

# Multifaceted Therapeutic Benefits of *Ginkgo biloba* L.: Chemistry, Efficacy, Safety, and Uses

S. MAHADEVAN AND Y. PARK

**ABSTRACT:** The new age of nutraceuticals is now embracing the centuries old herbal extract of *Ginkgo biloba* (Mantissa Plantarum Altera, 1771, Ginkgoaceae). The standardized preparation of the Ginkgo leaf extract (EGb 761) contained 2 main bioactive constituents, flavonoid glycosides (24%) and terpene lactones (6%), along with less than 5 ppm of the allergenic component, ginkgolic acid. The Ginkgo leaf extract has been reported to have neuroprotective, anticancer, cardioprotective, stress alleviating, and memory enhancing effects and possible effects on tinnitus, geriatric complaints, and psychiatric disorders. The therapeutic mechanisms of action of the Ginkgo leaf extract are suggested to be through its antioxidant, antiplatelet, antihypoxic, antiedemic, hemorrhheologic, and microcirculatory actions, where the flavonoid and the terpenoid constituents may act in a complementary manner. Toxicity studies show that the Ginkgo leaf extract is relatively safe for consumption, although a few side effects have been reported, that is, intracerebral hemorrhage, gastrointestinal disturbances, headaches, dizziness, and allergic skin reactions. The use of Ginkgo leaf extract may be promising for treatment of certain conditions, although its long-term use still needs to be evaluated.

**Keywords:** flavonoids, *Ginkgo biloba*, Ginkgo leaf extract, neuroprotective, terpenoids

## Introduction

Complementary and alternative medicine is defined as a “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine” (Ernst 2000). Over the past 15 y, there has been a steady growing trend of these unconventional therapies throughout the globe. The European and the U.S. market alone contributed to about \$7 and \$5 billion per annum, respectively, in 1999 (Calixto 2000). Until 2000, estimates showed that nearly 50% to 75% of the U.S. population have tried complementary and alternative medicine (Neldner 2000).

NIH broadly classifies complementary and alternative medicine into 6 categories; Mind-Body Interventions, Bioelectromagnetics Applications, Alternative Systems of Medical Practice, Manual Healing Methods, Herbal Medicine, and Diet and Nutrition (Wootton 2005). The category of herbal medicine has grown faster than any of the other forms of alternative treatment (Ernst 2002). Traditional Chinese medicine is a subsection of herbal medicine (Wootton 2005). The 12 most commonly used and best-studied medicinal herbs are listed in O’Hara (1998).

Over the past couple of decades, the Ginkgo leaf extract has stepped into the herbal spotlight mainly because of its proven benefits for treating Alzheimer’s disease (Bastianetto and others 2000; Zimmermann and others 2002; Smith and Luo 2003; Yao and others 2004). It also appears promising as a therapeutic for many other chronic and acute forms of diseases. Ginkgo leaf extract topped the list of the 7 best selling herbal products in 1998 with retail sales of US \$150 million (Izzo and Ernst 2001).

## *Ginkgo biloba*: botanical data

*Ginkgo biloba* L. (Mantissa Plantarum Altera, 1771, Ginkgoaceae) belongs to the botanical family of Ginkgoaceae with synonyms like *Salisburia adiantifolia*, *Salisburia macrophylla*, and *Pterophylla salisburiensis*. The ginkgo tree, known to be among the oldest living species on this planet, has flourished in forests for over 150 million y and hence it is called a “living fossil” (McKenna and others 2001). It is a dioecious tree with the male and female reproductive organs on separate trees. They have a large trunk with a girth of about 7 m and a height of about 30 m. Young trees are conifer like and exhibit branching dimorphism. Leaves that grow in clusters are golden yellow in fall during senescence. The leathery leaves are very uniquely shaped with 2 lobes and resemble the maidenhair fern in shape and venation. The pollination process involves the male microstrobilli bearing loosely distributed sporangiophores containing microspores with male gametophytes and the female pendulous pairs of ovules borne on the shoots. These trees begin to reproduce after about 20 y by developing naked seeds (nuts) with an outer fleshy layer (fruits). The outer fleshy layer of the fruit has a considerable amount of butanoic and hexanoic acids, which are responsible for the rotting flesh, fermented odor (McKenna and others 2001).

## History and traditional uses of *Ginkgo biloba*

The ginkgo tree is the only surviving member of Ginkgoaceae family, class of Ginkgoatae, rediscovered in Asian graded temple gardens by Kaempfer in 1670. The class of Ginkgoatae consists of approximately 15 genera, and among these, *Ginkgo*, *Baiera*, and *Ginkgoites* are the most important (Bilia 2002). The name ginkgo comes from the Chinese words *sankyo* or *yin-kuo*, which means a hill apricot or silver fruit, due to their apricot shaped mature fruits and yellow color (McKenna and others 2001). Englbart Kaempfer, a German surgeon, first used the term “Ginkgo” in 1712, but it was Linnaeus who termed it *Ginkgo biloba* in 1771 (Gertz and Kiefer 2004).

MS 20070614 Submitted 8/7/2007, Accepted 10/19/2007. Authors are with Dept. of Food Science, Univ. of Massachusetts, 100 Holdsworth Way, Amherst, MA 01003, U.S.A. Direct inquiries to author Park (E-mail: ypark@foodsci.umass.edu).

