Herbal Medicine

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Ginkgo Biloba leaf extract

Latin Name: *Ginkgo biloba L.*
Pharmacopeial Name: Ginkgo folium
Other Names: duck foot tree, maidenhair tree, silver apricot

Overview

There have been over four hundred scientific studies conducted on proprietary standardized extracts of the leaf of ginkgo in the past 30 years. Ginkgo is the world's most ancient extant tree, originating two hundred million years ago. Primary research was conducted by the W. Schwabe Co. of Karlsruhe, Germany, producer of the proprietary extract EGb 761. Ginkgo extract is a good example of a phytomedicine that must be standardized in order to deliver the intended benefits; the scientific literature does not support the clinical benefits of other dosage forms of crude ginkgo leaf or low-concentration extracts made from the leaf. The dry extract is pharmaceutically prepared to a 35–67:1 ratio of dried leaves to final extract; standardization is carried out to 24% ginkgo flavonol glycosides (based on flavones like quercetin, kaempferol, and isorhamnetin) and 6% terpene lactones (ginkgolides and bilobalide). A comprehensive, almost exhaustive, 401 page book reviewing the chemistry, pharmacology, toxicology, and all clinical studies conducted on EGb761 in various areas of clinical application has been published (DeFeudis, 1998).

Ginkgo biloba extract (GBE) has been popular in Europe and now is popular in the United States and other parts of the world for its neuroprotective properties and ability to aid circulatory problems in the elderly, especially cerebral insufficiency and the consequent cognitive effects, peripheral circulatory impairment, particularly intermittent claudication (poor circulation to the lower legs), and vertigo and tinnitus. New uses for protection against altitude sickness and to mediate erectile dysfunction in males have also been investigated.

Clinical studies demonstrate that daily doses of 120 to 240 mg of GBE can lead to an improvement in the symptoms associated with cerebral insufficiency, such as memory loss, depression, and tinnitus, within 8 to 12 weeks (Vorberg, 1985; Rai et al., 1991). An early review of 20 clinical studies concluded that many categories of elderly patients could benefit from GBE (Warburton, 1988). All of these trials used EGb 761.

In a later critical review of 40 ginkgo trials, the authors looked for evidence of the efficacy of GBE in cerebral insufficiency (Kleijnen and Knipschild, 1992a, 1992b). Four gingko preparations were used in the trials: Tebonin®, Tanakan®, rkan®, and Kaveri®. The first three are different names for EGb 761, the Schwabe product. Kaveri® (LI 1370; Lichtwer Pharma, Germany) is standardized in comparable percentages (25 and 6%). In accordance with German regulatory requirements, both products are purified to contain less than 5 parts per million ginkgolic acids. The standard dose was 120 mg/day for at least four to six weeks. Of the 40 trials, eight were deemed well performed. Shortcomings in the other trials included small patient numbers, inadequate description of randomization procedures, patient characteristics, effect measurement, and data presentation. In no trial was double-blindness checked. Virtually all trials reported positive results, and no serious side effects were reported in any trial. In a comparison of ginkgo with co-dergocrine, registered for the same indication, no marked differences were found in the quality of the evidence of the efficacy of ginkgo in cerebral insufficiency compared with co-dergocrine. The authors concluded that positive results have been reported for ginkgo in the treatment of cerebral insufficiency, but further studies should be conducted for a more detailed assessment of its efficacy.

In a meta-analysis of 11 placebo-controlled, randomized, double-blind trials in aged patients with cerebral insufficiency (Hopfenm ller, 1994), eight comparable trials were examined, most using a daily dose of 150 mg. Seven of the studies confirmed the effectiveness of ginkgo compared to placebo in cerebral insufficiency, while one study was inconclusive. Another double-blind trial tested the efficacy of LI 1370 on 90 patients with cerebral insufficiency caused by old age (Vesper and Hnsgen, 1994). A daily dose of 150 mg was administered for 12 weeks, with the ginkgo group showing significant improvement compared to

placebo.

A recent meta-analysis (Oken et al., 1998) systematically reviewed over 50 clinical studies on GBE for treatment of dementia and cognitive functions associated with Alzheimer's disease (AD). Only four studies met the inclusion criteria for the evaluation, because in many of the trials patients did not have a clear diagnosis of dementia and AD. There were 212 patients each in the ginkgo and placebo groups of the four studies. Based on a quantitative analysis of these trials, the researchers concluded that administration of 120 mg to 240 mg GBE (EGb 761, Tanakan®; Ipsen, France) for three to six months had a small but significant effect on objective measures of cognitive function in AD, without significant adverse effects in formal clinical trials.

