144 (1996): 501-11.
Sandhya P, Das UN. Vitamin C therapy for maturity onset diabetes mellitus: relevance to prostaglandin involvement. IRCS I Med Sci 9 (1981): 618.
Sarna S, Bhola RK. Chemo-immunotherapeutical studies on Dalton's lymphoma in mice using cisplatin and ascorbic acid: synergistic antitumor effect in vivo and in vitro. Arch Immunol Ther Exp (Warsz) 41 (1993): 327-33.
Sasazuki S et al. Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr 60 (2006): 9-17.
Schachter EN, Schlesinger A. The attenuation of exercise-induced bronchospasm by ascorbic acid. Ann Allergy 49.3 (1982): 146-51.
Schindler TH et al. [Effect of vitamin C on platelet aggregation in smokers and nonsmokers]. Med Klin 97.5 (2002): 263-9.
Schwenk TL, Costley CD. When food becomes a drug: nonanabolic nutritional supplement use in athletes. Am J Sports Med 30.6 (2002): 907-16.
Seddon JM et al. The use of vitamin supplements and the risk of cataract among US male physicians. Am J Public Health 84 (1994): 788-92.
Silvestro A et al. Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. Atherosclerosis 165.2 (2002): 277-83.
Simon JA, Hudes ES. Relation of ascorbic acid to bone mineral density and self-reported fractures among US adults. Am J Epidemiol 154.5 (2001): 427-33.
Singh N et al. Effects of a 'healthy' diet and of acute and long-term vitamin C on vascular function in healthy older subjects. Cardiovasc Res 56.1 (2002): 118-25.
Solzbach U et al. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulation 96.5 (1997): 1513-19.
Stoyanovsky DA et al. Endogenous ascorbate regenerates vitamin E in the retina directly and in combination with exogenous dihydrolipoic acid. Curr Eye Res 14.3 (1995): 181-9.
Tamayo C, Richardson MA. Vitamin C as a cancer treatment: state of the science and recommendations for research. Altern Ther Health Med 9 (2003): 94-101.
Taylor TV et al. Ascorbic acid supplementation in the treatment of pressure-sores. Lancet 304 (1974): 544-6.
Taylor A et al. Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. Am J Clin Nutr 75.3 (2002): 540-9.
Thompson D et al. Prolonged vitamin C supplementation and recovery from demanding exercise. Int J Sport Nutr Exerc Metab 11.4 (2001): 466-81.
Valero MP et al. Vitamin C is associated with reduced risk of cataract in a Mediterranean population. J Nutr 132.6 (2002): 1299-306.

Van Straten M, Josling P. Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey. Adv Ther 19.3 (2002): 151-9.
Vatassery GT. In vitro oxidation of alpha-tocopherol (vitamin E) in human platelets upon incubation with unsaturated fatty acids, diamide and superoxide. Biochim Biophys Acta 926.2 (1987): 160-9.
Vitetta L et al. Megadose vitamin C in treatment of the common cold: a randomised controlled trial. Med J Aust 176.6 (2002): 298-9.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wandzilak TR et al. Effect of high dose vitamin C on urinary oxalate levels. J Urol 151.4 (1994): 834-7.
Watanabe H et al. Randomized, double-blind, placebo-controlled study of the preventive effect of supplemental oral vitamin C on attenuation of development of nitrate tolerance. J Am Coll Cardiol 31.6 (1998a): 1323-9.
Watanabe H et al. Randomized, double-blind, placebo-controlled study of ascorbate on the preventive effect of nitrate tolerance in patients with congestive heart failure. Circulation 97.9 (1998b): 886-91.
Wilkinson IB et al. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. J Cardiovasc Pharmacol 34.5 (1999): 690-3.
Williams MJ et al. Vitamin C improves endothelial dysfunction in renal allograft recipients. Nephrol Dial Transplant 16.6 (2001): 1251-5.
Wilson CW et al. The metabolism of supplementary vitamin C during the common cold. J Clin Pharmacol 16.1 (1976): 19-29.
Wintergerst ES et al. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab 50 (2006): 85-94.
Wolf RL et al. Lack of a relation between vitamin and mineral antioxidants and bone mineral density: results from the Women's Health Initiative. Am J Clin Nutr 82 (2005): 581-8.
Yilmaz C et al. The contribution of vitamin C to healing of experimental fractures. Arch Orthop Trauma Surg 121.7 (2001): 426-8.
You WC et al. Gastric dysplasia and gastric cancer: Helicobacter pylori, serum vitamin C, and other risk factors. J Natl Cancer Inst 92.19 (2000): 1607-12.
Zamah NM et al. Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. Contraception 48.4 (1993): 377-91.
Zhang S et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 91.6 (1999): 547-56.
Zou W et al. Vitamin C inactivates the proteasome inhibitor PS-341 in human cancer cells. Clin Cancer Res 12 (2006): 273-80.

Vitamin D



Historical note Vitamin D was identified as a nutrient in the early 1900s when it was first realised that cod liver oil had an antirachitic effect in infants.

BACKGROUND AND RELEVANT PHARMACOKINETICS

The name 'vitamin D' actually refers to several related fat-soluble vitamin variants, all of which are sterol (cholesterol-like) substances. Cholecalciferol (D3) is the form found in animal products and fish oils, whereas ergocalciferol (D2) is the major synthetic form of provitamin D and usually found in supplements; however, other forms also exist. These ingested forms of vitamin D have 50–80% bioavailability and are emulsified by the bile salts, then enter through the small intestine into the lymphatic circulation. In the liver and kidneys, these forms are converted to 25-hydroxycholecalciferol and 1,25-dihydroxylcholecalciferol, the major circulating active form of vitamin D.

Vitamin D (as D3) is also produced in the body as a result of the conversion of a cholesterol-based precursor, 7-dehydrocholesterol, which is produced in the sebaceous glands of the skin. Exposure to sunlight (UVB) converts this precursor into cholecalciferol over a 2–3 day period. Prolonged exposure to UVB can inactivate some of the newly-formed vitamin D and its precursors so that eventually a state of equilibrium is reached between vitamin D synthesis and catabolism. Therefore, short periods of sun exposure are considered more efficacious than long periods (Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia 2005). Some vitamin D is stored in adipose tissue and can be mobilised during periods when exposure to sunlight is reduced or shortages develop (Nowson & Margerison 2002). Vitamin D and its metabolites are primarily excreted through bile and the degraded active form is removed via the kidney. Losses are believed to be minor, due to both reabsorption of vitamin D derivatives via the enterohepatic recirculation and limited filtration at the kidneys (Kohlmeier 2003). Parathyroid hormone (PTH), calcium and phosphorus are involved in the regulation of vitamin D metabolism.

CHEMICAL COMPONENTS

Cholecalciferol, or vitamin D3, is considered the most important dietary form and is identical to the form produced in the body. Ergocalciferol, or vitamin D2, is produced by fungi and yeasts and is rare in the diet, but a common supplemental form

(Nowson & Margerison 2002). Ergocalciferol has minor structural differences to D3 but is metabolised similarly and the two are considered to be equipotent (FAO/WHO 2002, Nowson & Margerison 2002, Wahlqvist 2002).

D2 also comes under the names 1-alpha-OHD2, calcifediol, calciferol, dihydrotachysterol (DHT), ergocalciferolum, ergosterol, whereas D3 may be referred to as 1-alpha-OHD3, alfacalcidiol, calcitriol or rocaltrol (Micromedex 2003).

Quantification of any of the vitamin D forms is expressed as either International Units (IU) or micrograms. The conversion is: 1 μg = 40 IU.

FOOD SOURCES

Small amounts are found in fatty fish, such as herring, salmon, tuna and sardines, beef and liver, butter, eggs and fortified foods such as margarine and milk (Groff & Gropper 2005). Cod liver oil is also a good source. Some foods are fortified with additional vitamin D, such as milk. Naturally occurring D2 is found only in mushrooms.

DEFICIENCY SIGNS AND SYMPTOMS

Although the traditional understanding of hypovitaminosis D revolves around its critical role in calcium metabolism, the extensive presence of 1,25-(OH)2D receptors throughout the body is providing the impetus for further research into actions, deficiency states and therapeutic applications (Groff & Gropper 2005).

PRIMARY DEFICIENCY

Unlike many other vitamins, vitamin D is not only ingested through the diet but is also produced and stored in the body. As such, endogenous production, which is reliant on adequate exposure to sunlight, will greatly influence whether deficiency states develop. It has been estimated that exposing the skin to UVB radiation produces approximately 90% of the vitamin D3 (cholecalciferol) that is bioavailable in the body. Currently, the NHMRC reports that it is almost impossible to get sufficient vitamin D from dietary sources alone, stressing the importance of UVB exposure.

Deficiency more prevalent than once thought Inadequate vitamin D is becoming recognised as a real concern, according to the 2005 position statement released by the Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. It states that there are a significant number of Australians who demonstrate a combination of poor dietary intake and inadequate sun exposure and who require supplementation.

Ongoing research in Australia investigating the prevalence of vitamin D deficiency supports this view and has identified that the wider community is at risk of mild deficiency. The results of a Tasmanian study revealed that although only 8% of 8-

year-olds were considered vitamin D deficient, the prevalence escalated with increasing age to peak at 85% for people aged 60 years (Proceedings from the RACGP Conference, Hobart, October 2003). Other studies have identified deficiencies in 80% of 'dark-skinned, veiled pregnant women', 76% of elderly residents in nursing homes and 53% of hostel residents (Grover & Morley 2001, Nowson & Margerison 2002, Sambrook et al 2002). The institutionalised elderly are of particular concern as they often have restricted exposure to sunlight, an estimated twofold reduction in capacity of the skin to produce D3 (Wilson et al 1991), compromised final conversion in the kidneys, reduced tissue response, and further reductions to calcium absorption independent of these pathways (Bouillon et al 1997, FAO/WHO 2002). At the other end of the age spectrum, a 2-year surveillance of infants presenting with vitamin D deficiency-related problems at the Monash Medical Centre in Clayton, Victoria found that of the 13 admitted to hospital, all were from migrant parents and predominantly or exclusively breastfed (Pillow et al 1995). Vitamin D deficiency is not restricted to Australia, as numerous international authors have concluded that it has become an epidemic in all age groups across America and Europe (Holick 2004).

Other populations at risk include hospitalised patients, people with a lifestyle or condition that precludes much sun exposure, such as those at risk of skin cancer, and adolescents and young children who are rapidly growing and are on marginal calcium intakes (FAO/WHO 2002, Wilson et al 1991, Working Group 2005).

Clinical note — The vitamin D dilemma

Determining an adequate dietary intake of vitamin D is complex, as multiple variables influence endogenous production and dietary requirements. Factors such as age, season, geographic latitude, time of day, part of body exposed to sunlight and use of sunscreen affect production of endogenous vitamin D. Researchers estimate that full body sun exposure in Australia, sufficient to induce mild erythema, is equivalent to consuming 15,000 IU orally (Working Group 2005). Hence, we have the dilemma.

Public health messages advocate exposure to UVB in order to prevent vitamin D deficiency, but this also exposes individuals to a wavelength that promotes skin cancer. The successful 'slip slop slap' campaign in Australia, which encourages covering up and reduced sun exposure, appears at odds with the vitamin D message and may have put many Australians at risk of poor vitamin D status.

Clearly, revision of the current public health messages regarding both vitamin D and safe sunlight exposure has been required for some time. In response, work has been undertaken to develop a message of compromise (Nowson & Margerison 2002, Working Group 2005). Recent evidence from a study by Samanek et al (2006)

supports the concept that safe sun exposure can yield vitamin D repletion. Their research concluded that from October to March only 10–15 minutes of unprotected exposure to 15% of the body outside of the hours 10 am to 3 pm was sufficient; however, during other seasons, up to 1 hour of exposure was required. In addition to this the authors themselves acknowledge that calculations were based on existing serum values, which have been widely contested by other researchers (Gomez et al 2003). In view of some of these concerns, the new NHMRC vitamin guidelines released in 2006 are now recommending an increased Adequate Intake of vitamin D, particularly for adults aged over 50 years. It also suggests varying lengths of time for sun exposure for different skin types in order to achieve adequate levels. Whether these initiatives are sufficient to prevent deficiency in the community remains to be seen.

SECONDARY DEFICIENCY

Malabsorption states such as coeliac disease, Crohn's disease, gastrectomy, intestinal resection, chronic cholestasis, cystic fibrosis and pancreatic disorders increase the risk of deficiency (Hendler et al 2001, Kumar & Clark 2002).

The use of certain anticonvulsants and chronic administration of glucocorticoids increase the risk of vitamin D deficiency. Several rare hereditary forms of rickets develop because the body cannot process (metabolise) vitamin D normally (Beers & Berkow 2003). Chronic liver disease will obstruct the first hydroxylation reaction, and end-stage kidney disease results in negligible conversion of 25-OHD into 1,25-OHD (Kumar & Clark 2002, Micromedex 2003). One large study also demonstrated that levels of serum 25-OHD are inversely correlated with percentage of body fat and as such morbidly obese individuals have increased requirements (Arunabh et al 2003).

SIGNS AND SYMPTOMS OF DEFICIENCY

The previously determined serum concentrations of 25-OHD believed to be indicative of deficiency (<20–25 nmol/L) are considered outdated (Gomez et al 2003). It is now apparent that much higher concentrations, deemed 'suboptimal' status, have deleterious effects (Nowson & Margerison 2002).

- Rickets and osteomalacia.
- Osteopenia and osteoporosis.
- Excess PTH secretion and parathyroid hyperplasia.
- Increased risk of fracture in the elderly (this is not just based on the influence of vitamin D on bone mass).
- Generalised muscle weakness.
- Stunted growth.

- Generalised muscle and bone pain.
- Chronic lower back pain (Al Faraj & Al Mutairi 2003).
- Cardiomegaly.
- Increased susceptibility to infections.
- Anaemia, decreased bone cellularity and extramedullary erythopoiesis.
- Impaired glucose-mediated insulin secretion (Brown et al 1999).

An association has been suggested between fibromyalgia presenting with generalised muscle weakness and pain and hypovitaminosis (Holick 2004).

MAIN ACTIONS

Whereas vitamin D is considered a fat-soluble vitamin, its active metabolite 1,25-(OH)2D3 is considered more like a steroid hormone because it can be produced by the body and moves through the systemic circulation to reach target tissues via receptors both at the cell membrane and at the nuclear receptor proteins.

REGULATION OF CALCIUM AND PHOSPHORUS LEVELS

In conjunction with PTH, which is released under conditions of low calcium levels, vitamin D can stimulate calcium and phosphorus absorption in the intestines, reabsorption in the kidneys and release of calcium from the bones back into the blood. 1,25-(OH)2D3 in turn is regulated by PTH, calcium, phosphorus and 1,25-(OH)2D3 itself (Wahlqvist 2002). To achieve the maximal efficiency of vitamin D-induced intestinal calcium transport, the serum 25(OH) D concentrations must be at least 78 nmol/L (30 ng/mL). In deficiency, intestinal absorption of calcium can be halved in adults (Holick 2004).

Modelling and remodelling of bone Besides influencing bone by maintaining calcium and phosphorus homeostasis, vitamin D may also contribute to bone health in other ways.

One pathway involves binding of 1,25 (OH)2D3 to DNA to promote transcription of specific mRNA, which codes for osteocalcin. Osteocalcin is then secreted by the osteoblasts, which bind calcium in new bone (Groff & Gropper 2005). Vitamin D also appears to play a role in oestrogen biosynthesis by increasing expression of the aromatase enzyme gene. It has demonstrated a synergistic effect in select tissues with the phyto-oestrogen genistein, with co-administration leading to a prolonged half-life of active vitamin D (Harkness & Bonny 2005, Swami et al 2005).

Cell differentiation, proliferation and growth Some of the actions already described are the result of the vitamin's capacity to affect cell differentiation, proliferation and growth in many tissues (e.g. differentiation of stem cells into osteoclasts to facilitate bone resorption). Alternatively, 1,25-(OH)2D3 can inhibit

proliferation in many cells, including lymphocytes, keratinocytes, mammary, cardiac and both skeletal and smooth muscle cells. This ability has led to its investigation as a treatment for proliferative disorders such as cancer (Brown et al 1999, Groff & Gropper 2005, Kohlmeier 2003).

Reduction of PTH and regulation of growth of the parathyroid gland Although PTH regulates the levels of 1,25-(OH)2D, its secretion is regulated by vitamin D, calcium and phosphorus. In deficiency, hypersecretion of this hormone can cause excessive growth of the parathyroid gland and secondary hyperparathyroidism (Brown et al 1999).

Immunomodulation Vitamin D enhances the immune system's response to both bacterial and viral agents, primarily through promoting differentiation and activity of the macrophages, which means that immune responses can be tailored through the appropriate cell response (Brown et al 1999). Vitamin D primarily influences the cytokine production of immune cells, suppressing the release of IL-2, IFN-gamma and TNF-alpha, products of the Th-1 line of cells, thereby reducing the propensity for a range of autoimmune conditions (Thien et al 2005). There is also some speculation that through this mechanism, vitamin D will promote a Th-2 dominance and may predispose to the atopic diathesis. Evidence in support of this hypothesis comes from two studies that reveal supplementation with vitamin D in early life to be a potential precipitator of allergic disease (Hypponen et al 2001).

OTHER ACTIONS

Our current understanding of the role of vitamin D appears to be only part of the picture. Ongoing discovery of previously unidentified receptors on tissues continues to broaden our understanding of its diverse effects.

HAEMATOPOIETIC TISSUES

Vitamin D appears to exert an effect on erythopoiesis and bone cellularity through unknown mechanisms. It has also been shown to inhibit clonal cell proliferation in some leukaemia lines and to promote differentiation (Brown et al 1999).

MUSCLE

Vitamin D maintains muscle strength and has an effect in skeletal muscle and myocardial function. Although it has been established that skeletal muscles have receptors for vitamin D, the specific actions of this steroid on muscle are largely unknown. Recently a link between fibromyalgia and vitamin D deficiency has been suggested, with an estimation of 40–60% of cases presenting with generalised muscle weakness and pain being undiagnosed hypovitaminosis (Holick 2004). Through unidentified mechanisms vitamin D exerts a direct effect on the myocardium:

1,25-(OH)2D3 controls hypertrophy in cardiac monocytes and, together with 25-OHD, improves the left ventricular function in patients with cardiomyopathies (Brown et al 1999).

PANCREAS

Vitamin D is essential for normal insulin secretion, as demonstrated in both animals and humans, and vitamin D receptors have been found in pancreatic beta-cells (Mathieu & Badenhoop 2005). Enhanced insulin synthesis may be due to vitamin D's role in controlling intracellular calcium flux in islet cells (Brown et al 1999).

BRAIN

Evidence is emerging about the specific role of vitamin D in the brain. Information to date implicates 1,25(OH)2D in the biosynthesis of neurotrophic factors, contribution to brain detoxification pathways with increased glutathione and reduced NO, neuroprotective effects, induction of glioma cell death and involvement in neurotransmitter synthesis including acetylcholine and the catecholamines (Garcion et al 2002). Preliminary studies in rats have demonstrated an anti-epileptic action (Kalueff & Tuohimaa 2005). There are tentative links being made between the aetiology/pathophysiology of Parkinson's disease and poor vitamin D status (Johnson 2001, Kim et al 2005).

CLINICAL USE

Vitamin D is administered using various routes and can be prescribed as either supplement or drug. This review will focus only on oral supplementation of D2 or D3 and not the variety of analogues that continue to be extensively studied. For many conditions that appear to require high doses, the race is on to develop and trial pharmaceutical analogues that retain in particular the antiproliferative nature of the vitamin, but are low-calcaemic in order to minimise the associated toxicity seen at such doses.

DEFICIENCY STATES

Frank vitamin D deficiency in infancy or childhood produces rickets, which results from reduced sun exposure, deficient diet, or metabolic or malabsorptive diseases. Vitamin D deficiency results in inadequate calcium and phosphorus levels for bone mineralisation (Beers & Berkow 2003). Diagnosis is confirmed with X-ray and serum assay of 25-OHD. When this condition occurs in adults it is called osteomalacia, and its first presentation is often chronic lower back pain (Al Faraj & Al Mutairi 2003).

Defective vitamin D metabolism may be another cause, and consequently will not respond to standard oral treatment. In this situation, extremely high doses may be required, which require careful monitoring for toxicity (Beers & Berkow 2003).

Pregnancy and lactation supplementation Vitamin D appears critical to both musculoskeletal and neurological growth and development of the infant. A recent Australian study investigated the well-documented seasonal variation in birth weight to determine the parameters of anthropometric changes associated with this seasonal variation (McGrath et al 2005). Comparison of over 350,000 mean monthly birth weights of neonates greater than 37 weeks' gestation revealed overall size, length, head size and skinfold thickness all display seasonal variation, but in particular greater limb length occurred with winter/spring births. Earlier animal studies imply that this may be a consequence of hypertrophy of the cartilage growth plates due to prenatal hypovitaminosis D (McGrath et al 2005).

Whether pregnant women require additional supplementation has been investigated in some studies. The Cochrane Controlled Trials Register has assessed only two trials, producing inconsistent results (Mahomed & Gulmezoglu 2000). However, trials involving over 500 women conducted by Marya et al (1981, 1987), not included in this review, have demonstrated statistically significant increased fetal birth weight, reduced prevalence of hypocalcaemia and hypophosphataemia detected in both maternal and cord blood and reduced blood pressure in non-toxaemic women. Additional evidence suggests a preventative role for a range of autoimmune conditions in the offspring when prenatal vitamin D levels are adequate (Holick 2004).

There is greater consensus regarding the need for vitamin D supplementation during lactation, with breastmilk being recognised as a poor source of this vitamin and that infants are largely dependent on stored vitamin D acquired in utero (Andiran et al 2002).

Treatment of deficiencies secondary to malabsorptive syndromes Numerous studies have confirmed a high prevalence (25–75%) of hypovitaminosis D in patients with coeliac disease, Crohn's disease, small bowel resection or cystic fibrosis. A positive correlation was detected in a majority of trials between low vitamin D status and clinical consequences, such as reduced bone mineral density (BMD) and osteopenia. Interestingly, trials investigating the benefits of oral vitamin D supplements (400–800 IU/day) found limited success in patients. Due to the theoretical advantage of supplementation in conditions associated with poor nutrient absorption, larger trials involving higher doses or different forms are expected to determine the most effective treatment (Buchman 1999, Congden et al 1981, Hanly et al 1985, Hoffmann & Zeitz 2000, Jahnsen et al 2002).

CANCER

Given the ability of vitamin D to inhibit abnormal proliferation, its chemoprotective potential has been investigated. Adding to this is the strong epidemiological evidence that suggests some forms of cancer show geographical distribution patterns similar to those reflecting poor UV radiation (Garland et al 1999). Advancing age, as well as ethnicity, have also been positively correlated with these cancers and have been explained again as related to reduced sun exposure.

Colorectal There is now strong evidence from several different lines of investigation supporting the hypothesis that vitamin D may reduce the risk of colorectal cancer (Garland et al 1991, Grant & Garland 2004, Holt et al 2002). A 2004 review of over 20 epidemiological studies into vitamin D and colorectal cancer concluded that the overwhelming majority of both serum and dietary intake assessment designs have demonstrated an inverse relationship. An estimate of daily requirements needed for prevention have been formulated using the data provided by these studies and it is suggested that an oral intake of >1000 IU/day of vitamin D or serum 25-hydroxyvitamin D levels >33 ng/mL (82 nmol/L) could reduce the risk of this cancer by as much as 50% (Garland et al 2004).

Prostate Epidemiological evidence from a number of substantial studies, including the Helsinki Heart Study involving 19,000 men, have illustrated that increased levels of circulating 1,25(OH)2D3 and low levels of 25-OHD are inversely associated with prostate cancer, in both incidence and aggressiveness, and are associated with an earlier age of onset (Chen & Holick 2003).

Experimental research with vitamin D has produced interesting results. Prostate cancer cells in vitro respond to vitamin D3 with reduced proliferation, increased differentiation and apoptosis. More recently, reduced activity of the 1-alpha(OH)ase enzyme in cancerous prostate cells was discovered, when compared to healthy prostate tissue, resulting in a reduced ability to convert vitamin D to its active form. Therefore, prostates with cancer display partial resistance to the tumour-suppressing activity of 1,25-(OH)2D3 (Ma et al 2004). Clinical trials using supplemental vitamin D at various stages of prostate cancer have yielded inconsistent results (Miller 1999).

Breast There is some epidemiological evidence to suggest an inverse association between vitamin D and breast cancer (Grant 2006). One study involving 179 breast cancer patients and 179 controls that assessed vitamin D status of patients and polymorphisms of vitamin D identified an inverse relationship, possibly as high as 7-fold, between 25 OHD levels and breast cancer risk (Lowe et al 2005). The vitamin D receptors in mammary tissue have been shown to oppose oestrogen-driven proliferation of cells (Welsh et al 2003).

DIABETES

Vitamin D deficiency has been linked to both type 1 and type 2 diabetes. To date the largest volume of evidence relates to prenatal and infant vitamin D levels and an inverse association with a child's overall risk of developing type 1. One birth cohort study published in the *Lancet* in 2001 involved the offspring of 12,055 pregnant Finnish women who gave birth in 1966. The families were assessed for vitamin D supplementation in the infant's first year of life and then the child was followed until 31 years of age to account for subsequent diagnoses of type 1 diabetes. It was shown that treatment of children with 2000 IU/day vitamin D from 1 year of age decreased the risk of developing type 1 diabetes mellitus by 80% throughout the next 20 years; furthermore, children from the same cohort who were vitamin D-deficient at 1 year of age had a 4-fold increased risk of developing type 1 diabetes (Hypponen et al 2001). Similar findings have been demonstrated in animal models, with pretreatment with 1,25(OH)2D being effective in mitigating or preventing the onset of type 1.

A case control study conducted in Norway involving 545 Norwegian children up to 15 years old with type 1 diabetes retrospectively assessed their cod liver oil and vitamin D use from birth to 12 months old. Children who had been given cod liver oil five times a week had a 26% lower incidence of the disease, whereas other forms of vitamin D appeared to bear no relationship (Stene & Joner 2003). Although this does not adequately assess vitamin D as a sole treatment agent and is not conclusive, it adds to the growing body of evidence implicating vitamin D in a preventive role.

Small interventional studies have also been conducted in populations with type 2 diabetes using vitamin D to enhance insulin secretion and activity. In one clinical trial, 10 adult women with type 2 diabetes were administered 1332 IU/day oral vitamin D for 1 month. Corresponding changes were observed in first-phase insulin secretion (34.3% increase) and serum 25-OHD levels. Improvements observed in second-phase insulin secretion and insulin resistance were deemed non-significant (Borrisova et al 2003).

HYPOPARATHYROIDISM

Vitamin D in combination with calcium has established benefits in the treatment of hypoparathyroidism, by promoting homeostasis of calcium, phosphorus 25-OHD and PTH levels (Mimouni et al 1986).

Secondary hyperparathyroidism In a controlled study involving 100 postmenopausal women with confirmed vitamin D deficiency (<18 nmol), supplementation with combination calcium and low-dose vitamin D showed the more significant reductions in PTH levels over the 90-day trial than calcium alone (Deroisy et al 2002).

HYPOPHOSPHATAEMIA

A combination of high-dose vitamin D and phosphorus results in improved phosphorus and calcium balance in these patients (Lyles et al 1982).

OSTEOPOROSIS

Although serum 1,25-(OH)2D levels are low in osteoporotic patients, vitamin D alone has not been shown to increase BMD (Hunter et al 2000, Wilson et al 1991). Alternatively, studies investigating vitamin D's role in the prevention of fractures associated with osteoporosis have produced some positive results. In a 2001 review on the use of minerals in the prevention of fractures associated with osteoporosis, combination treatment of calcium and vitamin D was considered to produce the greatest reductions.

REDUCING FALLS IN THE ELDERLY

Poor vitamin D status is independently associated with an increased risk of falling in the elderly, particularly in those aged 65–75 years (Snijder et al 2006). A 2004 review of double-blind RCTs of vitamin D in elderly populations conducted between 1960 and 2004 found that supplementation with vitamin D reduced the risk of a fall by more than 20% and that approximately 15 people needed to take vitamin D for up to 3 years to protect one person from a fall. The results were significant in women only and appeared to be independent of calcium administration, type of vitamin D and duration of therapy (Bischoff-Ferrari et al 2006). More recent research has suggested an even greater reduction in the incidence of falls. According to a double-blind randomised study involving 64 institutionalised elderly women (age range: 65–97 years; mean 25-hydroxyvitamin D levels: 16.4 ng/ml), treatment with 1200 mg/day calcium plus 800 IU/day cholecalciferol over a 3-month treatment period reduced the rate of falls by 60% compared with calcium supplementation alone (Bischoff-Ferrari et al 2006). After conducting a balance assessment, it was estimated that of the observed 60% reduction in the rate of falls, up to 22% of the treatment effect was explained by a change in postural balance and up to 14% by dynamic balance. A 60% reduction in the incidence of peripheral fractures was also identified by Cosman in 2005 for vitamin D supplementation (700–800 IU/day) with adequate or supplemented calcium. With regard to hip fracture specifically, a 40% reduction in incidence was observed. As a result of these impressive results, routine administration is recommended for those institutionalised or housebound elderly who are already at risk of deficiency (Sambrook & Eisman 2002).

ANTICONVULSANT-INDUCED OSTEOMALACIA

Preliminary evidence has shown vitamin D to be an effective treatment for this condition; however, much emphasis has been placed on establishing the most superior form of D, D2 or D3, as they exhibit important metabolic differences in these patients (Hartwell et al 1989, Tjellesen et al 1985, 1986). Results of the RCTs to date suggest that D2 may be the most effective form in the restoration of bone mineral content in patients on anticonvulsant treatment (Tjellesen et al 1985).

HEPATIC AND RENAL OSTEODYSTROPHY

Both chronic liver disease and those conditions exhibiting end-stage renal disease result in compromised hydroxylation of vitamin D to produce its active metabolite. It has been reported that 50% of patients with chronic liver disease, especially those with primary or secondary biliary cirrhosis, present with associated osteodystrophy. This frequently leads to a vitamin D deficiency and manifests most commonly as metabolic bone disorders, hypocalcaemia and secondary hyperparathyroidism (Wills & Savory 1984). The resultant hypovitaminosis D can result in bone loss, cardiovascular disease, immune suppression and increased mortality in patients with end-stage kidney failure (Andress 2006). Consequently, correction of this deficiency has been one of many first line treatments in these situations.

Although vitamin D2 supplementation in combination with calcium, phosphorus and magnesium (where indicated) has shown some success in those patients with hepatic osteodystrophy (Compston et al 1979, Long & Wills 1978), recent trials and emerging research implicate other factors in the aetiology of these sequelae (Klein et al 2002, Suzuki et al 1998). As such, therapy with D2 may need to be reviewed.

The treatment of renal osteodystrophy is reliant upon only the active forms or analogues of vitamin D and natural supplementation is ineffective due to the inability to convert these precursors into 1,25-alpha(OH)2D (Kim & Sprague 2002).

LOCALISED AND SYSTEMIC SCLERODERMA

Although patients suffering scleroderma do not show compromised D synthesis (Matsuoka et al 1991), vitamin D3 has been investigated as a therapeutic agent to moderate the excessive proliferation and collagen production typically seen in this condition. An in vitro study assessing the action of vitamin D3 on the behaviour of affected fibroblasts has confirmed a non-selective antiproliferative action (Boelsma et al 1995).

To date, clinical studies have produced mixed results. Clinical trials focusing on generalised scleroderma have involved small numbers and produced promising results, such as increased joint mobility, reduced induration and increased extensibility

of the skin, with benefits lasting at least 1 year after discontinuation of treatment (Caca-Biljanovska et al 1999, Hulshof et al 1994). However, the largest RCT involving 27 patients (the majority of whom suffered a localised condition) found that treatment over 9 months with a similar dose of D3 failed to produce any significant changes in any of the assessment criteria (Hulshof et al 2000). These results suggest that different therapies may be required for the two conditions; however, larger controlled studies are required to confirm those positive results from the preliminary open trials.

OTHER USES

MULTIPLE SCLEROSIS

There is reasonably strong ecologic and case–control evidence that vitamin D reduces the risk of multiple sclerosis (Grant 2006).

PSORIASIS

As a regulator of cellular growth and differentiation in various tissues, vitamin D has been investigated in psoriasis. The active form of vitamin D and its analogues have been found to suppress growth and stimulate the terminal differentiation of keratinocytes.

VAGINAL ATROPHY

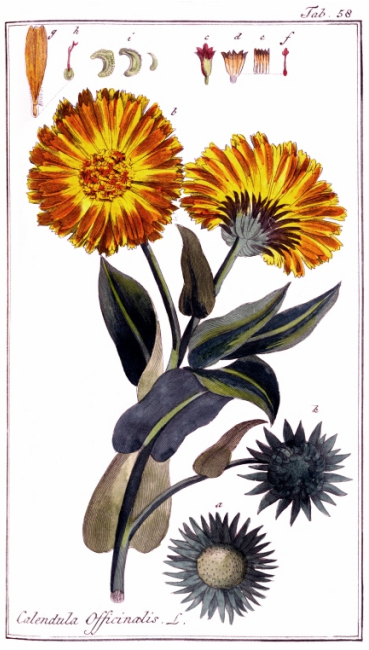
Animal studies have revealed the presence of vitamin D receptors in the cells lining the vagina (Yildirim et al 2004a). Given the established role of vitamin D in regulating growth and differentiation of tissues, especially those lining stratified squamous epithelium, a possible role for vitamin D in the prevention and treatment of vaginal atrophy associated with menopause is being considered (Yildirim et al 2004b). A number of studies involving co-administration with calcium have produced generally positive results.

Clinical note — A link between vitamin D and schizophrenia?

The epidemiological correlation between babies born in winter and spring and an increased prevalence of schizophrenia has been a long established phenomenon and presented many riddles for researchers (Kendell & Adams 2002). The association has also been observed in cities where air pollution reduces UV irradiation, and, more recently, a 7–10-fold increased risk in second-generation dark-skinned migrants. These observations have led to the emergence of a neurodevelopmental theory of schizophrenia, which suggests that low prenatal

vitamin D interferes with brain development by interacting with D responsive/susceptible genes to create the currently recognised polygenic effects of schizophrenia (Mackay-Sim et al 2004).

A significant contribution to the investigation of this theory has been made by the Queensland Centre for Schizophrenic Research led by Professor John McGrath. The Centre's work has taken the level of evidence beyond the early epidemiological findings, with research being conducted to assess the impact of vitamin D deficiency on animal brains and in vitro cultures. Research has also been conducted to measure third trimester serum 25(OH)D levels in schizophrenic and schizoaffective mothers, while investigating the impact of vitamin D supplementation prior to 1 year of age in the infants and the subsequent risk reduction for the disease in later life (McGrath et al 2003, 2004a, b). The preliminary evidence to date shows some support for this hypothesis, with a consistent positive relationship appearing for males and some evidence pointing towards a stronger relationship in dark-skinned populations compared to fairer skinned populations.



DOSAGE RANGE

The NHMRC vitamin guidelines released in 2006 make the following recommendations for ADI:

- Children and adults <50 years: 5 μg/day.
- Adults 51–70 years: 10 μg/day.
- Adults over 70 years: 15 μg/day.

The AI is based on the amount of vitamin D required to maintain serum 25(OH)D at a level of at least 27.5 nmol/L with minimal sun exposure. The level has been raised in the 51–70 year age group to account for the reduced capacity of the skin to produce vitamin D with ageing. The higher level recommended in the over 70 years group was made because this group tends to have less exposure to sunlight.

ACCORDING TO CLINICAL STUDIES

(D2 supplemental form unless otherwise indicated.)

- Uncomplicated rickets: 1600 IU/day for the first month, gradually reducing the dose to 400 IU.
- Osteomalacia: 36 000 IU/day with calcium supplementation.
- Rickets and osteomalacia due to defective metabolism: 50 000–300 000 IU/day.
- Pregnancy supplementation: two large doses of 600 000 IU in the 7th and 8th months (Marya et al 1981).

- Reduction in fractures associated with osteoporosis: prevention of fractures has resulted from as little as 200 IU/day in combination with calcium (Hunter et al 2000).
- Reduction in falls: 1200 mg/day calcium plus 800 IU/day cholecalciferol.
- Hyperparathyroidism: 2.5–6.25 mg/day.
- Hepatic osteodystrophy: 4000 IU/day.
- Anticonvulsant osteomalacia: 4000 IU D2/day for 105 days, followed by 1000 IU/day.
- Systemic scleroderma: 0.75–1.25 μg D3 for 6 months.

TOXICITY

Toxic ingestion of prescribed forms of vitamin D or excessive dietary consumption of either D2 or D3 has been reported in the vicinity of 50 000–100 000 IU/day or 10 000 IU taken routinely for several months. Obtaining such enormous amounts from unfortified foods is improbable. The resultant hypercalcaemia manifests as anorexia, nausea, vomiting, polyuria, muscle pain, unusual tiredness, dry mouth, persistent headache and secondary polydipsia. Over extended periods of time this state of hypervitaminosis can result in metastatic calcification of soft tissues including kidney, blood vessels, heart and lungs. Symptoms and signs at this later stage include cloudy urine, pruritis, drowsiness, weight loss, sensitivity to light, hypertension, arrhythmia, fever and abdominal pain. Toxic levels cannot be obtained from excessive sun exposure (FAO/WHO 2002, Groff & Gropper 2005).

ADVERSE REACTIONS

High doses of supplements may induce the following:

- arterial calcification
- arrhythmia
- gastrointestinal distress including nausea, vomiting and constipation
- hypercalcaemia
- nephrotoxicity, manifesting as polyuria, polydipsia and nocturia.

SIGNIFICANT INTERACTIONS

Only those interactions relevant to the oral supplemental forms of vitamin D will be reviewed.

A number of pharmacokinetic and pharmacodynamic interactions are possible with vitamin D and a range of medicines and minerals.

LIPID-LOWERING DRUGS
Drugs such as cholestyramine and colestipol may compromise the absorption of all fat-soluble vitamins. To avoid the interaction, administer the supplement at least 1 hour prior to or 4–6 hours after ingestion of the drug (Harkness & Bratman 2003).

MINERAL OIL
Mineral oil impairs absorption of all fat-soluble nutrients and may therefore deplete oral intake of vitamin D sources — separate doses by at least 2 hours.

ORLISTAT
Although orlistat has been shown to reduce the absorption of some fat-soluble nutrients, its effect on vitamin D specifically remains unclear. Concurrent supplementation of a multivitamin with D is advised — separate doses by a minimum of 4 hours either side of ingestion of orlistat (Harkness & Bratman 2003).

GLUCOCORTICOIDS
In high doses these drugs directly inhibit vitamin D-mediated calcium uptake in the gastrointestinal tract and through unknown mechanisms may deplete levels of active vitamin D (Wilson et al 1991). During long-term therapy with either oral or inhaled corticosteroids, calcium and vitamin D supplementation should be considered.

CALCIUM-CHANNEL BLOCKERS
Vitamin D supplementation may reduce effectiveness of these drugs — use with caution unless under medical supervision (Harkness & Bratman 2003).

OESTROGENS
Vitamin D works synergistically with oestrogens to prevent bone loss — beneficial interaction.

MAGNESIUM
Either an excess or inadequate level of magnesium can impact on vitamin D status. The final hydroxylation step to 1,25(OH)2D3 is dependent upon magnesium and a deficiency would compromise this. However, high levels of magnesium, mimicking calcium, can suppress PTH secretion, also suppressing the activation phase (Groff & Gropper 2005). Therefore magnesium levels within the normal range will enhance activation of vitamin D to its active form.

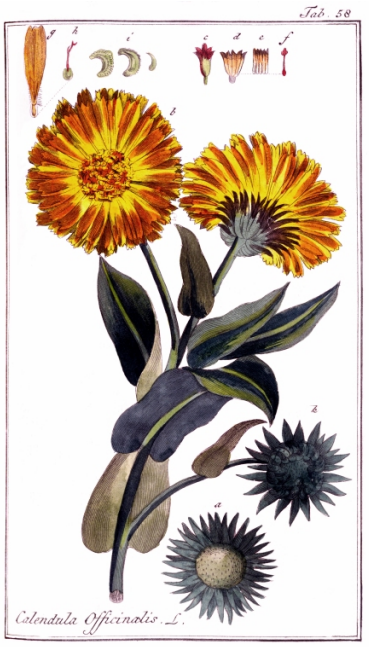
KETOCONAZOLE
This drug reduces the conversion of vitamin D to its active forms — increased vitamin D intake may be required with long-term drug use.

PHENYTOIN AND VALPROATE

The anticonvulsants, through liver induction, induce catabolism of vitamin D and prolonged use is associated with increased risk of developing rickets and osteomalacia.

ANTITUBERCULOSIS DRUGS

Drugs such as rifampicin and isoniazid have been reported to induce catabolism of vitamin D and in some cases manifest as reduced levels of metabolites. This may represent a concern in those patients already at risk of poor vitamin D status (Harkness & Bratman 2003).



CONTRAINDICATIONS AND PRECAUTIONS

- Hypersensitivity to vitamin D.
- Systemic lupus erythematosus.
- Hypercalcaemia.
- Not to be taken in sarcoidosis or hyperparathyroidism without medical supervision.
- Possible interference with the action of calcium-channel blockers.
- High doses require medical supervision in patients with arteriosclerosis and heart disease.
- High doses capable of inducing hypercalcaemia may precipitate arrhythmias in patients taking digitalis.

PREGNANCY USE

Vitamin D supplements as either D2 or D3 are exempt from pregnancy classification by the TGA, which reflects their safety in pregnancy and lactation (Australian Drug Evaluation Committee 1999).

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin D has a critical role in bone growth and development but has also diverse roles throughout the body, including inhibiting abnormal proliferation of cells.
- Most vitamin D is endogenously produced through sun exposure and an activation process that involves both the liver and the kidneys; food sources represent a secondary and often unreliable source. Those groups in the community who have restricted sun exposure are at the greatest risk of a deficiency, including the elderly, newborns, institutionalised, adolescents and young children with marginal calcium intake during rapid growth periods, and those with dark skins.
- Vitamin D supplements are most commonly given in combination with other nutrients, such as calcium, in the prevention of falls and prevention or treatment of osteoporosis.

- Other uses for vitamin D include supplementation during pregnancy to increase fetal levels, correction of deficiencies that may result from medications or malabsorptive diseases such as coeliac disease, Crohn's disease and cystic fibrosis, as a protective agent against breast, prostate and colorectal cancer, and for a variety of metabolic bone disorders.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin D is essential for health and wellbeing. It plays a critical role in regulating calcium and phosphorus levels in the body, and is important for healthy bones and preventing abnormal cell changes, which may increase the risk of some cancers.

When will it start to work?

This will depend on the condition being treated. In uncomplicated rickets, serum levels should begin to rise in 1–2 days and after 3 weeks signs of calcium and phosphorus mineralisation appear on X-ray.

Are there any safety issues?

Vitamin D is considered a safe supplement when used in recommended doses; however, it may interact with some other medicines.

REFERENCES

Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine 28(2): (2003) 177-9.

Andiran N, Yodam N, Ozon A. Risk factors for vitamin D deficiency in brest-fed newborns and their mothers. Nutrition 18 (2002): 47-50.

Andress DL. Vitamin D in chronic kidney disease: A systemic role for selective vitamin D receptor activation. Kidney Int 69.1 (2006): 33-43.

Arunabh S et al. Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endorinol Metab 88.1 (2003): 157-61.

Australian Drug Evaluation Committee. Prescribing Medicines in Pregnancy, 4th edn. Therapeutic Goods Administration, 1999.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Bischoff-Ferrari HA et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? Osteoporos Int 17.5 (2006): 656-63.

Boelsma E et al. Effects of calcitriol on fibroblasts derived from skin of scleroderma patients. Dermatology 191.3 (1995): 226-33.

Borissova AM et al. The effects of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 57(4) (2003): 258-61

Bouillon R et al. Ageing and calcium metabolism. Baillieres Clin Endocrinol Metab 11.2 (1997): 341-65.

Brown A et al. Vitamin D. Am J Phys 277 (1999): F157-75.

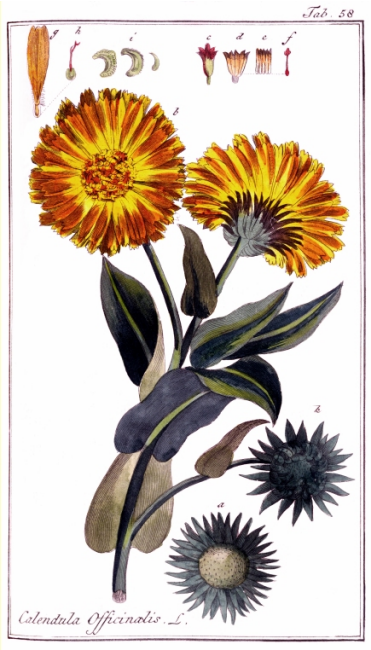
Buchman AL. Bones and Crohn's: problems and solutions. Inflamm Bowel Dis 5.3 (1999): 212-27.

Caca-Biljanovska NG et al. Treatment of generalized morphea with oral 1,25-dihydroxyvitamin D3. Adv Exp Med Biol 455 (1999): 299-304.

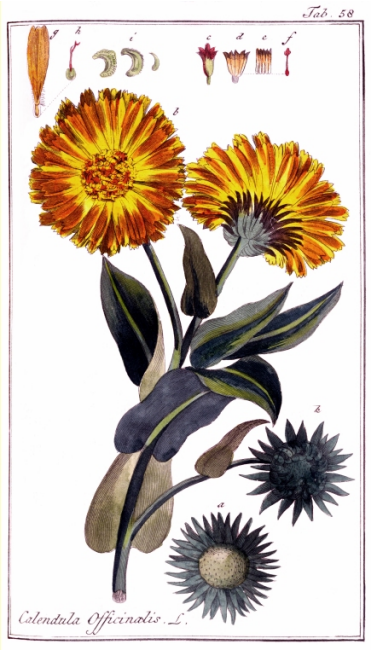
Chen TC, Holick MF. Vitamin D prostate cancer prevention and treatment. Trends Endocrinol Metabol 14.9 (2003): 423-31

Compston JE et al. Treatment of osteomalacia associated with primary biliary cirrhosis with parenteral vitamin D2 or 25-hydroxyvitamin D3. Gut 20 (1979): 133-6.
Congden PJ et al. Vitamin status in treated patients with cystic fibrosis. Arch Dis Child 56.9 (1981): 708-14.
Cosman F. The prevention and treatment of osteoporosis: a review. Med Gen Med 7.2 (2005): 73.
Deroisy R et al. Administration of a supplement containing both calcium and vitamin D is more effective than calcium alone to reduce secondary hyperparathyroidism in postmenopausal women with low 25(OH) vitamin D circulating levels. Aging Clin Exp Res 14.1 (2002): 13-17.
Food and Agriculture Organization/World Health Organization. Report of a Joint FAO/WHO Expert Consultation; Bangkok, Thailand. FAO/WHO: Rome, 2002.
Garcion E et al. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab 13.3 (2002): 100-5.
Garland CF et al. Can colon cancer incidence and death rates be reduced with calcium and vitamin D? Am J Clin Nutr 54.1 (Suppl) (1991): 193-201S.
Garland CF et al. Calcium and vitamin D: Their potential roles in colon and breast cancer prevention. Ann NY Acad Sci 889 (1999): 107-19.
Garland CF et al. An epidemiologic basis for estimating optimal vitamin D3 intake for colon cancer prevention and a public health recommendation for greater vitamin D intake. AEP 15.8 (2004): 630.
Giovannuci E. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer; a hypothesis. Cancer Causes Control 9.6 (1998): 567-82.
Gomez AC et al. Review of the concept of vitamin D 'sufficiency and insufficiency'. Nefrologia 23.2 (2003): 73-7.
Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. Prog Biophys Mol Biol 92.1 (2006): 65-79.
Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer 48.2 (2004): 115-23.
Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism. Belmont, CA: Wadsworth, 2005.
Grover SR, Morley R. Vitamin D deficiency in veiled or dark-skinned pregnant women. Med J Aust 175 (2001): 251-2.
Hanly JG et al. Hypovitaminosis D and response to supplementation in older patients with cystic fibrosis. Q J Med 56.219 (1985): 377-85.
Harkness LS, Bonny AE. Calcium and vitamin D status in adolescents: Key roles for bone, body weight, glucose tolerance and estrogen biosynthesis. J Pediatr Adolesc Gynecol 18 (2005): 305-11.
Harkness R, Bratman S. Mosby's Handbook of Drug-Herb and Drug-Supplements Interactions. St Louis: Mosby, 2003.
Hartwell D et al. Metabolism of vitamin D2 and vitamin D3 in patients on anti-convulsant therapy. Acta Neurol Scand 79.6 (1989): 487-92.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Hewison M et al. 1 alpha-hydroxylase and the action of vitamin D. J Mol Endocrinol 25 (2000): 141-8.
Hoffmann JC, Zeitz M. Treatment of Crohn's disease. Hepatogastroenterology 47.31 (2000): 90-100.
Holick MF. Vitamin D and health in the 21st century: bone and beyond: sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80.6 (2004): 1678-88S.
Holt PR et al. Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D. Cancer Epidemiol Biomarkers Prev 2002 11.1 (2002): 113-19.
Hulshof MM et al. Oral calcitriol as a new therapeutic modality for generalized morphea. Arch Dermatol 130.10 (1994): 12990-3.
Hulshof MM et al. Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. J Am Acad Dermatol 43.6 (2000): 1017-23.

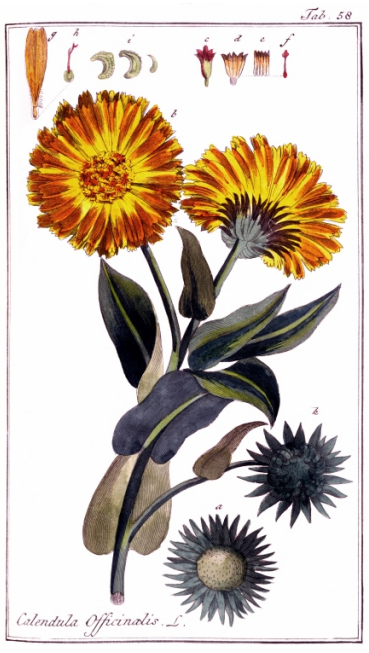
Hunter D et al. A randomized controlled trial of vitamin D supplementation on preventing postmenopausal bone loss and modifying bone metabolism using identical twin pairs. J Bone Miner Res 15(11) (2000): 2276-83.
Hypponen E et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358 (2001): 1500-3.
Jahnsen J et al. Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. Scand J Gastroenterol 37.2 (2002): 192-9.
Johnson S. Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease? Med Hypotheses 56.5 (2001): 641-5.
Kalueff AV, Tuohimaa P. Vitamin D: an antiepileptic neurosteroid hormone? Eur Neuropsychopharmacol 15 (Suppl 3) (2005): S618.
Kendell RE, Adams W. Exposure to sunlight, vitamin D and schizophrenia. Schizophrenia Res 54 (2002): 193-8.
Kim G, Sprague SM. Use of vitamin D analogs in chronic renal failure. Adv Renal Replace Ther 9.3 (2002): 175-83.
Kim JS et al. Association of vitamin D receptor gene polymorphism and Parkinson's disease in Koreans. J Korean Med Sci J 20.3 (2005): 495-8.
Klein EA. Chemoprevention of prostate cancer. Crit Rev Oncol Hematol 54 (2005): 1-10.
Klein GL et al. Hepatic dystrophy in chronic cholestasis: evidence for a multifactorial etiology. Pedriatr Transplant 6.2 (2002): 136-40.
Kohlmeier M. Nutrient Metabolism. London: Academic Press, 2003.
Kumar P, Clark M. Clinical Medicine, 5th edn. London: WB Saunders, 2002.
Latham NK et al. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. J Am Geriatr Soc 51.9 (2003): 1219-26.
Long RG, Wills MR. Hepatic osteodystrophy. Br J Hosp Med 20.3 (1978): 312-21.
Lowe C et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer 41 (2005): 1164-9.
Lyles KW et al. The efficacy of vitamin D2 and oral phosphorus therapy in X-linked hypophosphatemic rickets and osteomalacia. J Clin Endocrinol Metab 54 (1982): 307-15.
Ma JF et al. Mechanisms of decreased vitamin D 1 alpha hydrolase activity in prostate cancer cells. Mol Cell Endocrinol 221 (2004): 67-74.
Mackay-Sim A et al. Schizophrenia, vitamin D, and brain development. Int Rev Neurobiol 59 (2004): 351-80.
Mahomed K, Gulmezoglu AM. Vitamin D supplementation in pregnancy. Cochrane Database Syst Rev (2) (2000): CD000228.
Marya RK et al. Effects of vitamin D supplementation in pregnancy. Gynecol Obstet Invest 12.3 (1981): 155-61.
Marya RK et al. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Invest 24.1 (1987): 38-42.
Mathieu C, Badenhoop K. Vitamin D and type 1 diabetes mellitus: state of the art. Trends Endocrinol Metab 16.6 (2005): 262-6.
Matsuoka LY et al. Cutaneous vitamin D3 formation in progressive systemic sclerosis. J Rheumatol 18.8 (1991): 1196-8.
McGrath J. Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders? Med Hypotheses 56.3 (2001): 367-71.
McGrath J et al. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. Schizophrenia Res 63 (2003): 73-8.
McGrath JJ et al. Vitamin D3-implications for brain development. Steroid Biochem Mol Biol 89-90.1-5 (2004a): 557-60.
McGrath JJ et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophrenia Res 67 (2004b): 237-45.