Both the leaves and the nuts of this tree have been in use for the past several centuries in traditional Chinese medicine. In fact, the nuts are known to have a longer history of usage, being first mentioned in herbals in the Yuan dynasty [1280 to 1368 AD], published in 1350 AD (Goh and Barlow 2002). For over 5000 y, the seeds (nuts) have been known to treat pulmonary disorders (like asthma, cough, and enuresis), alcohol abuse, and bladder inflammation while the leaves have been mainly used to treat heart and lung dysfunctions and skin infections (Mahady 2002; Smith and Luo 2004). However, it was only in the last 20 to 30 y that the use of the ginkgo leaf and its standardized extract formulation, EGb 761, originated in Germany, and now is the most used form of supplement for cognitive ailments in the United States (Smith and Luo 2004).

Other uses of this tree include the fruit, prepared by fermentation and cooking, being a delicacy in weddings and feasts (McKenna and others 2001; Bilia 2002). The roasted or boiled ginkgo seeds are also considered a gourmet delicacy in Japan, China, Korea, and Malaysia. The tree is also grown in many parts of Europe and the United States mainly for its ornamental value. It grows well in most places due to such properties as pest, pollution, and disease resistance (McKenna and others 2001).

### Ginkgo leaf extract

Since the constituent composition of ginkgo leaf undergoes fluctuating changes with respect to their origin, species, and time of harvest like any other plant, it is essential to standardize the Ginkgo leaf extract to obtain consistent bioactivities. The culturing, harvesting, and extraction of the ginkgo leaves are rigorously standardized and controlled based on its known active components (Smith and Luo 2004). Typically, the leaves are collected during summer and fall between the months of July and September when they are still green. These leaves are then dried and analyzed for the presence of pollutants and toxic substances like heavy metals and aflatoxins. The crude dried leaves are then extracted using an acetone:water mixture (35 to 67:1). Standardization of Ginkgo leaf extract can be done by measuring flavonoids and terpenoids (Bilia 2002). The standardized extract preparation of the ginkgo leaf, EGb 761, developed by Beaufor-Ipsen Pharma (Paris, France) and Dr. Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany), contains 24% flavonoid glycosides, 6% terpene lactones, and less than 5 ppm ginkgolic acid (the constituent proposed to have allergenic properties) (Smith and Luo 2004). Recently, a new method to evaluate Ginkgo leaf extract using HPLC-fingerprinting has been suggested as a better method to monitor various preparation of the Ginkgo leaf extract (Sun and Liu 2007).

### Active components of *Ginkgo biloba* leaf

The 2 main pharmacologically active groups of compounds present in the Ginkgo leaf extract are the flavonoids and the terpenoids (Smith and Luo 2004).

Flavonoids, also called phenylbenzopyrones or phenylchromones, are a group of low molecular weight substances that are widely spread in the plant kingdom. Flavonoids present in the Ginkgo leaf extract are flavones, flavonols, tannins, biflavones (amentoflavone, bilobetol, 5-methoxybilobetol, ginkgetin, isoginkgetin and sciadopitysin), and associated glycosides of quercetin and kaempferol attached to 3-rhamnosides, 3-rutinosides, or p-coumaric esters (McKenna and others 2001). The flavonoid content in the Ginkgo leaf is known to vary between seasons; greater amounts are found in fall than in spring (McKenna and others 2001). These compounds are known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators (DeFeudis and Drieu 2000). In general, the bioavailability of flavonoids is relatively low due to

limited absorption and rapid elimination (Goh and Barlow 2004). Flavonoids in the glycosidic form are poorly absorbed in the intestine; only in the aglycone form can they be absorbed directly (Goh and Barlow 2004). Unabsorbed flavonoids that reach the colon may be subject to metabolism by bacterial enzymes, and then absorbed (DeFeudis and Drieu 2000). Once absorbed, flavonoids reach the liver where they are metabolized to conjugated derivatives (DeFeudis and Drieu 2000). It is known that the biological activities of flavonoid metabolites are not always the same as those of the parent compound (Manach and others 2004).

Two types of terpenoids are present in Ginkgo as lactones (non-saponifiable lipids present as cyclic esters): ginkgolides and the bilobalide (Smith and Luo 2004). Ginkgolides are diterpenes with 5 types A, B, C, J, and M, where types A, B, and C account for around 3.1% of the total Ginkgo leaf extract (DeFeudis and Drieu 2000). Bilobalide, a sesquiterpene trilactone, accounts for the remaining 2.9% of the total standardized Ginkgo leaf extract (Smith and Luo 2004).

There are no adequate studies determining the dose of Ginkgo extract needed to achieve beneficial effects, although the recommended dose of standardized extract, EGb 761, is 40 to 60 mg, 3 to 4 times daily based on clinical trials (Mahady 2001). For chronic conditions the German commission recommends a minimum 8-wk intake in order to observe the beneficial effects of the Ginkgo leaf extract (McKenna and others 2001).

