

# Ginkgo



Photo © Steven Foster  
*Ginkgo biloba* L.

Text by Armando González Stuart, Ph.D., 2005

**Other common names:** Maidenhair tree

**Botanical family:** Ginkgoaceae.

**Medicinal parts:** The leaves are used medicinally in western phytotherapy, but the “seed” or ovule is used both for cooking and medicine in many countries of the Orient (Schulz et al., 2004; Wichtl, 2004; Samuelsson, 1999).

## History

Ginkgo is a gymnosperm tree that is considered a living fossil, since all of its relatives died out during the last glacial period (Zhou et al., 2004; Zhou and Zheng, 2003; Libster, 2002; Mahdavi and Cupp, 2000). This tree is the only existing species of its genus. Some living specimens of this plant may be as much as 3,000 years old. (Spinella, 2001; Foster and Tyler, 2000).

The Ginkgo tree does not reproduce until it is about 20 years old and continues to do so after it has reached 1000 years of age. There are ginkgo plantations in the U.S. and France that contain an estimated 50 million trees (Spinella, 2001).

Ginkgo has been a part of traditional Chinese and Japanese medicine for many centuries (Evans, 2002; Samuelsson, 1999). The Ginkgo tree has also proven to be very resistant to environmental pollution and some pathogens (Libster, 2002).

The medicinal use of the leaves is of relatively recent origin and more common in western phytotherapy (Wichtl, 2004; Weiss and Fintelmann, 2000), in comparison to the culinary and

medicinal use of the seed (ovule), by the Oriental herbal tradition, which presumably dates back to the year 2800 BC (Schulz et al., 2004; Hoffmann, 2003; Evans, 2002; Mills and Bone, 2000).

### **Active Principles**

- Bioflavonoids (amentoflavone, bilobetin, ginkgetin)
- Flavonoids (quercetin, isorhamnetins, kaempferol)
- Proanthocyanidins
- Trilactonic diterpenes: Ginkgolides A,B,C
- Trilactonic sesquiterpene bilabolids (Bilobalide)  
(Barrett, 2004; Kraft and Hobbs, 2004; Deng and Zito, 2003; Evans, 2002; McKenna et al., 2001; Bruneton 2000; Samuelsson, 1999).
- Most Ginkgo extracts available on the European market are standardized to 24% flavone glycosides and 6% terpenoid lactones (Mahady et al., 2001; Ahlemeyer and Kriegelstein, 1998; Cott, 1995).
- Although some ginkgo preparations have also been applied parenterally, the great majority are ingested as tablets, capsules or extracts (Koltringer et al., 1989).

### **Applications in Herbal Therapy**

- For the treatment of bronchial asthma (Rottblatt and Ziment 2002; Mahmoud et al., 2000; Weiss and Fintelmann, 2000; Li et al., 1997).
- For the treatment of cerebral insufficiency, cognitive performance and memory loss (Cieza et al., 2003<sup>1,2</sup>; Kennedy et al., 2002; Rottblatt and Ziment, 2002; Hansel et al., 2001; Wesnes et al., 2000; Rigney et al., 1999; Brautigam et al., 1998; Kleijnen and Knipschild, 1992; Rai et al., 1991), especially in the elderly (Dongen et al., 2003, 2000; Tesch, 2003).
- For the treatment of Alzheimer's disease or senile dementia (Andrieu et al., 2003; Schulz, 2003; Smith and Luo, 2003; Loew, 2002; Luo et al., 2002; Keltner et al., 2001; McKenna et al., 2001; Spinella 2001; Ernst, 1999; Oken et al., 1998; Haase et al., 1996; Halama et al., 1988), although the exact therapeutic mechanism by which ginkgo may be effective is not yet known (Colciaghi et al., 2004).
- Anxiety and depression (Rottblatt and Ziment 2002; Ahlemeyer and Kriegelstein, 1998).
- Attention deficit-hyperactivity (ADHA) disorder (Cala et al., 2003; Lyon et al., 2001).
- Against diabetes and related circulatory disorders (Kudolo et al., 2002; Savickiene et al., 2002; Kudolo, 2001; Mahdavi and Cupp, 2000).
- Glaucoma and macular degeneration (Bartlett and Eperjesi, 2004; Fies and Dienel, 2002; Head, 2001).

- Intermittent claudication (Hansel et al. 2001; Pittler and Ernst, 2000; Ahlemeyer and Krieglstein, 1998; Draebeck et al., 1996).
- Impotence or erectile dysfunction of vascular origin (Moyad et al., 2004; Sohn and Sikora, 2001; Mahdavi and Cupp 2000) or due to secondary effects of antidepressant therapy (McKay, 2004; Ashton et al., 2000; Cohen and Bartlik, 1998).
- Tinnitus of vascular origin (Gruenwald, 2004; Rottblatt and Ziment, 2002; Spinella, 2001; Ahlemeyer and Krieglstein, 1998; Von Wedel et al., 1995).
- Some components in ginkgo leaves have antioxidant and free radical scavenging properties (Ferrari, 2004; Ellnaina-Wojtasek et al., 2003; Ikeda et al., 2003; Woo et al., 2003; Firenzuoli et al., 2004; Naidu et al., 2002; Mc Kenna et al., 2001; Yao et al., 2001; DeFeudis and Drieu, 2000; Mills and Bone, 2000; Marcocci et al., 1998).
- Ginkgo may offer a good option for the prevention and treatment of high altitude sickness (hypoxia) and related ailments (Basnyat and Murdoch, 2003; Gertsch et al., 2002; Leadbetter et al., 2001; Dumont et al., 2000; Roncin et al., 1996).
- For the treatment of slowly spreading vitiligo (Parsad et al., 2003).
- Against Raynaud's syndrome (Muir et al., 2003).
- For the treatment of depression (Fugh-Berman and Cott, 1999; Schubert and Halama, 1993).
- Ginkgo extracts may also have a role in the prevention and treatment of circulatory system/heart disease (Zhou et al., 2004; Mahady, 2002; Pietri et al., 1997; Mouren et al., 1994).
- The numerous active principles ( 26 or more) contained in ginkgo leaf affect various components of the circulatory system including arteries, veins, capillaries, red and white blood cells, capillary perfusion and venous tonicity (Hoffmann, 2003; McKenna et al., 2002; Mills and Bone, 2000).
- The compounds known as ginkgolides A, B and C have shown to be inhibitors of platelet activation factors (PAF). This action is important in the coagulation of blood, as well as in the potential treatment of hypertension (Chang and Chang, 1997; Braquet and Hosford, 2001). For this reason, caution should be exercised when using Ginkgo and other herbs or pharmaceuticals that have anticoagulant action (Mi (see section on safety and precautions below).
- The active principles in ginkgo reduce blood viscosity, antioxidant, vasodilator, stimulates neuronal activity. Ginkgo inhibits platelet function by lowering fibrinogen levels and decreasing plasma viscosity due to the action of flavonoids and terpenoids (ginkgolide B) that inhibit platelet activating factor. Terpene compounds, such as the ginkgolides, appear to inhibit platelet activating factor, decrease vascular resistance and improve circulatory flow without affecting blood pressure (Evans, 2002; MacIennan et al., 2002).
- A procedure known as coronary artery bypass grafting (CABG) could be a risk factor for a subtle decrease in cognitive functions. Preparations including ginkgo may be of value in

improving cognitive function in patients who have undergone this procedure, but further research is needed to prove their efficacy (Raja et al., 2004).