McGrath JJ et al. Seasonal fluctuations in birth weight and neonatal limb length: does prenatal vitamin D influence neonatal size and shape? Early Hum Dev 81 (2005): 609-18.
Micromedex. Vitamin D. Thomson 2003. Available at: www.micromedex.com.
Miller GJ. Vitamin D and prostate cancer: Biologic interactions and clinical potentials. Cancer Metastasis Rev 17 (1999): 353-60.
Mimouni F et al. Vitamin D2 therapy of pseudohypoparathyroidism. Clin Pediatr 25 (1986): 49-52.
Nowson CA, Margerison C. Vitamin D intake and vitamin D status of Australians. Med J Aust 177.3 (2002): 149-52.
Pillow JJ et al. Vitamin D deficiency in infants and young children born to migrant parents. J Paediatr Child Health 31.3 (1995): 180-4.
Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. Endocrinol Metab Clin North Am 27.2 (1998): 389-98.
Sambrook PN, Eisman JA. Osteoporosis prevention and treatment. Med J Aust 172 (2002): 226-9.
Sambrook PN et al. Vitamin D deficiency is common in frail institutionalized older people in northern Sydney. Med J Aust 176.11 (2002): 560.
Samanek AJ et al. Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres. Med J Aust 184.7 (2006): 338-41.
Snijder MB et al. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab 91 (2006): 2980-5.
Stene LC, Joner G. Use of cod liver oil during first year of life is associated with a lower risk of childhood-onset type 1 diabetes: a large population-based, case-control study. Am J Clin Nutr 78.6 (2003): 1128-34.
Suzuki K et al. Hepatic osteodystrophy. Nippon Rinsho 56.6 (1998): 1604-8.
Swami S et al. Genistein potentiates the growth inhibitory effects of 1,25-dihydroxyvitamin D3 in DU145 prostate cancer cells: role for the direct inhibition of CYP24 enzyme activity. Mol Cell Endocrinol 241 (2005): 49-61.
Thien R et al. Interactions of 1 alpha,25-dihydroxyvitamin D3 with IL-12 and IL-4 on cytokine expression of human T lymphocytes. J Allergy Clin Immunol 116 (2005): 683-90.
Tjellesen L et al. Different actions of vitamin D2 and D3 on bone metabolism in patients treated with phenobarbitone/phenytoin. Calcif Tissues Int 37.3 (1985): 218-22.
Tjellesen L et al. Different metabolism of vitamin D2/D3 in epileptic patients treated with phenobarbitone/phenytoin. Bone 7.5 (1986): 337-42.
Wahlqvist ML (ed.). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Welsh JE et al. Vitmain D3 receptor as a target for breast cancer prevention. J Nutr 133 (2003): 2425-33S.
Wills MR, Savory J. Vitamin D metabolism and chronic liver disease. Ann Clin Lab Sci 14.3 (1984): 189-97.
Wilson JD et al. Harrison's Principles of Internal Medicine, 12th edn. New York: McGraw-Hill, 1991.
Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust 182.6 (2005): 281-5.
Yildirim B et al. The effect of postmenopausal vitamin D treatment on vaginal atrophy. Maturitas 49 (2004a): 334-7.
Yildirim B et al. Immunohistochemical detection of 1,25-dihydroxyvitamin D receptor in rat epithelium. Fertil Steril 82.6 (2004b): 1602-8.



Vitamin E



Historical note Vitamin E was first discovered in 1922 at the University of California in Berkeley when it was observed that rats required the nutrient in order to maintain their fertility. In this way, vitamin E became known as the antisterility vitamin, which is reflected in its name, as *tokos* and *pherein* are the Greek words for 'offspring' and 'to bear'. Although considered an essential nutrient, it was not until the mid-1960s that deficiency states in humans were first identified. More specifically, deficiency was detected in children with fat malabsorption syndromes.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Alpha-tocopherol is absorbed from the intestinal lumen and is dependent upon adequate fat digestion. After micellisation, it enters the lymphatic circulation and then the systemic circulation where it is transported in chylomicrons. Breakdown of chylomicrons in the blood releases some vitamin E, which is then taken up by circulating lipoproteins such as LDL and HDL. The remaining vitamin E is transported via chylomicron remnants to the liver. Here, the RRR alpha-tocopherol form is preferentially secreted back into the circulation in VLDL. It is suspected that hepatic alpha-tocopherol transfer protein is responsible for discriminating between the different types of tocopherols at this point (with the natural form preferentially taken up). Vitamin E is ultimately delivered to tissues when chylomicrons and VLDL are broken down by lipoprotein lipase. Vitamin E transported by LDL is also taken up by tissues via the LDL receptor. The bulk of vitamin E is stored in adipose tissue, although some storage also occurs in the heart, muscles, testes, uterus, adrenal and pituitary glands, and blood. Vitamin E metabolites are mainly excreted in the faeces, although some is also excreted by the kidneys and the skin (Shils et al 1999).

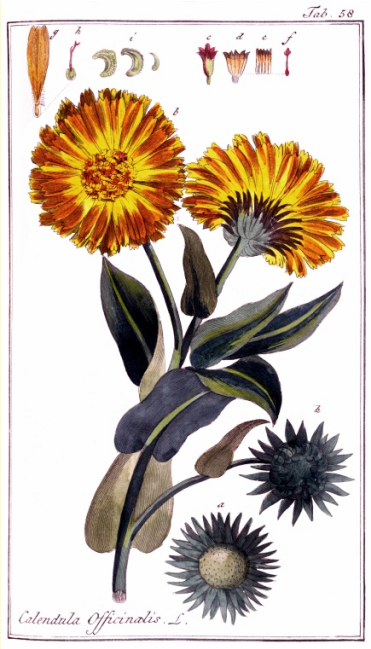
CHEMICAL COMPONENTS

To date, eight different naturally occurring compounds have been identified and named as alpha-, beta-, gamma- and delta-tocopherol and alpha-, beta-, gamma- and delta-tocotrienol. Acetate and succinate derivatives of natural and synthetic forms of vitamin E also have vitamin E-like activity, although the strength of activity varies between the different compounds and is less than the naturally occurring RRR stereoisomer D-alpha-tocopherol. The human diet generally provides a mixture of compounds with vitamin E activity.

RELATIVE STRENGTHS OF THE VARIOUS FORMS OF VITAMIN E

The relative strength of the different forms of vitamin E can be expressed as either alpha-tocopherol equivalents (alpha-TE) or international units (IU). One alpha-TE represents the activity of 1 mg RRR-alpha-tocopherol (D-alpha-tocopherol), and the alpha-TE of natural forms of vitamin E can be calculated using simple mathematics. The number of milligrams of beta-tocopherol should be multiplied by 0.5, gamma-tocopherol by 0.1, and alpha-tocotrienol by 0.3, whereas any of the synthetic all-*rac*-alpha-tocopherols (DL-alpha-tocopherol) should be multiplied by 0.74 (FAO/WHO 2002).

More commonly, activity is described in terms of International Units (IU) where 1 mg of synthetic all-*rac*-alpha-tocopherol (DL-alpha-tocopherol) acetate is equivalent to 1 IU of vitamin E. Relative to this, 1 mg of DL-alpha-tocopherol is equal to 1.1 IU, 1 mg of D-alpha-tocopheryl acid succinate is equal to 1.21 IU and 1 mg of D-alpha-tocopheryl acetate is equal to 1.36 IU. The natural form of D-alpha-tocopherol has the highest biopotency, which is equal to at least 1.49 IU (Meydani & Hayes 2003).



FOOD SOURCES

Vitamin E is found in various forms in both animal and plant foods. The richest food sources of vitamin E are cold pressed vegetable oils, particularly wheatgerm oil, nuts and seeds. Other sources include spinach, kale, sweet potatoes, yams, egg yolk, liver, soya beans, asparagus and dairy products such as butter and milk. Frying, processing, bleaching, milling and freezing foods will remove some of the vitamin E content. Overall, up to 55% can be lost through cooking (Wahlqvist et al 2002).

DEFICIENCY SIGNS AND SYMPTOMS

Due to the widespread availability of vitamin E in the food chain, it is generally accepted that primary vitamin E deficiency does not occur. However, deficiency has been reported in low birth weight infants given infant formula or cows' milk with low vitamin E levels, and in some intestinal malabsorption syndromes such as cystic fibrosis. Genetic abnormalities in alpha-tocopherol transport protein also result in vitamin E deficiency (Shils et al 1999).

Ultimately, it is tissue uptake, local oxidative stress levels and polyunsaturated fat content that influence whether symptoms of deficiency develop.

Symptoms of deficiency tend to be vague and difficult to diagnose due to the nutrient's widespread actions, but the following signs and symptoms have been reported in humans (FAO/WHO 2002, Meydani & Hayes 2003).

- Haemolytic anaemia.
- Immunological abnormalities.

- Neurological disturbances (e.g. peripheral neuropathies).
- Platelet dysfunction.
- Leakage of muscle enzymes such as creatine kinase and pyruvate kinase into plasma.
- Increased levels of lipid peroxidation products in plasma.

MAIN ACTIONS

Vitamin E is an electron donor (reducing agent or antioxidant), and many of its biochemical and molecular functions can be accounted for by this function. It is involved in many biochemical processes in the body, but its most important biological function is that of an antioxidant and working within the antioxidant network.

ANTIOXIDANT

Vitamin E is considered to be the most important and potent lipid-soluble antioxidant. It prevents free radical damage to the PUFAs within the phospholipid layer of each cell membrane and oxidation of LDL. It has been estimated that for every 1000–2000 molecules of phospholipid, one molecule of vitamin E is present for antioxidant defence (Sen & Packer 2000).

This is achieved by reacting with free radical molecules and forming a tocopheroxyl radical, which then leaves the cell membrane. Upon entering the aqueous environment outside the membrane, it reacts with vitamin C (or other hydrogen donors such as glutathione) to become reduced and, therefore, regenerated (Vatassery 1987). In this way, vitamin E activity is influenced by what has been called the 'antioxidant network', which restores vitamin E to its unoxidised state, ready to act as an antioxidant many times over (see Clinical note below for more information).

Taking a larger perspective, the collective antioxidant action at each cell membrane protects the body's tissues and organs from undue oxidative stress. Prolonged and/or excessive exposure to free radicals has been implicated in many conditions, such as cardiovascular disease, cancer initiation and promotion, degenerative diseases, and ageing in general (FAO/WHO 2002).

Clinical note — Free radicals, antioxidant recycling and the antioxidant network

Oxygen-containing free radicals (such as the hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet and nitric oxide radical) are highly reactive species, capable of damaging biologically important molecules such as

DNA, proteins, carbohydrates and lipids. Antioxidants can break the destructive cascade of reactions initiated by free radicals by converting them into harmless derivatives.

The term 'oxidative stress' refers to an imbalance of free radicals over antioxidants. Both endogenous and exogenous antioxidants work in a synergistic way to avoid this situation, but antioxidants such as vitamin E become oxidised themselves during this process. Other antioxidants, such as ubiquinone, ascorbate and glutathione, are then involved in recycling vitamin E back to its unoxidised state, allowing it to continue neutralising free radical molecules (Sen & Packer 2000). When these other antioxidants become oxidised in turn, they are also regenerated to their antioxidant forms by yet others such as alpha-lipoic acid and cysteine. In this way, the recycling of various antioxidants occurs in an orchestrated manner.

In the body, the antioxidant network comprises four parts that work together to provide a continuous defence against free radical damage (De Vita et al 2006).

- Enzymes that destroy or detoxify common oxidants (e.g. catalase, glutathione peroxidase, which needs selenium).
- Antioxidant vitamins, notably vitamins E and C, and coenzyme Q10, which are continuously recycled, as discussed earlier.
- Dietary antioxidants or phytochemicals (e.g. carotenoids, polyphenols and allyl sulfides).
- Proteins that sequester iron and copper so that free forms do not exist in the body.

The antioxidant network provides a basis for recommending combinations of foods and antioxidant nutrients to provide maximal benefits rather than single entities in high doses.

REGULATES IMMUNOCOMPETENCE

Vitamin E increases humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T-lymphocyte response, TNF production, and NK cell activity, thereby playing a role in immunocompetence. It also decreases PGE_2 production and therefore reduces its immunosuppressive effects and decreases levels of lipid peroxides that can also adversely affect immune function (Meydani 1995).

OTHER ACTIONS

- Regulates vascular smooth muscle cell proliferation.
- Inhibits smooth muscle cell proliferation by inhibiting protein kinase C activity.
- Inhibits phopholipase A2 activity, suppressing arachidonic acid metabolism.

- Antiplatelet activity: demonstrated in vitro, but in vivo tests have been inconsistent for D-alpha-tocopherol.
- Modulates vascular function by regulating the enzymatic activities of endothelial nitric oxide synthase (eNOS) and NAD(P)H oxidase (Ulker et al 2003).
- Analgesic activity: most likely mediated via effects on COX-2 and 5-lipooxygenase.
- Promotes wound healing.
- Influences signal transduction pathways and participates in the synthesis pathways of neurotransmitters.
- Exerts neuroprotective effects.
- Modulates the expression of genes that are involved in atherosclerosis (e.g. scavenger receptors, integrins, selectins, cytokines, cyclins) (Munteanu et al 2004).

CLINICAL USE

Although vitamin E supplementation is used to correct or prevent deficiency states, most uses are based on the concept of high-dose supplements acting as therapeutic agents to either prevent or treat various health conditions.

DEFICIENCY: PREVENTION AND TREATMENT

Traditionally, vitamin E supplementation has been used to treat deficiency or prevent deficiency in conditions such as genetic abnormalities with alpha-tocopherol transfer protein, apolipoprotein B, or microsomal triglyceride transfer protein (Shils et al 1999); and fat malabsorption syndromes (e.g. chronic cholestasis, cystic fibrosis, short bowel syndromes such as Crohn's disease, chronic steatorrhea, coeliac disease, chronic pancreatitis and TPN).

CARDIOVASCULAR DISEASE

Vitamin E is most well known for its effects on the cardiovascular system, as it inhibits platelet aggregation and adhesion, smooth muscle cell proliferation, has an anti-inflammatory effect on monocytes, improves endothelial function and decreases lipid peroxidation (Kaul et al 2001). It also modulates the expression of genes that are involved in atherosclerosis (e.g. scavenger receptors, integrins, selectins, cytokines, cyclins) (Munteanu et al 2004). Its ability to reduce oxidative stress both directly and indirectly as part of the antioxidant network is of particular importance because oxidation of LDL is a key process in atherogenesis, enhancing foam cell and early lesion formation (Terentis et al 2002).

As such, much investigation is being undertaken to determine whether it has a role in the primary and/or secondary prevention of cardiovascular disease.

Epidemiological and clinical studies In 1946 Canadian physicians first reported that vitamin E could protect against coronary heart disease; however, it was not until

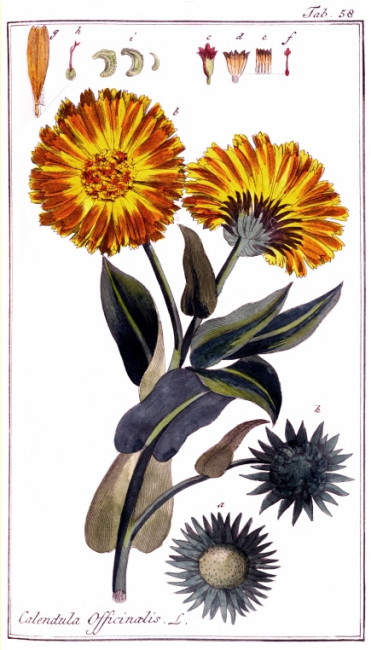
the results of two very large human studies were published nearly 50 years later that the greater scientific community and the public started to take note of vitamin E. In 1993, the prospective Nurses' Health Study and the Health Professionals Follow-up study both reported that vitamin E supplementation at a dose of at least 100 IU for at least 2 years significantly reduced the risk of coronary disease compared with non-users by an estimated 40% (Rimm et al 1993, Stampfer et al 1993).

The prospective Nurses Health Study followed 87,245 women aged 34–59 years without known coronary disease over 8 years and identified that those women with the highest intake of vitamin E had the lowest relative risk of non-fatal myocardial infarction (MI) or death from coronary disease compared with those with the lowest intake (Stampfer et al 1993). Interestingly, short-term use or dietary intake alone did not produce the same significant reduction. The Health Professionals Follow-up study observed 39,910 men aged between 40 and 75 years over 4 years and produced similar results, finding that long-term vitamin E (at least 100 IU/day) significantly reduced the relative risk of coronary disease compared with non-users (Rimm et al 1993).

Subsequently, a double-blind study conducted at Cambridge University and published in 1996 supported these results, but further suggested that higher doses could produce benefits more quickly and more dramatically (Stephens et al 1996). The placebo-controlled randomised study involved 2002 patients with angiographically proven coronary atherosclerosis and compared the effects of two different strengths of alpha-tocopherol supplementation (400 IU and 800 IU) and placebo over a median of 510 days. Treatment with either dose of vitamin E was seen to reduce the risk of cardiovascular death and non-fatal MI by over 75% with effects established after 12 months.

Since these early studies were published, newer intervention studies using vitamin E as a sole agent or in combination with other antioxidants have generally produced negative results; however, a number of important factors could account for some of the inconsistent results (see Clinical note below).

In 1999, results from the large GISSI trial were published, which produced conflicting results. The trial, involving 11,324 patients who had recently survived a MI (<3 months) investigated the effects of three different treatment protocols with placebo: 1 g omega-3 fatty acid/day, 300 IU synthetic vitamin E/day, fish oils plus vitamin E/day, or placebo. The four groups were observed for nearly 4 years for cardiovascular disease morbidity and mortality. Results showed that the fish oil treatment groups had significantly decreased combined end-points of death, non-fatal MI and stroke over this time, whereas the vitamin E treatment produced little



effect. The trial has since been criticised because the form of vitamin E used was synthetic, the dose used was relatively low compared with other studies involving patients with pre-existing disease. Subgroup analysis of cardiovascular deaths ultimately did detect a protective effect for vitamin E that was similar to the fish oil treatment.

The Heart Outcomes Prevention Evaluation (HOPE) study observed the effects of natural vitamin E 400 IU/day, the drug ramipril or placebo over 4.5 years in 9541 subjects (>55 years old) who were considered a high-risk group for cardiovascular events (Yusuf et al 2000).This study failed to detect a protective effect for vitamin E supplementation on the primary outcome, which was a composite end-point of MI, stroke, and death from cardiovascular disease. The study was extended for a mean of 7 additional years and renamed the HOPE-TOO study, which involved 3994 of the original subjects (Lonn et al 2005). Natural vitamin E (400 IU/day) failed to reduce the incidence of major cardiovascular events and there was suggestion it may increase the rate of heart failure.

The MRC/BHF study of 20,536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes found that a daily antioxidant supplement containing 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene produced no significant differences in all-cause mortality, or in deaths due to vascular or non-vascular causes (Parkinson Study Group 2002). Additionally, no significant differences in the numbers of participants having non-fatal MI or coronary death, non-fatal or fatal stroke or coronary or non-coronary revascularisation were observed.

A low-dose study investigating the effects of synthetic alpha-tocopherol at a dose of 50 mg/day failed to detect a significant protective effect against coronary disease (Virtamo et al 1998). The Alpha-Tocopherol Beta-carotene Cancer (ATBC) Prevention Study found that treatment with low-dose vitamin E produced a non-significant reduction of 8% on the incidence of fatal coronary disease in smokers ($n = 27,271$) but had no influence over non-fatal MI (Virtamo et al 1998). The population studied were Finnish male smokers aged 50–69 years with no history of MI.

In the Primary Prevention Project (PPP), 100 mg/day of aspirin or 300 mg/day of all-*rac*-alpha-tocopherol was investigated in 4495 people with hypertension, hypercholesterolaemia, diabetes, obesity, family history of premature MI, or the elderly (de Gaetano 2001). The study had a mean follow-up period of 3.6 years. Vitamin E had no significant effect on cardiovascular death, non-fatal MI, or non-fatal stroke; however, a significant 46% reduction in the incidence of peripheral artery disease was reported. The authors pointed out that the findings for vitamin E could

be regarded as a false-negative result because of the inadequate power of the prematurely interrupted trial.

Most recently, data from a major randomised study involving 39,876 healthy women of at least 45 years of age from the Women's Health Study found that long-term use of natural vitamin E (600 IU) taken on alternate days provided no overall benefit for major cardiovascular events (Lee et al 2005).

Alternatively, the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial demonstrated a striking 50% reduction in cardiac events in renal failure patients with established disease receiving 800 IU/day vitamin E (Boaz et al 2000). It is thought that the SPACE trial produced positive results because the dose was comparable to that used in the CHAOS study and it involved a population known to be under increased oxidative stress.

Clinical note — Confusing results for vitamin E

To date, many in vitro, animal and epidemiological studies support the use of vitamin E in the prevention of cardiovascular disease (Clarke & Armitage 2002). However, intervention studies are equivocal. Many factors could account for the lack of benefit on the primary end-point in the majority of trials.

1. Dose selection

A closer look at the evidence shows that dose selection varies enormously from levels just above the RDI (50 mg/day) to large doses of 800 IU/day. Clinical research shows that a daily dose of at least 400 IU is required for LDL to become less susceptible to oxidation (Brockes et al 2003) and an effective threshold dose may be as high as 800 IU/day (Jialal & Devaraj 2005a).

2. Measurement of biomarkers of oxidative stress

Just as the statin trials investigate subjects with high cholesterol levels rather than the general population, it can be reasonably assumed that antioxidant treatment is best suited to those people with increased oxidative stress rather then the general population, yet researchers consistently fail to consider this as a biochemical basis for patient inclusion (Meagher 2003). The levels of oxidised amino acids in urine and plasma can reflect those in tissues and identify people with high levels of oxidative stress and may be one method of subject selection (Heinecke 2002).

3. Type of vitamin E supplement

In the specific case of vitamin E, the form of tocopherol used is crucial, as synthetic forms have less biological activity than RRR D-alpha-tocopherol. According to a 2002 FAO/WHO report, cross-country correlations between coronary heart disease mortality in men and the supply of vitamin E homologues across 24

European countries shows a highly significant ($P < 0.001$) correlation for D-alpha-tocopherol, whereas all other forms of vitamin E do not achieve statistical significance.

In the past few years, it has further been proposed that the lack of efficacy of commercial tocopherol preparations in some clinical trials may be due to the absence of other natural tocopherols, primarily gamma- and delta-tocopherol. Preliminary studies provide some support for this view (Jialal & Devaraj 2005a, Saldeen & Saldeen 2005). Studies using different mixtures of alpha-, beta-, gamma- and delta-tocopherol have found that a mixture of gamma-, delta- and alpha-tocopherol with the ratio of 5:2:1 had a much better antioxidant effect than alpha-tocopherol alone. This mixture is similar to that found in nature. In human and animal studies, the mixed tocopherol preparation also had much more favourable effects on constitutive NO synthase (ecNOS) and superoxide dismutase activity than alpha-tocopherol and in a rat model was more effective in decreasing platelet aggregation and inhibiting thrombus formation. Mixed tocopherol preparation is also superior to alpha-tocopherol in terms of myocyte protection (Chen et al 2002).

4. Plasma vitamin E levels

The measurement of plasma vitamin E levels in the supplemented groups has been inconsistent in the studies, so it is uncertain whether levels significantly rose in response to treatment and subjects were compliant. For example, in the CHAOS, ASAP, ASAP follow-up and SPACE studies a significant increase in the plasma antioxidant levels was reported and all studies found a benefit on the primary end-point whereas measurement of plasma levels has been inconsistent in the negative studies (Jialal & Devaraj 2005a).

Clearly, the optimal form/s, dosage regimen, duration of use and subpopulation best suited to preventive treatment still needs to be clarified with future trials.

Slowing carotid atherosclerosis The ASAP study was a placebo-controlled, randomised study comparing the effects of vitamin E (136 IU twice daily) and/or slow release vitamin C (250 mg twice daily) on the 3-year progression of carotid artery disease in hypercholesterolaemic subjects ($n = 502$) (Salonen et al 2000). Combination treatment had the strongest effects and resulted in an average increase in common carotid artery intima–media thickness (IMT) of only 0.011 mm/year in men compared to 0.018 mm/year for vitamin E only, 0.017 mm/year for vitamin C only and 0.02 mm/year for placebo. The covariate-adjusted IMT increase in men was 45% less with both vitamins compared with placebo ($P = 0.049$), with the treatment effect being largest in smoking men (64% less) than in non-smoking men (30% less). This

suggests a synergistic effect when vitamins C and E are combined. Interestingly, no significant differences were observed in women.

A follow-up to the ASAP study was reported (Salonen et al 2003). It involved 440 of the original subjects and this time only used the combination of vitamin E (272 IU/day) and ascorbic acid (500 mg/day). Once again, a significant decrease in the rate of progression of carotid IMT was seen, with combination treatment compared with placebo. Those subjects with low baseline plasma vitamin C or common carotid artery plaque experienced the greatest effects. Just as reported in the original study, the effect was restricted to males only. It is worthwhile noting that both ASAP studies were of populations at high risk for oxidative stress, biomarkers of oxidative stress were measured and plasma levels of vitamins E and C were significantly increased with their respective treatments.

Restenosis Restenosis is a major limitation to the long-term success of angioplasty. Therefore, measures that prevent or delay this occurrence are being investigated to extend the beneficial effects of the procedure.

Studies in experimental models have identified vitamin E as helping to stabilise atherosclerotic plaque after angioplasty and favouring vascular remodelling, thereby suggesting it may be of benefit in preventing or slowing restenosis (Orbe et al 2003). An early double-blind study using oral synthetic vitamin E (1200 IU) for 4 months found that treatment did not significantly reduce the rate of restenosis after percutanous transluminal coronary angioplasty; however, a minor reduction was detected (DeMaio et al 1992).

Angina pectoris Low-dose vitamin E supplements (50 mg/day) produce a minor decrease in the incidence of angina pectoris in smokers without previous coronary heart disease according to a RCT (Rapola et al 1996). A smaller study of 29 subjects with variant angina identified six patients who did not respond to calcium-channel blockers and had lower plasma levels than normal, who responded positively to supplementation with 300 mg/day. Treatment resulted in significantly reduced incidence of angina episodes (Miwa et al 1996). Several years later, the same research group identified a transcardiac reduction in plasma vitamin E concentrations concomitant with lipid peroxide formation, suggesting that oxidative stress and vitamin E depletion may be involved in the pathogenesis of coronary artery spasm (Miwa et al 1999).

Nitrate tolerance Vitamin E supplements (200 mg three times daily) prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (NTG 10 mg/24 hours) according to one randomised, placebo-controlled study in which 24 patients with ischaemic heart disease were compared with 24 healthy volunteers over

a 6-day period (Watanabe et al 1997). New research indicates that continuous NTG infusion causes vitamin E depletion, as well as nitrate tolerance, and as the vitamin E levels continue to fall, NTG tolerance becomes greater (Minamiyama et al 2006).

Hypertension Vitamin E supplementation may reduce blood pressure, LDL oxidation and improve endothelial dysfunction in hypertension, according to current research.

An early double-blind, placebo-controlled study found that DL-alpha-tocopherol nicotinate (3000 mg) significantly reduced SBP pressure from 151.0 to 139.2 mmHg within 4–6 weeks in hypertensive subjects; however, DBP remain unchanged (Iino et al 1977). More recently, long-term vitamin E (200 IU/day) was shown to decrease SBP by 24% compared with a 1.6% reduction with placebo in mildly hypertensive patients, according to a triple-blind placebo-controlled study conducted over 27 weeks (Boshtam et al 2002). The study involved 70 hypertensive patients (SBP 140–160 mmHg; DBP 90–100 mmHg) aged 20–60 years without other cardiovascular risk factors. Besides reducing SBP, DBP was reduced by 12.5% compared with 6.2% with placebo.

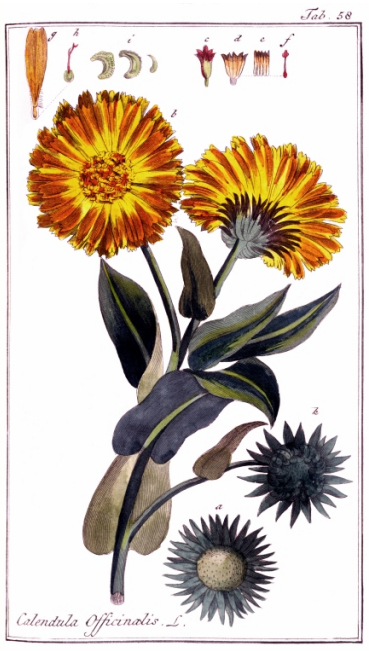
Some studies have revealed that hypertensive patients have a higher susceptibility to LDL oxidation than normotensive subjects and, therefore, increased atherogenic potential. One study measured the effect of vitamin E (400 IU/day) on the resistance of LDL to oxidation in 47 volunteers (Brockes et al 2003). Comparisons made before and after 2 months' supplementation showed that vitamin E caused a significant increase in the lag time in normotensive and hypertensive patients, ultimately bringing hypertensive patients up to the same point as the healthy controls.

Research with experimental models shows that vitamin E modulates vascular function by regulating enzymatic activities of eNOS and NAD(P)H oxidase and, therefore, may also have a role in normalising genetic endothelial dysfunction in genetic hypertension (Ilker et al 2003).

Clinical note — LDL oxidation and vitamin E

Oxidative stress affects lipid metabolism by producing an oxidised LDL that has greater atherogenic potential than its original form. In the past attention focussed was on investigating various antioxidants, such as vitamin E, for their ability to prevent LDL oxidation. In recent years, researchers have started to focus on identifying the biological oxidants responsible for initiating oxidation of LDL within the human arterial wall and better understand what makes oxidised LDL pro-atherogenic. In 2003, in vitro testing with LDL discovered that myeloperoxidase is a pathway that promotes LDL oxidation in the human artery wall, although others are also likely to exist. It is noteworthy that vitamin E failed to inhibit LDL oxidation by

myeloperoxidase in vitro (Heinecke 2003), although it does reduce LDL oxidation within animals and humans when given in doses well above RDI (Brockes et al 2003). If further testing confirms these results, it may mean that vitamin E reduces LDL oxidation in vivo, mainly through its role in the antioxidant network. In other words, its ability to regenerate antioxidants such as vitamin C, coenzyme Q10 and selenium may be more important than its direct antioxidant action.



ALL-CAUSE MORTALITY

In 2005, a meta-analysis of the dose–response relationship between vitamin E supplementation and total mortality was undertaken using data from 19 RCTs consisting of a large study population ($n = 135,967$) (Miller III et al 2005). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality. The authors suggested caution with doses of 400 IU/day or higher while acknowledging that the high-dose studies (≥400 IU/day) analysed in the report were often small and performed in patients with chronic diseases.

This meta-analysis has several serious flaws and has been criticised on a number of accounts, inspiring over 40 letters to the journal's Editor and hundreds of emails and phone calls to the authors (Jialal & Devaraj 2005b). In summary, these responses centre on six major flaws. First, results from 12 clinical studies that reported fewer than 10 deaths each were excluded from the meta-analysis, which created the appearance of bias and would have given an artificial weight to studies in which more people died. Second, the meta-analysis included trials of different designs, treatment times, doses, combinations and end-points. Pooling information together from such heterogeneous studies was considered inappropriate. Third, subjects in many studies had significant chronic diseases, such as Parkinson's disease, end-stage renal disease, coronary artery disease, diabetes mellitus and Alzheimer's dementia, which would have influenced their mortality risk. It also means the results do not necessarily apply to healthy adults taking these supplements. Next, studies used different forms of vitamin E (natural and synthetic) and sometimes used it in combination with other nutrients; however, results of all these studies were pooled and not separated. Furthermore, subject adherence to the treatment protocol was only considered in one study (the CHAOS study). Lastly, the use of some statistical models has been questioned.

ALZHEIMER'S DEMENTIA AND COGNITIVE DECLINE

The current standard of care for pharmacological management of the cognitive and functional disabilities of Alzheimer's dementia (AD) consists of the combination of a

cholinesterase inhibitor and high-dose vitamin E (Bonner & Peskind 2002). The inclusion of vitamin E is largely based on a 1997 double-blind study that compared a large dose of synthetic vitamin E (1000 IU twice daily) with selegiline (5 mg twice daily) and placebo in a group of patients with moderately severe AD. The 2-year study found that vitamin E significantly slowed down the progression of the disease, delayed institutionalisation and increased survival rate (Sano et al 1997).

Since the 1997 study, numerous dietary and intervention studies have sought to clarify whether vitamin E is protective against the development of various forms of dementia or can slow its progression.

Prevention Higher plasma vitamin E levels are associated with a significantly reduced risk of cognitive impairment and dementia in older adults. Protection is most consistently seen with vitamin E from food sources, but not always from vitamin E supplements (Cherubini et al 2005, Engelhart et al 2002, Morris et al 2005). According to one study, for every 5 mg/day increase in vitamin E intake, a significant 26% reduction in risk is possible (Morris et al 2005). It now appears that alpha-tocopherol is not the only form of vitamin E exhibiting protective effects. A comparison between the four different tocopherols found naturally in food identified that gamma-tocopherol was also beneficial.

Interventions studies using supplements have produced mixed results and only focus on alpha-tocopherol. The Cache County Study was a large study of 4740 people aged 65 years or older that found a combination of vitamins E (400 IU/day) and C (500 mg/day) taken for at least 3 years was associated with a reduced incidence of AD (Zandi et al 2004). No protective effects were seen when vitamin E or C was taken alone. In the Honolulu-Asia Aging Study, long-term use of vitamin E and C supplements was associated with an 88% reduction in the frequency of subsequent vascular dementia and appeared to improve cognitive function in later life; however, a protective effect against AD was not observed (Masaki et al 2000). A lack of association between dietary or supplemental vitamin E and risk of AD in elderly subjects was also found in the Washington Heights-Inwood Columbia Aging Project (WHICAP), which involved 980 older subjects (Luchsinger et al 2003). It must be noted that dietary intakes were assessed in this study with a limited food frequency questionnaire, which is likely to be less accurate than the more detailed surveys used in some other studies.

Slowing progression In contrast to the positive 1997 study, a more recent study involving 769 subjects with possible or probable AD using the same dose, found no significant effects in patients with mild cognitive impairment and no change to the rate of progression to AD over a 3-year period (Petersen et al 2005).

ENHANCES IMMUNITY IN THE ELDERLY

Immune cell function is influenced by the oxidant and antioxidant balance, so antioxidant supplements have been investigated clinically for their ability to enhance immune responses (Meydani et al 1998). Increased markers of T-cell-mediated immunity were enhanced with all doses of synthetic vitamin E tested, according to a randomised, double-blind study of 78 healthy elderly subjects. Doses used were 60, 200 and 800 mg/day for 4 months, with best overall responses obtained with the 200 mg dosage (Meydani et al 1997). Another double-blind study found no significant changes to either cellular or humoral immune responses with a low dose of 100 mg/day of synthetic vitamin E taken over 3 months (de Waart et al 1997).

HAEMODIALYSIS

Vitamin E supplementation may offer several benefits to patients on haemodialysis (HD), who typically experience high levels of oxidative stress, as there is some evidence that supplementation reduces oxidative stress and LDL oxidability in this population (Badiou et al 2003, Diepeveen et al 2005, Giray et al 2003, Galli et al 2001).

Haemodialysis patients also experience cramps, which appeared to respond to vitamin E supplementation according to a placebo-controlled, double-blind study of 60 subjects (Khajehdehi et al 2001). Treatment with vitamin E 400 mg/day for 8 weeks resulted in a 54% reduction in cramps, which increased to a 97% reduction when combined with vitamin C (250 mg/day). The benefits were not significantly associated with age, sex, aetiology of end-stage renal disease, serum electrolytes or HD duration, but showed a positive correlation ($P = 0.01$) with the type of therapy used.

According to one small study, vitamin E supplementation (500 mg/day) allowed for a reduction in erythropoietin dose (from 93 to 74 U/kg/week) while maintaining stable haemoglobin concentrations (Cristol et al 1997).

PREMENSTRUAL SYNDROME

Treatment with D-alpha-tocopherol (400 IU/day) over three menstrual cycles significantly alleviated some affective and physical symptoms of PMS according to one randomised double-blind study (London et al 1987). Symptoms of anxiety, food craving and depression responded to active treatment, whereas effects on other measured parameters such as weight gain were not significant.

A further study of 75 women with benign breast disease found that D-alpha-tocopherol (150–600 IU/day) significantly decreased some symptoms of PMS compared with placebo; however, the study involved subjective patient evaluation, which may have influenced the findings (London et al 1983).

INTERMITTENT CLAUDICATION

A Cochrane review of five placebo-controlled studies including a total of 265 volunteers (average age 57 years) concluded that although further research is required to determine its effectiveness, vitamin E may have beneficial effects in intermittent claudication with no serious side-effects (Kleijnen & Mackerras 2000). Treatment duration varied from 12 weeks to 18 months and dosage regimens varied between the studies, which were considered generally small and of poor quality. A closer look at the evidence suggests that doses of at least 600 IU/day for a minimum of 12 weeks are required.

More recently, a randomised, double-blind study found no benefits with vitamin E (400 IU/day) on perceived pain or treadmill walking duration in people with claudication (Collins et al 2003).

A small study of 16 patients with stable claudication revealed that administration of vitamin E (200 mg/day) and vitamin C (500 mg/day) for 4 weeks reduces oxidative stress in this population and therefore may also have an effect on the remote ischaemia–reperfusion damage (Wijnen et al 2001).

CANCER

Most of the epidemiological evidence suggests that vitamin E and other antioxidants decrease the incidence of certain cancers. Based on these observations, numerous prospective and intervention studies have been conducted in various populations. Very often, vitamin E is used in combination with other antioxidant nutrients and sometimes the form of tocopherol administered is not stated, thereby making it difficult to interpret study findings.

A review that systematically evaluated the scientific literature using guidelines developed by the US Preventative Services Task Force concluded that there is evidence to suggest that those individuals with higher serum vitamin E levels or receiving vitamin E supplementation have a decreased risk of some cancers, including lung, prostate, stomach and gastrointestinal carcinoma (Sung et al 2003). As can be expected, study design, differing treatment dose (nutritional levels or higher), form of vitamin used and population studied (general or high risk) had an influence on outcomes.

Mixed results have been obtained for vitamin E and primary prevention of breast cancer, although a recent study has detected a modest protective effect against recurrence of breast cancer and disease-related mortality in postmenopausal women previously diagnosed with the disease (Fleischauer et al 2001). Protective effects were established after 3 years' use, according to the study.

Vitamin E supplements were protective against the incidence of ovarian cancer whereas consumption of antioxidants from diet was unrelated to risk according to another study (Fleischauer et al 2001). In analyses combining antioxidant intake from diet and supplements, vitamins C (>363 mg/day) and E (>75 mg/day) were associated with significant protective effects.

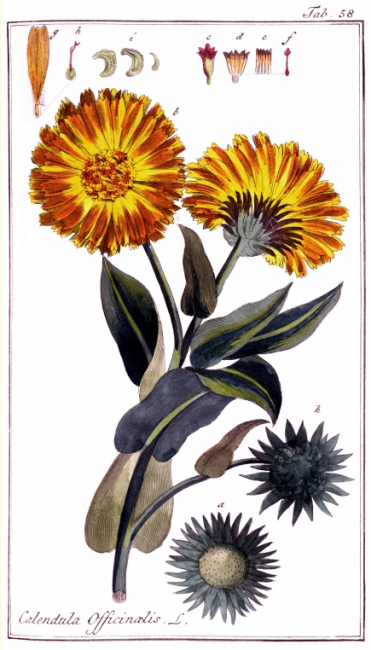
Studies investigating the association between vitamin E and incidence of colorectal cancer have produced inconsistent results. Prospective studies have shown that high serum levels of vitamin E are protective; however, only one of three intervention studies has produced positive results (Stone & Papas 1997). These results are difficult to interpret, as the studies have been criticised for not adequately distinguishing between cancer incidence and adenoma recurrence.

ATBC study One of the largest intervention studies to be published in recent years was the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study. It was a double-blind placebo-controlled trial of 29,133 male cigarette smokers aged 50–69 years. Participants were randomly assigned to four groups and received synthetic alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or a placebo daily for 5–8 years (Albanes et al 2000).

One of the most striking outcomes was a 34% decrease in the incidence of prostate cancer for volunteers receiving vitamin E ($n = 14{,}564$) compared with those not receiving it ($n = 14{,}569$) and a 41% reduction in mortality. Neither agent had any effect on the time interval between diagnosis and death (Heinonen et al 1998). A later study identified a decrease in serum androgen concentrations associated with long-term alpha-tocopherol supplementation, suggesting this may be one of the factors contributing to the observed reduction in incidence and mortality of prostate cancer (Hartman et al 2001).

The ATBC study also detected a somewhat lower incidence of colorectal cancer in the alpha-tocopherol arm compared with the no alpha-tocopherol arm, but this was not statistically significant. Neither treatment had a statistically significant effect on the rate of incidence of pancreatic carcinoma or the rate of mortality caused by this disease (Rautalahti et al 1999), the occurrence of neoplastic changes in cases of atrophic gastritis (Varis et al 1998), incidence of urinary tract cancers (Virtamo et al 2000) in this population.

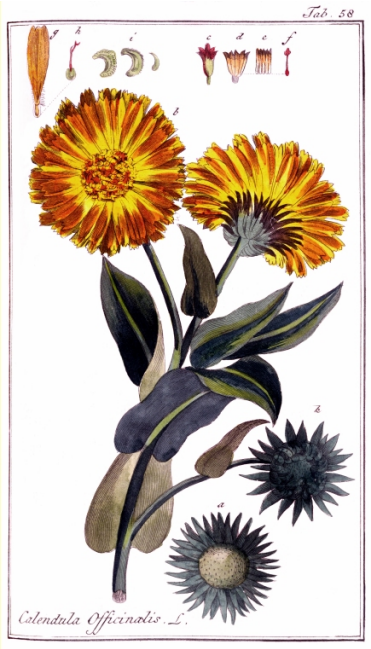
All cancers A large study of nearly 30,000 subjects was carried out in Linxian, China. It tested four combinations of vitamins and minerals (retinol and zinc, riboflavin and niacin, vitamin C and molybdenum and beta-carotene, vitamin E and selenium) over a 5-year period in a population with a persistently low intake of several micronutrients (Blot et al 1995). Although no statistically significant effect on cancer



incidence was achieved by any intervention, secondary analysis showed that the combination of selenium, beta-carotene and alpha-tocopherol was associated with a statistically significant lower total mortality rate, a 13% reduction (borderline significant) in total cancer mortality rate and a statistically significant lower mortality rate from stomach cancer (a major cancer in Linxian).

More recently three large studies have found no protective effect against cancer incidence for vitamin E supplementation. The MRC/BHF study of 20,536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes found that a daily antioxidant supplement containing 600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene produced no significant reduction in the incidence of cancer or in all-cause mortality (Parkinson Study Group 2002). The HOPE-TOO study, which used long-term natural vitamin E (400 IU/day) as a stand-alone supplement, failed to find a protective effect against cancer incidence or cancer deaths in people with pre-existing vascular disease or diabetes mellitus (Lonn et al 2005). Long-term use of natural vitamin E (600 IU) taken on alternate days provided no overall benefit for cancer incidence or total mortality in a large randomised study involving 39,876 healthy women of at least 45 years of age (Lee et al 2005).

Currently, the National Cancer Institute is conducting phase I, II and III chemoprevention trials for prostate, breast and colon cancers with vitamin E and the following micronutrients: isoflavones, lycopene, selenised yeast, selenomethionine, selenium, perillyl alcohol, folic acid, vitamin D, calcium, and curcumin. It is suspected that the response to micronutrients may vary not only in magnitude but also in direction (Greenwald et al 2002).



ARTHRITIS

High-dose vitamin E supplements may be effective in relieving pain in OA and RA, according to several double-blind studies, with some studies finding the effects are as strong as with diclofenac.

Osteoarthritis According to an early crossover study (Machtey & Ouaknine 1978), 52% of OA patients experienced less pain when treated with vitamin E (600 mg/day) compared with placebo. Several years later, a double-blind randomised study of 50 volunteers with OA confirmed these findings and showed that vitamin E (400 IU/day) was significantly superior to placebo in relieving pain, increasing mobility and reducing analgesic requirements (Blankenhorn 1986). Symptoms of pain at rest, during movement or with applied pressure all responded to treatment with vitamin E.

Vitamin E supplementation (500 IU/day) did not alter the loss of cartilage volume in knee OA according to a 2-year, double-blind, randomised placebo-controlled study of 138 patients (American College of Rheumatology clinical and radiographic criteria)

(Wluka et al 2002). Additionally, symptoms did not improve. Vitamin E also failed to alleviate symptoms in a shorter, 6-month double-blind study using the same dose (Brand et al 2001) and symptoms of pain, stiffness and function did not change at the 1, 3 or 6 month assessments.

Comparisons with diclofenac Scherak et al (1990) found that high-dose vitamin E (1200 mg/day) was as effective as diclofenac (150 mg/day) in improving swelling, walking ability and range of motion in patients with knee or hip OA under double-blind test conditions. Some 77% of patients experienced reduced or abolished pain with vitamin E, 67% had reduced pain on pressure and 62% had reduced pain on movement, which was considered as effective as diclofenac. Vitamin E was much better tolerated, with only 7.7% of patients reporting side-effects compared with 25.9% with diclofenac.

Rheumatoid arthritis According to several double-blind studies, a dose of 1200 mg/day vitamin E significantly reduces pain symptoms in people with RA but not always morning stiffness.

A double-blind study of 42 RA patients who received vitamin E (600 mg twice/day) over 12 weeks showed that pain parameters were significantly decreased with active treatment compared with placebo (Edmonds et al 1997). The same study also found no change in the Ritchie Articular Index, duration of morning stiffness, swollen joint count, or laboratory parameters with vitamin E supplementation compared with placebo. A further study using the same dose detected a significant inverse correlation between vitamin E levels and pain score whereas morning stiffness and sedimentation rate were not affected (Scherak & Kolarz 1991).

More recently, a combination of standard treatment (intramuscular methotrexate, oral sulfasalazine and indomethacin suppository at night) and vitamin E (400 mg three times daily) was compared with standard treatment and a combination of antioxidants or standard treatment alone (Helmy et al 2001). Standard treatment started to produce tangible improvements after 2 months, whereas additional treatment with either vitamin E or antioxidants improved symptoms more quickly, after 1 month.

Comparisons with pharmaceutical medication After 3 weeks' treatment with either high-dose vitamin E (400 mg RRR-alpha-tocopherol acetate three times daily) or diclofenac sodium, a significant improvement in all assessed clinical parameters was observed in hospitalised patients with established chronic RA ($n = 85$) according to a randomised, double-blind parallel group trial (Wittenborg et al 1998). Duration of morning stiffness, grip strength and the degree of pain, assessed by a 10 cm VAS,

reduced significantly with vitamin E as well as with diclofenac. Both treatments were considered equally effective by patients and physicians.

MENOPAUSAL SYMPTOMS

According to a review published by the Mayo clinic in the USA, behavioural changes in conjunction with vitamin E (800 IU/day) is a reasonable initial approach for menopausal women with mild symptoms that do not interfere with sleep or daily function (Shanafelt et al 2002). The recommendation is based on a double-blind, randomised, placebo-controlled, crossover clinical trial that found that vitamin E (800 IU/day) was more effective than placebo in controlling hot flushes in breast cancer survivors.

MALE INFERTILITY

Lipid-soluble antioxidants such as vitamin E have been studied for their effects in male reproductive physiology because the membranes of germ cells and spermatozoa are very sensitive to oxidation (Bhardwaj et al 2000, Bolle et al 2002).

According to three of four studies, oral vitamin E supplementation can effectively treat some forms of male infertility (Geva et al 1996, Kessopoulou et al 1995, Rolf et al 1999, Suleiman et al 1996). Doses used varied from 200 mg/day to 800 mg/day. As with many other conditions, treatment may be best suited to those individuals with elevated oxidative stress levels, although this requires further investigation.

DERMATOLOGICAL CONDITIONS

Vitamin E is used both as an oral supplement and as a topical preparation in a variety of dermatological conditions. It is a popular ingredient in many moisturising preparations used to alleviate dry and cracked skin, assist in the repair of abrasions, burns, grazes and skin lesions, prevent stretch marks and diminish scar tissue. Vitamin E oil is used as a stand-alone preparation or incorporated into a cream or ointment base for these purposes.

Sunburn protection Topical application of 1% alpha-tocopherol provided significant protection against erythema and sunburn in an experimental model. When combined with 15% ascorbic acid, the protective effect was enhanced (Lin et al 2003). Further improvements were seen when ferulic acid was added to the alpha-tocopherol (1%) and ascorbic acid (15%) solution, as this substance improves chemical stability of the antioxidants and doubles the photoprotective effect (Lin et al 2005).

Once again, it appears that not all forms of vitamin E exert a significant protective effect (McVean & Liebler 1999). According to an in vivo study, a 5% dispersion of alpha-tocopherol, gamma-tocopherol or delta-tocopherol in a neutral cream vehicle

produced a statistically significant inhibition of thymine dimer formation, whereas alpha-tocopherol acetate and alpha-tocopherol methyl ether had no effect. Further research revealed that gamma-tocopherol and delta-tocopherol were 5- to 10-fold less potent than alpha-tocopherol (McVean & Liebler 1997).

A comparison between topical vitamin E and C has demonstrated that vitamin E affords better protection against UVB radiation, whereas vitamin C is superior against UVA radiation (Baumann & Spencer 1999).

Although most research has focused on topical use, oral administration of a combination of high-dose vitamin E and C increases the threshold to erythema. The first study to show that the systemic administration of vitamins C and E reduces the sunburn reaction in humans was a small double-blind placebo-controlled trial that used ascorbic acid (2 g/day) combined with D-alpha-tocopherol (1000 IU/day) (Eberlein-Konig et al 1998). The effect was seen after 8 days. The next was a 50-day study of 40 volunteers (20–47 years old) that showed that supplemental vitamin E (2 g/day) and C (3 g/day) protected against sunburn and resulted in increased vitamin E levels in keratinocytes (Fuchs & Kern 1998). This was once again confirmed in a controlled study of 45 healthy volunteers (Mireles-Rocha et al 2002). The doses used were lower in this study, 1200 IU/day of D-alpha-tocopherol in combination with vitamin C (2 g/day).

Scar tissue Although vitamin E is widely used to diminish the appearance of scars, a small double-blind study of 15 patients who had undergone skin cancer removal found that applying an emollient preparation known as Aquaphor with added vitamin E after surgery either had no effect or worsened the appearance of scars compared with Aquaphor alone (Baumann & Spencer 1999). A larger study of 80 people with hypertrophic scars and keloids found that treatment with vitamin E and silicone gel sheets was successful in scar treatment (Palmieri et al 1995). After 2 months, 95% of patients receiving vitamin E and gel sheet treatment had improved by 50%, whereas 75% had improved by 50% without vitamin E.

PARKINSON'S DISEASE

Based on experimental and clinical data, it is well established that oxidative stress and lipid peroxidation is increased in the substantia nigra of people with Parkinson's disease (PD) and this may play an important role in the disease's aetiology. As such, vitamin E has been the focus of research as a potential treatment. Using both in vitro and in vivo experimental model systems for PD, studies have demonstrated both vitamin E-mediated protection and lack of protection (Fariss & Zhang 2003). Similarly, conflicting results have been obtained for vitamin E supplementation in the prevention and treatment of clinical PD. An open study using high doses of both

tocopherol (3200 UI/day) and ascorbic acid (3000 mg/day) delayed the use of levodopa or dopamine agonists for 2 years in subjects with early PD (Fahn 1992). In contrast, the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study found no effect on the progression of disability with alpha-tocopherol 2000 IU/day (Parkinson Study Group 1996). The same study found vitamin E had no effect on mortality (Parkinson Study Group 1998).