Until recently, market claims for the application of ginkgo for Alzheimer's disease were viewed as exaggerated and unfounded. However, three studies have suggested potential benefits in this area. Ginkgo has shown therapeutic potential in slowing some of the symptoms associated with early stages of Alzheimer's disease. In a randomized, double-blind, placebo-controlled study of 40 patients with senile dementia of the Alzheimer type, a daily dose of 240 mg of EGb 761 was given to the treatment group (Hofferberth, 1994). Battery tests were administered at baseline, one, two, and three months, with a significant improvement in memory and attention in the ginkgo group after only one month. No side effects were reported, and improvement continued over the three-month study.

Another study also suggests ginkgo's benefits for early stages of Alzheimer's (Kanowski et al., 1996, 1997). A randomized, double-blind, placebo-controlled study of 156 patients with presenile or senile primary degenerative dementia of the Alzheimer's type or multi-infarct dementia was conducted for 24 weeks using EGb 761. Seventy-nine subjects received 240 mg ginkgo extract per day; 77 received placebo. The ginkgo group was observed to have responded at a rate of 28% to three primary variables compared to only 10% for the placebo group. The authors concluded that GBE is "of clinical efficacy in the treatment of outpatients with dementia" of the two types noted.

Of considerable interest was the recent study published in *JAMA* on ginkgo's effects in preventing symptoms associated with Alzheimer's (Le Bars et al., 1997). This involved a placebo-controlled, double-blind, randomized, multicenter trial with 202 men and women 45 years of age or older, diagnosed with mild to moderately severe dementia. The trial lasted 52 weeks, with 97 subjects given 120 mg per day of EGb 761, and 105 given placebo. Using standardized assessment scales, patients were evaluated at baseline and at three-month intervals for cognitive function, daily living skills, social behavior, and overall impairment. Compared to placebo, the ginkgo group showed either improvement or a delay in progression of the disease with every assessment tool except that used for evaluation of overall impairment. The researchers concluded that EGb 761 was safe and appeared capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for six months to one year.

In an editor's note published with the Le Bars study, *JAMA* senior editor Margaret Winker, M.D., acknowledged that "Few treatments for Alzheimer's disease (AD) have been found to be both effective and acceptable to patients and their caregivers" (Winker, 1997). She noted the increase in popularity of natural substances for various conditions and lamented the lack of controlled clinical trials (presumably focusing on American medical journals) to test these products and the fact that, as natural products, their chemistry of "active ingredients" is variable. Dr. Winker stated that this trial used EGb 761, the chemically defined, standardized extract for treatment of dementia. She pointed out, "While the effect size was modest, EGb 761 reduced patients' cognitive decline and manifestations of dementia rated by the caregiver as compared with placebo, particularly for patients with a diagnosis of AD. The mechanism of action is unclear but it is postulated to be related to the agent's antioxidant properties. Only a single dose was studied, drop-out rates were high, and longer-term follow-up will be important; but this agent is an intriguing addition to the drugs thought to be helpful for patients with AD."

A recent review compared ginkgo with two conventional nootropic (cognitive-activating) medications (Letzel et al., 1996). Forty-four randomized, double-blind, placebo-controlled clinical trials were reviewed in which ginkgo extract, nimodipine, and tacrine were tested. Statistically significant results were obtained at three levels of efficacy (psychopathological, psychometric, and behavioral) for all three substances. The authors compared 25 studies on ginkgo, 9 on nimodipine, and 10 on tacrine. They noted that frequency of adverse events was lowest with ginkgo, confirming the previously established relative safety of ginkgo extract. They also compared study design to new standards set in Germany and the European Community, reporting that progress in the methodology of the studies has improved in the last decade and that "the efficacy of *Ginkgo biloba* special extract and tacrine has already been demonstrated according to the strictest criteria."

Another recent review investigated the use of ginkgo for dementia (Alzheimer type, multi-infarct dementia, or mixed types) (Ernst and Pittler, 1999). Eighteen double-blind, randomized, placebo-controlled trials were identified by the authors after extensive search on major databases. Nine were excluded, eight because patients were assessed with "cerebral insufficiency" and one due to assessment of cerebro-organic syndome. The authors concluded that the majority of randomized controlled trials support the idea that GBE is "efficacious in delaying the clinical deterioration of patients with dementia or in bringing about symptomatic improvement." The authors noted that none of the current studies were "flawless and ultimately convincing" but that the safety and tolerability profile of ginkgo is "reassuring." They called for more research to answer many questions that remain about ginkgo's efficacy.

