MEDI HERB®
a phytotherapist's perspective
Not for Public Distribution. For Professional Use Only.
No. 123 November 2010

Clinical Research & Applications of Standardised Ginkgo Extract

Key Points at a Glance

Actions

- antioxidant
- enhances cognition
- possibly antiatherosclerotic and neuroprotective
- stimulates circulation
- enhances blood flow, especially to the periphery and enhances tissue perfusion i.e. increases blood flow to tissues
- has anti-PAF (anti-platelet activating factor) activity
- does not have clinically-relevant antiplatelet activity
- not blood thinning
- very unlikely to cause bleeding
- very unlikely to increase the effects of aspirin or warfarin

Efficacy

- circulatory disorders: peripheral arterial occlusive disease, cerebral insufficiency, oedema, ischaemic ulcer, consequences of diabetes
- early stage of atherosclerosis and stroke
- dementia, supports healthy ageing, lowers mortality
- enhances cognitive function and quality of life
- dizziness, vertigo, hearing loss, glaucoma, macular degeneration, altitude sickness
- asthma,liver fibrosis, multiple sclerosis, stress, schizophrenia, anxiety, migraine
- congestive dysmenorrhoea, premenstrual syndrome, chronic obstructive pulmonary disease
- antioxidant

Safety

It is advisable to cease intake of Ginkgo at least a week prior to surgery. The risk of interaction with antiplatelet and anticoagulant medications is low, so monitoring is sufficient. (If prescribing Ginkgo under these circumstances, maintain close contact and review the patient's status on a regular basis.)

Dosage

For adults: usually 120 to 240 mg/day of a special 50:1 concentrated extract standardised to contain 24% flavonoid glycosides (ginkgo flavone glycosides) and 6% terpenoids (ginkgolides and bilobalide) – this corresponds to about 6 to 12 g/day of dried leaf.

In the 1960s German researchers found an extract of *Ginkgo biloba* leaves to be particularly beneficial for conditions characterised by disturbed blood flow. This led to the development of a special 50:1 concentrated extract (EGb 761) standardised to contain 24% flavonoid glycosides (ginkgo flavone glycosides) and eventually 6% terpenoids (ginkgolides and bilobalide), manufactured so as to not contain undesirable substances (ginkgolic acids, biflavones).[1] Since then a large number of Ginkgo products have become available. Not all of them, however, reflect the phytochemical profile of this clinically-trialled extract.

Clinical Studies

In most of the clinical trials outlined below a standardised Ginkgo extract was administered. This was usually the 50:1 concentrated extract discussed above, so the common dosage of 120 to 240 mg/day corresponds to the equivalent of 6 to 12 g of dried leaf, providing 24% (28.8-57.6 mg) of ginkgo flavone glycosides and 6% (7.2-14.4 mg) of terpenoids (ginkgolides and bilobalide).

Negative Results?

The Ginkgo Evaluation of Memory (GEM) trial which received funding support from several US health institutes and centres, was originally designed to evaluate the effectiveness of Ginkgo in *preventing* dementia. The trial failed to show benefit for Ginkgo. There was poor compliance: at the end of the trial, only about 60% were taking their tablets.[2] The trial has also been criticised for many other significant limitations.[3,4] For this reason, secondary analyses of the data reporting cognitive decline,[5] cardiovascular mortality,[6] hypertension[7] and risk of cancer[8] are not included in the discussion below.

Atherosclerosis, Ischaemia, Tissue Healing

Standardised Ginkgo extract:

- inhibited **atherosclerosis** at the very earliest stages in coronary bypass patients and patients with metabolic syndrome as measured by a reduction in nanoplaque formation, nanoplaque size and plasma concentration of the highly atherothrombic lipoprotein(a) (240 mg/day; 2 uncontrolled trials);[9]

- had a protective effect on **arteriosclerotic retinopathy** (120 mg/day; case reports);[1]
- improved vision in patients with **cerebral insufficiency** (120-160 mg/day; 2 uncontrolled trials).[1]

Standardised Ginkgo extract is widely used in the treatment of **acute ischaemic stroke** in China. A 2005 meta-analysis, conducted by the Cochrane Collaboration, assessed controlled trials for the effect on neurological deficit. Other measures of disability (such as the activities of daily living) and quality of life were not evaluated. Of the ten trials reviewed, in six trials Ginkgo extract was administered orally. Analysis of the results of all 10 trials indicated that Ginkgo was associated with a significant increase in the number of improved patients. Subgroup analysis showed there was no difference in efficacy between Ginkgo tablets and intravenous injections (compared to controls, both routes improve neurological impairment). The methodological quality of nine of the trials was however regarded as inferior. No deaths or major adverse events were reported during the follow-up period (14 to 35 days after stroke). The reviewers had planned to include non-randomised trials in the safety analysis, but no major side effects were reported in any of these trials.[10] Of the six oral trials (five conducted in China, one in India), four used standardised Ginkgo extract (120-160 mg/day, containing 24% ginkgo flavone glycosides and 6% terpenoids) for 20-28 days. The other two trials administered Ginkgo leaf extract (240 mg/day, standardisation unknown) for 20-21 days.

