Ginkgo

(Ginkgo biloba L.)

Synonyms

Maidenhair tree (Engl), Ginkgoblätter (Ger), arbre aux quarante écus (forty coin tree) (Fr), Ginkgo (Ital), tempeltrae (Dan).

What is it?

Ginkgo biloba is a deciduous tree that has survived unchanged for about 150 million years from when dinosaurs walked the earth. Described by Charles Darwin as a living fossil, it may have been saved from extinction by the Chinese who revered the tree and planted it around their temples. While Ginkgo nuts are used in traditional Chinese medicine (TCM, see below), the modern use of the green leaf (not the yellow autumn leaf) is entirely due to scientific discovery. In the 1960s a group of German scientists were investigating the effects of exotic herbs on circulation in vivo and found that the leaves of Ginkgo were particularly active. A special, highly concentrated extract standardised for flavonoid content was developed and patented soon after. In the years that followed, standardised extracts of Ginkgo leaf became widely used in Europe and elsewhere.

When the standardised extract of Ginkgo leaf was first developed by German scientists, the original therapeutic focus was improving peripheral circulation to the legs and brain. Later the neuroprotective effects were recognised and Ginkgo became an important herbal treatment for Alzheimer’s disease. In addition, a wide variety of other clinical effects have been discovered, making Ginkgo one of the most clinically versatile plants in the modern herbal materia medica, with all such uses underpinned by human evidence.

Effects

Increases blood flow, tissue oxygenation and tissue nutrition; platelet-activating factor (PAF) antagonism; prevention of cellular damage caused by free radicals; protects mitochondrial function during cellular stress; enhances memory and cognitive function, especially in the elderly; protects nervous tissue against damage; helps adaptation to stressors; modulates cardiovascular risk; allays anxiety.

Summary actions

Anti-PAF activity, antioxidant, tissue perfusion enhancer, circulatory stimulant, nootropic, neuroprotective, anxiolytic, adaptogen.

Can be used for

Indications supported by clinical trials

Disorders and symptoms due to restricted cerebral blood flow (memory and/or cognitive impairment, dizziness, tinnitus, headaches, anxiety/depression, fatigue, stroke); vertigo, acute cochlear deafness, tinnitus of vascular origin (mixed results); peripheral arterial disease (particularly intermittent claudication, mixed results); favourable modification of cardiovascular risk; early stages of primary degenerative dementia (Alzheimer-type); multi-infarct dementia; disorders due to reduced retinal blood flow and normal tension glaucoma, age-related macular degeneration (preliminary data); congestive dysmenorrhoea and premenstrual syndrome; effects of high altitude or hypoxia; anxiety, adjunct therapy in chronic schizophrenia; to improve cognitive function (mixed results); diabetic retinopathy and neuropathy; symptoms associated with multiple sclerosis; allergic conjunctivitis (topically), asthma; protection from radiation damage; idiopathic oedema; vitiligo; improving adaptation to stress.

Traditional therapeutic uses

Ginkgo leaf does not have well-documented traditional use.

May also be used for

Extrapolations from pharmacological studies

Disorders due to restricted peripheral blood flow (including diabetic vascular disease, atherosclerosis); anti-PAF activity.

Traditional view

Only Ginkgo nuts were widely used in TCM as an antiasthmatic and against polyuria.¹ The main information on the therapeutic use of Ginkgo leaf comes from clinical trials on the standardised extract conducted over the past 5 decades, backed up by data from experimental models. However, the Chinese have now incorporated the use of Ginkgo leaf into their materia medica.
Ginkgo (useful in the treatment of asthma, allergic reactions, immunological reactions, shock, ischaemia, thrombosis); antioxidant activity, protection against ischaemia and reperfusion injury. New uses may follow from the anti-PAF activity, such as prevention of migraine headaches.

**Preparations**

Standardised extract for internal and topical application.

**Dosage**

The dose of liquid extracts is uncertain if they have not been standardised for major active constituents. Because of potential adverse reaction to the ginkgolic acids, the use of normal galenical extracts (tinctures or fluid extracts) is not recommended.

The daily dose is typically 120 to 240 mg of a 50:1 Ginkgo standardised extract (containing 24% ginkgo flavone glycosides and about 6% terpenoids). This corresponds to 4 to 16 g of leaf, depending on the quality of original leaf. Ginkgolic acids are usually specified to be less than 5 parts per million. The extract can be incorporated into liquids or tablets, usually at 40 mg/mL or 40 to 60 mg/tablet, making the daily dose 3 to 6 mL or two to six tablets, depending on their strength.

**Duration of use**

There is no restriction on the long-term use of Ginkgo. Moreover, for most applications it should be given to patients for at least 6 weeks before any clinical benefit is assessed.

**Summary assessment of safety**

There is very low risk associated with the administration of Ginkgo. The risk of a bleeding event or interaction with blood thinning drugs is overstated in most articles and texts and not supported by controlled clinical trials.

**Technical data**

**Botany**

*Ginkgo biloba* is a member of the Ginkgoaceae family, a gymnosperm that has survived unchanged from the Triassic period. It can grow to a height of over 100 m, living for 1000 years. Ginkgo is dioecious (possessing male and female flowers on separate trees) and its leaves have open dichotomous venation and a characteristic fan-like appearance with two lobes (hence the species name, *biloba*). The leaf shape has been likened to the cerebral hemispheres The naked seed (or nut) is oily and edible, but the seed coat and embryo are bitter.

**Adulteration**

Considerable variability has been found in total terpene content and in individual terpene levels in commercial Ginkgo leaf extracts. A 2002 study by the Hong Kong Consumer Council found that 13 of 14 commercial products contained levels of ginkgolic acids exceeding WHO (World Health Organization) recommendations by 16 to 733 times. (Ginkgolic acid is potentially allergenic.) See also under Key constituents below.

**Key constituents**

- 0.5% to 1% mono-, di- and triglycosides of the flavonols quercetin, kaempferol and isorhamnetin, quercetin-3-beta-D-glucoside, quercitrin and rutin, including coumaric acid esters of these flavonoids
- Terpene lactones (terpenoids), including bilobalide and ginkgolides A, B, C and J.
- Biflavonoids, ginkgolic acids, sterols, procyanidins, polysaccharides.

The majority of the pharmacological studies and clinical trials have been conducted using a chemically complex, concentrated extract containing at least 26 identified components and standardised to 24% flavonol glycosides (ginkgo flavone glycosides) and 6% terpenoids (ginkgolides and bilobalide). The standardised extract allows the concentration of potentially active constituents and the elimination of undesirable substances. For this reason, many of the known constituents of Ginkgo leaves are present only in minute amounts or absent from these extracts, including the ginkgolic acids, biflavonoids and sterols. The German Commission E and WHO stipulate that extracts should contain less than 5 ppm ginkgolic acids.

The standardised extract also contains approximately 7% proanthocyanidins, 13% carboxylic acids, 2% catechins, 20% non-flavonol glycosides and 4% high molecular weight compounds. Around 5% of its content is inorganic in nature and about 13% contains other phytochemical constituents.
A 2003 quality control assessment of commercial standardised Ginkgo extracts using analysis of intact flavonol glycosides found one product had been adulterated with rutin in order to elevate the total flavonol levels.\(^\text{13}\)

A total of 16 Ginkgo products were assessed in a 2005 Belgian study, including four that were registered medicines, the others being food supplements.\(^\text{14}\) All the examined medicines complied with the pharmacopoeial standards and eight of the 12 food supplements contained the claimed level of flavonoids. The remaining four did not, and two of these contained unexpectedly low amounts. Seven food supplement products had an unexpectedly high proportion of rutin present, indicating that adulteration with this flavonoid had likely occurred.

Following this knowledge of the potential adulteration of Ginkgo extracts with rutin (and possibly other flavonoids), a test method was developed for its reliable detection. The application of this method in the quality control of standardised Ginkgo extracts is now a requirement of the United States Pharmacopoeia–National Formulary (USP32-NF27) and for product registration (listing) with the Australian Therapeutic Goods Administration.
Pharmacodynamics

The considerable number of pharmacological studies on Ginkgo biloba extract have not been comprehensively reviewed in this monograph. Rather, the results from important, unique or representative studies and reviews have been included.

PAF antagonism

Platelet-activating factor (PAF) is an ether-linked phospholipid formed by platelets, basophils, neutrophils, monocytes and macrophages. It is a potent platelet-aggregating agent (more so in animals than humans), inflammatory factor and inducer of systemic anaphylactic symptoms. The ginkgolides (particularly ginkgolide B) are potent and specific PAF receptor antagonists. Their effects are long-lived and are rapidly established after oral doses. No side effects have been recorded, even when given in high doses (120 mg of a ginkgolide mixture) to healthy human volunteers.

High doses of ginkgolides control mast cell degranulation, and have been used to treat systemic mastocytosis (high blood levels of mast cells). Ginkgolides partially countered PAF-induced and antigen-induced bronchoconstriction and inhibited the induction of airway hyperreactivity by PAF in vivo. Ginkgolides inhibit the response of eosinophils to PAF and decrease the IgE-mediated cytotoxicity of eosinophils. Ginkgolides and the standardised extract of Ginkgo have demonstrated a potent thrombolytic effect on the PAF-induced thrombus.

Standardised Ginkgo extract has improved peak flow rates in asthmatic children and caused significant clinical improvement in adults. More recent research has focused on analogues (chemical derivatives) of the ginkgolides as potential new drugs with PAF-inhibiting activity.

Effects on ischaemia and blood flow

Ginkgolides prevent the metabolic damage caused by experimental cerebral ischaemia and have a normalising effect when given 1 h after the event. They can reduce the infarct size in experimental myocardial occlusion. Arrhythmias induced by experimental myocardial ischaemia are significantly counteracted by the prior administration of ginkgolides. Bilobalide has demonstrated a potent neuroprotective effect against ischaemic damage, which was stronger than ginkgolide B.

There is experimental evidence to support the view that Ginkgo extracts have neuroprotective properties under conditions such as hypoxia/ischaemia, seizure activity and peripheral nerve damage (see also below). Standardised Ginkgo extract, as well as its non-flavonol fraction (probably the ginkgolides), but not the flavonol glycosides, conferred protection in mice against brain damage caused by hypoxia and retarded the breakdown of brain energy metabolism. Oral administration of Ginkgo extract produced slight to moderate changes in glucose utilisation in the brain structures of rats. Glucose utilisation was significantly decreased in the frontoparietal somatosensory cortex, nucleus accumbens, cerebellar cortex and pons when a 50 mg/kg dose of extract was administered. This may help explain the clinical efficacy of Ginkgo extract in treating problems associated with deficient somatosensory processing (such as impairment of vigilance) and vestibular mechanisms (such as vertiginous syndromes). One study investigated the effect of Ginkgo extract (up to 15 mg/kg) on the dynamic equilibrium of free radicals and amino acids in rats with cerebral ischemia/reperfusion injury. Ginkgo reduced levels of gamma-aminobutyric acid (GABA), glycine, glutamate, aspartate and malondialdehyde (a measure of oxidation) and increased antioxidant enzymes. These results indicate that Ginkgo can protect damaged neurons via balancing inhibitory/excitatory amino acids and enhancing the removal of free radicals.

Ginkgo has favourably influenced a number of the metabolic events that accompany cerebral ischaemia, including a preventative effect on ischaemic damage by inhibiting vasoconstriction and thrombus formation and improving cerebral blood flow to underperfused areas without robbing adjacent areas. It has increased cerebral perfusion after oral administration and improved hypoxia tolerance in humans. Also, Ginkgo has inhibited thrombus formation, promoted prostacyclin synthesis, reduced cerebral oedema, normalised brain ATP and glucose following ischaemia, improved neuronal function following infarction and inhibited arteriolar spasm in animals. A recent review concluded that the main mechanisms behind the protective effects of Ginkgo extract in brain ischaemia/reperfusion injury were antioxidation, enhanced free radical clearance, inhibition of excitatory amino acids, reduced inflammation and inhibition of neuronal apoptosis.

However, a recent study suggests that heme oxygenase 1 (HO-1) could represent a key aspect of the neuroprotective role of Ginkgo in transient ischaemia/reperfusion. HO-1 is an inducible enzyme (by the Nrf2/ARE pathway) that plays a vital role in cellular homeostasis in response to oxidative stress. Mice pretreated with Ginkgo extract (25 to 100 mg/kg, oral) had 50.9% less neurological dysfunction and 48.2% smaller infarct volumes, but this benefit was abolished in HO-1 knockout mice (lacking the enzyme). Acute post-treatment with Ginkgo also reduced infarct size. The same group had previously shown that Ginkgo extract induced HO-1 levels in neuronal cell cultures.

Standardised Ginkgo extract and bilobalide inhibited the hypoxia-induced decrease in ATP content in endothelial cells in vitro. After oral administration in an in vivo model of hypoxia, both compounds increased the respiratory control ratio of mitochondria isolated from rat hepatocytes. The authors concluded that these agents helped to retain the ability to form ATP, thereby reducing the cell’s need to induce glycolysis, probably via preserving ATP regeneration by mitochondria as long as oxygen was available. A protective effect of standardised Ginkgo extract on the hypoxic myocardium was demonstrated by the changes in enzyme activities in rat myocardium after pretreatment with Ginkgo for 3 months.

In a comparative study on stroke victims, intravenous standardised Ginkgo extract was more active at improving cerebral blood flow compared with 28 conventional drugs (see also under Clinical trials). Ginkgo biloba extract (240 mg/day) was evaluated in a 3-week randomised, double blind, placebo-controlled study of...
skin blood flow in 27 healthy middle-aged volunteers. Skin blood flow was measured on the forehead using laser Doppler flowmetry. Ginkgo exerted a modulating effect on haemodynamics, enhancing the skin blood flow of participants with impaired circulation, normalising excess skin blood flow in cases of hypercirculation, while not affecting normal flow. A randomised controlled study on the effect of Ginkgo extract on forearm haemodynamics in 16 healthy volunteers was conducted over 6 weeks. Forearm blood flow and venous capacity were measured by strain-gauge plethysmography. Forearm blood flow was significantly higher during active treatment after 3 and 6 weeks, as compared with placebo treatment (p<0.05), while mean arterial blood pressure was unchanged. In an earlier randomised placebo-controlled crossover study in 10 healthy volunteers, Ginkgo markedly decreased erythrocyte aggregation and increased blood flow in nail-fold capillaries.

Other neuroprotective effects
A 2007 review noted that ginkgolide B has demonstrated neuroprotective activity in several in vitro models including nitric-oxide-induced neurotoxicity and against beta-amyloid. An earlier review observed that bilobalide in vivo can reduce cerebral oedema produced by triethyltin and decrease cortical infarct volume in stroke models. Possible protective mechanisms included preservation of mitochondrial function, inhibition of apoptotic damage and suppression of hypoxia-induced cell membrane deterioration in the brain. Neurochemical modulation may also be responsible for neuroprotection, with an ex vivo study demonstrating that bilobalide antagonised the GABA-A receptor binding of TBPS (t-butylbicyclophosphorothionate), a molecule with a high affinity for GABA-A, to rat cortical membranes. TBPS binding was competitively inhibited by bilobalide in the low micromolar range (IC$_{50}$ 3.7 µM).

Research in one laboratory has focused on understanding the mechanism of action of Ginkgo in protecting against Alzheimer’s disease (AD) and this was reviewed in 2006. Ginkgo extract protects against beta-amyloid aggregation in vitro, attenuates beta-amyloid-induced reactive oxygen species in the roundworm and reduces its neuronal toxicity. Several other in vitro studies have observed that Ginkgo extract protects against beta-amyloid neurotoxicity.

Ginkgo has also demonstrated protective activity in murine models of AD. One study used a transgenic mouse model and found that Ginkgo extract (300 mg/kg diet) given for 16 months significantly lowered amyloid precursor protein levels in the cerebral cortex. Ginkgo biloba may possess a preventative role in Parkinson’s disease. A standardised extract of Ginkgo was tested on a Parkinson’s disease animal model (6-hydroxydopamine (6-OHDA)-induced neurotoxicity in the nigrostriatal dopaminergic system of the rat brain). At 8 weeks after the induced lesion, the number of contralateral forepaw adjusting steps was significantly higher in rats treated with the high dose of Ginkgo (100 mg/kg/day, ip) than in those treated with a low dose (50 mg/kg, ip) or with the control, denoting a neuroprotective and anti-Parkinson effect.

Antioxidant activity
As noted above, much of the neuroprotective activity of Ginkgo extract is probably predicated on its antioxidant activity. Flavonoids from Ginkgo extract scavenged free radicals and antagonised lipid peroxidation and cell necrosis of rat hepatocytes more potently than the terpeine lactones (ginkgolides, bilobalide) in vitro. Ginkgo extract scavenged various reactive oxygen species, such as hydroxyl and superoxide radicals, and also peroxyl radicals, which are involved in the propagation step of lipid peroxidation. Standardised Ginkgo extract inhibited or reduced functional and morphological retinal impairments observed after lipoperoxide release. The extract has demonstrated powerful antioxidant effects on copper-mediated human low-density lipoprotein oxidation in vitro.