A review of controlled studies on GBE in the treatment of intermittent claudication reported on 10 trials, finding most of poor methodological quality. All studies implied gingko was an effective therapy for intermittent claudication. The author recommended further trials with meticulous methodology, including studies on whether ginkgo can be usefully combined with walking exercise (Ernst, 1996). The Commission E reviewed some of these studies and concluded that there was sufficient evidence for approval for this indication. A recent trial on 111 patients with angiographically proven peripheral arterial disease and intermittent claudication was published on EGb 761 (Peters et al., 1998). A significant increase in pain-free walking distance was observed in the group taking 120 mg ginkgo extract over a 24-week study conducted in five centers. However, because Doppler index values did not change to indicate an increase in total

circulation to the legs, the authors of this study speculated that the improvement in walking distance may be due to improved nutrition to tissues and microcirculation, rather than changes in macrocirculatory parameters.

The use of GBE (EGb 761) was examined for the treatment of peripheral arterial occlusive disease in a randomized, placebo-controlled, double-blind study. Forty patients suffering from Fontaine stage IIb were given two 80 mg tablets per day and the difference in pain-free walking distance was measured after eight, sixteen, and twenty-four weeks of treatment. By twenty-four weeks, the changes in the mean pain-free walking distance were +47.7% and +14.3% (p=0.021). The study concluded that the tolerability of GBE was good and that it had demonstrated clinical efficacy for peripheral arterial occlusive disease (Blume et al., 1998).

An analysis of twelve placebo-controlled, randomized, double-blind studies (five on GBE, seven on pentoxifylline) found a relative increase in pain-free walking distance of 45% for GBE (EGb 761) and 57% for pentoxifylline, the most-frequently prescribed synthetic treatment for peripheral occlusive arterial disease (Letzel and Schoop, 1992).

A meta-analysis of EGb 761 in the treatment of peripheral arterial disease examined five placebo-controlled trials with similar design and inclusion criteria (Schneider, 1992). In all studies, treatment effect was quantified by the increase of walking distance measured in a standard treadmill exercise. The analysis revealed a highly significant therapeutic effect of EGb 761 for the treatment of peripheral arterial disease, based on a mean increase in walking distance of 0.75 times (of the standard deviation) higher than that achieved by placebo. A daily dose of 120 mg for six months was successful in the treatment of intermittent claudication in 79 patients (Bauer, 1984). The randomized, placebo-controlled, double-blind study found significant improvement in the ginkgo group compared to placebo after 24 weeks.

The results of studies on ginkgo's effectiveness in tinnitus (ringing of the ears) have been mixed. A recent study failed to substantiate ginkgo's efficacy in treating this condition. Eighty patients were given ginkgo in this open trial, with 21 patients reporting improvements. Twenty of the 21 patients reporting improvements were then included in a double-blind, placebo-controlled, crossover study, with discouraging results. Seven patients believed ginkgo effective, seven preferred placebo, and the other six found no difference between placebo and ginkgo. The authors concluded that while statistical group analysis in this study did not support the use of ginkgo for tinnitus, it is possible that GBE has an effect on some patients (Holgers et al, 1994). However, this study was not performed using the GBE EGb 761, and the dose was 29.2 mg of extract per day instead of the usual dose of 120–240 mg per day. The Commission E approved GBE for tinnitus of "vascular and involutive origin."

In a randomized, double-blind, placebo-controlled study on tinnitus, 99 patients were given a 40 mg tablet of GBE (EGb 761), 3 times daily for 12 weeks. Improvement in the sound volume (5 to 10 dB) of the ear with the worst tinnitus was shown after 8 and 12 weeks in the GBE group, while the placebo group remained unchanged. Statistically significant differences were not observed in the other measured parameters: the contralateral ear, click-evoked otoacoustic emissions, subjective assessment of intensity, or hearing loss (Morgenstern and Biermann, 1997).

An interesting study of mountain climbers was conducted in the Himalayas using EGb 761 (Tanakan®) (Roncin et al., 1996). This randomized, controlled study was based on 44 healthy men who had experienced symptoms of altitude sickness on previous climbs. Over a period of eight days, they ascended to a base camp at about 14,700 feet elevation, with periodic ascents to higher points. The daily dose for the ginkgo group was two tablets twice per day (160 mg total). According to the assessment of cerebral symptoms, none of the climbers in the ginkgo group experienced acute mountain sickness (headache, dizziness, shortness of breath, nausea, vomiting), compared to 41% of the placebo group. In the assessment by respiratory parameters, 14% of the ginkgo climbers experienced altitude sickness, compared to 82% in the placebo group. Ginkgo was also rated significantly more effective in preventing cold-related circulatory problems (numbness, tingling, aching, and swelling of extremities), based on evaluations of the functional disabilities and results obtained by plethysmography (measurement extremity circulation). Also, 18% of the ginkgo climbers reported moderate or severe impairment of diuresis, compared to 77% on placebo.