### Pharmacological effects of *Ginkgo biloba*

Ginkgo leaf extract has shown beneficial effects in treating neurodegenerative diseases like Alzheimer's, cardiovascular diseases, cancer, stress, memory loss, tinnitus, geriatric complaints like vertigo, age-related macular degeneration, and psychiatric disorders like schizophrenia (Ramassamy and others 2007). These multifaceted activities of the Ginkgo leaf extract may work through various mechanisms of action. The suggested mechanisms of the Ginkgo leaf extract are its antioxidant effect, anti-platelet activating factor (Anti-PAF) activity for cardio and cerebral vascular diseases, inhibition of beta amyloid peptide (A $\beta$ ) aggregation to reduce Alzheimer's progression, and decreased expression of peripheral benzodiazepine receptor (PBR) for stress alleviation and stimulation of endothelium derived relaxing factor to improve blood circulation (Amri and others 1996; Pietri and others 1997a; DeFeudis and Drieu 2000; Smith and Luo 2004).

**Antioxidant effects.** The underlying principle behind the therapeutic action of the Ginkgo leaf extract on chronic ailments (such as neurodegenerative diseases, cardiovascular diseases and cancer) has focused on its antioxidant properties. The 2 proposed mechanisms of action are (1) directly scavenging free radicals and (2) indirectly inhibiting formation of free radicals. The Ginkgo leaf extract can scavenge reactive oxygen species (ROS) such as hydroxyl radicals (OH $\cdot$ ), peroxy radical (ROO $\cdot$ ), superoxide anion radical (O $_2^{\cdot-}$ ), nitric oxide radical (NO $\cdot$ ), hydrogen peroxide (H $_2$ O $_2$ ), and ferryl ion species (Mahady 2002; DeFeudis and others 2003). The Ginkgo leaf extract can also enhance activities of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, catalase, and/or heme-oxygenase-1, thereby indirectly contributing as an antioxidant (Song and others 2000; DeFeudis and others 2003). It has been suggested that ginkgo leaf extract increases expression of mitochondrial enzymes like NADH dehydrogenases, which can influence ROS generation in the mitochondria. This is a protection against uncoupling of oxidative phosphorylation, thereby increasing ATP levels regulating energy metabolism (Janssens and others 1995; Tendi and others 2002). In comparison to other antioxidants, the Ginkgo leaf extract (EGb 761) is known

to be regulatory and adaptive, either dilating or contracting blood vessels, or controlling neurochemicals or neuroendocrine indicators according to the circumstances (Smith and Luo 2003). The main constituents implicated in all these actions are the flavonoids (quercetin and kaempferol) and the terpenoids (ginkgolides and bilobalide) (Bastianetto and others 2000; DeFeudis and others 2003; Smith and Luo 2004), where each contributes their antioxidant property differently. The flavonoids are known to exert their effects through inhibition of the cyclooxygenase-2 enzyme, which is a part of prostaglandin synthesis, and its inhibition is known to reduce colon carcinogenesis. The bilobalide increase the activities of the antioxidant enzymes (SOD and catalase) and improve cell viability (Watanabe and others 2000; DeFeudis and others 2003).

However, proanthocyanidins (present at about 7% in Ginkgo leaf extract) present in the whole leaf extract bind to proteins and inactivate antioxidant enzymes such as catalase, glutathione peroxidase, and lactate dehydrogenase (Pietri and others 1997a). Hence, the presence of these proanthocyanidins may hinder the antioxidant effects of the Ginkgo leaf extract.

**Prevention of neurodegenerative diseases.** Alzheimer's disease is a form of dementia that progressively deteriorates intellectual capacity of various domains of the brain, particularly with aging (Smith and Luo 2003). Alzheimer's disease affects about 4% of the population over 65 and 20% of those over 80 (Zimmermann and others 2002). Research has now found links between Alzheimer's disease and deposition of amyloid beta peptide ( $A\beta$ ) (Bastianetto and others 2000; Yao and others 2004; Ramassamy and others 2007).

$A\beta$  is a polypeptide with 39 to 43 amino acid residues and a major component of senile plaques and vascular amyloid deposits of the brains of patients suffering from Alzheimer's disease. Ginkgo leaf extract is known to inhibit the formation of  $A\beta$  from  $\beta$ -amyloid precursor protein (APP), a crucial process in the pathogenesis of Alzheimer's disease (Yao and others 2004). Formation of amyloid precursor protein has been indirectly linked to high cholesterol levels (Koudinov and Koudinova 2001; Wolozin 2002; Puglielli and others 2003). It has been postulated that the inhibition of  $A\beta$  is through the Ginkgo leaf extract's ability to compete with free cholesterol for interaction with  $A\beta$  and thereby decrease their aggregation (Yao and others 2004). Alternatively, the Ginkgo leaf extract inhibits ROS accumulation induced by  $A\beta$  (particularly flavonol quercetin) and also reduces neuron apoptosis, where apoptosis is considered to be one of the main causes for neurodegenerative diseases (Bastianetto and others 2000; Ahlemeyer and Krieglstein 2003; Ergun and others 2005; Ramassamy and others 2007) and thus help to relieve Alzheimer's disease. Ginkgolide B and bilobalide are reported to inhibit apoptosis induced by staurosporine (alkaloid anticancer drug) and serum deprivation (Ahlemeyer and Krieglstein 2003). Bilobalide also prevented DNA fragmentation due to hydroxyl radical  $\beta$ -amyloid and hydrogen peroxide (Ahlemeyer and Krieglstein 2003). In addition, Ginkgo leaf has also been reported to improve cerebral blood flow by stimulating norepinephrine secretion (Yang and others 2005) and increased the life span in a particular study of rats treated chronically with EGb 761, due to its antioxidant action in reducing oxidative stress and free radical production (Winter 1998).

