

Therapeutic role of *Ginkgo biloba* leaf extract

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In the past decade, interest by the general public in the use of herbal dietary supplements has risen exponentially. As throughout history, individuals are now turning to the use of “natural” therapies for the prevention, treatment and cure of almost every ailment and aging malady. One of the most popular herbal supplements is *Ginkgo biloba* leaf extract, taken for its perceived “memory enhancing” properties. Its purported biological effects include: scavenging free radical; lowering oxidative stress; reducing neural damages, reducing platelets aggregation; anti- inflammation; anti-tumor activities; and anti-aging. Clinically, it has been prescribed to treat central nervous system disorders such as Alzheimer’s disease and cognitive deficits. It exerts allergy and changes in bleeding time. There are no standards or guidelines regulating the constituent components of *Ginkgo biloba* leaf extract nor is exposure limits imposed. The use of *Ginkgo* leaf extract may be promising for treatment of certain conditions, although its long-term use still needs to be evaluated.

Key Words : *Ginkgo biloba*, Ginkgo leaf extracts, Terpenoids, Flavonoids, Ginkgolide

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INTRODUCTION

Ginkgo biloba L. comes from the leaves of the ginkgo tree. It is also known as the maidenhair tree because its leaves resemble with maidenhair fern. 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 colour (McKenna *et al.*, 2001). Englbart Kaempfer, a German surgeon, first used the term “Ginkgo”. The species was initially described by Carl Linnaeus in 1771, the *Biloba* derived from the Latin *Bis*, “two” and *Loba*, “lobed”, referring to the shape of the leaves (Gertz and

Kiefer, 2004). Native to China, the tree is widely cultivated and was introduced early to human history. Thus, it is one of the best known examples of a “living fossil”. A single ginkgo tree can live as long as 1,000 years and in 1945 six of the trees are said to have survived in Hiroshima in the devastated area around the impact of the atom bomb. The ginkgo tree is now cultivated extensively in Asia, Europe, North America, New Zealand, and Argentina due to such properties as pest, pollution, and disease resistance.

Now-a-days, extracts of ginkgo leaves in the form of film-coated tablets, oral liquids or injectable solutions can be used for therapeutic purposes. The uses of ginkgo include the fruit, prepared by fermentation and cooking, being a delicacy in weddings and feasts. The roasted or boiled ginkgo seeds are also considered a gourmet delicacy in Japan, China, Korea, and Malaysia (McKenna *et al.*, 2001 and Bilia, 2002). *Ginkgo biloba*, whose medicinal uses were described in the Chinese Materia Medica. The seeds (nuts) have been known to treat pulmonary disorders (like asthma, cough and enuresis), alcohol abuse,

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and bladder inflammation while the leaves have been mainly used to treat heart and lung dysfunctions and skin infections (Mahady, 2002 and Smith and Luo, 2004).

Commercial *Ginkgo biloba* leaves extracts :

Depending on the country of origin, time of harvest, etc., the percentages of individual constituents found in *Ginkgo biloba* can vary considerably. French and German companies have approved a standardized form of *Ginkgo biloba* leaf extract (EGb 761, developed by Beaufour-Ipsen Pharma (Paris, France) and Dr. Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany) that contains 24% flavonoid glycosides, 6% terpene lactones, and less than 5 ppm ginkgolic acid, the component that has allergenic properties. The leaves of *Ginkgo biloba* trees are collected while still green from July to September, dried, then analyzed morphologically, micro-biologically and chemically for an evaluation of the presence of heavy metals, pollutants and constituents. Next, a refinement process includes the extraction and concentration of the active constituents from the crude dried leaves formulation with an acetone-water mixture. Lastly, the flavonoid fraction is analyzed through HPLC/UV techniques, while the terpenes are identified and quantitated by HPLC coupled with a retention index detector (Sun and Liu, 2007 and Van Beek and Montoro, 2009).