Such passive in vitro antioxidant effects probably do not underlie the in vivo antioxidant activity of Ginkgo, which is more likely based on its activation of specific protector pathways, such as Nrf2/ARE. For example, an increase in catalase and superoxide dismutase (SOD) activities in the hippocampus, striatum and substantia nigra and a decrease of lipid peroxidation in the hippocampus was displayed in rats treated with Ginkgo. Ginkgo extract (100 mg/kg, oral) prevented mobile phone-induced oxidative stress in the brains of rats exposed to 900MHz radiation for 7 days (1 h/day). Cellular brain injury was also reduced.

Volunteers given standardised Ginkgo extract (200 mg/day) for 1 week also exhibited red blood cells that were more resistant to oxidative damage. Ginkgo extract decreased the clastogenic activity (a marker of oxidative stress) of blood taken from salvage personnel working on the Chernobyl reactor accident. In a further study, 30 recovery workers were treated with standardised Ginkgo extract (120 mg/day) for 2 months. The clastogenic activity of their plasma was reduced to control levels at the end of the treatment period and persisted for at least 7 months thereafter. This study also implies a radioprotective activity (see also under Clinical trials).

Mitochondrial effects
It has been suggested that effects on mitochondria exerted by Ginkgo extract could underpin several of its observed pharmacological activities, including AD prevention, neuroprotection, cardioprotection, attenuation of ischaemia/reperfusion injury and antioxidant activity. Cardioprotective activity observed in vitro using cardiomyocytes and isolated heart have been attributed to favourable effects on mitochondrial function. This cardioprotective aspect of Ginkgo extract has also been confirmed in vivo for the hearts of older rats.

Treatment of two different age groups of mice with Ginkgo extract (100 mg/kg/day for 14 days, oral) showed beneficial effects on complexes I, IV and V of the mitochondrial respiratory chain in brain cells against nitric oxide stress. Interestingly, these effects were only observed in the aged mice. In another study, favourable effects on mitochondrial dysfunction in the hippocampi of a senescence-accelerated strain of mice were observed after Ginkgo extract.
(100 mg/kg, oral), but again only in old mice. The authors attributed this enhanced effect to an age-associated increase in the permeability of the blood-brain barrier.

Neurotransmitter and other CNS effects
A review of the chemistry and biology of the terpene trilactones from Ginkgo observed that ginkgolide B is a potent and selective antagonist of the glycine receptor chloride channel in vitro. Glycine receptors are found primarily in the spinal cord and brain stem, but also in higher brain regions such as the hippocampus. The implications of this novel finding for ginkgolide B are not clear. Other ginkgolides also possess this activity, as well as being antagonists of the ion channels for GABA. Studies have also shown that the ginkgolides and bilobalide particularly modulate the peripheral benzodiazepine receptor (now called translocator protein). This may increase the risk of seizures. Several in vitro studies indicate that bilobalide also affects the major neurotransmitters in the brain, namely glutamate and GABA.

Another review noted that Ginkgo extract has exhibited mixed results on noradrenaline (norepinephrine) levels and receptor density in rats, inhibited the degeneration of dopaminergic neurons in the striatum of mice (an antiparkinsonism effect) and ameliorated the natural decline in acetylcholine receptors with age in rats. Favourable activity on serotonergic mechanisms in the brains of rats was also observed, especially with respect to 5-HT1A receptor density and function.

A single oral dose of Ginkgo extract (100 mg/kg) had no effect on monoamine levels in the prefrontal cortex and striatum of conscious rats. However, following chronic treatment for 14 days, the same daily dose significantly increased extracellular dopamine and noradrenaline (norepinephrine) levels, while serotonin levels were unaffected. Chronic treatment with Ginkgo showed dose-dependent increases in frontocortical dopamine levels and, to a lesser extent, in the striatum. Treatment with the main constituents of the herb revealed that the increase in dopamine levels was mostly caused by the flavonol glycosides and ginkgolide fractions, whereas bilobalide treatment was without effect. These observations may have implications for the effect of Ginkgo on cognitive function.

Ginkgo has demonstrated anxiolytic activity in several animal models, especially under conditions of stress (see also Antistress activity below). In an early study, intragastric administration of a preparation containing standardised extracts of Ginkgo and ginger demonstrated anxiolytic effects comparable to diazepam (by injection) in vivo. However, the herbal preparation demonstrated an anxiety-promoting effect at a higher dosage (100 mg/kg). A similar effect to diazepam was observed in a social interaction model in mildly stressed rats for Ginkgo extract (48 or 96 mg/kg/day for 8 days, oral) and there was an additive effect of its combination with the drug.

The anxiolytic-like effects of Ginkgo extract and its four key terpenoid components were assessed using the elevated plus-maze test in mice. Administration of Ginkgo extract as an acute oral dose (0.5 or 1 g/kg) caused a state of suppressed motor activity and shortened the time spent in the open-sided arms. However, when Ginkgo extract (0.063 to 1 g/kg, oral) was administered daily for 7 days and the plus-maze test carried out, the time spent in the open-sided arms was prolonged, with the peak anxiolytic-like effect at the 0.125 g/kg dose. A combination of 7-day administration of Ginkgo extract (0.125 g/kg) and a single dose of diazepam (1 mg/kg, oral, 10 min before testing) enhanced the anxiolytic-like effect. Flumazenil blocked the effect of diazepam, but not of Ginkgo. Daily administration of ginkgolide A (1 or 2 mg/kg, oral) resulted in an anxiolytic-like effect, but neither ginkgolide B, C, nor bilobalide produced any such activity. These results suggest that Ginkgo produces a significant anxiolytic-like effect following repeated administration, and that ginkgolide A is most likely responsible for this effect. Ginkgo exerts a sedative effect at comparatively higher doses.

There is also a suggestion from animal models that Ginkgo might possess antidepressant activity. This does not appear to be due to monoamine oxidase inhibition, despite some in vitro activity in that regard. Ginkgo demonstrated clear antidepressant effects in two behavioural models in rats at oral doses ranging between 10 and 100 mg/kg.

Antistress effects
Several animal studies have observed an antistress activity for Ginkgo extract. In fact, one group of researchers suggested that the improved cognitive functioning following sustained treatment with Ginkgo extract (see below) may be secondary to neuroprotective properties that buffer the animal from the harmful effects of stress.

A review of the research up to 2000 indicated that Ginkgo possesses an antistress action that differs from conventional drugs (antidepressants, anxiolytics). This action of Ginkgo appears to be linked to a modulation of adrenal activity, as it reduced circulating concentrations of adrenaline (epinephrine), noradrenaline (norepinephrine) and corticosterone in stressed old and young rats after chronic administration of oral extract doses ranging from 50 to 100 mg/kg/day. Such effects were demonstrated in various experimental models of stress, including studies that observed a suppression of the down-regulation of hippocampal glucocorticoid receptors induced by prednisolone or amphetamine, with a normalisation of learning and behavioural parameters. These studies demonstrate that Ginkgo in fact meets the definition of an adaptogen. These effects were due in part to the ginkgolides, and it appears that peripheral glucocorticoid biosynthesis serves as their molecular target.

Studies published since 2000 have confirmed these findings and added new insights. For example, catecholamines (norepinephrine, dopamine), serotonin and plasma corticosterone levels were studied in rat brains following 1, 2 and 4 h restraint stress. Ginkgo extract (14 mg/kg, oral) restored the restraint stress-induced elevations of catecholamines, serotonin and plasma corticosterone to near normal levels in the brain.

Like most adaptogens, Ginkgo has demonstrated effects on the immune response. Stress-induced suppression of the cellular immune response in rats was countered by Ginkgo extract (100 mg/kg/day for 7 days, oral). Another similar
study using the same dose confirmed this result and also found that Ginkgo improved innate immune responses in stressed rats.\textsuperscript{92}

A comparison of Ginkgo (30 mg/kg, oral) and Panax ginseng (100 mg/kg, oral) extracts in stressed rats found that Ginkgo was more effective in reversing the biochemical changes induced by acute stress, whereas ginseng was superior in chronic stress.\textsuperscript{93}

Exposure to chronic stress in humans alters cognitive function, possibly as a result of elevated glucocorticoids. One group has found that Ginkgo extract (100 mg/kg, oral) normalised stress- and corticosterone-induced impairment of recall and spatial memory in rats.\textsuperscript{94–96}

The adaptogenic activity of Ginkgo has been demonstrated in healthy volunteers. One study evaluated the effects of Ginkgo on salivary cortisol and blood pressure responses during stress in 70 healthy young volunteers in a double blind, placebo-controlled design.\textsuperscript{97} A stress model involving a combination of static exercise (handgrip) and mental stimuli was used. Single treatment with Ginkgo extract (120 mg) reduced the stress-induced rise in blood pressure without affecting heart rate. Salivary cortisol responses showed differences with respect to gender and time of day of the stress exposure, with the activation only in men in the afternoon. This activation was absent if they were first treated with Ginkgo.

Ginkgo extract at 120 mg/day for 3 months significantly dropped plasma cortisol levels during the stress caused by the glucose tolerance test in healthy volunteers.\textsuperscript{98} According to the scientists involved in the trial, Ginkgo might also reduce blood levels of cortisol in other types of stress.

**Effect on memory and/or learning**

Many in vivo models have demonstrated a positive effect of Ginkgo on cognitive function. In a controlled animal study, Ginkgo treatment (100 mg/kg/day, for 4 to 8 weeks prior to training and 10 weeks prior to testing, oral) enhanced performance on the tested task, indicating improved retrieval of the learned response.\textsuperscript{99} However, it did not affect performance in a passive avoidance test.\textsuperscript{100} Oral administration of Ginkgo extract to young and old rats facilitated behavioural adaptation, despite adverse environmental influences. Stress-induced detrimental changes in both discrimination learning and plasma hormones became significant after the third day of learning. Ginkgo was more effective in decreasing the number of inefficient lever presses and reaction times in the older animals.\textsuperscript{101}

A review of other studies up to 2000 indicated that Ginkgo had been found to enhance cognitive performance and learned responses in an eight-arm radial maze, to improve short-term memory in a passive avoidance paradigm and increase brain neuronal membrane fluidity.\textsuperscript{102} Results were most marked with chronic administration and in older animals, as noted in a slightly later review.\textsuperscript{102}

In later studies Ginkgo (50 to 200 mg/kg, oral) acutely reversed yohimbine-induced spatial working memory deficit in rats\textsuperscript{103} and with chronic administration (60 mg/kg/day for 30 days, oral) enhanced spatial learning and memory and hippocampal synaptic plasticity in aged rats.\textsuperscript{104} The countering effect on yohimbine was attributed to the action of Ginkgo on alpha-2-adrenoceptors.

A 2003 review provided an overview of much of this research and its relationship to key aspects of the other pharmacological research above. It observed that, while individual effects of cognition and behavioural assessment in all areas have been reported for adult animals and acute dosing, more pronounced effects are usually seen in aged animals and after subchronic treatment.\textsuperscript{105} Specifically for the cognition improving properties, pronounced beneficial effects are mainly present in those situations where cognition was impaired by ageing or other noxious stimuli. Since all these conditions are associated with mitochondrial dysfunction, the stabilising or even protective effect of Ginkgo on mitochondrial function seems to be a major mechanism associated with many of its behavioural effects. Bilobalide is most important in this respect. Moreover, bilobalide and the ginkgolides have been shown to affect chloride conductance by interfering with the function of membrane proteins related to receptor-gated chloride channels. These mechanisms are probably associated with behavioural effects requiring acute changes of neuronal activity, but might indirectly also improve mitochondrial function.

Most of the recent investigations on the cognitive activity of Ginkgo extract have been human studies. These are reviewed in the Clinical trials section under the relevant heading.

**Other activity**

The inflammatory response induced by intracolonic administration of acetic acid in rats was inhibited by 2 days of oral pretreatment with Ginkgo (30, 60, 120 mg/kg), significantly decreasing colonic myeloperoxidase activity, tumour necrosis factor (TNF)-alpha and interleukin (IL)-1beta levels and increasing the glutathione concentration. Ginkgo treatment also attenuated macroscopic colonic damage, as assessed by histopathological examination. An antioxidant action was regarded as being responsible for this antiulcerogenic activity.\textsuperscript{106} Another study involving an ethanol-induced gastric lesion rat model demonstrated that intravenous Ginkgo extract (8.75, 17.5 and 26.25 mg/kg) inhibited gastric ulcer formation.\textsuperscript{107}

The effects of various fractions of Ginkgo extract on human (obtained from impotent men) and rabbit penis corpus cavernosal tissue were investigated in vitro.\textsuperscript{108} One fraction was particularly active at relaxing corpus cavernosal tissues, suggesting a possible benefit in erectile dysfunction.

Oral administration of Ginkgo extract (10 mg/kg/day, for 12 weeks) in conjunction with a high-fat diet reduced disturbances of lipid metabolism and the severity of plaque formation in rabbits. In addition to hypolipidaemic and antioxidant (antiatherosclerotic) activities, Ginkgo also affected metabolic processes in the liver and may modify lipid deposition in major arteries.\textsuperscript{109}

Ginkgo extract showed a promoting effect on hair regrowth after cutaneous administration to shaved mice in a 1993 study.\textsuperscript{110} There appear to be no further studies on this theme. Ginkgo extract demonstrated an anti-inflammatory
activity with potency comparable to that of indomethacin after topical application in the croton oil test in mice.\textsuperscript{111} Unilateral vestibular deafferentation (UVD) causes ocular motor and postural disorders, some of which disappear over time in a process of behavioural recovery known as vestibular compensation. Vestibular compensation may be enhanced either by reducing the initial symptoms of UVD or by accelerating the compensation process. The positive impact of injected Ginkgo extract in UVD in vivo was suggested to be due to acceleration of compensation.\textsuperscript{112}

**Pharmacokinetics**

The first attempt to understand the pharmacokinetics of Ginkgo was undertaken using a radioactively labelled extract (with the carbon-14 isotope).\textsuperscript{113} After oral administration to rats, absorption of at least 60% was determined. The half-life of the radioactivity was about 4.5 h and after 72 h 22% was found in urine and 29% in faeces. Glandular and neuronal tissues and the eyes demonstrated a high affinity for the labelled substances (possibly ginkgolides and bilobalide). A site of absorption in the upper gastrointestinal tract was suspected, since specific activity in blood peaked after 1.5 h.

However, no flavonoid glycosides or aglycones were detected in urine, faeces or blood within 24 h of intragastric administration of Ginkgo extract to rats in another early study. Seven metabolites of flavonoid degradation were found.\textsuperscript{114} These were phenylalkyl acids formed by C-ring fission of the flavonoids by gut microorganisms (see Chapter 2).

Consistent with the above, Ginkgo flavonoids have exhibited a low bioavailability in mice. Oral administration of Ginkgo extract (about 36 mg/kg via the diet) resulted in plasma concentrations of quercetin, kaempferol andisorhamnetin (after hydrolysis with glucuronidase/sulphatase) of 12, 7 and 50 ng/mL, respectively, compared with levels of 5, 3 and 0 ng/mL in control mice.\textsuperscript{115} This low bioavailability of the intact flavonoids was confirmed in a later study in a beagle dog, after plasma concentrations following injection were compared against concentrations resulting from an oral dose.\textsuperscript{116,117}

A recent German study investigated the ability of Ginkgo flavonoid constituents to cross the blood-brain barrier in rats, after single (600 mg/kg) or repeated (8 days, 100 or 600 mg/kg) oral administration of Ginkgo extract.\textsuperscript{118} A highly sensitive method for the determination of the Ginkgo flavonoid metabolites (quercetin, kaempferol andisorhamnetin derivatives) in the brain and plasma was developed. The single dose of 600 mg/kg resulted in maximum plasma concentrations of 176, 341, and 183 ng/mL for quercetin, kaempferol, andisorhamnetin/tamarixetin, respectively, and in maximum brain concentrations of 291 ng/g protein for kaempferol and 161 ng/g protein forisorhamnetin/tamarixetin. In comparison, the repeated administration of the same dose for 8 days led to an approximate 4.5-fold increase in the plasma concentration of quercetin, an 11.5-fold increase for kaempferol and a 10-fold increase forisorhamnetin/tamarixetin. In the brain, an approximate 2-fold increase was observed for kaempferol andisorhamnetin/tamarixetin. About 90% of the determined flavonoids were distributed in the hippocampus, frontal cortex, striatum and cerebellum, which together represent only 38% of the whole brain.