In a somewhat novel application of ginkgo, researchers have studied its benefits in assisting patients suffering from anti-depression-induced sexual dysfunction, caused predominantly by selective serotonin reuptake inhibitors (SSRIs) (Cohen and Bartlik, 1998). The study was conducted in response to a case of a geriatric patient using *Ginkgo biloba* for memory enhancement who reported improved erections. The open study on 63 subjects found that women (33) were more responsive to the sexually enhancing effects than men (30), with relative success rates of 91% compared to 76% for the men. The ginkgo (product brand not noted) was given at a dosage range of 60 to 120 mg twice daily, within the normal range for the usual applications of ginkgo. The ginkgo reportedly had a positive effect on all four phases of the sexual response cycle: desire, excitement (erection and lubrication), orgasm, and resolution (afterglow). The authors note that the mechanism of action for this application is not yet clear. Postulated mechanisms include enhanced circulation to genitals by inhibition of PAF, direct effect on prostaglandins, known to enhance erectile function, and yet-to-be described norepinephrine receptor-induced effects on the brain.

In sum, there is a considerable degree of evidence from clinical trials to support the present use of GBE for a range of cognitive and peripheral vascular conditions. This conclusion was reinforced by the recent publication of a monograph on ginkgo by the World Health Organization (see Uses, below) (WHO, 1999).

Although most commercial ginkgo products sold as dietary supplements in the United States appear to be standardized to similar parameters (i.e., concentrated 50–1, standardized to 65 terpenes and 24% flavonol glycosides), it is possible that there may be differences in the biological activity of various brands. One study compared three commercial products in humans by measuring dynamic mapping of brain wave activity by computer-aided EEG (Itil and Mortorano, 1995). All three products increased alpha activity and decreased delta, theta, and beta waves. The study demonstrated that one product (Ginkgold®, Nature's Way, Utah; equivalent to EGb 761) was observed in all areas of the brain, while the effects of the others were limited to specific areas: one brand was limited to the temporal area and the other was limited

primarily to the frontal area and slightly in the left posterior temporal area. The authors concluded that Ginkgold® produced the most homogeneous central nervous system effects in healthy subjects, with 9 out of 12 showing central nervous system effects correlated with cognitive activating drugs, e.g., tacrine.

In 1994, the Commission E published a negative (unapproved) monograph for various types of ginkgo preparations that did not conform to the parameters for the approved dried standardized preparation (made with acetone and water). These unapproved preparations include crude ginkgo leaf and related preparations, plus non-standardized extracts and fluidextracts from ginkgo leaf made with water and ethanol or methanol. The approved monograph clearly focuses on a specific type of preparation; the two commercial extracts of this type being the preparations on which almost all the scientific and clinical studies on the effectiveness of GBE have been carried out (as noted above). Thus, only the specified acetone-water extract of ginkgo was approved.

In May 1997, the German Federal Institute for Drugs and Medical Devices (BfArM) sent a letter to manufacturers of ginkgo extracts and other preparations regarding the levels of ginkgolic acids in these products. The letter stated that, based on the present level of knowledge, the BfArM considered it necessary to reduce the content of ginkgolic acids in finished ginkgo preparations to a maximum level of five parts per million. If proof of this level cannot be documented, "the registration for these pharmaceuticals will be cancelled since in this case, there is the well-founded suspicion that the pharmaceuticals—when used in accordance with the instructions [in the monographs]—produce damaging effects which exceed a justifiable degree according to the knowledge of medical science" (Thiele, 1997).

Pharmacopeial grade ginkgo leaf, for use in manufacturing the standardized extracts described in this monograph, consists of the dried leaf of *Ginkgo biloba* L. The raw material may contain no more than 3.0% stems and not more than 2.0% other foreign organic matter. It must contain not less than 0.8% flavonol glycosides as determined by liquid chromatography. Botanical identity must be confirmed by a thin-layer chromatography (TLC) test, as well as macroscopic and microscopic examinations (USP 24–NF19, 1999). Additionally, the *British Herbal Pharmacopoeia* requires that the dried leaf contain not less than 18% water-soluble extractive (BHP, 1996).

Description

A dry extract from the dried leaf of *Ginkgo biloba* L. manufactured using acetone-water and subsequent purification steps without addition of concentrates or isolated ingredients. The preparation/extract ratio is 35–67:1, on average 50:1. The extract is characterized by: 22–27% flavonone glycosides, determined as quercetin and kaempferol, including isorhamnetin (via HPLC) and calculated as flavones with a molar mass of MMr = 756.7 (quercetin glycosides) and Mr = 740.7 (kaempferol glycosides); 5–7% terpene lactones, of which approximately 2.8–3.4% consists of ginkgolides A, B, and C, as well as approximately 2.6–3.2% bilobalide; below 5 ppm ginkgolic acids. The given ranges include manufacturing and analytical variances.