Addition of standardised Ginkgo extract to existing and/or local treatment:

- healed an **ischaemic ulcer** in a man with peripheral arterial disease (120 mg/day; case report);[11]
- significantly decreased the ulcer area in patients with **chronic leg ulcers** (160 mg/day; randomised controlled trial).[12]

Peripheral Circulation

A 2004 systematic review of randomised controlled trials found that standardised Ginkgo extract (120-240 mg/day, most frequently given for 24 weeks) increased pain-free walking distance for patients with peripheral arterial occlusive disease (**intermittent claudication**) in stage II according to Fontaine.[13]

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

- produced a modest, but not statistically significant, increase in maximal walking time (300 mg/day);[14]
- did not provide additional benefit when combined with supervised exercise training (240 mg/day).[15]

Note: A meta-analysis of randomised trials (those mentioned above, including in the 2004 review) conducted by the Cochrane Collaboration (2009) concluded that there is no evidence that Ginkgo has a clinically significant benefit for patients with peripheral arterial disease. People using standardised Ginkgo extract could walk 64.5 metres further, which was not significant in comparison with the placebo group.[16]

Many general practitioners (doctors) in South Korea have prescribed 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 (120-240 mg/day, standardisation unknown) showed a 30% improvement.[17]

Neuropsychological Effects: Overview

A review published in 2009 sought to find differential effects for the **cognition-enhancing effects** of standardised Ginkgo extract. Included in the analysis are 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 in review in sections below.) Objective psychometric test results were examined for 4 cognitive domains (memory, attention, executive functions, intelligence) comprising 14 subfunctions (e.g. for the domain of memory, the subfunctions were short- and long-term, visual and verbal memory). Key findings are outlined in the table below.[18]

There is consistent evidence 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) • 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 24-25% of ginkgo flavone glycosides and 6% of terpenoids was administered. Daily dosage ranged from 80 mg/day to 240 mg/day, with 120 mg/day the most common dosage (14 trials).
Future trials should be more comprehensive and use psychometric standards to evaluate cognitive function. A lack of investigation of some functions (e.g. divided attention, an early feature of Alzheimer's disease) tends to penalise Ginkgo and make it difficult to identify strengths and weakness in terms of functions sensitive to its treatment.

The results of a phase II, uncontrolled trial investigating Ginkgo in irradiated brain tumour survivors were briefly published in 2010. Ginkgo (extract undefined,

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, dose-limiting toxicity 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.[19]

Dementia

Treatment

A review published in 2008 assessed the efficacy of standardised Ginkgo extract in the treatment of **dementia of vascular origin** and **Alzheimer's disease**, 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 is sufficient evidence indicating the efficacy of Ginkgo for these conditions. The most frequent dosage was 120 mg/day, up to a maximum of 240 mg/day.[20] Three randomised, placebo-controlled trials published since this review have reported mixed results,[21-23] although subgroup analysis of one trial,[22] and the results of a trial with rigorous patient selection,[21] 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.)

In late 2008, the German Institute for Quality and Efficiency in Health Care (IQWiG) which assessed trials for meta-analysis, noted that there is evidence of a benefit of high dose standardised Ginkgo extract (240 mg/day, for at least 16 weeks) in patients with Alzheimer's disease, particularly for the goal of coping with daily activities. The results of the high dose trials are of higher relevance as they are more homogeneous (not much deviation).[24]

Note: An alternative interpretation is provided by the Cochrane Collaboration (2009). A meta-analysis of randomised, placebo-controlled trials concluded that the evidence that Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.[25] The analysis included trials mentioned above, including those covered in the review and the placebo comparison trials in the IQWiG meta-analysis. Criticism of some aspects of the methodology and conclusions of this Cochrane meta-analysis has been noted.

Unlike the Cochrane meta-analysis, a meta-analysis published in 2010 only included trials evaluating specifically defined dementia and Alzheimer's disease – trials of cognitive impairment were excluded. The results indicate standardised Ginkgo extract to be more effective than placebo in improving cognition in these patients. Treatment was at least 12 weeks in duration.[26] A meta-analysis that considered the influence of baseline risk on the treatment effect found that treatment with standardised Ginkgo extract for 6 months to be effective. The meta-analysis took into account the variation of changes in placebo group across the included trials.[27] (Baseline risk is the risk of the event (in this case, cognitive decline) occurring without the active treatment (i.e. in the placebo groups).)

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 effective in the treatment of dementia irrespective of the severity of neuropsychiatric symptoms. However, due to faster decline of the placebo group, the net effect of Ginkgo was larger in patients with more pronounced neuropsychiatric symptoms.[28]

Slowing the Progression

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 Alzheimer's disease. The review compared a trial of standardised Ginkgo extract with eight trials evaluating drugs (rivastigmine, donepezil, galantamine) published to 2000.[29] A 2006 trial confirmed this.[30] Slightly better outcomes and better tolerability were found in a 2009 preliminary study for a combination of standardised Ginkgo extract (240 mg/day) and donepezil compared to single therapy of either substance in patients with Alzheimer's disease and neuropsychiatric features.[31]

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.[2,32]

Results for the longest and largest European study for prevention of Alzheimer's disease ever conducted are emerging. 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 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 Alzheimer's disease vs 3.0% in the placebo group).[33]

Cognitive Function in the Healthy

A systematic review that assessed clinical research to January 2007 found 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 (7 trials) or over longer periods of time (8 trials, ranging from 2 days to 12 weeks).[34] A 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.[35]