Ginkgo leaf extract is known to improve memory complaints as well. Walesiuk and others (2005) used EGb 761 at a dose of 100 mg/kg and found improvements of spatial and nonspatial memory tested in rats using the maze and object recognition test. Not only was EGb761 responsible for memory response improvement but was also reported to improve response retrieval.

Similar effects on improvement of cognition, memory loss, or improved blood flow which may be beneficial for Alzheimer's disease, vertigo, dyslexia, and other neuropsychiatric disorders were exhibited in a number of human clinical trials using Ginkgo leaf extract (Hopfenmuller 1994; Hartley and others 2003; Smith and Luo 2004; Issing and others 2005; Akhondzadeh and Abbasi 2006; Donfrancesco and Ferrante 2007; Kennedy and others 2007b; Napryeyenko and others 2007; Ramassamy and others 2007; Scripnikov and others 2007). However, others showed no benefit of Ginkgo leaf extract on cognitive functions or memory (van Dongen and others 2000, 2003; Carlson and others 2007; Kennedy and others 2007a; Lovera and others 2007). Although there is a body of evidence showing the potentially beneficial effects of Ginkgo leaf extract on neurodegenerative diseases, it is still not conclusive whether Ginkgo leaf extract supplementation can improve cognitive functions in humans.

**Cardioprotective effects.** Ischemia, impaired blood circulation, is a common underlying condition of cardiovascular and cerebral vascular diseases. During an ischemic attack, there is an increased release of free radicals and lipid peroxidation causing tissue damage and resulting in chronic diseases (Mahady 2002). Cardioprotective effects of Ginkgo leaf extract are through antioxidant, antiplatelet activity and increased blood flow through release of nitric oxide and prostaglandins (Pietri and others 1997a, 1997b; Mahady 2002).

Pietri and others (1997b) showed that consumption of Ginkgo leaf extract prior to cardiac surgery helped in reducing reperfusion induced lipid peroxidation and prevented ascorbate depletion, tissue necrosis, and cardiac dysfunction. Moreover, they also showed that ginkgolide B reduces 50% to 60% of the posts ischemic production of ROS (Pietri and others 1997b). Pietri and others (1997a) also showed that reperfused hearts treated with terpene constituents alone recovered functionally better than those treated with EGb 761 (Pietri and others 1997a). This leads to the conclusion that terpene constituents decreased myocardial vulnerability to ischemic reperfusion.

The Ginkgo leaf extract is also known to improve coronary blood flow through antiplatelet activity (by ginkgolide B) and by improving contractile functions which are due to increased release of catecholamines from endogenous liver tissue reserves by flavonoids (quercetin, kaempferol, and isorhamnetin) (Mahady 2002).

**Anticancer effects.** Cancer is a disease characterized by uncontrolled division of cells and the ability of these cells to invade other tissues. The disease is of multifactorial origin that involves changes in gene expressions and aberrations in the cell signaling pathways. Ginkgo leaf extract is known to exhibit a chemopreventive action at various levels with antioxidant, antiangiogenic properties, and influence gene expression (Sagar and others 2006). The Ginkgo leaf extract's antioxidant ability contributes to improving cellular tolerance to oxidative stress (Smith and Luo 2004) as well as to reduce angiogenesis, which is blood vessel formation required for tumor metastasis (Monte and others 1994; DeFeudis and others 2003; Kim and others 2006; Sagar and others 2006). The nitric oxide (NO) involved in cancer progression also appears to be resolved through the terpenoids of the Ginkgo leaf extract by altering the expression of NO synthase enzymes (DeFeudis and others 2003). In addition, Ginkgo leaf extract is known to influence the expression of genes involved in cell proliferation, cell differentiation, and apoptosis at the mRNA levels in breast and bladder cancer models (Gohil and others 2000; Papadopoulos and others 2000; DeFeudis and others 2003), thus providing anticancer effects.

**Effects on stress modification, mood, and memory.** Anxiety syndromes such as stress, moods, and depression are becoming

common in the modern world. Complementary and alternative medicine is becoming popular as a prophylactic and/or therapeutic treatment for these symptoms. Stress involves a rise in the levels of glucocorticoids, and a subsequent memory dysfunction, increased anxiety, decreased immunity, gastrointestinal tract disturbances, myocardial infarction, or effects such as increased vigilance (Walesiuk and others 2005). Since mood and emotion are related to stress, the alleviating effects of Ginkgo leaf extract may result in improving mood, thus resulting in antidepressant activity (DeFeudis and Drieu 2004).

Ginkgolides A and B decreased the ligand binding capacity, protein, and mRNA expression of peripheral benzodiazepine receptor (PBR) which led to decreased corticosteroid synthesis and subsequently the circulating levels of glucocorticoids (Amri and others 1996). The memory enhancing effects of Ginkgo leaf extract through prevention of neuron degeneration are discussed in the previous section on prevention of neurodegenerative diseases.

