Ginkgo

Ginkgo biloba L.

[Fam. *Ginkgoaceae*]

Overview

Ginkgo is the oldest living species of tree on earth, dating back to the Paleozoic period (more than 225 million years ago). A standardized extract of ginkgo leaf is one of the most frequently used phytomedicines in Europe and has been one of the 10 best-selling herbs in the U.S. for about 6 years. *Ginkgo biloba* extract (GBE) is approved in Germany for treatment of cerebral insufficiency (memory loss that occurs with conditions such as Alzheimer's and vascular or multi-infarct dementia, as well as other conditions), tinnitus (ringing in the ears), vertigo, and intermittent claudication (poor circulation to the lower legs). In the U.S., ginkgo is widely used as a complementary therapy for Alzheimer's disease and vascular dementia. Ginkgo preparations consist of the dried green leaf of *Ginkgo biloba* L. [Fam. *Ginkgoaceae*]. The dry extract is pharmaceutically prepared using a 35–67:1 ratio of dried leaves to final extract (50:1 is the average level at which the leading German product is based). Standardization is carried out to 22–27% ginkgo flavonol glycosides (e.g., flavones quercetin, kaempferol, and isorhamnetin) and 5–7% terpene lactones (ginkgolides and bilobalide). In Germany, the content of ginkgolic acid is limited to a concentration of 5 ppm. The scientific literature shows little or no support for clinical benefits of other dosage forms of crude ginkgo leaf or low concentration extracts made from the leaf.

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Primary Uses

- Cerebral insufficiency: memory deficit, poor concentration, depression, and headache resulting from demential syndromes; attention and memory loss that occur with Alzheimer's disease and multi-infarct dementia
- Vertigo and tinnitus (ringing in the ear) of vascular and involutional origin
- Peripheral vascular disease: improvement of pain-free walking distance in Peripheral Arterial Occlusive Disease in Stage II according to Fontaine (intermittent claudication) in a regimen of physical therapeutic measures, in particular walking exercise

Other Potential Uses

- Sexual dysfunction associated with SSRI use
- Control of acute altitude sickness symptoms and vascular reactivity to cold exposure
- Protective action in hypoxia
- Acute cochlear deafness

Pharmacological Actions

Improvements in: cognition, working memory, short-term visual memory in dementia, short-term memory in cerebral insufficiency, social functioning in people with dementia, concentration in people with dementia, attention in people with dementia, tinnitus in people with dementia, intermittent claudication, activities of daily living (ADL) scores in people under 60 years old, mood and sleep in older individuals; increases in alpha wave brain activity; decreases in theta wave activity; inhibits binding of platelet activating factor (PAF) to platelets resulting in inhibited platelet aggregation and increased blood fluidity; reduces thrombosis, inflammation, allergy, and bronchoconstriction.

Dosage and Administration

The German Commission E makes the following recommendations: for chronic cognitive disorders, a minimum of 8 weeks with administration for more than 3 months subject to medical review; for intermittent claudication, not less than 6 weeks; for vertigo and tinnitus (vascular origin), use for more than 6–8 weeks has no therapeutic benefit.

Clinical studies suggest the following duration: for cerebral insufficiency, 4 weeks to one year as observed in clinical trials—improvements are usually seen after 8–12 weeks of treatment; 24 weeks for peripheral vascular disease.

DRY EXTRACT (STANDARDIZED): 40–60 mg in solid pharmaceutical form 2–3 times daily to treat dementia syndromes (120–240 mg/day); or 40–60 mg dry extract 2–3 times daily to treat intermittent claudication, vertigo, and tinnitus (120–160 mg/day).

Contraindications

Ginkgo should not be used in persons who have a history of allergy to ginkgo. It is also contraindicated in bleeding disorders due to increased bleeding potential associated with chronic use (6–12 months) or before elective surgery. The 120 mg dosage should not be used in children under 12 years. Clinicians are

advised to use all necessary precautionary measures in administering ginkgo extracts for treatment of depressive mood and headache not associated with demential syndromes since these conditions have not been sufficiently investigated.

PREGNANCY AND LACTATION: No known restrictions.

ADVERSE EFFECTS

Rare cases of stomach or intestinal upsets, headaches, or allergic skin reactions have been documented. Ginkgo has also been reported to cause dizziness and palpitations. In higher than recommended doses, diarrhea, nausea, vomiting, restlessness, and weakness may occur. Several case reports of bleeding associated with ginkgo use have been reported, including two reports of subdural hematoma, one report of subarachnoid hemorrhage, one report of intracerebral hemorrhage, and one report of anterior chamber bleeding in the eye (hyphema).

DRUG INTERACTIONS

Ginkgo extract may potentiate MAO-inhibiting drugs but the evidence is conflicting.

Ginkgo preparations may enhance the effect of antiplatelet agents (e.g., aspirin); in one case, a spontaneous hyphema occurred after combined intake of ginkgo and aspirin. Ginkgo may enhance the effect of warfarin, although no interaction was shown in a controlled trial. However, the true risks of these interactions are somewhat speculative and difficult to characterize due to the nature and limited number of existing reports. Ginkgo may also potentiate the effect of thiazide diuretics by increasing capillary permeability; however, no clinical relevance has been established as yet for this finding.

CLINICAL REVIEW

More than 120 clinical studies have been published on standardized ginkgo extract. Of 35 studies (3,541 participants) outlined in the table, "Clinical Studies on Ginkgo," only 2 trials found negative results: 1 study on dementia and 1 study on tinnitus. The remaining 33 studies demonstrated positive effects for indications including Alzheimer's disease and dementia, peripheral vascular disease (intermittent claudication), asthma, acute mountain (altitude) sickness, deafness, adjunct therapy in colorectal cancer, sexual dysfunction, and depression.

Eighteen studies (1,672 participants) supported the use of ginkgo in treating dementia due to cardiovascular insufficiency, Alzheimer's disease, or multi-infarct dementia; to slow the clinical deterioration of patients with dementia; or to improve cognitive symptoms. Of these 18 studies, 5 were randomized, double-blind, placebo-controlled, multi-center (R, DB, PC, MC) studies (663 participants); 11 were R, DB, PC (898 participants); and 2 were R, DB, PC, crossover (CO) studies (111 participants).

Three R, DB, PC studies (264 participants) showed positive results for treatment of peripheral arterial insufficiency/intermittent claudication with ginkgo.

Of the remaining studies investigating the use of ginkgo for various disorders, one R, DB, PC study (20 participants) found inconclusive results in the use of ginkgo for moderately severe depression; one R, DB, PC, CO study (8 participants) showed positive effects for hypoxia; three DB, PC studies (110 participants) found positive effects on altitude sickness; one R, DB, PC, MC study (103 patients) found ginkgo improved the evolution of tinnitus; one R, DB, C study (20 participants) found ginkgo superior to nicergoline for acute cochlear deafness; one PC study (61 patients) reported positive effects in asthma; one open-labeled study (63 participants) found positive effects for sexual dysfunction secondary to antidepressant use; one Phase II study (32 participants) suggests a good benefit-risk ratio of ginkgo combined with 5-FU therapy as second-line treatment for advance colorectal cancer; and one DB study (12 participants) investigating the effect of ginkgo extract on brain electrophysiology found significant pharmacological effects on the central nervous system; and one R, DB, PC, CO study (21 participants) concluded that warfarin and ginkgo do not interact.

NOTE: the reviews and meta-analyses discussed below are not listed in the table of Clinical Studies on Ginkgo.

In a review of 40 clinical studies conducted through 1991 on the use of ginkgo for symptoms associated with cerebral insufficiency, eight R, DB, PC trials met the inclusion criteria. All but one concluded that ginkgo extract was as effective as co-dergocrine and superior to placebo. Ginkgo was well-tolerated, and side-effects compared favorably to five studies assessing Hydergine®, another widely-used product for cerebral insufficiency. Ginkgo and Hydergine® were deemed equally effective for treatment of cerebral insufficiency.