The bioavailabilities of ginkgolides A and B and bilobalide were determined in rats after a single oral administration of 30, 55 and 100 mg/kg of Ginkgo extract.\textsuperscript{119} Their pharmacokinetics were found to be dose-linear, with maximum plasma concentrations for the lowest dose of 68, 40 and 159 ng/mL and half-lives of 1.7, 2.0 and 2.2 h, respectively. A study in rats found that ginkgolide B was metabolised to its hydroxyl metabolite, mainly via CYP2D6.\textsuperscript{120} Another rat study observed that ginkgolide B can pass through the blood-brain barrier, especially after ischaemia-reperfusion injury.\textsuperscript{121}

Results from human studies of the pharmacokinetics of Ginkgo extract tend to reflect the animal findings. After Ginkgo extract (4 g) was given to healthy volunteers observing a flavonoid-free diet, urine samples were collected for 3 days, and blood samples were withdrawn every 30 min for 5 h.\textsuperscript{122} Only urine samples contained detectable amounts of substituted benzoic acids, including a 4-hydroxybenzoic acid conjugate, 4-hydroxyhippuric acid, 3-methoxy-4-hydroxyhippuric acid, 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, hippuric acid and 3-methoxy-4-hydroxybenzoic acid (vanillic acid). In contrast to rats, no phenylacetic acid or phenylpropionic acid derivatives were found in urine, thus indicating that a more extensive metabolism takes place in humans. As for rats, the metabolites found in human urine accounted for less than 30% of the flavonoids given. When the same test procedure was applied to blood samples, no metabolites could be detected. A review of early pharmacokinetic studies of the Ginkgo flavonoids described evidence that intact flavonoids could in fact be identified in human urine following oral doses of Ginkgo extract, apparently as glucuronide metabolites.\textsuperscript{123} A later study did confirm the presence of quercetin and kaempferol, mainly as glucuronides, in human urine after a single dose of Ginkgo.\textsuperscript{124}

The pharmacokinetic properties of the terpenoids in humans have been more extensively studied than the flavonoids, probably because they exhibit better bioavailability and possibly also because they are more likely to explain much of the pharmacological activity of Ginkgo. Data obtained from an early human investigation suggested that ginkgolides A and B and bilobalide are excreted unchanged in the urine (70%, 40% and 30%, respectively of the administered dose) and exhibited relatively high bioavailability after oral ingestion (>80%, >80% and 70%, respectively).\textsuperscript{125} Ginkgolide C was not bioavailable.

This high bioavailability was also observed after the oral administration of 120 mg of Ginkgo extract to 12 healthy human volunteers. Elimination half-lives (after oral dosing while fasting) of 4.5, 10.6 and 3.2 h were measured for the three compounds, respectively.\textsuperscript{126} There was no relevant influence of food on the pharmacokinetics of the terpenoids. A 2003 review paper also included data from unpublished work.\textsuperscript{127} A study in 12 healthy male volunteers found that maximum plasma concentrations were reached within 1 h following a single dose of 80, 120 or 240 mg of Ginkgo extract. These concentrations were 15.2, 25.3 and 42.9 mg/mL, respectively, for ginkgolide A, 6.5, 9.1 and 18.1 mg/mL for ginkgolide B and 30.2, 35.2 and 58.6 mg/mL for bilobalide,
indicating an approximately dose-linear response. Another unpublished study included in the review investigated pharmacokinetics in 12 elderly volunteers after single (60mg) and multiple (60mg twice a day for 8 days) Ginkgo extract administration. There was no change in pharmacokinetics (for example, no accumulation) after multiple-dose administration. The steady-state concentrations of ginkgolide A and B and bilobalide were 9.4, 6.2 and 8.7ng/mL, respectively, and clearance rates in the elderly were lower than young volunteers, as might be expected.

A 2002 pharmacokinetic study of two different doses of Ginkgo extract involving 12 healthy volunteers discovered that twice daily administration of 40mg of the extract produced a higher serum half-life (t1/2) and mean residence time of bilobalide B than a single 80mg daily dose. A higher concentration peak (Cmax) was reached however with the 80mg dosage, while both dosages yielded a maximum concentration 2.3h (Tmax) after administration.127

Several studies have shown that the bioavailability of Ginkgo extracts (both in terms of flavonoids and terpenoids) can vary according to the pharmaceutical preparation. Complexing with soy phospholipids appears to enhance bioavailability based on animal128,129 and human130 studies. Higher dissolution rates of Ginkgo solid dose products also improved bioavailability in humans.131

Clinical trials

Cerebral insufficiency and stroke

Cerebral (not cerebrovascular) insufficiency is not strictly a medical condition and it is not accepted as being associated with any pathological change. Rather, it is a collection of symptoms associated with mental deterioration from ageing, and affects many elderly people who do not necessarily have dementia or a history of cerebral stroke. Typical symptoms of cerebral insufficiency include difficulties in concentration and memory, absentmindedness, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus and headaches. These symptoms can also be associated with the early stages of dementia, of either the Alzheimer (degenerative) or multi-infarct (circulatory) types.

The focus of the early Ginkgo clinical trials on cerebral insufficiency was a barrier to its wider acceptance as a treatment for the elderly. Subsequent trials have demonstrated the benefit of Ginkgo in dementia (see later); hence the review immediately below should be viewed in its historical context. One development in the field of pathology that could be relevant to the concept of cerebral insufficiency is the concept of ‘white matter ischaemia’. After computed tomography was introduced in clinical practice, it was realised that rarefaction or low attenuation of the white matter of the brain (the axons) was more common than previously thought. Although this can occur for several reasons (for example after head injury), age and ischaemia to the white matter are regarded as the commonest causes.132

The vulnerability of the white matter to ischaemia is due to the fact that it is supplied by long penetrating end arterioles from the surface and base of the brain that travel for a long distance with very few interconnections. Computed tomography of the brain shows that 30% of people aged 85 years have evidence of low attenuation of white matter. Magnetic resonance imaging (MRI) shows an incidence approaching 100% at age 85. Studies demonstrate that normal people with white matter ischaemia could have subtle neuropsychological deficits, such as a slower rate of mental processing and impaired attention and concentration. Hence a tentative link between white matter ischaemia and cerebral insufficiency has been established. Since Ginkgo has anti-ischaemic activity, it may prevent or ameliorate symptoms associated with white matter ischaemia. White matter ischaemia is also closely associated with vascular or so-called multi-infarct dementia. The key difference is that a patient need not show a history of strokes to have a cognitive impairment brought about by such ischaemia. A recent review has concluded that abnormalities in the small vessels caused by ageing and hypertension, together with systemic circulatory disturbances such as heart disease or abrupt variations in blood pressure, may lead to selective white matter injury. The damage is structurally characterised by incomplete infarction or selective cellular injury.133

A critical review of 40 clinical trials conducted from 1975 to 1991 on Ginkgo and cerebral insufficiency and other conditions found eight to be well conducted.134 Trials under this general heading also included the following conditions: primary degenerative dementia, dizziness associated with labyrinth and/or vestibular disorders, acute cochlear deafness, senile cognitive decline, vertigo, hearing loss and tinnitus.

The trials included Ginkgo versus placebo or registered drugs, mostly by oral route, and in one case combined with physical training. Shortcomings of the 40 trials included limited numbers of patients and incomplete description of randomisation procedures, patient characteristics, effect measurement and data presentation. All except one of the 40 trials showed positive results, 26 trials demonstrated significant results. The inconclusive result was obtained for a trial on senile dementia of vascular origin.135 In most trials the dosage was 120 to 160mg/day of Ginkgo extract, given for at least 4 to 6 weeks. No serious side effects were reported in any trial, and those that were reported were not significantly different from side effects observed in placebo-treated patients.

Eleven double blind, placebo-controlled trials using, in most cases, 150mg/day of standardised Ginkgo extract over 12 weeks for cerebral insufficiency were evaluated by meta-analysis. Global efficacy was confirmed in five studies, compared to one study that was inconclusive.136 Three studies were excluded on the basis of methodological or objective reasons and two were excluded because assessment by physician or patients was missing. Analysis of the total score of clinical symptoms from eight of the 11 studies indicated similar results (seven studies demonstrated Ginkgo was significantly better than placebo, one study was inconclusive).137 It was concluded that treatment with Ginkgo extract provided a better therapeutic effect compared with placebo in the treatment of cerebral insufficiency.138

In other early trials (uncontrolled, double blind, placebo and comparative), standardised Ginkgo extract was found
to be of benefit in the treatment of recent stroke victims. Improvement was observed in cerebral blood flow, motor recovery, intellectual performance, memory, mood and behaviour.137-140

A 2005 Cochrane review was conducted primarily to determine whether Ginkgo improved cognitive deficit and the functional outcome of patients with acute ischaemic stroke without causing deleterious side effects. The secondary outcome of effects on neurological impairment and quality of life in stroke sufferers was also reviewed. Ten trials involving a total of 792 patients met methodological standards and were included in the review (nine were conducted in China, where Ginkgo is used as a treatment for stroke). Analysing the trials together, Ginkgo was observed to significantly improve functional outcome in acute ischaemic stroke (OR 2.66; 95% CI –8.9 to 10.52). The authors concluded that, although Ginkgo shows promise in improving the functional outcome of stroke victims, most of the studies had some methodological failings, such as inadequate blinding and/or randomisation and an insufficient follow-up time (14 to 35 days).141 It should be noted that Ginkgo was administered by injection in four of the 10 trials and for several trials treatment was instituted within 48h.

In an early double blind, placebo-controlled trial not considered in the meta-analysis, 47 patients with acute ischaemic stroke received either Ginkgo extract (40mg) or placebo at 6-hourly intervals along with routine management over 4 weeks. Both groups showed significant improvement, with negligible difference in degree of change in either group. The study group did, however, consist of patients who were treated more than 48h after stroke and the treatment time was relatively short (4 weeks).142

The prevention of deleterious change in cerebral architecture and cognitive deficit in ageing humans was examined in a double blind, controlled study involving 48 men (aged 60 to 70 years). Single photon emission computed tomography (SPECT) and measurement of blood viscosity were employed after 8 months of Ginkgo extract (80mg/day). After the 8-month treatment period, the Ginkgo group showed a reduction in blood viscosity, improved cerebral perfusion in specific areas and improved global cognitive functioning. In contrast, the control group demonstrated the opposite (higher blood viscosity, a reduction in cerebral perfusion in specific areas and cognitive deterioration in different functions).143 A follow-up study compared a macerated garlic oil against Ginkgo extract (80mg/day) and placebo over 180 days in men and women and found Ginkgo was more effective in reducing blood viscosity from baseline.

Nine healthy men, of mean age 61±10 years, underwent a series of MRI scans at baseline and again after 4 weeks of treatment with Ginkgo extract (120mg/day).144 Cerebral blood flow was analysed at three different levels of spatial resolution in 10 brain regions. A small but statistically significant increase in cerebral blood flow was found in the left parietal-occipital white matter after Ginkgo administration (p≤0.001). The left parietal-occipital region has been implicated in visual memory and cognition. In other regions there was a (non-significant) trend of higher blood flow. There was also a small and statistically significant increase in global cerebral blood flow (all regions combined): 15% in white matter and 13% in grey matter (p≤0.0001).

Alzheimer’s disease and vascular dementia

Treatment

Ginkgo has been used successfully in the treatment of senile dementia of both the Alzheimer and vascular types. As a vast amount of literature exists regarding Ginkgo and dementia, only clinical trials and reviews of note are subsequently discussed.

A review published in 2008 assessed the efficacy of standardised Ginkgo extract in the treatment of dementia of vascular origin (VaD) and Alzheimer’s disease (AD) by considering the external validity (such as everyday life activities, patient evaluation, quality of life of patients and carers) in addition to the usual criteria of randomisation and trial blinding. The authors assessed 34 placebo-controlled clinical trials to 2002. Despite some methodological limitations, there was sufficient evidence indicating the efficacy of Ginkgo for these conditions. The most frequent dosage was 120mg/day, up to a maximum of 240mg/day.145 Three randomised, placebo-controlled trials published since this review have reported mixed results,146-148 although subgroup analysis of one trial149 and the results of a trial with rigorous patient selection,146 indicate standardised Ginkgo extract may be most beneficial to patients with neuropsychiatric symptoms. (The most frequent neuropsychiatric symptoms in dementia (Alzheimer and vascular) are apathy, depression and agitation/aggression. Up to 80% of patients with dementia, irrespective of cause, exhibit such symptoms.) A further subgroup analysis of this trial found that Ginkgo was equally effective for VaD and AD.149

In late 2008, the German Institute for Quality and Efficiency in Health Care (IQWiG) assessed trials for meta-analysis and noted there is evidence of a benefit for high-dose standardised Ginkgo extract (240mg/day, for at least 16 weeks) in patients with AD, particularly for the goal of coping with daily activities. The results of the high-dose trials are of greater relevance as they are more homogeneous (not much deviation in results).150 Four trials were included in the IQWiG meta-analysis of Ginkgo versus placebo.151

An alternative interpretation of the published data is provided by the Cochrane Collaboration (2009). A meta-analysis of randomised, placebo-controlled trials concluded the evidence for Ginkgo having a predictable and clinically significant benefit for people with dementia or cognitive impairment was inconsistent and unreliable.152 The analysis incorporated trials mentioned above, including those covered in the 2008 review and the IQWiG meta-analysis. Criticism of some aspects of the methodology and conclusions of this Cochrane meta-analysis has been noted below and in the feedback section of the review article.

In terms of specific results, 36 trials were included, but most were small and of less than 3 months’ duration. Results of the more recent trials showed inconsistent results. Of the four most recent trials, three found no difference between Ginkgo and placebo and one reported very large treatment effects in favour of Ginkgo. A subgroup analysis of only AD
patients (925 from nine trials) also showed no consistent pattern of benefit.

Unlike the Cochrane meta-analysis, a meta-analysis published in 2010 only included trials evaluating specifically defined dementia and AD; trials of just cognitive impairment were excluded. Results indicated Ginkgo extract to be more effective than placebo in improving cognition in these patients. The trials were at least 12 weeks in duration and nine trials were included (2372 patients).\textsuperscript{153} Effect sizes were moderate. Another 2010 meta-analysis that considered the influence of baseline risk on the treatment effect found Ginkgo extract for 6 months was effective in dementia. As mentioned, this meta-analysis took into account the variation of changes in the placebo groups across the included trials.\textsuperscript{154} (Baseline risk is the risk of the event (in this case, cognitive decline) occurring without the active treatment (i.e. in the placebo group).) Six trials were included in the analysis.

A retrospective analysis of one of the trials included in these 2010 meta-analyses investigated whether the effect of treatment correlated with the extent of neuropsychiatric symptoms at baseline. Standardised Ginkgo extract (240 mg/day) was found to be effective in the treatment of dementia irrespective of the severity of neuropsychiatric symptoms. However, due to a faster decline in the placebo group, the net effect of Ginkgo was larger in patients with more pronounced neuropsychiatric symptoms, similar to observations noted above.\textsuperscript{155}

A 2009 review identified 10 randomised, controlled, double-blind clinical trials of Ginkgo in the treatment of AD and VaD.\textsuperscript{156} In three of the four large trials, conducted in accordance with recent guidelines, Ginkgo extract was significantly superior to placebo with respect to cognitive performance and one or more other (global, functional or behavioural) outcomes. Only one trial was inconclusive, but was deemed to be of questionable external validity due to excessively rigorous patient selection.

Some of the key clinical trials included in the above reviews are discussed below.

The efficacy and safety of Ginkgo extract in the treatment of patients with mild-to-severe AD or VaD were assessed in a 52-week, randomised, double blind, placebo-controlled clinical trial.\textsuperscript{157} Patients received either 120 mg/day of the extract or placebo. Primary outcome measures were the Alzheimer’s Disease Assessment Scale (ADAS), Geriatric Evaluation by Relative’s Rating Instrument (GERRI) and Clinical Global Impression of Change (CGIC). Of the 309 patients who began the trial, 202 provided useful data for the endpoint analysis, with 27% of patients treated with Ginkgo achieving at least a 4-point improvement on the ADAS compared with 14% taking placebo (p=0.04). On the GERRI, 30% of the Ginkgo group improved and 17% worsened, while the placebo group displayed an opposite trend with 37% of patients worsening and 25% improved (p=0.006).\textsuperscript{158}

A later stratification of the ITT data set collected during this 52-week trial (using cut-off points of 23 and 14 for the Mini-Mental State Examination (MMSE) score) yielded interesting results.\textsuperscript{159} In the severity stratum 1 (MMSE >23), the placebo group did not demonstrate significant changes, while the Ginkgo group improved significantly by 1.7 points on the ADAS-Cog and by 0.09 points on the GERRI. In the severity stratum 2 (MMSE <24), the placebo group worsened by 4.1 points on the ADAS-Cog and 0.18 points on the GERRI, whereas the Ginkgo group showed 60% less decline on the ADAS-Cog (a treatment difference of 2.5 points) and no change on the GERRI (a treatment difference of 0.25 points). The most severely impaired subgroup (MMSE <15) displayed a slightly more pronounced worsening in both treatment groups. However, compared with placebo, Ginkgo induced virtually the same magnitude of effect as was observed in the entire stratum 2.

The results of this retrospective analysis further indicated that a treatment effect favourable to Ginkgo could be observed with respect to cognitive performance (p=0.02) and social functioning (p=0.001) regardless of the stage of dementia, whether mild or moderately severe. The authors believed their results reflected that Ginkgo ameliorated cognitive decline in cases of mild impairment, while in more severe cases it exerted a stabilisation or slowing-down of degeneration.

A 24-week randomised, controlled trial compared the efficacy of a standardised Ginkgo extract (160 mg/day) against a positive control group (donepezil, a cholinesterase inhibitor, 5 mg/day) and placebo in patients aged 50 to 80 years with mild to moderate dementia.\textsuperscript{160} Results demonstrated a comparable efficacy between donepezil and Ginkgo in attenuating the progression of dementia, as assessed by the Syndrom Kurztest (SKT), the MMSE and CGI score.

In a prospective, randomised, double blind, placebo-controlled multicentre study, 216 outpatients with presenile and senile dementia of Alzheimer type and VaD received either Ginkgo extract (240 mg/day) or placebo for 24 weeks. The data from the 156 patients who completed psychopathological, attention, memory and behavioural assessment indicated that the groups differed significantly in favour of Ginkgo.\textsuperscript{161} A later retrospective analysis of the ITT data estimated the cognitive performance and social function of patients with dementia.