### **Clinical Studies Using Ginkgo**

- Various ginkgo biloba extracts, especially EGb 761 have been studied in depth, both in animal and human trials, especially in Europe (Ulbricht and Basch, 2005; Barrett, 2004; Gertz and Kiefer, 2004; Wichtl, 2004; Anonymous, 2003; Blumenthal, 2003; Christen and Maixent, 2002; Ahlemeyer and Kriegelstein, 1998).
- Ginkgo leaf extracts such as Egb 761 and LI 1370, for example, are licensed in Germany for the treatment of various ailments, including cerebral dysfunction, intermittent claudication, tinnitus, anxiety, erectile dysfunction, macular degeneration and vertigo (Anonymous, 2003; Fies and Dienel, 2002; Horr and Kieser, 2002; Loew, 2002; Luo et al., 2002; Mclennan et al., 2002).
- Various reviews have evaluated evidence-based information related to the use of *Ginkgo biloba*, for the treatment of various conditions including dementia, intermittent claudication, tinnitus, and macular degeneration. Some of the reviewers criticized a number of the articles as having various flaws in methodology. With regard to the articles that did meet their selection criteria for adequate methodology (double-blind, placebo –controlled studies), the results indicated that ginkgo, in some instances, can be superior to placebo and may be useful in the treatment of some ailments, although, according to available evidence, a definitive conclusion as to its efficacy could not be made (Linde et al. 2003; Birks et al., 2002; Diamond et al., 2000; Pittler and Ernst, 2000; Kleijnen and Knipschild, 1992).
- In a review of based on meta-analyses of clinical trials using various products containing ginkgo, Kurz and Van Baeln (2004), concluded that ginkgo showed only a modest health benefit compared to cholinesterase inhibitors, in the treatment of patients suffering from dementia.
- It is important to note that ginkgo's purported activity is possibly due to a positive or synergistic interaction among its many components, rather than to any particular active ingredient. For example, a flavonoid-free Egb 761 extract had no neuromodulating effect on mice cerebral cortex synaptosomes (Ramassamy et al., 1992).
- In a study evaluating the hemodynamic and electrocardiographic effects of short-term Ginkgo use in young, healthy volunteers, Kalus and collaborators (2003), noted no immediate or short-term effects on blood pressure, heart rate, or electrocardiographic variables.
- In mice, at the behavioral level, these potent in vivo effects of Egb 761, ginkgolide B, and bilobalide, resemble those of certain antidepressants (Brochet et al., 1999).
- Studies in rats and humans have shown that ginkgo extracts may have a restorative action on 5-HT 1A receptor binding in the cerebral cortex (McKenna et al., 2002).

- Studies undertaken *in vitro* show that ginkgo extract EGb 761 possesses antioxidant activity, anti-ischemic activity on the central nervous system (CNS). Flavonoids reduce capillary permeability and fragility, and act as free radical scavengers, inhibiting lipid peroxidation and also cause the blood vessels to relax (McKenna et al., 2001).
- Two studies report possible beneficial effects of ginkgo in improving sleep patterns in patients with depressive illness (Hemmeter et al., 2001; Holsboer-Trachsler, 2000).
- Both *in vivo* and *in vitro* experiments have shown that ginkgo biloba extracts possess neuroprotective effects, which may have therapeutic applications for various nervous system disorders (Beal, 2003; Lin et al., 2003; Badianetto and Quirion, 2002; Chandrasekaran et al., 2002; Maclellan et al., 2002; Pierr et al., 2002; Roman, 2002; Sastre et al., 2002; Ternaux and Portalier, 2002; Zimmermann et al., 2002; Zhang et al., 2000; Ahlemeyer and Krieglstein, 1998).
- In a review of clinical trials comparing the efficacy of cholinesterase inhibitors and ginkgo on cognitive function in patients suffering from dementia or Alzheimer's disease, the data from the trials for cholinesterase inhibiting drugs were more consistent than those for ginkgo, especially with relation to the patient populations and outcome measures. The significant benefits on cognition compared to placebo were seen with the drugs donepezil, galantamine, and rivastigmine, for example. The preparations containing ginkgo were significant compared to placebo only when all doses were pooled (Evans et al., 2004; Kurz and Van Baelen, 2004).
- A review of a recent large trial with Ginkgo biloba showed that a product containing this plant was not effective in preventing acute mountain sickness (AMS) compared to the drug acetazolamide in a low dose of 2 x 125 mg. According to the reviewers, acetazolamide remains the drug of choice for prevention of this malady (Bartsch et al., 2004).
- According to some authors, ginkgo biloba extract, provides symptom relief comparable to pentoxifylline for the treatment of intermittent claudication (Jacoby and Mohler, 2004).
- In a review of results from clinical trials using a ginkgo biloba standardized extract (Egb 761) for the treatment of stage II peripheral arterial occlusive disease (PAOD), the majority of the studies (7 out of 9), showed that there was an advantage of Egb 761 in the increase of pain-free walking distance compared to placebo (Horsch and Walther, 2004).
- A review of clinical trials employing ginkgo for the treatment of tinnitus showed that there is little evidence that this plant can be useful for that condition (DeBisschop, 2003).
- Ginkgo biloba leaf extracts could have anticancer (chemopreventive) properties due to their antioxidant, anti-angiogenic and gene-regulatory effects. Both the antioxidant and associated anti-lipoperoxidative effects of Ginkgo biloba extracts seem to be due to their flavonoid and terpenoid constituents (De Feudis et al., 2003).
- *In vitro* studies have shown that ginkgo biloba extract (EGB761) significantly suppressed the proliferation and increased cytotoxicity in HepG2 and Hep3B in human cancer cells. Additionally, Ginkgo biloba extract decreased PCNA and increased p53 expression in HepG2 cells (Chao and Chu, 2004).

- Experimentally, ginkgo biloba exocarp polysaccharides (GBEP) can inhibit proliferation and induce apoptosis and differentiation of human gastric tumor cells (Xu et al., 2004).