In a review and meta-analysis of the scientific literature, researchers evaluated the effects of treatment with ginkgo extract on objective measures of cognitive function in elderly patients with vascular dementia, cognitive impairment, or both. Only 4 out of 50 articles met inclusion criteria. Standardized ginkgo extract produced a significant effect size of 0.40 on cognitive function in Alzheimer's ($p<0.0001$) comparable with the findings of a trial on donepezil. A comparison review of placebo-controlled efficacy studies evaluated the clinical relevance of acetylcholinesterase inhibitors and ginkgo special extract EGb 761 with respect to Alzheimer's dementia. The study concluded that EGb 761 and second generation cholinesterase inhibitors are equally effective in treating mild to moderate Alzheimer's dementia. A meta-analysis of nine DB, PC trials found that ginkgo extract was more effective for dementia than placebo, with few adverse side effects. A review of trials on the use of ginkgo for clinical improvement of memory and other cognitive functions concluded that ginkgo produces a significant therapeutic benefit; however, long-term studies have not evaluated ginkgo's sustained benefits in cognitive function, especially if drug therapy is subsequently interrupted. A Cochrane Review of 33 trials concluded that they showed "promising evidence" for treating dementia. The Cochrane Review concluded that in one identified trial on ginkgo and age-related macular degeneration, a beneficial effect was observed. However, the author encourages additional research due to the small number of patients included in the trial.

One meta-analysis of eight R, DB, PC studies concluded that ginkgo is effective for intermittent claudication but questioned the clinical relevance based on the modest size of the overall treatment effect.

Ginkgo

Ginkgo biloba L.
[Fam. *Ginkgoaceae*]

Overview

Ginkgo, the oldest living species of tree on earth, is more than 225 million years old. A standardized extract of ginkgo leaf is presently one of the most frequently used plant-based medicines in Europe. In the U.S., it has been one of the 10 best-selling herbs for more than five years. In Germany, ginkgo is also an approved therapy for the treatment of memory loss in conditions such as Alzheimer's, ringing in the ears, dizziness, and poor circulation in the lower legs resulting in pain during walking (intermittent claudication).

Uses

Poor memory, poor concentration, depression, and headache occurring with dementia diagnosed by a healthcare practitioner; attention and memory loss in Alzheimer's; ringing in ears (tinnitus); dizziness or whirling sensation (vertigo); peripheral vascular disease including poor circulation to the lower legs (intermittent claudication).

Other Potential Uses

Sexual dysfunction associated with use of SSRI drugs (selective serotonin reuptake inhibitors); control of acute symptoms of altitude sickness and vascular reactivity to cold exposure; protective action in hypoxia (insufficient oxygen in the body); acute deafness related to the cochlea (part of the inner ear).

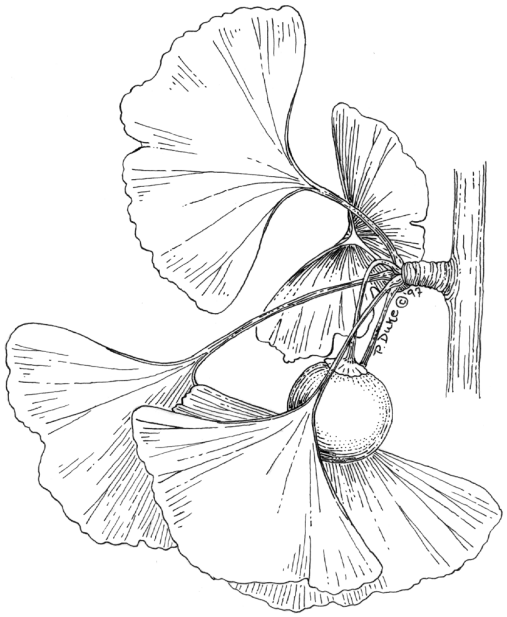
Dosage

Dry extract (standardized): a total of 120–240 mg per day, taken in dosage forms (e.g., tablets or capsules) of 40–60 mg each, 2 or 3 times daily to treat dementia; or a daily total of 120–160 mg, taken in 40–60 mg doses, 2 or 3 times daily to treat intermittent claudication, vertigo, and ringing in the ears (tinnitus).

Contraindications

Ginkgo should not be used before elective surgery or in persons who are allergic to ginkgo or have a bleeding disorder. The 120 mg dosage should not be used in children under 12 years.

Pregnancy and Lactation: No known restrictions.



Adverse Effects

Stomach or intestinal upsets, headaches, or allergic skin reactions occur rarely. Dizziness and pounding heartbeat may also occur. Isolated cases of bleeding (subdural hematoma, subarachnoid hemorrhage, intracerebral hemorrhage, anterior chamber bleeding in the eye [hyphema]) have been reported, but these reactions are extremely rare.

Drug Interactions

Ginkgo extract may possibly increase the effects of monoamine oxidase inhibiting (MAOI) drugs. Ginkgo preparations may increase the effect of blood-thinning drugs such as aspirin and warfarin. Gingko may also enhance the effect of thiazide diuretics.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Ginkgo

Ginkgo biloba L.

[Fam. *Ginkgoaceae*]

Overview

Ginkgo is the oldest living species of tree on earth, dating back to the Paleozoic period, over 225 million years ago. The medicinal use of ginkgo leaf is first mentioned in Chinese medicine in the Ming dynasty in 1436 (Foster, 1996). A standardized extract of ginkgo leaf is one of the most clinically tested and frequently prescribed phytomedicines in Europe, and has been one of the 10 best-selling herbal dietary supplements in the U.S. for about six years (Blumenthal *et al.,* 1998, 2001). *Ginkgo biloba* extract (GBE) is approved in Germany for the treatment of cerebral insufficiency (memory loss that occurs with conditions such as Alzheimer's disease, vascular or multi-infarct dementia, and other conditions), tinnitus (ringing in the ears), vertigo, and intermittent claudication (poor circulation to the lower legs). In the U.S, ginkgo is used widely as a complementary therapy for Alzheimer's disease and vascular dementia (Oken *et al.,* 1998). For comprehensive detailed reviews, see DeFeudis (1998) and McKenna *et al.* (2001).

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Description

Ginkgo preparations are derived from the dried, green leaf of *Ginkgo biloba* L. [Fam. *Ginkgoaceae*]. Ginkgo extracts are usually manufactured using acetone and water, and subsequent purification steps, without addition of concentrates or isolated ingredients. The dry extract is prepared pharmaceutically using a 35–67:1 ratio of dried leaves to final extract (50:1 is the average level at which the leading German product is based). Standardization is carried out to 22–27% ginkgo flavonol glycosides (e.g., the flavones quercetin, kaempferol, and isorhamnetin) and 5–7% terpene lactones (ginkgolides and bilobalide). In Germany, the content of ginkgolic acid is limited to a concentration of 5 parts per million (ppm). Scientific literature gives little or no support of the clinical benefits of other dosage forms of crude ginkgo leaf or low concentration extracts made from the leaf (Blumenthal *et al.*, 2000).

Primary Uses

Neurology

- Cerebral insufficiency:
  The German Commission E approved ginkgo for the following symptoms resulting from demential syndromes: memory deficit, poor concentration, depression, dizziness, tinnitus, and headache (Blumenthal *et al.,*1998)

  Treatment of attention and memory loss that occur with Alzheimer's disease and multi-infarct dementia (Arrigo, 1986; Brautigam *et al.*, 1998; Grässel, 1992; Halama *et al.*, 1988; Hofferberth, 1994; Hofferberth, 1989; Kanowski *et al.*, 1997; Kleijnen and Knipschild, 1992; Le Bars *et al.*, 1997; Oken *et al.*, 1998; Rigney *et al.*, 1999; Taillandier *et al.*, 1986; Vesper and Hansgen, 1994; Wesnes *et al.*, 1987)
- Vertigo and tinnitus (ringing in the ear) of vascular and involutional origin (Morgenstern and Biermann, 2002; Meyer, 1986; Dubreuil, 1986)

Vascular Disease

- Peripheral vascular disease: improvement of pain-free walking distance in Peripheral Arterial Occlusive Disease in Stage II according to Fontaine (intermittent claudication) in a regimen of physical therapeutic measures, in particular walking exercise (Bauer, 1984; Peters *et al.*, 1998; Schweizer and Hautmann, 1999; Pittler and Ernst, 2000) approved by Commission E (Blumenthal *et al.*, 1998)

Other Potential Uses

- Sexual dysfunction secondary to selective serotonin reuptake inhibitor (SSRI) use (Cohen and Bartlik,1998)
- Control of acute altitude sickness and vascular reactivity to cold exposure (Leadbetter *et al.*, 2001; Roncin *et al.*, 1996)
- Protective action in hypoxia (Schaffler and Reeh, 1985)
- Acute cochlear deafness (Dubreuil, 1986)

Dosage

Internal

Standardized Preparations

DRY EXTRACT: total of 120–240 mg solid pharmaceutical form per day, administered in small doses (e.g., 40–60 mg) 2–3 times daily to treat dementia syndromes (Blumenthal *et al.*, 1998), or total of 120–160 mg dry extract per day, administered in doses of 40–60 mg 2–3 times daily to treat intermittent claudication, vertigo, and tinnitus (Blumenthal *et al.*, 1998; WHO, 1999).