**Effects on tinnitus, geriatric, and psychiatric disorders.** Tinnitus, or “ringing in the ears,” is a common condition observed in almost 10% of the population (Drew and Davies 2001). One of the common causes for tinnitus is the inadequate blood supply to the inner ear (Ernst and Stevinson 1999). Thus, Ginkgo leaf extract was thought to have some potential beneficial effects in treating tinnitus.

There are a number of clinical trials discussing the effects of ginkgo leaf extract on tinnitus (Ernst and Stevinson 1999; Drew and Davies 2001; DeBisschop 2003; Rejali and others 2004). However, effects of Ginkgo leaf extract on tinnitus are inconclusive due to different commercial extract samples of the ginkgo leaf, different intervention methods, dosages of the extract, and use of different primary end points to evaluate the results (Ernst and Stevinson 1999).

Age-related macular degeneration is thought to be one of the common causes of age-related visual loss, possibly due to oxidative damage to the retina. Ginkgo has been reported to be effective against senile macular degeneration due to its free radical scavenging effect (Diamond and others 2000). Vertigo, which involves a sensation of movement when no movement is occurring, is another disorder which ginkgo has been found to be effective against (Issing and others 2005). Schizophrenia is a mental disorder involving impairments in the perception or expression of reality and by significant social or occupational dysfunction. The condition is characterized by excessive free radical formation in the brain. A clinical trial carried out by Atmaca and others (2005) showed a positive effect in treating schizophrenia patients through increase in the levels of antioxidant enzymes like SOD, catalase, and glutathione peroxidase.

### Safety profile

Studies show that a relatively low risk is associated with the consumption of Ginkgo leaf products. Occasional adverse effects with excessive consumption of Ginkgo leaf extract have been reported which include gastrointestinal disturbances, headaches, dizziness, excessive bleeding, allergic skin reactions, and occasional anaphylaxis-like reactions (only with intravenous administration) (Kleijnen and Knipschild 1992; Skogh 1998; Vale 1998; Benjamin and others 2001; De Smet 2002). Long-term safety of Ginkgo leaf extract is not clear.

Chinese and Japanese cuisines often involve ginkgo nut consumption as a part of their diet. A particular case study reported frequent vomiting and clonic convulsions in a 36-y-old woman with no prior history of epilepsy after consuming approximately 70 to 80 nuts over 1 meal. 4'-Methoxyppyridoxine, one of the components

present in the nuts, is suspected to cause convulsions by indirectly affecting an enzyme glutamate decarboxylase, resulting in a decrease of the  $\gamma$ -aminobutyric acid (GABA) level in the brain (Miwa and others 2001).

Hemorrhage or excessive bleeding caused by Ginkgo leaf extract is due to its inhibitory effects on PAF. At levels of 120 to 240 mg/d EGb 761 does not have significant effects on PAF antagonistic action; however, dosages greater than 100 times are reported to cause hemorrhage in rabbits and humans (Koch 2005). Due to its effect on PAF, Ginkgo has been known to interact with anticoagulant drugs (Lu and others 2006; Aruna and Naidu 2007), although Jiang and others (2005) did not observe any significant effects of Ginkgo in clotting status in healthy subjects. Ginkgo leaf extract also interacts with antidepressants (that is, Trazodone), antiepileptic, antidiabetic, diuretics, and nonsteroidal anti-inflammatory drugs, as well as other herbal drugs (Matthews 1998; Uchida and others 2006; Tang and others 2007). These interactions are believed to be affected mainly by the flavonoid glycosides and the terpenoids by selectively inhibiting particular enzymes, including cytochrome P450 (Gaudineau and others 2004). However, others reported no effect on clearance of cytochrome P450 substrates by Ginkgo leaf extract (Markowitz and others 2003; Greenblatt and others 2006; Mohutsky and others 2006). The apparent discrepancy has been suggested to be due to age-dependent responses (Gurley and others 2005).

The other components of Ginkgo leaf extract are the ginkgolic acids (alkyl phenols), which are considered to be toxic. They are bilobol, cardanol, cardols, and ginkgol and are known to cause gastrointestinal and allergic reactions. All commercial preparations of Ginkgo leaf extract must contain 5 ppm or less of ginkgolic acids to minimize these adverse reactions of Ginkgo leaf extract use (McKenna and others 2001).

German authorities report no side effects on pregnant and lactating women; however, data with respect to effects on fertility, lactation, and pregnancy, particularly near labor, are inadequate to be conclusive (McKenna and others 2001; Dugoua and others 2006).

### Conclusions

The standardized Ginkgo leaf extract preparation has been found to exhibit multifaceted therapeutic effects that include effects on neurodegenerative diseases, cancer, cardiovascular diseases, tinnitus, geriatric complaints, and psychiatric disorders. The main underlying mechanism of action in all these cases has been the antioxidant properties of the extract. There are other principles of action that include PAF antagonism, modulation of the peripheral benzodiazepine receptor, and endothelium relaxing factor improving the circulatory properties of blood. Thus, Ginkgo leaf extract has been shown to be a promising herbal dietary supplement with proven therapeutic benefits. However, its long-term safety needs to be properly addressed.