**Table 1. Selected Clinical Trials Employing Ginkgo\***

<b>Reference</b>	<b>Plant part / herbal product</b>	<b>Purpose of study</b>	<b>Number of subjects</b>	<b>Results</b>
Gertsch et al., 2004	Ginkgo supplement	Comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness	614	Not effective
Mattes and Pawlik, 2004	Ginkgo extract	To assess the effects of <i>Ginkgo biloba</i> on alertness and chemosensory function in healthy adults	39	Not effective
Nathan et al., 2004	An extract containing <i>Ginkgo biloba</i> (120 mg) and <i>Bacopa monniera</i> (300 mg)	To evaluate the effects of a combined extract of <i>Ginkgo biloba</i> and <i>Bacopa monniera</i> on cognitive function in healthy subjects	85	Not effective
Rejali et al., 2004	Ginkgo biloba tablets	To evaluate the efficacy of ginkgo for the treatment of tinnitus	66	Not effective
Singh et al., 2004	Capsules containing a combination of 75mg of <i>Codonopsis pilosula</i> total glycosides and 40 mg of ginkgo biloba extract	To test whether ginkgo biloba extract in combination with <i>Codonopsis pilosula</i> (dangshen) or ginkgo alone could enhance memory acquisition and retention of normal human subjects, better	60	The combination of <i>Codonopsis</i> and ginkgo extract was more effective than ginkgo extract alone in improving the cognitive function and overall health

		than placebo		
Sumboonnanonda and Lertsithichai, 2004	Ginko biloba-Troxerutin-Heptaminol Hce	To assess the clinical efficacy, and safety of Ginko biloba-Troxerutin-Heptaminol Hce in the treatment of patients with acute hemorrhoid attacks	22	Effective
Trick et al., 2004	Ginkgo biloba extract (120 mg/day)	To investigate the effects of continuing treatment with ginkgo on the activities of daily living (ADL), as well as improving various aspects of mood and sleep	1570	Effective
Chen et al., 2003	Ginkgo biloba exocarp polysaccharides (GBEP) capsule preparation taken orally	To observe the clinical efficacy of (GBEP capsule preparation in treating upper digestive tract malignant tumors of middle and late stage	86	The GBEP capsule preparation had positive therapeutic effects on upper digestive tract malignant tumors of middle and late stages
<sup>2</sup> Cieza et al., 2003	EGb 761 standardized extract	To evaluate the effects of ginkgo biloba extract on mental functioning and quality of life in healthy subjects	66	Effective

Kanowski and Hoerr, 2003	EGb 761 standardized extract	Use of ginkgo biloba extract for the treatment of dementia	Not available	Effective
Muir et al., 2003	Seredrin® (standardized Ginkgo biloba extract)	Treatment for Raynaud's syndrome	Not available	Effective
Prasad et al., 2003	Ginkocer® (Ginkgo biloba extract)	Treatment for vitiligo	47	Effective
Van Dongen et al., 2003	EGb 761 standardized extract	Treatment for dementia	214	Not effective
Gertsch et al., 2002	Ginkgo biloba extract	Treatment for acute mountain sickness	26	Effective (as pretreatment)
Kang et al., 2002	Ginkgo biloba extract	Treatment for antidepressant-induced sexual dysfunction	19	Not effective
Kennedy et al., 2002	Ginkgo biloba extract alone, Panax ginseng extract alone and a combination of ginkgo and ginseng extracts	Treatment for secondary memory performance and mood improvement	20	Effective
Le Bars, et al., 2002	EGb 761 standardized extract	Treatment for dementia	Not available	Effective
Nathan et al., 2002	EGb 761 standardized extract	To test acute effects on memory functioning in healthy older human subjects	Not available	Not effective
Burschka et al., 2001	EGb 761 standardized extract	Treatment for sudden unilateral hearing loss	106	Effective
Drew and Davies, 2001	LI 1370 standardized extract	Treatment for tinnitus	956	Not effective
Leadbetter et al.,	Ginkgo biloba	Treatment for	40	Effective (as



2001	extract	acute mountain sickness		pretreatment)
Stough et al., 2001	EGb 761 standardized extract	Memory enhancement	61	Effective
Kennedy et al., 2000	GK 501 (Ginkgo biloba extract)	Cognitive enhancement	20	Effective
Le Bars et al., 2000	EGb 761 standardized extract	Treatment for dementia	309	Effective
Van Dongen et al., 2000	EGb 761 standardized extract	Treatment for dementia	196	Not effective
Wesnes et al., 2000	Ginkgo biloba extract (GK501) combined with Panax ginseng extract (G115)	Cognitive function in healthy volunteers	256	Effective
Rigney et al., 1999	Kaveri®	Memory enhancement	31	Not effective
Brautigam et al., 1998	Geriaforce® (liquid extract)	Treatment for cerebral insufficiency	197	Effective (improvement of short term visual memory)
Cohen and Bartlik, 1998	Ginkgo biloba standardized extract	Treatment for sexual dysfunction related to SSRI antidepressants	63	Effective
Kanowski et al., 1997	EGb 761 standardized extract	Treatment for dementia	156	Effective
Le Bars et al., 1997	Ginkgold® (EGb 761 tablets)	Treatment for dementia	202	Effective
Li et al., 1997	Concentrated leaf liquid (Chinese product)	Treatment for asthma	61	Effective
Haase et al., 1996	EGb 761 standardized extract	Treatment for dementia	40	Effective
Roncin et al., 1996	Tanakan® (EGb 761 tablet)	Treatment for mountain altitude sickness	44	Effective
Brochet et al., 1995	Intravenous application of ginkgolide B	Treatment for exacerbations of multiple sclerosis	104	Not effective
Von Wedel et al., 1995	Soft-laser/Ginkgo therapy	Treatment for chronic tinnitus	Not available	Effective
Hofferberth, 1994	Tebonin® forte	Treatment for	40	Effective

	(EGb 761) standardized extract	dementia		
Mouren, et al., 1994	EGb 761 standardized extract	Treatment of peripheral arterial occlusive disease	20	Effective
Vesper and Hansgen, 1994	Kaveri® LI 1370	Treatment for cerebral insufficiency	86	Effective
Allain et al., 1993	EGb 761 (320 mg or 600 mg)	Dual coding test for memory	19	Effective
Grassel, 1992	Rokan ® (EGb 761)	Treatment for cerebral insufficiency	53	Effective
Bruchert et al., 1991	Kaveri® LI 1370	Treatment for cerebral insufficiency	209	Effective
Halama, 1991	Kaveri® LI 1370	Treatment for dementia of vascular origin	42	Effective
Rai et al., 1991	Tanakan®	Improvement of memory dysfunction	27	Effective
Schmidt et al., 1991	Kaveri® LI 1370	Treatment for Cerebral insufficiency	99	Effective
Eckmann, 1990	LI 1370 (standardized liquid extract)	Treatment for cerebral insufficiency	58	Effective

**\*Additional information about clinical trials and the products tested is available in the following publications:** Barrett, M. *Handbook of Clinically Tested Herbal Remedies* 2 Vols. New York: Haworth Herbal Press; 2004, Blumenthal, M. *ABC's Clinical Guide to Herbs*. New York: Thieme; 2003, Bratman S, Girman A. *Handbook of Herbal, Supplements and Their Therapeutic Uses*. St. Louis: Mosby; 2003, Bascom A. *Incorporating Herbal Medicine into Clinical Practice*. Philadelphia: F. A. Davis; 2002, Cassileth B, Lucarelli C. *Herb-Drug Interactions in Oncology*. London: BC Decker; 2003, Cupp M. *Toxicology and Clinical Pharmacology of Herbal Products*. Totowa, New Jersey: Humana Press; 2000 McKenna et al., *Botanical Medicines*. New York: Haworth Herbal Press; 2002, Rotblatt M, Ziment I. *Evidence-Based Herbal Medicine*. Philadelphia: Hanley and Belfus; 2002, Mahady et al., *Botanical Dietary Supplements*. The Netherlands: Swets and Zeitlinger; 2001; Ulbricht C, Basch E. *Natural Standard: Herbal and Supplement Reference*. New York: Elsevier; 2005; Werbach M, Murray M. *Botanical Influences on Illness* 2<sup>nd</sup> ed.; Tarzana CA: Third Line Press; 2000; Yarnell, E. et al., *Clinical Botanical Medicine*. New York: Mary Ann Liebert; 2003.