TYPE 1 DIABETES

Although the Heart Outcomes Prevention Evaluation (HOPE) study involving 3654 people with diabetes failed to detect a preventative effect for long-term vitamin E (400 IU/day) on cardiovascular disease outcomes or nephropathy, other studies have identified that long-term treatment improves metabolic control in type 1 diabetes and may be useful to reduce oxidative stress (Jain et al 1996, Lonn et al 2002).

CHRONIC HEPATITIS C

According to a 2004 systematic review, significant improvements in biochemical responses were seen for vitamin E compared with placebo (Coon & Ernst 2004). They report on one placebo controlled trial in which a statistically significant reduction in ALT was observed during vitamin E treatment but reductions were not consistent for all patients and complete normalisation of ALT levels did not occur.

ASTHMA AND ATOPY

Studies have consistently demonstrated beneficial associations between dietary vitamin E and ventilatory function, and a few have demonstrated beneficial associations with asthma and atopy (Devereux & Seaton 2005). However, benefits do not extend to vitamin E supplements, as a recent randomised study ($n = 72$) using natural vitamin E (500 mg/day) over 6 weeks found no clinical benefit in subjects with mild to moderate asthma (Pearson et al 2004).

OTHER USES

Oral supplements have been used to prevent or treat many other conditions such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.

Vitamin E prophylaxis in premature babies significantly reduces the risk of stage 3+ retinopathy by 52% according to a 1997 meta-analysis of six randomised studies (Raju et al 1997).

Infusions of vitamin E are being investigated as a means of preventing ischaemic reperfusion injury in liver and heart surgery (Bartels et al 2004, Jaxa-Chamiec et al 2005).

DOSAGE RANGE

The body's requirement for vitamin E changes according to the amount and type of fat eaten in the diet. For example, vitamin E requirements increase when there is a high intake of PUFAs (Wahlqvist et al 2002).

Many scientists believe it is difficult for an individual to consume more than 15 mg/day of alpha-tocopherol from food alone, without also increasing fat intake above recommended levels.

RECOMMENDATIONS FOR ADULTS (AUSTRALIAN ADEQUATE INTAKE)

- Men >18 years: 10 mg/day alpha-tocopherol.
- Women >18 years: 7 mg/day alpha-tocopherol.

Upper Level of intake: 300 mg/day alpha-tocopherol.

- Deficiency treatment: 800–1200 mg/day.

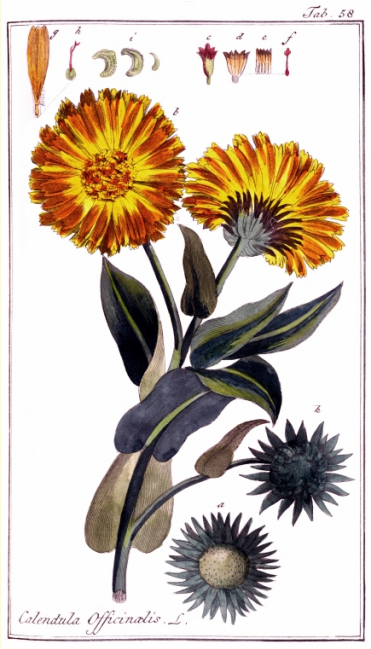
Based on clinical trials, the optimal dose for disease prevention that is considered safe for long-term use is 400 IU/day of RRR-alpha-tocopherol. However, there is considerable variation in short-term dosage used in the prevention or treatment of individual conditions.

ACCORDING TO CLINICAL STUDIES

Unless stated, dosages are for natural vitamin E (alpha-tocopherol).

- Alzheimer's disease: 2000 IU/day synthetic alpha-tocopherol.
- Anaemia in haemodialysis: 500 mg/day.
- Angina pectoris: 50–300 mg/day.
- Antioxidant effects: 400 IU/day.
- Cerebral infarction prevention: 50 mg/day synthetic vitamin E.
- Colorectal cancer prevention: 50 mg/day long term.
- Cardiovascular disease prevention: 100–800 IU/day long term.
- Carotid atherosclerosis, slowing progression: 136 IU twice daily and vitamin C 250 mg (slow release) twice daily.
- Dementia prevention: 400 IU/day alpha-tocopherol + vitamin C 500 mg/day.
- Haemodialysis, associated cramps: 400 mg/day alpha-tocopherol + vitamin C 250 mg/day.
- Hypertension: 200 IU/day long term.
- Immune system support in the elderly: 200 mg/day.
- Intermittent claudication: 600–1600 IU/day.
- Ischaemic stroke prevention in high-risk hypertension: 50 mg/day.
- Male infertility: 200–800 mg/day.
- Menopausal symptoms: 800 IU/day.
- Nitrate tolerance prevention: 200 mg three times daily.

- Osteoarthritis: 1200 IU/day.
- Ovarian cancer: >75 mg/day.
- Premenstrual symptoms: 400–600 IU/day.
- Prostate cancer prevention: 50 mg/day.
- Retinopathy of prematurity: 100 mg/kg/day.
- Rheumatoid arthritis: 1200 IU/day.
- Sunburn protection: 1000 IU/day up to 2000 mg/day + vitamin C 2000–3000 mg/day.



TOXICITY

Vitamin E is relatively non-toxic. It is not stored as readily in the body as other fat-soluble vitamins and up to 60–70% of a daily dose is excreted in the faeces. Doses as high as 3200 mg/day have been used for 12 years with few adverse effects (Fariss & Zhang 2003).

In April 2000, the Food and Nutrition Board of the Institute of Medicine in the United States set an upper tolerable limit of 1500 IU of RRR-alpha-tocopherol as the highest dose unlikely to result in haemorrhage in most adults.

ADVERSE REACTIONS

Adverse effects are dose related and tend to occur only at very high supplemental doses (>1200 IU/day); they include diarrhoea, flatulence, nausea and heart palpitations. Doses above this level should only be used under professional supervision.

SIGNIFICANT INTERACTIONS

Considering vitamin E is a fat-soluble vitamin, any medication that reduces the absorption of fats in the diet will also reduce the absorption of vitamin E. These include cholestyramine, colestipol, isoniazid, mineral oil, orlistat and sucralfate.

CHLOROQUINE

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown — observe patients taking this combination (Scuntaro et al 1996).

CHLORPROMAZINE

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown — observe patients taking this combination (Scuntaro et al 1996).

CISPLATIN

Oral vitamin E (300 mg/day) taken before cisplatin treatment and continued for 3 months after significantly reduced the incidence and severity of neurotoxicity

according to a randomised study — beneficial interaction but should be used under professional supervision (Pace et al 2003).

WARFARIN

Contradictory results have been obtained in clinical studies that have investigated whether vitamin E affects platelet aggregation or coagulation. A dose of 1200 IU/day (800 mg of D-alpha-tocopherol) taken for 28 days had no effects on platelet aggregation or coagulation according to one clinical study (Morinobu et al 2002). Similarly, a second clinical study found that a lower dose of 600 mg (900 IU) of RRR-alpha-tocopherol daily taken for 12 weeks did not alter coagulation activity (Kitagawa et al 1989). Alternatively, increased risk of gingival bleeding at doses of 50 mg/day was found by another study (Liede et al 1998).

Overall, it appears that people with reduced levels of vitamin K may be more susceptible to the effects of vitamin E potentiating warfarin activity. Until further research can clarify whether the interaction is clinically significant for most people, it is recommended that prothrombin time ratio or INR should be closely monitored with the addition and withdrawal of treatment with high-dose vitamin E supplements.

DOXORUBICIN

One study found that oral DL-alpha-tocopheryl acetate (1600 IU/day) prevented doxorubicin-induced alopecia (Wood 1985). The same dose of oral DL-alpha-tocopheryl acetate failed to prevent alopecia after doxorubicin treatment after mastectomy for breast cancer (Martin-Jimenez et al 1986). It also failed to prevent alopecia in a second study of 20 patients with different types of solid tumours (Perez et al 1986) — possible beneficial interaction but difficult to assess.

NITRATES

Oral vitamin E prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (10 mg/24 hours) according to one randomised placebo-controlled study (Watanabe et al 1997) — beneficial interaction possible.

NSAIDS AND SIMPLE ANALGESICS

Vitamin E may enhance pain modifying activity of drugs. Beneficial interaction possible — drug dosage may require modification.

PROPRANOLOL

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown — observe patients taking this combination (Scuntaro et al 1996).

CONTRAINDICATIONS AND PRECAUTIONS

Vitamin E is considered an extremely safe substance.

People with impaired coagulation, inherited bleeding disorders, history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision.

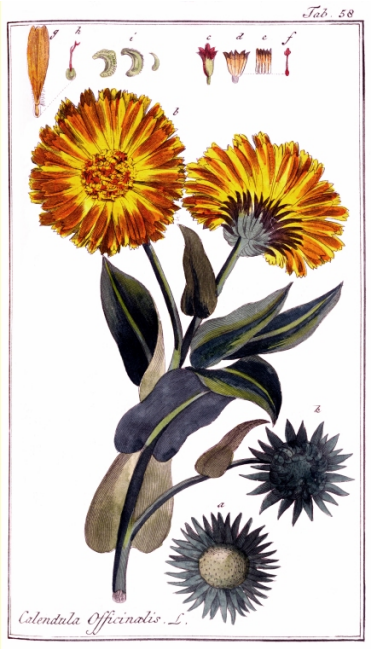
Although it was thought that people with hypertension wanting to take supplements should start with low doses, evidence does not support the concern that high-dose supplements will significantly elevate blood pressure. Suspend use of high doses (>1000 IU/day) 1 week before major surgery.

PREGNANCY USE

Vitamin E is considered safe in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin E is actually a generic term used to describe any chemical entity that displays the biological activity of RRR-alpha-tocopherol, the most abundant form found in nature. The 'natural' form is the most potent of all the eight forms of vitamin E, although there is evidence that other tocopherols also exhibit significant beneficial effects.
- It is involved in myriad biochemical processes such as immunocompetence and neurological function, but its most important biological function is that of an antioxidant.
- Vitamin E is used for many different indications. There is evidence to suggest that supplementation may be useful when meant for:
  - cardiovascular disease prevention, although effects are inconsistent
  - slowing down progression of Alzheimer's dementia, although effects are inconsistent
  - enhancing immune function in the elderly
  - preventing anaemia and treating cramps in patients on haemodialysis
  - reduce PMS and menopause symptoms
  - reducing pain in OA and RA
  - improving some forms of male infertility
  - reducing risk of stage 3+ retinopathy in premature babies
  - preventing ischaemic stroke in high-risk hypertensive patients
  - reducing incidence of some cancers, although effects are inconsistent
  - preventing sunburn (when used with vitamin C)
  - slowing down carotid atherosclerosis (when used with vitamin C)
  - reducing blood pressure



- reducing nitrate tolerance.
- Oral supplements have been used to prevent or treat many other conditions such as exerciser-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.
- It is a popular ingredient in many moisturising preparations used to alleviate dry and cracked skin, assist in the repair of abrasions, burns, grazes and skin lesions, prevent stretch marks and diminish scar tissue. Vitamin E oil is used as a stand-alone preparation or incorporated into a cream or ointment base for these purposes.
- People with impaired coagulation, inherited bleeding disorders, history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this vitamin do for me?

Vitamin E is essential for health and wellbeing. It is involved in many important biological processes in the body and may prevent serious diseases such as heart disease and some cancers. It is also used to reduce symptoms in common conditions such as arthritis, PMS and menopause. Vitamin E supplements enhance immune function in the elderly and may slow the progression of Alzheimer's dementia. Oral supplements have been used to prevent or treat many other conditions such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.

When will it start to work?

This depends largely on the reason for taking the supplement. In the case of disease prevention, studies suggest that long-term use is necessary (i.e. 2–3 years or longer). When using vitamin E to reduce symptoms, effects have generally been seen within 3 months.

Are there any safety issues?

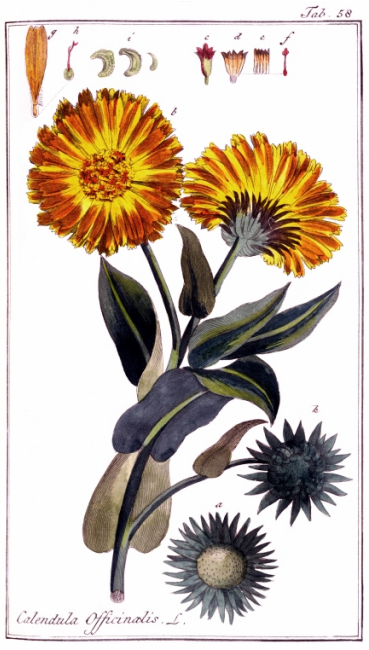
People with impaired coagulation, inherited bleeding disorders, history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision. Additionally, vitamin E can interact with some medicines, so professional advice is recommended when using high-dose supplements.

REFERENCES

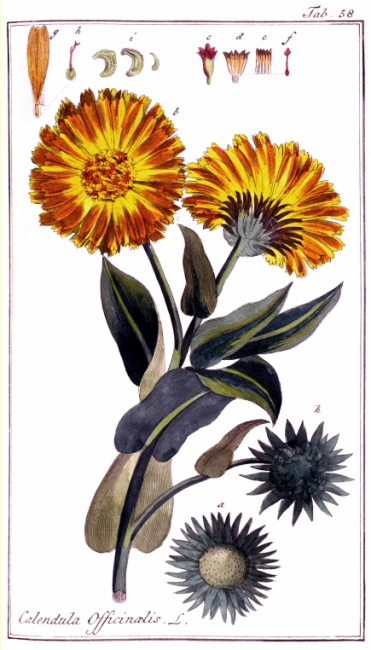
Albanes D et al. Effects of supplemental alpha-tocopherol and beta-carotene on colorectal cancer: results from a controlled trial (Finland). Cancer Causes Control 11(3) (2000): 197-205.

Badiou S et al. Vitamin E supplementation increases LDL resistance to ex vivo oxidation in hemodialysis patients. Int J Vitam Nutr Res 73(4) (2003): 290-6.
Bartels M et al. Pilot study on the effect of parenteral vitamin E on ischemia and reperfusion induced liver injury: a double blind, randomized, placebo-controlled trial. Clin Nutr 23(6) (2004): 1360-70.
Baumann LS, Spencer J. The effects of topical vitamin E on the cosmetic appearance of scars. Dermatol Surg 25(4) (1999): 311-15.
Bhardwaj A et al. Status of vitamin E and reduced glutathione in semen of oligozoospermic and azoospermic patients. Asian J Androl 2(3) (2000): 225-8.
Blankenhorn G. Clinical effectiveness of Spondyvit (vitamin E) in activated arthroses. A multicenter placebo-controlled double-blind study. Z Orthop Ihre Grenzgeb 124(3) (1986): 340-3.
Blot WJ et al. The Linxian trials: mortality rates by vitamin-mineral intervention group. Am J Clin Nutr 62(6 Suppl) (1995): 1424-6S.
Boaz M et al. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. Lancet 356(9237) (2000): 1213-18.
Bolle P et al. The controversial efficacy of vitamin E for human male infertility. Contraception 65(4) (2002): 313-15.
Bonner LT, Peskind ER. Pharmacologic treatments of dementia. Med Clin North Am 86(3) (2002): 657-74.
Boshtam M et al. Vitamin E can reduce blood pressure in mild hypertensives. Int J Vitam Nutr Res 72(5) (2002): 309-14.
Brand C et al. Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: a six month double blind, randomised, placebo controlled study. Ann Rheum Dis 60(10) (2001): 946-9.
Brockes C et al. Vitamin E prevents extensive lipid peroxidation in patients with hypertension. Br J Biomed Sci 60(1) (2003): 5-8.
Chen H et al. Mixed tocopherol preparation is superior to alpha-tocopherol alone against hypoxia-reoxygenation injury. Biochem Biophys Res Commun 291(2) (2002): 349-53.
Cherubini A et al. Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study. Neurobiol Aging 26(7) (2005): 987-94.
Clarke R, Armitage J. Antioxidant vitamins and risk of cardiovascular disease. Review of large-scale randomised trials. Cardiovasc Drugs Ther 16(5) (2002): 411-15.
Collins et al. PoleStriding exercise and vitamin E for management of peripheral vascular disease. Med Sci Sports Exerc 35(3) (2003): 384-93.
Coon JT, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. J Hepatol 40(3) (2004): 491-500.
Cristol JP et al. Erythropoietin and oxidative stress in haemodialysis: beneficial effects of vitamin E supplementation. Nephrol Dial Transplant 12(11) (1997): 2312-17.
Darr D et al. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. Acta Derm Venereol 76(4) (1996): 264-8.
de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice: Collaborative Group of the Primary Prevention Project. Lancet 357(9250) (2001): 89-95.
De Vita V (eds). Cancer: Principles and Practice in Oncology, 7th edn. Lipincott Williams and Wilkins. Online version available at: gateway.ut.ovid.com/gw2/ovidweb.cgi (accessed 12-06-06).
de Waart FG et al. Effect of 3 months vitamin E supplementation on indices of the cellular and humoral immune response in elderly subjects. Br J Nutr 78(5) (1997): 761-74.
DeMaio SJ et al. Vitamin E supplementation, plasma lipids and incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA). J Am Coll Nutr 11(1) (1992): 68-73.
Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 115(6) (2005): 1109-17.
Diepeveen SH et al. Effects of atorvastatin and vitamin E on lipoproteins and oxidative stress in dialysis patients: a randomised-controlled trial. J Intern Med 257(5) (2005): 438-45.
Drisko JA et al. The use of antioxidant therapies during chemotherapy. Gynecol Oncol 88(3) (2003): 434-9.

Eberlein-Konig B et al. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-[alpha]-tocopherol (vitamin E). J Am Acad Dermatol 38(1) (1998): 45-8.
Edmonds SE et al. Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis: Results of a prospective placebo controlled double blind trial. Ann Rheum Dis 56(11) (1997): 649-55.
Engelhart MJ et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 287(24) (2002): 3223-9.
Fahn S. A pilot trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's disease. Ann Neurol 32 (Suppl.) (1992): S128-32.
Fariss MW, Zhang JG. Vitamin E therapy in Parkinson's disease. Toxicology 189(1-2) (2003): 129-46.
Fleischauer AT et al. Antioxidant supplements and risk of breast cancer recurrence and breast cancer-related mortality among postmenopausal women. Nutr Cancer 46(1) (2003): 15-22.
Fleischauer AT et al. Dietary antioxidants, supplements, and risk of epithelial ovarian cancer. Nutr Cancer 40(2) (2001): 92-8.
Food and Agriculture Organization/World Health Organization. Vitamin E. In: Report of a Joint FAO/WHO Expert Consultation; Bangkok, Thailand. FAO/WHO: Rome, 2002.
Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by d-alpha-tocopherol and l-ascorbic acid: a clinical study using solar simulated radiation. Free Radic Biol Med 25(9) (1998): 1006-12.
Galli F et al. Vitamin E, lipid profile, and peroxidation in hemodialysis patients. Kidney Int Suppl 78 (2001): S148-54.
Geva E et al. The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. Fertil Steril 66(3) (1996): 430-4.
Giray B et al. The effect of vitamin E supplementation on antioxidant enzyme activities and lipid peroxidation levels in hemodialysis patients. Clin Chim Acta 338(1-2) (2003): 91-8.
GISSI-Prevenzione trial. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Lancet 354(9177) (1999): 447-55.
Greenwald P et al. Micronutrients in cancer chemoprevention. Cancer Metastasis Rev 21(3-4) (2002): 217-30.
Hartman TJ et al. Effects of long-term alpha-tocopherol supplementation on serum hormones in older men. Prostate 46(1) (2001): 33-8.
Heinecke JW. Oxidized amino acids: culprits in human atherosclerosis and indicators of oxidative stress. Free Radic Biol Med 32(11) (2002): 1090-101.
Heinecke JW. Oxidative stress: new approaches to diagnosis and prognosis in atherosclerosis. Am J Cardiol 91(3A) (2003): 12-16A.
Heinonen OP et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 90(6) (1998): 440-6.
Helmy M et al. Antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study. Arzneimittelforschung 51(4) (2001): 293-8.
Iino K et al. A controlled, double-blind study of dl-alpha-tocopheryl nicotinate (Juvela-Nicotinate) for treatment of symptoms in hypertension and cerebral arteriosclerosis. Jpn Heart J 18(3) (1977): 277-86.
Jain SK et al. Effect of modest vitamin E supplementation on blood glycated hemoglobin and triglyceride levels and red cell indices in type I diabetic patients. J Am Coll Nutr 15(5) (1996): 458-61.
Jaxa-Chamiec T et al. Antioxidant effects of combined vitamins C and E in acute myocardial infarction: The randomized, double-blind, placebo controlled, multicenter pilot Myocardial Infarction and VITamins (MIVIT) trial. Kardiol Pol 62(4) (2005): 344-50.
Jialal I, Devaraj S. Scientific evidence to support a vitamin E and heart disease health claim: research needs. J Nutr 135(2) (2005a): 348-53.
Jialal I, Devaraj S. High-dosage vitamin E supplementation and all-cause mortality. Ann Intern Med 143(2) (2005b): 155.
Kaul N et al. Alpha-tocopherol and atherosclerosis. Exp Biol Med 226(1) (2001): 5-12.



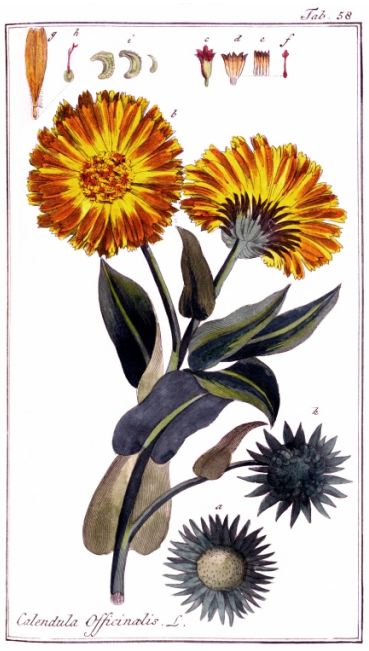
Kessopoulou E et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril 64(4) (1995): 825-31.
Khajehdehi P et al. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. Nephrol Dial Transplant 16(7) (2001): 1448-51.
Kitagawa M, Mino M. Effects of elevated d-alpha(RRR)-tocopherol dosage in man. J Nutr Sci Vitaminol (Tokyo) 35(2) (1989): 133-42.
Kleijnen J, Mackerras D. Vitamin E for intermittent claudication. Cochrane Database Syst Rev 2 (2000): CD000987.
Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev 4(5) (1999): 304-29.
Lee IM et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: The Women's Health Study: a randomized controlled trial. ACC Curr J Rev 14(10) (2005): 10-11.
Leppala JM, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP. Vitamin E and beta carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Arch Neurol 57(10) (2000): 1503-9.
Liede KE et al. Increased tendency towards gingival bleeding caused by joint effect of alpha-tocopherol supplementation and acetylsalicylic acid. Ann Med 30(6) (1998): 542-6.
Lin JY et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol 48(6) (2003): 866-74.
Lin FH et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J Invest Dermatol 125(4) (2005): 826-32.
London RS et al. Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. J Reprod Med 32(6) (1987): 400-4.
London RS et al. Evaluation and treatment of breast symptoms in patients with the premenstrual syndrome. J Reprod Med 28(8) (1983): 503-8.
Lonn E et al. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. Diabetes Care 25(11) (2002): 1919-27.
Lonn E et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 293(11) (2005): 1338-47.
Luchsinger JA et al. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 60(2) (2003): 203-8.
Machtey I, Ouaknine L. Tocopherol in osteoarthritis: a controlled pilot study. J Am Geriatr Soc 26(7) (1978): 328-30.
Martin-Jimenez M et al. Failure of high-dose tocopherol to prevent alopecia induced by doxorubicin. N Engl J Med 315(14) (1986): 894-5.
Masaki KH et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 54(6) (2000): 1265-72.
McCall MR, Frei B. Can antioxidant vitamins materially reduce oxidative damage in humans? Free Radic Biol Med 26(7-8) (1999): 1034-53.
McVean M, Liebler DC. Inhibition of UVB induced DNA photodamage in mouse epidermis by topically applied alpha-tocopherol. Carcinogenesis 18(8) (1997): 1617-22.
McVean M, Liebler DC. Prevention of DNA photodamage by vitamin E compounds and sunscreens: roles of ultraviolet absorbance and cellular uptake. Mol Carcinog 24(3) (1999): 169-76.
Meagher EA. Treatment of atherosclerosis in the new millennium: is there a role for vitamin E? Prev Cardiol 6(2) (2003): 85-90.
Meydani M. Vitamin E. Lancet 345(8943) (1995): 170-5.
Meydani M, Hayes KC. Vitamin E. Available at: http.jn.nutrition.org (accessed 02-06-03).
Meydani SN et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. JAMA 277(17) (1997): 1380-6.



Meydani SN et al. Antioxidant modulation of cytokines and their biologic function in the aged. Z Ernahrungswiss 37 (Suppl 1) (1998): 35-42.
Miller ER III et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 142(1) (2005): 37-46.
Minamiyama Y et al. Vitamin E deficiency accelerates nitrate tolerance via a decrease in cardiac P450 expression and increased oxidative stress. Free Radic Biol Med 40(5) (2006): 808-16.
Mireles-Rocha H et al. UVB photoprotection with antioxidants: effects of oral therapy with d-alpha-tocopherol and ascorbic acid on the minimal erythema dose. Acta Derm Venereol 82(1) (2002): 21-4.
Miwa K et al. Vitamin E deficiency in variant angina. Circulation 94(1) (1996): 14-18.
Miwa K et al. Consumption of vitamin E in coronary circulation in patients with variant angina. Cardiovasc Res 41(1) (1999): 291-8.
Morinobu T et al. The safety of high-dose vitamin E supplementation in healthy Japanese male adults. J Nutr Sci Vitaminol (Tokyo) 48(1) (2002): 6-9.
Morris MC et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr 81(2) (2005): 508-14.
Munteanu A et al. Anti-atherosclerotic effects of vitamin E: myth or reality? J Cell Mol Med 8(1) (2004): 59-76.
Orbe J et al. Antioxidant vitamins increase the collagen content and reduce MMP-1 in a porcine model of atherosclerosis: implications for plaque stabilization. Atherosclerosis 167(1) (2003): 45-53.
Pace A et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol 21(5) (2003): 927-31.
Palmieri B et al. Vitamin E added silicone gel sheets for treatment of hypertrophic scars and keloids. Int J Dermatol 34(7) (1995): 506-9.
Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa: Parkinson Study Group. Ann Neurol 39(1) (1996): 37-45.
Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. Parkinson Study Group. Ann Neurol 43(3) (1998): 318-25.
Parkinson Study Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360(9326) (2002): 23-33.
Pearson PJK et al. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. Thorax 59(8) (2004): 652-6.
Perez JE et al. High-dose alpha-tocopherol as a preventive of doxorubicin-induced alopecia. Cancer Treat Rep 70(10) (1986): 1213-14.
Petersen RC et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352(23) (2005): 2379-88.
Raju TN et al. Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. J Pediatr 131(6) (1997): 844-50.
Rapola JM et al. Effect of vitamin E and beta carotene on the incidence of angina pectoris: A randomized, double-blind, controlled trial. JAMA 275(9) (1996): 693-8.
Rautalahti MT et al. The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer 86(1) (1999): 37-42.
Rimm EB et al. Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 328(20) (1993): 1450-6.
Rolf C et al. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. Hum Reprod 14(4) (1999): 1028-33.
Saldeen K, Saldeen T. Importance of tocopherols beyond [alpha]-tocopherol: evidence from animal and human studies. Nutr Res 25(10) (2005): 877-89.
Salonen JT et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Intern Med 248(5) (2000): 377-86.

Salonen RM et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. Circulation 107(7) (2003): 947-53.
Sano M et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease: The Alzheimer's Disease Cooperative Study. N Engl J Med 336(17) (1997): 1216-22.
Scherak O et al. High dosage vitamin E therapy in patients with activated arthrosis. Z Rheumatol 49(6) (1990): 369-73.
Scherak O, Kolarz G. Vitamin E and rheumatoid arthritis. Arthritis Rheum 34(9) (1991): 1205-6.
Scuntaro I et al. Inhibition by vitamin E of drug accumulation and of phospholipidosis induced by desipramine and other cationic amphiphilic drugs in human cultured cells. Br J Pharmacol 119(5) (1996): 829-34.
Seifried HE et al. The antioxidant conundrum in cancer. Cancer Res 63(15)(2003): 4295-8.
Sen C, Packer L. Thiol homeostasis and supplements in physical exercise; Am J Clin Nutr 72(s) (2000): 653-69s.
Shanafelt TD et al. Pathophysiology and treatment of hot flashes. Mayo Clin Proc 77(11) (2002): 1207-18.
Shils M et al (eds). Modern Nutrition in Health and Disease, 9th edn. Baltimore: Lippincott Williams & Wilkins, 1999-2000.
Stampfer MJ et al. Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 328(20) (1993): 1444-9.
Stephens NG et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 347(9004) (1996): 781-6.
Stone WL, Papas AM. Tocopherols and the etiology of colon cancer. J Natl Cancer Inst 89(14)(1997): 1006-14.
Suleiman SA et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl 17(5) (1996): 530-7.
Sung L et al. Vitamin E: the evidence for multiple roles in cancer. Nutr Cancer 46(1) (2003): 1-14.
Terentis AC et al. Vitamin E oxidation in human atherosclerotic lesions. Circ Res 90(3) (2002): 333-9.
Ulker S et al. Vitamins reverse endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities. Hypertension 41(3) (2003): 534-9.
Varis K et al. Gastric cancer and premalignant lesions in atrophic gastritis: a controlled trial on the effect of supplementation with alpha-tocopherol and beta-carotene: The Helsinki Gastritis Study Group. Scand J Gastroenterol 33(3): (1998) 294-300.
Vatassery GT. In vitro oxidation of alpha-tocopherol (vitamin E) in human platelets upon incubation with unsaturated fatty acids, diamide and superoxide. Biochim Biophys Acta 926(2) (1987): 160-9.
Virtamo J et al. Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. Arch Intern Med 158(6) (1998): 668-75.
Virtamo J et al. Effects of supplemental alpha-tocopherol and beta-carotene on urinary tract cancer: incidence and mortality in a controlled trial (Finland). Cancer Causes Control 11(10) (2000): 933-9.
Wahlqvist ML (ed.). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Watanabe H et al. Randomized, double-blind, placebo-controlled study of supplemental vitamin E on attenuation of the development of nitrate tolerance. Circulation 96(8) (1997): 2545-50.
Wijnen MH et al. Antioxidants reduce oxidative stress in claudicants. J Surg Res 96(2) (2001): 183-7.
Wittenborg A et al. Effectiveness of vitamin E in comparison with diclofenac sodium in treatment of patients with chronic polyarthritis. Z Rheumatol 57(4) (1998): 215-21.
Wluka AE et al. Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. J Rheumatol 29(12) (2002): 2585-91.
Wood LA. Possible prevention of adriamycin-induced alopecia by tocopherol. N Engl J Med 312(16) (1985): 1060.
Yusuf S et al. Vitamin E supplementation and cardiovascular events in high-risk patients: The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342(3) (2000): 154-60.
Zandi PP et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 61(1) (2004): 82-8.

Wild yam



Historical note Wild yams have made a significant contribution as a root crop to tribal people in some parts of the world such as Nepal. Medicinally, wild yam has inaccurately been labelled 'natural progesterone'. Although wild yam does not contain progesterone or other hormones, it is the source of diosgenin, the raw material originally used to produce progesterone in the laboratory. Its traditional use is primarily as an antispasmodic.

COMMON NAME
Wild yam

OTHER NAMES
Atlantic yam, barbasco, China root, colic root, devil's bones, Mexican yam, natural DHEA, rheumatism root, wild Mexican yam, yuma

BOTANICAL NAME/FAMILY
Discorea composita, *D. floribunda*, *D. mexicana*, *D. macrostachya*, *D. villosa* (family Dioscoreaceae [yams])

PLANT PART USED
Root and rhizome

CHEMICAL COMPONENTS
The root of the wild yam contains diosgenin, dioscin, dioscorin and a range of vitamins and minerals such as vitamin C, beta carotene, vitamins B1, B2 and B3, iron, magnesium, potassium, selenium and zinc (US DA Phytochemical Database 2003) along with polyphenols (Bhandari & Kawabata 2004). Although diosgenin can be converted to dihydroepiandosterone (DHEA) and other steroid compounds in the laboratory, and has been used for commercial production of these compounds, this conversion does not occur in the human body. Additionally, wild yam does not contain progesterone or any other active steroid hormones.

MAIN ACTIONS

HORMONAL ACTIONS
The evidence for a hormonal action of wild yam varies. Wild yam extract may enhance oestradiol binding to oestrogen receptors and induce transcription activity in oestrogen-responsive cells (NMCD 2003) and diosgenin has been observed to have an

oestrogenic action on mouse mammary epithelium (Aradhana & Kale 1992). Alternatively, in an oestrogen competition assay using human breast cancer cell, diosgenin was found to cause an acute, endothelium-independent coronary artery relaxation, but did not interact with oestrogen or progesterone receptors (Au et al 2004) and extracts with an upper limit of 3.5% diosgenin have been found to have no oestrogenic activity (Hooker 2004).

One study looking at steroid hormone-regulated gene expression using an in vitro tissue culture indicator system suggests that wild yam extract does not have significant oestrogenic or progesteronal activity, but rather weak anti-oestrogenic and/or anti-androgenic activities (Rosenberg Zand et al 2001). A further study suggests that wild yam extract suppresses progesterone synthesis without direct effects on oestrogen or progesterone receptors (Zava 1998). In an in vivo study, supplementation with diosgenin protected the kidney from morphological changes associated with ovariectomy (Tucci & Benghuzzi 2003) and produced a significant decrease in the cortical and medullary adrenal areas of the ovariectomised rats (Benghuzzi et al 2003).

There is in vitro evidence that diosgenin up-regulates vascular endothelial growth factor-A and promotes angiogenesis in preosteoblast-like cells via pathways involving oestrogen receptors (Men et al 2005).

CHOLAGOGUE

There appears to be more consistent evidence for wild yam's effect on bile flow. Diosgenin has been shown to increase biliary secretion of cholesterol (Accatino et al 1998; Yamada et al 1997) and prevent oestrogen-induced bile flow suppression in rats (Accatino et al 1998), as well as increase elimination of indomethacin and reduce indomethacin-induced intestinal inflammation (Yamada et al 1997).

OTHER ACTIONS

Traditionally, wild yam is also believed to exert antispasmodic, anti-inflammatory and autonomic nervous system relaxant effects (Fisher & Painter 1996). Wild yam exhibits significant antioxidant activity (Bhandari & Kawabata 2004).

CLINICAL USE

The therapeutic effectiveness of wild yam has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

MENOPAUSAL SYMPTOMS AND OTHER FEMALE REPRODUCTIVE CONDITIONS

Although wild yam is a popular treatment for menopausal symptoms, there is currently no clinical research supporting its use for these indications.

Wild yam has been used as a 'natural alternative' to oestrogen replacement therapy, to treat postmenopausal vaginal dryness, PMS, osteoporosis, and to increase energy and libido in men and women, as well as for breast enlargement. The use of wild yam as a natural progesterone appears misguided because diosgenin is not converted to progesterone, DHEA or other steroid hormones in vivo. One small, double-blind, placebo-controlled crossover trial of topical wild yam extract showed no effect on menopausal symptoms (Komesaroff et al 2001). The study involved 23 healthy women suffering from troublesome symptoms of the menopause. After a 4-week baseline period, each woman was randomly assigned the active cream and matching placebo for 3 months. No changes in body weight, SBP or DBP, levels of total serum cholesterol, triglyceride, HDL-cholesterol, FSH, glucose, oestradiol, or serum or salivary progesterone were detected after 3 months' treatment.

OTHER USES

Wild yam has been used traditionally as an antispasmodic for treating diverticulosis, gall bladder colic, painful menstruation, cramp, nausea in pregnancy, rheumatoid arthritis, and for increasing energy (Fisher & Painter 1996), and may be useful when combined with other herbs for irritable bowel syndrome (Abascal & Yarnell 2005).

DOSAGE RANGE

- Decoction of dried root: 2–4 g three times daily.
- Tincture (1:5): 2–10 mL three times daily.
- Liquid extract (1:2): 3–6 mL/day.

TOXICITY

Considering that wild yams are widely consumed as food by several tribal groups, it appears that dietary ingestion is non-toxic. After assessment with short-term toxicity tests, dermal irritation tests, a sensitisation test, an ocular irritation test, a rat uterotropic assay, and genotoxicity tests wild yam was deemed safe for use in cosmetic products (Hooker 2004).

ADVERSE REACTIONS

In large doses, wild yam may cause nausea, vomiting and diarrhoea.

SIGNIFICANT INTERACTIONS

Insufficient reliable data are available to determine whether interactions may occur.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Wild yam is a popular root vegetable in some parts of the world.
- It is also a popular ingredient in commercial herbal formulas developed for menopausal women.
- Wild yam has been touted as having progesteronal and/or oestrogenic activity, but current evidence suggests this is unlikely.
- There is no clinical or scientific evidence to support the use of wild yam in treatment of conditions of the female reproductive system.
- Wild yam root may be useful as an antispasmodic. Its use as a natural hormone appears misguided.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Although the herb is used medicinally to treat menopausal symptoms, there is no scientific evidence to support this.

When will it start to work?

This cannot be answered based on scientific evidence.

Are there any safety issues?

Considering it is consumed as food, usual dietary intakes may be considered safe.

REFERENCES

Abascal K, Yarnell E. Combining herbs in a formula for irritable bowel syndrome. Altern Complement Ther 11.1 (2005): 17-23.

Accatino L, Pizarro M, Solis N, Koenig CS. Effects of diosgenin, a plant-derived steroid, on bile secretion and hepatocellular cholestasis induced by estrogens in the rat. Hepatology 28.1 (1998): 129-40.

Aradhana Rao AR, Kale RK. Diosgenin: a growth stimulator of mammary gland of ovariectomized mouse. Indian J Exp Biol 30.5 (1992): 367-70.

Au ALS et al. Activation of iberiotoxin-sensitive, Ca^{2+}-activated K^+ channels of porcine isolated left anterior descending coronary artery by diosgenin. Eur J Pharmacol 502.1-2 (2004): 123-33.

Benghuzzi H et al. The effects of sustained delivery of diosgenin on the adrenal gland of female rats. Biomed Sci Instrument 39 (2003): 335-40.

Bhandari MR, Kawabata J. Organic acid, phenolic content and antioxidant activity of wild yam (Dioscorea spp.) tubers of Nepal. Food Chem 88.2 (2004): 163-8.

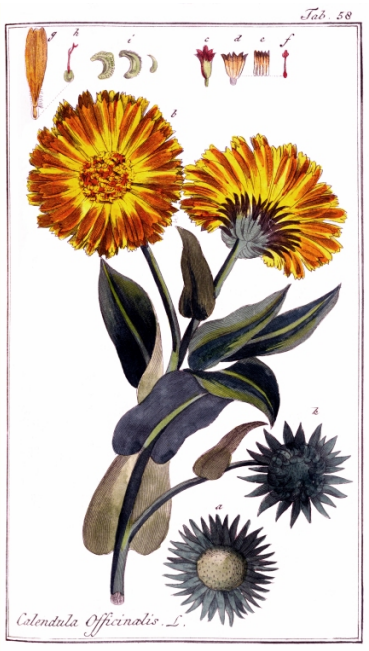
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.

Hooker E. Final report of the amended safety assessment of Dioscorea villosa (Wild yam) root extract. Int J Toxicol 23 (Suppl 2) (2004): 49-54.

Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. Climacteric 4.2 (2001): 144-50.

Men LY et al. Diosgenin induces hypoxia-inducible factor-1 activation and angiogenesis through estrogen receptor-related phosphatidylinositol 3-kinase/Akt and p38 mitogen-activated protein kinase pathways in osteoblasts. Mol Pharmacol 68.4 (2005): 1061-73.
Natural medicines comprehensive database (NMCD online) 2003. Wild yam. Available from: http://www.naturaldatabase.com
Rosenberg Zand RS, Jenkins DJ, Diamandis EP. Effects of natural products and nutraceuticals on steroid hormone-regulated gene expression. Clin Chim Acta 312.1-2 (2001): 213-19.
Tucci M, Benghuzzi H. Structural changes in the kidney associated with ovariectomy and diosgenin replacement therapy in adult female rats. Biomed Sci Instrument 39 (2003): 341-6.
US Department of Agriculture. Phytochemical Database. Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD, 2003.
Yamada T et al. Dietary diosgenin attenuates subacute intestinal inflammation associated with indomethacin in rats. Am J Physiol 273.2 (Pt 1) (1997): G355-64.
Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217.3 (1998): 369-78.

Willowbark



Historical note This herb has been used as a therapeutic agent since ancient times, with some reports stating that it was used in ancient China around 500 BC as a treatment for pain and fever and around 400 BC by Hippocrates, who recommended the bark be chewed for relief of fever and pain. As centuries passed, herbalists continued to prescribe the bark for many conditions and by the 18th century, it was widely used as an antipyretic and analgesic. Sometime during the late 1820s, French and German scientists extracted the glycosidic constituents, including salicin (Hedner & Everts 1998). The oxidation of salicin yields salicylic acid, which was produced in the mid 1800s but had limited clinical use due to the gastric irritation it caused. In 1853 a French chemist neutralised salicylic acid to create acetylsalicylic acid, but had no interest in marketing it and abandoned his discovery. A Bayer chemist called Hoffmann rediscovered acetylsalicylic acid in 1897 as a better tolerated treatment for his father's RA and within 2 years it was marketed by Bayer under the tradename of Aspirin (Setty & Sigal 2005). Since then it has become one of the most successful medicines in history. Although many believe aspirin was synthesised from the salicin found in willowbark, it was actually the salicin found in another herb, meadowsweet, from which aspirin was developed.

OTHER NAMES

White willowbark, brittle willow, bay willow, crack willow, purple willow, silberweide, violet willow

While white willow (*Salix alba*) is the willow species most commonly used for medicinal purposes, crack willow (*S. fragilis*), purple willow (*S. purpurea*), and violet willow (*S. daphnoides*) are all salicin-rich and are sometimes sold under the label of willow bark (Setty & Sigal 2005).

BOTANICAL NAME/FAMILY

Salix alba (family Salicaceae)

PLANT PART USED

Bark

CHEMICAL COMPONENTS

Phenolic glycosides, mainly salicylates including salicin and its derivatives, tannins, mainly catechin tannins, some gallontannins and condensed tannins (procyanidins), and flavonoids.

MAIN ACTIONS

ANTI-INFLAMMATORY AND ANALGESIC

Clinical studies using willowbark preparations standardised to salicin content have shown anti-inflammatory and analgesic activity (Chrubasik et al 2000, 2001a, b, Mills et al 1996, Schmid et al 2000). In vitro studies have demonstrated that *Salix* extract inhibits COX-2-mediated PGE_2 release and that it is a weak inhibitor of proinflammatory cytokines (Fiebich & Chrubasik 2004). While salicin is considered the main analgesic constituent, it is now thought that other constituents such as tannins, flavonoids, and salicin esters may contribute to its overall effect (Schmid et al 2001).

Clinical note — Lack of significant haemotological effects

It has largely been assumed that willowbark alters platelet aggregation and increases bleeding time, in much the same way as aspirin. Whether this is in fact correct and clinically significant has been investigated by Krivoy et al (2001). The clinical study found that consumption of *Salicis cortex* extract (containing 240 mg salicin per daily dose) only minimally affected platelet aggregation compared with a cardioprotective dose of acetylsalicylate (up to 100 mg/day). The particular preparation studied produced a total serum salicylate concentration bioequivalent to only 50 mg acetylsalicylate.

CLINICAL USE

In clinical practice, willowbark is generally used as a symptomatic treatment in osteoarthritic conditions and lower back pain. Of the five RCTs conducted to investigate its effects in these conditions, all but one have produced positive results (Biegert et al 2004, Chrubasik et al 2000, 2001a, Mills et al 1996, Schmid et al 2000).

JOINT PAIN AND INFLAMMATION

Osteoarthritis Three randomised double-blind trials have investigated the efficacy of willowbark in people with osteoarthritis, with the two earlier studies finding herbal treatment produced symptom relieving effects superior to placebo (Biegert et al 2004, Mills et al 1996, Schmid et al 2000). Seventy-eight subjects were randomly assigned willowbark extract (240 mg salicin/day) or placebo over a 2-week period, after which active treatment was found to produce a statistically significant improvement (Schmid et al 2000). Mills et al (1996), testing willowbark in 82 patients

with chronic arthritic pain, also found active treatment produced a statistically significant alleviation of pain symptoms.

However, willowbark failed to reduce WOMAC pain scores better than placebo in the largest and most recent study, which involved 127 outpatients with painful hip or knee osteoarthritis (Biegert et al 2004). Patients were randomised to receive willow bark extract, corresponding to 240 mg of salicin/day, diclofenac 100 mg/day, or placebo. Treatment with diclofenac produced the strongest pain reducing effects (WOMAC scores decreased by 47%) compared with willowbark (17% reduction) and placebo (10% reduction), with the difference between willow bark extract and placebo not statistically significant.

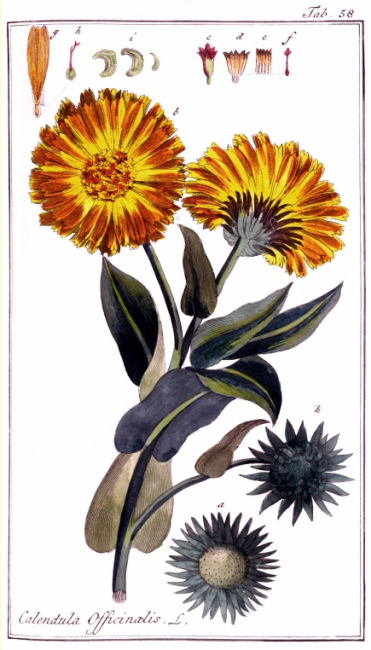
Rheumatoid arthritis Willowbark extract (corresponding to 240 mg salicin/day) failed to significantly reduce pain in people with active RA, according to a small, double-blind, randomised study of 26 volunteers (Biegert et al 2004). The main outcome measure used was the patient's assessment of pain rated on a 100-mm visual analogue scale.

LOWER BACK PAIN

Two randomised studies have investigated the use of oral white willowbark in people with acute episodes of chronic non-specific low-back pain (Chrubasik 2000, 2001a). According to a 2006 Cochrane systematic review, there is moderate evidence that a daily dose of 240 mg salicin from an extract of *S. alba* reduces pain more than either placebo or a daily dose of 120 mg of salicin in the short term for individuals with acute episodes of chronic non-specific low-back pain (Gagnier et al 2006).

One randomised placebo-controlled study involving 210 patients with chronic lower back pain found that 39% of those treated with 240 mg salicin became pain free after 4 weeks compared with 6% in the placebo group. This response was achieved after 1 week (Chrubasik et al 2000). Similar results were achieved in an open trial conducted over 18 months that compared willowbark extract containing 120 mg of salicin or 240 mg salicin with what the authors term 'conventional treatment' in 451 people with acute exacerbations of lower back pain. Those receiving 240 mg salicin experienced the best results, with 40% pain-free after 4 weeks compared with 19% in the 120 mg salicin group and 18% in the control group (Chrubasik et al 2001b).

Comparative trial with rofecoxib No significant differences in pain relieving effects were found between white willowbark standardised to provide a daily dose of 240 mg salicin and 12.5 mg of the synthetic COX-2 inhibitor rofecoxib according to a randomised trial of individuals with acute episodes of chronic non-specific low-back pain (Chrubasik et al 2001a). With regard to rescue treatments, the percentage of



patients requiring NSAIDs, tramadol or both was 10% for the willowbark group and 13% for the rofecoxib group. Approximately 90% of physicians and patients rated either treatment as effective and close to 100% rated either treatment as acceptable.

Considering some pharmaceutical treatments used in the management of pain and inflammatory conditions are costly, such as the newer COX-2 inhibitors, Chrubasik et al (2001b) also compared the cost savings associated with the use of willowbark. A dose of 120 mg salicin/day from willowbark reduced overall patient spending on additional drugs by about 35–50%. In comparison, 240 mg salicin/day produced superior pain relief that resulted in even less reliance on supplementary treatments, but savings were outweighed by the extra cost of the higher dose.

FEVER AND HEADACHES

Although no clinical trials are available for these indications, the known activity of the salicylate constituents suggests the herb may provide some symptomatic relief. Commission E has approved willowbark for these indications (Blumenthal et al 2000).

DOSAGE RANGE

- Tincture (1:1): 1–2 mL three times daily.
- Decoction: 1–3 g finely chopped herb in 1 cup of cold water, brought to the boil then reduced to simmer for 5 minutes, drunk 3–4 times daily.

ACCORDING TO CLINICAL STUDIES

- Osteoarthritic joint pain and inflammation — willowbark preparations standardised to total salicin content and providing 240 mg daily in divided doses.
- Acute episodes of chronic non-specific low-back pain — willowbark preparations standardised to total salicin content and providing 240 mg daily in divided doses

ADVERSE REACTIONS

None reported. Theoretically, the tannin and salicylate content may cause gastrointestinal disturbances.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are based on evidence of pharmacological activity and clinical significance is uncertain.

ANTICOAGULANTS

Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect. Caution with high dose > 240 mg salicin/day.

SALICYLATE DRUGS

Theoretically, concurrent use may result in additive effects, although this has yet to be tested — observe patients taking this combination.

ASPIRIN

Theoretically, willowbark may enhance the anti-inflammatory and antiplatelet effects at doses of salicin 240 mg/day — observe patients taking this combination; beneficial interaction may be possible.

An increased risk of bleeding is theoretically possible with high doses > 240 mg salicin — observe.

NSAIDS

A reduction in drug requirements may be possible with the use of white willowbark in lower back pain according to a randomised study — beneficial interaction possible.

CONTRAINDICATIONS AND PRECAUTIONS

Commission E states that there is no evidence that willowbark preparations should be contraindicated in small children due to the risk of Reye's syndrome, as the salicylates in the herb are metabolised differently to aspirin.

Due to the relatively high concentration of salicylates in this herb, it should not be used by people with salicylate sensitivity.

PREGNANCY USE

It is generally not advised to recommend salicylate-containing medicines during pregnancy or lactation, although no restrictions are known for willowbark directly.

PRACTICE POINTS/PATIENT COUNSELLING

- Evidence from several RCTs suggests that willowbark is an effective treatment for relieving pain in chronic backache and osteoarthritis.
- The results of one clinical study suggest it is as effective as 12.5 mg of the synthetic COX-2 inhibitor rofecoxib when used at a daily dose of 240 mg salicin.
- People using willowbark may find they have lowered requirements for traditional anti-inflammatory medicines such as NSAIDs.
- Currently, there is no evidence to suggest gastrointestinal side effects or significant platelet inhibition.
- Due to its salicylate content, people with salicylate sensitivity should avoid use of willowbark.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Scientific studies have found that willowbark is a useful treatment for relieving pain in osteoarthritis and chronic backache. It may also relieve symptoms of headache and fever.

When will it start to work?

Studies using willowbark preparations in diseases characterised by joint pain have found that effects start within 1 week's use.

Are there any safety issues?

Willowbark appears to be free of major side effects or drug interactions, but it should not be taken by people with salicylate sensitivity.

REFERENCES

Biegert C et al. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. J Rheumatol 31.11 (2004): 2121-30.

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.

Chrubasik S et al. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 109.1 (2000): 9-14.

Chrubasik S et al. Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study: willow bark extract for low back pain. Rheumatology (Oxford) 40.12 (2001a): 1388-93.

Chrubasik S et al. Potential economic impact of using a proprietary willow bark extract in outpatient treatment of low back pain: an open non-randomized study. Phytomedicine 8.4 (2001b): 241-51.

Fiebich BL, Chrubasik S. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. Phytomedicine 11.2-3 (2004): 135-8.

Gagnier JJ, van Tulder M, Berman B, Bombardier C. Herbal medicine for low back pain. Cochrane Database Syst Rev no. 2 (2006): CD004504.

