

A DETAIL OVERVIEW ON PHYTOCHEMISTRY, PHARMACOGNOSY AND PHARMACOLOGY OF MAIDENHAIR TREE (*Ginkgo biloba L*).

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Abstract- The brain is the platform for our mental health. But there is a growing body of evidence, and a number of significant voices are championing the role of diet in the care and treatment of people with mental health problems. Ginkgo biloba leaf extract has shown beneficial effect in treating impairments in memory, cognitive speed, activities of daily living (ADL), edema, inflammation and free radical toxicity associated with traumatic brain injury (TBI), Alzheimer's dementia, stroke, vaso occlusive disorders, and aging. The purpose of this chapter is to provide the mechanisms of action, clinical indications, and safety of Ginkgo biloba extract (GBE). Ginkgo biloba (Gb) has demonstrated antioxidant and vasoactive properties as well as clinical benefits in several conditions such as ischemia, epilepsy, and peripheral nerve damage. Additionally, Gb is supposed to act as potential cognitive enhancer in dementia. So far, several trials have been conducted to investigate the potential effectiveness of Gb in neuropsychiatric conditions. However, the results of these studies remain controversial. We conducted a systematic review and a meta-analysis of three randomised controlled trials in patients with schizophrenia and eight randomised controlled trials in patients with dementia. Gb treatment reduced positive symptoms in patients with schizophrenia and improved cognitive function and activities of daily living in patients with dementia. No effect of Gb on negative symptoms in schizophrenic patients was found. The general lack of evidence prevents drawing conclusions regarding Gb effectiveness in other neuropsychiatric conditions (i.e., autism, depression, anxiety, attention-deficit hyperactivity disorder, and addiction). Our data support the use of Gb in patients with dementia and as an adjunctive therapy in schizophrenic patients.

Key words: Ginkgo biloba, Pharmacology, Memory impairment, Safety issues, Dosage forms, Anti oxidants.

INTRODUCTION:

Ginkgo biloba (Gb) is one of the most ancient seed plant, often referred to as a "living fossil." This large tree may live over 1000 years and reach 40 m of height. Originally native to China, Gb is now cultivated worldwide. Extract from Gb leaves has been used in traditional Chinese medicine for centuries to treat circulatory disorders, asthma, tinnitus, vertigo, and cognitive problems

Ginkgo biloba, commonly known as the maidenhair tree, is a unique and ancient species that holds a special place in the realms of both nature and medicine. With distinctive fan-shaped leaves and a lineage dating back hundreds of millions of years, Ginkgo biloba is often considered a living fossil. This remarkable tree has garnered attention not only for its resilience and adaptability but also for its potential medicinal properties.

Ginkgo biloba is a tree species that has high medicinal value due to the presence of flavonoids, terpene trilactones, and phenolic compounds. However, ginkgo seeds contain toxic and allergenic alkylphenols. A recent review of the literature and patents on Ginkgo biloba extracts provides information on the chemical composition of extracts obtained from this plant and their use in medicine and food production. Despite the growing number of studies on its toxicity and interactions with synthetic drugs, its health-promoting properties are the reason for the interest of scientists and motivation to create new food products.

SCIENTIFIC CLASSIFICATION

Scientific name: *Ginkgo biloba L*

Kingdom: Plantae

Clade: Tracheophytes

Clade: Gymnospermae

Division: Ginkgophyta

Class: Ginkgoopsida

Order: Ginkgoales

Family: Ginkgoaceae

Genus: Ginkgo

Species: *G. biloba*

BIOLOGICAL SOURCE:

Ginkgo biloba comes from the maidenhair tree, the world's most ancient tree, thought to originate 200 million years ago. The leaves of *Ginkgo* are obtained from the dioecious tree *Ginkgo biloba*, belonging to family Ginkgoaceae. A standard preparation of *ginkgo biloba* is 24% *ginkgo flavonol glycosides* and 6% *terpene lactones*, which is referred to as *ginkgo biloba extract (GBE)* or *EGb761*.

GEOGRAPHICAL SOURCE:

It is native from China, Japan and Korea. Cultivated in India, Netherland, Australia, France, Germany, Italy, North America, New zealand and Argentina.