Mortality, Healthy Ageing

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 to non-consumers, even after adjustment for confounding factors.[36]

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 (Aβ42). Increased plasma Aβ42 may be a biological **risk factor related to age**. Plasma Aβ42 levels are elevated in both late onset Alzheimer's disease patients and their cognitively normal first-degree relatives. Users of Ginkgo for at least 2 years had significantly decreased Aβ42 plasma levels compared to non-users. This reduction was also independent of medial temporal lobe (brain) atrophy, as assessed by MRI scanning.[37] At follow-up, 2.5 years later, longer use of Ginkgo seemed to decrease plasma Aβ42 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 compared to those who had converted to mild cognitive impairment from cognitive health at baseline.[38]

Vertigo, Tinnitus, Hearing Loss

A review of randomised, double-blind clinical trials found that standardised Ginkgo extract (120-240 mg/day) was beneficial for vestibular and non-vestibular **vertigo**.[39]

An assessment of placebo-controlled trials to 2004 conducted by the Cochrane Collaboration, concluded that standardised Ginkgo extract (120-150 mg/day for 12 weeks) was not effective for tinnitus. This meta-analysis included trials of tinnitus as a primary complaint and as a feature of cerebral insufficiency/dementia.[40] A 2007 trial however, found it was beneficial for both **tinnitus and dizziness** in dementia patients when prescribed at 240 mg/day for 22 weeks.[41] In an address to Australian doctors in September 2007, the 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 three months of onset,[42] and a dosage of 240 mg/day is recommended.[43]

Three controlled trials using oral administration of standardised Ginkgo extract (120-320 mg/day) demonstrated benefit in **sudden hearing loss**.[44-46]

Acute Mountain Sickness, Hypoxia

Up until 2007 five randomised controlled trials had been conducted to evaluate the efficacy of standardised Ginkgo extract for the prevention of **mountain sickness**. Three of the trials demonstrated a beneficial effect.[47] The design of one of the negative result trials has been questioned. Mixed results were obtained from two small trials reported in 2009. Questions have been raised about the quality of the extracts used.[48]

In a Chinese trial, Ginkgo leaf extract tablets improved lung ventilation and physical work capacity in young volunteers at high altitude.[49]

In a randomised, double-blind, placebo-controlled, crossover study standardised Ginkgo extract demonstrated a protective effect when healthy volunteers were exposed to **hypoxia** (reduced oxygen).[50]

Anti-PAF Activity

Platelet activating factor (PAF) is a phospholipid which is formed by platelets, basophils, neutrophils, monocytes and macrophages. It is a potent platelet aggregating agent and inducer of systemic anaphylactic symptoms. Anti-PAF activity is regarded as useful in the treatment of asthma, allergic reactions, immunological reactions, shock, ischaemia and thrombosis.

Standardised Ginkgo extract:

- protected asthmatic patients exposed to challenge with an inhaled allergen (600 mg single dose pretreatment; uncontrolled trial);[51]
- improved **asthma** in adults, some of whom were able to stop corticosteroid therapy; normalised pulmonary function in children with atopic asthma, which was correlated with a significant improvement in flow parameters (uncontrolled trial).[50]

Compared to those treated only with inhaled corticosteroid, addition of standardised Ginkgo extract (oral, 240 mg/day) for 4 weeks decreased airway inflammation in asthmatics in a trial conducted in China.[52]

In a placebo-controlled trial in China, concentrated Ginkgo leaf liquor reduced airway hyperreactivity, improved clinical symptoms and pulmonary functions in asthmatic patients.[53,54]

In China, treatment with Ginkgo leaf tablets for 3 months significantly lowered the 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 flavone 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. Gingko treatment was superior to that of the control group.[55]

Multiple Sclerosis

Standardised Ginkgo extract (240 mg/day) was effective for relieving fatigue, symptom severity and functional performance in **multiple sclerosis**. It also improved concentration, selective attention and mental flexibility (3 small, controlled trials).[56-58]

Diabetes

Standardised Ginkgo extract:

- increased pancreatic **beta-cell function** in diet-controlled type 2 diabetics, leading to elevated blood glucose levels in those with overt hyperinsulinaemia (120 mg/day; uncontrolled trial);[59]
- improved peripheral nerve function and blood supply in patients with **diabetic neuropathy** (120 mg/day; controlled trial);[60]
- improved nerve conduction and thermal perception in patients with diabetic neuropathy (dosage undefined; controlled trial);[61]
- improved colour vision in early **diabetic retinopathy** (160 mg/day; controlled trial);[62]
- improved colour vision in children and adolescents with type 1 diabetes not yet exhibiting retinopathy (120 mg/day; uncontrolled trial);[63]
- improved a number of parameters which might facilitate blood perfusion (such as improved blood viscosity) and improved blood flow rate in the capillaries of the retina in type 2 diabetic patients with retinopathy (240 mg/day; uncontrolled trial).[64]

Ginkgo extract (120 mg/day, standardisation unknown) taken for 12 weeks improved motor nerve conduction velocities in diabetic patients with peripheral neuropathy, in a small, placebo-controlled trial conducted in Korea.[65]