Chemistry and Pharmacology

Ginkgo leaf contains diterpenes including ginkgolide A, ginkgolide B, ginkgolide C (Budavari, 1996), plus ginkgolide J, and the sesquiterpene bilobalide; flavonols, including kaempferol, quercetin, and isorhamnetin; flavones, including luteolin and tricetin; biflavones, mainly bilobetin, ginkgetin, isoginkgetin (Huang, 1999; Leung and Foster, 1996), and sciadopitysin (Gobbato et al., 1996); catechins; proanthocyanidins; sterols (Leung and Foster, 1996); and 6-hydroxykynurenic acid (6-HKA) (Grsel and Reuter, 1998).

According to the Commission E, the following pharmacological effects have been established experimentally:

Improvement of hypoxic tolerance, particularly in the cerebral tissue.

Inhibition of the development of traumatically or toxically induced cerebral edema, and acceleration of its regression.

Reduction of retinal edema and of cellular lesions in the retina.

Inhibition in age-related reduction of muscarinergic cholinoceptors and alpha-adrenoceptors as well as stimulation of choline uptake in the hippocampus.

Increased memory performance and learning capacity.

Improvement in the compensation of disturbed equilibrium.

Improvement of blood flow, particularly in the region of microcirculation.

Improvement of the rheological properties of the blood.

Inactivation of toxic oxygen radicals (flavonoids).

Antagonism of the platelet-activating factor (PAF) (ginkgolides).

Neuroprotective effect (ginkgolides A and B, bilobalide).

The pharmacokinetics have been investigated both in animal experiments and in trials involving humans.

An absorption rate of 60% was found in rats for a radioactively labeled extract (as specified under the Description section, above). In humans, after application of an extract specified as above, absolute bioavailability was 98100% for ginkgolide A, 7993% for ginkgolide B, and at least 70% for bilobalide.

Both the acute and the chronic toxicity of an extract as specified under Descriptionis very low; accordingly, the LD50 in the mouse was 7725 mg/kg body weight after oral application and 1100 mg/kg body weight after intravenous application.

Investigations with this extract as specified above showed no effects which were either mutagenic, carcinogenic, or toxic to reproduction (DeFeudis, 1998).

No evaluation was performed on the transferability of the experimental results to extracts other than those investigated.

> [Ed. note:This statement refers to the fact that only a few proprietary ginkgo extracts were used in the studies upon which this monograph is based. Whether these results can be extrapolated to other ginkgo extracts is uncertain.]

The vaso- and tissue-protective actions of ginkgo extract include the properties of relaxing blood vessels in spastic conditions, increasing tone of abnormally relaxed vessels, protecting against capillary permeability, inhibiting platelet aggregation and antithrombotic activity, and anti-ischemic and anti-edematous properties. The flavonoids present in GBE may be responsible for the cognitive-enhancing action of ginkgo extract. These flavonoids may enhance the release of catecholamines and other neurotransmitters, inhibit biogenic amine uptake, protect catechol-O-methyltransferase and monoamine oxidase, and protect endothelial-derived relaxing factor mechanisms in the brain (Van Beek et al., 1998).

Uses

The Commission E approved the internal use of ginkgo for the following conditions:

(a) For symptomatic treatment of disturbed performance in organic brain syndrome within the regimen of a therapeutic concept in cases of dementia syndromes with the following principal symptoms: memory deficits, disturbances in concentration, depressive emotional condition, dizziness, tinnitus, and headache. The primary target groups are dementia syndromes, including primary degenerative dementia, vascular dementia, and mixed forms of both.

> Note:Before starting treatment with ginkgo extract, clarification should be obtained as to whether the pathological symptoms encountered are not based on an underlying disease requiring a specific treatment.

(b) 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.

(c) Vertigo and tinnitus (ringing in the ear) of vascular and involutional origin.

The World Health Organization reiterated the Commission E approved uses noted above, adding the following specific conditions to peripheral arterial occlusive disease: Raynaud's disease (intermittent blue coloring of extremities due to restricted blood flow with no known direct cause, i.e., idiopathic, other than possible cold or emotion), acrocyanosis (i.e., Crocq's disease: persistently poor circulation to hands and sometimes the feet, resulting in cold, blue, sweaty condition), and post phlebitis syndrome (painful swelling of veins) (WHO, 1999).

Contraindications

The Commission E noted hypersensitivity to ginkgo preparations.

The product data sheet of the leading ginkgo preparation (EGb 761) notes that the 120 mg dosage (Tebonin intens 120 mg) should not be used in children under 12. 'Since Ginkgo extracts have not yet been sufficiently investigated in case of depressive mood and headache not occurring in relation with demential syndromes, [this product] may only be applied in these symptoms when taking into consideration all necessary precautionary measures' (Schwabe, 1999).

Side Effects

Very seldom cases of stomach or intestinal upsets, headaches, or allergic skin reaction.

Use During Pregnancy and Lactation

No restrictions known.

Interactions with Other Drugs

Commission E reported that none were known (based on data available before publication of the monograph in July, 1994).