Cultivation:

G. biloba is a perennial plant, which is raised with a plant to plant spacing of 3 to 6 m. It prefers full sunlight and well drained soil with mean soil temperature 15 to 27 °C.

Soil:

G. biloba prefer clayey loam soil rich in organic 1 matter and generally grows in acidic to neutral soil with soil pH value ranging from 5.11 to 8.05. Electrical conductivity of soil should be amid 0.07 M mhos/cm to 1.965 M mhos/ cm. Organic matter content should vary from 0.974 to 15.02 %. The available nitrogen, available phosphorus and available potassium in soil must be between 191.29 to 686.78 kg/ha, 12.30 to 846.89 ppm, and 45.89 to 456.10 ppm, respectively.

Climate:

G. biloba prefer temperature ranging from 10°C to maximum 25°C, relative humidity 60 - 85%, rainfall 1800-3200 mm and it likes bright sun shine. It is observed to grow well at the altitude of 500-3600 m. During the growing season drought, hail storm, D excessive rain fall, etc., affect the quality of the leaves.

INFORMATION ABOUT GINKGO BILOBA AS A MEDICINAL PLANT

1- **Basonym of Drug:** Ginkgo and Ginkgo

2-Main synonym:

- i. Ginkgo macrophylla
- ii. Pterophyllus salisburiensis.
- iii. Salisburia adiantifolia
- iv. Salisburia biloba (L.)
- v. Salisburia ginkgo
- vi. Salisburia macrophylla Reyn.

3- Botanical name: *Ginkgo biloba* L. (Ginkgoaceae)

4- Family: Ginkgoaceae

5- External morphology: Fissured bark is grayish, deeply furrowed on older trees, and has a corky texture and Leaves are fan shaped and possess open dichotomous venation.

6- Useful parts: leaves, tree bark and seeds.

7- Important phytoconstituents: flavonol glycosides, biflavones, proanthocyanidins and isoflavonoids.

8- Therapeutic Indication: cognition and memory in Alzheimer disease, age-associated dementia, cerebral insufficiency, intermittent claudication, schizophrenia, and multi-infarct dementia.

9- Therapeutical Uses:

- Treatment for anxiety.
- Treatment for certain types of dementia.
- Treatment for premenstrual symptoms.
- Treatment for vertigo (dizziness).
- Treatment for stroke

10- Dose: Adults 60-240 mg by mouth daily up to 6 months.

11- Adverse Effects:

1. Headache.
2. Dizziness.
3. Heart palpitations.
4. Upset stomach.
5. Constipation.
6. Allergic skin reactions.

12-Adaptogenic Properties:

Ginkgo biloba is sometimes classified as an adaptogen, a substance that may help the body adapt to stressors. Its potential to enhance resilience to various stressors is an area of interest in research.

13-Tree Characteristics:

Ginkgo biloba trees are known for their hardiness and resilience. They can tolerate various environmental conditions and are resistant to pests and diseases.

14- Gender Differences:

Male ginkgo trees are often preferred for ornamental purposes because female trees produce seeds that have a foul odor when they fall to the ground.

Pharmacological Activities of Ginkgo biloba:

In animals, EGb 761 possesses antioxidant and free radical-scavenging activities, it reverses age-related losses in brain alpha 1-adrenergic, 5-HT1A and muscarinic receptors, protects against ischaemic neuronal death, preserves the function of the hippocampal mossy fiber system, increases hippocampal high-affinity choline uptake, inhibits the down-regulation of hippocampal glucocorticoid receptors, enhances neuronal plasticity, and counteracts the cognitive deficits that follow stress or traumatic brain injury.

Pharmacological Actions:**Antioxidant:**

Ginkgo biloba extract may reduce inflammation and improve blood flow.

Free radical scavenger:

Ginkgo biloba extract protects neurons from oxidative damage and apoptosis.

Membrane stabilizer:

Ginkgo biloba functions as a neuroprotective agent and a membrane stabilizer.

Platelet-activating factor inhibitor:

Ginkgo biloba inhibits platelet-activating factor via the terpene ginkgolide B.

Blood circulation enhancer:

Ginkgo biloba extracts enhance blood circulation, inhibit clot formation, and strengthen capillary walls.

Neuroprotective agent:

Ginkgo biloba protects against hypoxic challenges and increased oxidative stress.