A later retrospective statistical analysis of this study used intent-to-treat (ITT) evaluation of all 309 patients that began the trial. It concluded that the placebo group showed a statistically significant worsening in all domains of assessment, while the group receiving Ginkgo was considered to be slightly improved on cognitive assessment, daily living and social behaviour. Mean treatment differences favoured Ginkgo, with 1.3 and 0.12 points, respectively, on the ADAS-Cog (p=0.04) and the GERRI (p=0.007). In the group receiving Ginkgo, 26% of the patients achieved at least a 4-point improvement on the ADAS-Cog, compared to 17% with placebo (p=0.04). On the GERRI, 30% of the Ginkgo group improved and 17% worsened, while the placebo group displayed an opposite trend with 37% of patients worsening and 25% improved (p=0.006).\textsuperscript{158}
ADAS-Cog and CGI-2 scores based on measured SKT scores.\textsuperscript{162} After 24 weeks of treatment, the ITT analysis of the SKT and estimated ADAS-Cog scores revealed a mean decrease in the total score by −2.1 (95% CI −2.7 to −1.5) points and −2.7 (95% CI −3.5 to −1.9) points, respectively, for the Ginkgo group, indicating an improvement in cognitive function. In contrast, the placebo group exhibited only a minimal change of −1.0 (95% CI −1.6 to −0.3) and −1.3 (95% CI −2.0 to −0.4) points, respectively. The changes from baseline differed significantly between treatment groups by 1.1 (SKT) and 1.4 (estimated ADAS-Cog) points, respectively (p<0.01). The CGI-2 score favoured the Ginkgo group compared with placebo, with a mean difference of 0.4 points (p=0.007). The results of this ITT analysis reflected the results of the 1996 trial, although such results should be interpreted cautiously, as the estimated ADAS-Cog and CGI-2 scores were reached via a subjective ITT analysis.\textsuperscript{161}

In contrast to the majority of trials displaying efficacy for Ginkgo in attenuating the progression of cognitive decline, a 24-week, randomised, double blind, placebo-controlled, parallel-group, trial involving 214 elderly participants with dementia (AD orVaD) or age-associated memory impairment, demonstrated equivocal results.\textsuperscript{163} Patients were randomly allocated Ginkgo (either 240mg/day or 160mg/day) or placebo after a 3-week placebo run-in. After 12 weeks, the patients in the two Ginkgo groups were randomised to continue Ginkgo treatment or placebo. No statistically significant differences in mean change of scores between Ginkgo and placebo were observed, as assessed via the primary outcomes measures involving the SKT, CGI-2 and the Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living. Although the authors noted there was a positive difference in favour of Ginkgo treatment, neither the dementia subgroup (n=36), nor the age-associated memory impairment subgroup (n=87), achieved a significant effect from Ginkgo treatment. The lack of a positive finding for the results of this methodologically rigorous study could be due to an ‘outlier by chance’, the fact that the study did not use the ADAS-Cog subtest (commonly used in dementia trials), or that this particular sub-population were non-responders to Ginkgo (as detailed in a neurological profile study of Ginkgo by Le Bars in 2003).\textsuperscript{164}

One interesting trial (not included in any of the reviews) examined the impact of a combination of Ginkgo and donepezil. A randomised, double blind, exploratory clinical trial was undertaken to compare Ginkgo against donepezil in patients with confirmed AD also exhibiting neuropsychiatric symptoms.\textsuperscript{165} Patients received either Ginkgo extract (240mg/day for 22 weeks, n=31), donepezil (5mg/day for 4 weeks and then 10mg/day for 18 weeks, n=33) or both treatments (n=32). The presence of neuropsychiatric symptoms was required, as indicated by a minimum score of 3 in at least one item (other than delusions or hallucinations) of the Neuropsychiatric Inventory (NPI) and a total composite score of at least 5. To exclude patients with severe depression, the total score of the 17-item Hamilton Rating Scale for Depression (HAM-D) had to be below 20.

Seven patients dropped out from the trial before week 12 and one after, but only one of these was from the Ginkgo group. At the end of the trial patients were assessed according to the HAM-D, NPI and a battery of cognitive tests assessing memory, attention/concentration, visuospatial abilities, executive functioning and verbal fluency. Activities of daily living and severity of tinnitus and dizziness were also evaluated.

During the 22 weeks of double blind treatment, patients in all three treatment groups showed, on average, improvements over baseline values in all tests and rating scales. No statistically significant or clinically relevant differences could be detected between treatments. However, on the short cognitive performance test (SKT) there was a trend (p=0.08) to greater improvement for the combined herbal and drug treatments. During the trial, 26 adverse events (AEs) were documented for 10 patients (32%) treated with Ginkgo, 51 AEs for 24 patients (73%) taking donepezil and 29 AEs for 18 patients (56%) receiving combined treatment. For three AEs in three patients in the Ginkgo group and 38 AEs in 21 patients in the donepezil group, a causal relationship to the treatment could not be ruled out. Of the AEs reported for the combined treatment group, four events in four patients were considered as possibly related to Ginkgo and 21 events in 14 patients as possibly related to donepezil. For treatment with Ginkgo alone significantly fewer patients suffered from adverse events potentially related to the study medication than under the other treatments (p<0.01). No serious treatment-related AEs were recorded.

The authors concluded that their exploratory findings have helped to develop three hypotheses that will need to be tested in further studies: (1) there is no significant difference in efficacy between Ginkgo and donepezil, (2) a combination therapy will be superior in efficacy to therapy with either one of both substances and (3) there will be fewer side effects for a combination therapy than under therapy with donepezil alone.

The authors noted in their discussion:

Relying on the proven efficacy of donepezil we did not include a placebo group. Estimating the natural deterioration of each patient of our sample using the relationship between deterioration and baseline severity as reported by Stern and co-workers a mean deterioration by 3.61 SKT points would result. The equation found by Stern and colleagues may tend to overestimate the natural progression of disease, but it highlights the fact that the real effect of drug treatment is not just the improvement over baseline, but improvement versus natural deterioration.

In other words, the observed average improvements in SKT scores of 1.8 points for the Ginkgo group and 3.5 points for the Ginkgo plus donepezil group must be added to a natural deterioration of up to 3.6 points over the treatment period. (SKT scores range between 0 and 27, with 27 being the weakest score).

Prevention

Despite its promising pharmacological properties, trials investigating the preventative role of Ginkgo in dementia and cognitive decline have yielded mixed results. A 2005 review concluded that standardised Ginkgo extract is likely to be of similar efficacy to cholinesterase inhibitors in delaying
progression of cognitive impairment in AD. The review compared a trial of standardised Ginkgo extract with eight trials evaluating drugs (rivastigmine, donepezil, galantamine) published to 2000. A 2006 trial tended to confirm this conclusion.

Two trials have investigated standardised Ginkgo extract (240 mg/day) for prevention of dementia in elderly individuals with normal cognition and those with mild cognitive impairment. Ginkgo was not effective, although in one trial a protective effect was found when medication compliance was taken into account (see below).

An earlier nested prospective case-controlled trial in the EPIDOS (EPIDeniology of OSteoporosis) study involving 1462 community-dwelling elderly women aged over 75 years was conducted to determine Ginkgo extract’s efficacy in attenuating cognitive decline over a 7-year period. Pfeiffer’s test was conducted at the start of the study to determine cognitive function, with volunteers being included with a reading of ≥8 (indicating normal cognitive function). A cohort of 714 women with assessed cognitive function was analysed after follow-up. Multivariate analysis including potential confounding factors showed that fewer women developed Alzheimer’s dementia if they had been prescribed pharmacological dementia treatment, including Ginkgo, for at least 2 years (OR 0.31, 95% CI 0.12 to 0.82, p=0.018).

Results for the longest and largest European study for prevention of AD ever conducted are emerging (the GuidAge study). Treatment with standardised Ginkgo extract (240 mg/day) did not significantly delay conversion to clinical disease in the randomised, double blind trial. However, in this ITT analysis, all patients, including those who did not complete the trial, were considered. A further analysis considering patients treated for at least 4 years found a clinically and statistically significant difference for treatment with Ginkgo (1.6% developed AD versus 3.0% in the placebo group). Interestingly the protective effect in this subset was most marked in men: AD incidence was 2.9% for the Ginkgo group versus 7.0% for placebo (p=0.007). The compliance rate for those who continued in the study was 93%.

However, the preventative study that received the most media attention was the GEM (Ginkgo Evaluation of Memory) trial. This study was designed as a dementia prevention trial and the final results were published in the Journal of the American Medical Association (JAMA) in 2008. The study failed to find any preventative effect for Ginkgo, but has been criticised because of the advanced age of participants (72 to 96 years), the relatively short treatment time (about 6 years) and the poor patient compliance with the treatment (only about 60%), which was 240 mg/day of Ginkgo extract.

In late 2009 a secondary analysis of the original GEM data was again published in JAMA. In this analysis, the impact of Ginkgo on cognitive decline among the participants in the GEM study was assessed. No benefit was found for Ginkgo.

A considered examination of the study design and results readily shows that they were not suitable to support any conclusions about the impact of regular Ginkgo intake on cognitive decline. There were five major weaknesses in the second published study:

- It was not originally designed to assess cognitive decline, hence for about the first 4 of the 6 years of treatment most participants were only assessed by very basic dementia scales, such as the MMSE, which are neither sensitive nor accurate measures of cognitive function.
- There was a very high dropout rate over the course of the study (approximately one-third) and yet the ITT analysis used would have included these dropouts as non-responders.
- There was poor compliance with the Ginkgo (as noted earlier), with only about 60% of participants actually taking the tablets regularly.
- The participants were of an advanced age (average 79 years at the beginning of the trial) and hence might not represent the effects of Ginkgo on cognition in younger people.
- Despite their high age, trial participants showed only a very low rate of cognitive decline in both the Ginkgo and placebo groups: the rate was in fact seven times slower than the reference rate used by the authors to plan their study. It would be very difficult for any active treatment to realistically impact a rate of cognitive decline that was already seven times lower than the typical norm for that age group.

A prospective, cohort study conducted in Vienna from 2000 to 2002 examined 526 individuals without dementia aged 75 years to investigate the influence of medication on plasma levels of amyloid beta protein 42 (Abeta42). Plasma Abeta42 levels are elevated in both late onset AD patients and their cognitively normal first-degree relatives. Users of Ginkgo for at least 2 years had significantly decreased Abeta42 plasma levels compared with non-users. This reduction was also independent of medial temporal lobe (brain) atrophy, as assessed by MRI scanning. At follow-up 2.5 years later, longer use of Ginkgo seemed to decrease plasma Abeta42 levels to a greater extent than shorter use. There was a weak association of Ginkgo use with the ability to remain cognitively healthy for the observation period.

Peripheral arterial disease

A 2004 systematic review of randomised, double blind, placebo-controlled clinical trials in patients with peripheral arterial occlusive disease (intermittent claudication) in stage II (according to Fontaine) treated with Ginkgo extract suggested positive benefit. Nine studies were found to be eligible for review. Although the methodological quality and design of the trials were heterogeneous, the majority of the studies reflected an advantage of Ginkgo in the increase of pain-free walking distance compared with placebo. For seven studies, the advantage was found to be statistically significant.

An earlier 2000 meta-analysis of eight randomised, placebo-controlled, double blind trials observed a statistically significant difference in the increase in pain-free walking distance in favour of Ginkgo extract compared with placebo (weighted mean difference 34 m, 95% CI 26 to 43 m). In studies with similar methodological features (ergometer speed 3 km/h, inclination 12%) this difference was 33 m in favour of Ginkgo (95% CI 22 to 43 m). Although the effect size
was considered by the authors as modest, the results of the meta-analysis supported the use of Ginkgo in the treatment of intermittent claudication.

In placebo-controlled trials published since the 2004 review, standardised Ginkgo extract:

- produced a modest, but not statistically significant, increase in maximal walking time (300 mg/day)\(^{178}\)
- did not provide additional benefit when combined with supervised exercise training (240 mg/day).\(^{179}\)

A 2009 meta-analysis of randomised trials (those mentioned above, including from the 2004 review) conducted by the Cochrane Collaboration concluded that there was no evidence that Ginkgo has a clinically significant benefit for patients with peripheral arterial disease. People using standardised Ginkgo extract could walk 64.5 m further, which was not considered to be significant in comparison with the placebo group.\(^{180}\)

A standardised Ginkgo extract (360 mg/day) was assessed in the treatment of Raynaud’s disease. In a 2-week assessment period, 22 patients recorded the frequency, severity and duration of attacks in diaries. Patients were then randomised to active or placebo treatments for 10 weeks, during which time ischaemic attacks were recorded in their diaries. The number of ischaemic attacks per day was significantly reduced after Ginkgo treatment versus placebo (56% versus 27%, respectively, p<0.00001). The mean duration of attacks reduced from 28 min pre-treatment to 17 min in the placebo intervention and to 10.3 min after Ginkgo administration.\(^{181}\)

Many doctors in South Korea prescribe Ginkgo extract for primary Raynaud’s disease. A clinical trial found patients treated for 8 weeks with slow release nifedipine showed a 50% improvement in the rate of attacks, and those treated with Ginkgo extract (120 to 240 mg/day) showed a 30% improvement.\(^{182}\) Hence the drug was more effective.

Addition of Ginkgo extract to existing and/or local treatment healed an ischaemic ulcer in a man with peripheral arterial disease (120 mg/day, case report),\(^{183}\) and significantly decreased the ulcer area in patients with chronic leg ulcers (160 mg/day, randomised controlled trial).\(^{184}\)

### Other vascular disorders

When the standardised extract of Ginkgo was developed by German scientists in the 1960s, the original therapeutic focus was on improving peripheral circulation to the legs and the brain. Later the neuroprotective effects of Ginkgo were recognised and it became an important herbal treatment to boost brain function and provide a benefit in AD. Always missing from the scenario was any potential impact of Ginkgo on heart function, especially in the prevention of heart disease. Given its known circulatory effects and its capacity to help body tissues survive a poor oxygen environment, it is likely that Ginkgo would exert some benefit here. Now some preliminary studies are suggesting that such a benefit might be unexpectedly profound.

A German and Swedish research team conducted an open label pilot trial in eight patients who had undergone coronary bypass surgery.\(^{185}\) They examined the impact of Ginkgo extract (240 mg/day) for 2 months on the capacity of blood samples to form nanoplques. Nanoplques are considered to be the very first stage of degeneration of the arterial wall that leads to atherosclerosis and eventually heart disease. In the case of bypass patients, the tendency to nanoplaque formation can determine how quickly the replacement blood vessels will become diseased.

The reduction in nanoplaque formation from the Ginkgo solution amounted to 11.9±2.5% (p<0.008) and nanoplaque size was reduced by 24.4±8.1% (p<0.023). Given these marked findings, the authors suggested that Ginkgo could be regularly consumed by heart patients as a complement to statin drugs to help prevent the redevelopment of atherosclerotic plaque following bypass surgery. They stressed that its mechanism of action and effects were unlike statin drugs.

But perhaps a more significant finding was the Ginkgo treatment lowered lipoprotein(a) by 23.4±7.9% (p<0.023). In a subsequent letter to the editor, another research group highlighted that this might represent a clinically remarkable outcome. This is because no conventional therapeutic approach has been identified so far capable of efficiently and safely lowering the plasma concentration of this intriguing lipoprotein.\(^{186}\)

Lipoprotein(a) is considered to be a significant independent cardiovascular risk factor.\(^{187,188}\) Despite this, it has not received much research attention until recently, presumably because there are no available drugs that can influence its levels. Attention has been on LDL-cholesterol (low-density lipoprotein cholesterol) and the statin drugs that lower this.

In the pilot study the Ginkgo treatment also upregulated superoxide dismutase (SOD) activity by 15.7±7.0% (p<0.039) and lowered the percentage of oxidised LDL by 17.0±5.5% (p<0.023). The authors concluded that the atherosclerosis-inhibiting effect of Ginkgo is possibly due to an upregulation of the body’s own radical scavenging enzymes (perhaps via the Nh2/ARE pathway) and a reduction in the risk factors of oxidised LDL and lipoprotein(a).

A letter to the editor on the study mentioned above suggested that the reduction in lipoprotein(a) might represent an anti-inflammatory effect, especially a reduction in IL-6 (interleukin-6).\(^{189}\) In response, the authors agreed with this possibility, but also stressed that a reduction in levels of reactive oxygen species might also play a role.\(^{189}\)

Continuing with the theme of Ginkgo coming into prominence as a herb for the heart, Chinese research is moving in this direction. In a clinical study in patients with coronary artery disease, Ginkgo extract (via injection) significantly improved distal left anterior descending (LAD) coronary blood flow.\(^{190}\) A similar trial in healthy elderly adults also observed an improvement in LAD blood flow.\(^{191}\) In both cases the increased response was proposed to result from an improved endothelium-dependent vasodilatory capacity, which is regulated by the enhanced release of nitric oxide.