The Tebonin product data sheet notes, 'The effect of platelet-aggregation inhibitors may be enhanced. The case of a spontaneous hyphema after combined intake of a Ginkgo-biloba-containing pharmaceutical and aspirin has been documented' (Schwabe, 1999).

Dosage and Administration

Unless otherwise prescribed: 120-240 mg standardized dry extract in liquid or solid pharmaceutical form for oral intake, given in two or three daily doses to treat indication (a) listed above in the Use section. Indications (b) and (c) require 120-160 mg native dry extract, given in two or three daily doses.

References

Bauer, U. 1984. Six-month double-blind randomized clinical trial of *Ginkgo biloba* extract versus placebo in two parallel groups of patients suffering from peripheral arterial insufficiency. *Arzneimforsch* 34(6):716720.

Blume, J., M. Kieser, U. Hlscher. 1998. [Efficacy of *Ginkgo biloba* special extract EGb 761 in peripheral arterial occlusive disease] [In German]. *Fortschr Med* 116:137-143.

British Herbal Pharmacopoeia (BHP). 1996. Exeter, U.K.: British Herbal Medicine Association. 8788.

Budavari, S. (ed.). 1996. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals,* 12th ed. Whitehouse Station, N.J.: Merck & Co, Inc. 751.

Cohen, A.J. and B. Bartlik. 1998. *Ginkgo Biloba* for antidepressant-induced sexual dysfunction. *J Sex Marital Ther* 24(2):139143.

DeFeudis, F.V. 1998. *Ginkgo biloba extract (EGb 761): From Chemistry to the Clinic.* Weisbaden, Germany: Ullstein Medical Verlagsgesellschaft.

Ernst, E. 1996. [*Ginkgo biloba* in treatment of intermittent claudication. A systematic research based on controlled studies in the literature] [In German]. *Fortschr Med* 114(8):8587.

Ernst, E. and M.H. Pittler. 1999. *Ginkgo biloba* Dementia: A systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 17(4):301308.

Gobbato, S., A. Griffini, E. Lolla, F. Peterlongo. 1996. HPLC quantitative analysis of biflavones in *Ginkgo biloba* leaf extracts and their identification by thermospray liquid chromatography-mass spectrometry. *Fitoterapia* 67(2):152158.

Grsel, I. and G. Reuter. 1998. Analysis of 6-hydroxykynurenic acid in *Ginkgo biloba* and Ginkgo preparations. *Planta Med* 64:566570.

Hofferberth, B. 1994. The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type: A double-blind, placebo-controlled study on different levels of investigation. *Hum Psychopharmacol* 9:215222.

Holgers K, A. Axelsson, I. Pringle. 1994. *Ginkgo biloba* extract for the treatment of tinnitus. *Audiology* 33 (2):8592.

Hopfenm ller, W. 1994. [Proof of the therapeutic effectiveness of a *Ginkgo biloba* special extract. Meta-analysis of 11 clinical trials in aged patients with cerebral insufficiency] [In German]. *Arzneimforsch* 44 (9):10051013.

Huang, K.C. 1999. *The Pharmacology of Chinese Herbs*. Boca Raton: CRC Press. 9799.

Itil, T. and D. Martorano. 1995. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharm Bull* 31(1):147158.

Kanowski, S., W.M. Hermann, K. Stephan, W. Wierich, R. Horr. 1997. Proof of the efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate dementia of the Alzheimer's type or multi-infarct dementia. *Phytomedicine* 4(1):313.

Kanowski, S., W.M. Hermann, K. Stephan, W. Wierich, R. Horr. 1996. Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry* 29:4756.

Kleijnen, J. and P. Knipschild. 1992a. *Ginkgo biloba* for cerebral insufficiency. *Br J Clin Pharmacol* 34 (4):352358.

. 1992b. *Ginkgo biloba. Lancet* 340(8828):11361139.

Le Bars, P.L. et al. 1997. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA* 278(16):13271332.

Letzel, H., J. Haan, W.B. Feil. 1996. Nootropics: Efficacy and tolerability of products from three active substance classes. *J Drug Dev Clin Pract* 8:7794.

Letzel, H. and W. Schoop. 1992. *Ginkgo biloba* extract EGb 761 and pentoxifylline in intermittent claudicaton: Secondary analysis of clinical efficacy studies. *Vasa* 21(4):403410.

Leung, A.Y. and S. Foster. 1996. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics,* 2nd ed. New York: John Wiley & Sons, Inc.

Morgenstern, C. and E. Biermann. 1997. *Ginkgo biloba* special extract EGb 761 in the treatment of tinnitus aurium: Results of a randomized, double-blind, placebo-controlled study. *Fortschr Med* 115(4):711.