External Morphology:

Leaves:

The leaves are simple, large, and fan-shaped or wedge-shaped. They are typically 5–10 cm (2–4 in) long, but can sometimes grow up to 15 cm (6 in). The leaves are flat and irregularly notched, and often have a deep groove in the middle that creates two distinct lobes. The leaves on the long shoots are deeply lobed, which is why the tree is named biloba. The leaves are rich green and turn bright yellow in the fall.

Branches:

The tree has long and short branches that grow at right angles to each other. As the tree ages, it may become more irregular in shape.

Roots:

The tree has a long tap root system with extensively branched roots that penetrate deep into the soil.

Chemical Constituents:

1 Flavonoids:

Liquid chromatography-mass spectrometry has been used to identify and separate several flavonoids found in *G. biloba*. To date, 110 flavonoids have been identified, including kaempferol 3-O- α -l-[6000-p-coumaroyl(β -d)-glucopyranosyl(1,2)-rhamnopyranoside]-7-O- β -d-glucopyranoside and isorhamnetin 3-O- α -l-[6000-p-coumaroyl(α -d)-glucopyranosyl(1,2)-rhamnopyranoside], which were identified in an n-Bu OH extract of *G. biloba* leaves. These flavonoids exhibit antioxidant properties when they bind with six other flavonol glycosides: quercetin 3-O- β -D-glucopyranoside, quercetin 3-O- β -rutinoside, quercetin 3-O- α -L-[6''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside], kaempferol 3-O- α -L-[6'''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside], quercetin 3-O- β -D-glucopyranosyl-(1-2)- α -L-rhamnopyranoside, and quercetin 3-O- α -L-[6'''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside]-7-O- β -D-glucopyranoside. The flavonol structures and other flavonoids. Flavonoids can be characterized into seven groups: flavanones, isoflavones, flavone, biflavones, flavan-3-ols, flavonols, and biginkgosides. Ma et al. first separated and described biginkgosides in 2016, describing the isolation of nine biginkgosides.

2 Terpenoids:

Ten diterpenoid lactones have been discovered, known as ginkgolides Q, P, N, M, L, K, J, C, B, and A. Until recently, bilobalide was thought to be the only sesquiterpene lactone in *G. biloba*, but Dong et al. announced a new bilobalide isomer in 2020 [28]. *G. biloba* also contains nor-terpenoids, including three nor-sesquiterpenoids discovered by Shu et al. in *G. biloba* L. The chemical structures of terpenoids.

3. Alkylphenols and Alkylphenolic Acids:

Alkylphenols can be divided into five groups: cardols, cardanols, α -hydroxycardanols, urushiols, isourushiols, and alkylphenolic acids. These chemical constituents of *G. biloba*. Although ginkgolic acids are known to be toxic, they have also been reported to display potential pharmacological effects.

Bioactive chemical constituents

The major bioactive compounds of Ginkgo are terpenoids, flavonoids, bi flavonoids, organic acids, polyphenols, and many others. ginkgolides and bilobalide are the major constituents of *G. biloba* that exhibit biological and/or pharmacological activities. Ginkgolides can be classified in five forms (A, B, C, J, and M), all having the same molecular geometrical skeleton but different numbers and geometric locations of hydroxyl functional groups. The flavonoids like quercetin, kaempferol, and isorhamnetin are also the principal flavonoids occurring as glycoside derivatives in *G. biloba*.

A standardized leaf extract of *G. biloba*, known as EGb 761, contains

flavonoid- 24%

glycosides-6% terpenoids-5%

organic acids-10%

And other constituents, and are responsible for numerous health benefits.

Cultural and symbolic significance:

The ginkgo tree has deep cultural significance in China and Japan. In Japanese culture, ginkgo leaves symbolize endurance and longevity, as ginkgo trees can live for thousands of years. In Chinese culture, ginkgo leaves are considered to be a symbol of longevity and resilience. In Western culture, ginkgo leaves are often associated with hope, peace, and love. The ginkgo leaf has been used extensively in Asian art but it is also valued around the world. Most notably the ginkgo has been used as a symbol of peace, hope and vitality and also as a symbol of love and duality.