Hedner T, Everts B. The early clinical history of salicylates in rheumatology and pain. Clin Rheumatol 17.1 (1998): 17-25.

Krivoy N et al. Effect of salicis cortex extract on human platelet aggregation. Planta Med 67.3 (2001): 209-12.

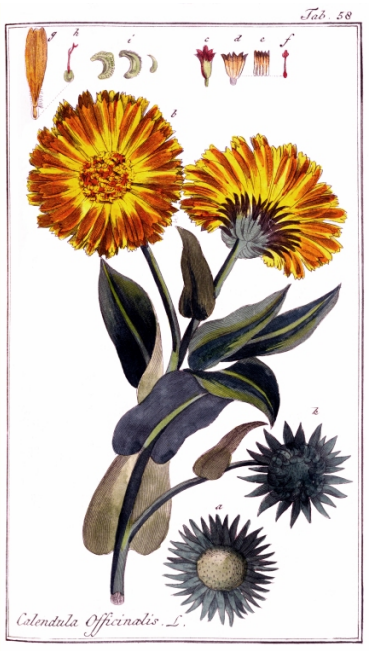
Mills SY et al. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. Br J Rheumatol 35.9 (1996): 874-7.

Schmid B et al. Effectiveness and tolerance of standardized willow bark extract in arthrosis patients. Randomized, placebo controlled double-blind study. Z Rheumatol 59.5 (2000): 314-20.

Schmid B et al. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. Phytother Res 15.4 (2001): 344-50.

Setty AR, Sigal LH. Herbal medications commonly used in the practice of rheumatology: mechanisms of action, efficacy, and side effects. Semin Arthritis Rheum 34.6 (2005): 773-84.

Withania



Historical note The name ashwagandha (one of the common names for this herb) comes from the sanskrit meaning 'horse-like smell'. Apparently, this name not only refers to the smell of the herb but also its strengthening and aphrodisiac qualities. It is often referred to as 'Indian ginseng' because it is used in much the same way in Ayurvedic medicine as *Panax ginseng* in TCM, although it is considered less stimulating.

OTHER NAMES

Ashwagandha (and a variety of spellings including ashvagandha, ashwaganda, asvagandha), Ayurvedic ginseng, Indian ginseng, winter cherry

BOTANICAL NAME/FAMILY

Withania somnifera (family Solanaceae)

Sometimes confused with *Physalis alkekengi*, also known as winter cherry.

PLANT PARTS USED

Primarily root, although berry, leaves and bark are sometimes used.

CHEMICAL COMPONENTS

Steroidal lactones (withanolides, withaferin A), alkaloids (including withanine, somniferine, isopelietierine, anaferine, tropine, pseudotropine), flavonoids, saponins, sitoindosides, iron, choline, acylsteryl glucosides, coumarins (scopoletin and aesculetin), triterpene (beta-amyrin), phytosterols (stigmasterol and beta-sitosterol), essential oils (ipuranol, withaniol) (Abou-Dooh 2002; Kulkarni & Verma 1993; Mills & Bone 2000).

MAIN ACTIONS

ADAPTOGEN (MODULATES STRESS RESPONSES)

Withania has been shown to attenuate the negative effects of chronic stress in rats, including hyperglycaemia, glucose intolerance, increase in plasma corticosteroid levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression (Bhattacharya & Muruganandam 2003).

Animal trials have shown that a withanolide-free hydrosoluble fraction of withania reduces the stress response induced both chemically and physically (Singh et al 2003). It suppresses stress-induced increases in dopamine receptors in the corpus striatum

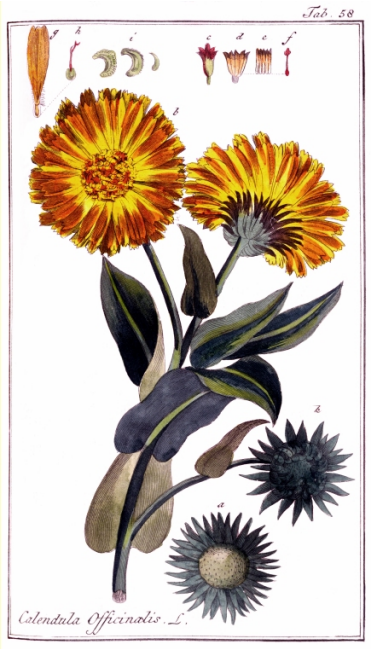
and acts as a GABA-mimetic agent by binding to GABA receptors (Mehta et al 1991, Upton 2000). Animal studies also suggest an ability to reduce adrenal weight and plasma cortisol levels (Kurandikar et al 1986), thus potentially protecting against the negative effects of elevated cortisol levels in chronic stress and allostasis.

NERVOUS SYSTEM ACTIVITY

Cognitive enhancement Memory enhancement has been confirmed by animal studies and appears to be mediated by a cholinergic effect (Dhuley 2001). Increased cortical muscarinic acetylcholine receptor capacity has been observed in animals and humans with extracts of withania (Schliebs et al 1997). Several withanolides exert calcium antagonistic ability, together with anticholinesterase activity, by inhibiting butyrylcholinesterase and acetylcholinesterase enzymes (Choudhary MI et al 2004, 2005). The presence of choline in the herb may also contribute to the production of acetylcholine and further increase cholinergic effects.

Neuroprotective Several animal studies indicate the potential for protection of neurons (Jain et al 2001), including protection from neuronal injury in Parkinson's disease (Ahmad et al 2005) and promotion of dendrite formation (Tohda et al 2000). One possible explanation is due to the antioxidant properties of withania (Parihar & Hemnani 2003).

In animal models of haloperidol-induced dyskinesia (chewing movements, tongue protrusion and buccal tremors), the reported benefits of withania appear to be due to its antioxidant rather than GABA-mimetic action (Bhattacharya SK et al 2002; Naidu et al 2003). In vitro results suggest that withanolide A is able to reconstruct neuronal networks, including axons, dendrites, pre- and postsynapses, in the neurons (Kuboyama et al 2002, 2005).



ANTIOXIDANT

Withania exerts an indirect antioxidant action in vivo (Bhattacharya SK et al 1997, Bhattacharya A et al 2001). Daily administration of *W. somnifera* root extract increases hepatic glucose-6-phosphatase activity and decreases hepatic lipid peroxidation, most likely by increasing the activity of endogenous antioxidant enzymes (Panda & Kar 1997, 1998, 1999). In vitro *W. somnifera* inhibits both the lipid peroxidation and the protein oxidative modification induced by copper (Gupta et al 2003). In animal studies the antioxidant actions have been proposed as a possible mechanism for withania preventing the negative effects of stroke induced by middle cerebral artery occlusion (Choudhary G et al 2003).

INCREASES HAEMATOPOIESIS

Animal trials indicate the herb increases haemoglobin and red blood cell levels (Ziauddin et al 1996) and increases haematopoiesis (Aphale et al 1998). The iron content of the herb may further contribute to its role in red blood cell formation.

IMMUNOMODULATION

Animal studies have shown immunomodulating effects of withania, including an increase in white blood cell, platelet and neutrophil counts (Agarwal et al 1999, Davis & Kuttan 2000, Gupta YK et al 2001, Ziauddin et al 1996), increases in IFN-gamma and IL-2 and a reduction in TNF (Davis & Kuttan 1999). In vitro, increased nitric oxide production by macrophages has also been reported (Iuvone et al 2003). Withaferin A and withanolide D may cause immunosuppression, but other factors have immunostimulant effects (NMCD 2006).

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

Animal and in vitro studies have shown antibacterial effects against *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus anthracis*, *Bacillus subtilis*, *Salmonella enteridis* (Akin et al 1986) and *Salmonella typhimurium* (Owais et al 2005). The methanol and hexane extracts of both the leaves and the roots have potent antibacterial activity against *S. typhimurium* and *Escherichia coli* (Arora et al 2004); and the steroidal withanolides from the related species *W. coagulens* have been found to have antifungal activity against *Allescheria boydii*, *Aspergillus niger*, *Curvularia lunata*, *Drechslera rostrata*, *Epidermophyton floccosum*, *Microsporum canis*, *Nigrospora oryzae*, *Pleurotus ostreatus* and *Stachybotrys atra* (Choudhary et al 1995).

ANTI-INFLAMMATORY ACTIVITY

The withanolides (steroidal lactones) are considered to have anti-inflammatory effects (Chevallier 1996). Several withanolides exert selective COX-2 enzyme inhibition (Jayaprakasam & Nair 2003) and withania has been found to decrease alpha-2-macroglobulin, a liver-synthesised plasma protein that increases during inflammation (Anbalagan & Sadique 1985). A reduction in the erythrocyte sedimentation rate has also been noted in a double-blind clinical trial of 50–59 year old males (Kupparajan et al 1980).

ANTICANCER (ANTINEOPLASTIC AND CHEMOPREVENTION)

Studies show that withania can stimulate the production of cytotoxic T-lymphocytes in vivo and in vitro, and that it may prevent or reduce tumour growth (Davis & Kuttan 2002; Jayaprakasam et al 2003). Withania was found in animal models to prevent skin carcinoma induced by UVB radiation (Mathur et al 2004) and forestomach

tumours (Padmavathi et al 2005); reduce the incidence, number and size of tumours; and to counteract the associated decrease in body weight (Singh et al 1996).

The withaferin A fraction appears to exert anti-angiogenic activity (Mohan et al 2004) and may be partly responsible for the antineoplastic effects observed in vitro and in vivo studies (Uma Devi 1995, 1996). The antioxidant effects aid in the prevention of DNA damage by mutagens (Khanam & Devi 2005) and this in combination with detoxifying properties, anti-inflammatory and immunomodulatory effects, determined in animal studies, are likely to contribute to its chemopreventive action (Prakash et al 2001, 2002).

ANXIOLYTIC AND ANTIDEPRESSANT

Animal studies have found glycowithanolides to exert anxiolytic effects comparable to those of lorazepam, and antidepressant effects comparable to those of the antidepressant drug, imipramine (Bhattacharya SK et al 2000).

OTHER ACTIONS

CARDIOPROTECTIVE

Cardioprotective effects have been noted in animal studies (Dhuley 2000, Mohanty et al 2004), significantly reducing myocardial injury after ischaemia and reperfusion (Gupta SK et al 2004). The alkaloids are considered to be sedative and reduce blood pressure and heart rate (Chevallier 1996, Malhotra et al 1965a). The withanolides have a chemical structure similar to cardiac glycosides and have demonstrated mild ionotropic and chronotropic effects on the heart (Roja et al 1991, Tripathi et al 1996).

THYROID MODULATING

An in vivo study reported that daily administration of *W. somnifera* root extract enhanced serum T_4 concentration (Panda & Kar 1998, 1999).

SEXUAL ENHANCER

Traditionally used for this purpose, one double-blind clinical trial found that a dose of 3 g taken daily for 1 year improved the sexual performance of 71.4% of healthy ageing males (Kupparajan et al 1980). Alternatively, animal studies have indicated that very high doses (3000 mg/kg) result in reduced sexual performance (Ilayperuma et al 2002).

HEPATOPROTECTIVE

Animal studies have demonstrated hepatoprotective effects (Bhattacharya A et al 2000, Sudhir et al 1986) and that withania inhibits phase I, and activates phase II and antioxidant enzymes in the liver (Padmavathi et al 2005).

CLINICAL USE

Overall, *W. somnifera* has not undergone significant scientific investigation in humans, therefore much of its use is based on pharmacological effects demonstrated in experimental models or traditional usage. In practice, it is often used in herbal combination treatments.

STRESS ADAPTATION

The pharmacological effects of the herb, which have been well established in animal studies, provide a theoretical basis for its use in situations characterised by stress (Archana & Namasivayam 1999; Bhattacharya & Muruganandam 2003; Dhuley 2000; Grandhi et al 1994).

More specifically, oral administration of an aqueous, standardised extract of *W. somnifera* (in a dose extrapolated from the human dose) has been found to offer protection against experimentally induced biological, physical and chemical stressors (Rege et al 1999).

In one in-vivo study, plasma cortisol levels and adrenal weight were significantly lower, while liver weight increased (Kurandikar et al 1986).

To date, controlled studies are unavailable to determine and clarify whether these effects are also significant in humans.

(For more information see 'Clinical note — Allostasis and adaptation to stress' in the Siberian ginseng monograph.)

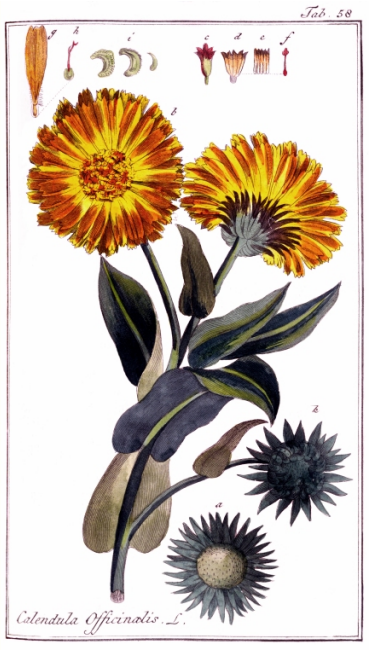
ANXIETY

Although controlled studies are lacking, the herb's pharmacological effects, such as its GABA-mimetic activity (Mehta et al 1991) and ability to lower cortisol levels (Kurandikar et al 1986), provide a theoretical basis for its use in anxiety states. One study used a herbal combination treatment known as Geriforte, which contains primarily *W. somnifera*. The product was taken by 34 subjects with anxiety neurosis, and after 12 weeks significant reductions in the frequency, duration and intensity of symptoms were observed (Ghosal et al 1990).

ANABOLIC AND WEIGHT GAIN PROMOTION

Both animal and human studies have shown significant improvements in weight gain during the growth phase with the use of withania (Sharma et al 1986; Ziauddin et al 1996). It is suspected that an anabolic effect is responsible.

Withania-fortified milk (2 g/day for 60 days) has been investigated in children and found to induce weight gain, increase total plasma proteins and haemoglobin levels (Venkatraghaven et al 1980).



ANAEMIA

The herb is used in the treatment of iron deficiency anaemia due to its effects on haemopoeisis and natural iron content (Aphale et al 1998; Ziauddin et al 1996). This use has been supported by studies showing increased haemoglobin levels in children, induced by withania.

CANCER THERAPY

Prevention of bone marrow depression Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy for the prevention of drug-induced bone marrow depression (Davis & Kuttan 1999; Gupta et al 2001).

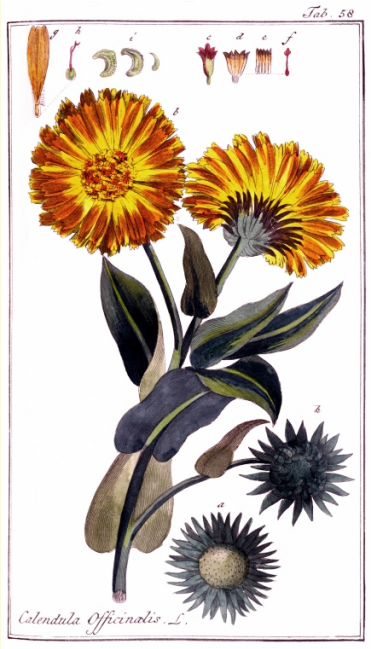
The ability to stimulate stem cell proliferation has led to concerns that *W. somnifera* could reduce cyclophosphamide-induced toxicity and therefore reduce its usefulness in cancer therapy (Davis & Kuttan 1998). However, preliminary animal studies indicate that withania could prove to be a potent and relatively safe radiosensitiser and chemotherapeutic agent (Uma Devi 1996).

DRUG WITHDRAWAL

In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence (Kulkarni & Ninan 1997). Based on this observation, and its ability to modulate stress responses in general, withania is used in herbal combination therapy during opiate withdrawal.

ARTHRITIS

Withania is traditionally incorporated into herbal combination formulations for symptom relief in osteoarthritis and rheumatoid arthritis. Its documented anti-inflammatory and antioxidant activities provide some support for this use, although controlled studies have not established efficacy.



OTHER USES

Traditionally used in convalescence for people who are stressed and both physically and emotionally exhausted. It is considered a non-stimulating tonic allowing for the restoration of vitality.

As the alkaloids are considered to be sedative and able to reduce blood pressure and heart rate (Chevallier 1996, Malhotra et al 1965a), it is also used in practice for insomnia, although controlled trials are lacking in this area.

DOSAGE RANGE

- Fluid extract (1:2): 5–13 mL/day.
- Dried root: 3–6 g/day in capsule or tea form.

ADVERSE REACTIONS

Large doses can cause gastrointestinal upset, diarrhoea and vomiting (Tierra 2005).

Central nervous system and respiratory depression (Malhotra et al 1965b), decreased body temperature (Malhotra et al 1965b), gastrointestinal upset (Lindner 1996) and kidney and liver abnormalities (Arseculeratne et al 1985) have been noted.

Acute toxicity studies in animals show a good margin of safety with a high therapeutic index (Aphale et al 1998, Rege et al 1999, Sharada et al 1993, Singh et al 2001, 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

BARBITURATES

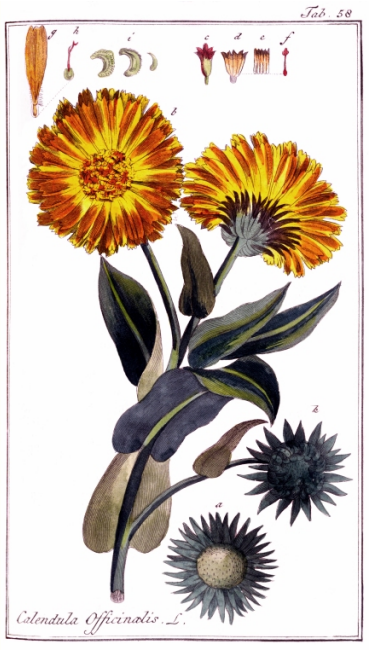
Additive effects are theoretically possible leading to increased sedation (NMCD 2006, Tierra 2005). Observe patients taking withania and barbiturates concurrently — beneficial interaction possible under medical supervision.

BENZODIAZEPINES

Additive effects are theoretically possible (Upton 2000). Observe patients taking withania and benzodiazepines concurrently — beneficial interaction possible under professional supervision.

CHEMOTHERAPY

Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy for the prevention of drug-induced bone marrow depression (Davis & Kuttan 1999, Gupta et al 2001). Observe — beneficial interaction possible under professional supervision.



IMMUNOSUPPRESSANTS (INCLUDING CYCLOPHOSPHAMIDE)

The ability to stimulate stem cell proliferation has led to concerns that *W. somnifera* could reduce cyclophosphamide-induced toxicity and its usefulness in cancer therapy (Davis & Kuttan 1998) although preliminary animal studies indicate a potential role as a potent and relatively safe radiosensitiser and chemotherapeutic agent (Uma Devi 1996). Theoretically it may also decrease the effectiveness of other immunosuppressant drugs. Caution should be exercised with patients taking immunosuppressants concurrently; however, a beneficial interaction may be possible under professional supervision.

MORPHINE

In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence (Kulkarni & Ninan 1997). For this reason it is sometimes used in opiate withdrawal. Beneficial interaction possible under professional supervision.

THYROID MEDICATION (E.G. LEVOTHYROXINE)

Additive effects are theoretically possible as an in vivo study reported that daily administration of withania enhanced serum T4 concentrations — observe patients taking withania and thyroid medications concurrently (Upton 2000).

CONTRAINDICATIONS AND PRECAUTIONS

Use with caution in peptic ulcer disease: withania may cause gastrointestinal irritation (Upton 2000). People who are sensitive to the Solanaceae family should use this herb with caution.

PREGNANCY USE

Contraindicated in pregnancy (Lindner 1996) due to a reputed abortifacient activity.

PRACTICE POINTS/PATIENT COUNSELLING

- Withania is an Ayurvedic herbal medicine also referred to as Indian ginseng or ashwaganda. Overall, it has not undergone significant scientific investigation in humans and therefore much of its use is based on pharmacological effects demonstrated in experimental models or traditional usage.
- It is traditionally used for improving stress adaptation responses in people who are both physically and emotionally stressed and exhausted and during periods of convalescence.
- Preliminary evidence suggests it increases haematopoiesis, promotes weight gain, reduces anxiety symptoms, increases cognitive function and exerts a neuroprotective effect.
- It has also demonstrated antioxidant, immunomodulating, antineoplastic, antifungal and antibacterial activity in animal or test tube studies.
- The herb should not be taken in pregnancy, and used with caution in people sensitive to the Solanaceae family of plants.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this herb do for me?

Withania has not undergone much scientific investigation in humans, so it is difficult to predict what effects will occur using this source of information. However, according to traditional usage and other studies, it may improve stress responses,

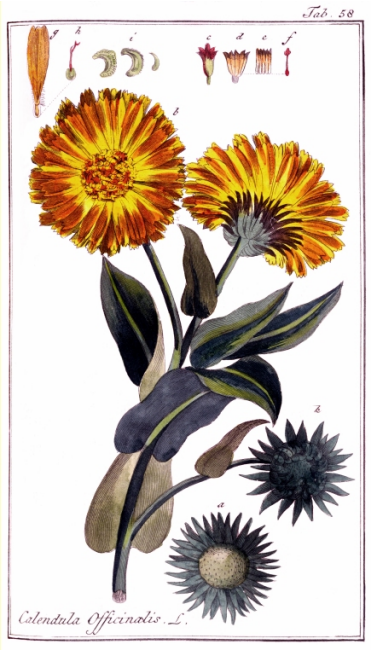
reduce symptoms of anxiety, improve memory and mood, increase red blood cell production, increase immune responses and promote weight gain and is useful in convalescence.

When will it start to work?

Symptoms of anxiety and stress improve within 3 months' continual use. It is not known when other effects start to develop.

Are there any safety issues?

The herb should not be taken in pregnancy, and used with caution in people sensitive to the Solanaceae family of plants.



REFERENCES

Abou-Douh AM. New withanolides and other constituents from the fruit of Withania somnifera. Arch Pharm (Weinheim) 335(6) (2002): 267-76.

Agarwal R et al. Studies on immunomodulatory activity of Withania somnifera (Ashwagandha) extracts in experimental immune inflammation. J Ethnopharmacol 67(1) (1999): 27-35.

Ahmad M et al. Neuroprotective effects of Withania somnifera on 6-hydroxydopamine induced Parkinsonism in rats. Hum Exp Toxicol 24(3) (2005): 137-47.

Akin S et al. Antibacterial effects of some higher plants. Gazi Ecz Fak Der 3(1) (1986): 65-80.

al-Hindawi MK et al. J Ethnopharmacol 37(1992): 113. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.

Anbalagan K, Sadique J. Int J Crude Drug Res 23 (1985): 177. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.

Andallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (Withania somnifera, Dunal) root. Indian J Exp Biol 38(6) (2000): 607-9.

Aphale AA et al. Subacute toxicity study of the combination of ginseng (Panax ginseng) and ashwagandha (Withania somnifera) in rats: a safety assessment. Indian J Physiol Pharmacol 42(2) (1998): 299-302.

Archana R, Namasivayam A. Antistressor effect of Withania somnifera. J Ethnopharmacol 64(1) (1999): 91-3.

Arora S et al. The in vitro antibacterial/synergistic activities of Withania somnifera extracts. Fitoterapia 75(3-4) (2004): 385-8.

Arseculeratne SN, Gunatilaka AAL, Panabokke RG. Studies on medicinal plants of Sri Lanka. Part 14: toxicity of some traditional medicinal herbs. J Ethnopharmacol 13(3) (1985): 323-35.

Begum VH, Sadique J. Effect of Withania somnifera on glycosaminoglycan synthesis in carrageenan-induced air pouch granuloma. Biochem Med Metab Biol 38(3) (1987): 272-7.

Bhattacharya A et al. Anti-oxidant effect of Withania somnifera glycowithanolides in chronic foot shock stress-induced perturbations of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. J Ethnopharmacol 74(1) (2001): 1-6.

Bhattacharya SK et al. Antioxidant activity of glycowithanolides from Withania somnifera. Indian J Exp Biol 35(3) (1997): 236-9.

Bhattacharya A et al. Effect of Withania somnifera glycowithanolides on iron-induced hepatotoxicity in rats. Phytother Res. 14(7) (2000): 568-70.

Bhattacharya SK et al. Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: an experimental study. Phytomedicine 7(6) (2000): 463-9.

Bhattacharya SK et al. Effect of Withania somnifera glycowithanolides on a rat model of tardive dyskinesia. Phytomedicine 9(2) (2002): 167-70.

Bhattacharya SK, Muruganandam AV. Adaptogenic activity of Withania somnifera: an experimental study using a rat model of chronic stress. Pharmacol Biochem Behav 75(3) (2003): 547-55.

Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.

Chevallier A. The Encyclopedia of Medicinal Plants. London, UK: Dorling Kindersley, 1996.
Choudhary G et al. Evaluation of Withania somnifera in a middle cerebral artery occlusion model of stroke in rats. Clin Exp Pharmacol Physiol 30(5-6) (2003): 399-404.
Choudhary MI et al. Antifungal steroidal lactones from Withania coagulance. Phytochemistry 40(4) (1995): 1243-6.
Choudhary MI et al. Cholinesterase inhibiting withanolides from Withania somnifera. Chem Pharm Bull (Tokyo) 52(11) (2004): 1358-61.
Choudhary MI et al. Withanolides, a new class of natural cholinesterase inhibitors with calcium antagonistic properties. Biochem Biophys Res Commun 334(1) (2005): 276-87.
Davis L, Kuttan G. Suppressive effect of cyclophosphamide-induced toxicity by Withania somnifera extract in mice. J Ethnopharmacol 62(3) (1998): 209-14.
Davis L, Kuttan G. Effect of Withania somnifera on cytokine production in normal and cyclophosphamide treated mice. Immunopharmacol Immunotoxicol 21(4) (1999): 695-703.
Davis L, Kuttan G. Immunomodulatory activity of Withania somnifera. J Ethnopharmacol 71(1-2) (2000): 193-200.
Davis L, Kuttan G. Effect of Withania somnifera on CTL activity. J Exp Clin Cancer Res 21(1) (2002): 115-18.
Dhuley JN. Effect of ashwagandha on lipid peroxidation in stress-induced animals. J Ethnopharmacol 60(2) (1998): 173-8.
Dhuley JN. Adaptogenic and cardioprotective action of ashwagandha in rats and frogs. J Ethnopharmacol 70(1) (2000): 57-63.
Dhuley JN. Nootropic-like effect of ashwagandha (Withania somnifera L.) in mice. Phytother Res 15(6) (2001): 524-8.
Ghosal S et al. Role of an indigenous drug Geriforte on blood levels of biogenic amines and its significance in the treatment of anxiety neurosis. Acta Nerv Super 32(1) (1990): 1-5.
Grandhi A, Mujumdar AM, Patwardhan B. A comparative pharmacological investigation of Ashwagandha and Ginseng. J Ethnopharmacol 44(3) (1994): 131-5.
Gupta S, Dua A, Vohra B. Withania somnifera (Ashwagandha) attenuates antioxidant defense in aged spinal cord and inhibits copper induced lipid peroxidation and protein oxidative modifications. Drug Metab Drug Interact 19(3) (2003): 211-22.
Gupta SK et al. Cardioprotection from ischemia and reperfusion injury by Withania somnifera: a hemodynamic, biochemical and histopathological assessment. Mol Cell Biochem 260(1-2) (2004): 39-47.
Gupta YK et al. Reversal of paclitaxel induced neutropenia by Withania somnifera in mice. Indian J Physiol Pharmacol 45(2) (2001): 253-7.
Hazeena Begum V, Sadique J. Long term effect of herbal drug Withania somnifera on adjuvant induced arthritis in rats. Indian J Exp Biol 26(11) (1988): 877-82.
Ilayperuma I, Ratnasooriya WD, Weerasooriya TR. Effect of Withania somnifera root extract on the sexual behaviour of male rats. Asian J Androl 4(4) (2002): 295-8.
Iuvone T et al. Induction of nitric oxide synthase expression by Withania somnifera in macrophages. Life Sci 72(14) (2003): 1617-25.
Jain S et al. Neuroprotective effects of Withania somnifera Dunn. in hippocampal sub-regions of female albino rat. Phytother Res 15(6) (2001): 544-8.
Jayaprakasam B, Nair MG. Cyclooxygenase-2 enzyme inhibitory withanolides from Withania somnifera leaves. Tetrahedron 59(6) (2003): 841-9.
Jayaprakasam B et al. Growth inhibition of human tumor cell lines by withanolides from Withania somnifera leaves. Life Sci 74(1) (2003): 125-32.
Khanam S, Devi K. Antimutagenic activity of Ashwagandha. J Nat Remed 5(2) (2005): 126-31.
Kuboyama T et al. Axon- or dendrite-predominant outgrowth induced by constituents from Ashwagandha. Neuroreport 13(14) (2002): 1715-20.
Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. Br J Pharmacol 144(7) (2005): 961-71.

Kulkarni SK, Ninan I. Inhibition of morphine tolerance and dependence by Withania somnifera in mice. J Ethnopharmacol 57(3) (1997): 213-17.
Kulkarni SK, Verma A. Aswagandha and brahmi: nootropic and de-addiction profile of psychotropic indigenous plants. Drugs Today 29(4) (1993): 257-63.
Kulkarni RR et al. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. J Ethnopharmacol 33(1-2) (1991): 91-5.
Kulkarni SK et al. GABA receptor mediated anticonvulsant action of Withania somnifera root extract. Indian Drugs 30(7) (1993): 305-12.
Kulkarni SK, George B, Nayar U. Amygdalid kindling in rats: protective effect of Withania somnifera (aswagandha) root extract. Indian Drugs 32(1) (1994): 37-49.
Kulkarni SK, George B, Mathur R. Protective effect of Withania somnifera root extract on electrographic activity in a lithium–pilocarpine model of status epilepticus. Phytother Res 12(6) (1998): 451-3.
Kupparajan K et al. J Res Ayu Sid 1 (1980): 247. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.
Kurandikar et al. Indian Drugs 23 (1986): 123. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.
Kuttan G. Use of Withania somnifera Dunal as an adjuvant during radiation therapy. Indian J Exp Biol 34(9) (1996): 854-6.
Lindner S. Withania somnifera. Aust J Med Herbalism 8(3) (1996): 78-82.
Malhotra CL et al. Studies on Withania – ashwagandha, Kaul. Part IV: The effect of total alkaloids on the smooth muscles. Indian J Physiol Pharmacol 9(1) (1965a): 9-15.
Malhotra CL et al. Studies on Withania – ashwagandha, Kaul. Part V: The effect of total alkaloids (ashwagandholine) on the central nervous system. Indian J Physiol Pharmacol 9(3) (1965b): 127-36.
Mathur S et al. The treatment of skin carcinoma, induced by UV B radiation, using 1-oxo-5[beta], 6[beta]-epoxy-witha-2-enolide, isolated from the roots of Withania somnifera, in a rat model. Phytomedicine 11(5) (2004): 452-60.
McGuffin M et al (eds). American Herbal Products Association's Botanical Safety Handbook. Boca Raton, FL: CRC Press, 1997.
Mehta AK et al. Pharmacological effects of Withania somnifera root extract on GABA receptor complex. Indian J Med Res 94(B) (1991): 312-15.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Mohan R et al. Withaferin A is a potent inhibitor of angiogenesis. Angiogenesis 7(2) (2004): 115-22.
Mohanty I et al. Mechanisms of cardioprotective effect of Withania somnifera in experimentally induced myocardial infarction. Basic Clin Pharmacol Toxicol 94(4) (2004): 184-90.
Naidu PS, Singh A, Kulkarni SK. Effect of Withania somnifera root extract on haloperidol-induced orofacial dyskinesia: possible mechanisms of action. J Med Food 6(2) (2003): 107-14.
Natural medicines comprehensive database (NMCD online) 2006. Withania. Available from: http://www.naturaldatabase.com (Accessed 10-11-05).
Owais M et al. Antibacterial efficacy of Withania somnifera (ashwagandha) an indigenous medicinal plant against experimental murine salmonellosis. Phytomedicine 12(3) (2005): 229-35.
Padmavathi B et al. Roots of Withania somnifera inhibit forestomach and skin carcinogenesis in mice. Evidence Based Complement Altern Med 2(1) (2005): 99-105.
Panda S, Kar A. Evidence for free radical scavenging activity of Ashwagandha root powder in mice. Indian J Physiol Pharmacol 41(4) (1997): 424-6.
Panda S, Kar A. Changes in thyroid hormone concentrations after administration of ashwagandha root extract to adult male mice. J Pharm Pharmacol 50(9) (1998): 1065-8.
Panda S, Kar A. Withania somnifera and Bauhinia purpurea in the regulation of circulating thyroid hormone concentrations in female mice. J Ethnopharmacol 67(2) (1999): 233-9.
Parihar MS, Hemnani T. Phenolic antioxidants attenuate hippocampal neuronal cell damage against kainic acid induced excitotoxicity. J Biosci 28(1) (2003): 121-8.

Prakash J et al. Chemopreventive activity of Withania somnifera in experimentally induced fibrosarcoma tumours in Swiss albino mice. Phytother Res 15(3) (2001): 240-4.
Prakash J, Gupta SK, Dinda AK. Withania somnifera root extract prevents DMBA-induced squamous cell carcinoma of skin in Swiss albino mice. Nutr Cancer 42(1) (2002): 91-7.
Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytother Res 13(4) (1999): 275-91.
Roja G, Heble MR, Sipahimalani AT. Tissue cultures of Withania somnifera: morphogenesis and withanolide synthesis. Phytother Res 5(4) (1991): 185-87.
Schliebs R et al. Systemic administration of defined extracts from Withania somnifera (Indian Ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain. Neurochem Int 30(2) (1997): 181-90.
Sharada AC, Solomon FE, Uma Devi P. Toxicity of Withania somnifera root extract in rats and mice. Int J Pharmacogn 31(3) (1993): 205-12.
Sharma S, Dahanukar S, Karandikar SM. Indian Drugs 23 (3) (1986): 133-9. Cited in Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Singh B et al. Adaptogenic activity of a novel, withanolide-free aqueous fraction from the roots of Withania somnifera Dun. Phytother Res 15(4) (2001): 311-18.
Singh B, Chandan BK, Gupta DK. Adaptogenic activity of a novel withanolide-free aqueous fraction from the roots of Withania somnifera Dun. Part II. Phytother Res 17(5) (2003): 531-6.
Singh N et al. Int J Crude Drug Res 24 (1986): 90. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Phytotherapy Press, 1996.
Sudhir S et al. Pharmacological studies on leaves of Withania somnifera. Planta Med 52(1) (1986): 61-3.
Tierra M. Ashwagandha: Wonder Herb of India. Available from: http://www.planetherbs.com/articles/ashwagandha.htm (Accessed 8-12-05).
Tohda C, Kuboyama T, Komatsu K. Dendrite extension by methanol extract of Ashwagandha (roots of Withania somnifera) in SK-N-SH cells. Neuroreport 11(9) (2000): 1981-5.
Tripathi AK, Shukla YN, Kumar S. Ashwagandha (Withania somnifera Dunal (Solanaceae)): A status report. J Med Aromatic Plant Sci 1(1996): 46-62.
Uma Devi P. Withania somnifera Dunal (ashwagandha): potential plant source of a promising drug for cancer chemotherapy and radiosensitization. Indian J Exper Biol 34(10) (1996): 927-32.
Uma Devi P, Sharada AC, Solomon FE. In vivo growth inhibitory and radiosensitizing effects of withaferin A on mouse Ehrlich ascites carcinoma. Cancer Lett 95(1-2)(1995): 189-93.
Upton R (ed.). Ashwagandha root (Withania somnifera): Analytical quality control and therapeutic monograph. Am Herbal Pharm, 2000, 1-25.
Venkatraghaven S et al. J Res Ayu Sid 1 (1980): 370. Cited in: Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Warwick, Qld: Phytotherapy Press, 1996.
Ziauddin M et al. Studies on the immunomodulatory effects of Ashwagandha. J Ethnopharmacol 50(2) (1996): 69-76.

Zinc

BACKGROUND AND RELEVANT PHARMACOKINETICS

Zinc is an essential trace element known to play an important role in all human living cells. The human body contains approximately 2 g zinc in total, with 60% found in skeletal muscle and 30% in bone mass, although it is found in all body tissues and fluids (Wahlqvist et al 1997). Dietary intake of zinc by healthy adults is 6–15 mg/day, but less than half of this is absorbed (Beers & Berkow 2003). It is now known that zinc absorption is influenced by many factors and adequate dietary intake is not necessarily indicative of adequate zinc status. High amounts of zinc in a meal cause a fractional decrease in zinc absorption and foods with high phytate content (e.g. wholegrains, corn and rice) significantly reduce zinc absorption due to the formation of strong and insoluble complexes (Lonnerdal 2000). Concerns have also been raised over the potential of calcium, iron, copper and cadmium to reduce zinc absorption. Alternatively, the amount of animal protein in a meal positively correlates to zinc absorption and the amino acids histidine and methionine, and various organic acids present in foods, such as citric, malic and lactic acids, can also increase absorption. As such, zinc is best absorbed from animal food sources (King 2003).

CHEMICAL COMPONENTS

Zinc sulfate and gluconate are the most commonly used forms in supplements.

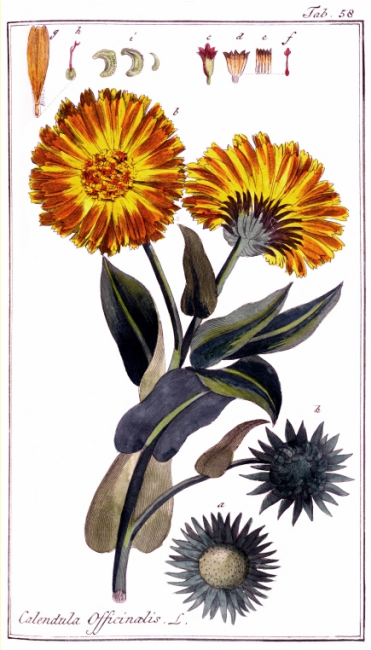
FOOD SOURCES

Meat, liver, eggs, seafood (especially oysters and shellfish) are the best sources, but zinc is also found in nuts, legumes, wholegrains, miso, tofu, brewers' yeast, mushrooms, green beans and pumpkin seeds.

DEFICIENCY SIGNS AND SYMPTOMS

Severe deficiency is rarely seen in industrialised countries, but marginal deficiency and inadequate intakes are not uncommon. According to a large national survey of over 29,000 people conducted in the USA, only 55.6% had adequate zinc intakes (based on total intakes of >77% of the 1989 US RDI levels). Young children aged 1–3 years, female adolescents and older people aged ≥71 years had the lowest percentage of 'adequate' zinc intake, and were identified at greatest risk of deficiency (Briefel et al 2000). Others at risk are alcoholics (especially those with liver disease), pregnant and lactating women, teenagers experiencing rapid growth, malnourished individuals

including those with anorexia nervosa, people with severe or chronic diarrhoea, malabsorption syndromes or inflammatory bowel diseases, and strict vegetarians.



SIGNS AND SYMPTOMS OF DEFICIENCY

- Anorexia and impaired sense of taste.
- Slowed growth and development, and delayed sexual maturation.
- Delayed sexual maturation, hypogonadism and hypospermia, and menstrual problems.
- Skin rashes.
- Alopecia.
- Chronic and severe diarrhoea.
- Immune system deficiencies and increased susceptibility to infection.
- Impaired wound healing due to decreased collagen synthesis.
- Night blindness; swelling and clouding of the corneas.
- Behavioural disturbances such as mental fatigue and depression (King 2003).
- Erectile dysfunction.

Zinc deficiency in pregnancy is associated with the following (Bedwal & Bahuguna 1994, Prasad 1996):

- Increased maternal morbidity, pre-eclampsia and toxaemia.
- Prolonged gestation.
- Inefficient labour.
- Atonic bleeding.
- Increased risk of abortion and stillbirths.
- Teratogenicity.
- Low birthweight infants.
- Diminished attention in the newborn and poorer motor function at 6 months (Higdon 2003).

PRIMARY DEFICIENCY

This can result from inadequate dietary intake of zinc; however, inhibition of zinc absorption is a common causative factor (Lonnerdal 2000). Strict vegetarians are at risk of deficiency if their major food staples are grains and legumes because the phytic acid in these foods will impair dietary zinc absorption.

SECONDARY DEFICIENCY

Zinc deficiency develops in some people with cirrhosis, malabsorption syndromes, sickle cell anaemia, conditions of increased zinc loss, such as severe burns or major surgery, chronic diarrhoea or diabetes, HIV and AIDS, and during prolonged parenteral nutrition (Prasad et al 1999). Additionally, strenuous exercise and elevated

ambient temperatures increase zinc losses through perspiration. A congenital disorder known as acrodermatitis enteropathica causes severe zinc deficiency.

Clinical note — Measuring zinc status is difficult

Currently, there is no universally accepted single measure of zinc status in humans. The most commonly used approach is the measurement of serum zinc levels, but this is a poor measure of marginal zinc deficiency because zinc is primarily found intracellularly and only a small portion is found in the circulation where it is mainly bound to plasma protein. Plasma zinc levels are affected by the homeostatic system and other factors, such as diurnal rhythm, stress, infection, starvation and plasma protein levels. As a consequence, it is not an accurate reflection of dietary zinc intake or true zinc status (Wood 2000). Estimation of hair zinc levels is another tool used, with low hair zinc levels indicative of zinc depletion. This method is costly and also subject to inaccuracies caused by variable hair growth and the presence of zinc in some shampoos. The zinc taste response test (also known as the Bryce-Smith taste test) is a popular measure among naturopathic practitioners. It relies on patients detecting a taste after oral administration of 10 mL of a zinc sulfate solution. Delayed taste perception or lack of taste is seen to indicate a zinc deficiency state. It is based on the theory that sense of taste is primarily influenced by the zinc dependent enzyme, gustin, in the saliva. As such, low zinc status should substantially affect taste discrimination. This method is not particularly accurate and hampered by variations in patients' subjective sense of taste and the fact that agents other thans zinc influence taste perception. Clinical studies with zinc taste tests have confirmed the inconsistency of the results (Birmingham et al 2005, Garg et al 1993, Mahomed et al 1993). Ultimately, this leaves the diagnosis of marginal deficiency up to a practitioner's clinical suspicion.

MAIN ACTIONS

IMPORTANT COFACTOR IN MANY BIOCHEMICAL REACTIONS

As a constituent of over 300 metalloenzymes, zinc is involved in myriad chemical reactions that are important for normal body functioning, such as carbohydrate metabolism, protein and DNA synthesis, protein digestion, bone metabolism and endogenous antioxidant systems (Beers et al 1999, Wahlqvist et al 1997, Wardlaw et al 1997). At the cellular level, the function of zinc can be divided into three categories: catalytic, structural and regulatory (King 2003).

Growth and development Zinc is important for the formation of biomembranes and zinc finger motifs found in DNA transcription factors (Semrad 1999).

Normal immune responses Zinc is involved in many aspects of immunological function. It is essential for the normal development and function of cells, mediating non-specific immunity such as neutrophils and natural killer cells and affecting development of acquired immunity and T-lymphocyte function. Deficiency rapidly diminishes antibody and cell-mediated responses in both humans and animals, leading to increases in opportunistic infections and mortality rates (Fraker et al 2000). Animal models have shown that suboptimal intake of zinc over 30 days can lead to 30–80% loss in defence capacity. Investigation using a human model has demonstrated that even mild deficiency in humans adversely affects T-cell functions (Prasad 1998). Conversely, high-dose zinc supplementation (20-fold RDI) can also produce immune dysfunction.

Neurological function Zinc ions are unevenly distributed in the CNS, acting as neurosecretory products or cofactors. Zinc is highly concentrated in the synaptic vesicles of specific neurons, known as 'zinc-containing' neurons (Frederickson and Danscher 1990, Frederickson and Moncrieff 1994, Frederickson et al 2000). Zinc-containing neurons are a subset of glutamatergic neurons and mostly located in the telencephalon. Zinc is released from zinc-containing neurons in a calcium- and impulse-dependent manner, producing a broad spectrum of neuromodulatory effects. Additionally, zinc appears to stabilise the storage of certain macromolecules in presynaptic vesicles.

Reproduction In humans, zinc is necessary for the formation and maturation of spermatozoa, for ovulation, and for fertilisation (Favier 1992). Zinc has multiple actions on the metabolism of androgen hormones, oestrogen and progesterone, and these, together with the prostaglandins and nuclear receptors for steroids, are all zinc finger proteins.

In adult males, zinc content is high in the testis and prostate, which have the highest concentration of zinc of any organ in the body (Bedwal & Bahuguna 1994).

In women, zinc deficiency in pregnancy has been associated with increased maternal morbidity, increased risk of abortion, stillbirth, teratogenicity and other unwanted outcomes (Bedwal & Bahuguna 1994).

Antioxidant Zinc limits oxidant-induced damage in a number of indirect ways, such as protecting against vitamin E depletion, controlling vitamin A release, contributing to the structure of the antioxidant enzyme extracellular superoxide dismutase, restricting endogenous free radical production, maintaining tissue concentrations of metallothionein, a possible scavenger of free radicals, and stabilising membrane structure (DiSilvestro 2000). More recently it was observed to decrease

lipid peroxidation, and protect mononuclear cells from TNF-alpha induced NF-kappa-B activation associated with oxidative stress (Prasad et al 2004).

Insulin-like activity One of the in vivo features of zinc is its insulin-like function, which is mediated via inhibition of endogenous GSK-3 (Ilouz et al 2002). This is important because GSK-3 inhibition appears essential for normal function of the insulin-activated signalling pathway.

CLINICAL USE

Many of the clinical uses of zinc supplements are for conditions thought to arise from a marginal zinc deficiency, but some indications are based on the concept that high-dose zinc supplements act as a therapeutic agent.

DEFICIENCY

Traditionally, zinc supplementation has been used to treat deficiency or prevent deficiency in conditions such as acrodermatitis enteropathica, anorexia nervosa, malabsorption syndromes, conditions associated with chronic diarrhoea, alcoholism, diabetes, HIV and AIDS, recurrent infections, severe burns, Wilson's disease and sickle cell anaemia. Zinc supplements are also popular among athletes in order to counteract the zinc loss that occurs through perspiration.

COMMON COLD

Oral zinc supplements, lozenges and nasal sprays and gels have been investigated in the treatment of the common cold. It has been demonstrated that a transient increase in zinc concentrations in and around the nasal cavity prevents rhinovirus binding to cells and disrupts infection (Novick et al 1996) and/or modulates inflammatory cytokines that may exacerbate cold symptoms.

Nasal preparations A randomised, double-blind placebo-controlled trial with 160 people tested the effects of a nasal spray of 0.12% zinc sulfate and found that it reduced the total symptom score, but had no effect on the duration of cold symptoms or the mean time to resolution (Belongia et al 2001). The effectiveness of intranasal zinc gluconate as a preventative agent against experimentally induced rhinovirus infection was tested in a study of 91 subjects (Turner 2001). It was administered for 3 days prior to rhinovirus inoculation followed by 6 days of treatment. This regimen had no effect on total symptom score, rhinorrhea, nasal obstruction, or the proportion of infected volunteers who developed clinical colds.

Two other trials using a dose of zinc in a nasal gel formulation showed that zinc treatment significantly reduced cold duration compared with placebo when used within 24–48 hours of symptom onset (Hirt et al 2000, Mossad 2003). The nasal gel spray contained either 33 mmol/L zinc gluconate or placebo and was administered as

one dose per nostril four times daily until symptoms resolved or for a maximum of 10 days. Symptoms that responded included nasal drainage, hoarseness and sore throat (Mossad 2003).

Oral supplements Both positive and negative results have been obtained for different forms of oral zinc supplements and specialised preparations. A 2000 Cochrane review analysed the results from seven trials involving 754 cases and concluded that current evidence is inconclusive as to whether zinc lozenges are an effective treatment for symptoms of the common cold (Marshall 2000). This conclusion is considered conservative, as an intention-to-treat analysis at 7 days found a statistically significant RR of 0.69 and the numbers needed to treat for one person to benefit ranged from 4 to 8 (Arroll 2005). The authors of the review were concerned about blinding of the studies and variation in doses used making a conclusive recommendation difficult.

Since then, several new studies have been published (Eby & Halcomb 2006, McElroy & Miller 2002, 2003, Turner & Cetnarowski 2000). McElroy and Miller (2002) showed that treatment with zinc gluconate glycine lozenges (Cold-Eeze) significantly decreased cold duration (7.5 vs 9.0 days for non use) and significantly reduced cold frequency and concomitant antibiotic use in school-aged subjects. A subsequent phase IV study by the same pair of researchers (2003) investigated the therapeutic and prophylactic effectiveness of Cold-Eeze for the common cold in a cohort of 134 subjects drawn from the previous study. Once again, zinc gluconate glycine lozenges shortened cold duration (6.9 vs 9.0 days) and the mean number of colds (1.7 vs 1.28), achieving a 25% reduction in cold incidence. Zinc lozenges were administered once daily during the cold season and four times daily as acute treatment. An adult study demonstrated that zinc gluconate (13.3 mg) or zinc acetate (5 or 11.5 mg) lozenges had no effect on duration or severity of cold symptoms (Turner & Cetnarowski 2000). A recent double-blind, placebo controlled study found that frequent administration of zinc orotate lozenges (37 mg zinc each) and intranasal zinc gluconate spray had no effects on severity of cold symptoms or their duration (Eby & Halcomb 2006).

It is not clear why some trials have produced positive results whereas others have not; however, it is suspected that the type of zinc and formulation used has an influence over effectiveness. A closer look at the evidence shows that zinc gluconate or zinc acetate are the forms generally associated with positive results whereas other forms are less effective. Additionally, lozenge additives such as sorbitol and citric acid are thought to decrease zinc ion release, which is necessary for zinc's virucidal activity. It has been suggested that zinc lozenges be allowed to completely dissolve in

the mouth without chewing and that citrus fruits or juices be avoided 30 minutes before or after dissolving each lozenge to avoid negating the therapeutic effects of zinc (Silk & Lefante 2005).

AGE-RELATED MACULAR DEGENERATION

Both dietary and supplemental zinc have been investigated in the prevention and/or progression of ARMD.

A 2002 Cochrane review assessed the effects of antioxidant vitamin and/or mineral supplementation on the progression of ARMD and found that evidence of effectiveness is currently dominated by one large trial that showed modest benefit in people with moderate to severe signs of the disease who were administered antioxidant vitamins and zinc together (Evans 2002). More recently, results of the Age-Related Eye Disease Study were published (AREDS 2001), which showed that high-dose vitamins C and E, beta-carotene, and zinc supplementation delayed the progression from intermediate to advanced disease by 25% over 5 years. The 11 centre, double-blind, prospective study involved 3640 volunteers aged between 55 and 80 years who were randomly divided into four treatment groups, receiving either antioxidant supplements (500 mg vitamin C, 400 international units (IU) vitamin E, and 15 mg beta carotene daily), zinc oxide and cupric oxide (80 mg elemental zinc, 2 mg elemental copper daily), antioxidants plus zinc, or placebo. The contribution of zinc to this result is unknown (see Lutein monograph for more information about ARMD).

Overall, the current available data are insufficient to conclusively state that zinc supplementation used as stand-alone treatment should be taken during the early signs of disease; however, when taken in combination with antioxidant vitamins the evidence is more supportive for its use in intermediate ARMD.

In terms of primary prevention, a 2005 study found that high dietary intake of zinc, beta-carotene and vitamins C and E was associated with a 35% reduced risk of ARMD in elderly persons (van Leeuwen et al 2005).

DIABETES MELLITUS

Zinc supplementation is sometimes used in diabetes in order to avoid deficiency, a state associated with both type 1 and 2 diabetes in numerous studies (Cunningham et al 1994). It is still unknown whether restoring zinc status to normal levels or using high-dose zinc to induce other effects will be beneficial in the clinical management of diabetes, its complications or its prevention, as current data from both animal and human studies have produced varied results (Baydas et al 2002, Cunningham et al 1994, Farvid et al 2004, Gupta et al 1998, Niewoehner et al 1986, Roussel et al 2003, Tobia et al 1998).

A prospective, double-blind, clinical interventional study of 56 obese women with normal glucose tolerance who were randomised to treatment with zinc, 30 mg/day, or placebo for 4 weeks (Marreiro et al 2002) found that zinc treatment decreased insulin resistance from 5.8 to 4.3 and insulin decreased from 28.8 to 21.2 mU/mL in the zinc group, but was unchanged in the placebo group. These results are particularly noteworthy because the women were not zinc deficient, suggesting a therapeutic role for zinc.