Duration of Administration

German Commission E made the following recommendations: for chronic cognitive disorders, a minimum of eight weeks with administration for more than three months subject to medical

review; for intermittent claudication, not less than six weeks; for vertigo and tinnitus (vascular origin), use for more than six to eight weeks has no therapeutic benefit (Blumenthal *et al.*, 1998).

Clinical studies suggest the following duration: for cerebral insufficiency, four weeks to one year as observed in clinical trials (Kanowski *et al.*, 1997; Grässel, 1992; Le Bars *et al.*, 1997; Taillandier *et al.*, 1986; Hofferberth, 1994; Vesper and Hansgen, 1994; Brautigam *et al.*, 1998; Halama *et al.*, 1988; Hofferberth, 1989; Wesnes *et al.*, 1987; Arrigo, 1986; Rigney *et al.*, 1999). Improvements are typically seen after eight to twelve weeks of treatment; 24 weeks for peripheral vascular disease (Bauer, 1984; Peters *et al.*, 1998; Schweizer and Hautmann, 1999; Pittler and Ernst, 2000).

Chemistry

Standardized Preparations

The active constituents in ginkgo extract are unique diterpene lactones, ginkgolides A, B, C, and J, and the sesquiterpene lactone bilobalide (WHO, 1999). Standardized dry ginkgo extract contains 22–27% ginkgo flavonol glycosides (based on flavones like quercetin, kaempferol, and isorhamnetin) and 5–7% terpene lactones of which 2.9% is bilobalide and 3.1% the ginkgolides A, B, and C (Kleijnen and Knipshild, 1992). The relative amounts of the various flavonoids or the ginkgolide and bilobalide components of the terpenoids may vary across different commercial preparations (Sticher, 1993). Ginkgo extract contains trace amounts of ginkgolic acid, a potential allergen, which is limited to a maximum of 5 ppm by German authorities (Blumenthal *et al.*, 1998). Extensive reviews of ginkgo chemistry have been written (Van Beek, 1998; Tang and Eisenbrandt, 1992; Braquet, 1988,1989).

Pharmacological Actions

Humans

Improves cognition (Rigney *et al.*, 1999; Le Bars *et al.*, 1997); improves working memory (Rigney *et al.*, 1999); improves short-term visual memory in people with dementia (Brautigam *et al.*, 1998); improves short-term memory in people with cerebral insufficiency (Grässel, 1992); improves social functioning in people with dementia (Le Bars *et al.*, 1997); improves concentration in people with dementia (Vesper and Hansgen, 1994); improves attention in people with dementia (Hofferberth, 1989); improves tinnitus in people with dementia (Halama *et al.*, 1988; Arrigo, 1986); improves intermittent claudication (Pittler and Ernst 2000; Schweizer and Hautmann, 1999; Peters *et al.*, 1998; Bauer, 1984); increases alpha wave brain activity and decreases theta wave activity (Brown, 1997); improves activities of daily living (ADL) scores in people under 60 years old, and improves mood and sleep in older individuals (Cock1e *et al.*, 2000). Inhibits binding of platelet activating factor (PAF) to platelets, which inhibits platelet aggregation and increases blood fluidity (Jung *et al.*, 1990; Guinot *et al.*, 1989); reduces thrombosis, inflammation, allergy, and bronchoconstriction (Smith *et al.,* 1996), increases pancreatic β-cell function with increased insulin and C-peptide levels (Kudolo, 2000).

Animal

Protects against cerebral ischemia (WHO, 1999; Larssen *et al.*, 1978; Rapin *et al.*, 1986; Le Poncin-Lafitte *et al.*, 1980); decreases cerebral edema induced by trauma or toxins (Chatterjee and Gabard, 1984; Otani *et al.*, 1986; Borzeix, 1985; Blumenthal *et al.*, 1998); improves memory and learning (WHO, 1999; Winter, 1991); increases arteriolar diameter in the pia mater and increases cerebral blood flow by intravenous infusion (WHO, 1999; Krieglstein *et al.*, 1986).

In vitro

Inhibits lipid peroxidation (Cott, 1995); flavonoids and terpenoid constituents are antioxidant and free radical scavenging (Pincemail *et al.*, 1989; WHO, 1999); attacks oxygen free radicals (Sastre *et al.*, 1998); inhibits monoamine oxidase A and B (White *et al.*, 1996) but more recent research has shown that ginkgo does not inhibit MAO *in vivo* (Fowler *et al.,* 2000; Porsolt, 2000); inhibits platelet aggregation (Van Beek *et al.*, 1998); protects against apoptosis (Ahlemeyer and Krieglstein, 1998); protects against cerebral hypoxia (Oberpichler *et al.*, 1988; Krieglstein, 1995; Blumenthal *et al.*, 1998).

Mechanism of Action

Ginkgolides (primarily ginkgolide B)

- Inhibit platelet activating factor (PAF) (WHO, 1999; Bracquet, 1988, 1989; Oberpichler, 1990).
- Inhibit 3'5'-cyclic GMP phosphodiesterase, leading to endothelium relaxation (WHO, 1999; DeFeudis, 1991).

Flavonoid fraction (especially quercetin)

- Increases serotonin release and uptake (Ahlemeyer and Krieglstein, 1998).
- Inhibits age-related reduction of muscarinergic cholinoceptors and alpha-adrenoceptors, and stimulates choline uptake in the hippocampus (DeFeudis, 1998; Blumenthal *et al.,* 1998).
- Acts as a free-radical scavenger (Smith *et al,* 1996).
- Inhibits nitric oxide formation, which may cause its neuroprotective effects. Pre-treatment (15 days) with ginkgo reduced significantly, in a dose-dependent manner, post-ischemic brain MDA levels and post-ischemic brain edema (Calapai *et al.*, 2000).
- Antagonism of PAF, antioxidant and metabolic actions, and effects on neurotransmitters may be due to the flavonoids and terpenoids, acting together or separately (Logani *et al.*, 2000).

Contraindications

Ginkgo should not be used by persons who have a history of allergy to the herb (this is considered rare) (Blumenthal *et al.,* 1998; Brinker, 2001). It is also contraindicated in bleeding disorders due to increased bleeding potential associated with chronic use (6–12 months) or before elective surgery (Brinker, 2001). The product sheet of the leading ginkgo preparation (EGb 761) notes that the 120 mg dosage should not be used in children under 12. In addition, it recommends to use all necessary precautionary measures in administering ginkgo extracts for treatment of depressive mood and headache not associated with demential syndromes since these conditions have not been sufficiently investigated (Schwabe, 2001).

Pregnancy and Lactation: According to Commission E, no known restrictions (Blumenthal *et al.,* 1998) although no long-term studies have been conducted on pregnant or lactating woman.

