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SHORT COMMUNICATION

Pharmaceutical Benefits of Ginkgo Biloba (Tree Of Life): A Review.

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ABSTRACT

Ginkgo biloba is the oldest living tree species and can live as long as 1,000 years and grow to a height of 120 feet. For thousands of years, leaves from the *Ginkgo biloba* tree have been a common treatment in Chinese medicine. In the U.S., many take ginkgo supplements in the belief that they will improve memory and sharpen thinking. Flavonoids and terpenoids are the mainly pharmacologically active groups of compounds present in the Ginkgo leaf extract. Different herbal dosage form like extract, Infusion, capsule and tincture are available in market.

KEY WORDS: *Ginkgo biloba,* Flavonoids, Maidenhair Tree, Antioxidant

INTRODUCTION:

Ginkgo biloba (Fig 1) is also known as Maidenhair Tree, Golden Fossil Tree and Stinkbomb Tree etc. **[1]**. Ginkgo is a relatively shade-intolerant species that (at least in cultivation) grows best in environments that are well-watered and well-drained **[2]**. Research has focused on the standardized Ginkgo extract which is produced from the leaves. The mechanism of action of ginkgo is believed to be produced by its functions as a neuroprotective agent, an antioxidant, a free-radical scavenger, a membrane stabilizer, and an inhibitor of platelet-activating factor via the terpene ginkgolide B. Other pharmacologic effects include the following: endothelium relaxation mediated by inhibition of 3', 5'-cyclic GMP (guanosine monophosphate) phosphodiesterase; inhibition of age-related loss of muscarinergic cholinoceptors and α-adrenoceptors; and stimulation of choline uptake in the hippocampus. Ginkgo extract also has been shown to inhibit beta-amyloid deposition **[1]**.

Ginkgo is made up of ginkgo flavone glycosides, several terpene molecules unique to ginkgo and organic acids. These molecules are thought to have the ability to fight the many effects of aging which include improving blood circulation, reducing inflammation and protecting brain cells from damage caused by lack of oxygen. Its strong antioxidant properties may protect central nervous and cardiovascular systems from damage and the effects of aging **[3]**.

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TAXONOMY:

Table 1: Taxonomy of *Ginkgo biloba* [2]

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Ginkgophyta
Class	Ginkgoopsida
Order	Ginkgoales
Family	Ginkgoaceae
Genus	Ginkgo
Species	Biloba

GENERAL DESCRIPTION [4]:

- **Botanical name:** *Ginkgo biloba L.*
- **Family:** *Ginkgoaceae*
- **Height:** 50 to 75 feet
- **Spread:** 50 to 60 feet
- **Crown uniformity:** Irregular outline or Silhouette
- **Crown shape:** Round; Pyramidal
- **Growth rate:** slow
- **Texture:** Medium
- **Leaf arrangement:** alternate (Fig. 2)
- **Leaf type:** simple
- **Leaf margin:** lobed
- **Leaf shape:** fan-shaped
- **Leaf venation:** parallel; palmate
- **Leaf type and persistence:** deciduous
- **Leaf blade length:** 2 to 4 inches
- **Leaf color:** green
- **Fall characteristic:** showy
- **Flower color:** green
- **Flower characteristics:** pleasant fragrance; inconspicuous and not showy; spring flowering
- **Fruit shape:** oval; round (Fig. 3)
- **Fruit length:** 1 to 3 inches
- **Fruit covering:** fleshy
- **Fruit color:** green; yellow

Fruit characteristics: Does not attract wildlife; inconspicuous and not showy; fruit, twigs, or foliage cause significant litter.

Figure 1: *Ginko biloba* tree [5]

Figure 2: *Ginko biloba* leaves [6]

Figure 3: *Ginko biloba* fruits [7]

ACTIVE COMPONENTS PRESENT IN *GINKGO BILOBA* LEAF [8]:

Mainly two pharmacologically active groups of compounds present in the Ginkgo leaf extract are flavonoids and terpenoids.

Flavonoids present in the Ginkgo leaf extract are flavonols, flavones, tannins, biflavones (amentoflavone, bilobetol, 5-methoxybilobetol, ginkgetin, isoginkgetin and sciadopitysin), and associated glycosides of quercitin and kaempferol attached to 3-rhamnosides, 3-rutinosides, or p-coumaric esters. The flavonoid content in the Ginkgo leaf is known to vary between seasons; greater amounts are found in fall than in spring. These compounds are known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators. Flavonoids in the glycosidic form are poorly absorbed in the intestine; only in the aglycone form can be absorbed directly. Unabsorbed flavonoids that reach the colon may be subject to metabolism by bacterial enzymes, and then absorbed. Once absorbed, flavonoids reach the liver where they are metabolized to conjugated derivatives.

Two types of terpenoids are present in Ginkgo as lactones: Ginkgolides and the Bilobalide. 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. Bilobalide, a sesquiterpene trilactone, accounts for the remaining 2.9% of the total standardized Ginkgo leaf extract.

PHARMACOLOGICAL EFFECTS OF *GINKGO BILOBA* [8]:

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 ($OH^{\cdot}$), peroxyl radical ($ROO^{\cdot}$), superoxide anion radical ($O2^{-\cdot}$), nitric oxide radical ($NO^{\cdot}$), hydrogen peroxide (H2O2), and ferryl ion species. The Ginkgo leaf extract can also enhance activities of antioxidant enzymes such as superoxide distmutase (SOD), 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. 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. The main constituents implicated in all these actions are the flavonoids (quercitin and kaempferol) and the terpenoids (ginkgolides and bilobalide), 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. 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. Hence, the presence of these proanthocyanidins may hinder the antioxidant effects of the Ginkgo leaf extract.