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### References

- Ahlemeyer B, Krieglstein J. 2003. Neuroprotective effects of *Ginkgo biloba* extract. *Cell Mol Life Sci* 60:1779–92.
- Akhondzadeh S, Abbasi SH. 2006. Herbal medicine in the treatment of Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 21:113–8.
- Amri H, Ogwuegbu SO, Boujrad N, Drieu K, Papadopoulos V. 1996. In vivo regulation of peripheral-type benzodiazepine receptor and glucocorticoid synthesis by *Ginkgo biloba* extract EGb 761 and isolated ginkgolides. *Endocrinology* 137:5707–18.

- Aruna D, Naidu MU. 2007. Pharmacodynamic interaction studies of *Ginkgo biloba* with clostazol and clopidogrel in healthy human subjects. *Br J Clin Pharmacol* 63:333-8.
- Atmaca M, Tezcan E, Kuloglu M, Ustundag B, Kirtas O. 2005. The effect of extract of *Ginkgo biloba* addition to olanzapine on therapeutic effect and antioxidant enzyme levels in patients with schizophrenia. *Psychiatry Clin Neurosci* 59:652-6.
- Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R. 2000. The *Ginkgo biloba* extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. *Eur J Neurosci* 12:1882-90.
- Benjamin J, Muir T, Briggs K, Pentland B. 2001. A case of cerebral haemorrhage—can *Ginkgo biloba* be implicated? *Postgrad Med J* 77:112-3.
- Bilia AR. 2002. *Ginkgo biloba* L. *Fitoterapia* 73:276-9.
- Calixto JB. 2000. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Braz J Med Biol Res* 33:179-89.
- Carlson JJ, Farquhar JW, DiNucci E, Ausserer L, Zehnder J, Miller D, Berra K, Hagerty L, Haskell WL. 2007. Safety and efficacy of a *Ginkgo biloba*-containing dietary supplement on cognitive function, quality of life, and platelet function in healthy, cognitively intact older adults. *J Am Diet Assoc* 107:422-32.
- DeBisschop M. 2003. *Ginkgo* ineffective for tinnitus. *J Fam Pract* 52:766-9.
- DeFeudis FV, Drieu K. 2000. *Ginkgo biloba* extract (EGb 761) and CNS functions: basic studies and clinical applications. *Curr Drug Targets* 1:25-58.
- DeFeudis FV, Drieu K. 2004. "Stress-alleviating" and "vigilance-enhancing" actions of *Ginkgo biloba* extract (EGb 761). *Drug Dev Res* 62:1-25.
- DeFeudis FV, Papadopoulos V, Drieu K. 2003. *Ginkgo biloba* extracts and cancer: a research area in its infancy. *Fundam Clin Pharmacol* 17:405-17.
- De Smet PA. 2002. Herbal remedies. *N Engl J Med* 347:2046-56.
- Diamond BJ, Shifflett SC, Feiwei N, Matheis RJ, Noskin O, Richards JA, Schoenberger NE. 2000. *Ginkgo biloba* extract: mechanisms and clinical indications. *Arch Phys Med Rehabil* 81:668-78.
- Donfrancesco R, Ferrante L. 2007. *Ginkgo biloba* in dyslexia: a pilot study. *Phytotherapy* 14:367-70.
- Drew S, Davies E. 2001. Effectiveness of *Ginkgo biloba* in treating tinnitus: double blind, placebo controlled trial. *BMJ* 322:73-5.
- Dugoua JJ, Mills E, Perri D, Koren G. 2006. Safety and efficacy of ginkgo (*Ginkgo biloba*) during pregnancy and lactation. *Can J Clin Pharmacol* 13:e277-84.
- Ergun U, Yurtcu E, Ergun MA. 2005. Protective effect of *Ginkgo biloba* against gossypol-induced apoptosis in human lymphocytes. *Cell Biol Int* 29:717-20.
- Ernst E. 2000. The role of complementary and alternative medicine. *Br Med J* 321:1133-5.
- Ernst E. 2002. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. *Ann Intern Med* 136:42-53.
- Ernst E, Stevinson C. 1999. *Ginkgo biloba* for tinnitus: a review. *Clin Otolaryngol Allied Sci* 24:164-7.
- Gaudineau C, Beckerman R, Welbourn S, Auclair K. 2004. Inhibition of human P450 enzymes by multiple constituents of the *Ginkgo biloba* extract. *Biochem Biophys Res Commun* 318:1072-8.
- Gertz HJ, Kiefer M. 2004. Review about *Ginkgo biloba* special extract Egb 761 (*Ginkgo*). *Curr Pharm Des* 10:261-4.
- Goh LM, Barlow PJ. 2002. Antioxidant capacity in *Ginkgo biloba*. *Food Res Int* 35:815-20.
- Goh LML, Barlow PJ. 2004. Flavonoid recovery and stability from *Ginkgo biloba* subjected to a simulated digestion process. *Food Chem* 86:195-202.
- Gohil K, Moy RK, Farzin S, Maguire JJ, Packer L. 2000. mRNA expression profile of a human cancer cell line in response to *Ginkgo biloba* extract: induction of antioxidant response and the Golgi system. *Free Radic Res* 33:831-49.
- Greenblatt DJ, von Moltke LL, Luo Y, Perloff ES, Horan KA, Bruce A, Reynolds RC, Harmatz JS, Avula B, Khan IA, Goldman P. 2006. *Ginkgo biloba* does not alter clearance of flurbiprofen, a cytochrome P450-2C9 substrate. *J Clin Pharmacol* 46:214-21.
- Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. 2005. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and *Ginkgo biloba*. *Drugs Aging* 22:525-39.
- Hartley DE, Heinze L, Elsbagh S, File SE. 2003. Effects on cognition and mood in postmenopausal women of 1-week treatment with *Ginkgo biloba*. *Pharmacol Biochem Behav* 75:711-20.
- Hopfenmuller W. 1994. Evidence for a therapeutic effect of *Ginkgo biloba* special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age. *Arzneimittelforschung* 44:1005-13.
- Issing W, Klein P, Weiser M. 2005. The homeopathic preparation Vertigoheel versus *Ginkgo biloba* in the treatment of vertigo in an elderly population: a double-blind, randomized, controlled clinical trial. *J Altern Complement Med* 11:155-60.
- Izzo AA, Ernst E. 2001. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 61:2163-75.
- Janssens D, Michiels C, Delaive E, Eliaers F, Drieu K, Remacle J. 1995. Protection of hypoxia-induced ATP decrease in endothelial cells by *Ginkgo biloba* extract and bilobalide. *Biochem Pharmacol* 50:991-9.
- Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. 2005. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 59:425-32.
- Kennedy DO, Haskell CF, Mauri PL, Scholey AB. 2007a. Acute cognitive effects of standardised *Ginkgo biloba* extract complexed with phosphatidylserine. *Hum Psychopharmacol* 22:199-210.