Clinical note — Zinc deficiency and diabetes
Diabetes affects zinc homeostasis in many ways and is associated with increased urinary loss, decreased absorption and decreased total body zinc (Chausmer 1998, Cunningham et al 1994). The role of zinc and zinc deficiency in diabetes and its complications or prevention is currently unclear. It has been suggested that deficiency may exacerbate destruction of islet cells in type 1 diabetes and may adversely affect synthesis, storage and secretion of insulin, a process that requires zinc. Furthermore, evidence indicates that patients with type 1 diabetes mellitus have a higher concentration of free radicals than healthy controls, which is due to increased oxidant production and/or decreased efficiency of endogenous antioxidant systems (Davison et al 2002). It is suspected that deficiency of key micronutrients (i.e. zinc, copper, manganese and selenium), which are integral components of important antioxidant systems, may be partly responsible.

IMPROVES WOUND HEALING
Zinc is an essential cofactor in wound healing and immune function. Therefore, zinc deficiency retards both fibroplasia and epithelialisation, and results in delayed wound healing. Zinc supplements are used to restore zinc status in cases of wound healing associated with malnutrition and deficiency. Additionally, zinc administered orally or topically to wounds can promote healing and reduce infection, according to one major review (Lansdown 1996).

In 2001, a randomised study demonstrated that oral zinc sulfate significantly improved healing of cutaneous leishmaniasis (Sharquie et al 2001). Results showed that the cure rate for a dose of 2.5 mg/kg was 83.9%, for 5 mg/kg it was 93.1% and for 10 mg/kg it was 96.9%, whereas no lesions showed any sign of healing in the control group.

Topical application Topical zinc oxide promotes cleansing and re-epithelialisation of ulcers and reduces the risk of infection and deterioration of ulcers compared with placebo, according to one double-blind trial of leg ulcer patients with low serum zinc levels (Agren 1990). Evidence from animal and in vitro research suggests that topically

applied zinc solution is more effective when combined with iron than when used alone, and can effectively enhance healing in acute partial-thickness and second-degree burn wounds (Feiner et al 2003).

ARTERIAL AND VENOUS LEG ULCERS

A 2000 Cochrane review assessed six placebo-controlled trials of zinc sulfate supplementation in arterial and venous leg ulcers and concluded that overall there is no evidence of a beneficial effect on the number of ulcers healed. However, there is some evidence that oral zinc might improve healing of venous ulcers in people with low-serum zinc levels (Wilkinson & Hawke 2000).

Double-blind studies producing encouraging results have used oral zinc (600 mg/day) combined with topical treatment and compression bandages (Haeger & Lanner 1974, Hallbook & Lanner 1972).

ACNE AND OTHER SKIN CONDITIONS

Over the past 2–3 decades, tetracyclines and macrolide antibiotics have been widely prescribed for the treatment of acne; however, resistance has been reported, especially to erythromycin and clindamycin with cross-resistance being widespread among strains of *Propionibacterium acnes*. As a result, non-antibiotic treatments such as topical and oral zinc preparations have been investigated as both alternatives and adjuncts to these treatments.

Overall, studies have yielded conflicting results, possibly due to considerable placebo effects, with better effects generally seen on inflammatory lesions than other lesion types. This is most likely due to the fact that zinc has a marked anti-inflammatory effect, which was first observed with zinc sulfate and later with zinc gluconate, which is a better tolerated form.

Oral supplementation Numerous studies have been conducted investigating the effects of zinc supplementation in acne vulgaris (Dreno et al 1989, 1992, 2001, Goransson et al 1978, Hillstrom et al 1977, Orris et al 1978, Weimar et al 1978, Weismann et al 1977, Verma et al 1980). Doses between 90 mg and 200 mg (30 mg elemental zinc) daily taken over 6–12 weeks have been associated with generally positive results, whereas larger doses tend to be poorly tolerated. More recently, an open study involving 30 subjects with inflammatory acne found that a lower dose of oral zinc gluconate (30 mg) taken daily reduced the number of inflammatory lesions after 2 months regardless of whether *P. acnes* was present (Dreno et al 2005).

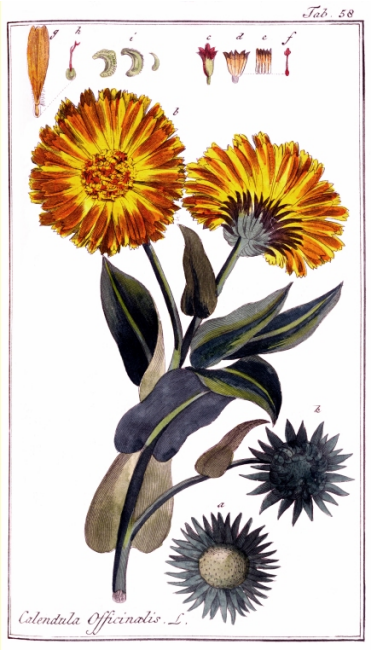
Two double-blind studies have compared the effects of oral zinc supplementation with two antibiotic medicines, minocycline or oxytetracycline, over 3 months (Dreno et al 1989, Cunliffe et al 1979). Zinc sulfate (135 mg) was as effective as

oxytetracycline after 12 weeks' use, decreasing acne scores by 65% in one study, whereas the same dose was not as effective as minocycline (500 mg) in the second study.

Zinc has also been investigated as an adjunct to antibiotic therapy under laboratory conditions. When administered in combination with erythromycin, it inhibits erythromycin-resistant propionibacteria according to two in vitro studies (Dreno et al 2005, Oprica et al 2002).

Topical application A number of studies have investigated the effects of a topical erythromycin–zinc acetate formulation (Bojar et al 1994, Feucht et al 1980, Habbema et al 1989, Morgan et al 1993, Pierard & Pierard-Franchimont 1993, Pierard-Franchimont et al 1995, Schachner et al 1990).

Statistically significant effects have been observed within the first 12 weeks of treatment for acne severity grades, and for papule, pustule and comedo counts, with the effect of the combination superior to preparations containing erythromycin alone (Habbema et al 1989, Schachner et al 1990). Human studies have identified antibacterial activity against *Propionibacterium* spp. in short-term treatment, which is mostly attributed to zinc (Fluhr et al 1999) and sebosuppressive effects (Pierard & Pierard-Franchimont 1993).



REDUCED MALE FERTILITY

Zinc deficiency leads to several clinical signs, such as decreased spermatogenesis and impaired male fertility. When zinc deficiency is not present, a 2002 survey found no statistically significant relationship between zinc in seminal plasma or serum and semen quality or local antisperm antibody of the IgG or IgA class (Eggert-Kruse et al 2002). Furthermore, zinc levels did not influence sperm capacity to penetrate cervical mucus in vitro or in vivo, and did not affect subsequent fertility.

IMPOTENCE

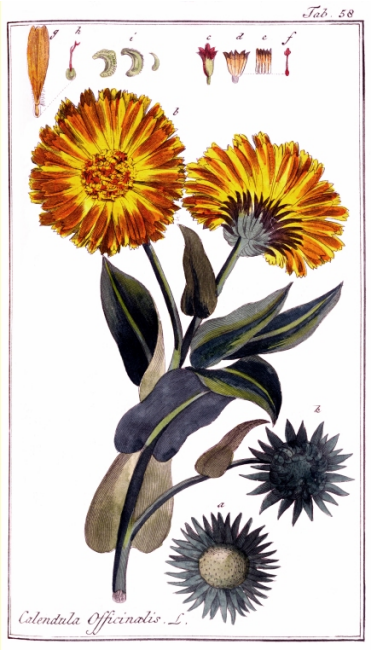
In men, zinc deficiency may lead to impaired testosterone synthesis, resulting in hypogonadism and impotency. One placebo-controlled study has investigated whether oral zinc supplementation improves erectile dysfunction. The study involved 20 uraemic haemodialysis patients and showed that 6 months treatment with oral zinc acetate (25 mg elemental zinc) taken twice daily 1–2 hours before meals resulted in greater libido, improved potency and more frequent intercourse compared to placebo (Mahajan et al 1982). Active treatment also resulted in significant increases in plasma zinc, serum testosterone, and sperm count and decreases in serum levels of LH and FSH.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

In 1990, Arnold et al observed that boys aged 6–12 years with ADHD with a higher baseline hair zinc level had better responses to amphetamine therapy than children with mild zinc deficiency. At the time it was suggested that children responding poorly to drug therapy and presenting with mild zinc deficiency would require zinc supplementation instead of amphetamine treatment to address the condition. Since then, numerous controlled studies have identified that children with ADHD have lower zinc tissue levels (serum, red cells, hair, urine, nails) than normal children (Arnold 2005). It is not certain why this occurs, but may result from not sitting at the kitchen table long enough to consume a balanced diet, picky eating, stimulant-related appetite suppression, malabsorption or biochemical changes.

Two double-blind studies have investigated whether oral zinc supplementation has a beneficial effect in ADHD, producing promising results. One randomised study involving 400 Turkish children with a mean age of 9.6 years found that treatment with 150 mg zinc sulfate (equivalent to 40 mg of elemental zinc) daily for 12 weeks resulted in significant reductions in hyperactive, impulsive and impaired socialisation symptoms, but not in reducing attention deficiency symptoms, as assessed by the ADHD Scale (Bilici et al 2004). A significant difference between zinc and placebo were already evident by week 4 ($P = 0.01$). Older children with low zinc and free fatty acid levels and high BMI responded best to treatment. A second placebo-controlled trial used a combination of 55 mg zinc sulfate (equivalent to 15 mg elemental zinc) and methylphenidate (1 mg/kg) daily for 6 weeks in Iranian children aged 5–11 years and reported significant benefits with the combination (Akhondzadeh et al 2004).

It is important to note that both studies were conducted with children from countries with suspected zinc deficiency and further investigation is required to determine whether the same beneficial results will occur in children living in Western countries.



DEPRESSION

Twenty patients with unipolar depression had an improved response to antidepressant medication when taken with zinc aspartate supplements (equivalent to 25 mg elemental daily), according to a small, double-blind pilot study (Nowak et al 2003). Significantly greater reductions in Hamilton Depression Rating Scale scores were achieved with zinc treatment compared to placebo by the 6th week and maintained until the end of the 12-week study.

CROHN'S DISEASE

Although reduced zinc status has been associated with chronic diarrhoea and Crohn's disease (Sturniolo et al 1980), the results from a small open study demonstrated that oral zinc sulfate (110 mg three times daily) resolved intestinal permeability problems in people with increased permeability and decreases relapse rates (Sturniolo et al 2001).

HERPES SIMPLEX

Overall, application of zinc preparations greatly reduces or eliminates recurrence of genital herpes infections and resolves symptoms of herpes simplex infections (Kneist et al 1995, Finnerty 1986). Zinc sulfate gel applied every 2 hours was a more effective treatment than placebo in herpex simplex labialis in a double-blind study of 80 subjects (Kneist et al 1995). Another study of 200 volunteers with herpes simplex found that 0.25% zinc sulfate solution started within 24 hours of lesion appearance and applied 8–10 times daily cleared lesions within 3–6 days (Finnerty 1986). A randomised placebo-controlled study using a weak zinc solution (0.05% or 0.025% zinc sulfate) found no effects on frequency, duration or severity of herpes attacks, suggesting that stronger concentrations are required for effectiveness (Graham et al 1985).

ANOREXIA NERVOSA

There is evidence that suggests zinc deficiency may be intimately involved with anorexia in humans, if not as an initiating cause, then as an accelerating or 'sustaining' factor for abnormal eating behaviours that may deepen the pathology of the anorexia (McClain et al 1992, Shay & Mangian 2000). Zinc status is compromised in anorexia nervosa due to an inadequate zinc intake, with supplementation (50 mg elemental zinc/day) shown to decrease depression and anxiety, stop body weight loss and improve weight gain (Katz et al 1987, Safai-Kutti 1990). According to one randomised, double-blind, placebo-controlled trial, 100 mg of zinc gluconate doubled the rate of subjects with anorexia nervosa increasing their BMI compared to placebo (Birmingham et al 1994).

IMPROVES TASTE PERCEPTION

Dysfunctional taste perception, or dysgeusia, is a condition that can at the least affect QOL and occasionally can become life-threatening. Zinc supplementation using 140 mg of zinc gluconate (20 mg elemental) per day can improve dysgeusia (Heckmann et al 2005).

TINNITUS

In 1987, a report was published suggesting a link between reduced zinc status and intermittent head noises in people suffering with tinnitus (Gersdorff et al 1987). This has been further investigated in several studies; however, the poorly defined patient groups and use of serum zinc as the means of measuring zinc status makes interpretation of results difficult to assess.

In 1991 Paaske et al reported the results of a randomised, double-blind study of 48 patients with tinnitus that had failed to find a significant effect on symptoms with sustained-release zinc sulfate tablets. Of note, only one subject had low zinc serum levels. More recently, a study of 111 subjects aged 20–59 years found individuals with tinnitus who had normal hearing had significantly lower serum zinc levels than controls, whereas zinc levels were normal for those with accompanying hearing loss (Ochi et al 2003). In addition, a significant correlation between average hearing sensitivity and serum zinc level was observed. Yetiser et al (2002) investigated serum zinc levels and response to supplementation in 40 patients with severe tinnitus of various origins. Some relief in tinnitus symptoms was reported by 57.5% of all subjects who received 220 mg of zinc daily for 2 months; however, the effect was considered minor. When results were divided by age, a different finding emerged as 82% of people over 50 years of age experienced an improvement on the tinnitus scale compared to only 48% of younger subjects. There was no correlation between severity of tinnitus and serum zinc levels. Zinc supplementation (50 mg/day) was further studied in a randomised, placebo-controlled trial involving 41 Turkish patients with tinnitus of no known cause. Active treatment for 2 months produced clinically favourable progress in 46.4% of subjects; however, this result was not statistically significant (Arda et al 2003).

WARTS

Oral zinc sulfate (10 mg/kg) supplements administered in three divided doses per day (up to 600 mg/day) for 2 months completely cleared recalcitrant viral warts in 87% of patients, according to a single-blind, placebo-controlled trial of 80 volunteers with at least 15 viral warts that were resistant to other treatments (Al Gurairi et al 2002). Warts were completed cleared in 61% of patients after 1 month of treatment, whereas none of the patients receiving placebo reported a successful response and some developed new warts. In both placebo and treatment groups the drop-out rates were high: 50% and 45% respectively. Interestingly, patients in the treatment group with low serum zinc baseline levels (mean 62.4 μg/100 mL) exhibited no signs or symptoms of deficiency and zinc serum levels failed to rise in the patients who remained resistant to zinc therapy. Treatment with high-dose zinc supplements was

accompanied by nausea and in some cases vomiting and mild epigastric pain, although these symptoms were described as mild and transient.

OTHER USES

REDUCING THE RISK OF CANCER

Epidemiological studies suggest that zinc deficiency may be associated with increased risk of cancer (Prasad & Kucuk 2002).

HIV AND AIDS

Low plasma zinc concentration occurs in HIV infection, especially with advancing illness (Wellinghausen et al 2000). The balance of evidence favours the view that a low plasma zinc level is a marker for disease progression (Siberry et al 2002). Large intervention trials are not available to determine whether zinc supplementation in HIV infection produces positive outcomes.

MALARIA

Zinc supplementation (10 mg elemental) randomly allocated to preschool children residing in a malaria-endemic region of Papua New Guinea for 6 days a week over 46 weeks showed this intervention reduced morbidity due to *Plasmodium falciparum* (Shankar et al 2000). Duggan et al (2005) also identified low plasma zinc levels in children with acute malaria, including a significant correlation between evidence of illness severity and zinc status.

PNEUMONIA

A randomised, controlled trial involving 270 children aged between 6 and 12 months, hospitalised with pneumonia, found that those given 20 mg/day of zinc (as acetate) showed significant reductions in recovery time from severe pneumonia. Overall hospital stay duration was also reduced when used with standard antimicrobial therapy (Brooks et al 2004). Furthermore, a randomised, placebo-controlled trial in which 1665 children aged less than 12 months were given 70 mg of zinc prophylactically found a reduced incidence of pneumonia (17%), with severe pneumonia incidence reducing by 49%. It also reduced URTI by 8% and reactive airways disease (bronchiolitis) by 12% (Brooks et al 2005).

WILSON'S DISEASE

Patients with diagnosed Wilson's disease have increased hepatic glutathione and reduced oxidation when supplemented with zinc sulfate (220 mg three times daily) for 3 months, compared with those using penicillamine (Farinati et al 2003).

ALZHEIMER'S DEMENTIA

Cognitive performance was temporarily improved after 3 months of zinc supplementation (zinc chelate 15 mg) taken twice daily by six subjects with Alzheimer's disease (Potocnik et al 1997). Although the initial improvement was not maintained in this small open study, a modest cognitive improvement on psychometric testing was observed at 12 months for the four patients evaluated.

DOSAGE RANGE

AUSTRALIAN RDI

Children

- 1–3 years: 3 mg/day.
- 4–8 years: 4 mg/day.
- 9–13 years: 6 mg/day.
- Males 14–18 years: 13 mg/day.
- Females 14–18 years: 7 mg/day.

Adults

- Males >19 years: 14 mg/day.
- Females >19 years: 8 mg/day.

Pregnancy

- <19 years: 10 mg/day.
- ≥19 years: 11 mg/day.

Deficiency

- 25–50 mg elemental zinc daily.

ACCORDING TO CLINICAL STUDIES

- Common cold — zinc gluconate lozenges (free of sorbitol, mannitol or citric acid).
  - Adults: 9–24 mg elemental zinc dissolved in the mouth, without chewing every 2 hours for acute treatment.
  - School-aged children: dissolved in the mouth once daily as prophylaxis and four times daily for acute treatment.

  *It is recommended that citrus fruits or juices be avoided 30 minutes before or after dissolving each lozenge to avoid negating the effects of zinc.
- Common cold — nasal gel spray containing either 33 mmol/L zincum gluconicum administered four times a day for a maximum of 10 days.
- ARMD — zinc oxide (equivalent to 80 mg elemental zinc), together with 500 mg vitamin C, 400 IU vitamin E, and 15 mg beta-carotene, taken daily.
- ADHD — 55–150 mg zinc sulfate daily.
- Diabetes — 30 mg/day (type of zinc unknown).

- Wound healing — 2.5 mg/kg zinc sulfate daily.
- Leg ulcers — 600 mg zinc sulfate daily.
- Acne vulgaris — 90–200 mg (50 mg elemental) daily.
- Crohn's disease — 110 mg zinc sulfate taken three times daily.
- Herpes infection — 0.25% zinc sulfate solution applied 8–10 times daily.
- Anorexia nervosa — 50 mg elemental zinc daily.
- Dysgeusia — 140 mg zinc gluconate daily.
- Tinnitus — 50–200 mg daily of zinc (salt unknown).
- Warts —10 mg/kg zinc sulfate taken orally in three divided doses (up to 600 mg/day) for 1–2 months.

TOXICITY

Signs of toxicity are nausea, vomiting, diarrhoea, fever and lethargy and have been observed after ingestion of 4–8 g zinc according to a 2002 WHO report. Single doses of 225–450 mg of zinc usually induce vomiting (King 2003).

Doses of zinc ranging from 100 to 150 mg/day interfere with copper metabolism and cause hypocuprinaemia, red blood cell microcytosis and neutropenia if used long term.

ADVERSE REACTIONS

Mild gastrointestinal distress has been reported at doses of 50–150 mg/day of supplemental zinc (King 2003). According to a randomised, double-blind study, zinc gluconate glycine lozenge (104 mg equivalent to 13.3 mg ionic zinc) taken every 3–4 hours is well tolerated (Silk & Lefante 2005). Of the side-effects that were reported, dry mouth and a burning sensation on the tongue were probably related to use, whereas symptoms of nausea, dizziness, lightheadedness and upset stomach were considered as possibly related.

SIGNIFICANT INTERACTIONS

CALCIUM

High levels of dietary calcium impair zinc absorption in animals, but it is uncertain whether this occurs in humans — separate doses by 2 hours.

CAPTOPRIL AND ENALOPRIL

These drugs increase urinary excretion of zinc (Golik et al 1990). Monitor for signs and symptoms of zinc deficiency. Increased zinc intake may be required with long-term drug treatment.

COFFEE

Coffee reduces zinc absorption — separate intakes by 2 hours (Pecoud et al 1975).

COPPER
High zinc intakes (100–150 mg/day) interfere with copper metabolism and can cause hypocuprinaemia with long-term use. Avoid using high-dose zinc supplements long term, or increase intake of copper.

FOLATE
Folate intake may reduce zinc levels — observe patient for signs and symptoms of zinc deficiency with long-term folate supplementation.

IRON
Supplemental (38–65 mg/day elemental) iron decreases zinc absorption (King 2003) — separate doses by 2 hours.

NSAIDS
Zinc interacts with NSAIDs by forming complexes with these drugs (Dendrinou-Samara et al 1998) — separate dose by 2 hours.

TETRACYCLINES AND QUINOLONES
Complex formation between zinc and tetracycline results in reduced absorption of both substances with potentially reduction in efficacy — separate dose by 2 hours.

THIAZIDE AND LOOP DIURETICS
These diuretics increase urinary zinc loss — monitor for signs and symptoms of zinc deficiency with long-term drug use. Increased zinc intake may be required with long-term therapy.

METHYLPHENIDATE
The efficacy of this drug is improved by supplementation with zinc sulfate (15 mg elemental zinc) for 6 weeks in children with ADHD. There is no change to side-effects reported (Akhondzadeh et al 2004).

VACCINATIONS
Zinc acetate improved seroconversion of vibriocidal antibodies in children given a cholera vaccination (Albert et al 2003) in both faecal and serum titres (Karlsen et al 2003).

RADIOTHERAPY
Radiotherapy reduces plasma zinc levels (Ertkin et al 2004). Supplementation may be required with intensive radiotherapy treatment.

INTERFERON-ALPHA/RIBAVIRIN

Interferon-alpha and ribavirin treatment for hepatitis C patients is not affected by zinc supplementation (Ko et al 2005).

ORLISTAT

Orlistat has no significant effect on zinc levels (Zhi et al 2003).

TRICYCLIC ANTIDEPRESSANTS AND SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Zinc supplementation (25 mg elemental zinc daily) improves the efficacy of antidepressants such as tricyclic antidepressants and SSRIs after 2 weeks of intervention (Nowak et al 2003) — beneficial interaction possible.

CONTRAINDICATIONS AND PRECAUTIONS

Amiloride reduces zinc excretion and can lead to zinc accumulation (Reyes et al 1983). Therefore, supplementation should be used with caution.

PREGNANCY USE

Zinc is safe in pregnancy and may improve fetal heart rate in zinc deficient mothers (in conjunction with iron and folic acid) (Merialdi et al 2004).

PRACTICE POINTS/PATIENT COUNSELLING

- Zinc is involved in many chemical reactions that are important for normal body functioning and it is essential for health and wellbeing.
- Although zinc supplements are traditionally used to treat deficiency, they are also used to prevent deficiency in conditions associated with low zinc status or deficiency, such as acrodermatitis enteropathica, anorexia nervosa, malabsorption syndromes, conditions associated with chronic diarrhoea, alcoholism, diabetes, HIV and AIDS, recurrent infections, severe burns, Wilson's disease and sickle cell anaemia.
- Zinc supplements are also popular among athletes in order to counteract zinc loss that occurs through perspiration.
- Zinc lozenges have been used to prevent and treat the symptoms of the common cold and oral supplements have been used to treat acne vulgaris, improve wound healing and chronic leg ulcers, resolve intestinal permeability problems and reduce recurrences in Crohn's disease, treat recalcitrant warts, reduce symptoms of tinnitus and improve ADHD.
- Topical applications of zinc have been used to treat acne vulgaris (in combination with erythromycin), herpes simplex and to promote wound healing.

- Numerous interactions exist between other minerals, foods and medicines and zinc.

ANSWERS TO PATIENTS' FREQUENTLY ASKED QUESTIONS

What will this supplement do for me?

Zinc is found in every cell of the body and is essential for health and wellbeing. Some studies have found that supplements are not only useful to treat and prevent deficiency, but may also be useful in conditions such as the common cold, poor wound healing and leg ulcers, diabetes, Crohn's disease, acne vulgaris, warts, ADHD and tinnitus. Topical preparations may be useful in acne vulgaris (with erythromycin), herpes infection and chronic wounds.

When will it start to work?

This depends on the indication (refer to monograph for more details).

Are there any safety issues?

Used in high doses, zinc can cause nausea, vomiting, gastrointestinal discomfort and if used long term, reduce copper levels. Zinc also interacts with a number of other minerals, foods and medicines.

REFERENCES

Age-Related Eye Disease Study. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta-carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 119.10 (2001): 1417-36.

Agren MS. Studies on zinc in wound healing. Acta Derm Venereol Suppl (Stockh) 154 (1990): 1-36.

Akhondzadeh S, Mohammadi M-R, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial. BMC Psychiatry 4.1 (2004): 9.

Al Gurairi FT, Al Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. Br J Dermatol 146 (2002): 423-31.

Albert MJ et al. Supplementation with zinc, but not vitamin A, improves seroconversion to vibriocidal antibody in children given an oral cholera vaccine. J Infect Dis 187.6 (2003): 909-13.

Arda HN et al. The role of zinc in the treatment of tinnitus. Otol Neurotol 24 (2003): 86-9.

Arnold LE, DiSilvestro RA. Zinc in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 15 (2005): 619-27.

Arnold LE et al. Does hair zinc predict amphetamine improvement of ADD/hyperactivity? Int J Neurosci 50 (1990): 103-7.

Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). Resp Med 99 (2005): 1477-84.

Baydas B, Karagoz S, Meral I. Effects of oral zinc and magnesium supplementation on serum thyroid hormone and lipid levels in experimentally induced diabetic rats. Biol Trace Elem Res 88.3 (2002): 247-53.

Bedwal RS, Bahuguna A. Zinc, copper and selenium in reproduction. Experientia 50.7 (1994): 626-40.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.

Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. Am J Med 111.2 (2001): 103-8.

Bilici M et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry 28 (2004): 181-90.
Birmingham CL et al. Controlled trial of zinc supplementation in anorexia nervosa. Int J Eat Disord 15.3 (1994): 251-5.
Birmingham CL et al. Reliability of the AccuSens Taste Kit(c) in patients with eating disorders. Eat Weight Disord 10.2 (2005): e45-8.
Bojar RA et al. Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. Br J Dermatol 130.3 (1994): 329-36.
Briefel RR et al. Zinc intake of the U.S. population: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Nutr 130 (2000): 1367-73S.
Brooks WA et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 363.9422 (2004): 1683-8.
Brooks WA et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomized controlled trial. Lancet 366.9490 (2005): 999-1004.
Chausmer AB. Zinc, insulin and diabetes. J Am Coll Nutr 17.2 (1998): 109-15.
Cunliffe WJ et al. A double-blind trial of a zinc sulphate/citrate complex and tetracycline in the treatment of acne vulgaris. Br J Dermatol 101.3 (1979): 321-5.
Cunningham JJ et al. Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation. Metabolism 43.12 (1994): 1558-62.
Davison GW et al. Exercise, free radicals, and lipid peroxidation in type 1 diabetes mellitus. Free Radic Biol Med 33.11 (2002): 1543-51.
Dendrinou-Samara C et al. Anti-inflammatory drugs interacting with Zn(II), Cd(II) and Pt(II) metal ions. J Inorg Biochem 71(3-4) (1998): 171-9.
DiSilvestro RA. Zinc in relation to diabetes and oxidative disease. J Nutr 130.5S Suppl (2000): 1509-11S.
Dreno B et al. Low doses of zinc gluconate for inflammatory acne. Acta Derm Venereol 69.6 (1989): 541-3.
Dreno B et al. Zinc salts effects on granulocyte zinc concentration and chemotaxis in acne patients. Acta Derm Venereol 72.4 (1992): 250-2.
Dreno B et al. Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. Dermatology 203.2 (2001): 135-40.
Dreno B et al. Effect of zinc gluconate on propionibacterium acnes resistance to erythromycin in patients with inflammatory acne: in vitro and in vivo study. Eur J Dermatol 15 (2005): 152-5.
Duggan C et al. Plasma zinc concentrations are depressed during the acute phase response in children with Falciparium Malaria. J Nutr 135.4 (2005): 802.
Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. Alt Ther Health Med 12.1 (2006): 34-8.
Eggert-Kruse W et al. Are zinc levels in seminal plasma associated with seminal leukocytes and other determinants of semen quality? Fertil Steril 77.2 (2002): 260-9.
Ertekin MV et al. The effects of oral zinc sulphate during radiotherapy on anti-oxidant enzyme activities in patients with head and neck cancer: A prospective, randomized, placebo-controlled study. Int J Clin Pract 58.7 (2004): 662-8.
Evans JR. Antioxidant vitamin and mineral supplements for age-related macular degeneration. Cochrane Database Syst Rev 2 (2002): CD000254.
Farinati F et al. Zinc treatment prevents lipid peroxidation and increases glutathione availability in Wilson's disease. J Lab Clin Med 141.6 (2003): 372-7.
Farvid MS et al. The impact of vitamin and/or mineral supplementation on lipid profiles in type 2 diabetes. Diabetes Res Clin Pract 65.1 (2004): 21-8.
Favier AE. The role of zinc in reproduction: Hormonal mechanisms. Biol Trace Elem Res 32 (1992): 363-82.

Feiner AM et al. Evaluation of the effects of a zinc/iron solution on the migration of fibroblasts in an in-vitro incisional wound healing model. Wounds 15(4) (2003): A23-34.
Feucht CL et al. Topical erythromycin with zinc in acne: A double-blind controlled study. J Am Acad Dermatol 3.5 (1980): 483-91.
Finnerty EF. Topical zinc in the treatment of herpes simplex. Cutis 37.2 (1986): 130-1.
Fluhr JW et al. In-vitro and in-vivo efficacy of zinc acetate against propionibacteria alone and in combination with erythromycin. Zentralbl Bakteriol 289.4 (1999): 445-56.
Fraker PJ et al. The dynamic link between the integrity of the immune system and zinc status. J Nutr 130 (2000): 1399-406S.
Frederickson CJ, Danscher G. Zinc-containing neurons in hippocampus and related CNS structures. Prog Brain Res 83 (1990): 71-84.
Frederickson CJ, Moncrieff DW. Zinc-containing neurons. Biol Signals 3.3 (1994): 127-39.
Frederickson CJ et al. Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr 130.5S Suppl (2000): 1471S-83S.
Garg HK, Singal KC, Arshad Z. Zinc taste test in pregnant women and its correlation with serum zinc level. Indian J Physiol Pharmacol 37.4 (1993): 318-22.
Gersdorff M et al. A clinical correlation between hypozincemia and tinnitus. Arch Otorhinolaryngol 244 (1987): 190-3.
Golik A et al. Zinc metabolism in patients treated with captopril versus enalapril. Metabolism 39.7 (1990): 665-7.
Goransson K, Liden S, Odsell L. Oral zinc in acne vulgaris: a clinical and methodological study. Acta Derm Venereol 58.5 (1978): 443-8.
Graham RM, James MP, Bennett S. Low concentration zinc sulphate solution in the management of recurrent herpes simplex infection. Br J Dermatol 112.1 (1985): 123-4.
Gupta R et al. Oral zinc therapy in diabetic neuropathy. J Assoc Physicians India 46.11 (1998): 939-42.
Habbema L et al. A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. Br J Dermatol 121.4 (1989): 497-502.
Haeger K, Lanner E. Oral zinc sulphate and ischaemic leg ulcers. Vasa 3.1 (1974): 77-81.
Hallbook T, Lanner E. Serum-zinc and healing of venous leg ulcers. Lancet 2.7781 (1972): 780-2.
Heckmann S et al. Zinc gluconate in the treatment of dysgeusia: a randomized clinical trial. J Dent Res 84.1 (2005): 35-8.
Higdon J. An Evidence-Based Approach to Vitamins and Minerals. New York: Thieme, 2003: 197-205.
Hillstrom L et al. Comparison of oral treatment with zinc sulphate and placebo in acne vulgaris. Br J Dermatol 97.6 (1977): 681-4.
Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. Ear Nose Throat J 79.10 (2000): 778-80, 782.
Ilouz R et al. Inhibition of glycogen synthase kinase-3beta by bivalent zinc ions: insight into the insulin-mimetic action of zinc. Biochem Biophys Res Commun 295.1 (2002): 102-6.
Karlsen TH et al. Intestinal and systemic immune responses to oral cholerz toxoid B subunit whole-cell vaccine administered during zinc supplementation. Infect Immun 71.7 (2003): 3909-13.
Katz RL et al. Zinc deficiency in anorexia nervosa. J Adolesc Health Care 8.5 (1987): 400-6.
King J. Zinc. Oregon: The Linus Pauling Institute, 2003.
Kneist W, Hempel B, Borelli S. Clin double-blind trial of topical zinc sulfate for herpes labialis recidivans. Arzneimittelforschung 45.5 (1995): 624-6.
Ko W-S et al. The effect of zinc supplementation on the treatment of chronic hepatitis C patients with interferon and ribavirin. Clin Biochem 38 (2005): 614-20.
Lansdown AB. Zinc in the healing wound. Lancet 347.9003 (1996): 706-7.
Lonnerdal B. Dietary factors influencing zinc absorption. J Nutr 130 (2000): 1378-83S.
Mahajan SK et al. Effect of oral zinc therapy on gonadal function in hemodialysis patients: A double-blind study. Ann Intern Med 97 (1982): 357-61.

Mahomed K et al. Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. Eur J Obstet Gynecol Reprod Biol 48.3 (1993): 169-75.
Marreiro DN et al. Abstracts 1644-P, 569-P. In: Proceedings of the American Diabetes Association Annual Meeting, June 16-17, 2002.
Marshall I. Zinc for the common cold. Cochrane Database Syst Rev 2 (2000): CD001364.
McClain CJ et al. Zinc status before and after zinc supplementation of eating disorder patients. J Am Coll Nutr 11.6 (1992): 694-700.
McElroy BH, Miller SP. Effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) against the common cold in school-aged subjects: a retrospective chart review. Am J Ther 9.6 (2002): 472-5.
McElroy BH, Miller SP. An open-label, single-center, phase IV clinical study of the effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) in reducing the duration and symptoms of the common cold in school-aged subjects. Am J Ther 10 (2003): 324-9.
Merialdi et al. Randomized controlled trial of prenatal zinc supplementation and the development of fetal heart rate. Am J Obstet Gynecol 190.4 (2004): 1106-12.
Morgan AJ et al. The effect of zinc in the form of erythromycin-zinc complex (Zineryt lotion) and zinc acetate on metallothionein expression and distribution in hamster skin. Br J Dermatol 129.5 (1993): 563-70.
Mossad SB. Effect of zincum gluconium nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. Q J Med 96.1 (2003): 35-43.
Niewoehner CB et al. Role of zinc supplementation in type II diabetes mellitus. Am J Med 81.1 (1986): 63-8.
Novick SG et al. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. Med Hypotheses 46 (1996): 295-302.
Nowak G et al. Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. Polish J Pharmacol 55.6 (2003): 1143-7.
Ochi K et al. Zinc deficiency and tinnitus. Auris Nasus Larynx 30 (Suppl) (2003): S25-8.
Oprica C, Emtestam L, Nord CE. Overview of treatments for acne. Dermatol Nurs 14 (2002): 242-6.
Orris L et al. Oral zinc therapy of acne. Absorption and clinical effect. Arch Dermatol 114.7 (1978): 1018-20.
Paaske PB et al. Zinc in the management of tinnitus: Placebo-controlled trial. Ann Otol Rhinol Laryngol 100 (1991): 647-9.
Pecoud A, Donzel P, Schelling JL. Effect of foodstuffs on the absorption of zinc sulfate. Clin Pharmacol Ther 17(4) (1975): 469-74.
Pierard GE, Pierard-Franchimont C. Effect of a topical erythromycin-zinc formulation on sebum delivery. Evaluation by combined photometric-multi-step samplings with Sebutape. Clin Exp Dermatol 18.5 (1993): 410-13.
Pierard-Franchimont C et al. A double-blind controlled evaluation of the sebosuppressive activity of topical erythromycin-zinc complex. Eur J Clin Pharmacol 49.1-2 (1995): 57-60.
Potocnik FCV et al. Zinc and platelet membrane microviscosity in Alzheimer's disease: the in vivo effect of zinc on platelet membranes and cognition. S Afr Med J 87.9 (1997): 1116-19.
Prasad AS. Zinc deficiency in women, infants and children. J Am Coll Nutr 15.2 (1996): 113-20.
Prasad AS. Zinc and immunity. Mol Cell Biochem 188.1-2 (1998): 63-9.
Prasad AS, Kucuk O. Zinc in cancer prevention. Cancer Metastasis Rev 21.3-4 (2002): 291-5.
Prasad AS et al. Effect of zinc supplementation on incidence of infections and hospital admissions in sickle cell disease (SCD). Am J Hematol 61.3 (1999): 194-202.
Prasad AS et al. Antioxidant effect of zinc in humans. Free Radic Biol Med 37.8 (2004): 1182-90.
Reyes AJ et al. Urinary zinc excretion, diuretics, zinc deficiency and some side-effects of diuretics. S Afr Med J 64.24 (1983): 936-41.
Roussel A-M et al. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. J Am Coll Nutr 22.4 (2003): 316-21.
Safai-Kutti S. Oral zinc supplementation in anorexia nervosa. Acta Psychiatr Scand Suppl 361 (1990): 14-17.
Schachner L et al. Topical erythromycin and zinc therapy for acne. J Am Acad Dermatol 22.2 (1990): 253-60.
Semrad CE. Zinc and intestinal function. Curr Gastroenterol Rep 1.5 (1999): 398-403.

Shankar AH et al. The influence of zinc supplementation on morbidity due to Plasmodium falciparum: a randomized trial in preschool children in Papua New Guinea. Am J Trop Med Hyg 62.6 (2000): 663-9.
Sharquie KE et al. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. Clin Exp Dermatol 26.1 (2001): 21-6.
Shay NF, Mangian HF. Neurobiology of zinc-influenced eating behavior. J Nutr 130.5S Suppl (2000): 1493-9S.
Siberry GK, Ruff AJ, Black R. Zinc and human immunodeficiency virus infection. Nutr Res 22.4 (2002): 527-38.
Silk R, LeFante C. Safety of zinc gluconate glycine (Cold-Eeze) in a geriatric population: a randomized, placebo-controlled, double-blind trial. Am J Ther 12 (2005): 612-17.
Sturniolo GC et al. Zinc absorption in Crohn's disease. Gut 21.5 (1980): 387-91.
Sturniolo GC et al. Zinc supplementation tightens leaky gut in Crohn's disease. Inflamm Bowel Dis 7.2 (2001): 94-8.
Tobia MH et al. The role of dietary zinc in modifying the onset and severity of spontaneous diabetes in the BB Wistar rat. Mol Genet Metab 63.3 (1998): 205-13.
Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. Clin Infect Dis 31.5 (2000): 1202-8.
Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. Clin Infect Dis 33.11 (2001): 1865-70.
van Leeuwen R et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 294 (2005): 3101-7.
Verma KC, Saini AS, Dhamija SK. Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. Acta Derm Venereol 60.4 (1980): 337-40.
Wahlqvist M et al. Food and Nutrition. Sydney: Allen & Unwin, 1997.
Wardlaw GM et al. Contemporary Nutrition: Issues and Insights, 3rd edn. Boston: McGraw-Hill, 1997.
Weimar VM et al. Zinc sulfate in acne vulgaris. Arch Dermatol 114.12 (1978): 1776-8.
Weismann K, Wadskov S, Sondergaard J. Oral zinc sulphate therapy for acne vulgaris. Acta Derm Venereol 57.4 (1977): 357-60.
Wellinghausen N et al. Zinc serum level in human immunodeficiency virus-infected patients in relation to immunological status. Biol Trace Elem Res 73.2 (2000): 139-49.
Wilkinson EA, Hawke CI. Oral zinc for arterial and venous leg ulcers. Cochrane Database Syst Rev 2 (2000): CD001273.
Wood RJ. Assessment of marginal zinc status in humans. J Nutr 130 (2000): 1350-4S.
World Health Organization. Zinc: Report of a joint FAO/WHO expert consultation, Bangkok, Thailand. Rome: WHO, 2002.
Zhi J, Moore R, Kanitra L. The effect of short-term (21-day) orlistat treatment on the physiologic balance of six selected macrominerals and microminerals in obese adolescents. J Am Coll Nutr 22.5 (2003): 357-62.

APPENDIX 1

GLOSSARY AND ABBREVIATIONS

Abortifacient – Substance used to terminate a pregnancy.
ACE – angiotensin-converting enzyme
ACTH – adrenocorticotropic hormone
Active constituents – Chemical components that exhibit pharmacological activity and contribute to the agent's overall therapeutic effects.
Acute – Beginning abruptly; sharp and intense; subsiding after a short period.
Adaptogen – Innocuous agent, non-specifically increasing resistance to physical, chemical, environmental, emotional or biological factors ('stressors') and having a normalising effect independent of the nature of the pathological state.
ADHD – attention deficit hyperactivity disorder
ADI – Acceptable Daily Intake
Adjuvant – Substance added to a mixture to enhance the effect of the main ingredient.
ADRAC – Adverse Drug Reactions Advisory Committee (Australia)
Adverse reaction – Unintended harmful, undesirable or seriously unpleasant response to a medicine at doses intended for prophylaxis, diagnosis or therapeutic effect.
Aerial parts – All parts of a plant that are above the ground. Very often, plants that have useful aerial parts are harvested when flowering (e.g St John's wort (*Hypericum perforatum*) of the Hypericaceae family).
Agonist – Substance that binds to and activates a receptor, thereby causing a response.
Alkaloid – Naturally occurring cyclic organic compound containing nitrogen in a negative oxidation state, which has limited distribution in living organisms. Based on their structures, alkaloids are divided into several subgroups: non-heterocyclic alkaloids and heterocyclic alkaloids, which are again divided into 12 major groups according to their basic ring structure. They tend to have marked physiological effects in vivo (e.g. morphine, codeine, nicotine).
Allostatic responses – Changes that occur in the body in order to adapt and respond to physical or psychological change (e.g. standing, sitting, stress). They are critical to survival, have broad boundaries and involve the sympathetic nervous system and the HPA axis.
ALT – alanine aminotransferase
Amino acid – Organic compound composed of one or more basic amino groups and one or more acidic carboxyl groups; form the basic structural units of protein.
AMP – adenosine monophosphate

Analgesic – Substance that relieves the symptoms of pain.
ANF – atrial natriuretic factor
Antagonist – Substance that binds to a receptor (blocking others from doing so), but does not activate it, causing a diminished response.
Anthelmintic – Substance that destroys or assists in the expulsion of intestinal worms.
Anthocyanins – Compounds responsible for the bright colours of most flowers and fruits; water-soluble pigments that occur as glycosides and their aglycones (anthocyanidins) and have significant anti-oxidant activity.
Anti-allergic – Substance that reduces the allergic response (e.g. antihistamine activity or mast cell stabilisation).
Anti-asthmatic – Substance that prevents asthma attacks and/or reduces their severity.
Anticholinergic – Agent that blocks cholinergic receptors (e.g. atropine), which results in inhibition of transmission of parasympathetic nerve impulses.
Anticoagulant – Substance that prevents or delays blood coagulation (e.g. warfarin).
Antidiabetic – Substance that aids in blood glucose management or improves management of diabetes via other mechanisms.
Anti-emetic – Substance or procedure that prevents or alleviates nausea and vomiting.
Antigen – Substance that the body recognises as foreign and to which it can evoke an immune response; often it is a protein.
Antimicrobial – Substance that kills microorganisms or inhibits their growth or replication.
Anti-oxidant – Substance that inhibits or delays the oxidation of a second substance; also described as scavenging free radical molecules.
Antiplatelet – Substance that inhibits platelet aggregation and thereby prolongs bleeding time (e.g. aspirin).
Antipruritic – Substance or procedure that relieves or prevents itching.
Antipyretic – Substance or procedure that reduces fever.
Antispasmodic – Substance that reduces smooth muscle spasms.
Antitussive – Substance that suppresses the cough reflex.
Anxiolytic – Substance used to treat and relieve anxiety states.
Apolipoprotein – Protein on the surface of lipoproteins that may bind to receptors, activate enzymes involved in lipoprotein metabolism and provide structure.

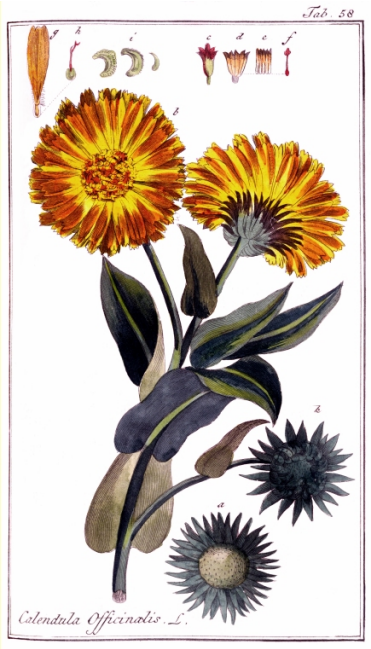
Apoptosis – Programmed cell death.
ARMD – age-related macular degeneration
AST – aspartate aminotransferase
Astringent – Substance that precipitates proteins, causes vasoconstriction and constriction of mucous membranes, and reduces cell permeability when applied topically.
ATP – adenosine triphosphate
Bark – Outermost protective layer of a tree trunk, formed by layers of living cells just above the wood itself. There are usually high concentrations of the active ingredients in the bark (e.g. cinnamon from *Cinnamomum camphora* of the Lauraceae family).
Bioavailability – Proportion of an administered dose that reaches the systemic circulation intact.
Bitter tonic – Herbs with a bitter taste, which are used to stimulate the upper gastrointestinal tract (i.e. stomach, liver, pancreas). They stimulate appetite and digestive function.
BMI – Body mass index
BPH – benign prostatic hypertrophy
Bulb – Fleshy structure made up of numerous layers of bulb scales, which are leaf bases. Bulbs that are popular for medicinal use include onion and garlic (*Allium cepa* and *A. sativum*, respectively, both of the Liliaceae family).
CAM – complementary and alternative medicine
Cardioprotective – Substance that protects the heart from damage by toxins or ischaemia (oxygen deficiency).
Carminative – Substance that relieves flatulence, abdominal distension, spasm and discomfort by relaxing the intestinal muscles and sphincters.
Carotenoid – Group of red, yellow or orange highly unsaturated pigments found naturally in foods. Some are converted to vitamin A in the body and most exhibit anti-oxidant properties.
Chelation – Chemical interaction of a metal ion with another substance, which results in the formation of a molecular complex with the metal firmly bound and isolated.
Chemoprevention – Substance or intervention that reduces the incidence of cancer.
CFS – chronic fatigue syndrome
Cholagogue – Substance that stimulates the release of stored bile from the gall bladder.

Choleretic – Substance that stimulates both the production and the flow of bile.
Chronic – Persisting for a long period of time.
Chylomicrons – Large particles that transport dietary cholesterol and fatty acids from the gastrointestinal tract to the liver.
CNS – central nervous system
Cognitive activator – Substance or procedure that stimulates the mental processes such as memory, judgement, reasoning and comprehension.
Cohort study – Study concerning a specific population that shares a common characteristic (e.g. same age, same gender).
Cold extraction – Plant material is extracted in a solvent of differing polarity at room temperature, which enables maximum extraction of most components.
Contraindication – Any factor that makes it undesirable or dangerous to administer a medicine or perform a procedure on a specific patient.
Corticosteroids – Steroidal hormones that are synthesised and released from the adrenal cortex; includes both glucocorticoids and mineralocorticoids.
COX – cyclo-oxygenase
Crude herb – Raw plant before it is processed or dried.
CVD – cerebrovascular disease
Cytochrome P450 (CYP) – Proteins involved in extra-mitochondrial electron transfer, chiefly in the liver and during detoxification. There are many CYPs, which are named by the root symbol CYP, followed by a number for family, a letter for subfamily, and another number for the specific gene.
DBP – diastolic blood pressure
Decoction – Aqueous medicine made from an extract of water-soluble substances, usually with the aid of boiling water.
Decongestant – Substance or procedure that reduces or eliminates congestion and swelling, usually of mucous membranes.
Debridement – Removal of foreign objects, damaged tissue, cellular debris and dirt from a wound or burn to prevent infection and promote healing.
Demulcent – Substance that soothes and reduces irritation of tissues such as skin or mucous membranes.
DHA – docosahexanoic acid
DHEA – dehydroepiandrosterone
Diuretic – Substance that modifies kidney function to increase the rate of urine flow.
DMBA – 7,12-dimethylbenz[a]anthracene

Double-blind study – Both the test subject and clinician do not know whether a placebo or active medicine is being administered. The substances are often identifiable by a code that is revealed after results are obtained. This method is widely used in clinical studies to confer greater objectivity.
DSM-IV – Diagnostic and Statistical Manual [of Mental Health Disorders], 4th edn.
ECG – electrocardiogram
EEG – electroencephalogram
Emmenagogue – Substance that increases the strength and frequency of uterine contractions and initiates and promotes menstrual flow (some are also abortifacients).
Emollient – Substance that softens tissue and reduces irritation, usually of the skin and mucous membranes.
Endogenous – Originating from within the body; synthesised by the body.
Epidemiological study – Study of occurrence and distribution of disease in large human populations.
Ergogenic aid – Substance that improves energy utilisation with the expectation that it will enhance physical performance.
Erythropoiesis – Process of erythrocyte production in the bone marrow.
ESADDI – estimated safe and adequate daily dietary intake
ESCOP – European Scientific Cooperative on Phytotherapy
ESR – erythrocyte sedimentation rate
Essential amino acids – Eight amino acids that are required for health and must be obtained from the diet: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine.
Essential fatty acids (EFA) – Polyunsaturated acids required for growth and general health, and must be obtained from the diet (e.g. omega 3 EFAs found in fish oils).
Essential oil – Volatile oils usually extracted from plants through a process of either steam distillation or microwave extraction. They consist of terpenes (mono- and sesquiterpenoids and coumarins) and are of considerable importance as active ingredients (e.g. peppermint oil from *Mentha* × *piperita* from the Lamiaceae family).
Expectorant – Substance that promotes the expulsion of mucus, fluids or sputum from the respiratory tract.
Extract – Substance prepared by the use of solvents or evaporation to separate it from the original material.

Fatty oils – Non-volatile, insoluble oils pressed from either the seeds or the fruits of a plant (e.g olive oil).
FDA – Food and Drug Administration (USA)
FEV1 – forced expiratory volume in 1 second
Flavonoids – Compounds responsible for the colour of flowers, fruits and sometimes leaves. The name refers to the Latin *flavus*, meaning yellow. Some may contribute to the colour as co-pigment. Flavonoids protect the plant from UV damage and play a role in reproduction by attracting pollinators.
Flowers – Commonly used in medicine (e.g. cloves *(Syzygium aromaticum*, Myrtaceae family), chamomile (*Chamomilla recutita*, Asteraceae family) and marigold (*Calendula officinalis*, Asteraceae family)).
Fluid extract – Hydro-ethanolic extract of crude herbal material with a drug solvent ratio of 1:1 or 1:2 (e.g. 1 part herb to 1 or 2 parts solvent).
Free radical – Unstable organic compound with at least one unpaired electron.
Fresh plant tincture – Herbal extract made from fresh plant instead of dried material.
Fruit – Most commonly used seeds are anis (*Pimpinella anisum*) and fennel (*Foeniculum vulgare*), both of the Apiaceae family. In some instances, the fruit peel is used specifically (e.g. citrus spp, from the Rutaceae family).
FSH – follicle stimulating hormone
FVC – forced vital capacity
GABA – gamma-aminobutyric acid
GAD – generalised anxiety disorder
Galactogogue – Substance that promotes the production and flow of breast milk.
GI – glycaemic index
Glycoside – Sugar-containing compound with a glycone (sugar) and aglycone (non-sugar) component that can be cleaved on hydrolysis.
Gum – Solids consisting of mixtures of polysaccharides that are water-soluble and are partially digested by humans. Gums sometimes flow from a damaged plant stem as a defence mechanism or sometimes as a protective system against the invasion of bacteria and fungi. Well-known examples are gum arabic (*Acacia senegal*, Leguminosae), and aloe gel (*Aloe vera* (Liliaceae family): gum mixed with water).
Gy – gray (unit of radiation)
Haemostasis – Physiological process that stops bleeding (i.e. vessel constriction, platelet plug formation and blood coagulation).