Adverse Effects

In general, ginkgo extract has produced few adverse effects in clinical trials, with effects for ginkgo being the same as for

placebo. Rare cases of stomach or intestinal upsets, headaches, or allergic skin reaction have been documented (Blumenthal *et al.,* 1998). Ginkgo has also been reported to cause dizziness and palpitations. Several case reports of bleeding associated with ginkgo use have been reported, including two reports of subdural hematoma (Rowin and Lewis, 1996; Gilbert, 1997), one report of subarachnoid hemorrhage (Vale, 1998), one report of intracerebral hemorrhage (Matthews, 1998), and one report of anterior chamber bleeding in the eye (hyphema) (Rosenblatt and Mindel, 1997). However, animal experiments have suggested a protective effect of ginkgo extract on subarachnoid hemorrhage-induced vasospasm and vasculopathy (Kurtsoy *et al.,* 2000).

Drug Interactions

MAO-Inhibition

A safety review suggested that ginkgo extract may potentiate MAO-inhibiting drugs (McGuffin *et al.,* 1997), but the evidence is questionable. Recent studies have concluded that ginkgo does not inhibit MAO *in vivo,* and that a different mechanism may be responsible for some of ginkgo's effects on the central nervous system (Fowler *et al.,* 2000; Porsolt *et al.,* 2000).

Anticoagulants and antiplatelet drugs

Interaction with drugs inhibiting blood coagulation cannot be excluded. A single case of a spontaneous hyphema after combined intake of a ginkgo-containing pharmaceutical preparation and aspirin has been documented (Rosenblatt and Mindel, 1997). However, in a placebo-controlled double-blind study carried out in 50 subjects over a period of 7 days, interactions of ginkgo special extract EGb 761 (daily dose 240 mg) with acetyl salicylic acid (aspirin, daily dose 500 mg) could not be demonstrated (Schwabe, 2001). There is a single case of an intracerebral hemorrhage after concomitant intake of warfarin and ginkgo described in the literature (Matthews, 1998). However, further investigation revealed that the patient received two other drugs (amiodarone and lovastatin) with known interactions with warfarin (Schwabe, 1998). A recent randomized, double-blind, placebo-controlled crossover study has concluded that ginkgo does not interact with warfarin (Engelsen *et al.*, 2002).

Diuretics

One old case report of intravenous use of ginkgo (300 mg/day) speculated the possibility that ginkgo may potentiate the effect of thiazide diuretics by increasing capillary permeability, but the clinical relevance, if any, is not clear (Lagrue *et al.,* 1986). A review of this case suggests that ginkgo did not increase capillary permeability but decreased the shock-induced hyperpermeability (Busse, 2001).

Anticonvulsants

One paper reported the presence of a potential neurotoxin (4'-*O*-methylpyroxidine) in both the ginkgo leaf and seed; the author suggests that ginkgo should thus be used with caution by epileptic patients being treated with anticonvulsants (Arenz *et al.,* 1996). However, an analysis of this case report shows that the toxic concentration of this compound after oral administration of ginkgo is 11 mg/kg of body weight (BW). Thus, the toxic dose is an estimated 11,000 times higher than the maximum daily dose of commercial ginkgo extract (60 mcg) corresponding to 1 mcg/kg BW (Leistner, 1997). Further, the bilobalide in ginkgo has anticonvulsant effects (Sasaki *et al.*, 1995). Thus, there is no clinical evidence to support cautions regarding use of ginkgo extract with anticonvulsants.

Antidepressant

Ginkgo can offset sexual dysfunction symptoms in patients taking antidepressants (SSRIs, MAOIs, and tricyclics) (Brinker, 2001).

Other

Use of ginkgo for 12–18 months potentiated papaverine intracavernosal injections in men where papaverine alone was previously ineffective (Sikora *et al.*, 1989). Use of ginkgo before and after kidney transplant helped prevent PAF-induced organ rejection when used with cyclosporine (Brinker, 2001). In one case report, ginkgo used with trazodone resulted in coma that was immediately resolved by injection of 1 mg flumazenil (Brinker, 2001).

American Herbal Products Association (AHPA) Safety Rating

Class 1: Herbs that can be safely consumed when used appropriately.

Regulatory Status

Argentina: Standardized extracts (Ginkgo NF) are approved for peripheral and cerebrovascular disorders.

Austria: A standardized extract (EGb 761) is approved for cerebral and nutritional insufficiencies, dementia, intermittent claudication, and supportive treatment of hearing deficits.

Brazil: Standardized extracts (Ginkgo NF) are approved for cerebrovascular deficits; peripheral vascular disorders; neurosensorial disorders of vascular origin in the ears, eyes, and nose, and migraine headaches.

Canada: New Drug if claims made. Extract form is unacceptable as food ingredient (HPB, 1993). Permitted as a homeopathic drug requiring premarket authorization and assignment of a Drug Identification Number (DIN). Thirty-two ginkgo homeopathic preparations are listed in the Drug Product Database (DPD) (Health Canada, 2001).

Denmark: Standardized ginkgo extracts (most of which comply with Ginkgo NF) are approved for memory and concentration deficits, tiredness, continuing dizziness, and tinnitus in the elderly, tendency to cold extremities, and intermittent claudication.

France: Marketed under the brand name Tanakan® (EGb 761) is a prescription medication (Itil *et al.*, 1996). The standardized extract (EGb 761) is approved for treating symptoms of cerebral insufficiencies, intermittent claudication, Raynaud's disease, certain dizziness and/or tinnitus syndromes, and retinal conditions due to probable ischemia.

Germany: Only semi-purified normalized (standardized) dry extracts (35–67:1) with less than 5 ppm ginkolic acids are approved drugs of the German Commission E; Active Ingredient Classification ASK No. 05939 (Blumenthal *et al.*, 1998). Dry extract, (35–67:1) is official in the *German Pharmacopoeia,* standardized to contain no less than 22.0% and no more than 27.0% flavone glycosides, as well as no less than 5.0% and no more than 7.0% terpene lactones, of which 2.8–3.4% are ginkgolides A, B, and C and 2.5–3.2% are bilobalide (DAB, 2000). Licensed for the treatment of cerebral dysfunction with attendant memory loss, dementia, poor concentration, etc., plus vertigo and tinnitus of vascular origin, and for intermittent claudication (Blumenthal *et al.,* 1998). Marketed both as a prescription and a nonprescription drug.

MEXICO: Standardized extracts (Ginkgo NF) are approved for treating diminished mental capacities, demential syndromes, dizziness, and tinnitus.

SPAIN: A standardized extract (Ginkgo NF) is approved for cerebral insufficiencies (such as dizziness, headache, and memory deficits), and peripheral vascular disorders.

SWEDEN: Classified as Natural Remedy, requiring premarket authorization. As of January, 2001, six ginkgo products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies," and a monograph is published with the approved indication: "Herbal remedy for the treatment of long-standing symptoms in elderly people such as difficulties of memory and concentration, vertigo, tinnitus and feeling of tiredness. Prior to treatment other serious conditions should have been ruled out by doctor" (MPA, 1998, 2001; Tunón, 1999).

SWITZERLAND: Herbal medicine with positive classification (List D) by the *Interkantonale Konstrollstellefar Heilmittel* (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; Ruppanner and Schaefer, 2000). There are nine ginkgo monopreparation phytomedicines, nine polypreparations and three ginkgo homeopathic preparations listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2000). Standardized ginkgo extracts, most of which comply with Ginkgo NF, are approved for concentration difficulties, forgetfulness, and dizziness (due to arteriosclerotic complaints).

U.K.: Not entered in the *General Sale List* (GSL). Standardized extracts, are available.

U.S.: Dietary supplement (USC, 1994). Dried leaf containing no less than 0.8% flavonol glycosides is official in the *National Formulary* 19th edition (USP 25-NF 20, 2002). Standardized extracts are commonly sold.

Clinical Review

More than 120 clinical studies have been published on standardized ginkgo extract. The table "Clinical Studies on Ginkgo" outlines 35 studies including 3,541 participants. Two trials found negative results: one on dementia (Van Dongen *et al.*, 2000) and one on tinnitus (Drew and Davies, 2001). The remaining 33 studies found positive effects for indications including Alzheimer's disease and dementia, peripheral vascular disease (intermittent claudication), asthma, acute mountain (altitude) sickness, deafness, adjunct therapy in colorectal cancer, sexual dysfunction, and depression.