In a randomised, controlled trial in China, Ginkgo leaf extract tablets taken for 3 months had a protective effect on early diabetic nephropathy.[66] In a later trial, also conducted in China, treatment with standardised Ginkgo extract (providing 57.6 mg/day of ginkgo flavone glycosides and 14.4 mg/day of terpenoids) for 8 weeks improved vascular endothelial function in patients with early stage **diabetic nephropathy**.[67]

Glaucoma & Macular Degeneration

Significant improvement in visual field indices was recorded in a randomised, double-blind, placebo-controlled trial of patients with normal tension **glaucoma** (a form of primary open-angle glaucoma). Patients received standardised Ginkgo extract (120 mg/day) for 4 weeks.[68] Beneficial results with standardised Ginkgo extract were demonstrated in another controlled trial. Patients were followed up and tests conducted over a period of at least 4 years.[69]

Standardised Ginkgo extract (80 mg/day) for at least 6 months did not improve visual field indices of patients with primary open-angle glaucoma. In this trial, treated patients were retrospectively matched with control patients.[70]

Some positive effects for standardised Ginkgo extract (60-240 mg/day, for 6 months) on vision in patients with age-related **macular degeneration** have been reported from two small trials.[71]

Schizophrenia

Four randomised, controlled trials have demonstrated that Ginkgo improved clinical symptom scores and blood levels of antioxidant enzymes in patients with **schizophrenia** who were taking antipsychotic medication (haloperidol or olanzapine). Blood levels of antioxidant enzymes such as superoxide dismutase have been found to be elevated in schizophrenics. Treatment with Ginkgo reduced these elevated levels. Overall, the results suggested to the authors that Ginkgo increased the effectiveness of the drugs. In one trial, scores for behavioural toxicity and nervous system symptoms were reduced, suggesting that Ginkgo treatment may reduce the extrapyramidal side effects of haloperidol. Ginkgo also improved the decrease in immune function by improving T cell subsets (CD3+ (T lymphocytes), CD4+ (T helper cells) and IL-2 (interleukin 2) secreting cells). Many of these trials administered standardised Ginkgo extract (300-360 mg/day, containing 24% ginkgo flavone glycosides and 6% terpenoids) for 12 weeks.[72-76] A placebo-controlled trial found standardised Ginkgo extract (120 mg/day, for 12 weeks) was effective in decreasing negative symptoms in schizophrenics taking clozapine.[77]

Long-term treatment with antipsychotics and neuroleptic drugs may lead to side effects such as tardive dyskinesia. A randomised, placebo-controlled trial in China found standardised Ginkgo extract (240 mg/day, for 12 weeks) significantly reduced the symptoms of tardive dyskinesia in schizophrenia patients.[78]

Cancer

Standardised Ginkgo extract:

- was associated with a reduced risk of **ovarian cancer**, especially of the non-mucinous type (epidemiological study);[79]
- improved cognitive function, mood and quality of life in long-term survivors (of 6 or more months) of **brain tumour** who had received radiation therapy and were radiographically stable – the beneficial effect on mood was mostly due to reductions in fatigue and confusion (120 mg/day; uncontrolled trial);[80,81]
- **neutralised genotoxic damage** induced by radioiodine treatment in Graves' disease patients (120 mg/day; randomised controlled trial)[82] and in Chernobyl accident recovery workers (120 mg/day; uncontrolled trial).[83]

Other Conditions

Standardised Ginkgo extract:

- decreased anxiety in patients with defined **anxiety disorders** (240 mg/day; randomised controlled trial);[84]
- had a beneficial effect on **sleep patterns** in patients with major depression being treated with trimipramine (240 mg/day; pilot trial);[85]
- relieved congestive and psychological symptoms of **premenstrual syndrome** (120-160 mg/day; two randomised controlled trials);[86,87]
- decreased capillary hyperpermeability in women with idiopathic **oedema** (160-240 mg/day; uncontrolled study);[1,88]
- helped prevent retinal oedema following cataract surgery (160 mg/day; uncontrolled study);[89]
- improved word recognition and reading in children with **dyslexia** (80 mg/day; pilot trial);[90]
- improved cognitive function and social behaviour in children with **Down syndrome** (80-120 mg/day; two cases);[91]
- reduced the active progression of depigmentation in patients with **vitiligo** (120 mg/day; randomised controlled trial);[92]
- had beneficial effects in **migraine** (120-240 mg/day; 2 uncontrolled studies).[1]

Standardised Ginkgo extract (200 mg/day) improved behaviour, hyperactivity, inattention and immaturity in 6 young adults with **attention deficit disorder** (ADHD).[93] In an open trial, 56% of ADHD children improved with Ginkgo treatment.[94] Ginkgo was not as effective as methylphenidate in a randomised, double-blind trial conducted in Iran.[95]

Administration of standardised Ginkgo extract (120 mg/day) significantly reduced plasma cortisol levels during 2-hour glucose-induced **stress** (oral glucose tolerance test) in healthy volunteers. In this double-blind, placebo-controlled, crossover trial participants received Ginkgo or placebo for 3-month periods. The author suggests that Ginkgo also may reduce blood cortisol levels in other types of stress.[96]

In additional trials conducted in China:

- addition of Ginkgo leaf extract tablets to paroxetine provided better therapeutic effect than paroxetine alone in patients with **depression**;[97]
- Ginkgo leaf extract tablets improved pulmonary function in patients with **chronic obstructive pulmonary disease** (controlled trial).[98]

Addition of Ginkgo extract to treatment with prednisolone in patients with postviral olfactory loss showed a tendency toward greater efficacy than prednisolone alone.[99] Standardised Ginkgo extract was not beneficial for winter depression (seasonal affective disorder),[100] cocaine dependence[101] or autistic disorder (three cases).[102] Mixed results were found overall from several clinical studies and case reports for men and women with sexual dysfunction due to the use of antidepressant drugs.[103-108] It was not beneficial in women with sexual problems not induced by antidepressant medications.[109]

Topical Application

In a controlled trial, topical application of standardised Ginkgo extract relieved signs and symptoms of seasonal allergic **conjunctivitis**.[110] A similar concentration to that used in the controlled trial can be achieved by adding 2 to 3 drops of a 2:1 standardised liquid extract to 5 mL of sterile saline. The eye can then be bathed in this diluted solution using an eye bath (eye cup). (Concentrated liquid extracts should never be applied directly to the eye.)

Actions with Safety in Perspective

The main actions of standardised Ginkgo extract have been identified by experimental studies:[94,95]

- antioxidant,
- increases blood flow/tissue perfusion enhancing, circulatory stimulant,
- cognition enhancing,
- neuroprotective,
- anti-PAF (anti-platelet activating factor) activity,
- life-span extending.

Many of these activities have been confirmed in clinical studies.

Anti-PAF but not Antiplatelet?

Although a constituent of Ginkgo, ginkgolide B, is a potent *in vitro* anti-PAF agent,[113] **Ginkgo cannot be said to have significant antiplatelet activity.**[114] See table below for more details.

PAF is a weak activator of platelets, and not of primary importance to the process of haemostasis (the normal process by which bleeding in the body is stopped), and will not cause haemorrhage.[111]
PAF-mediated aggregation of human platelets *in vitro* was half-maximally inhibited by ginkgolide B at a concentration of 2.5 microg/mL. (Ginkgolide B is present to about 0.5% in standardised Ginkgo extract.) Higher concentrations were required for the other ginkgolides. These concentrations are more than 100 times higher that the peak plasma levels measured after oral intake of standardised Ginkgo extract at doses of 120-240 mg.[111] The anti-PAF activity demonstrated by oral doses of standardised Ginkgo extract in humans (*see Clinical Studies above*) is mild.
Oral doses in humans have found conflicting results for inhibition of PAF-induced platelet aggregation *ex vivo*. • No effect found in two trials (120-240 mg/day, 7 days and 3 months, healthy volunteers and type 2 diabetics).[115,116] • Inhibition was demonstrated (240 mg/day, for 7 days, healthy volunteers).[1,117] • Inhibition demonstrated (high single dose: 600 mg/day), but bleeding time (which assesses platelet function) and coagulation were not affected.[118]

A review of studies in human volunteers, diabetics and elderly patients with cognitive impairment indicates oral doses have produced conflicting results for *ex vivo* inhibition of platelet aggregation induced by agents other than PAF (6 trials, single-dose trials excluded, 4 were placebo-controlled). There was no effect on spontaneous platelet aggregation or other aspects of platelet function such as platelet membrane glycoproteins.[119]

Ginkgo has been shown to modify circulating platelet aggregates in pathological conditions. In a small, randomised, placebo-controlled trial, standardised Ginkgo extract (120 mg/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).[120] Ginkgo appears to have turned a system of elevated platelet aggregates towards normal. Note: The test system used did not assess the capacity of platelets to aggregate under normal physiological conditions.

Blood Thinning?

Most 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.

Ginkgo has also decreased blood viscosity in healthy volunteers[121,122] and patients (often with initially elevated levels),[63,97,123,124] but blood viscosity is related to friction among red blood cells and is a measure of blood flow and tissue perfusion. In the trial involving healthy elderly volunteers, in addition to reducing blood viscosity, Ginkgo improved cerebral perfusion and cognitive function.[120]

Ginkgo does not have clinically-relevant 'blood thinning' (anticoagulant) activity. A review of studies in human volunteers, diabetics and elderly patients with cognitive impairment did not find that oral doses of standardised Ginkgo extract adversely affected bleeding time (3 trials) or other aspects of coagulation such as thrombin time, international normalised ratio (INR) or fibrinolysis (6 trials).[117]

Combined with Antiplatelet or Anticoagulant Drugs

Associate Professor Kerry Bone in a review published in 2008, investigates the evidence to March 2007 in humans of the safety of standardised Ginkgo extract (*also referred to in section above*). There is little evidence to suggest that Ginkgo significantly adversely affects the safety of coadministered aspirin or warfarin. The information assessed includes four controlled clinical trials and a large database study. See table below for more details.[112]

• Aspirin (2 trials): no interaction found; bleeding time of aspirin not extended and no impact on platelet aggregation *ex vivo*. • Warfarin (2 trials): no effect on INR, no cases of bleeding observed, no impact on platelet aggregation *ex vivo*; no effect on pharmacokinetics (1 trial).
The database study examined information for 320 644 patients and found no increase in the frequency of bleeding events when Ginkgo was combined with antiplatelet or anticoagulant medications.