HbA_{1c} – haemoglobin A_{1c}
HBeAg – hepatitis B early antigen
HDL – high-density lipoprotein
Hepatoprotective – Substance that reduces or prevents liver damage; protects against the destructive effect of hepatotoxins.
High-performance liquid chromatography – Very popular and widely used method for the analysis and isolation of bioactive natural products.
HIV – human immunodeficiency virus
HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A
HPA – hypothalamus–pituitary–adrenal [axis]
HRT – hormone replacement therapy
HSV – herpes simplex virus
Hypnotic – Substance that induces sleep or the feeling of dreamy sleepiness.
Hypoglycaemic – Substance that reduces blood glucose levels.
Hypolipidaemic – Substance that reduces blood levels of lipids (e.g. cholesterol, triglycerides).
Iatrogenic – Condition caused by medical or surgical treatment or diagnostic procedures.
IBS – irritable bowel syndrome
IFN – interferon
Ig – immunoglobulin
IL – interleukin
Immunomodulation – Substance that alters the immune response; also described as having a balancing effect on immune responses.
Immunostimulant – Substance that augments the immune response.
Immunosuppressant – Substance that inhibits the immune response.
Infused oil – Herbal extract using a fixed oil as the solvent.
Infusion (herbal) – Herbal tea prepared by pouring boiling water over plant parts and steeping for a short time.
iNOS – inducible nitric oxide synthase
Inotrope – Substance that has an effect on the force of myocardial contractility. A positive inotrope increases the force of contraction whereas a negative inotrope decreases the force of contraction.
INR – international normalised ratio
Interaction – Pharmacological interaction is said to occur when the response to one medicine varies from what is usually predicted because another substance has altered the response. An interaction may lead to drug toxicity or a loss of



drug effect; however, it can also be manipulated to benefit the patient by improving outcomes, reducing side-effects or reducing drug dose and costs.
IP – intraperitoneal
IQ – intelligence quotient
Ischaemia – oxygen deficiency.
IV – intravenous
IVF – in vitro fertilisation
Laxative – Substance that causes bowel evacuation.
LD50 – median lethal dose
LDL – low-density lipoprotein
LH – luteinising hormone
Maceration – Method of herbal extraction in which cut herb is soaked in solvent (such as cold water) for a period of time before draining, straining and pressing.
Meta-analysis – Quantitative statistical procedure for combining the results of independent studies to better analyse the efficacy of a specific treatment.
Mineral – Compound containing a non-metal, metal, radical or phosphate required for proper body functioning and health maintenance.
Mineral oil – Faecal softener and laxative.
MND – motor neurone disease
MOA – monoamine oxidase
MRSA – methicillin-resistant *Staphylococcus aureus*
MSSA – methicillin-sensitive *Staphylococcus aureus*
Mucilage – Sticky mixture of carbohydrates produced by plant cell activity. Herbs with a high mucilaginous content are often used as demulcents (e.g. *Ulmus fulvus* (slippery elm), *Althea officinalis* (marshmallow)).
Mucolytic – Substance that dissolves or destroys mucus.
Myocardial infarction – Necrosis (death) of a portion of the heart muscle; also called a heart attack.
NADPH – nicotinamide adenine dinucleotide phosphate
Narrow therapeutic index (NTI) – The dose required to produce a toxic effect in 50% of test animals (TD_{50}) is close to the dose required to produce an effective therapeutic response in 50% of test animals (ED_{50}); such drugs are particularly susceptible to adverse interactions (e.g. digoxin).
Nervine – Substance that exerts a relaxant effect; described as nourishing and strengthening the nervous system.

Neurotransmitter – Chemical that acts as a messenger, enabling transmission of nerve impulses across synapses and neuromuscular junctions. The most important are acetylcholine, catecholamines (noradrenaline, adrenaline and dopamine), serotonin, some amino acids and neuro-active peptides.
NK – natural killer [cell]
NO – nitric oxide
NSAID – non-steroidal anti-inflammatory drug
Nutritive – Substance that contains numerous nutrients such as vitamins, minerals, carbohydrates and fats.
NYHA – New York Heart Association Classification
OA – osteoarthritis
OCP – oral contraceptive pill
OTC – over-the-counter
Oxytocic – Substance that exerts similar effects to oxytocin (i.e. stimulates smooth muscle, usually of the uterus, to contract).
PCOS – polycystic ovaries syndrome
PEF – peak expiratory flow
Peri-operative – Pertaining to the time of surgery.
PG – prostaglandin
P-glycoprotein (P-gp) – P-gp is a transport protein found on the surface of hepatocytes, renal tubular epithelial cells, epithelial cells in the intestine and placenta and capillary epithelial cells in the brain. It has a counter-transport activity (i.e. can transport medicines from the blood back into the gastrointestinal tract, thereby reducing bioavailability).
Pharmacodynamics – Study of the effects of drugs on living organisms.
Pharmacokinetics – Study of the actions of drugs within the body (i.e. absorption, distribution, metabolism and excretion, onset of action and duration of effect).
Phytochemical – Naturally occurring chemical found in a plant.
Phytotherapy – Study and application of plant medicine; a modern term used to describe scientifically investigated and validated herbal medicine.
Placebo – Harmless inactive substance that does not contain an active medicine; used in clinical studies for comparison with medicines suspected of exerting a clinical effect to determine whether in fact a significant response does occur.
PMS – premenstrual syndrome
PO – per os (oral)

Polypharmacy – Use of many medicines by a patient with one or more health conditions.
Polysaccharide – Carbohydrate polymer formed from three or more sugar molecules.
Postprandial – After a meal.
Poultice – Paste made from crushed fresh plant, either mixed with oil or alcohol or simply made in water and applied to the parts of the body.
PPI – proton-pump inhibitors
ppm – parts per million
Prospective study – Study designed to determine the relationship between a condition and a characteristic shared by some members of a group. Usually the population selected is healthy at the beginning of the study and are observed over a period of time for the development of certain conditions in the different subgroups (e.g. smokers and non-smokers).
PUFA – polyunsaturated fatty acids
PUVA – psoralen ultraviolet A
QOL – quality of life
RA – rheumatoid arthritis
RAST – radioallergosorbent test
RCT – randomised controlled trial
RDI – recommended daily intake
Resin – Excreted from specialised cells or ducts in plants and consists of a mixture of essential oils and polymerised terpenes; usually insoluble in water. Well-known examples include frankincense (*Boswellia sacra*) and myrrh (*Commiphora molmol*), both of the Burseraceae family
Restorative – Restores or renews a person's state of health or consciousness to normal.
Rhizome – Root; underground fleshy stem that grows horizontally and acts as food storage for the plant.
Risk factor – Factor that increases a person's susceptibility to an unwanted, unpleasant or unhealthy event or disease.
Root – Fleshy or woody, usually underground, part of a plant; may be fibrous (e.g. *Urtica dioica* or *U. radix* of the Urticaceae family, stinging nettle), solid (e.g. *Glycyrrhiza glabra* of the Leguminosae family, licorice) or fleshy (e.g. *Harpagophytum procumbens* of the Pedaliaceae family, devil's claw).
Salicylate – Substance that contains or is derived from salicylic acid.

Saponin – Vast group of glycosides that occur in many plants; dissolve in water and form a soapy solution when shaken; used in demulcents.
SBP – systolic blood pressure
SC – subcutaneous
Seeds – Contained within the fruit and used medicinally (e.g. fennel seed (*Foeniculum vulgare*, Apiaceae)).
SLE – systemic lupus erythematosus
SSRI – selective serotonin reuptake inhibitor
Synergistic – Several components acting or working together in a coordinated manner to produce an effect greater than that of the sum of the individual effects.
Tannin – Substance that forms a precipitate with proteins, nitrogenous bases, polysaccharides and some alkaloids and glycosides (e.g. *Camellia sinensis*, the herb commonly used to make 'tea' is a rich source of tannins).
TCM – traditional Chinese medicine
TGA – Therapeutic Drugs Administration (Australia)
Th – T helper cell
Therapeutic index – Measure of the safety of a medicine based upon the dose required to produce a toxic effect in 50% of test animals (TD_{50}) divided by the dose required to produce an effective therapeutic response in 50% of test animals (ED_{50}) i.e. TI = TD_{50}/ED_{50}.
Thin layer chromatography – Analytical method using glass or aluminium plates precoated with the sorbent (e.g. silica gel) to separate a compound mixture according to the polarity of its components.
Tincture – Hydro-ethanolic extraction of crude herbal material; usually extracted in the ratio of 1:5 (1 part herb to 5 parts solvent). Glyceride tinctures may be prepared by using glycerol rather than alcohol.
TNF – tumour necrosis factor
TPN – total parenteral nutrition
TSH – thyroid stimulating hormone
URTI – upper respiratory tract infection
UTI – urinary tract infection
UV – ultraviolet
VAS – visual analogue scale
Vitamin – Organic compound essential to life. With few exceptions, they cannot be synthesised in the body and must be obtained from the diet.
VLDL – very low-density lipoprotein

WOMAC – Western Ontario and McMasters University Osteoarthritis Index

APPENDIX 2

HERB/NUTRIENT–DRUG INTERACTIONS

ASSUMPTIONS MADE WHEN COLLATING AND ASSESSING INFORMATION FOR THIS TABLE

- Information is compiled from the 120 monographs included in this book.
- The clinical significance of many interactions is still unknown because controlled trials are lacking in most cases. In these instances, interactions are based on evidence of pharmacological activity and case reports, and have a sound theoretical basis, although remain to be tested.
- All information refers to oral dose forms unless otherwise specified.
- Information is correct at the time of writing; however, because of the ever-expanding knowledge base developing in this area, new research is constantly being published.
- The interaction table is provided as a guide only and should not replace the use of professional judgement. It has been developed to assist clinicians when advising patients.

USING THIS GUIDE IN PRACTICE

- Refer to Chapter 8: Interactions with Herbal and Natural Medicines for background information.
- Commonly used prescription and over-the-counter medications are organised by therapeutic class and subclass and are listed alphabetically.
- Common names have been used when referring to herbs.
- Refer to the original monograph for more information about a particular substance.

RECOMMENDATIONS

Avoid — there may be insufficient information available to be able to advise using the two substances safely together, so avoid until more is known. The drug may have a narrow therapeutic index and there is sufficient evidence to suggest that the interaction may be clinically significant. Consider an alternative treatment that is unlikely to produce an undesirable interaction.

Avoid use unless under medical supervision — harmful effects of the potential interaction can be avoided if doses are altered appropriately under professional supervision or the patient is closely monitored. Some of these interactions can be manipulated to the advantage of the patient. Changes to the dosage regimen may be required for safe combined use.

Caution — the possibility exists of an interaction that may change effects clinically; be aware and monitor. It is prudent to tell patients to be aware and seek advice if they are concerned.

Observe — interaction may not be clinically significant at the usual recommended doses and theoretical; however, the clinician should be alert to the possibility of an interaction.

Beneficial interaction possible — prescribing the interacting substance may improve clinical outcomes; for example, reducing drug requirements, complementing drug effects, reducing drug side-effects, counteracting nutritional deficiencies caused by drugs, alleviating drug withdrawal symptoms, and enhancing patient wellbeing.

Key to the Table by Herb/Supplement

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
ALLERGIC DISORDERS				
Antihistamines				
Antihistamines and mast-cell-stabilising drugs	Albizia	Additive effects	Beneficial interaction possible	Both in vitro and in vivo tests have reported significant mast-cell-stabilisation effects similar to those of cromoglycate
	Baical skullcap	Additive effects	Beneficial interaction possible	Luteolin and baicalein have been shown to inhibit IgE antibody-mediated immediate- and late-phase allergic reactions in mice
	Perilla	Additive effects	Observe	Perilla seed extract has been shown to inhibit histamine release from mast cells in a dose-dependent manner — drug dosage may need modification
ANALGESIA				
Narcotic analgesics				
Codeine	Adhatoda	Additive effects	Beneficial interaction possible	Theoretically will increase antitussive effects of drug
	Kava kava	Additive effects	Caution	Increased CNS depression theoretically possible
Morphine	Kava kava	Additive effects	Caution	Increased CNS depression theoretically possible
	Tyrosine	Additive effects	Observe	Tyrosine potentiates morphine-induced analgesia by 154% in mice
	Withania	Reduced morphine tolerance/ dependence	Beneficial interaction possible with professional supervision	In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence, so it is sometimes used in opiate withdrawal
Simple analgesics and antipyretics				
Simple analgesics and antipyretics	Meadowsweet	Additive effects	Observe Beneficial interaction possible	Additive anti-inflammatory and analgesic effects theoretically possible

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin E	Additive effects	Beneficial interaction possible Drug dosage may require modification	Vitamin E may enhance the pain-modifying effects of drug in RA
	Willowbark	Additive effects	Observe Beneficial interaction possible	Additive anti-inflammatory and analgesic effects theoretically possible
Aspirin	Grapeseed extract	Increased bruising and bleeding	Observe Beneficial interaction possible	Theoretically may enhance antiplatelet and anti-inflammatory activity of aspirin
	Meadowsweet	Increased bruising and bleeding	Observe Beneficial interaction possible	Theoretically may enhance anti-inflammatory and antiplatelet effects
	Policosanol	Increased bruising and bleeding	Observe	Doses >10 mg/day may inhibit platelet aggregation
	Vitamin C	Decreased vitamin C effects	Beneficial interaction	Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements, as observed in animal and human studies. Increased vitamin C intake may be required with long-term therapy
	Willowbark	Increased bruising and bleeding	Observe Beneficial interaction possible Caution with high-dose (> 240 mg salicin daily)	Theoretically may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect
Paracetamol	Andrographis	Reduced side-effects	Beneficial interaction possible	Andrographis may exert hepatoprotective activity against liver damage induced by paracetamol
	Garlic	Reduced side-effects	Beneficial interaction possible	Garlic may exert hepatoprotective activity against liver damage induced by paracetamol

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Quercetin	Reduced side-effects	Beneficial interaction possible	Quercetin may exert hepatoprotective activity against liver damage induced by paracetamol
	St Mary's thistle	Reduced side-effects	Beneficial interaction possible	St Mary's thistle may exert hepatoprotective activity against liver damage induced by paracetamol
	SAMe	Reduced side-effects	Beneficial interaction possible	SAMe may exert hepatoprotective activity against liver damage induced by paracetamol
	Schisandra	Reduced side-effects	Beneficial interaction possible	Schisandra may exert hepatoprotective activity against liver damage induced by paracetamol
CARDIOVASCULAR SYSTEM				
Anti-angina agents				
Nitroglycerin/ glyceryl trinitrate (e.g. anginine)	Vitamin E	Prevention of drug tolerance	Beneficial interaction possible	Oral vitamin E prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (10 mg/24 h) according to one randomised placebo-controlled study
Anti-arrhythmic agents				
	Astragalus	Additive effects	Observe	Additive effects are theoretically possible with IV administration of astragalus, based on positive inotropic activity identified in clinical studies; the clinical significance of these findings for oral dose forms is unknown
	Devil's claw	Additive effects	Observe	Devil's claw has demonstrated anti-arrhythmic activity, but interaction is theoretical and clinical significance is unclear
	Hawthorn	Additive effects	Observe	Hawthorn has demonstrated anti-arrhythmic activity in vitro and in vivo, but interaction is theoretical and clinical significance is unclear
	Magnesium	Additive effects	Observe	High-dose oral magnesium has demonstrated anti-arrhythmic activity according to one clinical trial
Anticoagulants, antiplatelets				
Monitor bleeding time and signs and symptoms of excessive bleeding				

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Anticoagulants (e.g. warfarin)	Andrographis	Increased bruising and bleeding	Caution — monitor bleeding time	Andrographolide clinically confirmed to inhibit platelet-activating-factor-induced platelet aggregation
	Carnitine	Increased bruising and bleeding	Caution — monitor bleeding time and signs and symptoms of excessive bleeding	According to one case report, L-carnitine 1 g/day may potentiate the anticoagulant effects of acenocoumarol
	Celery	Increased bruising and bleeding	Observe with concentrated extracts	Although it contains naturally occurring coumarins, interaction is unlikely
	Chondroitin	Increased bruising and bleeding	Observe with high-dose supplements	Theoretical risk; not observed in clinical trials
	Coenzyme Q10	Reduced drug effects	Caution	A double-blind crossover study found that oral CoQ10 100 mg/day had no significant effect on INR or warfarin levels; however, in vivo tests using 10 mg/kg/day CoQ10 decreased serum concentrations of warfarin by increasing drug metabolism
	Cranberry	Increased bruising and bleeding	Caution	Based on case reports
	Devil's claw	Increased bruising and bleeding	Caution	Case reports suggest possible anticoagulant activity
	Dong quai	Increased bruising and bleeding	Caution with high-dose supplements	A controlled trial using an IV preparation of dong quai found that it prolonged prothrombin times, but it is unknown whether this effect occurs with oral dose forms
	Evening primrose oil	Increased bruising and bleeding	Caution with high-dose supplements	Gamma-linoleic acid in evening primrose oil affects prostaglandin synthesis, leading to inhibition of platelet aggregation — clinical significance is unknown
	Fenugreek	Increased bruising and bleeding	Observe	Contains naturally occurring coumarins, but a placebo-controlled study found no effect on platelet aggregation, fibrinogen or fibrinolytic activity
	Feverfew	Increased bruising and bleeding	Observe	Although feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in a clinical study

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Fish oils	Increased bruising and bleeding	Caution with doses < 12 g Avoid with very high doses (> 12 g) unless under medical supervision	Bleeding time is increased at doses of 12 g/day, according to a clinical study
	Garlic	Increased bruising and bleeding	Avoid at high dose (>4 g) unless under medical supervision	Large doses may increase INR
	Ginger	Increased bruising and bleeding	Avoid at high dose (>10 g) unless under medical supervision	Inhibits platelet aggregation at high doses
	Ginkgo biloba	Increased bruising and bleeding	Caution	Although case reports suggest possible anticoagulant effect, two recent clinical studies indicate no effect on pharmacokinetics, pharmacodynamics or clinical effects of warfarin
	Ginseng — Korean	Increased bruising and bleeding	Avoid unless under medical supervision	Inhibits platelet aggregation both in vitro and in vivo; clinical significance unknown
	Ginseng — Siberian	Increased bruising and bleeding	Observe	In vivo study demonstrated that an isolated constituent in Siberian ginseng has anticoagulant activity and a clinical trial found a reduction in blood coagulation induced by intensive training in athletes — whether these effects also occur in non-athletes is unknown
	Grapeseed extract	Increased bruising and bleeding	Caution	Inhibits platelet aggregation in vitro — clinical significance unknown
	Green tea	Reduced drug effects	Caution with high doses	A case report of excessive intake (2.25–4.5 L green tea daily) was reported to inhibit warfarin activity and decrease INR
	Guarana	Increased bruising and bleeding	Caution	In vitro and in vivo research has identified antiplatelet activity
	Horseradish	Increased bruising and bleeding risk	Observe with high-dose supplements	Although it contains coumarins, interaction unlikely, but this has not been established clinically

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Licorice	Increased bruising and bleeding	Caution with high doses	Isoliquiritigenin inhibits platelet aggregation, and glycyrrhizin inhibits prothrombin, according to in vitro and in vivo tests — clinical significance unknown
	Meadowsweet	Increased bruising and bleeding	Observe	In vitro tests have indicated anticoagulant activity — clinical significance unknown
	Myrrh	Increased bruising and bleeding	Observe with myrrh preparations Caution with guggul preparations	Guggul inhibited platelet aggregation in vitro and in a clinical study, so concurrent use may theoretically increase the risk of bleeding — implications for *Commiphora molmol* use unclear
	Policosanol	Increased bruising and bleeding	Caution with doses >10 mg daily	Current evidence is contradictory, as one study failed to detect an interaction between policosanol and warfarin, but others have found that doses >10 mg/day may inhibit platelet aggregation
	Psyllium	Decreased drug absorption	Separate doses by at least 1 hour	
	Rosemary	Increased bruising and bleeding	Caution	Rosemary demonstrates antithrombotic activity in vitro and in vivo
	St John's wort	Decreased drug effects	Avoid unless under medical supervision to monitor for signs of reduced drug effectiveness and adjust dose if necessary Prothrombin time or INR should be closely monitored with addition or withdrawal of St John's wort	St John's wort increases metabolism of drug
	St Mary's thistle	Increased drug effects	Caution — monitor for signs of increased drug effectiveness	Possible CYP (liver cytochrome) inhibition effects, but conflicting evidence makes evaluation difficult
	Turmeric	Increased bruising and bleeding	Caution with concentrated extracts	Curcumin inhibits platelet aggregation in vitro and in vivo — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin E	Increased bruising and bleeding	Caution with high-dose supplements (>1000 IU daily) Until clinical significance can be established prothrombin time or INR should be closely monitored with addition or withdrawal of high-dose vitamin E supplements	Clinical studies have produced conflicting results: several found no effects of platelet aggregation or coagulation, although others found an increased bleeding risk People with reduced levels of vitamin K may be more susceptible to the effects of vitamin E potentiating warfarin activity
Antiplatelet drugs (e.g. aspirin)	Andrographis	Increased bruising and bleeding	Observe	Herb inhibits platelet aggregation, observed in animal and clinical studies
	Bilberry	Increased bruising and bleeding	Caution with high-dose (>170 mg) anthocyanadins unless under medical supervision	Dose is extremely high and not relevant to clinical practice
	Evening primrose oil	Increased bruising and bleeding	Observe, although beneficial interaction possible	Theoretically may enhance anti-inflammatory and antiplatelet effects
	Feverfew	Increased bruising and bleeding	Observe	Although feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in a clinical study
	Fish oils	Additive effects	Observe — beneficial interaction possible under professional supervision	No haemorrhagic effects were seen in a clinical study — theoretical concern
	Garlic	Increased bruising and bleeding	Caution at doses >4 g/day	

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Ginger	Increased bruising and bleeding	Caution at high dose (>10 g) unless under professional supervision	Inhibits platelet aggregation at very high doses
	Ginkgo biloba	Increased bruising and bleeding	Observe	Theoretically possible because of platelet-activating-factor inhibitor activity, but three trials cast doubt on the clinical significance of this effect
	Grapeseed extract	Increased bruising and bleeding	Observe	Theoretically may enhance antiplatelet activity
	Guarana	Increased bruising and bleeding	Observe	Decreases platelet aggregation
	Myrrh	Increased bruising and bleeding	Observe	Guggul inhibited platelet aggregation in vitro and in a clinical study, so concurrent use may theoretically increase the risk of bleeding. It is uncertain what implications this observation has for use of *Commiphora molmol*
	Turmeric	Increased bruising and bleeding	Observe with concentrated extracts	Curcumin inhibits platelet aggregation in vitro and in vivo — clinical significance unknown
Aspirin	Grapeseed extract	Additive effects	Beneficial interaction possible	Theoretically may enhance antiplatelet and anti-inflammatory activity of aspirin
	Meadowsweet	Increased bruising and bleeding	Observe — beneficial interaction possible	Theoretically may enhance anti-inflammatory and antiplatelet effects
	Policosanol	Increased bruising and bleeding	Observe	Doses >10 mg/day may inhibit platelet aggregation
	Vitamin C	Decreased vitamin C effects	Observe	Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements, as observed in animal and human studies. Increased vitamin C intake may be required with long-term therapy
	Willowbark	Increased bruising and bleeding	Caution with high dose (>240 mg/day)	Theoretically may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Antihypertensive agents				
Antihypertensive drugs	Essential fatty acids — omega-3 and omega-6	Increased drug effects	Observe — beneficial interaction possible	Both omega-3 and omega-6 fatty acids exhibit antihypertensive activity
	Evening primrose oil	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	Evening primrose oil has been shown to enhance the effects of several antihypertensive drugs, including dihydralazine, clonidine and captopril in rats under experimental conditions
	Guarana	Antagonistic effects	Caution	Theoretical concern
	Garlic	Additive effects	Caution — monitor drug requirements (interaction may be beneficial)	Clinical trials have shown garlic to reduce blood pressure
	Hawthorn	Additive effects	Caution — monitor drug requirements (interaction may be beneficial)	Mild antihypertensive activity has been reported with long-term use of hawthorn
	Licorice	Reduced drug effect	Caution — monitor blood pressure when high-dose licorice preparations are taken for more than 2 weeks	High-dose glycyrrhizin taken long-term can lead to increased blood pressure
	Oats (oat-based cereals)	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	A clinical trial has shown that ingestion of oat-based cereals decreased blood pressure in 73% of hypertensive patients and reduced drug requirements
	Olive leaf and olive oil	Additive effects	Beneficial interaction possible	
Hydralazine (e.g. Apresoline, Alphapress)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B6 (pyridoxine)	Reduced vitamin B6 absorption	Separate doses by at least 2 hours	A clinical trial has shown that the drug may induce B6 deficiency, so increased intake may be required with long-term therapy
Methyldopa (e.g.Aldomet)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy
ACE inhibitors (e.g. captopril, enalapril)	Iron	Reduced drug effect	Separate doses by at least 2 hours	A small clinical trial found that concomitant iron administration reduced area-under-the-curve plasma levels of unconjugated captopril by 37%
	Zinc	Reduced zinc levels	Monitor for zinc efficacy and zinc status	Increased zinc intake may be required with long-term therapy
Verapamil	St John's wort	Reduces drug levels via increased metabolism	Monitor and adjust dose as necessary	
Beta-adrenergic-blocking agents	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy
Propranolol	Myrrh	Reduced drug effect	Observe	A clinical trial has shown that guggulipid reduces bioavailability of propranolol. It is uncertain what implications this has for use of *Commiphora molmol*
	Vitamin E	Reduced drug effect	Observe	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown
Calcium-channel blockers (e.g. verapamil)	Calcium	Reduced drug effect	Avoid high-dose supplements unless under medical supervision	Calcium may reduce antihypertensive effect of drug
	Magnesium	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	A meta-analysis of 20 randomised trials showed that magnesium has a modest antihypertensive activity
	Vitamin D	Reduced drug effect	Caution unless under medical supervision	
Felodipine	Peppermint oil	Increased drug effects	Caution	Peppermint oil has been shown to increase the oral bioavailability of felodipine in animal studies

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Nifedipine	Ginseng — Korean	Increased drug effects	Caution	
Diltiazem	Myrrh	Reduced drug effect	Prudent to avoid guggulipid preparations	A clinical trial has shown that guggulipid reduces bioavailability of diltiazem. It is uncertain what implications this has for use of *Commiphora molmol*
	Quercetin	Increased drug effects	Caution	Increased drug bioavailability observed in vivo
Antimigraine preparations				
Antimigraine preparations	Coenzyme Q10	Additive effects	Beneficial interaction possible	CoQ10 demonstrated migraine prevention activity in a clinical study
	Feverfew	Additive effects	Beneficial interaction possible	Feverfew demonstrated migraine prevention activity in several clinical studies
	Vitamin B2 (riboflavin)	Additive effects	Beneficial interaction possible	Vitamin B2 has demonstrated migraine prevention activity in several clinical studies
Clonidine (e.g. Catapres)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	In vivo study indicates that clonidine reduces serum CoQ10 levels. Increased CoQ10 intake may be required with long-term therapy
Cardiac inotropic agents				
Cardiac glycosides	Hawthorn	Additive effects	Caution — monitor drug requirements (interaction may be beneficial)	Theoretical interaction, as in vitro and in vivo studies indicate that hawthorn has positive inotropic activity Small clinical study found interaction not clinically signficant when digoxin 0.25 mg taken with Hawthorn (WS1442) 450 mg twice daily

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Digoxin (e.g. Lanoxin) Adverse effects of high-dose digoxin include: nausea, vomiting, diarrhoea, confusion, fainting, palpitations, irregular heart beat, visual disturbances	Aloe vera	Increased drug toxicity	Avoid long-term use of high-dose preparations	Long-term oral use of aloe can deplete potassium levels and reduced potassium status lowers the threshold for drug toxicity
	Ginseng — Siberian	Interferes with therapeutic drug monitoring for digoxin	Caution — drug assay may produce false-positive results	Refer to Chapter 8 on interactions for further information
	Guarana	Increased drug toxicity	Avoid long-term use of high-dose preparations	Long-term guarana use can deplete potassium levels and reduced potassium status lowers the threshold for drug toxicity
	Licorice	Increased drug toxicity	Avoid long-term use of high-dose preparations (>100 mg glycyrrhizin daily >2 weeks) unless under medical supervision	Reduced potassium status lowers the threshold for drug toxicity
	Quercetin	Increased drug toxicity	Avoid concurrent use	Increased drug bioavailability possible

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	St John's wort	Reduced drug effects	Avoid unless under medical supervision Monitor for signs of reduced drug effectiveness and adjust dose if necessary When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort induces CYP enzymes and P-glycoprotein. A clinical trial shows that St John's wort significantly decreases serum levels of drug within 10 days of concomitant use
Diuretics				
Diuretics	Dandelion leaf	Additive effects	Observe	Theoretically increased diuresis is possible — clinical significance is unknown
	Guarana	Additive diuretic effects but decreased hypotensive effects of drug	Caution Monitor potassium status	Theoretically increased diuresis and decreased hypotensive effects are possible — clinical significance is unknown
	Licorice	Increased potassium excretion	Avoid long-term use unless under medical supervision Monitor potassium status	Potassium loss may become significant when licorice is used in high dose (>100 mg glycyrrhizin daily) for longer than 2 weeks
Loop diuretics	Magnesium	Increased magnesium excretion	Monitor magnesium efficacy and status — beneficial interaction possible	Increased magnesium intake may be required with long-term therapy
	Stinging nettle	Additive effects	Observe	Theoretically increased diuresis is possible — clinical significance is unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B1 (thiamin)	Reduced B1 levels	Monitor B1 efficacy and status — beneficial interaction possible	Increased B1 intake may be required with long-term therapy
	Zinc	Increased urinary zinc excretion	Monitor zinc efficacy and status — beneficial interaction possible	Increased zinc intake may be required with long-term therapy
Potassium-sparing diuretics	Magnesium	Increased magnesium effects	Observe	
Thiazide diuretics	Calcium	Decreased urinary calcium excretion	Observe Monitor serum calcium and look for signs of hypercalcaemia	
	Magnesium	Increased magnesium excretion	Monitor magnesium efficacy and status — beneficial interaction possible	Increased magnesium intake may be required with long-term therapy
	Zinc	Increased urinary zinc excretion	Monitor zinc efficacy and status — beneficial interaction possible	Increased zinc intake may be required with long-term therapy
Hydrochlorothiazide (e.g. Diclotride)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy
	Vitamin B12	Reduces hyperhomocysteinaemia	Beneficial interaction possible in conjunction with folate	Hydrochlorothiazide may increase homocysteine levels
Hypolipidaemic agents				
Hypolipidaemic agents	Chromium	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	Clinical trials indicate that chromium reduces total cholesterol levels

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Garlic	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	A meta-analysis of 13 clinical trials concluded that garlic significantly reduces total cholesterol levels — effects are described as modest
	Myrrh	Additive effects	Observe — monitor drug requirements (interaction may be beneficial for guggul preparations)	Guggul has demonstrated cholesterol-lowering activity in several clinical studies
	Oats (oat-based cereals)	Additive effects	Beneficial interaction possible — monitor drug requirements	Clinical trials indicate that oat-based cereals reduce total cholesterol levels
	Policosanol	Additive effects	Caution, although beneficial interaction possible under medical supervision	Policosanol may theoretically increase cholesterol-lowering effects of statins, but a theoretical concern exists as to whether concurrent use will also increase incidence of adverse effects
	Vitamin B3 (niacin)	Additive effects	Beneficial interaction possible — caution with sustained-release form	Several clinical trials confirm the cholesterol-lowering activity of niacin and the safety of niacin with statins, but the sustained-release form may be unsafe
Cholestyramine (e.g. Questran lite, colestipol [e.g. Colestid])	Fat-soluble vitamins (A, D, E, K, beta-carotene)	Reduced vitamin absorption	Separate doses by at least 4 hours and monitor vitamin status	Increased vitamin intake may be required with long-term therapy
	Folate	Reduced folate absorption	Separate doses by at least 4 hours and monitor iron status	Increased vitamin intake may be required with long-term therapy
	Iron	Reduced iron absorption	Separate doses by at least 4 hours and monitor iron status	Increased iron intake may be required with long-term therapy
	Vitamin E	Reduced vitamin absorption	Separate doses by at least 4 hours and monitor vitamin status	Increased vitamin intake may be required with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Chitosan	Vitamin C	May increase cholesterol-lowering effect	Beneficial interation possible	
Fibric-acid derivatives (e.g. gemfibrozil)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible — separate doses by 4 hours	Increased CoQ10 intake may be required with long-term therapy
HMG-CoA reductase inhibitors (statins)	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Clinical study indicates several statin drugs reduce CoQ10 levels — increased CoQ10 intake may be required with long-term therapy
	Vitamin A	Increased vitamin A activity	Observe	A clinical trial has reported increased serum levels of vitamin A — clinical significance unclear
	Vitamin B3 (niacin)	Additive effects	Beneficial interaction possible — caution with sustained-release form	Several clinical trials confirm the cholesterol-lowering activity of niacin and the safety of niacin with statins, but the sustained release form may be less safe
Pravastatin (e.g. Pravachol)	Fish oils	Additive effects	Beneficial interaction possible	A clinical trial suggests improved lipid-lowering effects when used concurrently
Simvastatin (e.g. Lipex, Zocor)	Peppermint oil	Additive effects	Observe — monitor drug requirements (interaction may be beneficial)	Peppermint oil has been shown to increase the oral bioavailability of simvastatin in animal studies
	St John's wort	Reduced drug effects	Monitor for signs of reduced drug effectiveness and adjust the dose if necessary When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort increases metabolism of simvastatin
	St Mary's thistle	Increased drug effect	Observe — monitor drug requirements	May reduce metabolism of drug resulting in increased serum levels and adverse effects (difficult to evaluate evidence)

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
CENTRAL NERVOUS SYSTEM				
Anticonvulsants				
Anticonvulsants	Carnitine	Reduced side-effects	Beneficial interaction possible	L-Carnitine deficiency may cause or potentiate valproic acid toxicity, and supplementation is known to reduce the toxicity of valproate as well as symptoms of fatigue — concurrent use is recommended, as a beneficial interaction is possible
	Folate	Reduced side-effects	Monitor for drug effectiveness Beneficial interaction possible	Requires close supervision to ensure that drug efficacy is not substantially reduced
	Ginkgo biloba	Reduced drug effects	Observe	Based on case reports
	St John's wort	Reduced drug effects	Avoid unless under medical supervision to alter doses appropriately When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort may increase drug metabolism, resulting in reduced drug efficacy
Carbamazepine (e.g. Tegretol) NTI: signs of overdose include CNS and respiratory depression, hypotension, vomiting, fluid retention	St Mary's thistle	Increased drug effects	Caution — monitor drug requirements	May reduce metabolism of drug resulting in increased serum levels and adverse effects (difficult to evaluate evidence)

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B12	Decreased B12 levels	Observe for signs and symptoms of B12 deficiency Beneficial interaction possible	In studies with children, long-term carbamazepine use led to a decrease in vitamin B12 levels. Increased intake may be required with long-term therapy
Phenobarbitone	Celery	Prolonged action	Caution	Celery juice has been found to prolong the action of phenobarbitone in rats — clinical significance unknown
	Kava kava	Increased sedation	Caution	
	Withania	Increased sedation	Observe although beneficial interaction possible	
Phenobarbitone and phenytoin	Kava kava	Increased sedation	Caution	
	St John's wort	Decreased drug effects (increased drug metabolism)	Avoid — monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	
	Vitamin B12	Increased serum B12 levels	Observe	One clinical study reported that combined long-term use of phenobarbital and phenytoin resulted in significantly increased serum B12 levels — clinical significance unknown
Phenytoin	Vitamin B6 (pyridoxine)	Reduced drug effects	Caution — monitor for reduced drug effectiveness	B6 in high doses may lower plasma levels and efficacy of drug and decrease seizure control
Phenytoin and valproate	Vitamin D	Reduced side-effects	Beneficial interaction possible	Anticonvulsants induce catabolism of vitamin D through liver induction — prolonged use is associated with increased risk of developing rickets and osteomalacia, therefore increased intake may be useful with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Antidepressants				
Antidepressants including SSRIs, SNRIs, tricyclics and MAOIs	Albizia	Additive effects	Observe	Increased risk of serotonergic syndrome is theoretically possible, as the herb increases serotonin levels, according to in vivo studies — clinical significance unknown
	Ginkgo biloba	Reduced side-effects	Beneficial interaction possible	Reduced sexual dysfunction side-effects reported in a clinical study and may also improve sleep continuity
	St John's wort	Additive effects	Avoid unless under medical supervision	Risk of serotonergic syndrome if combined use is not carefully monitored
	SAMe	Additive effects	Caution	Theoretically may increase risk of serotonergic syndrome, and a case report exists; however, an experimental study found that brain SAMe levels were significantly reduced after chronic treatment with imipramine
	Tyrosine	Additive effects	Avoid unless under medical supervision	Tyrosine is a precursor for several neurotransmitters, which theoretically increases risk of serotinin syndrome
MAOIs	Tyrosine	Increased side-effects	Avoid	Some tyrosine may be metabolised to tyramine Concurrent use with MAOIs may lead to hypertensive crisis
Tricyclic antidepressants	Andrographis	Reduced side-effects	Beneficial interaction possible	Andrographis may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants
	Coenzyme Q10	Reduced CoQ10 serum levels	Beneficial interaction possible	Increased CoQ10 intake may be required with long-term therapy
	St John's wort	Additive effects	Avoid unless under medical supervision	Although St John's wort decreases drug plasma levels of tricyclic antidepressants, it may increase available serotonin
	St Mary's thistle	Reduced side-effects	Beneficial interaction possible	St Mary's thistle may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants
	Vitamin B2 (riboflavin)	Decreased B2 levels	Monitor for signs and symptoms of B2 deficiency Beneficial interaction possible	Tricyclic antidepressants may reduce the absorption of riboflavin. Increased B2 intake may be required with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Imipramine	Vitamin B3 (niacin)	Additive effects	Beneficial interaction possible	A combination of imipramine with L-tryptophan 6 g/day and niacinamide 1500 mg/day has been shown to be more effective for people with bipolar disorder than imipramine alone
Antipsychotic agents				
Haloperidol (e.g. Serenace)	Ginkgo biloba	Increased drug effects and reduced side-effects	Observe — beneficial interaction possible under professional supervision	Three clinical trials demonstrate that ginkgo increases drug effectiveness
	Iron	Reduced iron effect	Monitor iron status	May cause decreased blood levels of iron — clinical significance unclear. Increased iron intake may be required with long-term therapy
	Quercetin	Reduced drug side-effects	Beneficial interaction possible	According to in vivo studies, reduced chewing movements and tongue protrusions possible with concurrent use
Phenothiazines (e.g. chlorpromazine, trifluoperazine)	Evening primrose oil	Reduced drug effects	Avoid concomitant use until safety can be established	Several case reports suggest that evening primrose oil may reduce seizure threshold and reduce drug effectiveness in patients with schizophrenia treated with phenothiazines
Chlorpromazine (e.g. Largactil)	Vitamin E	Reduced drug effects	Observe	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown
CNS agents				
Cholinergic drugs Tacrine (e.g. Cognex)	Brahmi	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for brahmi, so increased drug activity is theoretically possible
	Ginkgo biloba	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for ginkgo, so increased drug activity is theoretically possible
	Lemon balm	Additive effects	Observe Beneficial interaction possible	Cholinergic activity has been identified for lemon balm, so increased drug activity is theoretically possible

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	St Mary's thistle	Reduced side-effects	Beneficial interaction possible	St Mary's thistle may exert hepatoprotective activity against liver damage induced by tacrine
CNS stimulants	Guarana	Additive effects	Caution	Herb has demonstrated CNS stimulant activity
	Tyrosine	Additive effects	Caution	Tyrosine is a precursor for several neurotransmitters (theoretical concern)
Movement disorders				
L-Dopa (levodopa)	Calcium	Reduced drug absorption	Separate doses by 2 hours	L-dopa can form an insoluble complex with calcium
	Iron	Reduced drug absorption	Separate doses by 2 hours	L-dopa can form an insoluble complex with iron
	Kava kava	Reduced drug effects	Avoid unless under medical supervision	Theoretical interaction, as dopamine antagonist effects have been reported for kava kava
	Magnesium	Reduced drug absorption	Separate doses by 2 hours	L-dopa can form an insoluble complex with magnesium
	Tyrosine	Decreased drug and tyrosine effect	Avoid unless under medical supervision	L-Dopa competes with tyrosine for uptake, so concurrent use may decrease uptake of both substances, thereby reducing efficacy
	Vitamin B6 (pyridoxine)	Reduced drug effects	Observe Monitor for reduced drug effectiveness	Interaction does not occur with combination L-dopa products
	Vitamin C	Reduced side-effects	Beneficial interaction possible	A case report of co-administration with vitamin C suggests this may reduce drug side-effects
	Zinc	Reduced drug absorption	Separate doses by 2 hours	L-Dopa can form an insoluble complex with zinc
L-Dopa with carbidopa	Iron	Reduced drug effects	Separate doses by at least 2 hours	May reduce bioavailability of carbidopa and L-dopa

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Sedatives, hypnotics				
CNS sedatives	Guarana	Reduced drug effects	Observe	Theoretically guarana may reduce the sedative effects of drug via its CNS stimulation effects; however, an in vivo study found no interaction with pentobarbital
	Hops	Additive effects	Caution	
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
	Lavender oil	Additive effects	Observe	
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
	Valerian	Additive effects	Caution Beneficial interaction possible under medical supervision	May be useful in benzodiazepine withdrawal
Midazolam (e.g. Hypnovel)	St John's wort	Reduced drug effects	Caution Monitor for signs of reduced drug effectiveness and adjust the dose if necessary	St John's wort may increase drug metabolism and so reduce serum levels of drug
Barbiturates	Albizia	Additive effects	Caution Beneficial interaction possible under medical supervision	Potentiation of phenobarbitone-induced sleeping was observed in vivo — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Andrographis	Additive effects	Observe Beneficial interaction possible under medical supervision	Potentiation effects observed in vivo — clinical significance unknown
	Folate	Reduced drug effects	Caution Monitor for signs of reduced drug effectiveness	Concomitant folic acid use can reduce seizure control
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision — monitor drug dosage	Increased sedation
	Lemon balm	Additive effects	Observe Beneficial interaction possible under medical supervision	Increased sedation
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision — monitor drug dosage	Increased sedation
	St John's wort	Reduced drug effects	Avoid — monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required	St John's wort induces CYP enzymes and P-glycoprotein, so can reduce drug serum levels
	Valerian	Additive effects	Caution Beneficial interaction possible under medical supervision	Increased sedation

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B6 (pyridoxine)	Reduced plasma levels and drug effects	Caution Monitor for drug effectiveness	Concomitant B6 use can reduce seizure control
	Withania	Additive effects	Observe Beneficial interaction possible under medical supervision	Theoretically may increase sedation
Benzodiazepines	Chamomile	Additive effects	Observe Beneficial interaction possible under medical supervision	Theoretically an additive effect can occur with concurrent use
	Kava kava	Additive effects	Caution Beneficial interaction possible under medical supervision — monitor drug dosage	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision
	Passionflower	Additive effects	Caution Beneficial interaction possible under medical supervision — monitor drug dosage	Increased sedation
	Valerian	Additive effects	Observe Beneficial interaction possible under medical supervision	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision
	Withania	Additive effects	Observe Beneficial interaction possible under medical supervision	

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
CONTRACEPTIVE AGENTS				
Combined oral contraceptive agents				
Oral contraceptive pill	Chaste tree	Reduced herb effects	Observe	There has been speculation as to whether chaste tree is effective when OCPs are being taken. Several clinical studies conducted in women taking the OCP have confirmed that chaste tree still reduces symptoms of premenstrual syndrome
	Folate	Reduced folate levels	Beneficial interaction possible	Folate levels are reduced with long-term use. Increased intake may be required with long-term therapy
	Licorice	Increased side-effects	Observe Caution with high-dose licorice (>100 mg/day glycyrrhizin) or long-term use (> 2 weeks)	Increased risk of side-effects such as hypokalaemia, fluid retention and elevated blood pressure have been noted in case reports
	St John's wort	Reduced drug effects	Caution — avoid use with low-dose OCP	Breakthrough bleeding has been reported in 12 cases, which may indicate decreased effectiveness. Caution related to hyperforin
	Vitamin A	Increased vitamin A levels	Observe	OCP increases serum vitamin A levels
	Vitamin B2 (riboflavin)	Reduced vitamin B2 levels	Beneficial interaction possible	OCP may increase demand for vitamin B2. Increased intake may be required with long-term therapy
	Vitamin B3 (niacin)	Reduced vitamin B3 levels	Beneficial interaction possible	Increased intake may be required with long-term therapy
	Vitamin B5 (pantothenic acid)	Reduced vitamin B5 levels	Beneficial interaction possible	Increased intake may be required with long-term therapy
	Vitamin B6 (pyridoxine)	Reduced vitamin B6 levels	Beneficial interaction possible	OCP may induce pyridoxine deficiency. Increased intake may be required with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B12	Reduced vitamin B12 levels	Observe for signs and symptoms of B12 deficiency Beneficial interaction possible	OCP users showed significantly lower concentrations of cobalamin than controls in a clinical study. Increased intake may be required with long-term therapy
ENDOCRINE AND METABOLIC DISORDERS				
Adrenal steroid hormones				
Corticosteroids	Calcium	Reduced side-effects	Beneficial interaction possible	Through inhibiting vitamin D-mediated calcium absorption, overall levels may be decreased. Increased calcium intake may be required with long-term therapy
	Chromium	Reduced side-effects	Beneficial interaction possible	Corticosteroids increase urinary losses of chromium, and chromium supplementation has been shown to aid in recovery from steroid-induced diabetes mellitus
	Licorice	Additive effects	Beneficial interaction possible but patients should be monitored closely for corticosteroid excess	Concurrent use of licorice preparations potentiates the effects of topical and oral corticosteroids (e.g. prednisolone) as glycyrrhizin inhibits the metabolism of prednisolone. Some practitioners use licorice to minimise requirements for, or to aid in withdrawal of, corticosteroid medications
	Vitamin C	Reduced vitamin C effects	Beneficial interaction possible	May increase requirement for vitamin C. Increased intake may be required with long-term therapy
	Vitamin D	Reduced vitamin D absorption	Beneficial interaction possible	Increased vitamin D intake may be required with long-term therapy
Betamethasone	Carnitine	Additive effects	Beneficial interaction possible	RCT has shown that a combination of low-dose betamethasone (2 mg/day) and L-carnitine (4 g/5 days) was more effective in preventing respiratory distress syndrome (7.3% vs 14.5%) and death (1.8% vs 7.3%) in preterm infants than high-dose betamethasone given alone (8 mg/2 days)

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Agents affecting calcium and bone metabolism				
Alendronate (e.g. Fosamax) and Etidronate (e.g. Didronel)	Calcium	Reduced drug absorption	Separate doses by at least 2 hours	Calcium may reduce drug absorption; however, adequate calcium is required for optimal drug effects
	Iron	Reduced drug absorption	Separate doses by at least 2 hours	
	Magnesium	Reduced drug absorption	Separate doses by at least 2 hours	Magnesium may reduce drug absorption; however, adequate magnesium is required for optimal drug effects
	Zinc	Reduced drug absorption	Separate doses by at least 2 hours	
Gonadal hormones				
Oestrogen	Hops	Additive effects	Observe	Theoretical interaction, based on mild oestrogenic effect of hops
	Red clover	Reduced drug effects	Observe	Theoretically, if taken in large quantities phyto-oestrogens may compete with synthetic oestrogens for receptor binding — clinical significance unknown
Oestrogen and progesterone	Calcium	Additive effects	Beneficial interaction possible	Possible beneficial interaction on bone mineralisation
	Licorice	Increased side-effects	Observe Caution with high-dose licorice or long-term use (> 2 weeks)	OCP can increase sensitivity to glycyrrhizin side-effects such as hypertension, fluid retention, hypokalaemia
Testosterone	Licorice	Altered testosterone effect	Observe Monitor testosterone levels	Contradictory evidence suggests possible effects on testosterone levels
Haemopoietic agents				
Erythropoietin	Ginseng — Korean	Enhanced drug effects	Beneficial interaction possible	The total saponin fraction has been shown to promote haemopoiesis — clinical significance for total herb unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Iron	Enhanced drug effects	Beneficial interaction possible	
	Withania	Enhanced drug effects	Beneficial interaction possible	Animal studies indicate herb increases haematopoiesis — clinical significance unknown
Hypoglycaemic agents				
Hypoglycaemic (e.g. metformin) agents Adverse effects associated with increased hypoglycaemic effects include sweating, hunger, depression, tremor and headaches	Aloe vera	Additive effects	Observe	Oral aloe vera may have hypoglycaemic activity, so additive effects are theoretically possible
	Andrographis	Additive effects	Caution — blood glucose levels should be checked regularly Beneficial interaction possible under professional supervision	Andrographis has hypoglycaemic activity comparable to that of metformin in vivo, so additive effects are theoretically possible
	Bilberry	Additive effects	Observe	Animal study identified the constituent myrtillin as exerting hypoglycaemic actions — relevance for bilberry unclear
	Bitter melon	Additive effects	Caution Monitor drug requirements Possible beneficial effect under professional supervision	

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Chromium	Additive effects	Caution Monitor drug requirements Beneficial interaction possible under professional supervision	Clinical studies have shown that chromium has hypoglycaemic activity in some individuals
	Cinnamon	Additive effects	Observe — potentially beneficial interaction	Clinical studies have produced contradictory results
	Damiana	Additive effects	Observe	
	Fenugreek	Additive effects	Caution — blood glucose levels should be checked regularly Beneficial interaction possible under professional supervision	
	Ginseng — Siberian	Additive effects	Observe	Speculation is based on IV use in animal studies and has not been observed in humans with oral dose forms
	Green tea	Additive effects	Observe	Clinical significance unknown
	Myrrh	Additive effects	Caution — blood glucose levels should be checked regularly Beneficial interaction possible	Myrrh has been shown to increase glucose tolerance in both normal and diabetic rats — clinical significance unknown
	Olive leaf extract	Additive effects	Beneficial interaction possible — drug dose may need modification	
	Psyllium	Additive effects	Drug dose may need modification	
	Vitamin B3 (niacin)	Increased drug requirement	Caution Monitor drug effectiveness	Niacin may affect glycaemic control and increase fasting blood glucose levels, so medication doses may need to be reviewed

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Metformin	Vitamin B12	Decreased vitamin B12 levels	Observe	Increased B12 intake may be required with long-term drug use
Thyroid hormones and antithyroid agents				
Levothyroxine (e.g. Oroxine)	Calcium	Reduced drug absorption	Separate doses by 2–4 hours	Calcium and thyroxine form an insoluble complex
	Celery	Decreased drug effect	Observe	One case report suggests that celery extract may reduce drug effects. Clinical significance unknown
	Horseradish	Increased drug requirement	Observe Monitor thyroid function. Dose may need to be adjusted	Isothiocyanates may inhibit thyroxine formation and be goitrogenic, although this has not been demonstrated clinically
	Iron	Decreased drug absorption	Separate doses by 2–4 hours	Iron supplements may decrease absorption of thyroid medication; however, iron deficiency may impair the body's ability to make thyroid hormones
	Magnesium	Reduced drug absorption	Separate doses by 2–4 hours	Magnesium and thyroxine form an insoluble complex together
	Tyrosine	Additive effects	Observe	Additive effects theoretically possible, as tyrosine is a precursor to thyroid hormones
	Withania	Additive effects	Observe	An in vivo study reported that daily administration of *Withania somnifera* root extract enhanced serum T4 concentration
	Zinc	Reduced drug absorption	Separate doses by 2–4 hours	Zinc and thyroxine form an insoluble complex together
EYE				
Glaucoma preparations				
Timolol eye drops	Coenzyme Q10	Reduced side-effects	Beneficial interaction possible	A clinical trial of people with glaucoma found that oral CoQ10 reduced cardiovascular side-effects of timolol eye drops without affecting intraocular pressure