The beneficial effects of Ginkgo on nanoplaque formation were investigated in a second observational trial involving 11 patients with metabolic syndrome.\(^{192}\) After 2 months of treatment with Ginkgo extract (240 mg/day), nanoplaque formation and nanoplaque size were reduced by 14.7% and 21.5% respectively. These results were highly statistically significant.
Ginkgo lowered the percentage of oxidised LDL (by 21.0%), lowered lipoprotein(a) concentration (by 26.3%) and upregulated the activities of SOD and glutathione peroxidase (19.6% and 11.6%, respectively).

An extensive range of other biomarkers were measured, which led the authors to conclude that the atherosclerosis-inhibiting effect of Ginkgo can be attributed to:

- a stimulation of radical scavenging enzymes in the body
- a restriction of certain risk factors (lipoprotein(a), percentage of oxidised LDL)
- an increase in nitric oxide/cyclic GMP release (having a vasodilatory effect).

Interestingly, treatment with Ginkgo resulted in a significant increase in both mean corpuscular haemoglobin levels and concentration. In conjunction with the observed vasodilation, this will result in improved oxygen supply and enhanced organ perfusion.

In an earlier double blind, placebo-controlled trial, 15 patients undergoing aortic valve replacement (in cardiopulmonary bypass) received either Ginkgo extract (320 mg/day) or placebo for 5 days before surgical intervention. Plasma samples taken at crucial stages of the operation indicated that Ginkgo limited free radical-induced oxidative stress generated throughout the surgery. Recovery of the Ginkgo patients was improved (but not significantly) compared with placebo, and Ginkgo was considered useful in limiting oxidative stress. The protective activity was attributed to a membrane-protective mechanism rather than a direct scavenging effect. Earlier in vitro and in vivo studies suggest the cardioprotective effects of the Ginkgo terpenoids involve an inhibition of free radical formation rather than direct free radical scavenging.

In an early uncontrolled trial, 20 outpatients with a long history of elevated plasma viscosity and fibrinogen levels and a variety of underlying diseases received 240 mg/day Ginkgo extract for 12 weeks. Steady and significant reductions in fibrinogen levels and blood viscosity were observed over the treatment period.

A short-term 7-day, crossover, placebo-controlled, double blind study found that Ginkgo extract (240 mg/day) had no impact on blood pressure, heart rate or electrocardiographic variables in young, healthy volunteers.

### Ear, nose, throat problems

Ginkgo extract is the most clinically tested herbal therapy for disorders involving the ear. However, results from clinical trials have not always been consistent.

#### Hearing loss

Deafness of sudden onset (acute cochlear deafness) is often due to ischaemia of the cochlea and the metabolic derangement that accompanies this. The first study on the use of Ginkgo in acute cochlear deafness was published in 1986. The author suggested that prognosis in acute cochlear deafness is entirely dependent on the rapid initiation of an effective treatment. Hence a relatively high dose of Ginkgo extract of 320 mg/day was employed in the study. The efficacy of Ginkgo was compared to nicergoline, an alpha-adrenoreceptor blocker, and the study involved 18 patients in a double blind design over 30 days. Audiometric analyses and labyrinth tests demonstrated that all of the patients in the Ginkgo group had normal values at the end of the trial, whereas one-third of the patients in the nicergoline group still had inconclusive tests. The significance of this trial was hampered by the small patient numbers.

In another trial, Ginkgo extract (intravenous 200 mg/day for 9 days, followed by oral 160 mg/day for 6 weeks) was found to be superior to the drug piracetam for the treatment of sudden deafness (one-sided hearing loss). Median values for hearing thresholds in the range 250 to 3000 Hz were significantly lower with Ginkgo treatment.

In a randomised comparative study, 80 patients with idiopathic sudden hearing loss of no longer than 10 days were treated with either Ginkgo extract or naftidrofuryl (a vasodilator). After 1 week, 40% of patients in each group experienced a complete remission. After 3 weeks there was a significant borderline benefit for Ginkgo over naftidrofuryl. Ginkgo treatment was preferred due to a lack of side effects, unlike the naftidrofuryl.

A study conducted in India examined the value of Ginkgo extract against a combined drug treatment for acquired sensorineural hearing loss in 52 patients. Probable aetiologies included presbycusis (36.5%), followed by unknown causes (28.8%). Outcomes for Ginkgo were better than the conventional treatment in responding patients. Response rates were similar between the two treatments.

In a relatively large trial involving 106 patients, the efficacies of two different dosages of Ginkgo for unilateral idiopathic sudden hearing loss were compared in a randomised, double blind design. The higher dose of Ginkgo (240 mg/day) appeared to accelerate and secure the recovery of patients, with a good chance for complete recovery (p=0.006). Positive results were observed after 1 week of treatment.

In a randomised, prospective, double blind study involving 72 patients, the therapeutic efficacy of Ginkgo extract (n=37) was compared with pentoxifylline (n=35) for the treatment of sudden deafness. The dose of Ginkgo extract was 200 mg/day via intravenous infusion. The two treatments were equally well tolerated and showed a statistically significant equivalence in terms of either improvement or a return to normal of the auditory thresholds. Subjective assessment of the treatment (with regard to improvement in hearing and reduction in tinnitus) suggested that Ginkgo extract was more beneficial than pentoxifylline.

#### Vestibular disorders

Most of the trials assessing the value of Ginkgo in vertigo date to the 1980s, although there is one trial of more recent origin. In one early trial, which had an open phase with Ginkgo extract followed by a double blind, placebo-controlled phase, results were compiled for 50 patients complaining of dizziness. These results showed a clear benefit for Ginkgo in the open phase as well as over the placebo, except for patients with Ménière’s disease.
A randomised, placebo-controlled, double blind trial in 35 patients assessed the value of Ginkgo extract at 160 mg/day for vestibular vertigo.\textsuperscript{204} The primary outcome measured was performance using posturography (assessment of body sway with eyes open or closed) and there was a statistically significant benefit from baseline observed for therapy with Ginkgo, which was also superior to placebo.

A study conducted in three centres included 70 patients with vertigo of recent and idiopathic onset in a double blind, placebo-controlled trial.\textsuperscript{205} The efficacy of Ginkgo extract (160 mg/day) on both the frequency and duration of vertigo achieved statistical significance, with 47% of patients in the Ginkgo group free of symptoms at the end of the trial compared with 18% for the placebo group (p<0.05).

A trial conducted in Poland compared Ginkgo extract plus physical therapy against physical therapy alone for the treatment of vestibular organ peripheral lesion syndrome in an open label design.\textsuperscript{206} Patients in both groups improved, but improvement was more marked and faster, as assessed by dynamic posturography, for the group receiving Ginkgo.

A 2007 systematic review of randomised, double blind clinical trials identified five studies (including those reviewed above) and concluded that Ginkgo extract (120 to 240 mg/day) was a beneficial treatment for vestibular and non-vestibular vertigo (see also below).\textsuperscript{207}

**Tinnitus or combined syndromes**

After vertigo, nausea and hearing loss, tinnitus is one of the most important symptoms in the field of disorders of the ear. In most cases the origin of the tinnitus is not identifiable, although it is recognised that it can arise in any part of the hearing pathway. It is frequently associated with vertigo, nausea and hearing loss. An age predominance exists and identifiable causes include presbycusis, atherosclerosis, chronic otitis media, otosclerosis, acoustic trauma, Ménière’s disease and ototoxicity. Given such a wide range of causes, known and unknown, it is likely that clinical trials in this field will be fraught with difficulties and prone to conflicting results. This is certainly the case for trials involving Ginkgo treatment.

Since the pathophysiology and treatment of tinnitus is still under debate and is relatively obscure, it is likely that Ginkgo may assist in the treatment of specific sub-populations of tinnitus sufferers. The difficulty is determining potential responders to Ginkgo treatment.

An early trial conducted in 1979 included 60 patients with hearing loss and/or vertigo and tinnitus.\textsuperscript{208} Ginkgo extract (120 mg/day) was compared with nicergoline and found to be superior. Another early open design trial found good efficacy for Ginkgo extract in patients with hearing impairment and tinnitus due to a variety of causes, mainly involving ischaemia.\textsuperscript{209}

In 1986 Meyer conducted a defining study on 103 patients that clearly established a reputation for Ginkgo in the treatment of tinnitus (deserved or otherwise).\textsuperscript{210} A randomised, double blind, placebo-controlled trial with Ginkgo extract included only patients with tinnitus of recent onset (less than one year). Improvement or cure was observed after an average of 70 days in patients treated with Ginkgo compared with 119 days in patients receiving placebo. Tinnitus of recent onset, unilateral and intermittent seemed to be particularly responsive to Ginkgo.

Soft laser therapy in combination with Ginkgo for the treatment of tinnitus was found to be effective in one open trial\textsuperscript{211} and ineffective in another.\textsuperscript{212} In a double blind, placebo-controlled trial involving 100 elderly patients (with at least four symptoms out of poor memory, anxiety, vertigo, tinnitus and headaches), therapy with Ginkgo extract (112 mg/day) or placebo was assessed after 12 weeks.\textsuperscript{213} Improvement in tinnitus from baseline was 37% for the Ginkgo group versus 12% for the placebo group.

The 20 patients reporting a positive effect on persistent severe tinnitus in an open study involving 80 patients were included in a double blind placebo-controlled crossover study.\textsuperscript{214} They received either Ginkgo extract (29.2 mg/day, 2 weeks) or placebo. The success of the treatment was based on patient preference (as there is no objective measurement) and on this basis Ginkgo did not demonstrate a significant effect. However, the dose of Ginkgo extract used was subtherapeutic.

A study published in the BMJ found no advantage for Ginkgo extract (150 mg/day) in treating tinnitus in a double blind, placebo-controlled trial using postal questionnaires in 1121 healthy people with a comparatively stable condition.\textsuperscript{215}

In contrast, a trial involving 60 patients with chronic tinnitus observed a positive result for Ginkgo extract (200 mg/day by intravenous infusion for 10 days followed by oral therapy of 160 mg/day) compared with placebo after 12 weeks of therapy.\textsuperscript{216} While results achieved statistical significance, the absolute difference between the two treatment groups was only moderate.

A systematic search of the literature identified 19 clinical trials (many early) investigating the effect of Ginkgo extract on tinnitus.\textsuperscript{217} The results of eight controlled studies were found for the most part to show a statistically significant superiority of Ginkgo extract over placebo or reference drugs. Tinnitus of recent onset had a better prognosis.

A 12-week randomised, double blind trial of Ginkgo extract (120 mg/day, slow release tablet) involving 66 patients with tinnitus was conducted with Tinnitus Handicap Inventory (THI), Glasgow Health Status Inventory (GHSI) and average of hearing threshold at 0.5, 1, 2, 4 kHz being used as the outcome measures.\textsuperscript{218} Results showed that the mean difference in changes of the THI, GHSI and hearing between Ginkgo (n=31) and placebo (n=29) were 2.51 (CI −10.1 to 5.1, p=0.51), 0.58 (CI −4.8 to 3.6, p=0.38) and 0.68 dB (CI −4.13 to 2.8, p=0.69), respectively, indicating no statistically significant difference between Ginkgo and placebo. The researchers conducted and published a meta-analysis in the same paper of five previously conducted studies. Meta-analysis revealed 21.6% of Ginkgo-treated patients (107 of 552) gained benefit versus 18.4% (87 of 504) of placebo-treated patients with an odds ratio of 1.24 (CI 0.89 to 1.71) indicating only a small benefit.\textsuperscript{219}

A 2004 Cochrane systematic review of Ginkgo in the treatment of tinnitus was conducted to determine evidence of efficacy.\textsuperscript{218} Although 12 trials were initially located, 10
were excluded from the review on methodological grounds. The interventions assessed were Ginkgo versus placebo, with no ‘gold standard’ treatment available for an active control. Most studies involved a dosage of 120 to 200 mg/day of standardised Ginkgo extract, using outcome measures such as changes in loudness of tinnitus, severity and impact on quality of life. The exclusion of 10 of the studies was due to a variety of methodological failings, including a high drop-out rate, cohort number reporting and concealment, and unsatisfactory rating scales. After a later update, another acceptable study was located and three randomised placebo-controlled studies were included. One was a 12-week trial involving 99 patients given 120 mg/day Ginkgo extract that demonstrated improvement in the sound volume (5 to 10 dB) of the ear with the worst tinnitus in the Ginkgo group, while the placebo group remained unchanged. The other two studies have been reviewed above. The Cochrane review concluded that limited evidence does not demonstrate Ginkgo was effective for tinnitus.

Part of a double blind, placebo-controlled trial of Ginkgo extract in dementia investigated effects on dizziness and tinnitus. The trial involved outpatients aged 50 years or older with mild-to-moderate dementia with neuropsychiatric symptoms. After receiving Ginkgo extract (240 mg/day) for 22 weeks, the mean severity score for dizziness improved from 4.35 to 2.09 and the severity score for tinnitus decreased from 4.02 to 1.91. There were only slight improvements in the placebo group, from 4.22 to 3.88 for dizziness and from 3.90 to 3.75 for tinnitus. Dizziness was improved in 86% of Ginkgo recipients and in 28% of the placebo group. Improvement rates for tinnitus were 84% of the Ginkgo-treated patients versus 20% of the placebo group. The differences were significant between Ginkgo and placebo on all measures (p<0.001).

Since hypercholesterolaemia might promote the development of tinnitus, a retrospective study was performed to assess whether simvastatin might impact this disorder. Remission rates in 58 patients were investigated after 4 months of simvastatin (40 mg/day) and compared to results for Ginkgo (120 mg/day) in 36 patients as a control group. Only small reductions in tinnitus scores were observed in both groups, casting doubt on the efficacy of either treatment.

In an address to Australian clinicians in September 2007, a spokesperson of the European Federation of Tinnitus Associations advised that European doctors had a high degree of success treating tinnitus with standardised Ginkgo extract. It is most successful if administered within the first 3 months of onset, and a dose of 240 mg/day was recommended.

Olfactory disorders

Seventy-one patients who were diagnosed with postviral olfactory loss participated in a randomised trial conducted in South Korea. Patients did not have sinus inflammation, nasal discharge, allergic rhinitis or chronic rhinosinusitis. They were treated with oral prednisolone (2 weeks) or oral prednisolone (2 weeks) plus Ginkgo extract (240 mg/day, 4 weeks). All patients could take two puffs of mometasone furoate (a corticosteroid) nasal spray per nostril twice daily for 4 weeks. Olfactory function tests, including the butanol threshold test (tests odour threshold) and the cross-cultural smell identification test (CCSIT, tests odour identification) were performed at baseline and after treatment.

Although not statistically different between the two groups, the addition of Ginkgo showed a tendency toward greater efficacy (for example, for CCSIT response rate p=0.08). The results of CCSIT are considered more relevant, as odour identification is a more complex and higher-level olfactory function than odour threshold.

Eye disorders

As Ginkgo exerts vascular protective, antioxidant and circulatory enhancing activity, it is posited that it can have a therapeutic role in treating age-related macular degeneration. A 2000 Cochrane review was conducted evaluating its efficacy in treating macular degeneration. Two studies were identified by the review. A trial involving 20 people found that visual acuity improved in Ginkgo treated patients more than the control over a 6-month period. The other study reviewed tested the visual acuity of 99 participants with macular degeneration, finding no statistical difference between the low-dose (60 mg/day) and high-dose (240 mg/day) Ginkgo groups. Further work is needed in this area, given that these trials did indicate some benefits.

A US research team evaluated a possible therapeutic effect of Ginkgo extract that might benefit glaucoma patients through improvement in ocular blood flow. A phase I crossover trial of Ginkgo with placebo control in 11 healthy volunteers was performed. Patients were treated with either Ginkgo extract (120 mg/day) or placebo for 2 days. Colour Doppler imaging was used to measure ocular blood flow before and after treatment. There was a 2-week washout period between Ginkgo and placebo treatments. Ginkgo extract significantly increased end diastolic velocity in the ophthalmic artery (baseline versus Ginkgo treatment; 6.5±0.5 versus 7.7±0.5 cm/sec, 23% change, p=0.023), with no change seen in placebo (baseline versus placebo; 7.2±0.6 versus 7.1±0.5 cm/sec, 3% change, p=0.892). No side effects related to Ginkgo were found. Ginkgo extract did not alter arterial blood pressure, heart rate or intraocular pressure. The authors concluded that the extract deserves further investigation for possible application in the treatment of optic neuropathy linked to glaucoma as well as other ischaemic ocular diseases.

Significant improvements in visual field indices, but not intraocular, pressures were recorded in a randomised, double blind, placebo-controlled trial involving patients with normal tension glaucoma (a form of primary open-angle glaucoma). Patients received standardised Ginkgo extract (120 mg/day) for 4 weeks. Beneficial results with Ginkgo were demonstrated in another controlled trial of the same disorder, with tests conducted over a period of at least 4 years.