A study published after March 2007 confirmed that standardised Ginkgo extract (300 mg/day) combined with aspirin did not have an impact on coagulation among older adults at risk of cardiovascular disease.[125] 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.[126]

An interaction has been observed in a 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. 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.[127] 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.[128]

In Korea, Ginkgo extract is administered with ticlopidine (an antiplatelet, chemically similar to clopidogrel) for the prevention of ischaemic stroke or acute coronary syndrome.[129] In a single-dose study, standardised Ginkgo extract (80 mg) combined with ticlopidine had no significant additional effect on bleeding time or platelet aggregation.[130] No effect on pharmacokinetics of the drug was found when standardised Ginkgo extract (120 mg/day) was taken for 3 days.[131] Both trials involved healthy volunteers.

Bleeding Episodes?

The quality of case reports citing adverse bleeding events in connection with consumption of Ginkgo has in general been very low (casting doubt on the causality). The large database study (*see previous section*) found the frequency of reported bleeding events in patients taking Ginkgo was the same as that in patients not taking Ginkgo. Ginkgo did not increase the likelihood of experiencing a bleeding event. Similar to most medicinal herbs, the possibility of a rare idiosyncratic bleeding event due to Ginkgo use is very unlikely, but cannot be excluded.[114] From 2000 to 2008 a randomised trial assessed 3069 healthy volunteers treated with standardised Ginkgo extract (240 mg/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 individuals taking aspirin. However, compliance during the trial was low.[2]

Indications

- Impaired peripheral and cerebral circulation, atherosclerosis, peripheral arterial occlusive disease, Raynaud's disease.
- To promote healing, particularly in peripheral tissues such as those in the arms and legs.
- May improve concentration, cognitive function and memory.
- To assist healthy ageing and as a tonic for the elderly.
- Tinnitus, dizziness, sudden hearing loss.
- Altitude sickness, hypoxia.
- Conditions requiring mild anti-PAF activity e.g. adjunctive treatment for asthma, liver fibrosis.
- Multiple sclerosis, diabetes, stress.
- Disorders due to reduced retinal blood flow, normal tension glaucoma, age-related macular degeneration.
- May assist schizophrenia and cancer as adjunctive treatment.
- Congestive dysmenorrhoea, oedematous conditions, migraine, chronic obstructive pulmonary disease, vitiligo.
- To provide antioxidant activity and protect against genotoxic damage.
- Topically, in a suitable preparation, for allergic conjunctivitis.

Cautions and Contraindications

Caution is advised in patients taking anticoagulant drugs, but the risk of adverse effect is low (and has been exaggerated in scientific literature). Although not demonstrated to have a pharmacokinetic effect, monitoring is recommended for Ginkgo coadministered with warfarin. It is advisable to cease intake of Ginkgo at least a week prior to surgery.

REFERENCES

[1] DeFeudis FV. *Ginkgo biloba Extract (EGb 761): Pharmacological Activities and Clinical Applications*. Elsevier, Amsterdam, 1991. [2] DeKosky ST et al. *JAMA* 2008; **300**: 2253 [3] American Botanical Council, News Release December 29, 2009. cms.herbalgram.org/press/2009/JAMAGinkgoResponse.html. Accessed April 14, 2010. [4] Dr Willmar Schwabe GmbH & Co. KG. Schwabe Statement on Article by Snitz et al, *JAMA* 2009. www.npicenter.com/anm/templates/newsATemp.aspx?articleid=26040&zoneid=2. Accessed April 14, 2010. [5] Snitz BE et al. *JAMA* 2009; **302**: 2663 [6] Kuller LH et al. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 41 [7] Brinkley TE et al. *Am J Hypertens* 2010; **23**: 528 [8] Biggs ML et al. *Pharmacoepidemiol Drug Saf* 2010; **19**: 694 [9] Siegel G et al. *Z Phytother* 2008; **29**(S1): S16 [10] Zeng X et al. *Cochrane Database Syst Rev* 2005; (4): CD003691 [11] Steins A et al. *Eur J Dermatol* 1997; **7**: 109 [12] Maillet P et al. In: Clostre F, DeFeudis FV (eds). *Advances in Ginkgo biloba Extract Research*, Vol 3, Paris, Elsevier, 1994, pp 151-160. [13] Horsch S, Walther C. *Int J Clin Pharmacol Ther* 2004; **42**: 63 [14] Gardner CD et al. *J Cardiopulm Rehabil Prev* 2008; **28**: 258 [15] Wang J et al. *Clin Rehabil* 2007; **21**: 579 [16] Nicolai SP et al. *Cochrane Database Syst Rev* 2009; (2): CD006888 [17] Choi WS et al. *Clin Rheumatol* 2009; **28**: 553 [18] Kaschel R. *Hum Psychopharmacol* 2009; **24**: 345 [19] Attia A et al. *J Clin Oncol* 2010; **28**: e12523 [20] Bornhoeft G et al. *Z Gerontol Geriatr* 2008; **41**: 298 [21] Napryeyenko O et al. *Arzneim Forsch* 2007; **57**: 4 [22] Schneider LS et al. *Curr Alzheimer Res* 2005; **2**: 541 [23] McCarney R et al. *Int J Geriatr Psychiatry* 2008; **23**: 1222[24] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). *Ginkgo in Alzheimer's disease*. IQWiG Reports - Commission No. A05-19B, Executive Summary, Version 1.0, September 2008. English version available online: www.iqwig.de/download/A05-19B_Executive_Summary_Ginkgo_in_Alzheimers_disease.pdf. November 16, 2010. [25] Birks J, Grimley Evans J. *Cochrane Database Syst Rev* 2009; (1): CD003120 [26] Weinmann S et al. *BMC Geriatr* 2010; **10**: 14 [27] Wang BS et al. *Pharmacopsychiatry* 2010; **43**: 86 [28] Ihl R et al. *J Neurol Sci* In Press. [29] Hoerr R. *Phytomedicine* 2005; **12**: 598 [30] Mazza M et al. *Eur J Neurol* 2006; **13**: 981 [31] Yancheva S et al. *Aging Ment Health* 2009; **13**: 183 [32] Dodge HH et al. *Neurology* 2008; **70**: 1809 [33] Ipsen. *Encouraging results of GuidAge®, large scale European trial conducted in the prevention of Alzheimer's Dementia*. Available online: www.ipsen.com/sites/default/files/communiques-presse/PR%20GuidAge%20Results%20FINAL%20EN.pdf. Accessed November 16, 2010. [34] Canter PH, Ernst E. *Hum Psychopharmacol* 2007; **22**: 265 [35] Page JW et al. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1246 [36] Dartigues JF et al. *J Am Geriatr Soc* 2007; **55**: 395 [37] Blasko I et al. *Neurobiol Aging* 2005; **26**: 1135 [38] Blasko I et al. *J Psychiatr Res* 2008; **42**: 946 [39] Hamann KF. *HNO* 2007; **55**: 258 [40] Hilton M, Stuart E. *Cochrane Database Syst Rev* 2004; (2): CD003852 [41] Hoerr R et al. *Focus Altern Complement Ther* 2007; **12**: 26 [42] Schapowal S, Spokesperson of the European Federation of Tinnitus Associations. National Health News, Australian Healthcare & Hospitals Association, September 4, 2007. Available online: www.aushealthcare.com.au/news/news_details.asp?nid=9688. Accessed July 22, 2009. [43] [No authors listed]. *Forsch Komplementarmed* 2008; **15**:

115 [44] Burschka MA et al. *Eur Arch Otorhinolaryngol* 2001; **258**: 213 [45] Dubreuil C. *Presse Med* 1986; **15**: 1559 [46] Kumar A et al. *Indian J Otolaryngol Head Neck Surg* 2000; **52**: 212 [47] Moraga FA et al. *Wilderness Environ Med* 2007; **18**: 251 [48] Leadbetter G et al. *Wilderness Environ Med* 2009; **20**: 66 [49] Wang W et al. *Chin J Clin Rehab* 2005; **9**: 36 [50] Schaffler K, Reeh PW. *Arzneimittelforschung* 1985; **35**: 1283 [51] Braquet P. *Adv Prostaglandin Thromboxane Leukot Res* 1986; **16**: 179 [52] Tang Y et al. *J Huazhong Univ Sci Technolog Med Sci* 2007; **27**: 375 [53] Li MH et al. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1997; **17**: 216 [54] Huntley A, Ernst E. *Thorax* 2000; **55**: 925 [55] He Y et al. *Chin J Integr Med* 2002; **8**: 90 [56] Kenney C et al. *Neurology* 2002; **58**(7, Suppl 3): A458 [57] Johnson SK et al. *Explore* 2006; **2**: 19 [58] Lovera J et al. *Mult Scler* 2007; **13**: 376 [59] Kudolo GB. *J Clin Pharmacol* 2001; **41**: 600 [60] Smirnova V et al. *Diabetologia* 1999; **42**(Suppl 1): A293, Abstract No. 1109 [61] Thajeb P et al. *Neurol* 1996; **46**(2, Suppl): A132 [62] Lanthony P, Cosson JP. *J Fr Ophtalmol* 1988; **11**: 671 [63] Bernardczyk-Meller J et al. *Klin Oczna* 2004; **106**: 569 [64] Huang SY et al. *Clin Nutr* 2004; **23**: 615 [65] Choi KM et al. *J Korean Diabetes Assoc* 2000; **24**: 375 [66] Zhu HW et al. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2005; **25**: 889 [67] Li XS et al. *Chin J Integr Med* 2009; **15**: 26 [68] Quaranta L et al. *Ophthalmology* 2003; **110**: 359 [69] Ha SJ, Rho SH. *J Korean Ophthalmol Soc* 2003; **44**: 2047 [70] Vessaini RM et al. *3rd International Glaucoma Symposium*, Prague, Czech Republic, March 21-25, 2001. [71] Evans JR. *Cochrane Database Syst Rev* 2000; (2): CD001775. Updated 2008. [72] Zhang XY et al. *Psychopharmacology* 2006; **188**: 12 [73] Zhang XY et al. *J Clin Psychopharmacol* 2001; **21**: 85 [74] Zhang XY et al. *J Clin Psychiatry* 2001; **62**: 878 [75] Atmaca M et al. *Psychiatry Clin Neurosci* 2005; **59**: 652 [76] Zhou D et al. *Chin Med J* 1999; **112**: 1093 [77] Doruk A et al. *Int Clin Psychopharmacol* 2008; **23**: 223 [78] Zhang WF et al. *J Clin Psychiatry* In Press. [79] Ye B et al. *Cancer Lett* 2007; **251**: 43 [80] Gehring K et al. *Lancet Neurol* 2008; **7**: 548 [81] Shaw E et al. *Society for Integrative Oncology 2nd International Conference*, San Diego, California, November 10-12, 2005. Available online: www.integrativeonc.org/images/F1100aEShaw.pdf. Accessed June 2008. [82] Dardano A et al. *J Clin Endocrinol Metab* 2007; **92**: 4286 [83] Emerit I et al. *Radiat Res* 1995; **144**: 198 [84] Woelk H et al. *J Psychiatr Res* 2007; **41**: 472 [85] Hemmeter U et al. *Pharmacopsychiatry* 2001; **34**: 50 [86] Tamborini A, Taurelle R. *Rev Fr Gynecol Obstet* 1993; **88**: 447 [87] Ozgoli G et al. *J Altern Complement