## Safety/Precautions

- Standardized ginkgo leaf extracts are usually regarded as being safe (Mills and Bone, 2005; Gertz and Kiefer, 2004; Kraft and Hobbs, 2004; Rottblatt and Ziment 2002; Mc Kenna et al., 2001; Le Bars and Kastelan, 2000; Brinker, 2001; Mills and Bone, 2000).
- There may be great variability in the content and quality of ginkgo's active principles in herbal extracts available on the market today (Ganzera et al., 2001).
- Although with normal therapeutic dosages, the risk of bleeding is uncommon (Rottblatt and Ziment 2002), ginkgo preparations should be used with caution in patients with known bleeding disorders (Mills and Bone, 2005; Schneider et al., 2002; Harkness and Bratman, 2003; Purroy-Garica et al., 2001; Brinker, 2001; Smolinske, 1999).
- Avoid during pregnancy and lactation. (Gruenwald, 2004; Herr 2002; Libster, 2002).
- Cardiac patients should consult with their health care provider before taking this plant, due to possible ventricular arrhythmia associated with Ginkgo use (Cianfrocca et al., 2002).
- Patients who are at risk for intracranial hemorrhage should avoid using Ginkgo preparations due their inhibition of Platelet Activating Factors (PAF) (Harkness and Bratman, 2003).
- There is one report that mentions the presence of the toxic alkaloid, colchicine, in a commercial herbal preparation containing Ginkgo (Petty et al., 2001), but after subsequent chemical analyses, that statement was later refuted (Li et al., 2002<sup>a, b</sup>).
- Avoid using the ovule (seed) for medicinal or culinary purposes, due to its potential toxicity (Burrows and Tyrl, 2001; Brinker, 2000) Ingestion of the ovules (seeds) is associated with intoxication, known as *Gin-nan poisoning*, which has occurred primarily in children in the Orient, where the ovules are employed both for culinary and medicinal purposes (Mills and Bone, 2005; Rottblatt and Ziment, 2002; Mahdavi and Cupp, 2000; Samuelsson, 1999).
- The commercial extracts do not contain the poisonous principles contained in the ovules or "seeds" (Mills and Bone, 2005; Rottblatt and Ziment, 2002; Mahdavi and Cupp, 2000).
- Ginkgo may cause allergic reactions in susceptible people (Mossabeb et al., 2001).
- Parenteral use may be related to blood pressure problems, phlebitis and allergic reactions (Gruenwald, 2004).
- Due to the fact that Ginkgo preparations delay blood clotting, suspend ingestion of this herb product at least 36 hours before you plan to undergo surgery (Herr, 2002; Skogh, 1998).

## **Potential Herb/Drug Interactions**

- Although some authors mention that ginkgo preparations may potentially interfere with certain anticancer medications (Sparreboom et al., 2004), other researchers have found that ginkgo does not seem to possess significant effect on CYP activity (Markowitz et al., 2003; Gurley et al., 2002).
- The anti inflammatory effect present in extract of ginkgo biloba has been used therapeutically, since it is a known inhibitor of platelet activating factor (PAF), which is important in the pathogenesis of asthma. This effect could be synergistic with cyclosporin A, in order to inhibit pathogenic immune activation in asthmatic patients (Mahmoud et al., 2000).
- The scientific literature on herb-drug interactions usually warns that ginkgo may increase the blood-thinning effects of warfarin (Collins and Dufresne, 2002; Herr 2002; Boniel and Dannon, 2001; Brinker, 2001; Izzo and Ernst, 2001; Argento et al., 2000; Evans, 2000; Heck et al., 2000; Miller, 1998), although evidence of this particular interaction may not always be conclusive (Vaes and Chyka, 2000).
- A double-blind, placebo-controlled clinical trial employing Coenzyme Q-10, Ginkgo and warfarin was conducted. The results showed no interactions between ginkgo's components and warfarin. (Engelsen et al., 2003).
- A single case of spontaneous hyphema was associated with the concomitant ingestion of aspirin and ginkgo (Rosenblatt and Mondel, 1997), however, a controlled trial investigating the possible interactions between aspirin and ginkgo failed to produce any negative effects (Schwabe, 2001, cited by Blumenthal, 2003).
- A fatal case of cerebral hemorrhage associated with an interaction between ibuprofen and Ginkgo has been reported (Meisel et al., 2003).
- Ginkgo extract (EGb 761) enhanced the antithrombotic activity of ticlopidine in animal experiments (Kim et al., 1998).
- One case of an interaction between thiazide diuretics and ginkgo has been reported, which presumably caused an increase in blood pressure. However, the ginkgo preparation had been injected, which is an unusual way of administering this herb (Izzo et al., 2005; Izzo and Ernst, 2001).
- Avoid using together with therapeutic amounts of other herbs that could theoretically interfere with blood coagulation, such as garlic, uña de gato ("cat's claw"), dong quai (Chinese Angelica) or ginger (Brinker, 2001).
- In studies with rats, EGb 761 standardized extract was regarded as a facilitating drug for the development of amikacin ototoxicity. Although the effects of this combination in humans is unknown at this time, the results of the study warn against concomitant use of aminoglycosides,

specifically amikacin, together with EGb 761, without medical supervision (Miman et al., 2002).

### **Literature Cited**

- Ahlemeyer B, Krieglstein J. Neuroprotective Effects of Ginkgo biloba Extract. In; Lawson L, Bauer R. (Eds) *Phytomedicines of Europe*. Washington, D.C.: American Chemical Society; 1998.
- Andrieu S, Gillette S, Amouyal K. et al. Association of Alzheimer's disease onset with ginkgo biloba and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study. *J Gerontol A Biol Sci Med Sci*. 2003; 58(4):372-377.
- Allain H, Raoul P, Lieury A. et al. Effect of two doses of ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. *Clin Ther*. 1993; (3):549-558.
- Anonymous. EGb 761: ginkgo biloba extract, Ginkor. *Drugs R D*. 2003; 4(3):188-193.
- Argento A, Tiraferri E, Marzaloni M. Oral anticoagulants and medicinal plants. An emerging interaction. [Article in Italian] *Ann Ital Med Int*. 2000; 15(2):139-143.
- Ashton AK, Ahrens K, Gupta S, Masand PS. Antidepressant-induced sexual dysfunction and Ginkgo Biloba. *Am J Psychiatry*. 2000 May;157(5):836-837.
- Barrett M. *Handbook of Clinically Tested Herbal Remedies, 2 Vols*. New York: Haworth Herbal Press; 2004, pp. 547-672.
- Bartlett H, Eperjesi F. An ideal ocular nutritional supplement? *Ophthalmic Physiol Opt*. 2004;24(4):339-49.
- Bartsch P, Bailey DM, Berger MM. et al. Acute mountain sickness: controversies and advances. *High Alt Med Biol*. 2004; 5(2):110-24.
- Basnyat B, Murdoch DR. High-altitude illness. *Lancet*. 2003; 361(9373):1967-1974.
- Bastianetto S, Quirion R. EGb 761 is a neuroprotective agent against beta-amyloid toxicity. *Cell Mol Biol (Noisy-le-grand)*. 2002; 48(6):693-697.
- Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol*. 2003; 53 Suppl 3:S39-47.
- Birks J, Grimley EV, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2002 ;( 4):CD003120.
- Braquet P, Hosford D. Ethnopharmacology and the development of natural PAF antagonists as therapeutic agents. *J Ethnopharmacol*. 1991; 32(1-3):135-139.