Oken, B.S., D.M. Storzbach, J.A. Kaye. 1998. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. *Arch Neurol* 55(11):14091415.

Peters, H., M. Kieser, U. Holscher. 1998. Demonstration of the efficacy of *Ginkgo biloba* special extract EGb 761 on intermittent claudicationa placebo-controlled, double-blind multicenter trial. *Vasa* 27(2):105110.

Rai, G.S., C. Shovlin, K.A. Wesnes. 1991. A double-blind, placebo controlled study of *Ginkgo biloba* extract (Tanakan) in elderly out-patients with mild to moderate memory impairment. *Curr Med Res Opin* 12 (6):350355.

Roncin, J.P., F. Schwartz, P. D'Arbigny. 1996. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. *Aviat Space Environ Med* 67(5):44552.

Schneider, B. 1992. *Ginkgo biloba* extract in peripheral arterial diseases. Meta-analysis of controlled clinical studies. *Arzneimforsch* 42(4):428436.

Thiele, A. 1997. Averting of drug-induced risks, grade II: pharmaceuticals containing *Ginkgo biloba* leaves. Communication to Dr. Willmar Schwabe GmbH & Co., May 27.

United States Pharmacopeia, 24th rev. and *National Formulary*, 19th ed. (USP 24NF19). 1999. Rockville, MD: United States Pharmacopeial Convention, Inc. 24582459.

Van Beek, T.A., E. Bombardelli, P. Morazzoni, F. Peterlongo. 1998. *Ginkgo biloba* L. *Fitoterapia* 49 (3):195244.

Schwabe. 1999. Tebonin intens 120 mg Data Sheet. Karlsruhe, Germany: Willmar Schwabe Arzneimittel GmbH & Co.

Vesper, J. and K.D. Hnsgen. 1994. Efficacy of *Ginkgo biloba* in 90 outpatients with cerebral insufficiency caused by old age. *Phytomedicine* 1:916.

Vorberg, G. 1985. *Ginkgo biloba* extract (GBE): A long-term study of chronic cerebral insufficiency in geriatric patients. *Clin Trials J* 22:149157.

Warburton, D.M. 1988. Clinical psychopharmacology of *Ginkgo biloba* extract. In: Funfgeld, E.W. (ed.). *Rokan (Ginkgo biloba): Recent Results in Pharmacology and Clinic.* Berlin-Heidelberg: Springer Verlag. 327345.

Winker, M.A. 1997. Aging: A global issue [Editor's Note]. *JAMA* 278(16):1378b.

World Health Organization (WHO). 1999. Ginkgo folium. *WHO Monographs on Selected Medicinal Plants,* Vol. 1. Geneva: World Health Organization.

Additional Resources

Ahlemeyer, B. and J. Kriglstein. 1998. Neuroprotective Effects of *Ginkgo biloba* Extract. In: L.D. Lawson and R. Bauer (eds.). *Phytomedicines of Europe: Chemistry and Biological Activity.* Washington, DC: American Chemical Society. 210220.

Auguer, M. et al. 1994. *Advances in Ginkgo biloba Extract Research,* Vol. 3. Elsevier: Paris. 3137.

Blume J., M. Kieser, U. Hlscher. 1996. [Placebo-controlled double-blind study on the efficacy of *Ginkgo biloba* special extract EGb 761 in maximum-level-trained patients with intermittent claudication] [In German]. *Vasa* 25(3):265274.

Bone, K. 1996. GinkgoRecent Research. *Can J Herbalism* Spring:2941.

Braquet, P. 1987. The ginkgolides: potent platelet-activating factor antagonists isolated from *Ginkgo biloba* L.: Chemistry, pharmacology and clinical applications. *Drugs of the Future* (12):643699.

Brown, D. 1997. *Ginkgo Biloba* Extract for Age-Related Cognitive Decline and Early-stage DementiaA Clinical Overview. *Quarterly Rev Nat Med* Summer:9196.

Bruneton, J. 1995. *Pharmacognosy, Phytochemistry, Medicinal Plants.* Paris: Lavoisier Publishing.

Chatterjee, S.S. et al. 1985. *Effects of* Ginkgo Biloba *Extract on Organic Cerebral Impairment.* London: John Libbey Eurotext, Ltd.

Chung, K.F. et al. 1987. Effect of a ginkgo-like mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man. *Lancet* (1):218219.

DeFeudis, F.V. 1991. *Ginkgo biloba extract (EGb 761):Pharmacological Activities and Clinical Applications.* Elsevier Editions Scientifiques: Paris. 5051.

Della Loggia, R. et al. 1996. Anti-inflammatory activity of some *Ginkgo biloba constituents* and their phospholipid-complexes. *Fitoterapia* 67(3):257264.

Foster, S. 1991. *Ginkgo biloba. Botanical Booklet Series,* No. 304. Austin, TX: American Botanical Council.