Many other companies in Asia, Europe, and the United States manufacture or distribute *Ginkgo biloba* extracts and dietary supplements containing extracts of the ginkgo leaves. Ginkgo leave extract is also used in combination products to provide “special nutrients for the brain”.

Active chemical components of *Ginkgo biloba* leaves:

There are numerous chemical constituents contained

in *Ginkgo biloba* leaves (Table 1). The two main pharmacologically active groups of compounds present in the ginkgo leaf extract are the flavonoids and the terpenoids (Smith and Luo, 2004). Both the terpenes and the flavonoids, having separate properties, are responsible for giving this extract its unique polyvalent pharmacological action. The terpene lactones are represented by the ginkgolides A, B, C, J and M and bilobalide. The ginkgolides are platelet activating factor antagonists, able to reduce platelet activation and aggregation, and therefore having the potential to improve blood circulation. Bilobalide, a sesquiterpene trilactone constituent of Ginkgo leaf extracts, can reduce cerebral edema and decrease cortical infarct volume in certain stroke models, and reduce damage from cerebral ischemia (Defeudis, 2002). The increase in blood circulation allows increased delivery of oxygen and glucose to the brain following an ischemic event.

The antioxidant effect of the flavonoid fraction may be achieved by direct attenuation of reactive oxygen species (ROS) (Smith and Luo, 2003), chelating prooxidant transitional metal ions, expression of antioxidant proteins such as superoxide dismutase (SOD), and increase in antioxidant metabolites such as glutathione (Gohil and Packer, 2002). The flavonoid fraction of the extract appears to be more effective against hydroxyl radicals than the terpene fraction (Chan *et al.*, 2007 and Zimmermann *et al.*, 2002).

Therapeutic benefits of *Ginkgo biloba*:

Ginkgo biloba leave extract may act through several mechanisms including antioxidant effects, inhibition of platelet activating factor, alterations in membrane fluidity (signal transduction), and inhibition of glucocorticoid synthesis (Smith and Luo, 2004). The beneficial effects of *Ginkgo biloba* leave extract used

Table 1 : The main constituents of *Ginkgo biloba* leaves extracts

Sr. No.	Class	Major chemical constituents
1.	Terpenoids	Diterpenes: ginkgolides A, B, C, J (M is found in the root) Sesquiterpene: bilobalide Triterpenes: sterols
2.	Flavonoids (flavone, flavonol glycosides and aglycones)	Kaempferol, quercetin, isorhamnetin, rutin, luteolin, delphinidin, myricetin
3.	Biflavonoids	Sciadopitysin, ginkgetin, isoginkgetin, amentoflavone, bilobetin, 5'-methoxybilobetin
4.	Organic acids	Benzoic acid derivatives (ginkgolic acid), N-containing acids
5.	Polyphenols	di- <i>trans</i> -poly- <i>cis</i> -octadecaprenol
6.	Others	Waxes, steroids, 2-hexenal, cardanols, sugars, catechins, proanthocyanidins, phenols, aliphatic acids, rhamnose

in treating neuro degenerative 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 *et al.*, 2007).

Antioxidant effects:

The Ginkgo leaf extract can scavenge Reactive Oxygen Species (ROS) such as Hydroxyl Radicals (OH[•]), Peroxyl Radical (ROO[•]), Superoxide Anion Radical (O₂^{•-}), Nitric Oxide Radical (NO[•]), Hydrogen Peroxide (H₂O₂) (Mahadevan and Park, 2008; Mahady, 2002 and DeFeudis *et al.*, 2003). The Ginkgo leaf extract can also enhance activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, catalase, and/or heme-oxygenase-1, thereby indirectly contributing as an antioxidant. 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 (Abdel-Kader *et al.*, 2007).

In comparison to other antioxidants, the Ginkgo leaf extract is known to be regulatory and adaptive, either dilating or contracting blood vessels, or controlling neurochemicals or neuroendocrine indicators according to the circumstances. The main constituents implicated in all these actions are the flavonoids (quercetin and kaempferol) and the terpenoids (ginkgolides and bilobalide), where each contributes their antioxidant property differently (Smith and Luo, 2003).