Ginkgo extract (80 mg/day) for at least 6 months did not improve visual field indices in patients with primary open-angle glaucoma. In this trial, treated patients were retrospectively matched with control patients.
In earlier research in 24 patients suffering from blockage of veins in the retina, Ginkgo extract produced improvements in blood vessels, visual acuity and field of vision in a double blind, placebo-controlled trial. Where the blood supply to the retina was deficient, Ginkgo improved many aspects of vision such as near and far vision, colour recognition and field of vision.\textsuperscript{231} In an uncontrolled trial, 35 patients with poor blood supply to the retina, or to those parts of the brain that interpret the signals from the eyes, were treated with Ginkgo extract (120mg/day) over a 3-month period; 86% of patients with reduced vision improved markedly.\textsuperscript{234}

Two open label studies demonstrated that standardised extract of Ginkgo (120 to 240mg/day for 3 months) reduced the abnormal blood parameters seen in diabetic retinopathy including a decrease in lipid peroxidation,\textsuperscript{235,236} a decrease in clotting factors and red blood cell deformity, and improved blood viscosity and elasticity, resulting in improved retinal capillary blood flow rate.\textsuperscript{236}

A total of 60 patients with symptomatic allergic conjunctivitis were enrolled and randomly assigned to 15 days of treatment with Ginkgo and hyaluronic acid (GB-HA) eye drops or hyaluronic acid ophthalmic solution (HA) alone for 1 month.\textsuperscript{237} Clinical symptoms such as conjunctival hyperaemia (redness), conjunctival discharge and chemosis (swelling or oedema of the conjunctiva), and subjective signs as itching, photophobia, stinging and lacrimation were evaluated before and after the treatment. Patients treated with GB-HA, compared with patients treated with HA alone, showed a significant decrease in the appearance of conjunctival hyperaemia, conjunctival discharge and chemosis. Hyperaemia was particularly responsive to the GB-HA eye drops, dropping by 85%. In addition, all patients treated with GB-HA showed a significant improvement in subjective symptoms. Itching was substantially reduced.

**Psychiatric and learning disorders**

Although Ginkgo is commonly used to treat dementia, cognitive decline, peripheral arterial disease and tinnitus, studies have noted that mood modulation can also occur in cognitively impaired patients. A 2006 randomised, double blind trial (n=107) was conducted using Ginkgo extract (480mg or 240mg/day) or placebo for 4 weeks in adults with general anxiety disorder or adjustment disorder with anxious mood as assessed via DSM-III-R.\textsuperscript{238} ITT analyses were performed on the primary outcome measure the Hamilton anxiety scale (HAMA-A), and the secondary outcome measures, the CGI, the Erlangen anxiety tension and aggression scale and the patient’s global rating of change. The patients’ HAM-A total scores decreased by $-14.3$ ($\pm 8.1$), $-12.1$ ($\pm 9.0$) and $-7.8$ ($\pm 9.2$) in the 480mg/day Ginkgo group, the 240mg/day Ginkgo group and the placebo group, respectively. Results indicated dose-dependent anxiolysis compared with placebo (p=0.0003 in the higher-dose group, p=0.01 in the lower-dose group).

A methodologically rigorous 10-week pilot study involving 27 adults assessed whether a Ginkgo extract may prevent the symptoms of winter depression in patients with seasonal affective disorder.\textsuperscript{239} Results demonstrated that Ginkgo did not prevent the seasonally provoked depressive symptoms as assessed via an extended Montgomery-Asberg Depression Rating Scale and various self-assessed key symptoms on a visual analogue scale.

A systematic review and meta-analysis of the role of Ginkgo as an adjunct therapy in chronic schizophrenia found six clinical trials published between 1996 and 2008 comprising a total of 828 patients.\textsuperscript{240} Five of the trials were placebo-controlled and the dose of Ginkgo extract ranged from 120 to 360mg/day. The trials lasted from 8 to 16 weeks, with four being conducted in East Asia and the remainder in Eastern Europe. Ginkgo treatment was combined with the following drugs: chlorpromazine, haloperidol, olanzapine and clozapine.

All trials used the Scale for the Assessment of Negative Symptoms to measure negative symptoms, and the Scale for the Assessment of Positive Symptoms or the Brief Psychiatric Rating Scale to measure total symptoms. The difference between Ginkgo and control groups from their pre- and post-trial scores and the pooled standard deviation were used to compute the standardised mean difference (SMD). Ginkgo as an add-on therapy to antipsychotic medication produced a statistically significant moderate improvement (SMD=-0.50) in total and negative symptoms associated with chronic schizophrenia. The authors concluded that Ginkgo has a statistically significant moderate therapeutic benefit with acceptable safety limits as an add-on therapy for chronic schizophrenia, but that more research is needed, especially in terms of its potential interactions with psychotropic drugs.

Ginkgo extract improved word recognition and reading in children with dyslexia (80mg/day, pilot trial),\textsuperscript{241} and improved cognitive function and social behaviour in children with Down syndrome (80 to 120mg/day, two cases).\textsuperscript{242} Ginkgo extract (200mg/day) improved behaviour, hyperactivity, inattention and immaturity in six young adults with attention deficit hyperactivity disorder (ADHD).\textsuperscript{243} In an open trial, 56% of ADHD children improved with Ginkgo treatment.\textsuperscript{244} However, Ginkgo was not as effective as methylphenidate in a randomised, double blind trial conducted in Iran.\textsuperscript{245}

**Asthma and PAF-related disorders**

Platelet activating factor (PAF) is a phospholipid formed by platelets, basophils, neutrophils, monocytes and macrophages. Anti-PAF activity is regarded as useful in the treatment of asthma, allergic reactions, immunological reactions, shock, ischaemia and thrombosis.

Ginkgo extract protected asthmatic patients exposed to challenge with an inhaled allergen (600mg single dose pre-treatment; uncontrolled trial).\textsuperscript{23} It also improved asthma in adults, some of whom were able to stop corticosteroid therapy, and normalised pulmonary function in children with atopic asthma, which was correlated with a significant improvement in flow parameters (uncontrolled trial).\textsuperscript{24} Compared with those treated only with inhaled corticosteroid, addition of Ginkgo extract (oral, 240mg/day) for 4 weeks decreased airway inflammation in asthmatic patients in a trial conducted in China.\textsuperscript{246} In a placebo-controlled trial, also from China,
concentrated Ginkgo leaf liquor reduced airway hyper-reactivity, improved clinical symptoms and pulmonary function in asthmatic patients.247,248

Treatment with Ginkgo leaf tablets for 3 months significantly lowered elevated serum PAF levels in chronic hepatitis B patients. Indices of liver fibrosis were also significantly lowered. The daily dose of Ginkgo provided 86.4 mg/day of ginkgo flavonol glycosides and 21.6 mg/day of ginkgolides. A control group received a tablet containing mostly silybin, at a daily dose of 315 mg/day. Ginkgo treatment was deemed superior to the control.249

**Acute mountain sickness**

Two randomised, double blind, placebo-controlled clinical trials were undertaken to assess the efficacy of 240 mg/day of two different Ginkgo standardised extracts in reducing the incidence and severity of acute mountain sickness (AMS) following rapid ascent to a high altitude.250 The trial was conducted at Pike’s Peak in Colorado, which has over 300,000 visitors a year who rapidly ascend from 2000 to 4300 m in 2 h via train or car. As might be expected, many of these visitors experience AMS, which includes symptoms such as extreme shortness of breath (due to pulmonary oedema) and confusion (due to cerebral oedema) in its more severe manifestations. Symptoms associated with mild-to-moderate AMS include difficulty sleeping, dizziness, fatigue, headache, loss of appetite, nausea, rapid pulse and shortness of breath with exertion. The cause is unknown, although theories implicating oxidative stress have been suggested.251 The drug acetazolamide is used as a preventative treatment, but is not tolerated by some people and is associated with side effects such as nausea and paraesthesia.

An oral dose of 120 mg of Ginkgo or placebo was self-administered by participants twice per day, morning and evening, for 4 days (study 1) or 3 days (study 2) prior to ascent and during 24 h at altitude, for a total treatment time of 5 days in study 1 and 4 days in study 2. Results were conflicting: Ginkgo significantly reduced the incidence and severity of AMS in study 1 but not in study 2 (p = 0.027 versus p = 0.247 for incidence, p = 0.029 versus p = 0.272 for severity, respectively). The authors suggested that despite the weaknesses in their study design, which included low patient numbers (40 in study 1 and 37 in study 2), differing pretreatment times (4 versus 3 days) and a greater placebo effect in study 2, the main reason for the observed difference between the two studies was the source of Ginkgo. The extract used in study 1 contained a much higher level of ginkgolides A, B and C than the one used in study 2, even though the total level of terpene lactones was similar at around 6.5%. They concluded that the source and composition of the Ginkgo extract may determine the efficacy of Ginkgo for the prevention of AMS.250

This study adds to the controversy around using Ginkgo for the prevention of AMS, a controversy that was highlighted by the same authors when they published a review of all the other Ginkgo trials in this context.251 From this review it was concluded that, given the mixed results, more studies are required in AMS, especially focusing on what is active in Ginkgo extracts.

**Cognitive function**

A review published in 2009 sought to find differential effects for the cognition-enhancing activity of standardised Ginkgo extract.252 Included in the analysis were 29 randomised, double blind, placebo-controlled studies of chronic (greater than 4 weeks) administration providing data on function-specific cognitive tests in healthy and cognitively impaired volunteers of any age. (Some of the trials in this review are also covered individually or by review below.) Objective psychometric test results were examined for four cognitive domains (memory, attention, executive functions, intelligence) comprising 14 subfunctions (for example, for the domain of memory, the subfunctions were short- and long-term, visual and verbal memory). There was consistent evidence found from studies investigating mild cognitive impairment, depression, multiple sclerosis and healthy young and elderly volunteers that Ginkgo improves selective attention, some executive processes (working memory, cognitive flexibility) and long-term memory for verbal and non-verbal (visual) material. Little specific information could be obtained from trials for treatment of dementia. Except for one trial, standardised extract providing 24% to 25% ginkgo flavonol glycosides and 6% terpenoids was administered. Daily doses ranged from 80 to 240 mg/day, with 120 mg/day the most common dosage (14 trials). The reviewers suggested that future trials should be more comprehensive and use psychometric standards to evaluate cognitive function. A lack of investigation of some functions (such as divided attention, an early feature of AD) tends to penalise Ginkgo and make it difficult to identify its strengths and weakness in terms of functions sensitive to its influence.

However, a systematic review that assessed clinical research to January 2007 concluded that standardised Ginkgo extract did not have a beneficial effect on cognitive function in healthy people under the age of 60 years. The review assessed randomised clinical trials in which Ginkgo was ingested as a single dose (seven trials) or over longer periods of time (eight trials, ranging from 2 days to 12 weeks).253

One placebo-controlled trial not included in this review measured the effect of Ginkgo (240 mg/day for 4 weeks) on vision-related neural function using electroencephalography in healthy adults aged from 41 to 83 years. No effect was found on the lower level physiological function of the visual system, but significant improvement was found when assessing higher order neural changes. The higher order visual system relies on additional cognitive processing, and may include cognitive aspects such as attention, recognition and memory.254 Other key trials are reviewed below.

To elucidate the mechanism of clinical benefit of Ginkgo in the treatment of symptoms of impaired brain function in advanced age, its effect on cognitive information processing was investigated by means of long-latency auditory event-related potentials (P300). In a double blind, placebo-controlled study, 48 elderly patients with age-associated memory impairment received 120 mg/day of Ginkgo extract or placebo for 57 days. P300 latency was shortened in the Ginkgo group and this may reflect shorter stimulus-evaluation times.255

A 12-week, double blind, placebo-controlled study assessed the effects of Ginkgo extract (120 mg/day) on a wide range of
A short-term double blind, placebo-controlled design involved 98 men and 132 women (>60 years of age) in general good health with MMSE scores greater than 25. Participants were randomly assigned to receive a standardised Ginkgo extract (120mg/day, n=20) or placebo (n=20) for a 6-week period. After 6 weeks of treatment, there were no significant effects of Ginkgo on mood or any of the cognitive tests, with the authors commenting that tolerance may develop in young healthy people with normal cognition. A 4-week, randomised, double blind, placebo-controlled, parallel-group, monocentric study involving 66 healthy volunteers (aged 50 to 65 years) testing Ginkgo extract (240mg/day) revealed that self-estimated quality of life significantly favoured Ginkgo treatment. A 6-week randomised, double blind, placebo-controlled, parallel-group trial was conducted involving 98 men and 132 women (>60 years of age) in general good health with MMSE scores greater than 25. Participants were randomly assigned to receive a standardised Ginkgo extract (120mg/day, n=115), or matching placebo (n=115) and were evaluated by a variety of cognitive outcome measures. Analysis of the modified ITT population of 219 participants indicated that there were no significant differences between treatment groups on any cognitive outcome measures as assessed via standard neuropsychological tests of learning, memory, attention, concentration and verbal fluency. A double blind, placebo-controlled study testing the acute effects of Ginkgo extract (120mg) on the memory function in healthy older volunteers using the cognitive drug research battery of memory tests and the Rey auditory verbal learning task, discovered no acute effects of Ginkgo in any of the memory tests conducted.

A short-term double blind, placebo-controlled design involving 60 healthy male volunteers was conducted to determine the nootropic effect of Ginkgo extract (120mg/day for 5 days). On the fifth day, after a 2h waiting period, all volunteers were given the Sternberg Memory Scanning Test, a reaction time control test, the vocabulary and digit span subtests of the WAIS-R and a prose recall test. No significant changes occurred with Ginkgo intervention on all the tests except the Sternberg Memory Scanning Test. A 30-day randomised, double blind, placebo-controlled clinical trial involving 61 participants was conducted using Ginkgo extract to assess nootropic activity. Volunteers were administered a battery of validated neuropsychological tests before and after treatment, with results indicating significant improvements in speed of information processing working memory and executive processing.

A placebo-controlled, multi-dose, double blind, crossover study using 20 participants receiving Ginkgo extract (120mg, 240mg and 360mg) or a matching placebo was conducted to assess cognitive performance via the Cognitive Drug Research computerised test battery immediately prior to dosing, and at 1, 2.5, 4 and 6h after. Compared with the placebo, the acute administration of Ginkgo produced a number of significant changes in performance measures, most noticeably in speed of attention which was evident at 2.5h and was still present at 6h. Another study investigated the effects of acute doses of Ginkgo extract on memory and psychomotor performance in a randomised, double blind and placebo-controlled five-way crossover design. Thirty-one volunteers with normal cognition (aged 30 to 59 years) received varying dosages of Ginkgo extract (120, 150, 240 or 300mg/day) for 2 days. Psychometric tests concluded a more pronounced effect occurred on memory (particularly working memory) in the Ginkgo group compared with placebo. The study noted that the cognitive-enhancing effects of Ginkgo were more apparent in the 50 to 59 year-old sub-population.

Although the overall evidence of Ginkgo’s nootropic effect on healthy volunteers is equivocal, it is likely that acute or short-term Ginkgo administration (which was assessed in the majority of studies) may not be long enough to influence cognitive enhancement in people with pre-existing optimum cognition. Ginkgo also appears to demonstrate the most profound enhancement in cases of cognitive deficit, which presents more commonly in older patients. A number of clinical trials have found a beneficial effect on cognitive function for a combination of Ginkgo and ginseng (Panax ginseng). (These studies are reviewed in the ginseng monograph.)

**Diabetes**

Ginkgo extract improved peripheral nerve function and blood supply in patients with diabetic neuropathy (120mg/day; controlled trial) and enhanced nerve conduction and thermal perception in patients with diabetic neuropathy (dosage undefined; controlled trial). It also improved colour vision in children and adolescents with type 1 diabetes not yet exhibiting retinopathy (120mg/day; uncontrolled trial).

Ginkgo extract (120mg/day, taken for 12 weeks) improved motor nerve conduction velocities in diabetic patients with peripheral neuropathy in a small, placebo-controlled trial conducted in Korea.

In a randomised, controlled trial from China, Ginkgo extract taken for 3 months had a protective effect on early diabetic nephropathy. In a later trial, also from China, treatment with standardised Ginkgo extract (providing 57.6mg/day of Ginkgo flavone glycosides and 14.4mg/day of terpenoids) for 8 weeks improved vascular endothelial function in 64 patients with early stage diabetic nephropathy.

**Multiple sclerosis**

After limited success in an open trial using intravenous ginkgolide B with multiple sclerosis (MS) patients in acute relapse, a double blind, placebo-controlled study was undertaken with 104 patients. There was no significant difference between placebo and the low or high-dose ginkgolide B groups.
A blinded, controlled pilot trial using a Ginkgo extract (240 mg/day) in ameliorating the presentation of MS was conducted with 22 patients diagnosed via Poser criteria. Results demonstrated that the Ginkgo group contained significantly more improved patients compared with placebo, as assessed via the outcome measures of fatigue (p<0.024), symptom severity (p<0.06) and functionality. Although the results should be interpreted with caution due to the small sample size, they indicate a therapeutic role of Ginkgo in treating MS. Another small trial (n=38) found that Ginkgo (240 mg/day for 12 weeks) significantly improved cognitive function in the Stroop test compared with placebo (p=0.008) in MS patients.

**Cancer**

Regular use of Ginkgo extract was associated with a reduced risk of ovarian cancer, especially of the non-mucinous type, in an epidemiological study. Ginkgo improved cognitive function, mood and quality of life in long-term survivors (6 months or more) of brain tumour who had received radiotherapy and were radiographically stable. The beneficial effect on mood was mostly due to reductions in fatigue and confusion (120 mg/day; uncontrolled trial). Ginkgo also neutralised genotoxic damage (induced by radiiodine treatment) in Graves’ disease patients (120 mg/day; randomised controlled trial) and in Chernobyl accident recovery workers (120 mg/day; uncontrolled trial).