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 mutifactorial 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. 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. 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. 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, thus providing anticancer effects.

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. Cardioprotective effects of Ginkgo leaf extract are through antioxidant, antiplatelet activity and increased blood flow through release of nitric oxide and prostaglandin. 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 postischemic production of ROS. 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 (quercitin, kaempferol, and isorhamnetin).

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. Alzheimer's disease affects about 4% of the population over 65 and 20% of those over 80. Research has now found links between Alzheimer's disease and deposition of amyloid beta peptide (Aβ). Aβ 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*β* from *β*-amyloid precursor protein (APP), a crucial process in the pathogenesis of Alzheimer's disease. Formation of amyloid precursor protein has been indirectly linked to high cholesterol levels. It has been postulated that the inhibition of A*β* is through the Ginkgo leaf extract's ability to compete with free cholesterol for interaction with A*β* and thereby decrease their aggregation. Alternatively, the Ginkgo leaf extract inhibits ROS accumulation induced by A*β* (particularly flavonol quercitin) 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. Ginkgolide B and bilobalide are reported to inhibit apoptosis induced by staurosporine (alkaloid anticancer drug) and serum deprivation. Bilobalide also prevented DNA fragmentation due to hydroxyl radical *β*-amyloid and hydrogen peroxide. In addition, Ginkgo leaf has also been reported to improve cerebral blood flow by stimulating norepinephrine secretion 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. Ginkgo leaf extract is known to improve memory complaints as well. 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.

EFFECTS ON TINNITUS, GERIATRIC, AND PSYCHIATRIC DISORDERS:

Tinnitus, or "ringing in the ears," is a common condition observed in almost 10% of the population. One of the common causes for tinnitus is the inadequate blood supply to the inner ear. 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. 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. 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. Vertigo, which involves a sensation of movement when no movement is occurring, is another disorder which ginkgo has been found to be effective against. 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 showed a positive effect in treating schizophrenia patients through increase in the levels of antioxidant enzymes like SOD, catalase, and glutathione peroxidase.

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. 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. 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. The memory enhancing effects of Ginkgo leaf extract through prevention of neuron degeneration are discussed in the previous section on prevention of neurodegenerative diseases.

BENEFITS OF *GINKGO BILOBA* [3]

- Ginkgo is a powerful aid to circulatory problems, particularly a lack of blood to the brain that may be associated with memory loss, vertigo, tinnitus, disorientation, headaches and depression, especially in the elderly.
- Ginkgo improves blood circulation by reducing the stickiness of blood platelets. This improved blood flow may help inhibit or treat heart disorders as well as stroke.
- Ginkgo may be effective in preventing the onset of age-related mental deterioration. It is often recommended for older people suffering from dementia.
- Ginkgo, as well as rhodiola and cordyceps, have all been effectively used for impotence and erectile dysfunction.
- Ginkgo may help reduce certain premenstrual symptoms for women such as fluid retention and breast tenderness.

➢ It is considered safe and rare side effects; it has blood thinning properties and should not be used with blood thinning medications.

HERBAL FORMS OF *GINKGO BILOBA* [9]:

- *Extract:* An extract made from ginkgo leaves is available in Europe and is used for cerebral arteriosclerosis in peripheral circulatory disorders of the elderly.
- *Infusion:* Infusions of ginkgo are used for arteriosclerosis, varicose veins and hemorrhoids.
- *Capsules:* Powdered forms of ginkgo can be used to enhance brain function and memory.
- *Tincture:* Ginkgo tincture is often combined with other herbs such as periwinkle and used for circulatory problems and venous disorders.

DOSAGE [1]:

The dosage for patients who have tinnitus and peripheral vascular disease is no more than 160 mg per day, taken in two or three doses. For patients who have memory problems and dementia, the dosage of ginkgo is 120 to 240 mg daily, taken in two to three doses. An initial period of six to 12 weeks is recommended to assess the effectiveness of ginkgo, although results have been seen as early as four weeks. The monthly cost for the usual daily dose of 120 mg is approximately $15 to $20.

APPLICATIONS OF *GINKGO BILOBA* [9]:

1. PRIMARY APPLICATIONS:

The following are general areas that ginkgo biloba can be used effectively:

- Alzherimer's Disease
- Antioxidant
- Attention Span
- Blood Clots
- Brain Booster
- Cardiovascular Problems
- Cerebrovascular Insufficiency
- Circulatory Disorders
- Dementia
- Dizziness
- Edema
- Hypoxia
- Inflammation
- Impotence
- Ischemia
- Longevity
- Memory Loss
- Multiple Sclerosis
- Muscular Degeneration
- PMS
- Raynaud's Disease
- Senility
- Stress
- Stroke
- Tinnitus
- Vascular Disease

2. SECONDARY APPLICATIONS:

The following are areas of secondary application for ginkgo biloba:

- Allergies
- Angina
- Anxiety
- Arthritis
- Asthma
- Bronchial Infections
- Cancer
- Carpal Tunnel Syndrome
- Cough
- Depression
- Epilepsy
- Eye Problems
- Hemorrhoids
- High Blood Pressure
- Lung Conditions
- Migraines
- Toxic Shock Syndrome
- Transplant Rejection
- Urinary Tract Disorders
- Varicose Veins
- Vascular Impotence
- Vertigo

CONCLUSION:

Ginkgo is a relatively shade-intolerant species that grows best in environments that are well-watered and well-drained. 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.

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