Med* 2009; **15**: 845 [88] American Herbal Pharmacopoeia. Ginkgo Leaf, Ginkgo Leaf Dry Extract – *Ginkgo biloba* L.: Standards of Analysis, Quality Control, and Therapeutics. American Herbal Pharmacopoeia, Santa Cruz, 2003. [89] Keita CT. *Med Afr Noire* 1997; **44**: 490 [90] Donfrancesco R, Ferrante L. *Phytomedicine* 2007; **14**: 367 [91] Donfrancesco R, Dell'umomo A. *Phytomedicine* 2004; **11**: 469 [92] Parsad D et al. *Clin Exp Dermatol* 2003; **28**: 285 [93] Niederhofer H. *Phytother Res* 2010; **24**: 26 [94] Frei H. *Schweiz Z Ganzheitsmed* 2002; **14**: 10 [95] Salehi B et al. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34**: 76 [96] Kudolo GB. *Clin Chem* 2007; **53**(6, Suppl S): A186 [97] Guo KF et al. *Chin J Clin Rehab* 2006; **10**: 43 [98] Li Y. *Chin J Clin Rehab* 2006; **10**: 79 [99] Seo BS et al. *Arch Otolaryngol Head Neck Surg* 2009; **135**: 1000 [100] Lingaerde O et al. *Acta Psychiatr Scand* 1999; **100**: 62 [101] Kampman K et al. *Addict Behav* 2003; **28**: 437 [102] Niederhofer H. *Phytother Res* 2009; **23**: 1645 [103] Cohen AJ, Bartlik B. *J Sex Marital Therapy* 1998; **24**: 139 [104] Ellison JM, DeLuca P. *J Clin Psychiatry* 1998; **59**: 199 [105] Ashton AK et al. *Am J Psychiatry* 2000; **157**: 836 [106] Kang BJ et al. *Hum Psychopharmacol* 2002; **17**: 279 [107] Wheatley D. *Hum Psychopharmacol* 1999; **14**: 512 [108] Wheatley D. *Hum Psychopharmacol* 2004; **19**: 545 [109] Meston CM et al. *Arch Sex Behav* 2008; **37**: 530 [110] Russo V et al. *Eur J Ophthalmol* 2009; **19**: 331 [111] Ponto LL, Schultz SK. *Ann Clin Psychiatry* 2003; **15**: 109 [112] Smith JV, Luo Y. *Appl Microbiol Biotechnol* 2004; **64**: 465 [113] Koch E. *Phytomedicine* 2005; **12**: 10 [114] Bone KM. *Mol Nutr Food Res* 2008; **52**: 764 [115] Kudolo GB et al. *Thromb Res* 2002; **108**: 151 [116] Kohler S et al. *Blood Coagul Fibrinolysis* 2004; **15**: 303 [117] Mahady GB. *J Cardiovasc Nurs* 2002; **16**: 21 [118] Guinot P et al. *Haemostasis* 1989; **19**: 219 [119] Bone KM. *Mol Nutr Food Res* 2008; **52**: 764. Additional details from individual studies cited therein. [120] Hofferberth B. In: Christen Y, Courtois Y, Droy-Lefaix MT (eds). *Advances in Ginkgo biloba Research*, Volume 4. Paris, Elsevier, 1995, pp 141-148. [121] Galduroz JC et al. *Phytomedicine* 2007; **14**: 447 [122] Santos RF et al. *Pharmacopsychiatry* 2003; **36**: 127 [123] Witte S et al. *Fortschr Med* 1992; **110**: 247 [124] Witte S. *Clin Hemorheol* 1989; **9**: 323 [125] Gardner CD et al. *Blood Coagul Fibrinolysis* 2007; **18**: 787 [126] Lai CF et al. *Pharmacotherapy* 2002; **22**: 1326 [127] Aruna D, Naidu MU. *Br J Clin Pharmacol* 2007; **63**: 333 [128] Yeo C et al. *Clin Pharm Ther* 2010; **87**: S43 [129] Kim TE et al. *Clin Ther* 2009; **31**: 2249 [130] Kim BH et al. *Clin Ther* 2010; **32**: 380 [131] Lu WJ et al. *J Clin Pharmacol* 2006; **46**: 628

Author: Michelle Morgan