- Kennedy DO, Jackson PA, Haskell CF, Scholey AB. 2007b. Modulation of cognitive performance following single doses of 120 mg *Ginkgo biloba* extract administered to healthy young volunteers. *Hum Psychopharmacol* [Epub ahead of print].
- Kim JD, Liu L, Guo W, Meydani M. 2006. Chemical structure of flavonols in relation to modulation of angiogenesis and immune-endothelial cell adhesion. *J Nutr Biochem* 17:165-76.
- Kleijnen J, Knipschild P. 1992. *Ginkgo biloba*. *Lancet* 340:1136-9.
- Koch E. 2005. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: considerations on possible bleeding complications after oral intake of *Ginkgo biloba* extracts. *Phytotherapy* 12:10-6.
- Koudinov AR, Koudinova NV. 2001. Essential role for cholesterol in synaptic plasticity and neuronal degeneration. *FASEB J* 15:1858-60.
- Lovera J, Bagert B, Smoot K, Morris CD, Frank R, Bogardus K, Wild K, Oken B, Whitham R, Bourdette D. 2007. *Ginkgo biloba* for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial. *Mult Scler* 13:376-85.
- Lu WJ, Huang JD, Lai ML. 2006. The effects of ergoloid mesylates and *Ginkgo biloba* on the pharmacokinetics of ticlopidine. *J Clin Pharmacol* 46:628-34.
- Mahady GB. 2001. *Ginkgo biloba*: a review of quality, safety, and efficacy. *Nutr Clin Care* 4:140-7.
- Mahady GB. 2002. *Ginkgo biloba* for the prevention and treatment of cardiovascular disease: a review of the literature. *J Cardiovasc Nurs* 16:21-32.
- Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. 2004. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 79:727-47.
- Markowitz JS, Donovan JL, Lindsay De Vane C, Sipkes L, Chavin KD. 2003. Multiple-dose administration of *Ginkgo biloba* did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. *J Clin Psychopharmacol* 23:576-81.
- Matthews MK, Jr. 1998. Association of *Ginkgo biloba* with intracerebral hemorrhage. *Neurology* 50:1933-4.
- McKenna DJ, Jones K, Hughes K. 2001. Efficacy, safety, and use of *Ginkgo biloba* in clinical and preclinical applications. *Altern Ther Health Med* 7:70, 86, 88-90.
- Miwa H, Iijima M, Tanaka S, Mizuno Y. 2001. Generalized convulsions after consuming a large amount of ginkgo nuts. *Epilepsia* 42:280-1.
- Mohutsky MA, Anderson GD, Miller JW, Elmer GW. 2006. *Ginkgo biloba*: evaluation of CYP2C9 drug interactions in vitro and in vivo. *Am J Ther* 13:24-31.
- Monte M, Davel LE, de Lustig ES. 1994. Inhibition of lymphocyte-induced angiogenesis by free radical scavengers. *Free Radic Biol Med* 17:259-66.
- Napryeyenko O, Borzenko I, GINDEM-NP Study Group. 2007. *Ginkgo biloba* special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittelforschung* 57:4-11.
- Neldner KH. 2000. Complementary and alternative medicine. *Dermatol Clin* 18:189, 93, xi.
- O'Hara M, Kiefer D, Farrell K, Kemper K. 1998. A review of 12 commonly used medicinal herbs. *Arch Fam Med* 7:523-36.
- Papadopoulos V, Kapsis A, Li H, Amri H, Hardwick M, Culty M, Kasprzyk PG, Carlson M, Moreau JP, Drieu K. 2000. Drug-induced inhibition of the peripheral-type benzodiazepine receptor expression and cell proliferation in human breast cancer cells. *Anticancer Res* 20:2835-47.
- Pietri S, Maurelli E, Drieu K, Culcasi M. 1997a. Cardioprotective and anti-oxidant effects of the terpenoid constituents of *Ginkgo biloba* extract (EGb 761). *J Mol Cell Cardiol* 29:733-42.
- Pietri S, Seguin JR, d'Arbigny P, Drieu K, Culcasi M. 1997b. *Ginkgo biloba* extract (EGb 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther* 11:121-31.
- Puglielli L, Tanzi RE, Kovacs DM. 2003. Alzheimer's disease: the cholesterol connection. *Nat Neurosci* 6:345-51.
- Ramassamy C, Longpre F, Christen Y. 2007. *Ginkgo biloba* extract (EGb 761) in Alzheimer's disease: is there any evidence? *Curr Alzheimer Res* 4:253-62.
- Rejali D, Sivakumar A, Balaji N. 2004. *Ginkgo biloba* does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clin Otolaryngol Allied Sci* 29:226-31.
- Sagar SM, Yance D, Wong RK. 2006. Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1. *Curr Oncol* 13:14-26.
- Scripnikov A, Khomeenko A, Napryeyenko O, GINDEM-NP Study Group. 2007. Effects of *Ginkgo biloba* extract Egb 761 on neuropsychiatric symptoms of dementia: findings from a randomised controlled trial. *Wien Med Wochenschr* 157:295-300.
- Skogh M. 1998. Extracts of *Ginkgo biloba* and bleeding or haemorrhage. *Lancet* 352:1145-6.
- Smith JV, Luo Y. 2003. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract Egb 761. *J Alzheimers Dis* 5:287-300.
- Smith JV, Luo Y. 2004. Studies on molecular mechanisms of *Ginkgo biloba* extract. *Appl Microbiol Biotechnol* 64:465-72.
- Song W, Guan HJ, Zhu XZ, Chen ZL, Yin ML, Cheng XF. 2000. Protective effect of bilobalide against nitric oxide-induced neurotoxicity in PC12 cells. *Acta Pharmacol Sin* 21:415-20.
- Sun G, Liu J. 2007. Qualitative and quantitative assessment of the HPLC fingerprints of *Ginkgo biloba* extract by the involution similarity method. *Anal Sci* 23:955-8.
- Tang J, Sun J, Zhang Y, Li L, Cui F, He Z. 2007. Herb-drug interactions: effect of *Ginkgo biloba* extract on the pharmacokinetics of theophylline in rats. *Food Chem Toxicol* 45:2441-5.
- Tendi EA, Bosetti F, Dasgupta SF, Stella AM, Drieu K, Rapoport SI. 2002. *Ginkgo biloba* extracts Egb 761 and bilobalide increase NADH dehydrogenase mRNA level and mitochondrial respiratory control ratio in PC12 cells. *Neurochem Res* 27:319-23.
- Uchida S, Yamada H, Li XD, Maruyama S, Ohmori Y, Oki T, Watanabe H, Umegaki K, Ohashi K, Yamada S. 2006. Effects of *Ginkgo biloba* extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. *J Clin Pharmacol* 46:1290-8.
- Vale S. 1998. Subarachnoid haemorrhage associated with *Ginkgo biloba*. *Lancet* 352:36.
- van Dongen MC, van Rossum E, Kessels AG, Sielhorst HJ, Knipschild PG. 2000. 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* 48:1183-94.
- van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P. 2003. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol* 56:367-76.