The former trial assessed the effect of standardised Ginkgo extract on the appearance of micronuclei (MN) in lymphocytes from patients with Graves’ disease after radioactive iodine therapy. Twenty-five patients were randomly assigned to receive Ginkgo extract (120 mg/day) or placebo from 3 days before and up to 30 days after iodine therapy. During this time period all patients took the same dose of methimazole (an antithyroid drug).

The peak increase of MN and the mean increase of MN were significantly higher in the placebo group than in Ginkgo-treated patients. An early and sustained MN increase was observed in the placebo group, but in the Ginkgo-treated patients the increase never reached statistical significance. The protective effect of Ginkgo extract was still present after correcting the data for age, gender, thyroid hormone profile and bone marrow dose. Administration of Ginkgo did not have any adverse effect on the efficacy of the radiotherapy.

The summary results of a phase II, uncontrolled trial investigating Ginkgo in irradiated brain tumour survivors were published in 2010. Ginkgo extract (120 mg/day) was prescribed to 34 patients for 24 weeks. There was a high drop-out rate (56% completed the trial) due to perceived lack of efficacy and development of either intercurrent medical illness or brain tumour progression. Of the 19 remaining patients, there were significant improvements in some measures of cognitive function and quality of life.

**Premenstrual syndrome**

In a controlled, multicentre, double blind study involving 165 women with congestive symptoms of premenstrual syndrome (PMS), patients received either 160 mg/day of Ginkgo extract or placebo. The medication was taken from day 16 of the menstrual cycle to day 5 of the following cycle. Ginkgo significantly improved breast tenderness. There were marked improvements in other symptoms for the Ginkgo group including oedema, anxiety, depression and headaches.

The efficacy of 120 mg/day of Ginkgo standardised extract for the amelioration of the symptoms of PMS was also assessed in a later randomised, single blind, placebo-controlled clinical trial. Trial participants were 90 students (average age around 22 years) with PMS living in dormitories of a medical university (Tehran). Participants took the Ginkgo or placebo from the day 16 of the menstrual cycle to the fifth day of the next cycle for two consecutive cycles.

Eighty-five (94.4%) participants completed the study. The two groups were similar in terms of demographic characteristics and overall severity of symptoms at baseline. After the intervention, there was a significant decrease in the overall severity of symptoms and physical and psychological symptoms in both the Ginkgo (23.68%) and placebo (8.74%) groups (p<0.01). However, the mean decrease in the severity of symptoms was significantly more in the Ginkgo group compared with the placebo group (p<0.001). The authors concluded that Ginkgo can reduce the severity of PMS symptoms.

**Antidepressant-induced sexual dysfunction**

A triple blind (investigator, patient, statistician), randomised, placebo-controlled, trial of Ginkgo extract (240 mg/day) was conducted in 24 patients (male and female) with sexual impairment due to antidepressant drugs. A validated, sex (gender)-orientated questionnaire was recorded throughout the 12-week trial. The researchers commented that, although spectacular individual responses occurred in both groups, no statistically significant differences between Ginkgo and placebo were apparent. Another 8-week controlled study involving 37 men examined Ginkgo in the treatment of SSRI-evoked sexual dysfunction. (SSRI is selective serotonin re-uptake inhibitor.) It revealed a high response in both placebo and Ginkgo groups, with no difference between the two.

In an uncontrolled trial, Ginkgo extract (average dose 207 mg/day) was found to be 84% effective in alleviating sexual dysfunction secondary to antidepressant drug use in 33 female and 30 male patients. No adverse effects were reported. The inconsistency of results involving sexual dysfunction is conceivably due to small sample sizes, differing classes of antidepressants, the psychological component of the condition yielding a high placebo effect and individual psycho-physiological sexual responses. Essentially, the promising results of an earlier uncontrolled trial have not been supported by controlled studies.

**Other conditions**

An epidemiological study conducted in France assessed 3534 elderly people from 1988 to 2001. Participants aged 65 years or over and without dementia were included in the study. Those who took Ginkgo had a significantly lower risk of mortality in the long term, compared with non-users, even after adjustment for confounding factors.
Ginkgo extract had a beneficial effect on sleep patterns in patients with major depression being treated with trimipramine (240 mg/day, pilot trial). 286

In two separate trials, Ginkgo extract decreased capillary hyperpermeability in women with idiopathic oedema (160 to 240 mg/day, uncontrolled study) 287, 288 and helped prevent retinal oedema following cataract surgery (160 mg/day, uncontrolled study). 289

In a double blind, placebo-controlled trial involving 52 patients with vitiligo (with 47 evaluated), Ginkgo extract (120 mg/day) for 6 months induced a significant cessation of active progression and depigmentation (p=0.006). 290 Repigmentation was observed in 10 patients in the Ginkgo group versus two patients receiving placebo. The extract was well tolerated.

Toxicology and other safety data

Toxicology

The following LD50 data have been recorded for Ginkgo extract and its constituents:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Route, model</th>
<th>LD50</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardised Ginkgo extract</td>
<td>Oral, mice</td>
<td>7.7 g/kg</td>
<td>291, 292</td>
</tr>
<tr>
<td>Standardised Ginkgo extract</td>
<td>ip mice</td>
<td>1.9 g/kg</td>
<td>292</td>
</tr>
<tr>
<td>Standardised Ginkgo extract</td>
<td>iv mice</td>
<td>1.1 g/kg</td>
<td>292</td>
</tr>
<tr>
<td>Standardised Ginkgo extract</td>
<td>ip rats</td>
<td>2.1 g/kg</td>
<td>292</td>
</tr>
<tr>
<td>Standardised Ginkgo extract</td>
<td>iv rats</td>
<td>1.1 g/kg</td>
<td>292</td>
</tr>
<tr>
<td>Ginkgo leaf extract fraction (ginkgolic acids 16%; biflavones 6.7%)</td>
<td>Injection, hen’s eggs</td>
<td>1.8 mg/egg (33 ppm)</td>
<td>293</td>
</tr>
<tr>
<td>Ginkgo leaf extract fraction (ginkgolic acids 58%; biflavones 0.02%)</td>
<td>Injection, hen’s eggs</td>
<td>3.5 mg/egg (64 ppm)</td>
<td>293</td>
</tr>
<tr>
<td>Ginkgo leaf extract fraction (ginkgolic acids 1%; biflavones 16%)</td>
<td>Injection, hen’s eggs</td>
<td>250 mg/egg (4540 ppm)</td>
<td>293</td>
</tr>
</tbody>
</table>

The toxicity data indicate standardised Ginkgo extract has very low toxicity. No deaths occurred in rats orally administered up to 10 g/kg of standardised extract. Chronic oral toxicity studies indicated no evidence of biochemical, haematological or histological damage or impairment of hepatic or renal function in rats and dogs orally administered standardised Ginkgo extract for 6 months. Doses began at 20 and 100 mg/kg/day and gradually increased to 500 mg/kg/day in rats and 400 mg/kg/day in dogs. Light and transient vasodilatory effects were observed in dogs at the 100 mg/kg dose and became more pronounced with increasing dose. 291, 292, 294

No carcinogenic effects were observed in rats orally administered standardised leaf extract for 104 weeks at doses of 4, 20 and 100 mg/kg, 292 or in rats fed Ginkgo seed for almost a year. 295 Standardised leaf extract did not demonstrate mutagenic activity using in vitro tests with and without metabolic activation, or in vivo tests in mice after oral administration of doses up to 20 g/kg. 291, 292

No adverse effects were observed in human volunteers administered pure ginkgolides at doses of 720 mg (acute) or 360 mg/day for 1 week. 296

Fractions of Ginkgo leaf extract containing high concentrations of ginkgolic acids have been shown to be cytotoxic against human and animal cell lines in vitro 297 and immunotoxic in vivo after subplantar injection. 298, 299 They were also embryotoxic in the hen’s egg test (see left). The authors of the last study did not exclude the possibility that other constituents such as the biflavones may amplify the adverse effects of ginkgolic acids. 292 Ginkgolic acids demonstrated neurotoxic, 300 genotoxic and tumour promoting 301 activities in vitro.

Contraindications

Ginkgo preparations are contraindicated in those with a known sensitivity.

Special warnings and precautions

Caution should be observed when prescribing Ginkgo to patients with coagulation disorders or concomitantly with anticoagulant or antiplatelet medication. (See Side effects and Interactions.) This is based on poorly described case reports and adverse effects are not typically expected.

Patients about to undergo surgery are advised to stop taking Ginkgo 5 to 7 days beforehand due to possible (but very minor) risk of increased bleeding tendency. 302, 303

Ginkgo preparations that contain appreciable quantities of ginkgolic acids may pose a risk of allergic reaction.

Interactions

See Appendix C for the data and recommendations regarding potential herb-drug interactions for Ginkgo that are deemed to be clinically relevant.

A 2002 publication listed 185 reports of adverse effects in connection with Ginkgo, with 20 reports related to bleeding disorders. It was concluded that patients using Ginkgo extracts are at risk of suffering complications during surgery or spontaneous bleeding, and there is an increased danger of bleeding with concomitant use of anticoagulant or antiplatelet agents. 304 However, there is still no strong evidence for this. Treatment with standardised Ginkgo extract (100 mg/day) for 4 weeks in patients who were stabilised on long-term warfarin had no significant influence on their response to warfarin in a randomised, double blind, placebo-controlled,
crossover trial (average age of patients was 64.5 years). The stability of international normalised ratio (INR) values was confirmed and major bleeds or thromboembolic events were not observed.\textsuperscript{305}

Another clinical study investigated the effect of Ginkgo on the pharmacokinetics and pharmacodynamics of warfarin and clotting status.\textsuperscript{306} The open label, three-way crossover study involved 12 healthy male volunteers who received a single 25 mg dose of warfarin alone or after 7 days of pretreatment with Ginkgo. The trial determined that INR values and platelet aggregation were not affected by administration of Ginkgo. The mean ratio of apparent clearance for S-warfarin was 1.05 and for R-warfarin was 1.00 when co-administered with Ginkgo. Other pharmacokinetic parameters for warfarin were not affected by Ginkgo. These results were replicated later in a similar trial by the same research team, demonstrating that the S-warfarin concentration and response (prothrombin complex activity) data from 24 healthy volunteers who received a single warfarin dose (25 mg) were not altered by Ginkgo administration.\textsuperscript{307}

A randomised, controlled study involving 24 outpatients on stable, long-term warfarin treatment was undertaken, assessing the impact of Ginkgo extract (100 mg/day) on INR over a 4-week period. Results indicated that INR was stable during all treatment periods, with no bleeding episodes occurring.\textsuperscript{308}

A substudy within the National Institutes of Health-funded Dementia Prevention (GEM) Study investigated whether Ginkgo standardised extract would affect platelet function. Fifty-one patients had platelet function analysis performed at baseline and at 6-month follow-up. Patients were randomised to receive Ginkgo (240 mg/day) or placebo. There was no significant difference between the placebo and Ginkgo groups. Fifteen patients were taking aspirin but there was no difference in closure time at either time point, and aspirin did not show any interaction with Ginkgo.\textsuperscript{309} A double blind, double-dummy procedure involving 50 healthy male volunteers (20 to 44 years) using 120 or 240 mg/day of Ginkgo extract in combination with acetylsalicylic acid (aspirin) demonstrated no additional effect on bleeding time, coagulation parameters or platelet activity in response to various anticoagulant-provoking agonists.\textsuperscript{310} Aspirin given alone clearly prolonged bleeding time, whereas the combination of aspirin and Ginkgo exerted similar effects to aspirin alone on all coagulation parameters measured, including bleeding time (aspirin alone: 4.1 min before therapy, 6.2 min after therapy; aspirin plus Ginkgo: 4.2 min before therapy, 6.3 min after therapy; ratio of means: 1.01, 90% CI 0.86 to 1.19) and agonist-induced platelet aggregation (collagen-induced platelet aggregation: 84.5% before therapy, 81.0% after aspirin therapy; aspirin plus Ginkgo: 86.6% before therapy, 81.0% after therapy; ratio of means: 1.00, 90% CI 0.95 to 1.05; adenosine diphosphate-induced platelet aggregation with aspirin: 72.6% before therapy, 47.2% after therapy; with aspirin plus Ginkgo: 71.7% before therapy, 44.8% after therapy; ratio of means: 0.95, 90% CI 0.85 to 1.06).

A study in Taiwan in 2002 found no clinically significant change in coagulation parameters (including INR, bleeding time and clotting time) in healthy volunteers taking standardised Ginkgo extract (120 mg/day) and warfarin. In 21 clinical cases, no significant change in INR was found after adding Ginkgo to existing warfarin therapy.\textsuperscript{311} A 2008 review of studies published up to March 2007 found four trials (included above) and seven case reports pertaining to the potential interaction of drugs that can elevate the risk of bleeding with Ginkgo.\textsuperscript{312} As noted above, the trials did not provide any evidence for an interaction of aspirin or warfarin with Ginkgo. Establishing causality from the case reports was difficult due to the generally low quality of the reports and the presence of confounding factors, with scant evidence to suggest any adverse interaction. An excerpt from the Mediplus database in Germany failed to show an increased bleeding risk from the combination of Ginkgo with antiplatelet or anticoagulant drugs.

Studies published since the March 2007 cut-off date of this review are consistent with its overall conclusions. For example, it was confirmed that standardised Ginkgo extract (300 mg/day) combined with aspirin did not have an impact on bleeding parameters among older adults at risk of cardiovascular disease.\textsuperscript{313}

An interaction was observed in one clinical study for a single dose of Ginkgo extract (120 mg) combined with the antiplatelet drug cilostazol. The bleeding time prolongation of cilostazol was extended by Ginkgo. There was no change in platelet aggregation ex vivo or clotting time. Also there was no significant correlation between prolongation of bleeding time and inhibition of platelet aggregation. No interaction was found between Ginkgo and the antiplatelet drug clopidogrel.\textsuperscript{314} Dosing of Ginkgo (extract undefined, 160 mg/day) to healthy volunteers over 7 days found no effect on the pharmacokinetics of cilostazol or on platelet aggregation or bleeding time.\textsuperscript{315}

In Korea, Ginkgo extract is administered with ticlopidine (an antiplatelet drug, chemically similar to clopidogrel) for the prevention of ischaemic stroke and acute coronary syndrome.\textsuperscript{316} In a single-dose study, standardised Ginkgo extract (80 mg) combined with ticlopidine exerted no significant additional effect on bleeding time or platelet aggregation.\textsuperscript{317}

No effect on the pharmacokinetics of the drug was found when Ginkgo extract (120 mg/day) was taken for 3 days.\textsuperscript{318} Both trials involved healthy volunteers.

Concerns have also been expressed about the potential interaction of Ginkgo with antiepileptic drugs. In an innocuously entitled paper, “Ginkgo biloba and Gingotoxin”, two German scientists drew the rather radical conclusion that the low levels of ginkgotoxin found in products containing Ginkgo leaf extracts “… can have a detrimental effect on a person’s health condition”. Gingotoxin should not be confused with the ginkgolic acids. The latter are irritant and allergenic compounds controlled to quite low levels in appropriately made standardised extracts of Ginkgo leaves (as noted previously). Ginkgotoxin is 4’-O-methylpyridoxine, a vitamin B6 antagonist. It occurs in relatively high levels in Ginkgo nuts and is believed to be responsible for the poisoning that occurs after the ingestion of unprocessed nuts. It is also found at much lower levels in Ginkgo leaves.

On the basis of their in vitro research, the authors proposed that ginkgotoxin primarily acts as a toxicant by inhibiting vitamin B6 phosphorylation.\textsuperscript{319} This could deplete the
brain of phosphorylated B6 vitamers, resulting in a reduction of glutamate metabolism which in turn would increase neuronal excitability due to lower levels of GABA. Poisoning with Ginkgo nuts certainly causes epileptiform seizures, unconsciousness and leg paralysis. Children are especially vulnerable to the toxin and vitamin B6 administration typically leads to full recovery with no serious complications.

The major thesis of the authors was that even the very low levels of ginkgotoxin found in typical daily doses of standardised Ginkgo leaf extract, estimated by them to be 11.4 to 58.6 μg, might increase the risk of seizures in epileptic patients. In support of this, they cited adverse event reports linking Ginkgo leaf to seizures. In the closing paragraphs, a rather tangential argument was proposed that Ginkgo leaf might also present a risk to epileptic patients by interacting with their medications.

One commentary expressed doubts over the relevance of conclusions from test tube research involving high doses of ginkgotoxin, when a pharmacokinetic study found that the compound was below detection limits (1 nM/mL) in human plasma after normal oral doses of Ginkgo extract. Supporting this contention, documentation from extensive clinical trial experience and records for 150 million daily doses per year for more than two decades have not recorded one case of epileptic seizure attributed to Ginkgo extract.

Reports of seizures linked to Ginkgo essentially come from three sources: the US FDA Nutritionals database, which has been shut down due to its poor accuracy and reliability, and the articles by Granger in 2001 and Kupiec and Raj in 2005. However, the latter two publications could be describing a heroin-drug interaction. Kupiec and Raj certainly provide some evidence that Ginkgo might reduce the levels of some anticonvulsants drugs via increased hepatic metabolism. Ginkgo has been found in a clinical trial to induce CYP2C19 activity, an enzyme involved in the metabolism of some anticonvulsants. For this reason the herb should be used with caution in epileptic patients controlled by medication, despite the relatively low number of reported cases.