Helps to increase brain power and memory :

Ginkgo is now accepted as a brain booster which improves memory, mental efficiency, cognitive function, communication, orientation and the ability to concentrate. One of the most impressive aspects of ginkgo is its ability to stimulate circulation and oxygen flow to neural tissue, there by improving cognitive functions and memory. In addition, ginkgo increases oxygen transport at the blood-brain barrier site, while inhibiting the permeability of toxins into brain tissue. As well as boosting blood supply to the brain and increases the nerve transmission rate (Snitz *et al.*, 2009; Donfrancesco and Ferrante, 2007 and Ramassamy *et al.*, 2007).

Prevention of neurodegenerative diseases:

Ginkgo leaf extract is known to inhibit the formation of A β from β -amyloid precursor protein (APP), a crucial process in the pathogenesis of Alzheimer's disease (Yao *et al.*, 2004). Alternatively, the Ginkgo leaf extract inhibits ROS accumulation induced by A β (particularly flavonol quercetin) and also reduces neuron apoptosis, where apoptosis is considered to be one of the main causes for neurodegenerative diseases and thus help to relieve Alzheimer's disease (Ramassamy *et al.*, 2007 and Bate *et al.*, 2008). It was reported that *Ginkgo biloba* leave extract can reduce corticosteroid production, improve cerebral blood flow, increase glucose uptake and utilization, ATP production, mitochondrial metabolism, and intra and extra-cellular ionic gradients (Ihl *et al.*, 2012).

Cardio protective effects :

Cardioprotective effects of Ginkgo leaf extract are through antioxidant, antiplatelet activity and increased blood flow through release of nitric oxide and prostaglandins (Mahady, 2002 and Carlson *et al.*, 2007). It is the bioflavonoid content of ginkgo which enables the compound to scavenge free radicals so effectively. The flavonoids in ginkgo help protect cells against free radical contact. The antioxidant action of ginkgo helps to prevent damage to heart muscle. Ginkgo reduces the formation of free radicals and also provides some protection from exposure to damaging ultraviolet light (Bone, 2008).

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 (Oskouei *et al.*, 2013)].

Anticancer effects :

Ginkgo leaf extract is known to exhibit a chemo preventive action at various levels with antioxidant, anti angiogenic properties, and influence gene expression (Sagar *et al.*, 2006). The Ginkgo leaf extract's antioxidant ability contributes to improving cellular tolerance to oxidative stress as well as to reduce angiogenesis, which is blood vessel formation required for tumor metastasis (Smith and Luo, 2004). 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 thus providing anticancer effects (DeFeudis *et al.*, 2003).

A natural anti stress and anti depressant Herb:

Research has shown that ginkgo can help relieve the adverse effects of stress and depression. It is considered that ginkgo helps boost stamina is by helping the body conserve energy through the increased biosynthesis of protein and nucleic acids. Ginkgo also helps to increase glucose and ATP level at the cellular level which helps to sustain higher energy output, especially under periods of mental or physical stress. Frequently, stress impairs cognitive ability, and because ginkgo facilitates better blood flow to brain neurons, coping abilities may be enhanced (Sener *et al.*, 2007). Ginkgo may work the same way that exercise does for people suffering from depression. Exercise helps to oxygenate the blood and by so doing, elevates mood. Ginkgo accomplishes a similar action by boosting brain blood flow (DeFeudis and Drieu, 2004 and Woelk *et al.*, 2007).

Circulatory system enhancer :

Ginkgo biloba dilates the blood vessels, allowing greater blood flow to the tissues. It also provides better drainage of waste products, especially through arteries that have been partially blocked because of atherosclerosis. Ginkgo also inhibits the clumping of blood platelets, which can contribute to heart and artery problems. Ginkgolides inhibit Platelet Activating Factor, which controls the formation of clots. It is purported that *Ginkgo biloba* leave extract can improve blood flow by increasing red blood cell deformability and decreasing red cell aggregation, and thus, improves red blood cell fluidity and decreases whole blood viscosity (Bastianetto *et al.*, 2000).