- Walesiuk A, Trofimiuk E, Braszko JJ. 2005. Ginkgo biloba extract diminishes stress-induced memory deficits in rats. *Pharmacol Rep* 57:176–87.
- Watanabe K, Kawamori T, Nakatsugi S, Wakabayashi K. 2000. COX-2 and iNOS, good targets for chemoprevention of colon cancer. *Biofactors* 12:129–33.
- Winter JC. 1998. The effects of an extract of *Ginkgo biloba*, EGb 761, on cognitive behavior and longevity in the rat. *Physiol Behav* 63:425–33.
- Wolozin B. 2002. Cholesterol and Alzheimer's disease. *Biochem Soc Trans* 30: 525–9.
- Wootton JC. 2005. Classifying and defining complementary and alternative medicine. *J Altern Complement Med* 11:777–8.
- Yang YL, Su YW, Ng MC, Chang CL, Lu KT. 2005. Extract of *Ginkgo biloba* EGb 761 facilitates fear conditioning measured by fear-potentiated startle. *Neurosci Lett* 383:145–50.
- Yao ZX, Han Z, Drieu K, Papadopoulos V. 2004. *Ginkgo biloba* extract (Egb 761) inhibits beta-amyloid production by lowering free cholesterol levels. *J Nutr Biochem* 15:749–56.
- Zimmermann M, Colciaghi F, Cattabeni F, Di Luca M. 2002. *Ginkgo biloba* extract: from molecular mechanisms to the treatment of Alzheimer's disease. *Cell Mol Biol (Noisy-le-grand)* 48:613–23.
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