A brief review of the potential interaction of Ginkgo with other drugs follows. An elderly patient with AD developed a coma a few days after starting the SSRI antidepressant trazodone (40 mg/day), which has hypnotic and sedative effects, in conjunction with Ginkgo extract (160 mg/day). Previously she had been taking bromazepam (3.5 mg/day), donepezil (5 mg/day) and vitamin E (1200 mg/day). It was postulated that sedation was caused by increased GABAergic activity via ginkgo flavonols acting directly at the benzodiazepine receptor and indirectly by inducing CYP3A4 to increase the metabolism of trazodone to an active compound that also has GABAergic activity. However, this case certainly does not provide conclusive evidence of a drug interaction with Ginkgo.

An elderly patient started treatment with a thiazi diuretic for elevated blood pressure. She then started taking Ginkgo and after a week her blood pressure was found to have increased further. Her blood pressure decreased gradually when both medications were ceased. It was unclear how soon the Ginkgo was started after the thiazi diuretic and the interpretation of this case as a herb-drug interaction is highly questionable, although it has been widely recorded as such.

Concerns have been raised that Ginkgo extract may increase the hepatic metabolic clearance rate of insulin and hypoglycaemic agents in type 2 diabetes mellitus patients, resulting in reduced insulin-mediated glucose metabolism and elevated blood glucose. However, no adverse effects of any significance have been reported for blood glucose levels and for laboratory results of glucose control in 10 trials conducted from 1980 to 1998 where Ginkgo extract was administered to diabetic and non-diabetic patients.

There are many published in vitro, in vivo and human studies investigating the potential impact of Ginkgo extract on the metabolism of drugs (some are mentioned above and several are included in Appendix C). A 2010 review concluded that the findings in humans (which must be given priority) were conflicting and further studies are needed to elucidate the role of Ginkgo in altered drug absorption due to cytochrome P450 (CYP) and P-glycoprotein (P-gp) inhibition. Three clinical studies excluded any effect of Ginkgo on CYP3A4, but two other studies with the probe drugs alprazolam and midazolam suggest an inhibition of this enzyme. Ginkgo did not interact with drug substrates of CYP1A2, CYP2E1 or CYP2D6 (as reported in three studies). One study found that Ginkgo altered the metabolism of the CYP2C19 substrate omeprazole in a genotype-dependent manner, but a different study did not find this for a different CYP2C19 probe drug (voriconazole).

The review did note that drugs that are P-gp substrates should be monitored in conjunction with Ginkgo. Some studies have reported a high between-subject variability of the bioavailability of digoxin (a P-gp substrate) and the pharmacokinetics of talinol (another P-gp substrate) was modified by long-term intake of Ginkgo in two different studies by the same research group.

Use in pregnancy and lactation

Category B1 – no increase in frequency of malformation or other harmful effects on the fetus from limited use in women. No evidence of increased fetal damage in animal studies.

One review hypothesised that Ginkgo may be a risk factor for excessive blood loss during delivery, but there are no reports of this in the literature.

Oral administration of standardised Ginkgo extract to rats (up to 1600 mg/kg/day) and rabbits (up to 900 mg/kg/day) did not cause teratogenicity or embryotoxicity or affect reproduction. In contrast, a study from Pakistan attributed malformations in the offspring of mice to Ginkgo extract at 100 mg/kg/day, but found no teratogenic effects at 78 mg/kg/day.

A commercial Ginkgo extract and fractions of Ginkgo extract containing high concentrations of ginkgolic acids demonstrated embryotoxic effects in the hen’s egg test when injected into freshly fertilised chick eggs (see Toxicology). The dose of the commercial Ginkgo extract was not specified.
A study claimed to have identified the highly toxic alkaloid colchicine in a commercial Ginkgo preparation and linked this to their discovery of the presence of colchicine in the placental blood of women who had used herbal supplements. The herbal supplements taken by the women were not identified and it was not clear whether Ginkgo was one of them. Colchicine has never been detected in Ginkgo previously and studies conducted since the findings were released have failed to detect colchicine in commercial preparations. The validity of the colchicine findings and the conclusions drawn from them have been vigorously criticised. (See Chapter 5 for a further discussion of this issue.)

Pretreatment of hamster oocytes in vitro with Ginkgo (1 mg/mL) significantly reduced penetration by human sperm compared to a control. However, significant reduction of sperm penetration was not observed at a concentration of 0.1 mg/mL, which represents typical human exposure for in vitro research. (See Chapter 5 for further discussion of this issue.)

No data are available regarding the use of Ginkgo in breastfeeding mothers. However, only small amounts of flavon glycosides and terpene lactones accumulate in the serum and the serum half-life of terpene lactones is relatively short. This would reduce the amount available to enter the breast milk and the possibility of accumulation in the infant.

A 2006 systematic review examined the literature for evidence on the use, safety and pharmacology of Ginkgo in the context of pregnancy and lactation. The review found some weak scientific evidence that Ginkgo has antiplatelet activity that might be of concern during labour because of prolonged bleeding times. It concluded that the safety of Ginkgo in lactation is unknown and recommended that it be avoided during breastfeeding until more safety information is generated.

**Effects on ability to drive or operate machinery**

Possible improvement of these functions, especially in older subjects.

**Side effects**

Reviews and meta-analyses of clinical trials have shown that standardised Ginkgo extract has a remarkably low incidence of side effects and there were no differences between Ginkgo and placebo in adverse event profiles. Two adverse events were reported in 314000 patient years of use in 1988. Only 0.5% of 9772 patients reported adverse events over 44 clinical trials. Adverse events reported have included mild gastrointestinal complaints, headache, dizziness, allergic skin reactions and palpitations. Palpitations and ventricular arrhythmia have been associated with Ginkgo use in a case report.

More than 5 million units of Ginkgo preparations were sold in Germany in 1998 alone. German authorities recorded 117 reports of adverse effects in connection with preparations containing Ginkgo from 1990 to 2000, including non-standardised extracts, homeopathics and multi-ingredient preparations. Ginkgo was indicated as the only medication in 65 cases. By 2002 the number of adverse reactions was 185. In fact, given the widespread use of Ginkgo, the number of published adverse reactions is remarkably low.

The primary concern of an adverse reaction occurring with Ginkgo commonly expressed in the literature is an increase of bleeding or an initiation of spontaneous bleeding, as documented in several case studies (discussed below). A 2005 review of spontaneous bleeding associated with Ginkgo use reported 15 published cases of purported Ginkgo-induced bleeding events, including one new case report described in the publication. The review, however, commented there was very limited evidence to support Ginkgo being a risk factor for bleeding due the documented cases involving concomitant drug use, inadequate reporting or a lack of re-challenge to establish causation. The review did document a new case, where re-challenge with Ginkgo evoked spontaneous bleeding in a 73-year-old Caucasian male who reported haemorrhoidal bleeding and increased bleeding from minor skin trauma. He was taking a standardised Ginkgo preparation (75 mg/day). After stopping Ginkgo (6-week washout period) his bleeding time was assessed via a ‘blinded’ laboratory test at 5.5 min (normal range 2.5 to 9.5 min). When Ginkgo use was re-initiated, his bleeding time increased to >15 min and he started noticing occasional ecchymoses, although coagulation studies were still normal. After discontinuing Ginkgo, the patient experienced no further haematological abnormalities (although over the next few years he developed Alzheimer’s dementia).

Other cases of spontaneous cerebral or extracerebral bleeding attributed to the intake of Ginkgo preparations have also been reported. It was not possible to establish Ginkgo as the cause in any of these cases. Prolonged bleeding times were noted in two of the bleeding cases, although the bleeding time quoted in one is widely considered to be within the normal range. In another case involving spontaneous hyphema, the authors state that, after extensive ophtalmological and haematological investigations, no putative causes were recorded other than Ginkgo intake. Use of Ginkgo has also been attributed to one case of postoperative bleeding following laparoscopic cholecystectomy. Other isolated cases of spontaneous bleeding have been attributed to drug interactions with Ginkgo (see Interactions above).

Contrary to these isolated case histories, a 7-day haematological study involving 40 elderly subjects (65 to 79 years of age) who were administered a Ginkgo extract (240 mg/day) demonstrated no change on primary haemostasis. The complete set of PFA-100 in vitro bleeding time and coagulation parameters including prothrombin time, activated partial thromboplastin time and INR confirmed no statistically significant prolongation in bleeding time or coagulation parameters in patients. A prospective, double blind, randomised, placebo-controlled trial tested a Ginkgo extract (120, 240 or 480 mg over 14 days) in 32 healthy men to evaluate any haematological abnormalities (although over the next few years he developed Alzheimer’s dementia).
available evidence does not demonstrate that Ginkgo extract causes significant changes in blood coagulation parameters.\textsuperscript{356}

The 2008 review cited under Interactions also sought to understand the evidence for the impact of Ginkgo on haemostasis and the case reports of increased bleeding.\textsuperscript{312} None of the trials reviewed (including some summarised above) demonstrated any convincing evidence for the impact of Ginkgo on haemostasis. The 21 case reports identified were of low quality. Not only was there variability in Ginkgo products, but also the documentation of key factors such as product name, standardisation and other potentially active ingredients were generally absent. The low quality of these case reports casts doubts on causality. The large Medipus database study found the frequency of reported bleeding events in patients taking Ginkgo was the same as in patients not taking Ginkgo. The review concluded that, similar to most medicinal herbs, the possibility of a rare idiosyncratic bleeding event due to Ginkgo use is very unlikely, but cannot be excluded.\textsuperscript{312}

From 2000 to 2008 the GEM study assessed 3069 healthy volunteers treated with standardised Ginkgo extract (240mg/day) or placebo for incident dementia. There were no statistically significant differences in the rate of major bleeding, and no difference between the groups for the incidence of bleeding in the patients taking aspirin. However, compliance during the trial was low.\textsuperscript{317}

To date, the balance of the evidence indicates that Ginkgo has an extremely low chance of provoking spontaneous bleeding, if at all. Rare cases of idiosyncratic increases in bleeding may occur in certain individuals, hence monitoring is advised in cases of known haematological abnormalities, close to surgery or in high-dose use with concomitant use of anticoagulants and antiplatelet drugs.

A substantial part of the misunderstanding that Ginkgo alters haemostasis probably arises from knowledge of its capacity to enhance tissue perfusion and inhibit PAF. But these are both quite separate phenomena.

PAF is a weak activator of platelets not of primary importance to the process of haemostasis, and its inhibition is unlikely to cause haemorrhage.\textsuperscript{312} PAF-mediated aggregation of human platelets in vitro was half-maximally inhibited by ginkgolide B at a concentration of 2.5 μg/mL. (Ginkgolide B is present at about 0.5% in standardised Ginkgo extract.) Higher concentrations were required for the other ginkgolides. These concentrations are more than 100 times higher than peak plasma levels measured after oral intake of Ginkgo extract at doses of 120 to 240mg.

Some clinical studies show that standardised Ginkgo extract increases blood flow to and within an organ, and to tissues, or it may have a regulatory effect (dilating or constricting blood vessels depending upon the condition). Increases in blood flow mean Ginkgo improves oxygen and nutrient supply to the organs and tissues, but this does not mean it increases the risk of haemorrhage.

Ginkgo has also decreased blood viscosity in healthy volunteers\textsuperscript{324,357} and patients (often with initially elevated levels),\textsuperscript{105,267,358,359} but blood viscosity is related to friction among red blood cells and is a measure of blood flow and tissue perfusion. In a trial involving healthy elderly volunteers, in addition to reducing blood viscosity, Ginkgo improved cerebral perfusion and cognitive function.\textsuperscript{360}

Ginkgo has been shown to modify circulating platelet aggregates in pathological conditions. In a small, randomised, placebo-controlled trial, Ginkgo extract (120mg/day) over a period of 12 weeks reduced the elevated platelet reactivity index (a measure of platelet aggregates) in elderly patients with cerebral insufficiency and ‘cerebral vascular risk’ (risk of stroke).\textsuperscript{360} Ginkgo appears to have shifted elevated platelet aggregates towards normal. Note that the test system used did not assess the capacity of platelets to aggregate under normal physiological conditions.

Cases of Stevens-Johnson syndrome associated with the use of preparations containing Ginkgo have been reported.\textsuperscript{344,361} Stevens-Johnson syndrome is an acute inflammatory skin disease that affects the skin and mucous membranes of the face and mouth.

Severe circulatory disturbances, local phlebitis, allergic skin reactions and anaphylactic shock may occur with parenteral use of standardised Ginkgo extracts.\textsuperscript{338} Injectable preparations have been disallowed in some European countries.\textsuperscript{362}

Hypersensitivity reactions to standardised extracts of Ginkgo leaf are extremely rare, indicating that it has a very low potential for sensitisation.\textsuperscript{201,363} However, cases of allergic contact dermatitis to Ginkgo fruit pulp have been repeatedly reported.\textsuperscript{364} Gastrointestinal disturbances (tenesmus, stomatitis and proctitis) have also been reported after consumption of the fruit.\textsuperscript{338,365} Provocation tests in patients and animal experiments have identified alkylphenols such as ginkgolic acids as the causative constituents.\textsuperscript{288} Tests in guinea pigs have shown that, although sensitisation developed with purified ginkgoligic acids, it failed to occur to leaf extract containing approximately 1000 ppm ginkgoligic acids\textsuperscript{364} which is 200 times higher than the level deemed acceptable for standardised extracts. Nonetheless, consumption of Ginkgo extracts containing ginkgolic acids above acceptable levels may constitute a risk to those who are allergic to plants from the Anacardiaceae family, such as poison ivy and cashew, because of cross-reactivity between the alkylphenols of the two families.\textsuperscript{299}

A diffuse morbilliform eruption occurred in a 66-year-old woman about 1 week after the ingestion of a Ginkgo preparation that was suspected to be due to alkylphenols.\textsuperscript{366} The alkylphenol level of the preparation was not measured.

Manic psychosis has been questionably associated with the use of Ginkgo in two sisters who had been consuming the herb for approximately 2 years at a dosage twice that recommended. A few months before onset of symptoms the dose had been further increased. Family psychiatric history was significant for paranoid schizophrenia on the paternal side. They were stabilised on medication and 6 months later were free of all medications and were not manifesting psychiatric symptoms. Almost 1 year after the first episode one sister had a relapse while not taking Ginkgo.\textsuperscript{367} One case of hypomania has been reported; however, the patient (with a history of mild traumatic brain injury) combined an unknown Ginkgo preparation with St John’s wort, fluoxetine and buspirone. Hence the exact cause of the adverse reaction cannot be determined.\textsuperscript{294}
Overdosage

Intoxication generally occurs after ingestion of large numbers of Ginkgo seeds and young children are more vulnerable to poisoning. Those under the age of 6 comprise about 74% of cases.368 Symptoms include vomiting, diarrhoea, irritability, seizure and in some cases death.369-372 The number of seeds consumed in reported fatalities ranged from 15 to 574 pieces.369 The neurotoxin 4’-O-methylpyroxidine, which can cause vitamin B6 deficiency symptoms as noted previously, is thought to be responsible.371,372 Intravenous vitamin B6 (2 mg/kg) has been used to treat Ginkgo seed poisoning.369

As mentioned previously, the stems and leaves of Ginkgo also contain 4’-O-methylpyroxidine (ginkgotoxin).373,374 This toxin has been measured at levels of 42 μg/g fresh weight of stem373,374 and up to 80 μg/g in raw seed.368 The highest concentration of 4’-O-methylpyroxidine in medicinal preparations tested conferred a daily dose of 60 μg.374 In contrast, the acute oral toxic dose was measured at 11 mg/kg in guinea-pigs.371,372 The ingestion of normal quantities of Ginkgo extracts and of boiled Ginkgo seeds (eaten in Japan) is not expected to cause detrimental effects,373,374 although ingestion of seeds should be limited, particularly in children. In extreme cases of overdosage of Ginkgo extract the phytochemicals noted above may cause toxic effects, but even this is unlikely given the low toxicity observed for the extract.

Safety in children

No side effects were observed in infants (2 to 7 months old) with hypoxic-ischaemic encephalopathy treated with standardised Ginkgo extract (0.5 mL/day, oral) for 2 months.375

Standardised Ginkgo extract has also been used to treat asthma in children (see previous).

Cases of poisoning have been reported in young children after ingestion of a large number of Ginkgo seeds, 50 or more in some cases (see Overdosage).369-372 Japanese authorities advise that children should not eat more than five seeds (nuts) per day and that they should not eat seeds every day.368 However, the risk of toxic or adverse effects in children for Ginkgo leaf extract is very low.

Regulatory status in selected countries

Ginkgo is included on the General Sale List in the UK. Standardised Ginkgo leaf extract is covered by a positive German Commission E monograph, but Ginkgo leaf is covered by a negative Commission E monograph. Ginkgo is official in the British Pharmacopoeia 2012 and the European Pharmacopoeia 2012.

In the USA Ginkgo is official in the United States Pharmacopeia-National Formulary (USP 34-NF 29, 2011).

Ginkgo does not have GRAS status. However, it is freely available as a ‘dietary supplement’ in the USA under DSHEA legislation (Dietary Supplement Health and Education Act of 1994).

Ginkgo is not included in Part 4 of Schedule 4 of the Therapeutic Goods Act Regulations of Australia and is freely available for sale.

References