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
GASTROINTESTINAL SYSTEM				
Digestive supplements				
Pancreatin	Folate	Reduced folate absorption	Monitor for folate efficacy and folate status	
Hyperacidity, reflux and ulcers				
Aluminium-based antacids	Vitamin C	Increased aluminium absorption	Separate doses by at least 2 hours	Vitamin C increases the amount of aluminium absorbed
Antacids	Folate	Reduced folate absorption	Separate doses by 2–3 hours	
	Iron	Reduced iron absorption	Separate doses by at least 2 hours	
Antiulcer drugs				
Sucralfate (e.g. Carafate, Ulcyte)	Vitamin E	Reduced vitamin absorption	Separate doses by at least 4 hours Monitor vitamin status	Increased vitamin intake may be required with long-term therapy
	Calcium	Reduced calcium absorption	Monitor calcium status	Calcium supplementation may be required
Gastric-acid inhibitors (proton-pump inhibitors [e.g. omeprazole], H_2-receptor antagonists [e.g. ranitidine])	Folate	Reduced folate absorption	Separate doses by 2–3 hours	

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Iron	Reduced drug and iron effect	Monitor for iron efficacy and iron status	Drug reduces gastric acidity and therefore iron absorption
	Vitamin B12	Reduced B12 absorption	Beneficial interaction possible Monitor B12 status	B12 supplementation may be required with long-term therapy
Helicobacter pylori triple-therapy	Garlic	Additive effects	Interaction may be beneficial	Garlic inhibits growth of *H. pylori* in vitro and in vivo and two studies have shown a synergistic effect with omeprazole
Laxatives				
	Aloe vera	Additive effects	Caution	Anthraquinones have significant laxative activity and may increase adverse effects of griping
GENITOURINARY SYSTEM				
Bladder function disorders				
5-alpha-reductase inhibitors (e.g. finasteride [e.g. Proscar])	Pygeum	Additive effects	Beneficial interaction possible	
	Saw palmetto	Additive effects	Beneficial interaction possible	Meta-analyses show that herb is beneficial for BPH and in vitro tests show it may also inhibit 5-alpha-reductase activity
	Stinging nettle root	Additive effects	Beneficial interaction possible	Clinical studies show nettle root to improve symptoms of BPH
IMMUNOLOGY				
Immune modifiers				
Cyclosporin	Peppermint	Additive effects	Avoid unless under medical supervision	Peppermint oil has been shown to increase the oral bioavailability of cyclosporin in animal studies — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Echinacea	Decreased drug effects	Caution	Theoretically, the immunostimulant activity of the herb may reduce drug effects — clinical significance unknown
	Goldenseal	Increased drug effects	Caution	RCT conducted with berberine constituent — clinical relevance for goldenseal difficult to assess
	St John's wort	Reduced drug effects	Avoid	Decreases plasma levels significantly within 3 days of concomitant use
	St Mary's thistle	Reduced drug side-effects but may increase drug effects	Caution	Decreases hepatotoxicity; however, herb may reduce drug metabolism leading to increased effects — clinical significance unknown
Interferon	Baical skullcap	Increased side-effects	Caution	There have been reports of acute pneumonitis due to a possible interaction between Sho-saiko-to preparation (containing baical skullcap) and interferon, which appears to be due to an allergic–immunological mechanism rather than direct toxicity
Interferon-alpha	Carnitine	Reduced side-effects	Beneficial interaction possible	Clinical trials with patients being treated with interferon-alpha for hepatitis C found a reduction in fatigue associated with treatment when carnitine 2 g/day was co-administered
Tacrolimus (e.g. Prograf)	St John's wort	Reduced drug effects	Avoid unless under medical supervision	Decreased drug serum levels
Vaccines				
Influenza virus vaccine	Ginseng — Siberian	Reduced side-effects	Beneficial interaction possible	May reduce the risk of post-vaccine reactions
INFECTIONS AND INFESTATIONS				
Antibiotics	Probiotics	Reduced side-effects	Beneficial interaction possible	Reduces gastrointestinal and genitourinary side-effects. A meta-analysis of nine studies found that *Lactobacilli* and *Saccharomyces boulardii* successfully prevent antibiotic-induced diarrhoea. Increase intake with antibiotic therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Soy	Reduced phyto-oestrogen effect	Inhibits metabolism of isoflavones to equol through inhibition of intestinal microflora	
	Vitamin B1 (thiamin)	Reduces endogenous vitamin production	Beneficial interaction possible	Increase dietary intake or consider supplementation with long-term therapy
	Vitamin B5 (pantothenic acid)	Reduces endogenous vitamin production	Beneficial interaction possible	Increase dietary intake or consider supplementation with long-term therapy
Aminoglycosides (e.g. gentamicin)	Magnesium	Decreased magnesium absorption	Caution Monitor for signs and symptoms of magnesium deficiency	Aminoglycosides may deplete magnesium levels and result in neuromuscular weakness. Increased magnesium may be required with long-term therapy
Quinolone antibiotics (e.g. norfloxacin [e.g. Noroxin])	Calcium	Reduced drug absorption	Separate antibiotic dose by at least 2 hours before or 4 hours after oral calcium	
	Dandelion	Reduced drug absorption	Separate doses by at least 2 hours	Reduced drug absorption observed in an experimental study
	Iron	Reduced drug absorption	Separate antibiotic dose by at least 2 hours before or 4–6 hours after oral iron	
	Magnesium	Reduced drug absorption	Separate antibiotic dose by at least 2 hours before or 4 hours after oral magnesium	
	Quercetin	Reduced drug effect	Caution	Theoretical concern based on test tube studies

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Zinc	Reduced drug and zinc absorption	Separate doses by at least 2 hours	Complex formation between zinc and quinolones results in reduced absorption of both substances, with potential reduction in efficacy
Tetracycline antibiotics (e.g. minocycline [e.g. Minomycin], doxycycline)	Calcium	Reduced drug and calcium absorption	Separate doses by at least 2 hours	Tetracyclines form insoluble complexes with calcium, thereby reducing its absorption
	Iron	Reduced drug and iron absorption	Separate doses by at least 4 hours	Tetracyclines form insoluble complexes with iron, thereby reducing its absorption
	Magnesium	Reduced drug and magnesium absorption	Separate doses by at least 2 hours	Tetracyclines form insoluble complexes with iron, thereby reducing its absorption
	Vitamin B12	Reduced drug absorption	Separate doses by at least 2 hours	B complexes containing B12 may significantly reduce the bioavailability of tetracycline hydrochloride
	Zinc	Reduced drug and zinc absorption	Separate doses by at least 2 hours	Complex formation between zinc and tetracycline results in reduced absorption of both substances, with potential reduction in efficacy
Other antibiotics and anti-infectives (Trimethoprim [e.g. Triprim])	Folate	Reduced folate levels	Caution Monitor folate status with long-term or high-dose therapy Beneficial interaction possible	Increased folate intake may be required with long-term or high-dose therapy
Antimalarials				
Pyrimethamine (e.g. Daraprim)	Folate	Reduced folate effects	Beneficial interaction possible with folinic acid	Impaired folate utilisation occurs with drug use — supplementation may be required
Chloroquine (e.g. Chlorquin)	Vitamin E	Reduced drug effects	Observe	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Antituberculotics and Antileprotics				
Cycloserine and isoniazid	Vitamin B6 (pyridoxine)	Reduced B6 levels	Beneficial interaction possible	Drug may induce pyridoxine deficiency. Increased intake may be required with long-term therapy
Isoniazid	Vitamin B3 (niacin)	Reduced B3 levels	Beneficial interaction possible	Prolonged isoniazid therapy (the drug replaces niacinamide in NAD) may induce pellagra. Increased intake may be required with long-term therapy
	Vitamin E	Reduced vitamin absorption	Separate doses by at least 4 hours and monitor vitamin status	Increased vitamin intake may be required with long-term therapy
Rifampicin	Vitamin D	Reduced vitamin D levels	Beneficial interaction possible	Increase vitamin D intake with long-term therapy
Antiviral agents				
HIV drugs (e.g. zidovudine [AZT, e.g. Retrovir])	Carnitine	Reduced carnitine levels	Beneficial interaction possible	In vitro studies indicate prevention of muscle damage due to carnitine depletion. Increased intake may be required with long-term therapy
HIV non-nucleoside transcriptase inhibitors	St John's wort	Reduced drug effects	Avoid	St John's wort increases drug metabolism, thereby reducing drug serum levels
HIV protease inhibitors	St John's wort	Reduced drug effects	Avoid	St John's wort increases drug metabolism, thereby reducing drug serum levels
Saquinavir	Garlic	Reduced drug effects	Avoid	A clinical study found that garlic reduces serum levels of saquinavir and therefore drug efficacy
MUSCULOSKELETAL SYSTEM				
Non-steroidal anti-inflammatory drugs				
	Celery seed extract	Reduced side-effects	Beneficial	Gastroprotective activity seen in animal model

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Chamomile	Reduced side-effects	Beneficial interaction	Gastroprotective activity seen in animal model
	Chondroitin	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of the NSAID
	Colostrum	Reduced side-effects	Beneficial interaction	Gastroprotective activity
	Devil's claw	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of the NSAID
	Fish oils	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of the NSAID
	Ginger	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of NSAIDs at high doses
	Glucosamine	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of the NSAID
	Glutamine	Reduced side-effects	Beneficial interaction	May ameliorate the increased intestinal permeability caused by indomethacin
	New Zealand green-lipped mussel	Additive effects	Beneficial interaction possible Drug dosage may require modification	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Stinging nettle	Additive effects	Beneficial interaction possible Drug dosage may require modification	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID
	SAMe	Additive effects	Beneficial interaction possible Drug dosage may require modification	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID
	Vitamin E	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the pain-modifying effects of the NSAID when used in high doses for RA
	Willowbark	Additive effects	Beneficial interaction possible Drug dosage may require modification	May enhance the anti-inflammatory effects of the NSAID
	Zinc	Reduced absorption	Separate doses by at least 2 hours	
Aspirin	Grapeseed extract	Additive effects	Observe Beneficial interaction possible	Theoretically may enhance antiplatelet and anti-inflammatory activity of aspirin and may increase risk of bleeding
	Meadowsweet	Increased bruising and bleeding	Observe Beneficial interaction possible	Theoretically may enhance anti-inflammatory and antiplatelet effects
	Policosanol	Increased bruising and bleeding	Observe	Doses >10 mg/day may inhibit platelet aggregation
	Vitamin C	Decreased vitamin C effects	Beneficial interaction	Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements, as observed in animal and human studies. Increased vitamin C intake may be required with long-term therapy

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Willowbark	Increased bruising and bleeding	Observe Beneficial interaction possible Caution with high dose (>240 mg salicin daily)	Theoretically may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect
Diclofenac sodium (topical)	Licorice	Additive effects	Beneficial interaction possible	In vitro studies have shown that the addition of glycyrrhizin enhanced the topical absorption of diclofenac sodium — significance for licorice unknown
Sulfasalazine (e.g. Salazopyrin)	Folate	Reduced drug absorption	Separate doses by 2–3 hours	
	Iron	Reduced drug and iron effects	Separate doses by at least 2 hours	
NEOPLASTIC DISORDERS				
Chemotherapy	Ginseng — Siberian	Improved treatment tolerance	Caution — possible beneficial interaction under medical supervision	Co-administration may increase drug tolerance and improve immune function
	Rosemary	Increased drug effects of Pgp substrates	Caution	Inhibits P-glycoprotein so may affect the bio-availability of Pgp substrates
	Vitamin C	May enhance anti-tumour activity	Beneficial interaction possible	Controversial
	Withania	Reduced side-effects	Observe Beneficial interaction possible under medical supervision	Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy for the prevention of drug-induced bone marrow suppression — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Alkylating agents				
Cyclo-phosphamide	Turmeric	Reduced drug effects	Avoid	
Immuno-suppressants (e.g. cyclo-phosphamide)	Withania	Reduced drug effects Reduced side-effects/toxicity	Caution — possible beneficial interaction	The ability to stimulate stem cell proliferation has led to concerns that withania could reduce cyclophosphamide-induced toxicity, although preliminary animal studies indicate a potential role as a potent and relatively safe radiosensitiser and chemotherapeutic agent. Theoretically it may also decrease the effectiveness of other immunosuppressant drugs
	Herbs with immunostimulant properties (e.g. echinacea, andrographis, astragalus, baical skullcap, garlic, Korean ginseng, Siberian ginseng)	Reduced drug effects	Observe	Theoretically, immunostimulating agents may reduce drug effectiveness; however clinical significance is unknown
Antibiotic cytotoxics				
Doxorubicin (e.g. Adriamycin)	Carnitine	Reduced side-effects	Beneficial interaction possible	Animal and human studies suggest that long-term carnitine administration may reduce the cardiotoxic side-effects of adriamycin
	Coenzyme Q10	Reduced side-effects	Beneficial interaction possible	Animal and human studies suggest that the cardiotoxic side-effects of adriamycin are reduced with CoQ10 supplementation
	Ginkgo biloba	Reduced side-effects	Beneficial interaction possible	In vivo research suggests that ginkgo can prevent doxorubicin-induced cardiotoxicity, although no human studies are available to confirm this
	Vitamin C	Reduces side-effects and enhances therapeutic action	Beneficial interaction possible	Encouraging — further evidence required

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin E	Reduced side-effects	Beneficial interaction possible	One study found that oral DL-alpha tocopheryl acetate (1600 IU/day) prevented doxorubicin-induced alopecia; however, the same dosage failed to prevent alopecia after doxorubicin treatment after mastectomy for breast cancer
Antimetabolites				
Methotrexate	Folate	Reduced side-effects but may reduce drug response	Caution in cancer treatment Observe in other conditions	Methotrexate is a folate antagonist drug, supplementation may reduce toxicity. This action may be problematic in cancer treatment and reduce drug response, but beneficial in other uses
Paclitaxel	Licorice	Additive effects	Observe	A constituent of licorice has been demonstrated to significantly potentiate the effects of paclitaxel in vitro — clinical significance for licorice unknown
	Quercetin	Increased drug effects	Caution	Increased drug bio-availability seen in animal study
Immunosuppressant drugs				
	Andrographis	Reduced drug effects	Caution	Immunostimulant activity has been demonstrated in vivo
	Astragalus	Reduced drug effects	Caution	Due to known immunostimulant effects observed clinically
	Baical skullcap	Reduced drug effects	Caution	Due to known immunostimulant effects observed clinically
	Echinacea	Reduced drug effects	Caution	Due to known immunostimulant effects observed clinically
	Garlic	Reduced drug effects	Caution	Due to known immunostimulant effects observed clinically
	Ginseng – Korean and Ginseng – Siberian	Reduced drug effects	Caution	Due to known immunostimulant effects observed clinically

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
Cisplatin	Carnitine	Reduced side-effects	Beneficial interaction possible under professional supervision	Research into the use of L-carnitine 4 g/day for 7 days showed reduced fatigue from treatment with cisplatin
	Ginkgo biloba	Reduced side-effects	Beneficial interaction possible under professional supervision	
	Quercetin	Increased drug effects	Beneficial interaction theoretically possible under professional supervision	Pre-treatment may sensitise human cervix carcinoma cells to drug according to preliminary research
	St Mary's thistle	Increased drug effects Reduced side-effects	Beneficial interaction possible under professional supervision	Preliminary research has shown that this combination may reduce toxicity effects yet enhance antitumour activity
	Selenium	Reduced side-effects	Beneficial interaction possible under professional supervision	In vitro and in vivo studies indicate that selenium may reduce drug-associated nephrotoxicity, myeloid suppression and weight loss
	Vitamin E	Reduced side-effects	Beneficial interaction possible under professional supervision	Oral vitamin E (300 mg/day) taken before cisplatin treatment and continued for 3 months significantly reduced the incidence and severity of neurotoxicity, according to a randomised study
Interleukin-2-immunotherapy	Carnitine	Reduced side-effects	Beneficial interaction possible under professional supervision	Clinical trials using L-carnitine (1000 mg/day orally) found that it may successfully prevent cardiac complications during IL-2-immunotherapy in cancer patients with clinically relevant cardiac disorders
Vinca alkaloids				
Vinblastine	Licorice	Additive effects	Observe Beneficial interaction possible under medical supervision	A constituent of licorice has been demonstrated to significantly potentiate the effects of vinblastine in vitro — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
NUTRITION				
Anorectics and weight-reducing agents				
Orlistat (e.g. Xenical)	Vitamin A	Reduced vitamin absorption	Separate doses by at least 4 hours Monitor vitamin status	Increased vitamin intake may be required with long-term therapy
	Vitamin D	Reduced vitamin absorption	Separate doses by at least 4 hours Monitor vitamin status	Increased vitamin intake may be required with long-term therapy
	Vitamin E	Reduced vitamin absorption	Separate doses by at least 4 hours Monitor vitamin status	Increased vitamin intake may be required with long-term therapy
POISONING, TOXICITY AND DRUG DEPENDENCE				
Agents used in drug dependence				
Methadone	Kava kava	Additive effects	Caution	Increased sedation theoretically possible
	St John's wort	Reduced drug effects	Avoid	Decreases serum levels
Detoxifying agents, antidotes				
Penicillamine (e.g. D-penamine)	Calcium	Reduced drug effects	Separate doses by 2 hours	Combination forms insoluble complex
	Iron	Reduced drug and iron effects	Separate doses by at least 2 hours. Do not suddenly withdraw iron	Sudden withdrawal of iron during penicillamine use has been associated with penicillamine toxicity and kidney damage
	Magnesium	Reduced drug effects	Separate doses by 2 hours	Combination forms insoluble complex

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B6 (pyridoxine)	Reduced B6 effect	Beneficial interaction possible	Drug may induce pyridoxine deficiency — increase intake with long-term therapy
	Zinc	Reduced drug effects	Separate doses by 2 hours	Combination forms insoluble complex
RESPIRATORY SYSTEM				
Broncospasm relaxants				
Ephedrine	Tyrosine	Increased side-effects	Observe	Tyrosine (200 and 400 mg/kg) has been shown to increase side-effects of anorexia caused by ephedrine and amphetamine in a dose-dependent manner in rats — clinical significance unknown
Theophylline	St John's wort	Reduced drug effects	Monitor for signs of reduced drug effectiveness and adjust the dose if necessary	Decreased drug serum levels
	Vitamin B6 (pyridoxine)	Reduced B6 levels	Beneficial interaction possible	Drug may induce pyridoxine deficiency. Increased intake may be required with long-term therapy
Expectorants, antitussives, mucolytics and decongestants				
	Adhatoda	Increased drug effects	Observe	Results from animal studies show that *Adhatoda vasica* extract exerts considerable antitussive activity when administered orally and is comparable to codeine when cough is due to irritant stimuli
Phenyl-propanolamine (found in Neo-Diophen)	Tyrosine	Increased side-effects	Observe	Tyrosine (200 and 400 mg/kg) has been shown to increase side-effects of anorexia caused by phenylpropanolamine in a dose-dependent manner in rats — clinical significance unknown

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
SKIN				
Acne, keratolytics and cleansers				
Isotretinoin (e.g. Roaccutane)	Vitamin A	Additive effects	Avoid	Isotretinoin is a vitamin A derivative, so adverse effects and toxicity may be increased
Psoriasis, seborrhoea and ichthyosis				
Ketoconazole (e.g. Nizoral)	Vitamin D	Reduced vitamin D effects	Beneficial interaction possible	Ketoconazole reduces the conversion of vitamin D to its active forms. Increased intake may be required with long-term therapy
Topical corticosteroids				
Topical corticosteroids (e.g. hydrocortisone)	Aloe vera (topical)	Additive effects	Beneficial interaction possible	In addition to its own anti-inflammatory effects, animal studies have shown that aloe vera increases the absorption of hydrocortisone by hydrating the stratum corneum, inhibits hydrocortisone's antiwound-healing activity and increases wound tensile strength
OTHER				
Alcohol	Andrographis	Reduced side-effects	Beneficial interaction possible	May reduce hepatic injury
	Ginseng — Korean	Reduced side-effects	Beneficial interaction possible	May reduce hepatic injury
	Kava kava	Additive effects	Observe	Potentiation of CNS sedative effects have been reported in an animal study; however, one double-blind placebo-controlled study found no additive effects on CNS depression or safety-related performance
	St Mary's thistle	Reduced side-effects	Beneficial interaction possible	May reduce hepatic injury
	SAMe	Reduced side-effects	Beneficial interaction possible	May reduce hepatic injury caused by such agents as paracetamol, alcohol and oestrogens

Drug	Herb/Supplement	Potential outcome	Recommendation	Evidence/Comments
	Schisandra	Reduced side-effects	Beneficial interaction possible	May reduce hepatic injury
Dopamine antagonists	Chaste tree	Reduced drug effects	Observe	Reduced drug effects theoretically possible
Hepatotoxic drugs	Andrographis	Reduced side-effects	Beneficial interaction possible	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol and tricyclic antidepressants
	Garlic	Reduced side-effects	Beneficial interaction possible	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol
	Quercetin	Reduced side-effects	Beneficial interaction	Hepatoprotective activity
	St Mary's thistle	Reduced side-effects	Beneficial interaction possible	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol
	SAMe	Reduced side-effects	Beneficial interaction possible	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol
	Schisandra	Reduced side-effects	Beneficial interaction possible	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol
Lipophilic drugs	Chitosan	Reduced drug absorption	Separate doses by at least 2 hours	Binds to dietary fats and reduces their absorption and so can also affect the absorption of lipophilic drugs
PUVA therapy	Celery	Additive effects	Caution	While celery has been found to contain psoralens, celery extract does not seem to be photosensitising, even after ingestion in large amounts; however, it may increase the risk of phototoxicity with concurrent PUVA therapy
	St John's wort	Additive effects	Caution	Hypericin may increase sensitivity to UV radiation

APPENDIX 3

POISONS INFORMATION CENTRES

Call **131 126** (24 hour line) for information and advice on emergency treatment of poisoning, bites and stings in all States and Territories of Australia.

New South Wales
The Children's Hospital at Westmead
Locked Bag 4001
WESTMEAD 2145
Tel: (02) 9382 1367

Victoria
Royal Children's Hospital
Flemington Road
PARKVILLE 3052
Tel: (03) 9345 5680

Queensland
Brisbane Royal Children's Hospital
Herston Road
HERSTON 4029
Tel: 131 126

South Australia
Women's and Children's Hospital
72 King William Road
ADELAIDE 5006
Tel: (08) 8161 7222

Western Australia
Sir Charles Gairdner Hospital
Hospital Avenue
NEDLANDS 6009
Tel: (08) 9346 2923

Tasmania
Royal Hobart Hospital
48 Liverpool Street,
HOBART 7001
Tel: (03) 6222 8737

Northern Territory
Royal Darwin Hospital
Rocklands Drive
TIWI 0810
Tel: (08) 8922 8424

Australian Capital Territory
The Canberra Hospital
Yamba Drive
GARRAN 2605
Tel: (02) 6244 3333

Australian Sports Drug Agency
Tel: 1800 020 506

Specialised Drug Information Service
National Prescribing Service
- Health professionals — 1300 138 677
- Consumers — 1300 888 763

New Zealand
Tel: 0800 764 766
(0800 POISON)

APPENDIX 4

RESOURCES: TRAINING, MANUFACTURERS AND INFORMATION

Universities, schools and colleges in Australia and New Zealand offering undergraduate or postgraduate courses in nutritional medicine, herbal medicine, naturopathy or complementary medicine.

VICTORIA

Southern School of Natural Therapies
39 Victoria St, Fitzroy 3065

Melbourne College of Natural Medicine (branch of the Australian College of Natural Medicine based in Queensland)
City Campus: 368 Elizabeth St,
Melbourne 3000
Box Hill Campus: 2A Cambridge St, Box Hill 3128

Australian College of Natural Medicine
609-611 Camberwell Rd, Camberwell 3124

RMIT School of Health Sciences
Bundoora West Campus, Plenty Rd, Bundoora 3083

Victoria University
TAFE School of Health Sciences
Ballarat Rd, Footscray 3011

Australian College of Nutritional and Environmental Medicine (ACNEM)
13 Hilton St, Beaumaris 3193

Australian College of Herbal Medicine
38/487 Toorak Rd, Toorak 3142

National College of Traditional Medicine
1st Floor, 25-29 Devonshire Rd,
Sunshine 3020

ACT

ACT College of Natural Therapies
Unit 1 Lynnwood, 31 Mugglestone Place, Bruce 2617

Canberra Institute of Technology
GPO Box 826, Canberra 2601

National Institute of Health Sciences
PO Box 279, Deakin West 2600

NSW

Nature Care College of Natural Therapies and Life Studies
46 Nicholson St, St Leonards 2065

Australasian College of Natural Therapies
PO Box K1356, Haymarket 1240

International Academy of Nutrition
Suite 4/21, Sydney Rd, Manly 2095
(PO Box 370, Manly 2095)

College of Nepean Natural Therapeutics
Suite 12/20 Castlereagh St, Penrith 2750

NSW School of Natural Medicine
202 North Boambee Rd,
Coffs Harbour 2450

Gracegrove College
Level 1/723 Hunter St
(PO Box 108), Newcastle 2300

Endeavour College of Natural Therapies
Cnr Henson and Short Sts,
Summer Hill 2130

Charles Sturt University
School of Biomedical Sciences
PO Box 588, Wagga Wagga 2678

University of Sydney
Faculty of Pharmacy
Sydney 2006

University of Western Sydney
(in conjunction with Endeavour College, Sydney)
4 Hensen St, Summer Hill 2130

University of Newcastle
School of Applied Sciences
University Drive, Callaghan 2308

University of Technology Sydney
College of Traditional Chinese Medicine
Faculty of Science (incorporates the College of TCM)
Broadway, Sydney 2000

Southern Cross University
School of Health & Human Sciences
Natural and Complementary Medicine
PO Box 157, Lismore 2480

SA

University of South Australia
Division of Health Sciences
City East Campus, North Terrace,
Adelaide 5000

South Australian Health Education Centre
88 Currie St, Adelaide 5000

Wholistic Learning Centre
308A Pulteney St, Adelaide 5000

Adelaide Training College of Complementary Medicine
Division 3/297 Montacute Rd,
Newton 5074

QUEENSLAND

Australian College of Natural Medicine (ACNM)
Brisbane Campus: 362 Water St,
Fortitude Valley 4006
Gold Coast Campus: 1 Nerang St, Southport 4215

Australian College of Phytotherapy
PO Box 661, Warwick 4370

Health Schools Australia
111 Crescent Ave, Hope Island 4212

Queensland Institute of Natural Sciences
PO Box 5608, Maroochydore BC 4558

Australian Institute of Applied Sciences
PO Box 124, Stones Corner 4120

Academy of Natural Therapies (TAFE Gold Coast Institute)
PO Box 5547, Gold Coast Mail Centre 9726

Academy of Safe Therapies
PO Box 2060, Burleigh Junction 4220

Aromatherapy College of Australia
Suite 3, 16-36 Nile St,
Woolloongabba 4102

Robynn Morro's College of Natural Medicine
64-66 Thuringowa Dve, Kirwan 4817

WA

Australian College of Natural Medicine (ACNM)
Perth Campus: Piccadilly Square, Nash St, East Perth 6004

The AMRA College of Natural Sciences
PO Box 664, Kalamunda 6076

Australian Institute of Holistic Medicine
862 North Lake Rd, Jandakot 6164

TASMANIA

TAFE Tasmania
PO Box 2015, Hobart 70001

NEW ZEALAND

Naturopathic College of New Zealand Ltd
4-6 Lynton St, New Plymouth

The International College of Herbal Medicine
18-B Sirrah St, Wainui, Gisborne

COMPLEMENTARY MEDICINE ASSOCIATIONS OF AUSTRALIAN AND NEW ZEALAND PRACTITIONERS AND INDUSTRY

Australasian Integrative Medicine Association (AIMA)
AIMA Office, located within the Royal Australian College of General Practitioners Building, 1 Palmerston Cres, South Melbourne, Vic 3205
- Chiefly represents medical doctors; however, other healthcare professionals may become associate members.

Australian Natural Therapies Association (ANTA)
PO Box 657, Maroochydore, Qld 4558
- Major association representing complementary medicine practitioners.

Australian Naturopathic Practitioners Association (ANPA)
609-611 Camberwell Rd, Camberwell, Vic 3124
- Longest standing association of naturopathy in Australia.

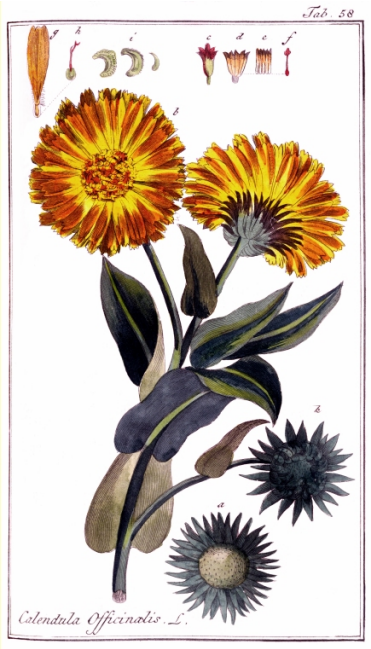
Australian Traditional Medicine Society (ATMS)
12/27 Bank St, Meadowbank, NSW 2114
- Currently Australia's largest professional association of complementary medicine practitioners, representing about 65% of the total complementary medicine profession.

Complementary Medicine Association (CMA)
PO Box 6412, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153

The Federation of Natural and Traditional Therapists Ltd (FNTT)
PO Box 168, North Adelaide, SA 5006
- Comprises several professional associations.

National Herbalists Association of Australia (NHAA)
33 Reserve St, Annandale, NSW 2038
- Largest association specialising in herbal medicine.

Complementary Healthcare Council (CHC)
Unit 2, 1 Napier Close, Deakin, ACT 2600
- Peak body representing the complementary healthcare industry (suppliers, retailers, healthcare professionals and consumers).



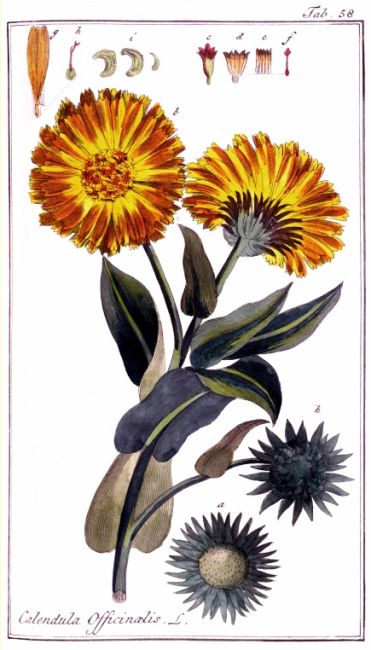
Australian Self Medication Industry (ASMI)
Level 4, 140 Arthur St, North Sydney, NSW 2060

- Represents companies involved in the manufacture and distribution of over-the-counter consumer healthcare products; peak industry body for the Australia self-care industry.

Australian Complementary Health Association
Ross House, 4th Floor, 247 Flinders Lane, Melbourne, Vic 3000

- Represents consumers and practitioners.

International Federation of Aromatherapists
14 Fawkner Cr, Hurstbridge, Vic 3099



MANUFACTURERS OF HERBAL MEDICINES AND NATURAL SUPPLEMENTS IN AUSTRALIA AND NEW ZEALAND

DFC Thompson Australia Pty Ltd
23-25 Sefton Rd, Thornleigh, NSW 2120

Healtheries of Australia Pty Ltd
PO Box 22045, Otahuhu, New Zealand

Lipa Pharmaceuticals Pty Ltd
21 Reaghs Farm Rd, Minto, NSW 2566

MediHerb Pty Ltd
PO Box 713, Warwick, Qld 4370

Nutrition Care Pharmaceuticals Pty Ltd
PO Box 153, Dingley, Vic 3172

Tabco Pty Ltd
26 Roseberry St, Balgowlah, NSW 2093

RESOURCES USED TO COMPILE THIS BOOK

A book of this type requires careful research and access to quality resources in order to provide balanced and accurate information. Here is a list of many of the reference texts and electronic databases on which the information is based.

Reference Texts

Atkinson AJ (ed). Principles of Clinical Pharmacology. California: Academic Press, 2001.
Battaglia S. The Complete Guide to Aromatherapy. Brisbane: The Perfect Potion, 1995.

Beers MH, Berkow R (eds). The Merck Manual of Diagnosis and Therapy, 17th edn. Whitehouse, NJ: Merck and Co. Inc., 2003.
Blumenthal M et al (eds). Herbal Medicine: Expanded Commission E Monographs. Austin, TX: Integrative Medicine Communications, 2000.
Blumenthal M et al. The ABC Clinical Guide to Herbs. Texas: American Botanical Council, 2003.
Bratman S, Kroll D. Natural Health Bible. Rocklin, CA: Prima Health, 2000.
Braunwald E et al. Harrison's Principles of Internal Medicine. New York: McGraw Hill, 2003.
Brinker F. Herb Contraindications and Drug Interactions, 2nd edn. Portland: Eclectic Medical Publications, 1999.
Bryant B et al. Pharmacology for Health Professionals. Sydney: Elsevier, 2003.
Como D (ed). Mosby's Medical, Nursing and Allied Health Dictionary, 6th edn. Philadelphia: Mosby, 2003.
Ernst E et al. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach. St Louis: Mosby, 2001.
Fetrow CW, Avila JR. Professionals Handbook of Complementary and Alternative Medicines. Springhouse Corp, USA, 1999.
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.
Grieve M. A Modern Herbal. London: Penguin Books, 1980.
Hendler SS, Rorvik D (eds). PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Co., 2001.
Hoffmann D. The New Holistic Herbal. Dorset, UK: Element Books, 1990.
Kumar P, Clark M. Clinical Medicine, 5th edn. London: WB Saunders, 2002.
Lininger SW (ed). A-Z Guide to Drug-Herb-Vitamin interactions. California: Prima Health, 1999.
Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone, 2000.
Mills S, Bone K. The Essential Guide to Herbal Safety. Sydney: Elsevier, 2005.
Mills S. The Essential Book of Herbal Medicine. London: Penguin Books, 1991.
Mosby's Medical, Nursing and Allied Health Dictionary. 6th edn. Mosby, USA, 2002.
Murray M. The Healing Power of Herbs. Rocklin, CA: Prima Health, 1995
Newell CA et al. Herbal Medicines: A Guide for Health Care Professionals. London: The Pharmaceutical Press, 1996.
Nissen D (ed). Mosby's Drug Consult. St Louis: Mosby, 2003.
Pelton R et al. Drug-induced Nutrient Depletion Handbook 1999-2000. Hudson, OH: Lexi-Comp Inc., 2000.
Pizzorno J, Murray M. Textbook of Natural Medicine. St Louis: Elsevier, 2006.
Price S, Price L. Aromatherapy for Health Professionals, 2nd edn. London: Churchill Livingstone, 2002.
Rang HP et al. Pharmacology, 4th edn. Edinburgh: Churchill Livingstone, 2001.
Shils M (ed). Modern Nutrition in Health and Disease, 9th edn. Baltimore: Williams and Wilkins, 2000.
Skidmore-Roth L. Mosby's Handbook of Herbs and Natural Supplements. St Louis: Mosby, 2001.
Thomsen M. Phytotherapy Desk Reference, 2nd edn. Institute for Phytotherapy, 2001.
Ulbricht CE et al. Natural Standard Herb and Supplement Reference. St Louis: Mosby, 2005.
Wahlqvist ML (ed). Food and Nutrition, 2nd edn. Sydney: Allen & Unwin, 2002.
Waller DG et al. Medical Pharmacology and Therapeutics. London: WB Saunders, 2001.
Williamson EM. Dabur Research Foundation and Dabur Ayurvet Ltd. Edinburgh: Churchill Livingstone, 2002.

Public Access Electronic Databases

(some may require fee for access)
Entrez-PubMed (National Library of Medicine USA): www.ncbi.nlm.nih.gov/PubMed/
Arbor Nutrition Guide: www.arborcom.com
Integrative Medicine Gateway (IMG; Unity Health Pty Ltd, Australia): www.imgateway.net/wheel.htm
Herbmed: www.herbmed.org
Medscape from WebMD: www.medscape.com
Merck Manual, 17th edn, 1999-2003 (Merck & Co., Inc): www.merck.com

Dr Duke's Phytochemical and Ethnobotanical Databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. www.ars-grin.gov/duke.

Specialist Databases

EMBASE.com
FullText Clinicans' Health Channel
Health and Medical Complete
Journals @ OVID (OVID technologies)
Medical Library and Health Module
Micromedex (Thomson Healthcare Series)
Natural Medicines Comprehensive Database (Therapeutic Research Facility): www.naturaldatabase.com
ProQuest
Science Direct (Elsevier Publishing): www.sciencedirect.com
The Cochrane Library: www.nicsl.com.au/cochrane

APPENDIX 5

GUIDE TO THE SAFE USE OF COMPLEMENTARY MEDICINES DURING THE PREOPERATIVE PERIOD

Common name	Botanical name (where applicable)	Comments	Recommendation
Andrographis	*Andrographis paniculata*	Andrographolide inhibits platelet-activating-factor-induced platelet aggregation in a dose-dependent manner (confirmed clinically) (Amroyan et al 1999, Zhang et al 1994)	Suspend use 1 week prior to surgery
Bilberry	*Vaccinium myrtillus*	Bilberry extract inhibits platelet aggregation according to ex vivo tests (Pulliero et al 1989). The anthocyanin content is responsible.	Suspend use of high dose supplements 1 week prior to surgery
Chondroitin		There is a theoretical risk of anticoagulant activity, but it has not been investigated in clinical trials (Chavez 1997). There are no reports of excessive bleeding	Likely to be safe
Devil's claw	*Harpagophytum procumbens*	Case reports suggest possible anticoagulant activity	Suspend use of concentrated extracts 1 week prior to surgery
Evening primrose oil (EPO)	Omega-6 essential fatty acids or n-6 fatty acids	Gamma linolenic acid in EPO affects PG synthesis leading to inhibition of platelet aggregation – clinical significance unknown	Suspend use of high-dose concentrated products 1 week prior to surgery; however, safety is difficult to assess
Feverfew	*Tanacetum parthenium*	Inhibition of platelet aggregation has been observed in several in vitro studies (Groenewegen & Heptinstall 1990, Marles et al 1992, Voyno-Yasenetskaya et al 1988); however, a small human study found no effects on platelet aggregation (Biggs et al 1982)	Likely to be safe; however, safety is difficult to assess
Fish oils	Omega-3 essential fatty acids or n-3 fatty acids	High doses of dietary omega-3 essential fatty acids modestly reduce thrombotic responses in vivo (Harker et al 1993). Bleeding times increased at doses of 12 g/day of n-3 fatty acids (Harris et al 1990)	Usual dietary intakes likely to be safe. Suspend use of high-dose products 1 week prior to surgery
Garlic	*Allium sativum*	Inhibition of platelet aggregation is clinically significant – two case reports of postoperative bleeding after excessive dietary intake have been reported (Burnham 1995, German et al 1995). One clinical study found reduced haematocrit values and plasma viscosity (Jung et al 1991)	Usual dietary intakes likely to be safe. Suspend use of concentrated extracts 1 week prior to surgery

Common name	Botanical name (where applicable)	Comments	Recommendation
Ginger root	*Zingiber officinale*	Oral doses of 4 g/day did not alter platelet aggregation or fibrinogen levels in one clinical study, whereas a high dose of 10 g/day significantly reduced platelet aggregation in another clinical study (Bordia et al 1997)	Usual dietary intakes likely to be safe. Suspend use of high-dose (10 g/day) concentrated extracts 1 week prior to surgery
Ginkgo	*Ginkgo biloba*	Case reports of postoperative bleeding (Fessenden et al 2001, Hauser et al 2002). However, three placebo-controlled studies failed to detect a significant effect on platelet function or coagulation (Bal Dit et al 2003, Jiang et al 2003, Kohler 2004)	Suspend use 1 week prior to surgery; however, safety is difficult to assess
Ginseng Korean	*Panax ginseng*	Inhibition of platelet aggregation has been identified in both in vitro and in vivo tests (Kuo et al 1990) but not human studies	Suspend use 1 week prior to surgery; however; safety is difficult to assess
Grapeseed extract	*Vitis vinifera*	Shown to inhibit platelet aggregation, and combining extracts of grape seed and grape skin produced a far greater antiplatelet effect in test tube and ex vivo tests (Shanmuganayagam et al 2002)	Suspend use of concentrated extracts 1 week prior to surgery; however, safety is difficult to assess
Guarana	*Paullinia cupana*	In vitro and in vivo research has identified antiplatelet activity (Bydlowski et al 1991)	Suspend use of concentrated extracts 1 week prior to surgery
Licorice root	*Glycyrrhizae radix*	Isoliquiritigenin inhibits platelet aggregation (Tawata et al 1992) and glycyrrhizin inhibits prothrombin (Francischetti et al 1997) according to in vitro tests – clinical significance unknown	Usual dietary intakes likely to be safe
Meadowsweet	*Filipendula ulmaria*	In vitro and in vivo tests have identified anticoagulant activity (Liapina and Koval'chuk 1993) – clinical significance of these findings is unknown	Suspend use of concentrated extracts 1 week prior to surgery
Myrrh	*Commiphora molmol*	Guggul inhibited platelet aggregation in vitro and in a clinical study (Bordia & Chuttani 1979)	Suspend use of guggul preparations 1 week prior to surgery
Policosanol		Doses of 10 mg/day and greater reduce platelet aggregation according to clinical studies (Arruzazabala et al 2002, Castano et al 1999). Effect of 20 mg/day is similar to aspirin 100 mg stat.	Suspend use of doses 10 mg/day or greater 1 week prior to surgery

Common name	Botanical name (where applicable)	Comments	Recommendation
Turmeric root	*Curcuma longa*	Curcumin, a major component of turmeric, inhibits platelet aggregation in vitro (Shah et al 1999, Srivastava et al 1995) – clinical significance unknown	Usual dietary intakes likely to be safe. Suspend use of concentrated extracts 1 week prior to surgery
Vitamin E	Alpha-tocopherol	Clinical studies in recent years have produced conflicting results – 200 IU daily (800 mg of D-alpha-tocopherol) taken for 28 days had no effects on platelet aggregation or coagulation according to one clinical study (Morinobu et al 2002). A lower dose of 600 mg (900 IU) of RRR-alpha-tocopherol daily taken for 12 weeks did not alter coagulation activity in a second clinical study (Kitagawa & Mino 1989). However, increased risk of gingival bleeding at doses of 50 mg/day was found by a further clinical study (Liede et al 1998)	Suspend use of high-dose supplements (>1000 IU/day) 1 week prior to surgery; however, safety is difficult to assess
Willowbark	*Salix* spp.	Although it has been assumed that willowbark affects platelet aggregation due to its salicylate content, one clinical study found that consumption of *Salicis cortex* (240 mg salicin daily) produced minimal effects on platelet aggregation (Krivoy et al 2001)	Likely to be safe

See Chapter 9 for references.

APPENDIX 6

CLINICAL USE AND SAFETY OF VITAMINS AND MINERALS

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
VITAMINS						
Vitamin A	Women: 700 μg Men: 900 μg	10,000–50,000 IU/day orally in divided doses Not recommended for more than 2 weeks without medical supervision	Treating deficiency Prevention of secondary deficiency (e.g. coeliac disease, cystic fibrosis, pancreatic disease) Reducing severity of infectious diseases in children Dermatology — many uses Slowing progression of retinitis pigmentosa	Hypersensitivity Pregnancy Hypervitaminosis A Retinoid analogue use Lactation Chronic renal failure or liver disease	**Early signs** Dry rough skin and mucous membranes, desquamation Coarse sparse hair, alopecia of eyebrows Diplopia Bone and joint pain **Later signs** Irritability Increased intracranial pressure and headache Dizziness Hepatotoxicity	Cumulative toxicity if >100,000 IU long term Acute toxicity possible if >2,000,000 IU taken If taken long term in pregnancy, >1500 IU may be teratogenic, causing craniofacial abnormalities
Vitamin B1 (thiamin)	Women: 1.1 mg Men: 1.2 mg	5–3000 mg	Treating deficiency Prevention of secondary deficiency (e.g. hyperemesis and malabsorption states) Acute alcohol withdrawal Alzheimer's dementia Dysmenorrhoea	Hypersensitivity None	Well tolerated	Non-toxic

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin B2 (riboflavin)	Women: 1.1 mg <70 yo: 1.3 mg Men: 1.3 mg >70 yo: 1.6 mg	10–400 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. chronic diarrhoea, liver disease, chronic alcoholism) Prevention of migraine headaches Reducing incidence of both nuclear and cortical cataract	Hypersensitivity None	Well tolerated	Non-toxic
Vitamin B3 (niacin)	Women: 14 mg Men: 16 mg	1500–2000 mg crystalline niacin or sustained-release forms daily	Treating deficiency Prevent secondary deficiency (e.g. anorexia nervosa) Hypercholesterolaemia and hypertriglyceridaemia Syndrome X	Hypersensitivity Diabetes Peptic ulcer disease Gout Hepatitis Liver function should be monitored and patients observed for symptoms of myopathy	Flushing is a common side-effect (not with nicotinamide). Night-time administration, ER niacin or concurrent administration of aspirin can reduce these effects Palpitations	Tachycardia, chills, sweating, shortness of breath, nausea, vomiting, myalgias, hepatotoxicity ER niacin is considered the safest form

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin B6 (pyridoxine)	Women: 1.3 mg >50 yo: 1.5 mg Men: 1.3 mg >50 yo: 1.7 mg	5–500 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. malabsorption syndromes, cancer, liver cirrhosis and alcoholism, hyperthyroidism) Relieving symptoms of PMS and morning sickness Hyperhomocysteinaemia (often with folic acid and B12) Reducing repeated febrile convulsions in children Autism (with magnesium)	Hypersensitivity Long-term use of high-dose pyridoxine supplements (>100 mg, although this level varies between individuals) should be used with caution	Nausea, vomiting, headache, paraesthesias, sleepiness and low serum folic acid levels have been reported If taken at night, may induce vivid dreams	Paraesthesia, hyperaesthesia, bone pain, muscle weakness, numbness and fasciculation most marked at the extremities Dose and time frame at which toxicity occurs varies significantly
Vitamin B6 (pyridoxine)						Studies involving large populations found minimal or no toxicity with 100–150 mg/day over 5–10 years, whereas women self-medicating for PMS taking 117 ± 92 mg for 2.9 ± 1.9 years have reported increased incidence of peripheral neuropathy

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin B12 (cobalamin)	2.4 μg	2–2000 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. atrophic gastritis, achlorhydria) Pernicious anaemia Hyperhomocysteinaemia (with B6 and folate) Depression HIV infection Cognitive impairment Diabetic retinopathy Sleep disorders Tinnitus	Hypersensitivity Avoid in cases of altered cobalamin metabolism or deficiency associated with chronic cyanide intoxication	None known	Well tolerated
Folate	400 μg	1–15 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. malabsorption syndromes such as coeliac and Crohn's disease, HIV infection) Preconception care and pregnancy (prevention of neural tube defects) Hyperhomocysteinaemia Cognitive impairment Reducing incidence of cancer Vitiligo Topical: periodontal disease	Hypersensitivity Use may mask B12 deficiency by correcting the apparent microcytic anaemia without altering the potential for or progression of neurological damage	Doses >5 mg/day: generalised urticaria, nausea, flatulence and bitter taste in the mouth and some CNS activation in the form of irritability and excitability, altered sleep pattern	Non-toxic

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin C	45 mg	250–12,000 mg/day orally in divided doses More is used when administered IV	Treating deficiency Prevention of secondary deficiency (e.g. heavy smokers, achlorhydria, chronic diarrhoea, major surgery) Treat iron deficiency anaemia (with iron) Preventing and treating common URTI such as colds and influenza and mild allergic responses Prevention and adjunctive treatment of cardiovascular disease and cancer	Hypersensitivity Increases iron, and decreases copper, absorption Renal impairment Interacts with numerous laboratory tests (e.g. serum cholesterol and triglycerides and urinary oxalate)	None expected if <3000–4000 mg/day but this varies between individuals Gastrointestinal upset: nausea, diarrhoea, flatulence, distension Hyperoxaluria and renal stones now considered doubtful	Considered non-toxic
Vitamin C			Management of diabetes and asthma Oral and topical forms used for various dermatological conditions (e.g. wound healing, photo-aged skin, prevention of sunburn (with vitamin E))			

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin D	5 μg >50 yo: 10 μg >70 yo: 15 μg	2000–300,000 IU/day	Treating deficiency Prevention of secondary deficiency (e.g. malabsorption states) Hypoparathyroidism (with calcium) Hypophosphataemia (with phosphorus) Prevention of bone fracture and osteoporosis (with calcium) Hepatic and renal osteodystrophy Scleroderma	Hypersensitivity Hypercalcaemia Sarcoidosis Hyperparathyroidism SLE Vitamin D toxicity Pregnancy Lactation Renal failure Use of cardiac glycosides, thiazide diuretics, calcium-channel blockers	Not seen with doses <2400 IU/day Doses >3800 IU: hypercalcaemia, soft tissue calcification Fatigue, headache, nausea, vomiting, metallic taste, abdominal cramps, myalgia, tinnitus, arthralgia, constipation, polyuria, polydipsia	Cumulative toxicity possible Between 50,000 and 200,000 IU/day: signs of hypercalcaemia 50,000–200,000 IU daily: nausea, vomiting, anorexia, calcification of soft tissue and organs, cardiac arrhythmias

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Vitamin E	Women: 7 mg alpha-tocopherol Men: 10 mg alpha-tocopherol	50–3200 IU/day	Treating deficiency Prevention of secondary deficiency (e.g. malabsorption syndromes, cystic fibrosis) Prevention of cardiovascular disease, certain cancers, ischaemic stroke in high-risk hypertensive patients, nitrate tolerance Enhancing immune function in the elderly Slowing progression of Alzheimer's dementia Improving symptoms in PMS, menopause, intermittent claudication Reducing pain in OA and RA	Hypersensitivity People with impaired coagulation, inherited bleeding disorders, history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis Suspend use of supplements 1–2 weeks before major surgery	Adverse effects are dose-related and tend to occur only at very high doses (>1200 IU/day) Side-effects include diarrhoea, flatulence, nausea and heart palpitations Increased risk of bleeding if vitamin K deficiency present	Vitamin E is relatively non-toxic Doses as high as 3200 mg/day have been used for 12 years without signs of toxicity
Vitamin E			Treating some forms of male infertility Oral and topical use for many dermatological states Prevention or treatment of many other conditions such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia			

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
MINERALS						
Calcium	Women: 1000 mg >50yo 1300 mg Men: 1000 mg >70 yo 1300 mg	250–2000 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. achlorhydria and malabsorption syndromes) Prevention of osteoporosis, pre-eclampsia, maintenance of bone density, colorectal cancer Symptoms of PMS Hypertension and hyperlipidaemia Dyspepsia	Hypersensitivity Hyperparathyroidism Chronic kidney disease Hypercalcaemia	Gastrointestinal discomfort, nausea, loss of appetite, constipation, flatulence, metallic taste, muscle weakness	Increased serum calcium level may be associated with hypotonia, depression, lethargy and coma Prolonged hypercalcaemic state, especially if normal or elevated serum phosphate; can precipitate ectopic calcification of blood vessels, joints, gastric mucosa, cornea and renal tissue
Chromium	Women: 25 μg Men: 35 μg	50–1000 μg	Treating deficiency Diabetes Hypoglycaemia Hyperlipidaemia Obesity Atypical depression Polycystic ovary syndrome Syndrome X	Hypersensitivity	Irritability and insomnia have been reported with chromium yeast supplementation Chromium picolinate is well tolerated	Chromium IV is used in industry and is highly toxic, whereas Cr III, which is used in supplements, is well tolerated

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Iodine	150 μg	0.5–6 mg	Treating deficiency Preventing deficiency in high-risk groups Fibrocystic breast disease Mastalgia	Hypersensitivity Hyperthyroidism	Symptoms of iodine hypersensitivity are fever, painful joints, lymph node enlargement, eosinophilia, urticaria, angio-oedema, cutaneous and mucosal haemorrhage and fatal peri-arteritis	Chronic iodine toxicity when intake is >2 mg/day Symptoms: brassy taste in mouth, burning sensation in mouth and throat, increased salivation, gastric irritation, acneiform skin lesions, pulmonary oedema, depression
Iron	Women: 18 mg >50 yo: 8 mg Men: 8 mg	10–100 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. menorrhagia, cystic fibrosis) Unexplained fatigue without anaemia Improving athletic performance	Hypersensitivity Haemochromatosis Haemosiderosis Iron-loading anaemias (thalassaemia, sideroblastic anaemia) Liquid iron preparations can discolour teeth (brush teeth after use)	Gastrointestinal disturbances such as nausea, diarrhoea, constipation, heartburn, upper gastric discomfort	Haemochromatosis can develop from long-term excessive intake Iron toxicity causes severe organ damage and death The most pronounced effects are haemorrhagic necrosis of the gastrointestinal tract and liver damage

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Magnesium	Women: 310 mg >30 yo: 32 mg Men: 400 mg >30 yo 420 mg	200–750 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. inflammatory bowel diseases, diabetes, hyperthyroidism) Alleviating symptoms of coronary heart disease, reducing hypertension, reducing plasma lipid levels, reducing incidence of arrhythmias in congestive heart failure Prevention of migraine headache, premenstrual headache, osteoporosis	Hypersensitivity Renal failure and heart block (unless pacemaker present)	**Most common** Diarrhoea and gastric irritation; usually not seen at doses <350 mg/day (elemental) Overuse of magnesium hydroxide or magnesium sulfate may cause deficiencies of other minerals or lead to toxicity **Other side-effects** Decreased heart rate, hypotension, muscle weakness	Most commonly seen in patients with renal insufficiency Symptoms: muscle weakness, sedation, ECG changes, confusion, hypotension
Magnesium			Relieving symptoms of PMS, dyspepsia, constipation, asthma, dysmenorrhoea, leg cramps in pregnancy, muscular cramps in general Improving diabetic control			

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Selenium	Women: 60 μg Men: 70 μg	80–200 μg/day	Treating deficiency Prevention of secondary deficiency (e.g. cirrhosis, malabsorption syndromes, cystic fibrosis, coeliac disease, HIV infection) Reducing total cancer incidence and mortality (especially lung, colorectal and prostate cancers), adjunctive treatment HIV infection Cardiovascular disease Autoimmune thyroiditis Symptoms of RA, asthma Male infertility Anxiety and depression	Hypersensitivity NHMRC upper level of intake is 400 μg/day	Nausea, vomiting, nail changes, irritability, fatigue Organic form of selenium found in high-selenium yeast is less toxic and safer than other forms	Long-term use of excessive doses (>1000 μg/day) can produce fatigue, depression, arthritis, hair or fingernail loss, garlicky breath or body odour, gastrointestinal disorders and irritability

Vitamin/ mineral	Australian and New Zealand RDI for adults (>18 yo)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side-effects	Toxicity
Zinc	Women: 8 mg Men: 14 mg	25–200 mg/day	Treating deficiency Prevention of secondary deficiency (e.g. cirrhosis, malabsorption syndromes, severe burns, major surgery) Treating the common cold and reducing symptoms (lozenges) Diabetes Enhancing wound healing (e.g. leg ulcers) Decreasing relapse rates in Crohn's disease Acne vulgaris Topical: herpes simplex infection	Hypersensitivity	Mild gastrointestinal upset at doses of 50–150 mg/day	Single doses of 225–450 mg usually induce vomiting Nausea, vomiting, diarrhoea, fever and lethargy, which have been observed after ingestion of 4–8 g Doses ranging from 100 to 150 mg/day interfere with copper metabolism and cause hypocupraemia, red blood cell microcytosis, and neutropenia if used long-term

ER, extended release; yo, years old.