Eighteen studies involving a total of 1,672 participants supported the use of ginkgo in treating dementia due to cardiovascular insufficiency, Alzheimer's disease, or multi-infarct dementia, or to slow the clinical deterioration of patients with dementia or to improve cognitive symptoms. Of these 18 studies, five were randomized, double-blind, placebo controlled, multi-center (R, DB, PC, MC) studies involving a total of 663 participants (Le Bars *et al.*, 1997; Kanowski *et al.*, 1997; Grässel, 1992; Vesper and Hansgen, 1994; Taillandier *et al.*, 1986); 11 were R, DB, PC with a total of 898 participants (Brautigam *et al.*, 1998; Hofferberth, 1994, 1989; Halama, 1991; Rai *et al.*, 1991; Schmidt *et al.*, 1991; Brüchert *et al.*, 1991; Eckmann, 1990; Vorberg *et al.*, 1989; Halama *et al.*, 1988; Wesnes *et al.*, 1987); and two were R, DB, PC, crossover (CO) studies involving a total of 111 participants (Rigney *et al.*, 1999; Arrigo, 1986).

Three R, DB, PC studies (Bauer, 1984; Peters *et al.*, 1998; Schweizer and Hautmann, 1999), with a total of 264 participants, focused on ginkgo for treatment of peripheral arterial insufficiency/intermittent claudication, with positive results.

Of the remaining studies investigating the use of ginkgo for various disorders, one R, DB, PC study (20 participants) found inconclusive results for the use of ginkgo for moderately severe depression (Halama, 1990); one R, DB, PC, CO study (8 participants) found positive effects for hypoxia (Schaffler and Reeh 1985); two R, DB, PC studies and one DB, PC study on altitude sickness (total 110 participants) had positive results (Gertsch *et al.*, 2002; Roncin *et al.*, 1996; Leadbetter *et al.*, 2001); one R, DB, PC, MC study (Meyer, 1986) on 103 patients found ginkgo improved the evolution of tinnitus; one R, DB, C study (20 participants) (Dubreuil, 1986) found ginkgo superior to nicergoline for acute cochlear deafness; one PC study of 61 patients with asthma reported positive effects (Li *et al.*, 1997); one open-labeled study (63 participants) investigating sexual dysfunction secondary to antidepressant use found positive effects (Cohen and Bartlik, 1998); one Phase II study (32 participants) suggests a good benefit-risk ratio of ginkgo combined with 5-FU therapy as second line treatment for advance colorectal cancer (Hauns et al., 2001); and one DB study (12 participants) investigating the effect of ginkgo extract on brain electrophysiology found that pharmacological effects on the central nervous system are statistically significant when compared to placebo (Itil *et al.*, 1996). One R, DB, PC, CO study (21 participants) concluded that warfarin and ginkgo do not interact (Engelsen *et al.*, 2002).

NOTE: the reviews and meta-analyses discussed below are not listed in the table "Clinical Studies on Ginkgo." In a review of 40 clinical studies conducted through 1991 on the use of ginkgo for symptoms associated with cerebral insufficiency, eight R, DB, PC trials of the 40 studies met inclusion criteria for a well-designed study (Kleijnen and Knipschild, 1992). All but one (Hartmann and Frick, 1991) of these eight studies concluded that ginkgo extract was as effective as co-dergocrine and superior to placebo. Symptoms most often reported improved were concentration and memory, anxiety, dizziness, tinnitus, and headache. Ginkgo was well-tolerated and side effects compared favorably to five studies assessing Hydergine®, another widely-used product for cerebral insufficiency. Ginkgo and Hydergine® were deemed equally effective for treatment of cerebral insufficiency.

A recent Cochrane review of 33 trials on ginkgo extract found that the trials showed "promising evidence of improvement in cognition and function" (Birks *et al.*, 2002).

In a review and meta-analysis of the scientific literature, researchers evaluated the effects of treatment with ginkgo extract on objective measures of cognitive function in elderly patients with vascular dementia, cognitive impairment, or both (Oken *et al.*, 1998). Of more than 50 articles, only four met reasonable inclusion criteria for adequate clinical trial design, with a total of 212 subjects in each of the placebo and ginkgo treatment groups (Le Bars *et al.*, 1997; Hofferberth, 1994; Kanowski *et al.,* 1997; Wesnes *et al.*, 1987). Standardized ginkgo extract produced a significant effect size of 0.40 on cognitive function in Alzheimer's ($p<0.0001$) comparable with the findings of a trial on donepezil (Rogers *et al.*, 1998). The clinical trials reviewed did not determine whether there is improvement in noncognitive behavior or daily function. A comparison review of PC efficacy studies evaluated the clinical relevance of acetylcholinesterase inhibitors and

ginkgo special extract EGb 761 for Alzheimer's dementia. The study concluded that EGb 761 and second generation cholinesterase inhibitors are equally effective in treating mild to moderate Alzheimer's dementia (Wettstein, 2000). A meta-analysis of nine DB, PC trials found ginkgo extract more effective for dementia than placebo, with few adverse side effects (Ernst and Pittler, 1999). A review of trials on ginkgo use for clinical improvement of memory and other cognitive functions found that ginkgo produces a significant therapeutic benefit; however, long-term studies have not evaluated its sustained benefits in cognitive function, especially if drug therapy is subsequently interrupted. The author cites the need for further studies to test the relative efficacy of different doses of ginkgo (Soholm, 1998).

The Cochrane Review selected R, controlled trials (C) that studied ginkgo and age-related macular degeneration. The review concluded that in the one identified trial on that condition, a beneficial effect was observed on 20 patients. However, the author encourages additional research due to the small number of patients included in the trial (Evans, 2000).

One meta-analysis of eight R, DB, PC studies (Pittler and Ernst, 2000) concluded that ginkgo is effective for intermittent claudication but questioned the clinical relevance based on the modest size of the overall treatment effect; patients in the ginkgo groups had a longer distance of pain-free walking than those in the placebo groups (average increase of 34 meters).

Shortly after completion of this monograph, a new study on ginkgo extract for cognitive abilities in healthy older adults (over 60) was published finding no significant improvement in various measured parameters at a dose of 120 mg/day for four weeks (Solomon *et al.*, 2002). Previously, at least four trials of various sizes and designs had suggested that ginkgo extract did contribute to increased mental performance in asymptomatic subjects (Mix and Crews, 2002; Stough *et al.*, 2001; Mix and Crews, 2000).

The most comprehensive review of research and clinical information on ginkgo is compiled by DeFeudis (1998).

Branded Products*

Bio-Biloba®: Pharma Nord ApS / Sadelmagervej 30-32, DK-7100 / Vejle / Denmark / Tel: +43-75-85-7400 / Fax: +43-75-85-7474 / www.pharmanord.com.

Concentrated Ginkgo leaf liquid: Quindao Fengyi Biotechnology Limited. Contact information not available. Each milliliter contains 14.5 mg flavone glycosides and 2.8 mg terpene lactones.

EGb-761: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4, D-76227 / Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / www.schwabepharma.com / Email: melville-eaves@schwabe.de. The standardized mono-extract of dried leaves from ginkgo (50:1) consists of 24% ginkgo flavonol glycosides and 6% terpene lactones, of which 2.9% is bilobalide and 3.1% is the ginkgolides A, B, and C. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

Geriaforce®: CH-9325 Roggwil TG / Switzerland / Tel: +41 71 454 61 61 / Fax: +41 71 454 61 62 / www.bioforce.com / Email: info@bioforce.ch. Each tablet contains an ethanolic extract of fresh leaves 1:4, with a content of flavonol glycosides of 0.20 mg/ml and ginkgolides 0.34 mg/ml.