Guinot, P., E. Caffrey, R. Lambe, A. Darragh. 1989. Tanakan inhibits platelet-activating-factor-induced platelet aggregation in healthy male volunteers. *Haemostasis* 19(4):219223.

Haguenauer, J.P., F. Cantenot, H. Koskas, H. Pierart. 1988. Treatment of disturbed equilibrium with *Ginkgo Biloba* extract: Multicenter double-blind study versus placebo. In: F ngfeld, E.W. (ed.). *Rkan (Ginkgo Biloba).Recent Results in Pharmacology and Clinic.* New York: Springer Verlag.

Itil, T.M., E. Erlap, E. Tsambis, K.Z. Itil, U. Stein. 1996. Central nervous system effect of *Ginkgo Biloba*, a plant extract. *Am J Therapeutics* 3(63):6373.

Itil, T.M., S.H. Kornhauser, I. Ahmed. 1996. Early diagnosis and treatment of memory disturbances. *Am J Electromed* Jun:8185.

Janssens, D. et al. 1995. Protection of hypoxia-induced ATP decrease in endothelial cells by *Ginkgo biloba* extract and bilobalide. *Biochem Pharmacol* 50(7):991999.

Jung, F., C. Mrowietz, H. Kiesewetter, E. Wenzel. 1990. Effect of Gingko Biloba on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimforsch* 40(5):589593.

Maurer, K., R. Ihl, T. Dierks, L. Frolich. 1997. Clinical efficacy of *Gingko biloba* special extract EGb 761 in dementia of the Alzheimer type. *J Psychiatr Res* 31(6):645655.

Meyer, B. 1988. A multicenter randomized double-blind study of *Ginkgo biloba* extract versus placebo in the treatment of tinnitus. In: F nfgeld, E.W. (ed.). *Rkan (Ginkgo Biloba).Recent Results in Pharmacology and Clinic.* New York: Springer Verlag.

Pietri, S., J.R. Seguin, P. d'Arbigny, K. Drieu, M. Culcasi. 1997. Gingko biloba extract (EGb 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther* 11(2):121131.

Pincemail, J. and C. Deby. 1986. Proprietes antiradiclaites de l'extraite de *Ginkgo biloba* [Antiradical properties of *Ginkgo biloba* extract]. *Presse Med* 15(31):14751479.

Pincemail, J. et al. 1989. Superoxide anion scavenging effect and superoxide dismutase activity of *Ginkgo biloba* extract. *Experientia* 45:708712.

Robben Batre, P. et al. 1996. Phase II study with 5-FU plus *Gingko biloba* extract (GBE 761 ONC) in 5-FU pretreated patients with advanced colorectal cancer. (Annual Congress of the German and the Austrian Society of Hematology) *Ann Hematol* 73(2):A73.

Schulz, V., R. Hnsel, V.E. Tyler. 1998. *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine.* New York: Springer. 38-50.

Scorolli, L. et al. 1997. Evolution of color vision in early diabetic retinopathy treated by *Ginkgo biloba* extract. *Ann Ottalmol Clin Ocul* 123(68):245251.

Smith, P.F., K. Maclennan, C.L. Darlington. The neuroprotective properties of *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor. 1996. *J Ethnopharmacol* 50(3):131139.

Soholm, B.1998. Clinical improvement of memory and other cognitive functions by *Gingko biloba:* Review of relevant literature. *Adv Ther* 15(1):5465.

Tang, W. and G. Eisenbrand. 1992. *Chinese Drugs of Plant Origin: Chemistry, Pharmacology, and Use in Traditional and Modern Medicine.* New York: Springer Verlag.

Wesnes, K.A. et al. 1997. The cognitive, subjective, and physical effects of a *Ginkgo biloba/Panax ginseng* combination in healthy volunteers with neurasthenic complaints. *Psychopharmacol Bull* 33(4):677683.

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1) The Overview section is new information.

2) Description, Chemistry and Pharmacology, Uses, Contraindications, Side Effects, Interactions with Other Drugs, and Dosage sections have been drawn from the original work. Additional information has been added in some or all of these sections, as noted with references.

3) The dosage for equivalent preparations (tea infusion, fluidextract, and tincture) have been provided based on the following example:

- Unless otherwise prescribed: 2 g per day of [powdered, crushed, cut or whole] [plant part]
- Infusion: 2 g in 150 ml of water
- Fluidextract 1:1 (g/ml): 2 ml
- Tincture 1:5 (g/ml): 10 ml

4) The References and Additional Resources sections are new sections. Additional Resources are not cited in the monograph but are included for research purposes.

This monograph, published by the Commission E in 1994, was modified based on new scientific research. It contains more extensive pharmacological and therapeutic information taken directly from the Commission E.

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