MULTIVITAMINS

Overall, acute toxicity is unlikely with combination vitamin supplements unless huge amounts have been ingested. In the case of toxicity or side-effects, signs and symptoms will relate to the individual nutrient ingested. In general, gastrointestinal symptoms such as discomfort, nausea and diarrhoea are the most frequent adverse effects.

Of all the nutrients listed, extra special care must be taken when supplementing with vitamins A and D and the mineral iron. The forms of selenium and niacin used in practice also have a major influence on their safety profile and should be taken into consideration.

For more details regarding RDI for specific age groups: www.nhmrc.gov.au/publications/synopses/n35syn.htm

APPENDIX 7

EVIDENCE BASE FOR PHYSIOLOGICAL ACTIVITIES OF HERBS AND SUPPLEMENTS

Evidence codes

AS	Animal studies
CT	Clinical trial
EP	Based on epidemiological studies
IV	In vitro studies
PH	Based on known pharmacological activity of constituents
TH	Theoretical
TU	Traditional use

Assumptions made when collating the information for this table

- Information is compiled from the 120 monographs included in this book
- All information refers to oral dose forms unless otherwise specified
- Information listed here is correct at time of writing; however, because of the ever-expanding knowledge base developing in this area, new research is constantly being published
- Not all actions referred to in the text are covered; see monographs for more detail

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Adaptogenic			
	Ginseng — Korean	AS, CT	
	Ginseng — Siberian	IV, AS	
	Tyrosine	CT	
	Withania	AS	
Analgesic			
	Brahmi	AS	Antinociceptive activity identified when used in combination with other herbs
	Chondroitin	CT	Musculoskeletal pain
	Clove oil	AS, CT	Effects due to the eugenol, beta-caryophyllene component. Clinical trials used tiger balm
	Dandelion (root)	AS	Mild effects reported
	Devil's claw	CT	Musculoskeletal pain
	Fenugreek	AS	Antinociceptive activity identified
	Feverfew	AS, CT	Inhibits prostaglandin production and acts at nociceptors
	Ginger	CT	Inhibits prostaglandin and thromboxane production and topically depletes substance P
	Glucosamine	CT	Musculoskeletal pain — effects seen in osteoarthritis
	Kava kava	IV, AS	Local anaesthetic
	Lemon balm	AS	High doses
	Meadowsweet	TH	Based on its high salicylate content
	Peppermint	CT	Observed for oil applied topically
	St John's wort	IV, AS	Binds opioid receptors
	SAMe	CT	Musculoskeletal pain — effects seen in osteoarthritis (not prostaglandin mediated)
	Shark cartilage	AS	Mechanism does not appear to involve the opioid system

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Stinging nettle	CT	Probably due to counter-irritant effect
	Vitamin E	CT	Established in clinical trials using high doses of 1200 mg daily in rheumatoid arthritis
	Willowbark	CT	Musculoskeletal pain
Antacid			
	Magnesium	TU	
	Meadowsweet	TU	
Anti-allergic			
	Adhatoda	IV, AS	Asicine and vasicinone possess bronchodilatory activity and inhibit allergen-induced bronchial obstruction, with effects comparable to those of sodium cromoglycate
	Albizia	IV, AS	Significant mast-cell-stabilisation effects, similar to those of sodium cromoglycate
	Baical skullcap	IV, AS	Inhibits histamine release
	Brahmi	IV	Potent mast-cell-stabilising activity (methanolic fraction) comparable to that of disodium cromoglycate
	Clove oil	IV, AS	Inhibits histamine release
	Feverfew	IV, AS	Inhibits histamine release (different mechanism to cromoglycate)
	Ginger	IV	Inhibits histamine release
	Ginseng — Korean	IV	Stabilises cell membrane
	Ginseng — Siberian	IV	Inhibits histamine release
	Peppermint	IV, AS	Inhibits histamine release
	Perilla	IV, AS, CT	Various mechanisms
	Probiotics	CT	Reduces antigen transport through the intestinal mucosa
	Quercetin	IV, AS	
	St Mary's thistle	AS	Mast-cell stabilisation

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Stinging nettle	CT	Freeze-dried preparation showed activity
	Vitamin C	CT	Reduces histamine levels
Anti-anxiety/anxiolytic			
	Baical skullcap	IV, AS	Certain constituents bind with the benzodiazepine-binding site of the GABA-A receptor
	Brahmi	CT	
	Chamomile	AS	Binds benzodiazepine receptors
	Ginger	AS	In combination with ginkgo biloba
	Ginseng — Korean	IV	Regulates GABA-A receptors in vitro
	Kava kava	CT	Various mechanisms
	Lavender	CT	
	Lemon balm	AS, CT	Eugenol and citronellol bind to GABA-A receptors and increase the affinity of GABA to receptors
	Passionflower	AS, CT	Unknown mechanism — possibly acts via GABA
	St John's wort	AS	Various mechanisms
	Valerian	IV, CT	Stimulates the release of GABA, inhibits GABA reuptake and may have an effect at GABA receptors; low-dose valerian (100 mg) reduces situational anxiety without causing sedation
	Withania	AS, CT	Unknown mechanism — possibly acts via GABA
Anti-atherogenic — See listing under Lipid-lowering			
Antibacterial — See listing under Antimicrobial			
Anticancer (e.g. antimutagenic, antineoplastic and/or anti-angiogenic activity has been identified)			
	Astragalus	IV, AS, CT	Tested in combination with other herbs
	Baical skullcap	IV, AS	May induce apoptosis, inhibit proliferation, prevent metastases and inhibit angiogenesis
	Bilberry	IV	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Chamomile	IV, AS	Apigenin has been shown to inhibit carcinogenesis in a variety of experimental models
	Cranberry	IV	Due to proanthocyanidins
	Creatine	AS	Antitumour
	Fenugreek	IV, AS	Antineoplastic
	Garlic	IV	Antineoplastic in breast, prostate, endometrial, stomach and colon cancer
	Ginseng — Korean	IV, AS	Antitumour, antimetastatic and apoptosis-inducing
	Goldenseal	IV, AS	Demonstrated for the berberine constituent
	Grapeseed extract	IV	Suppresses tumour growth and has cytotoxic activity against a range of cancer cells, including breast, lung, prostate, and gastric adenoma cells
	Green tea	IV, EP	Reduction in proliferation, increase in apoptosis and possible anti-angiogenic properties identified; supported by epidemiological studies
	Lavender	IV, AS, PH	Preliminary evidence of activity for several constituents
	Lavender oil	IV, AS	Antineoplastic in cancer of the colon, liver, lung, breast, pancreas, prostate, as well as melanoma
	Licorice	IV, AS	Antitumour
	Lutein	CT	Possibly endometrial, lung, breast, bowel
	Mullein	IV	Antitumour
	Perilla	IV, AS	
	Quercetin	IV, AS	Multiple mechanisms involved
	Red clover	IV, AS, CT	Antimutagenic as well as protecting against chemical-induced DNA damage
	St John's wort	IV, AS	Selective photosensitisation of tumour cells
	St Mary's thistle	IV	Anti-angiogenic and antitumour
	Shark cartilage	IV, AS	Anti-angiogenic and antitumour

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Turmeric	IV, AS, CT	Promotes apoptosis, reduces proliferation, reduces angiogenesis and metastases
	Vitamin A	CT	Stimulates epithelial cell differentiation, preventing the proliferation of dedifferentiated or undifferentiated carcinoma cells in skin, breast, liver, colon, cervical, prostate, oral, pharyngeal, oesophageal and lung carcinomas
	Withania	IV, AS	Antineoplastic
Chemoprotection			
	Beta-carotene	EP	Effect associated with 'natural' beta-carotene and natural sources
	Celery	AS	May reduce incidence of stomach and colon cancer
	Fish oils	IV, AS	Especially breast, prostate and colorectal cancers
	Flaxseed oil	CT	Increased levels of ALA associated with reduced risk of breast cancer
	Folate	EP, AS, CT	Especially cervix, colorectal, lung, oesophagus, brain, pancreas and breast
	Garlic	IV	Including breast, prostate, endometrial, stomach and colon cancer
	Ginseng — Korean	IV, AS, CT	
	Guarana	AS	
	Hops	IV	
	Lutein and Zeaxanthin	EP	various cancers
	Lycopene	IV, AS, CT	Especially prostate, stomach and cervical
	Probiotics	IV, AS, CT	Antimutagenic, anticarcinogenic (e.g. nitrosamines), immune enhancing
	Rosemary	IV, AS, TU	
	St Mary's thistle	AS	
	Selenium	CT, EP	Significantly reduces total cancer mortality, total cancer incidence and incidences of lung, colorectal, and prostate cancers
	Stinging nettle	IV, CT	Antiproliferative in prostate cells

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Turmeric	AS, CT	Against skin cancer, stomach cancer, colon cancer and oral cancer
	Vitamin A	IV, AS	
	Vitamin B3	IV, AS	
	Vitamin C	EP	
	Vitamin D	EP	Inverse association with colorectal cancer and breast cancer
	Vitamin E	EP	
	Withania	AS	Multiple mechanisms
	Zinc	EP	
Antifibrotic			
	Baical skullcap	IV, AS	In combination; chemopreventive role in the development of hepatocellular carcinoma
	Ginger	CT	
Anticoagulant — See listing under Blood thinning			
Anticonvulsant			
	Albizia	AS	
	Lavender oil	AS	
Antidepressant/neurotransmitter effects			
	Albizia	AS	Influences GABA, serotonin and dopamine levels
	Brahmi	AS	Mechanism unknown
	Folate	CT	Effectiveness may be restricted to only those patients with an existing deficiency
	Ginkgo biloba	IV, AS	Greater inhibition of MAO-A than MAO-B, increases uptake of serotonin, direct and indirect cholinergic activity, competitive antagonist for GABA-A receptors; moderation of corticosterone levels
	Licorice	IV	Inhibits serotonin reuptake

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Perilla	AS	Mechanism unknown — does not appear to involve monoamines
	St John's wort	CT	Various mechanisms
	SAMe	CT	Various mechanisms
	Selenium	CT	Low dietary intakes of selenium have been linked with greater incidence of anxiety, depression and tiredness
	Tyrosine	CT	Precursor to neurotransmitters
	Vitamin B6 (pyridoxine)	TH	Supplementation can elevate GABA and serotonin levels by increasing production
	Withania	AS	Effects comparable to those of imipramine
Antidiarrhoeal			
	Bilberry	TH, PH	Due to tannins and astringent activity
	Calcium		
	Colostrum	CT	Effective against some forms of infectious diarrhoea
	Goldenseal	IV, AS, CT	Due to berberine constituent
	Probiotics	CT	Includes infant, travellers', infectious, acute and antibiotic-induced diarrhoea
	Raspberry	TU, PH	Due to tannins and astringent activity
	Sage	TU, PH	Due to tannins and astringent activity
	Thyme	TU, PH	Due to tannins and astringent activity
Anti-emetic			
	Ginger	AS, CT	Multiple mechanisms
	Peppermint	CT	Peppermint oil inhalation
Antifibrotic — See listing under Anticancer			
Antifungal — See listing under Antimicrobial			

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Antihypertensive/hypotensive			
	Andrographis	AS	Involves adrenoceptors, autonomic ganglia receptors and a reduction in circulating angiotensin-converting enzyme
	Astragalus	AS	Intravenous administration in rats
	Baical skullcap	AS	Mechanism unknown
	Calcium	CT	Results variable, possibly in 'salt sensitive' hypertension
	Coenzyme Q10	CT	Mechanism unknown but may reduce total peripheral resistance
	Evening primrose oil	CT	Mechanism unknown
	Fish oils	CT	Mechanism unknown but may reduce total peripheral resistance
	Garlic	AS	Renin–angiotensin and NO may be involved
	Ginseng — Korean	IV, AS, CT	May not be clinically significant
	Hawthorn	TU, IV, AS	Mechanism unknown but may reduce total peripheral resistance
	Magnesium	CT	Affects NO release and vascular tone
	Oats	CT	Mechanism unknown
	Olive oil and Olive leaf		
	Quercetin	AS	
	Stinging nettle	AS	Administered IV
	Vitamin C	CT	Results overall positive
	Vitamin E	CT	Modulates vascular function possibly via NO
Anti-inflammatory			
	Adhatoda		Alkaloid fraction shown to be equivalent to hydrocortisone in one study

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Aloe	AS	Aloe vera gel reduces oxidation of arachidonic acid, thereby reducing prostaglandin synthesis and inflammation
	Andrographis	IV	May involve promotion of ACTH and enhancement of adrenocortical function
	Baical skullcap	IV, AS	May bind a variety of chemokines and limit their biological function; inhibits COX-2, PGE_2, 5-lipoxygenase and NO
	Bilberry	AS	Reduces oedema
	Brahmi	IV	Effect is mediated via inhibition of PGE_2
	Calendula	IV, AS	Reduces oedema
	Celery	AS	Mechanism unknown
	Chamomile	AS	Most research uses topical application
	Cinnamon	IV, AS	
	Clove oil	AS	Due to the eugenol, beta-caryophyllene component
	Damiana	AS	Mechanism unknown
	Dandelion (root)	AS	Mild activity
	Devil's claw	IV, AS, CT	Various mechanisms
	Echinacea	IV, AS	Inhibits COX-1 and COX-2 and possibly other mechanisms (topical)
	Evening primrose oil	AS, CT	Precursor to PGE_1
	Fenugreek	AS	Mechanism unknown
	Feverfew	IV	Inhibits prostaglandin production
	Fish oils	AS, CT	Chiefly prostaglandin mediated
	Flaxseed oil	AS	
	Garlic	IV, AS	Fresh extract and oil — inhibits COX activity
	Ginger	IV, AS, CT	Inhibits prostaglandin and thromboxane production and topically depletes substance P

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginkgo biloba	AS	Reduces oedema
	Ginseng — Korean	AS	Inhibition of NF-kappa-B and COX-2
	Goldenrod	AS	Mechanism unknown
	Goldenseal	IV, AS	Due to the berberine content
	Grapeseed extract	IV	Non-specific inhibitory activity against COX-1 and -2
	Hawthorn	IV, AS	Chiefly due to the flavonoid constituents
	Honey	CT	Topical use
	Hops	IV	
	Lavender		
	Licorice	PH, IV, AS	Largely mediated by cortisol, although other mechanisms likely to exist
	Meadowsweet	TH	High salicylate content
	Myrrh	AS	Mechanism unknown
	New Zealand green-lipped mussel	IV, AS, CT	Possibly via effects on prostaglandins and leukotrienes
	Noni	IV	
	Olive oil and Olive leaf	PH	
	Perilla	IV	Refined oil and seed extract
	Pygeum		Effect due to multiple constituents
	Quercetin	IV, AS	
	Raspberry	TU, PH	Topically, due to tannins
	Rosemary	IV	Possibly via effects on prostaglandins and leukotrienes
	St John's wort	IV, AS	Various mechanisms

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	St Mary's thistle	IV, AS	Various mechanisms
	SAMe	CT	Not prostaglandin mediated
	Saw palmetto	IV	Dual inhibitor of the cyclo-oxygenase and 5-lipoxygenase pathways and decreases COX expression
	Schisandra	IV	Leukotriene inhibitor
	Selenium	IV, AS	Possibly via effects on prostaglandins and leukotrienes
	Shark cartilage	AS	Mechanism unknown — does not affect opioid system
	Slippery elm	TU, TH	High mucilage content; soothes irritated and inflamed tissues
	Stinging nettle	IV, EP, CT	Various mechanisms
	Turmeric	AS	Various mechanisms
	Willowbark	CT	Chiefly due to salicylate content
	Withania	IV	May reduce ESR, mechanism unknown
Antimicrobial			
	Albizia	IV, AS	Antifungal and antibacterial
	Aloe vera	IV	Activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Escherichia coli*
	Baical skullcap	IV	Dose dependent
	Bitter melon	IV	Antibacterial and antiviral — activity against *E. coli*, *Salmonella paratyphi*, *Shigella dysenterae* and *Streptomyces griseus*, *Helicobacter pylori*, *Mycobacterium tuberculosis*
	Brahmi	IV	Significantly inhibited *H. pylori*
	Calendula	IV	Antibacterial, antiviral and antifungal
	Chamomile	IV	Bactericidal and fungicidal activities against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and *Candida albicans*, *Escherichia coli*, *Streptococcus mutans*; inhibitory activity against HIV activation; inhibits herpes virus in vitro

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Chitosan	AS	May exert antibacterial activity against *Bifidobacterium* and *Lactobacillus* spp.
	Cinnamon	IV	Broad-spectrum antibacterial and antifungal activities
	Citrus aurantium	IV	Tuberculosis
	Clove oil	IV, AS	Demonstrated activity against Gram-negative anaerobic periodontal oral pathogens, including *Porphyromonas gingivalis*, *Prevotella intermedia*; also *Bacillus subtilis*, *Listeria monocytogenes*, *Salmonella enterica*, *Escherichia coli* and *Saccharomyces cerevisiae*; hepatitis C virus protease; human cytomegalovirus, herpes simplex virus 1
	Cloves	IV	Antibacterial, antifungal and antiviral
	Colostrum	IV	Hyperimmune colostrums exhibit widespread antimicrobial activity
	Cranberry	IV, AS, CT	Bacteriostatic — reduced adhesion of *Escherichia coli*, Gram-negative and Gram-positive bacteria to uroepithelial tissues, and of *Helicobacter pylori* to human gastrointestinal cells
	Echinacea	IV	Various
	Garlic	IV, AS	Antibacterial, antifungal, antiviral and antiparasitic
	Ginger	IV, AS	Antibacterial, antiviral and antifungal
	Goldenrod		Antibacterial and antifungal
	Goldenseal	IV	Demonstrated for the whole extract and berberine constituent against *S. aureus*, *Streptococcus sanguis*, *E. coli*, *Pseudomonas aeruginosa* Methanolic extract of rhizome inhibited *H. pylori* in vitro Also demonstrated for berberine, activity against *Shigella dysenteriae*, *Bacillus subtilis*
	Green tea	IV	Active against certain strains of *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, *Salmonella* spp.; also *Corynebacterium suis*, *Helicobacter pylori*, *Porphyromonas gingivalis* and *Prevotella* spp.; Green tea is more active than black
	Guarana	IV	Active against *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*
	Gymnema sylvestre		Active against *Bacillus purnilis*, *B. subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Honey	IV, CT	Leptospermum (manuka) honey can inhibit the growth of several important bacterial pathogens, including *Escherichia coli*, *Salmonella typhimurium*, *Shigella sonnei*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Streptococcus mutans*. Also useful against certain strains of methicillin-resistant *Staphylococcus aureus* and vancomycin-sensitive and resistant enterococci. Topical use
	Hops	IV	Activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* A, but almost no activity against the Gram-negative bacterium *Escherichia coli*
	Horseradish	IV	Gram-negative and Gram-positive bacteria
	Lavender oil	IV	Antibacterial, antifungal and mitocidal
	Lemon balm	IV	Eugenol has antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*
	Licorice	IV, AS	
	Meadowsweet	IV	Bacteriostatic activity has been reported against *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa*
	Mullein	IV	Antiviral and antibacterial
	Myrrh	IV, CT	Activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* Successful trials in acne Topical use
	Noni	IV	
	Peppermint	IV	Peppermint oil is active against *Helicobactor pylori*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enteritidis*, *Listeria monocytogenes*, *Shigella sonnei* and *Micrococcus flavus*, and a variety of fungi
	Perilla		
	Rosemary	IV	Activity against a variety of bacteria and fungi
	Sage	IV	Active against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., *Shigella sonnei*, *Klebsiella ozanae*, *Bacillus subtilis* and various fungi, including *Candida albicans* Antimicrobial activity also reported for sage oil
	St John's wort	IV	Active against MRSA and other Gram-positive bacteria

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Shark cartilage	IV	Activity against protozoa, fungi, and both Gram-positive and Gram-negative bacteria
	Tea tree oil	IV, CT	Activity against *Corynebacterium* spp., *Klebsiella pneumoniae*, *Micrococcus luteus*, *Micrococcus varians*, *Micrococcus* spp., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Serratia marcescens*, *Staphylococcus aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. saprophyticus*, *S. warneri*, and *S. xylosus* Successful trials in acne, methicillin-resistant *Staphylococcus aureus.* Topical use
	Thyme	IV	Activity against *Escherichia coli*, *Listeria monocytogenes*, *Salmonella enterica*, *Helicobacter pylori*
	Turmeric		
	Withania	IV	Activity against *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus anthracis*, *Bacillus subtilis*, *Salmonella enteridis* and *Salmonella typhimurium*
Antifungal			
	Baical skullcap	IV	Including *Candida albicans*
	Calendula	IV	Activity against *Aspergillus niger*, *Rhizopus japonicum*, *Candida albicans*, *Candida tropicalis* and *Rhodotorula glutinis*
	Cinnamon	IV	
	Citrus aurantium essential oil		
	Clove oil	IV	
	Echinacea	IV	Activity observed against *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatulytica* and *C. tropicalis*
	Goldenrod	IV	Inhibitory effects on *Candida* and *Cryptococcus* spp. have been demonstrated for triterpenoid glycosides
	Goldenseal	PH	Berberine constituent inhibits *Candida* spp.
	Hops	IV	Activity against the fungus *Trichophyton mentagrophytes* var. *interdigitale* but almost no activity against the yeast *Candida albicans*

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Myrrh	IV	Activity against *Candida albicans*
	Rosemary	IV	
	Sage	IV	
	Tea tree oil	IV, CT	*Candida*, toenail onychomycosis
	Withania	IV	*Withanolides coagulens*, *Allescheria boydii*, *Aspergillus niger*, *Curvularia lunata*, *Drechslera rostrata*, *Epidermophyton floccosum*, *Microsporum canis*, *Nigrospora oryzae*, *Pleurotus ostreatus* and *Stachybotrys atra*
Antiviral			
	Aloe vera	IV, CT	Virucidal against herpes simplex 1 and 2, vaccinia virus, parainfluenza virus and vesicular stomatitis virus
	Baical skullcap	IV, AS	
	Bitter melon	IV	
	Calendula	IV	Virucidal activity against influenza viruses and suppresses the growth of herpes simplex virus
	Echinacea	IV	Activity against herpes simplex virus
	Ginseng — Siberian	IV	Inhibits the replication of RNA-type viruses such as human rhinovirus, respiratory syncytial virus and influenza A virus
	Green tea	IV	Interferes with virus absorption; antiviral activity has been identified against HIV, herpes simplex 1, influenza A and B, rotavirus and enterovirus, Epstein-Barr virus
	Gymnema sylvestre		
	Hawthorn	IV	Herpes simplex 1
	Lemon balm	IV, AS, CT	Herpes simplex 1, HIV
	Licorice	IV, AS	Activity against SARS-CV, HIV, influenza, ebola virus, herpes simplex virus 1, Epstein-Barr virus
	L-Lysine	IV, CT	Clinical trials show inconsistent results against herpes simplex virus
	Rosemary	IV	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	St John's wort	IV, AS	Antiretroviral activity appears to be photo-activated
	Stinging nettle	IV	Activity against HIV-1, HIV-2, human cytomegalovirus, respiratory syncytial virus and influenza A
	Tea tree oil	IV	Activity against herpes simplex 1 and 2
Antimalarial			
	Andrographis	IV, AS	
Antiparasitic			
	Goldenseal	PH	Berberine inhibits *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis*
	Myrrh	CT	Effective against schistosomiasis, fascioliasis
Antimigraine (i.e. reducing frequency and/or severity of attacks)			
	Coenzyme Q10	CT	Mechanism unknown — possibly via mitochondrial stabilisation
	Feverfew	CT, AS	Reduced frequency and severity of migraine headache Reduces serotonin release from platelets; possibly other mechanisms
	Magnesium	CT	Mechanism unknown — possibly via mitochondrial stabilisation
	SAMe	CT	Reduced pain reported
	Vitamin B2 (riboflavin)	CT	Reduced frequency and duration of migraines with large doses
Antioxidant			
	Adhatoda	IV	Induces glutathione S-transferase and DT-diaphorase in lungs and forestomach, and superoxide dismutase and catalase in kidneys
	Andrographis	AS	Increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver
	Astragalus	AS	Raises superoxide dismutase activity in the brain and liver
	Baical skullcap	IV, AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Beta-carotene		
	Bilberry	PH	Contains anthocyanosides
	Brahmi	IV, AS	Direct free radical-scavenging activity and increases endogenous anti-oxidant systems
	Calendula		Reduces levels of superoxide and hydroxyl radicals, suggesting a free radical-scavenging effect; reduces lipid peroxidation
	Carnitine	IV	
	Chamomile	IV	Inhibits lipid peroxidation
	Cinnamon	IV	
	Clove oil	PH	
	Cocoa	IV, AS, CT	
	Coenzyme Q10		
	Cranberry	IV	Antioxidant activity of flavonol glycosides comparable or superior to that of vitamin E
	Creatine	AS	
	Dandelion	AS	
	Echinacea		Activity attributed to numerous antioxidant constituents found in echinacea, such as vitamin C, beta-carotene, flavonoids, selenium and zinc
	Garlic		Capable of directly scavenging free radicals, and indirect activity by enhancing endogenous anti-oxidant systems such as glutathione, superoxide dismutase, catalase and glutathione peroxidase
	Ginger	AS	
	Ginkgo biloba	IV	The extract and several of its individual constituents (quercetin, kaempferol) have demonstrated significant anti-oxidant properties; used topically, increases the activity of superoxide dismutase within skin
	Glutamine		Precursor to glutathione

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Grapeseed extract	IV, AS	Significantly greater effects than vitamins C and E and beta-carotene; procyanidins prevent vitamin E loss and regenerate alpha-tocopherol radicals back to their anti-oxidant form
	Green tea	IV, AS, CT	Inhibits lipid peroxidation, scavenges hydroxyl and superoxide radicals
	Hawthorn	IV	Direct and indirect activities
	Honey	IV	
	Lavender	IV	
	Lemon balm		
	Licorice	IV, CT	
	Lutein and Zeaxanthin		
	Lycopene	IV	
	Meadowsweet	IV	
	Mullein	IV	
	Noni	IV, CT	
	Olive leaf and Olive oil		
	Perilla	IV	
	Policosanol	IV	Reduces oxidation of LDL-cholesterol
	Quercetin		
	Raspberry		
	Rosemary	IV, AS	Chiefly due to carnosol and carnosic acid
	Sage	AS	Chiefly due to labiatic acid and carnosic acid
	St Mary's thistle	AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	SAMe	IV	
	Schisandra	IV	Direct activity and increases glutathione levels
	Selenium		Essential component of glutathione peroxidase
	Shark cartilage	IV	
	Slippery elm	IV	
	Stinging nettle	IV, AS	
	Thyme		
	Turmeric	IV	Direct and indirect activity
	Tyrosine		
	Vitamin A		
	Vitamin B2 (riboflavin)		By itself, but also as part of the enzyme glutathione reductase
	Vitamin B3	IV	
	Vitamin C	IV	
	Vitamin E		Considered to be the most important and potent lipid-soluble anti-oxidant. It prevents free radical damage to polyunsaturated fatty acids within the phospholipid layer of each cell membrane and oxidation of LDL-cholesterol
	Withania	AS	Direct and indirect anti-oxident activities
	Zinc		
Antiparasitic — See listing under Antimicrobial			
Antiplatelet — See listing under Blood thinning			
Antipruritic			
	Chickweed	TU	Topical use; effect due to saponins

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Oats	CT	Topical use
Antipyretic			
	Andrographis	AS, CT	
	Fenugreek	AS	
	Willowbark	PH	Effect chiefly due to salicylate content
Antispasmodic			
	Adhatoda	AS	Essential oil
	Brahmi	AS	Acts on smooth muscle; effect due to inhibition of calcium influx into the cell
	Chamomile	IV	
	Cinnamon		
	Clove oil	PH	Effect due to the eugenol, beta-caryophyllene component
	Feverfew	IV	
	Hops	TU	
	Horseradish		
	Kava kava	IV, AS	Acts on skeletal muscles
	Magnesium		
	Myrrh	EV	Due to T-cadinol, and several minor components
	Peppermint	IV, CT	
	Rosemary	TU	Used for mild cramp-like gastrointestinal and biliary upsets, as well as for tension headache, renal colic and dysmenorrhoea
	Sage	AS	
	St John's wort	AS	Most likely mediated via GABA activity

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Saw palmetto	IV	
	Thyme	IV	
	Turmeric	AS	Smooth muscle
	Valerian	IV, AS	Acts on smooth muscle
Antithrombotic — See listing under Blood thinning			
Antitussive			
	Adhatoda	AS	Comparable to codeine when cough is due to irritant stimuli
	Chickweed	TU	Saponins irritate mucous membranes
	Cocoa		
	Licorice	AS	
	Passionflower	AS	
	Thyme	AS	
Anti-ulcer/anti-ulcerogenic (i.e. prevention and/or treatment)			
	Brahmi	AS	Fresh juice of whole plant
	Chamomile	AS	
	Fenugreek	AS	
	Ginger	AS	
	Ginseng — Korean	AS	
	Lemon balm	AS	Activity associated with reduced acid output and increased mucin secretion, an increase in prostaglandin E_2 release and a decrease in leukotrienes
	Licorice	CT	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Meadowsweet	IV, AS	Protective effects against stomach ulcers induced by acetylsalicylic acid; however, no protection was seen against ulcers produced under high-acid environments or due to stimulation by histamine. Effect may be prostaglandin-mediated
	St Mary's thistle	AS	Associated with reduced acid output, increased mucin secretion, increased prostaglandin E_2 release and decreased leukotriene release
	Turmeric	CT	May reduce symptoms
Antiviral — See listing under Antimicrobial			
Anxiolytic — See listing under Anti-anxiety			
Blood thinning			
Anticoagulant			
	Dong quai	CT	
	Meadowsweet	IV, AS	
	Ginseng — Siberian	CT	Decreases blood coagulation normally induced by intensive training of athletes
Antiplatelet			
	Andrographis	AS, CT	Andrographolide inhibits platelet-activating-factor-induced human blood platelet aggregation in a dose-dependent manner
	Baical skullcap	IV	
	Clove oil	IV	Due to the eugenol component
	Cocoa	IV, CT	Due to polyphenol content
	Feverfew	IV, AS, CT	No significant effects were seen in a clinical study of 10 patients receiving feverfew
	Fish oils	AS	Observed for high doses
	Garlic	CT	
	Ginger	CT	Observed for high doses >10 g
	Ginkgo biloba	CT	Platelet-activating-factor antagonist

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginseng — Korean	IV, AS	
	Ginseng — Siberian	IV	3,4-dihydroxybenzoic acid constituent
	Grapeseed extract	IV	Combination of grapeseed and grape skin produces a greater effect
	Guarana	IV, AS	
	Licorice	IV, AS	Clinical relevance yet to be determined
	Myrrh	CT	Gum guggul fraction
	Policosanol	AS, CT	
	Rosemary	IV, AS	
	Schisandra	IV	Several lignans inhibit platelet-activating factor
	Turmeric	IV, AS	Demonstrated for curcumin
	Vitamin E		Demonstrated in vitro, but in vivo tests have been inconsistent; likely only at very high doses
Antithrombotic			
	Andrographis	AS, CT	
	Baical skullcap	IV	
	Evening primrose oil	TH	PGE_1 production results in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation
	Fish oils	AS	
	Garlic	CT	
Bone density protection			
	Calcium	CT	
	Magnesium	CT	
	Red clover	CT	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Soy	CT	
	Vitamin C	CT	
	Vitamin D	CT	
Capillary stabilisation			
	Bilberry	AS	Stabilises membrane phospholipids; increases the synthesis of mucopolysaccharides of the connective ground substance and restores altered mucopolysaccharidic pericapillary sheath; improves ischaemic damage and preserves capillary perfusion; inhibits increased permeability of reperfusion and saves arteriolar tone
	Ginkgo biloba	AS	Due to proanthocyanidin content
	Grapeseed extract	AS, CT	Cross-links collagen fibres, reducing capillary permeability
	Hawthorn		Flavonoid content improves vascular repair
	Vitamin C		
Cardioprotective			
	Cocoa	EP	Polyphenol content responsible for protective effects
	Coenzyme Q10	CT	
	Dong quai	IV, AS	
	Fish oils	CT	
	Folate		
	Glutamine	IV	
	Hawthorn	AS, CT	
	Lycopene	EP	
	Magnesium	AS, CT	
	Quercetin	IV, AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Schisandra	AS	Activity seen for schisandrin B constituent
	Selenium	CT	
	Vitamin C	EP	
	Vitamin E	CT	
	Withania	AS	
Chemoprotection — See listing under Anticancer			
Choleretic (i.e. increased bile production and flow)			
	Andrographis	AS	Dose-dependent increase in bile flow and bile salt and acid production
	Chamomile	AS	Chamomile increases bile production
	Dandelion (root)	TU	
	Ginger	AS	
	Globe artichoke	AS, CT	
	Peppermint	AS, CT	
	St Mary's thistle	AS	
	Wild yam	AS	
Chologogue (i.e. increased bile flow)			
	Celery	AS	
	Globe artichoke	AS	
	Turmeric	AS	Stimulates contraction of the gall bladder and promotes the flow of bile
Chondroprotective			
	Chondroitin	AS, CT	
	Devil's claw	IV, AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Glucosamine	IV, CT	May stimulate proteoglycan and hyaluronic acid synthesis
	SAMe	IV, AS	
	Vitamin B3	CT	
CNS sedative			
	Chamomile	AS, CT	
	Hops	TU, CT, AS	
	Lavender oil	AS, CT	Inconsistent results
	Lemon balm	CT	High doses
	Kava kava	IV, AS	
	Passionflower	AS	Mechanism unknown
	Peppermint	AS	
	Valerian	IV, AS, CT	
CNS stimulant			
	Guarana	CT	Possibly due to caffeine content
Cognitive enhancement/activator			
	Albizia	AS	Effects due to saponins
	Astragalus	AS	In combination with other herbs
	Bilberry		
	Brahmi	CT	Possible mechanism of action are anti-oxidant and anticholinesterase activity
	Ginkgo biloba	IV, AS, CT	Cholinergic activity
	Ginseng — Korean	CT	
	Guarana	AS, CT	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Lemon balm	CT	Dose dependent, cholinergic
	Licorice	AS	
	Tyrosine	CT	
	Withania	AS	Cholinergic effects
Diuretic			
	Celery	TU	
	Dandelion (leaf)	TU	Considered a potassium-sparing diuretic
	Globe artichoke	AS	
	Goldenrod	AS	Excretion of calcium can increase whereas excretion of potassium and sodium decreases
	Green tea	PH	Chiefly due to caffeine content
	Guarana	PH	Chiefly due to caffeine content
	Horseradish	TU	
	Stinging nettle leaf	AS	
	Tribulus	AS	With high dose
Expectorant			
	Chickweed	TU	Saponins irritate mucous membranes
	Licorice	TU, TH	Stimulates tracheal mucus secretion, facilitating elimination of mucus from the respiratory tract
	Mullein	PH	Due to saponins
	Thyme	AS	Due to saponins
Gastrointestinal effects			
	Astragalus	AS	Improves gastrointestinal motility; strengthens the movement and muscle tone of the small intestine

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Cinnamon	AS	
	Citrus aurantium essential oil	TU	Carminative action
	Colostrum	IV, AS, CT	Improves gut permeability and reduces NSAIDs-induced damage
	Fenugreek	AS	Enhances pancreatic lipase activity, intestinal lipase activity and the disaccharides sucrase and maltase
	Gentian	CT	Stimulates the flow of saliva, gastric juice and bile secretion
	Ginger	AS, CT	Stimulates the flow of saliva, bile and gastric secretions; increases gastrointestinal motility without affecting gastric emptying anti-ulcer activity
	Glutamine	IV, AS	Aids in the proliferation and repair of intestinal cells
	Guarana	CT	Increases gastric acid secretion and delays gastric emptying time in combination with Yerbe mate and damiana
	Lavender	TU	Carminative action
Hepatoprotective			
	Andrographis	AS	Increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver; hepatoprotective effect of andrographolide is more potent than that of silymarin
	Astragalus	AS	Increases liver glutathione levels
	Baical skullcap	AS	
	Clove oil	AS	
	Garlic	IV	
	Ginger	AS	
	Hawthorn	AS	
	Licorice	IV, AS	
	Perilla	AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Quercetin	IV, AS	
	Rosemary	AS	
	St Mary's thistle	IV, AS, CT	Protective against carbon tetrachloride-induced liver cirrhosis, paracetamol-induced liver peroxidation, and side-effects of cyclosporin, phenothiazine, butyrophenone, erythromycin, amitriptyline and nortriptyline, oestradiol, amanita phalloides, tacrine and iron overload
	SAMe	CT	Significantly increases hepatic glutathione levels
	Schisandra	IV, AS, CT	Gomisin A inhibits elevation of serum aminotransferase activity and hepatic lipoperoxides content, and the appearance of histological changes such as degeneration and necrosis of hepatocytes
	Turmeric	IV, AS	
Hepatorestorative (i.e. liver repair)			
	Ginseng — Korean	AS	
	St Mary's thistle	AS, CT	
	Schisandra	AS	Gomisin A increases ornithine decarboxylase activity, which is important during the early stages of regeneration and suppresses fibrosis proliferation
Homocysteine level reduction			
	Folate	CT	
	Vitamin B6	CT	
	Vitamin B12	CT	With B6 and folic acid
Hypertensive			
	Guarana	PH	Effects due to caffeine content
Hypoglycaemic/improving blood sugar control			
	Aloe vera	CT	One clinical study found that blood sugar levels reduce steadily in people treated with aloe gel, compared with a control group

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Andrographis	AS	Does not appear to involve the stimulation of insulin release from the pancreas; may alter glucose absorption from the gut
	Bilberry	AS	Bilberry extracts contain myrtillin, which has been shown to possess hypoglycaemic actions
	Bitter melon	CT, AS	Delay in progression of diabetic complications seen in experimental models
	Calendula	AS	
	Carnitine	CT	Improves insulin sensitivity
	Chromium	CT	Blood glucose regulation; multiple mechanisms
	Cinnamon	CT	Contradictory results in clinical studies
	Damiana	AS	
	Devil's claw	AS	
	Fenugreek	AS, CT	Delays glucose absorption and enhances its utilisation; may increase insulin sensitivity
	Gymnema sylvestre	CT	Multiple mechanisms involved
	Hawthorn	AS	
	Myrrh	AS	Increased glucose tolerance
	Oats	CT	
	Olive leaf	AS	
	Stinging nettle	AS	
Hypotensive — See listing under Antihypertensive			
Male fertility			
	Astragalus	IV	Stimulates sperm motility
	Carnitine	CT	Increasing semen quality, sperm concentration and total and forward sperm motility
	Ginseng — Korean	CT	Improves erectile dysfunction

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Selenium	CT	Required for human sperm maturation and sperm motility; positive correlation between selenium levels and sperm density, number, motility and viability
	Tribulus	AS	Androgenic; protodioscin converts to DHEA; observed pro-erectile effects with protodioscin, due to increased release of NO from the endothelium and nitronergic nerve endings
	Zinc		Deficiency affects spermatogenesis
Immunomodulating			
	Aloe vera	IV, AS	Immune stimulant, antiviral, antitumour and non-specific immunostimulant activity; protective against a variety of fungi and bacteria
	Andrographis	AS, CT	Immune stimulant; antigen-specific and non-specific immune responses in vivo; immunostimulant activity of the whole extract is greater than the isolated andrographolide constituent
	Astragalus	IV, AS, CT	Immune stimulant; stimulates macrophage activity and enhances antibody responses
	Baical skullcap	IV, AS, CT	Immune stimulant
	Beta-carotene	CT	Multiple mechanisms involved
	Calendula	IV	Stimulates phagocytosis of human granulocytes
	Chamomile	IV	Immune stimulant
	Chromium	IV	Chromium has both immunostimulatory and immunosuppressive effects, as shown by its effects on T- and B-lymphocytes, macrophages and cytokine production
	Coenzyme Q10		Immune stimulant
	Dong quai	IV, AS	Immune stimulant
	Echinacea	CT	Immune stimulant; acts mainly on non-specific cellular immunity
	Fenugreek	AS	Immune stimulant — enhanced humoral immunity, significant increases in macrophage activity and a stimulatory effect on lymphoproliferation
	Fish oils		
	Garlic	CT	Immune stimulant

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginger	IV, AS	In vitro and in vivo research suggests that ginger extract exerts some degree of immunomodulatory activity
	Ginkgo biloba	AS	Immune stimulant
	Ginseng — Korean	IV, CT	Based on the production of cytokines, activation of macrophages, stimulation of bone marrow cells and stimulation of inducible NO synthesis
	Ginseng — Siberian	IV, AS, CT	Stimulates general non-specific resistance and influences T-lymphocytes, natural killer cells and cytokines
	Goldenseal	IV	
	Glutamine	AS, CT	
	Lutein		
	Probiotics	IV, AS, CT	Probiotics bind to intestinal epithelial cells and inhibit the binding of pathogenic bacteria to the gut wall by producing inhibitory substances such as bacteriocins, lactic acid and toxic oxygen metabolites
	Quercetin	IV, AS	Contradictory evidence
	Selenium	AS, CT	Confirmed in both animal studies and human trials, immune modulation is in part due to improved activation and proliferation of B-lymphocytes and enhanced T-cell function. Selenium concentrations significantly decrease during stages of acute infection, suggesting either increased utilisation and/or excretion or decreased absorption during this period
	Shark cartilage	IV	Immune stimulant
	Turmeric	IV, AS	Curcumin has demonstrated both immunostimulating and immunosuppressing activity
	Vitamin A	AS	Immune-stimulant role includes expression of mucins and keratins, lymphopoiesis, production of antibodies, and the function of neutrophils, natural killer cells, macrophages and T- and B-lymphocytes. Potentiates antibody responses and lymphocyte proliferation in response to antigens. Restores the integrity and function of mucosal surfaces
	Vitamin C	IV, CT	Immune stimulant — favourably modulates lymphocytes and phagocytes, regulates natural killer cells and can influence antibody and cytokine synthesis under certain situations

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Vitamin E	CT	Regulates immunocompetence — increases humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T-lymphocyte response, tumour necrosis factor production and natural killer cell activity
	Withania	AS	Immunomodulating effects include an increase in white blood cell, platelet and neutrophil counts, increases in interferon-gamma and interleukin-2 levels, and a reduction in tumour necrosis factor level
	Zinc	AS, CT	Essential for normal development and function of cells mediating non-specific immunity, such as neutrophils and natural killer cells, and affects development of acquired immunity and T-lymphocyte function
Laxative			
	Aloe vera	AS	Anthraquinones increase intestinal water content, stimulate mucus secretion and induce intestinal peristalsis
	Dandelion (root)	TU	Mild activity
	Magnesium	PH	In high doses
Lipid-lowering			
	Astragalus	CT	In combination with other herbs
	Baical skullcap	AS	
	Bilberry	AS	Decreases plasma triglyceride levels
	Calcium	CT	Reduced LDL-cholesterol levels by 4.4%, increased HDL-cholesterol levels 4.1% in one study
	Calendula	AS	
	Carnitine	CT	Reduced serum lipoprotein-a levels; changes in other lipid parameters inconsistent
	Celery	AS	
	Chitosan	CT	
	Chromium	CT	
	Cocoa	CT	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Fenugreek	AS, CT	
	Fish oils	CT	Decreases triglyceride levels
	Flaxseed oil	CT	
	Flaxseeds	CT	
	Garlic	IV, CT	May inhibit cholesterol synthesis, increase HDL-cholesterol and decrease triglyceride levels
	Ginger	AS, EV	May reduce cholesterol and triglyceride levels and development of atherosclerotic lesions
	Ginseng — Korean	AS, CT	
	Globe artichoke	CT	
	Goldenseal	CT	Demonstrated for berberine constituent
	Grapeseed extract	AS, CT	LDL- and triglyceride-lowering activities
	Gymnema sylvestre	AS, CT	Serum cholesterol and triglyceride lowering activity
	Hawthorn	AS, CT	
	Lycopene	IV, CT	Reduced LDL-cholesterol level
	Magnesium	CT	Increase molar ratio of apolipoprotein A1:apolipoprotein B; reduces triglyceride levels
	Myrrh	CT, AS	Guggul or certain constituents within *Commiphora mukul* reduce triglyceride and cholesterol levels
	Oats	CT	
	Policosanol	AS, CT	Lowers total cholesterol levels, increases HDL and reduces LDL levels
	Probiotics	CT	
	St Mary's thistle	AS, CT	
	Turmeric	AS, CT	Demonstrated for curcumin
	Vitamin B3	CT	Reduce total cholesterol, LDL, triglycerides and lipoprotein-a levels and also markedly raises HDL levels

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Vitamin B5	AS, CT	
Anti-atherogenic			
	Andrographis	AS	Significantly improves atherosclerotic iliac artery stenosis induced by both de-endothelialisation and a high-cholesterol diet
	Garlic	AS, CT	
	Selenium	AS	
Nephroprotection			
	Goldenrod	TU	Believed to stabilise the microarchitecture of the kidneys
	St Mary's thistle	IV, AS	
Neuroprotection			
	Baical skullcap	AS, IV	Attributed to the flavonoids
	Brahmi	AS	
	Carnitine	AS	
	Creatine	AS	
	Fish oils	CT	
	Folate		
	Ginkgo biloba	IV, AS, CT	
	Ginseng — Korean	IV	
	Ginseng — Siberian	AS	
	Quercetin		
	Schisandra	IV	Demonstrated for some of the herbs lignans
	Vitamin E		

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Withania	IV, AS	
Neurotransmitter effects —See listing under Antidepressant			
Reproductive hormonal effects			
	Black cohosh	IV, AS, CT	Reduces level of luteinising hormone; oestrogenic activity is controversial
	Chaste tree	IV, CT	Inhibits prolactin release by selective stimulation of pituitary dopamine D_2 receptors; however, low dose may increase secretion; stimulates progesterone-receptor expression in vitro
	Damiana	IV, AS	Weak oestrogen agonist activity reported; possibly works via progesterone receptors
	Hops	IV	Significant competitive binding to oestrogen receptors alpha and beta and up-regulation of progesterone receptors
	Red clover	IV, AS	Weak oestrogenic effects; anti-androgenic
	Rosemary	AS	Anti-oestrogenic
	SAMe	CT	Reduces prolactin levels
	Saw palmetto	AS	Reduces prolactin levels
	Tribulus	AS	Androgenic; protodioscin converts to DHEA; observed pro-erectile effects with protodioscin due to increased release of nitric oxide from the endothelium and nitronergic nerve endings
	Wild yam	IV, AS	Inconsistent results
Thermogenic effects			
	Ginger	AS	
	Green tea	CT	Interaction between catechin polyphenols and caffeine stimulates noradrenaline release and reduces noradrenaline catabolism
Thyroid modulation			
	Brahmi	AS	Increases T_4 concentration
	Fenugreek	AS	Reduces conversion of T_4 to T_3, resulting in increased T_4 concentration

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Iodine	PH	
	Lemon balm		Inhibits binding of thyroid-stimulating hormone to thyroid plasma membranes and extra-thyroidal enzymic T4-5'-deiodination to T_3
	Selenium	CT	Required for normal thyroid hormone synthesis, activation and metabolism
	Withania	AS	Root extract enhanced serum T_4 concentration
Wound healing/enhancement			
	Aloe vera	IV, AS, CT	Inhibits thromboxane, which would normally inhibit wound healing in vitro; improves collagen composition and cross-linking
	Calendula	AS, CT	
	Chamomile	CT	
	Chickweed	TU	
	Chitosan	PH	
	Echinacea	CT	Topically
	Grapeseed extract	IV, AS	Accelerates wound contraction and closure; resveratrol facilitates oxidant-induced vascular endothelial-growth-factor expression in keratinocytes
	Honey	AS, CT	Topical use, accelerates wound healing
	Myrrh	TU	
	St John's wort	TU	May be based on anti-inflammatory, analgesic and antimicrobial activities
	Slippery elm	TU, PH	High mucilage content
	Vitamin B2	AS	Deficiency lengthens the time to epithelialisation of wounds, slows the rate of wound contraction and reduces the tensile strength of incision wounds
	Vitamin B5	AS	
	Vitamin C	IV	
	Vitamin E		

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Zinc	IV, AS, CT	May be more effective in combination with iron

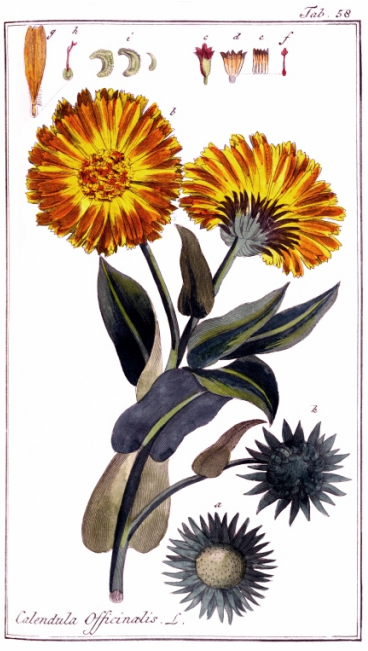
INDEX

This is an index to the herbal medicines, conditions and main actions (clinical uses) discussed in this book. Minor actions and drug interactions have not been indexed for each medicine (although drug interactions are indexed when discussed in the chapters).

Related information might be found under clinical uses and effects for each condition of interest (eg under 'hyperlipidaemia' and 'lipid-lowering activity').

Page locators indicate the first page number only, but not a page range for a continual discussion of a topic.

Index entries for special groups (eg 'elderly') are used when drugs are specifically recommended for a group of people, but not when the medicine is used for general purposes and aspects of its use for special groups is discussed. For example, a drug for morning sickness is indexed under 'pregnancy', but the safety of a general drug in pregnancy is not.



— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— continued next page

— *continued next page*

— continued next page

— continued next page

— continued next page