Ginkgold®: Nature's Way Products, Inc. / 10 Mountain Spring Parkway / Springville, Utah 84663 / U.S.A. / Tel: (801) 489-1500 / www.naturesway.com. The standardized mono-extract (EGb-761) of dried leaves from ginkgo (50:1) consists of 24% ginkgo flavonol glycosides and 6% terpene lactones, of which 2.9% is bilobalide and 3.1% is the ginkgolides A, B, and C. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

Kaveri®: Lichtwer Pharma AG / Wallenroder Strasse 8-14 / 13435 / Berlin / Germany / Tel: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. Prepared from the standardized mono-extract (LI-1370) of dried leaves from ginkgo (50:1) containing at least 25% flavonol glycosides and 6% terpene lactones. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

LI-1370: Lichtwer Pharma AG, Berlin, Germany. The standardized mono-extract of dried leaves from ginkgo (50:1) contains at least 25% flavonol glycosides and 6% terpene lactones (Vesper and Hansgen, 1994) and conforms to the German Commission E specifications. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

Rökan®: Spitzner GmbH / Postfach 763, 76261 Ettlingen, Germany / Tel. +49 72 43 – 106 01 / Fax +49 72 43 – 106 333 / www.spitzner.de / Email: info@spitzner.de. The standardized mono-extract (EGb-761) of dried leaves from ginkgo (50:1) consists of 24% ginkgo flavonol glycosides and 6% terpene lactones, of which 2.9% is bilobalide and 3.1% is the ginkgolides A, B, and C. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

Tanakan®: 4. Beaufor-Ipsen / Paris, France / Tel.: +33 (0) 1 44 30 42 15 / Fax: +33 (0) 1 44 30 42 04 / www.beaufour-ipsen.com/ / Email: contact.web@beaufour-ipsen.com. The standardized mono-extract (EGb-761) of dried leaves from ginkgo (50:1) consists of 24% ginkgo flavonol glycosides and 6% terpene lactones, of which 2.9% is bilobalide and 3.1% is the ginkgolides A, B, and C. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

Tebonin® forte: Dr. Willmar Schwabe Pharmaceuticals. The standardized mono-extract (EGb-761) of dried leaves from ginkgo (50:1) consists of 24% ginkgo flavonol glycosides and 6% terpene lactones, of which 2.9% is bilobalide and 3.1% is the ginkgolides A, B, and C. Contains less than 5 ppm ginkgolic acids and conforms to the German Commission E requirements for GBE.

*American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Ginkgo (*Ginkgo biloba* L.)

Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Van Dongen *et al.*, 2000	Dementia and age-associated memory impairment (AAMI)	R, DB, PC, MC, PG n=196 older patients with mild to moderate dementia or AAMI; intention to treat analysis	Total 24 weeks. Patients randomized to usual dose, high dose, or placebo for 3 months, then randomized again for next 3 months	80 mg, 2x/day or 120 mg, 2x/day or placebo	EGb-761	In 24 weeks, ginkgo group showed no improvement compared to placebo in outcome measures (neuropsychological testing, digit memory span, verbal learning, depressive mood, self-evaluated health and memory, and behavioral evaluation). No benefit was seen for higher dose or extended duration of ginkgo. Ginkgo did not benefit any subgroups. Authors concluded that ginkgo is not effective to treat mild to moderate dementia or AAMI.
Rigney *et al.*, 1999	Memory and psychomotor performance	R, DB, PC, CO (5-way) n=31 asymptomatic individuals (30-59 years old)	Each treatment was taken for 2 days and separated by a washout period of 5 days or more	50 mg, 3x/day; or 100 mg 3x/day; or 120 mg, 1x/day in a.m.; or 240 mg/day in a.m.; or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	Ginkgo produced a non-significant cognitive improvement in overall word recall (short-term working-memory task) (p=0.318) and significantly increased integrative capacity of the central nervous system (based on the critical flicker fusion threshold test) (p=0.043). There was no improvement in choice reaction time. Authors concluded that improvements in asymptomatic controls are most pronounced for working memory, and in individuals over 50 years of age.
Brautigam *et al.*, 1998	Cerebral insufficiency	R, DB, PC n=197 elderly patients with cognitive impairment	6 months	1.9 ml, 3x/day undiluted; or 1.9 ml, 3x/day (1:1 dilution) or placebo	Geriaforce® (liquid extract)	Low-dose ginkgo treatment significantly improved short-term visual memory more than high dose or placebo treatment (based on contrast statistical analysis of the Benton Test of Visual Retention-Revised task) (p=0.0076). There was no improvement in the following parameters: attention or concentration (based on Expended Mental Control Test); short-term memory or learning curve (based on Rey Test part 2). Overall, ginkgo had limited efficacy in this battery of subjective and objective tests. [Note: The ginkgo extract used in this trial is not phyto-equivalent with the 2 preparations upon which most of the studies on ginkgo have been conducted.]
Kanowski *et al.*, 1997	Dementia	R, DB, PC, MC, P n=156 elderly patients with Alzheimer's disease or multi-infarct dementia	6 months	120 mg 2x/day or placebo	EGb-761 (120 mg capsule)	Per protocol and intent-to-treat analyses significantly favored EGb-761 over placebo (p=0.012). Clinical Global Impressions scores, a measure of psychopathological assessment, increased 15% (p<0.05). Syndrom-Kurztest, for the assessment of attention and memory, improved 20% (p<0.05). Overall, EGb-761 was well-tolerated and effective in treatment of Alzheimer's disease and multi-infarct dementia.
Le Bars *et al.*, 1997	Dementia	R, DB, PC, MC, P n=202 elderly patients with mild to severe Alzheimer's disease or mulit-infarct dementia	13 months	40 mg, 3x/day or placebo	Ginkgold® (EGb-761 40 mg tablet)	Patients receiving ginkgo had no significant change in ADAS-Cog score (evaluates memory, language skill, and orientation), but by comparison there was significant worsening in placebo group (p=0.04). Patients taking ginkgo had mild improvement on GERRI test, (assesses daily living and social behavior) while placebo group had significant worsening (p=0.04). Both groups had slight worsening in CGIC, (assesses overall psychopathology). It was concluded that ginkgo is safe and capable of stabilizing or improving cognitive performance and social functioning of demented patients for 6 months to 1 year.
Hofferberth, 1994	Dementia	R, DB, PC n=40 elderly patients with Alzheimer's disease	3 months	80 mg per day (2x 40 mg) or placebo	EGb-761 film-coated tablets (Tebonin® forte)	Of individuals treated with ginkgo, 90.5% had significant improvement in memory and attention as assessed by Syndrom-Kurztest total value at end of study (p=0.00017). Improvements were seen in all 5 subsets of the SCAG (cognitive disturbances, emotional disturbances, lack of drive, social behavior, and somatic disturbances) (p<0.01). Authors concluded treatment improved memory, attention, psychopathology, psychomotor performance, functional dynamics, and neurophysiology after one month. Ginkgo was well-tolerated.

KEY: ADAS-Cog – Alzheimer's Disease Assessment Scale-cognitive subscale, **C** – controlled, **CC** – case-control, **CGIC** – Clinical Global Assessment of Change, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **GERRI** – Geriatric Evaluation by Relative's Rating Instrument, **GLC** – concentrated ginkgo leaf product, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **MMSE** – Mini Mental Status Exam, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **QPEG** –quantitative pharmaco-electroencephalogram, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** - single-center, **SCAG** – Sandoz Clinical Assessment Scale, **SKT** – Syndrom-Kurztest, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled, **WAIS** – Wechsler Adult Intelligence Scale.

Clinical Studies on Ginkgo (*Ginkgo biloba* L.) (cont.)

Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Vesper and Hansgen, 1994	Cerebral insufficiency	R, DB, PC, MC n=86 elderly patients with cerebral insufficiency	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	Target parameters and results were established with help of computer diagnostics and demonstrated improved reaction time, concentration ($p<0.05$), and mental flexibility ($p<0.05$), and improved memory ($p<0.05$), improved concentration power ($p<0.05$) after several weeks of ginkgo treatment.
Grässel, 1992	Cerebral insufficiency	R, DB, PC, MC n=53 elderly patients with cerebral insufficiency	24 weeks	80 mg, 2x/day or placebo	Rökan® EGb-761 (80 mg film-coated tablets)	Computer aided measurements revealed improved short-term memory and learning rate after treatment for 6 weeks or 24 weeks, respectively.
Brüchert *et al*., 1991	Cerebral insufficiency	R, DB, PC n=209 patients with typical symptoms of cerebral insufficiency	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After 12 weeks, statistically significant improvements were demonstrated on 8 out of 11 typical symptoms. In ginkgo group, period for figure connection test was improved by 25% vs. only 14% in placebo group ($p<0.01$) Both physicians and patients judged highly significant differences between ginkgo and placebo.
Halama, 1991	Dementia of degenerative or vascular origin	R, DB, PC n=42 patients with presenile, senile, and arteriosclerotic dementia	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After 12 weeks, significant differences between ginkgo and placebo group for 7 out of 11 typical symptoms. Ginkgo group was significantly faster in carrying out figure configuration test after 6 and 12 weeks. Authors concluded that ginkgo treatment resulted in improvement in cerebral functional capacity in patients with degenerative and vascular dementia.
Rai *et al*., 1991	Memory impairment	R, DB, PC, P n=27 elderly patients with mild to moderate memory impairment	6 months	40 mg, 3x/day or placebo	Tanakan® EGb-761 (40 mg tablets)	Ginkgo improved performance on digit-copying subtest of Kendrick battery at both 12 ($p=0.022$) and 24 ($p=0.017$) weeks, and improved speed of response on computerized classification task ($p=0.02591$), and mean reaction time ($p=0.0502$). Although the digit recall task at 24 weeks showed much lower scores ($p=0.032$), further analysis indicated that ginkgo has beneficial effects on mental efficiency.
Schmidt *et al*., 1991	Cerebral insufficiency	R, DB, PC n=99 patients with cerebral insufficiency	3 months	150 mg/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After only 4 weeks, 8 of 12 typical symptoms of cerebral insufficiency improved significantly ($p<0.05$ to $p<0.01$) compared to placebo. Ginkgo was very well-tolerated.
Eckmann, 1990	Cerebral insufficiency	R, DB, PC n=58 patients with cerebral insufficiency with leading symptom of depressive mood.	6 weeks	160 mg/day or placebo	LI 1370 liquid form	Marked differences in improvement of 11 of 12 symptoms in ginkgo group compared to placebo group. Largest number of improvements observed between 2nd and 4th week of treatment.
Hofferberth, 1989	Cerebro-organic syndrome	R, DB, PC n=36 elderly patients with cerebro-organic syndrome	2 months	40 mg, 3x/day or placebo	Rökan® EGb-761 (40 mg film-coated tablets)	Psychometric tests showed improved visual response speed with reduced saccade (eye movement) duration and latency (Saccade test) ($p<0.0001$), and improved reaction time (Vienna determination test and trail making test) ($p<0.0001$). Researchers concluded ginkgo is well-tolerated and of clinical efficacy.
Vorberg *et al*., 1989	Cerebral insufficiency	R, DB, PC n=96 patients with typical symptoms of cerebral insufficiency	3 months	15 ml, 3x/day (112 mg/day) or placebo	LI 1370 liquid form (Kaveri®)	Severity of symptoms improved in ginkgo group by 50% compared to only 25% with placebo. Statistically significant differences between ginkgo and placebo could be demonstrated for these symptoms: loss of memory, lack of concentration, anxiety, dizziness, and headache ($p<0.05$ to $p<0.001$).

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Clinical Studies on Ginkgo (*Ginkgo biloba* L.) (cont.)

Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Halama *et al.*, 1988	Cerebro-vascular insufficiency	R, DB, PC n=40 elderly patients with mild to medium cere-brovascular insufficiency	3 months	40 mg, 3x/day or placebo	Tebonin® forte EGb-761 (40 mg film-coated tablets)	After 12 weeks of ginkgo treatment, there was signifi-cant improvement in SCAG scale (p=0.00005), dizziness, (p<0.001), tinnitus (p=0.035), and lessened indifference to surroundings.
Wesnes *et al.*, 1987	Idiopathic cognitive impairment	R, DB, PC n=54 elderly patients with idiopathic cognitive impairment	3 months	40 mg, 3x/day or placebo	Tanakan® EGb-761 (40 mg film-coated tablets)	Treatment improved cognitive function and mental efficiency based on a battery of computerized and pen-cil-and-paper tasks (number matching, p=0.0183; word recognition, p=0.026), and increased interest in everyday life. Researchers concluded that ginkgo may be poten-tially helpful in treating early stages of primary degener-ative dementia.
Taillandier *et al.,* 1986	Cerebral insufficiency	R, DB, PC, MC n=166 elderly patients with cerebral insufficiency	12 months	2 ml, 3x/day (160 mg /day), or placebo	Tanakan® EGb-761 liquid form (40 mg/ml)	Scores on geriatric clinical evaluation scale test (meas-uring intellectual functions, mood, social insertion, and neurosensory disorders) were improved after 3 months of ginkgo treatment (p<0.05) and reached 17% improve-ment for placebo (p=0.01). Authors concluded that ginkgo is effective in ameliorating cerebral disorders due to aging.
Arrigo, 1986	Cerebro-vascular insufficiency	R, DB, PC, CO n=80 elderly patients with chronic cere-brovascular insufficiency	45 days drug; 15 days wash-out; vs. 45 days control; 15 days wash-out	40 mg, 3x/day or placebo	Tebonin® forte EGb-761	Ginkgo improved memory (p<0.0001), logical thinking, and vigilance, based on WAIS (p<0.01), a Word Recognition task and a Memory Table (p<0.0001). In addition, ginkgo lessened headache, dizziness, tinnitus, visual impairment, and asthenia, based on self-assessment by patients.

Peripheral Vascular Disease (Intermittent Claudication)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Schweizer and Hautmann, 1999	Peripheral Arterial Occlusive Disease; Fontaine's Stage IIb	R, DB, MC, P n=74	6 months	120 mg/day (n=38); 240 mg/day (n=36)	Rökan®	Pain-free walking distance improved with both 120 mg and 240 mg treatments, with a mean increase of 60.6 meters, and 107 meters, respectively (p=0.0253). The superiority of the higher dose was statistically significant and demonstrated a substantial therapeutic benefit.
Peters *et al.*, 1998	Intermittent claudication	R, DB, PC, MC n=111	6 months	40 mg, 3x/day or placebo	Tebonin® forte EGb-761 40 mg film-coated tablets	Ginkgo group experienced a significant decrease of pain associated with walking and increased walking distance, at 8 (p=0.017), 16 (p=0.007), and 24 (p=0.016) weeks.
Bauer, 1984	Peripheral arterial insufficiency, Fontaine's Stage IIb	R, DB, PC, PG n=79	6 months	40 mg, 3x/day or placebo	Rökan® EGb-761 40 mg film-coated tablets	Ginkgo group experienced decreased pain associated with walking, improved walking distance, and increased limb perfusion. Ginkgo was concluded to be a beneficial clinical treatment.

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Clinical Studies on Ginkgo (*Ginkgo biloba* L.) (cont.)