Brochet D, Chermat R, DeFeudis FV, Drieu K. Effects of single intraperitoneal injections of an extract of *Ginkgo biloba* (EGb 761) and its terpene trilactone constituents on barbital-induced narcosis in the mouse. *Gen Pharmacol*. 1999; 33(3):249-256.

Brochet B, Guinot P, Orgogozo JM et al. Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis. The Ginkgolide Study Group in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1995; 58(3):360-362.

Blumenthal, M. *The Complete Commission E Monographs*.  
Boston: Integrative Medicine Publications; 1998.

Blumenthal, M. *Expanded Commission E Monographs*.  
Boston: Integrative Medicine Publications; 2000.

Boniel T, Dannon P. The safety of herbal medicines in psychiatric practice. [Article in Hebrew] *Harefuah*. 2001; 140(8):780-783, 805.

Brinker F. *Herb Contraindications and Drug Interactions* 3<sup>rd</sup> ed.  
Sandy, Oregon: Eclectic Medical Publications; 2001.

Brinker F. *Toxicology of Botanical Medicines* 3<sup>rd</sup> ed.  
Sandy, Oregon: Eclectic Medical Publications; 2000.

Bruneton, J. *Pharmacognosy, Phytochemistry, Medicinal Plants*. 3<sup>rd</sup> ed.  
Paris: Intercept; 2000.

Burrows G, Tyrl R. *Toxic Plants of North America*.  
Ames, Iowa: Iowa State Press; 2001.

Burschka MA, Hassan HA, Reineke T. et al. . Effect of treatment with *Ginkgo biloba* extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients. *Eur Arch Otorhinolaryngol*. 2001; 258(5):213-219.

Cala S, Crismon ML, Baumgartner J. A survey of herbal use in children with attention-deficit-hyperactivity disorder or depression. *Pharmacotherapy*. 2003; 23(2):222-230.

Chandrasekaran K, Mehrabian Z, Spinnewyn B. et al. Bilobalide, a component of the *Ginkgo biloba* extract (EGb 761), protects against neuronal death in global brain ischemia and in glutamate-induced excitotoxicity. *Cell Mol Biol (Noisy-le-grand)* 2002; 48(6):663-669.

Chao JC, Chu CC. Effects of *Ginkgo biloba* extract on cell proliferation and cytotoxicity in human hepatocellular carcinoma cells. *World J Gastroenterol*. 2004;10(1):37-41.

Chen HS, Zhai F, Chu YF et al. Clinical study on treatment of patients with upper digestive tract malignant tumors of middle and late stage with *Ginkgo biloba* exocarp polysaccharides capsule preparation [Article in Chinese] *Zhong Xi Yi Jie He Xue Bao*. 2003;1(3):189-91.

Christen Y, Maixent JM. What is Ginkgo biloba extract EGb 761? An overview--from molecular biology to clinical medicine. *Cell Mol Biol (Noisy-le-grand)*. 2002; 48(6):601-661.

Cianfrocca C, Pelliccia F, Auriti A, Santini M. Ginkgo biloba-induced frequent ventricular arrhythmia. *Ital Heart J*. 2002; 3(11):689-691.

<sup>1</sup>Cieza A, Maier P, Poppel E. Effects of Ginkgo biloba on mental functioning in healthy volunteers. *Arch Med Res*. 2003;34(5):373-81.

<sup>2</sup>Cieza A, Maier P, Poppel E. Ginkgo biloba works in healthy persons, too. Older people feel more mentally fit. [Article in German]. *MMW Fortschr Med*. 2003; 145(10):51.

Cockle SM, Kimber S, Hindmarch I. The effects of Ginkgo biloba extract (LI 1370) supplementation on activities of daily living in free living older volunteers: a questionnaire survey. *Hum Psychopharmacol*. 2000; 15(4):227-235.

Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Sex Marital Ther*. 1998; 24(2):139-143.

Colciaghi F, Borroni B, Zimmermann M. et al. Amyloid precursor protein metabolism is regulated toward alpha-secretase pathway by Ginkgo biloba extracts. *Neurobiol Dis*. 2004;16(2):454-60

Collins SC, Dufresne RG Jr. Dietary supplements in the setting of Mohs surgery. *Dermatol Surg*. 2002; 28(6):447-452.

Cott J. NCDEU update. Natural product formulations available in Europe for psychotropic indications. *Psychopharmacol Bull*. 1995; 31(4):745-751.

Cupp MJ. Herbal remedies: adverse effects and drug interactions. *Am Fam Physician*. 1999; 59(5):1239-1245.

DeBisschop M. Ginkgo ineffective for tinnitus. *J Fam Pract*. 2003; 52(10):766, 769.

DeFeudis FV, Papadopoulos V, Drieu K. Ginkgo biloba extracts and cancer: a research area in its infancy. *Fundam Clin Pharmacol*. 2003; 17(4):405-17.

DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. *Curr Drug Targets*. 2000; 1(1):25-58.

Deng F, Zito SW. Development and validation of a gas chromatographic-mass spectrometric method for simultaneous identification and quantification of marker compounds including bilobalide, ginkgolides and flavonoids in Ginkgo biloba L. extract and pharmaceutical preparations. *J Chromatogr A*. 2003; 986(1):121-127.

Diamond BJ, Shiflett SC, Feiwel N. et al. Ginkgo biloba extract: mechanisms and clinical indications. *Arch Phys Med Rehabil*. 2000; 81(5):668-678.

Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: double blind, placebo controlled trial. *BMJ*. 2001; 322(7278):73.

Dumont L, Mardirosoff C, Tramer MR. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ*. 2000; 321(7256):267-272.

Eckmann F. Cerebral insufficiency treatment with Ginkgo-biloba extract. Time of onset of effect in a double-blind study with 60 inpatients. [Article in German] *Fortschr Med* 1990; 108:557-560.

Ellnain-Wojtaszek M, Kruczynski Z, Kasprzak J. Investigation of the free radical scavenging activity of *Ginkgo biloba* L. leaves. *Fitoterapia*. 2003; 74(1-2):1-6.

Ernst E. Herbal medications for common ailments in the elderly. *Drugs Aging*. 1999; 15(6):423-428.