Effect on tinnitus, geriatric and psychiatric disorders:

Tinnitus, or “ringing in the ears,” is a common condition of inadequate blood supply to the inner ear. Ginkgo helps to oxygenate tissues more effectively which can enhance nutrient transport to the nerves of the inner ear. Thus, Ginkgo leaf extract was thought to have some potential beneficial effects in treating tinnitus. One of the main advantages of using ginkgo over other drugs for hearing loss is that it is considered safe with minimal side effects (Donfrancesco and Ferrante, 2007).

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 (Diamond *et al.*, 2000).

Schizophrenia is a mental disorder involving impairments in the perception or expression of reality and by significant social or occupational dysfunction. A clinical trial showed a positive effect in treating schizophrenia patients through increase in the levels of antioxidant enzymes like SOD, catalase, and glutathione peroxidase (Atmaca *et al.*, 2005).

Diabetic retinopathy :

There is evidence to suggest that ginkgo extract may be beneficial for people with diabetes who risk damage to their optic nerves. Diabetes causes the membranes of capillaries located in the retina to thicken, there by obstructing blood flow and reducing vision. The retina is particularly susceptible to free radical damage. A three months of oral administration of ginkgo leaf extract in type 2 diabetic patients with retinopathy significantly reduced malondialdehyde levels of erythrocytes membranes, decreased fibrinogen levels, promoted erythrocytes deformability, and improved blood viscosity and viscoelasticity, which may facilitate blood perfusion. Furthermore, it effectively improved retinal capillary blood flow rate in type 2 diabetic patients with retinopathy (Huang *et al.*, 2004).

Impotence and Ginkgo :

Ginkgo may prove to be very important in treating erectile dysfunctions of penis. Recent tests have indicated that improving the arterial blood flow to penile tissue was accomplished by ginkgo therapy without changing blood pressure (Sohn and Sikora, 1991).

Raynaud’s disease :

Raynaud’s disease is believed to be caused by blood vessels that over react to the cold and spasm, reducing blood flow and there by depriving extremities of oxygen. Ginkgo biloba may help this condition by widening the small blood vessels, which would keep these spasms from completely blocking the blood flow and may be effective in reducing the number of Raynaud’s attacks per week in patients suffering from Raynaud’s disease (Muir *et*

al., 2002).

Safety profile and safe level to human exposure :

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) (Benjamin *et al.*, 2001 and De Smet, 2002). Long-term safety of Ginkgo leaf extract is not clear.

Hemorrhage or excessive bleeding caused by Ginkgo leaf extract is due to its inhibitory effects on platelet activating factor. At levels of 120 to 240 mg/d EGb 761 does not have significant effects on platelet activating factor antagonistic action; however, dosages greater than 100 times are reported to cause hemorrhage in rabbits and humans (Koch, 2005). Due to its effect on platelet activating factor, Ginkgo has been known to interact with anticoagulant drugs (Lu *et al.*, 2006 and Aruna and Naidu, 2007). Ginkgo leaf extract also interacts with antidepressants (that is, Trazodone), antiepileptic, antidiabetic, diuretics, and nonsteroidal anti-inflammatory drugs, as well as other herbal drugs (Abad *et al.*, 2010 and Tang *et al.*, 2007). These interactions are believed to be affected mainly by the flavonoidic glycosides and the terpenoids by selectively inhibiting particular enzymes, including cytochrome P450 (Mohutsky *et al.*, 2006).

The other components of Ginkgo leaf extract are the ginkgolic acids (alkyl phenols), which are considered to be toxic. They 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 (Mahadevan and Park, 2008).

Conclusion :

Ginkgo biloba leaf extract is a complex mixture derived from a natural product. As one of the top five most selling dietary supplements in the world. Although it is perceived that “natural green” products are safe, clinical and scientific data from epidemiological and rodent experimental studies. The standardized Ginkgo leaf extract 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 platelet activating factor, antagonism 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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