Respiratory Conditions (Asthma and Acute Mountain [Altitude] Sickness)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Gertsch *et al*., 2002	Acute mountain sickness (AMS)	R, DB, PC n=26 sea level residents	1 day prior to ascent	60 mg or placebo, 3x/day	*Ginkgo biloba* extract (brand not stated)	Participants traveled by air from sea level to 4,205 meters over 3 hrs with 1 hr at 2,835 m. Ginkgo group showed significantly lower median Lake Louise Self-report scores (LLSR) than placebo (4, range 1–8 vs. 5, range 2–9, p=0.03). Ginkgo lowered the incidence of AMS but this effect was not deemed statistically significant compared with placebo (58.3% vs. 92.9%, p=0.07). Authors conclude pretreatment with ginkgo one day prior to rapid ascent may reduce severity of AMS.
Leadbetter *et al*., 2001	Acute mountain sickness (AMS)	DB, PC n=40	5 days prior to ascent	120 mg or placebo, 2x/day	*Ginkgo biloba* extract (brand not stated)	Ginkgo reduced the incidence and severity of AMS when taken 5 days prior to an ascent of 4,300 meters. The ginkgo group demonstrated a decrease in incidence of AMS of 33% compared with 68% in the placebo group (p<0.02).
Li *et al*., 1997	Asthma	PC n=61	2 months	45 g crude herb, 10 ml, 3x/day (15 g/10 ml) (equates to 1,400 mg of standard extract) or placebo	Concentrated ginkgo leaf liquid product (produced by Quindao Fengyi Biotechnology Limited). Contains 14.5 mg/ml flavone glycosides and 2.8 mg/ml terpene lactones	Improved airway reactivity test at 4 and 8 weeks (p<0.05). Improved pulmonary function test at 8 weeks (p<0.05) including forced expiratory volume and peak expiratory flow rate.
Roncin *et al*., 1996	Control of acute mountain (altitude) sickness (AMS) and vascular reactivity to cold exposure	R, DB, PC n=44	30 days	80 mg, 2x/day or placebo	Tanakan® EGb-761 80 mg tablets	Ginkgo was effective in preventing AMS. No individuals receiving prophylactic experienced AMS, compared to 41% taking placebo (p=0.0014). Respiratory symptoms of altitude sickness occurred in 13.6% of the ginkgo group (p=0.000012), compared to 81.8% of the placebo group. Of ginkgo subjects, 18% reported moderate or severe impairment of diuresis at high altitude compared with 77% of placebo subjects. Ginkgo also reduced vasomotor disorders of the extremities, as demonstrated by plethysmography (p<10–8) and questionnaire (p<10–9). Authors concluded ginkgo treatment was effective.

Tinnitus and Acute Cochlear Deafness

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Drew and Davies, 2001	Tinnitus	DB, PC n=956	12 weeks	50 mg, 3x/day or placebo	LI 1370 or placebo	The researchers concluded that 50 mg ginkgo extract LI 1370 given 3 times daily for 12 weeks is no more effective than placebo. This conclusion was based upon participant's assessment of tinnitus before, during, and after treatment.
Meyer, 1986	Tinnitus	R, DB, PC, MC n=103 patients with recent tinnitus (appearing within the previous 12 months)	13 months	2 ml, 2x/day or placebo	Rökan® EGb-761 liquid form	Ginkgo treatment significantly improved symptoms of tinnitus compared to placebo (p=0.05). The time before disappearance or distinct improvement in 50% of tinnitus cases was 70 days in ginkgo group, compared to 119 days for placebo. Authors concluded that treatment with ginkgo improves the evolution of tinnitus.

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Clinical Studies on Ginkgo (*Ginkgo biloba* L.) (cont.)

Tinnitus and Acute Cochlear Deafness (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Dubreuil, 1986	Acute cochlear deafness	R, DB, C n=20 individuals with acute cochlear deafness (partial or complete) within the preceding week	30 days	4 ml liquid ginkgo extract 2x/day or 2 tablets nicergoline 3x/day	Rökan® EGb-761 or nicergoline	Ginkgo was superior over nicergoline, an alpha-blocker commonly prescribed for the same indication. By day 10, ginkgo group had an average gain of 30 decibels/frequency, compared to a 21-decibel gain with nicergoline treatment. By day 30, ginkgo patients had gained on average 34 decibels/frequency, compared to 23 decibels for nicergoline patients. After one month of treatment, ginkgo group registered a total gain exceeding the nicergoline group by 67 decibels, (6-15 decibels, depending on frequency). The small sample size demands cautious conclusions; however, ginkgo demonstrated much greater efficacy than nicergoline. Therapeutic results were obtained as early as day 10; however, several weeks of treatment are suggested to consolidate the result.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Engelsen *et al*., 2002	Drug interaction (long-term warfarin use in patients with recurrent venous thromboembolism, mechanical heart valves) or chronic atrial fibrillation)	R, DB, PC, CO n=21	4 weeks each phase with 2 week washout between each phase	100 mg ginkgo daily, 100 mg coenzyme Q10 daily or placebo	Bio-Biloba® (Ginkgo); Bio-Quinone® (CoQ10); placebo	The stability was confirmed by linear regression of INR values and geometric mean doses of warfarin did not change during treatment. The study concluded that CoQ10 and ginkgo do not interact with warfarin.
Hauns *et al*., 2001	Advanced colorectal cancer	Phase II n=32	Every 3 weeks, for 4 treatments (12 weeks)	350 mg ginkgo as a 30-minute i.v. infusion (days 1–6) followed by 500 mg/m2/d 5-FU as a 30-minute i.v. infusion (days 2–6)	EGb-761 and 5-Fluorouracil (5-FU)	The results suggested a good benefit-risk ratio of combining 5-FU and EGb 761 therapy as the second line treatment. Patients showed an overall response rate of 6.3%, with the disease progressing in 22 patients. Of these, the disease progressed in 17 patients after one course of treatment, 2 patients after 3 treatments, and 3 patients after 4 treatments. The study saw no change in 8 patients and a partial response in 2 patients.
Cohen and Bartlik, 1998	Sexual dysfunction secondary to SSRI use	O n=63	1 month	Average dose: 207 mg/day 40-60-120 mg, 2x/day (dosage range: 40–60 mg, 4x/day to 120 mg 2x/day)	Ginkgo extract (brand not stated) 40 or 60 mg capsules	Ginkgo was 84% effective in treating antidepressant-induced sexual dysfunction predominantly caused by selective serotonin reuptake inhibitors. Women were more responsive than men, with relative success rates of 91% versus 76%. Ginkgo had positive effects on desire, excitement, orgasm, and resolution phases of the sexual response cycle.
Itil *et al*., 1996	Effect on electrophysiological characteristics of the central nervous system	R, DB, PC, CO n=12	Acute treatment followed by a minimum 3-day washout	40 mg/day or 120 mg/day or 240 mg/day or placebo	Ginkgold® EGb-761	The higher doses had more pharmacological effects than the 40 mg dose, and the 120 or 240 mg dose may be clinically more beneficial (changes in alpha activity, p=0.002; change in coefficient of CEEG response, p=0.008). Ginkgo extract has electrophysiological effects in the central nervous system similar to other well-known cognitive activators.

KEY: ADAS-Cog – Alzheimer's Disease Assessment Scale-cognitive subscale, **C** – controlled, **CC** – case-control, **CGIC** – Clinical Global Assessment of Change, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **GERRI** – Geriatric Evaluation by Relative's Rating Instrument, **GLC** – concentrated ginkgo leaf product, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **MMSE** – Mini Mental Status Exam, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **QPEG** –quantitative pharmaco-electroencephalogram, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** - single-center, **SCAG** – Sandoz Clinical Assessment Scale, **SKT** – Syndrom-Kurztest, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled, **WAIS** – Wechsler Adult Intelligence Scale.

Clinical Studies on Ginkgo (*Ginkgo biloba* L.) (cont.)

Other (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Halama, 1990	Depression	R, DB, PC n=20 elderly patients with moderately severe depression	2 months	80 mg, 3x/day or placebo. Patients continued taking existing antidepressive medication (75–100 mg/day Stangyl®, n=12; 75–100 mg/day Ludiomil®, n=5; 50–75 mg/day Pertrofan®, n=3).	Tebonin® forte EGb-761 (40 mg tablets)	Severity of depression lessened in 3 patients, was unchanged in 4, and became worse in 3 patients. Placebo-treated groups showed no lessened depression, while depression remained unchanged in 5 and worsened in 5 patients. Authors conclude that results are inconclusive.
Schaffler and Reeh, 1985	Hypoxia	R, DB, PC, CO n=8	5 weeks drug; 2-week washout, 1 week placebo	4 ml (80 drops), 2 ml 2x/day or placebo	Tebonin® forte EGb 761 liquid form	The oculomotor system was used to test effectiveness of ginkgo. Hypoxia-induced increase of corneoretinal resting potential and the augmented respiratory drive were reduced. Compared with placebo, saccadic eye movements and choice reaction times were significantly reduced under cumulative hypoxic stress. These findings were interpreted as indicative of a protective action against hypoxia, relevant to the treatment of cardiovascular insufficiency.

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