Evans JG, Wilcock G, Birks J. Evidence-based pharmacotherapy of Alzheimer's disease. *Int J Neuropsychopharmacol*. 2004;7(3):351-69.

Evans V. Herbs and the brain: friend or foe? The effects of ginkgo and garlic on warfarin use. *J Neurosci Nurs*. 2000; 32(4):229-232.

Evans WC. *Pharmacognosy* 17<sup>th</sup> ed. Philadelphia: W.B. Saunders; 2002.

Ferrari CK. Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging. *Biogerontology*. 2004; 5(5):275-89.

Fies P, Dienel A. Ginkgo extract in impaired vision--treatment with special extract EGb 761 of impaired vision due to dry senile macular degeneration. [Article in German] *Wien Med Wochenschr*. 2002; 152(15-16):423-6.

Firenzuoli F, Gori L, Crupi A, Neri D. Flavonoids: risks or therapeutic opportunities? [Article in Italian] *Recenti Prog Med*. 2004; 95(7-8):345-51.

Fugh-Berman A. Herb-drug interactions. *Lancet*. 2000; 355(9198):134-138.

Fugh-Berman A, Cott JM. Dietary supplements and natural products as psychotherapeutic agents. *Psychosom Med*. 1999; 61(5):712-728.

Ganzera M, Zhao J, Khan IA. Analysis of terpenelactones in Ginkgo biloba by high performance liquid chromatography and evaporative light scattering detection. *Chem Pharm Bull (Tokyo)*; 2001 ;49(9):1170-1173.

Gertsch JH, Basnyat B, Johnson EW, Onopa J, Holck PS. Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). *BMJ*. 2004 ;328 (7443):797.



Gertsch JH, Seto TB, Mor J, Onopa J. Ginkgo biloba for the prevention of severe acute mountain sickness (AMS) starting one day before rapid ascent. *High Alt Med Biol.* 2002; 3(1):29-37.

Gertz HJ, Kiefer M. Review about Ginkgo biloba special extract EGb 761 (Ginkgo). *Curr Pharm Des.* 2004;10(3):261-4.

Grassel E. Effect of Ginkgo-biloba extract on mental performance. Double-blind study using computerized measurement conditions in patients with cerebral insufficiency. [Article in German] *Fortschr Med.* 1992; 110(5):73-76.

Gruenwald J. *PDR for Herbal Medicines 3<sup>rd</sup> ed.*  
Montvale, NJ: Thomson PDR; 2004.

Gurley BJ, Gardner SF, Hubbard MA et al. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin Pharmacol Ther.* 2002; 72(3):276-287.

Haase J, Halama P, Horr R. Effectiveness of brief infusions with Ginkgo biloba Special Extract EGb 761 in dementia of the vascular and Alzheimer type. [Article in German] *Z Gerontol Geriatr.* 1996; 29(4):302-309.

Halama P, Bartsch G, Meng G. Disorders of brain performance of vascular origin. Randomized double-blind study of the effectiveness of Ginkgo biloba extract. [Article in German] *Fortschr Med.* 1988; 106(19):408-412.

Head KA. Natural therapies for ocular disorders, part two: cataracts and glaucoma. *Altern Med Rev.* 2001; (2):141-166.

Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health Syst Pharm.* 2000; 57(13):1221-7; quiz 1228-30.

Hemmeter U, Annen B, Bischof R. et al. Polysomnographic effects of adjuvant ginkgo biloba therapy in patients with major depression medicated with trimipramine. *Pharmacopsychiatry.* 2001; 34(2):50-59.

Herr S. *Herb-Drug Interaction Handbook.*  
Nassau, NY: Church Street Books; 2002.

Hofferberth B. The effect of Ginkgo biloba extract on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome. A double-blind study against placebo [Article in German]. *Arzneimittelforschung.* 1989; 39(8):918-922.

Hoffmann D. *Medical Herbalism.*  
Rochester, VT: Inner Traditions; 2003; pp. 174-175; 553-554.

Holsboer-Trachsler E. Phytotherapeutic drugs and sleep. [Article in German] *Schweiz Rundsch Med Prax.* 2000;89(51-52):2178-82.

Horr R, Kieser M. Pharmaco-economic evaluation of Ginkgo special extract EGb 761 for dementias in Austria [Article in German]. *Wien Med Wochenschr.* 2002; 152(15-16):427-31.

- Horsch S, Walther C. Ginkgo biloba special extract EGb 761 in the treatment of peripheral arterial occlusive disease (PAOD)--a review based on randomized, controlled studies. *Int J Clin Pharmacol Ther.* 2004; 42(2):63-72.
- Ikeda K, Negishi H, Yamori Y. Antioxidant nutrients and hypoxia/ischemia brain injury in rodents. *Toxicology.* 2003; 189(1-2):55-61.
- Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. *Int J Cardiol.* 2005;98(1):1-14.
- Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs.* 2001;61(15):2163-2175.
- Jacoby D, Mohler ER. Drug treatment of intermittent claudication. *Drugs.* 2004;64(15):1657-70.
- Kalus JS, Piotrowski AA, Fortier CR. et al. Hemodynamic and electrocardiographic effects of short-term Ginkgo biloba. *Ann Pharmacother.* 2003; 37(3):345-349.
- Kang BJ, Lee SJ, Kim MD, Cho MJ. A placebo-controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. *Hum Psychopharmacol.* 2002; 17(6):279-284.
- Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. *Pharmacopsychiatry.* 2003; 36(6):297-303.
- Kanowski S, Herrmann WM, Stephan K. et al. 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.* 1996; 29(2):47-56.
- Keltner NL, Zielinski AL, Hardin MS. Drugs used for cognitive symptoms of Alzheimer's disease. *Perspect Psychiatr Care.* 2001; 37(1):31-4.
- Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of Ginkgo biloba, ginseng, and a ginkgo/ginseng combination to healthy young adults. *Physiol Behav.* 2002; 75(5):739-751.
- Kennedy DO, Scholey AB, Wesnes KA. Differential, dose dependent changes in cognitive performance following acute administration of a Ginkgo biloba/Panax ginseng combination to healthy young volunteers. *Nutr Neurosci.* 2001; 4(5):399-412.
- Kim YS, Pyo MK, Park KM. et al. Antiplatelet and antithrombotic effects of a combination of ticlopidine and ginkgo biloba ext (EGb 761). *Thromb Res.* 1998;91(1):33-38.
- Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. *Br J Clin Pharmacol.* 1992; 34(4):352-358.
- Koltringer P, Eber O, Klima G. et al. Microcirculation in parenteral Ginkgo biloba extract therapy. [Article in German] *Wien Klin Wochenschr.* 1989; 101(6):198-200.

Kraft K, Hobbs C. Pocket Guide to Herbal Medicine. New York: Thieme; 2004; pp. 71-73.

Kudolo GB, Dorsey S, Blodgett J. Effect of the ingestion of Ginkgo biloba extract on platelet aggregation and urinary prostanoid excretion in healthy and Type 2 diabetic subjects. *Thromb Res.* 2002; 108(2-3):151-160.

Kudolo GB. The effect of 3-month ingestion of Ginkgo biloba extract (EGb 761) on pancreatic beta-cell function in response to glucose loading in individuals with non-insulin-dependent diabetes mellitus. *J Clin Pharmacol.* 2001; 41(6):600-611.

Kurz A, Van Baelen B. Ginkgo biloba compared with cholinesterase inhibitors in the treatment of dementia: a review based on meta-analyses by the Cochrane collaboration. *Dement Geriatr Cogn Disord.* 2004; 18(2):217-26.

Le Bars PL, Velasco FM, Ferguson JM et al., Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer's disease. *Neuropsychobiology.* 2002; 45(1):19-26.

Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 in dementia. *Dement Geriatr Cogn Disord.* 2000;11(4):230-237.

Le Bars PL, Kastelan J. Efficacy and safety of a Ginkgo biloba extract. *Public Health Nutr.* 2000; 3(4A):495-9.

Le Bars PL, Katz MM, Berman N. et al., A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. *JAMA.* 1997; 278(16):1327-1332.

Li MH, Zhang HL, Yang BY. Effects of ginkgo leave concentrated oral liquor in treating asthma [Article in Chinese] *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 1997; 17(4):216-218.

<sup>a</sup>Li W, Fitzloff JF, Farnsworth NR, Fong HH. Evaluation of commercial Ginkgo biloba dietary supplements for the presence of colchicine by high-performance liquid chromatography. *Phytomedicine.* 2002; 9(5):442-446.

<sup>b</sup>Li W, Sun Y, Fitzloff JF, van Breemen RB. Evaluation of commercial ginkgo and echinacea dietary supplements for colchicine using liquid chromatography-tandem mass spectrometry. *Chem Res Toxicol.* 2002; 15(9):1174-1178.

Lin CC, Cheng WL, Hsu SH, Chang CM. The effects of Ginkgo biloba extracts on the memory and motor functions of rats with chronic cerebral insufficiency. *Neuropsychobiology.* 2003; 47(1):47-51

Linde K, Ter Riet G, Hondras M. et al. For The Cochrane Complementary Medicine Field. [In Process Citation] [Article in German] *Forsch Komplementarmed Klass Naturheilkd.* 2003; 10 Suppl 1:17-27.

Loew D. Value of Ginkgo biloba in treatment of Alzheimer dementia. [Article in German]. *Wien Med Wochenschr.* 2002; 152(15-16):418-22.

- Luo Y, Smith JV, Paramasivam V. et al. Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. *Proc Natl Acad Sci U S A*. 2002; 99(19):12,197-202.
- Lyon MR, Cline JC, Totosy de Zepetnek J. et al. Effect of the herbal extract combination Panax quinquefolium and Ginkgo biloba on attention-deficit hyperactivity disorder: a pilot study. *J Psychiatry Neurosci*. 2001; 26(3):221-228.
- MacLennan KM, Darlington CL, Smith PF. The CNS effects of Ginkgo biloba extracts and ginkgolide B. *Prog Neurobiol*. 2002; 67(3):235-257.
- Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. *J Cardiovasc Nurs*. 2002; 16(4):21-32.
- Mahady G, Fong H, Farnsworth N. *Botanical Dietary Supplements: Quality, Safety and Efficacy*. The Netherlands: Swets and Zeitlinger; 2001.
- Mahdavi F, Cupp M. Ginkgo. In: Cupp M. *Toxicology and Clinical Pharmacology of Herbal Products*. Totowa, New Jersey: Humana Press; 2000.
- Mahmoud F, Abul H, Onadeko B. et al. In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A. *Jpn J Pharmacol*. 2000;83(3):241-245.
- Marcocci L, Packer L, Droy-Lefaix MT, et al. Antioxidant action of Ginkgo biloba extract EGb 761. *Methods Enzymol* 1994; 234:462-475.
- Markowitz JS, Donovan JL, Lindsay DeVane C et al. Multiple-dose administration of Ginkgo biloba did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. *J Clin Psychopharmacol*. 2003; 23(6):576-81.
- Mattes RD, Pawlik MK. Effects of Ginkgo biloba on alertness and chemosensory function in healthy adults. *Hum Psychopharmacol*. 2004; 19(2):81-90.
- Matthews MK Jr. Association of Ginkgo biloba with intracerebral hemorrhage. [letter] *Neurology*. 1998; 50(6):1933-1934.
- McKay D. Nutrients and botanicals for erectile dysfunction: examining the evidence. *Altern Med Rev*. 2004; 9(1):4-16.
- McKenna DJ, Jones K, Hughes K. Efficacy, safety, and use of ginkgo biloba in clinical and preclinical applications. *Altern Ther Health Med*. 2001; (5):70-86, 88-90.
- Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. *Atherosclerosis*. 2003; 167(2):367.
- Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med*. 1998; 158(20):2200-2211.
- Mills S, Bone K. *The Essential Guide to Herbal Safety*. New York: Elsevier-Churchill-Livingstone; 2005; pp.425-432.

Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill-Livingstone; 2000.

Miman MC, Ozturan O, Iraz M. et al. Amikacin ototoxicity enhanced by Ginkgo biloba extract (EGb 761). *Hear Res.* 2002; 169(1-2):121-129.

Mossabeb R, Kraft D, Valenta R. Evaluation of the allergenic potential of Ginkgo biloba extracts. *Wien Klin Wochenschr.* 2001;113(15-16):580-587.

Mouren X, Caillard P, Schwartz F. Study of the antiischemic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. *Angiology.* 1994;45(6):413-7.

Moyad MA, Barada JH, Lue TF et al. Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II. *Urol Clin North Am.* 2004; 31(2):259-73.

Muir AH, Robb R, McLaren M. et al. The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial. *Vasc Med.* 2002; 7(4):265-267.

Naidu MU, Kumar KV, Mohan IK. et al. Protective effect of Ginkgo biloba extract against doxorubicin-induced cardiotoxicity in mice. *Indian J Exp Biol.* 2002;40(8):894-900.

Nathan PJ, Tanner S, Lloyd J. et al. Effects of a combined extract of Ginkgo biloba and Bacopa monniera on cognitive function in healthy humans. *Hum Psychopharmacol.* 2004;19(2):91-6.

Nathan PJ, Ricketts E, Wesnes K. et al. The acute nootropic effects of Ginkgo biloba in healthy older human subjects: a preliminary investigation. *Hum Psychopharmacol.* 2002; 17(1):45-49.

Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol.* 1998; 55(11):1409-1415.

Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol.* 2003; 28(3):285-287.

Petty HR, Fernando M, Kindzelskii AL et al. Identification of colchicine in placental blood from patients using herbal medicines. *Chem Res Toxicol.* 2001; 14(9):1254-1258.

Pierr S, Jamme I, Robert K. et al., Ginkgo biloba extract (EGb 761) protects Na,K-ATPase isoenzymes during cerebral ischemia. *Cell Mol Biol (Noisy-le-grand).* 2002; 48(6):671-679.

Pietri S, Seguin JR, d'Arbigny P. et al. Ginkgo biloba extract (EGb 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther.* 1997;11(2):121-131.

Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med.* 2000; 108(4):276-281.

Purroy Garcia F, Molina C, Alvarez Sabin J. Spontaneous cerebellar haemorrhage associated with Ginkgo biloba ingestion. [Article in Spanish] *Med Clin (Barc).* 2002; 119(15):596-597.

- Raja PV, Blumenthal JA, Doraiswamy PM. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. *CNS Spectr*. 2004; 9(10):763-72.
- Rigney U, Kimber S, Hindmarch I. The effects of acute doses of standardized Ginkgo biloba extract on memory and psychomotor performance in volunteers. *Phytother Res*. 1999; 13(5):408-415.
- Roman G. Perspectives in the treatment of vascular dementia. *Drugs Today (Barc)*. 2000; 36(9):641-653.
- Roncin JP, Schwartz F, D'Arbigny P. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. *Aviat Space Environ Med*. 1996; 67(5):445-452.
- Rosenblatt M, Ziment I. *Evidence-Based Herbal Medicine*. Philadelphia: Hanley and Belfus; 2002.
- Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. *N Engl J Med*. 1997; 336(15):1108.
- Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. [letter] *Neurology*. 1996; 46(6):1775-1776.
- Samuelsson G. *Drugs of Natural Origin* 4<sup>th</sup> ed. Stockholm: Swedish Pharmaceutical Society; 1999.
- Sastre J, Lloret A, Borrás C. et al. Ginkgo biloba extract EGb 761 protects against mitochondrial aging in the brain and in the liver. *Cell Mol Biol (Noisy-le-grand)*. 2002; 48(6):685-692.
- Savickiene N, Dagilyte A, Lukosius A, Zitkevicius V. Importance of biologically active components and plants in the prevention of complications of diabetes mellitus. [Article in Lithuanian] *Medicina (Kaunas)*. 2002; 38(10):970-975.
- Schneider C, Bord C, Misse P. et al. Spontaneous hyphema caused by Ginkgo biloba extract. [Article in French]. *J Fr Ophtalmol*. 2002; 25(7):731-732.
- Schulz V. Ginkgo extract or cholinesterase inhibitors in patients with dementia: what clinical trials and guidelines fail to consider. *Phytomedicine*. 2003; 10 Suppl 4:74-79.
- Schulz V, Hansel R, Tyler V, Blumenthal, M. *Rational Phytotherapy* 5<sup>th</sup> ed. Berlin: Springer-Verlag; 2004.
- Singh B, Song H, Liu XD, Hardy M et al. Dangshen (*Codonopsis pilosula*) and Bai guo (Ginkgo biloba) enhance learning and memory. *Altern Ther Health Med*. 2004; 10(4):52-6.
- Skogh M. Extracts of Ginkgo biloba and bleeding or haemorrhage. *Lancet*. 1998;352(9134):1145-1146.
- Smith JV, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by Ginkgo biloba extract EGb 761. *Alzheimers Dis*. 2003;5(4):287-300.

- Smolinske SC. Dietary supplement-drug interactions. *J Am Med Womens Assoc.* 1999;54(4):191-192,195.
- Sohn M, Sikora R. *Ginkgo biloba* extract in the therapy of erectile dysfunction. *J Sex Educ Ther* 1991; 17: 53-61.
- Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol.* 2004 ;22(12):2489-503.
- Spinella, M. *The Psychopharmacology of Herbal Medicine.* Cambridge, MS: MIT Press; 2001.
- Stough C, Clarke J, Lloyd J, Nathan PJ. Neuropsychological changes after 30-day *Ginkgo biloba* administration in healthy participants. *Int J Neuropsychopharmacol.* 2001; 4(2):131-134.
- Sumboonnanonda K, Lertsithichai P. Clinical study of the *Ginkgo biloba*--Troloxerutin-Heptaminol Hcl in the treatment of acute hemorrhoidal attacks. *J Med Assoc Thai.* 2004;87(2):137-42.
- Ternaux JP, Portalier P. Effect of quercetine on survival and morphological properties of cultured embryonic rat spinal motoneurons. *Neurosci Lett.* 2002 ;332(1):33-36.
- Tesch BJ. Herbs commonly used by women: an evidence-based review. *Am J Obstet Gynecol.* 2003; 188(5 Suppl):S44-55.
- Trick L, Boyle J, Hindmarch I. The effects of *Ginkgo biloba* extract (LI 1370) supplementation and discontinuation on activities of daily living and mood in free living older volunteers. *Phytother Res.* 2004; 18(7):531-7.
- Ulbricht C, Basch E. *Natural Standard: Herbal and Supplement Reference.* New York: Elsevier: 2005.
- Vaes LP, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: nature of the evidence. *Ann Pharmacother.* 2000; 34(12):1478-1482.
- van Dongen M, van Rossum E, Kessels A. et al. *Ginkgo* for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol.* 2003; 56(4):367-376.
- van Dongen MC, van Rossum E, Kessels AG. et al. The efficacy of *ginkgo* for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. *J Am Geriatr Soc.* 2000; 48(10):1183-1194.
- von Wedel H, Calero L, Walger M. et al. Soft-laser/*Ginkgo* therapy in chronic tinnitus. A placebo-controlled study. *Adv Otorhinolaryngol.* 1995; 49:105-108.
- Weiss,V, Fintelmann J. *Herbal Medicine* 2<sup>nd</sup> ed.. Stuttgart: Thieme; 2000.
- Wettstein A. Cholinesterase inhibitors and *Ginkgo* extracts--are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. *Phytomedicine.* 2000; 6(6):393-401.

Wichtl M. Herbal Drugs and Phytopharmaceuticals 3<sup>rd</sup> ed.  
Boca Ratón, FL: CRC Press; 2004.

Woo CW, Cheung F, Chan VW. Et al. Homocysteine stimulates inducible nitric oxide synthase expression in macrophages: antagonizing effect of ginkgolides and bilobalide. *Mol Cell Biochem.* 2003; 243(1-2):37-47.

Xu AH, Chen HS, Sun BC et al. Therapeutic mechanism of ginkgo biloba exocarp polysaccharides on gastric cancer. *World J Gastroenterol.* 2003; 9(11):2424-7.

Yao Z, Drieu K, Papadopoulos V. The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. *Brain Res.* 2001;889(1-2):181-190.

Zhang WR, Hayashi T, Kitagawa H. et al. Protective effect of ginkgo extract on rat brain with transient middle cerebral artery occlusion. *Neurol Res.* 2000; 22(5):517-521.

Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical Use and Molecular Mechanisms of Action of Extract of Ginkgo biloba Leaves in Cardiovascular Diseases. *Cardiovasc Drug Rev.* 2004; 22(4):309-19.

Zhou Z, Zheng S. The missing link in Ginkgo evolution.  
*Nature.* 2003; 423(6942):821-822.

Zimmermann M, Colciaghi F, Cattabeni F, Di Luca M. Ginkgo biloba extract: from molecular mechanisms to the treatment of Alzheimer's disease. *Cell Mol Biol (Noisy-le-grand).* 2002; 48(6):613-623.