Medicinal Uses:

Mental health: Treating dementia, Alzheimer's disease, anxiety, depression, and memory loss

Circulatory health: Improving blood flow and regulating blood pressure

Other conditions: Treating altitude sickness, cerebral vascular insufficiency, cognitive disorders, dizziness, intermittent claudication, macular degeneration, glaucoma, premenstrual syndrome, and Raynaud's phenomenon.

Therapeutical uses:

Memory and cognitive function: Ginkgo biloba extract may help improve memory and cognitive function in people with dementia and Alzheimer's disease.

Eye health: Ginkgo biloba extract may help improve vision and slow down the progression of age-related macular degeneration.

Anxiety and depression: Ginkgo biloba extract may help alleviate symptoms of anxiety and depression.

Peripheral artery disease: Ginkgo biloba extract may help improve blood flow and reduce pain in people with peripheral artery disease.

Asthma: Ginkgo biloba extract may help reduce inflammation and improve lung function in people with asthma.

Tinnitus: Ginkgo biloba extract may help reduce the severity and frequency of tinnitus.

It's important to note that while ginkgo biloba extract is generally considered safe, it may interact with certain medications and cause side effects such as headache, dizziness, and upset stomach. It's always best to consult with a healthcare professional before taking any new supplements or medications.

Traditional Uses:

Ginkgo Biloba has been traditionally used for various purposes, including improving cognitive function, alleviating symptoms of anxiety, and enhancing blood circulation. Additionally, it's believed to have anti-inflammatory and antioxidant properties, making it a popular choice in traditional medicine for conditions like asthma and bronchitis. Always consult with a healthcare professional before using it for medicinal purposes.

Preventing bed wetting

Increasing sexual energy

Soothing bladder irritation

Treating intestinal worms

Treating gonorrhoea Ginkgo biloba has many health benefits and is often used to treat mental health conditions, Alzheimer's disease, and fatigue. It is one of the oldest living tree species in the world and has a long history in traditional Chinese medicine. It has also been used in Japan and Korea to manage age-related symptoms and improve blood circulation.

Medicinal uses:

Ginkgo biloba is an herb that has been used in alternative medicine to improve mental function or treat anxiety, dementia, leg pain caused by blood circulation problems, premenstrual symptoms, vision problems caused by glaucoma or diabetes, vertigo, or a movement disorder caused by taking certain antipsychotic drugs. Some evidence suggests that the herb may offer health benefits such as improving symptoms of dementia and supporting eye health. Other medicinal uses of Ginkgo biloba include treating anxiety, depression, asthma, PCOS, and fatigue. However, more research is needed to confirm these benefits. It is important to note that Ginkgo biloba can interact with certain medications, including blood thinners, antidepressants, and anticonvulsants. Therefore, it's essential to consult a healthcare professional before taking Ginkgo biloba supplements.

Neuroprotective Effect:

Ginkgo biloba extract has been studied for its potential neuroprotective effects against Alzheimer's disease and other neurological disorders. The extract has been shown to have antioxidant properties that may help prevent the formation of senile plaques and neurofibrillary tangles, which are hallmarks of Alzheimer's disease. Ginkgo biloba extract has also been investigated for its potential use in the prevention of Alzheimer's disease. However, the efficacy of Ginkgo biloba extract in the prevention and treatment of dementia remains controversial. According to a study, Ginkgo biloba extract has neuroprotective properties under conditions such as hypoxia/ischemia, seizure activity, and peripheral nerve damage. However, the macromolecular targets in the brain require further study.

Therapeutic effects:

G. biloba has been used in traditional Chinese medicine for many years for the treatment of asthma, bronchitis, tuberculosis, cognitive dysfunction, stomach pain, been tested and clinically found effective as a dietary supplement and medication for the improvement of memory, treatment or prevent of Alzheimer's disease and other neurological disorders, and treatment of cardiovascular disorders through its neuroprotective, immunomodulatory, anti-inflammatory, and antioxidant activities.

Anti inflammatory:

G. biloba extract was found to be effective in helping rats recover from colitis by significantly reducing macroscopic and histological damage. The effect of G. biloba leaf extract on the chronic inflammatory condition found in the colons of mice showed that the extract effectively suppresses the activation of macrophages and downregulates inflammation (iNOS, COX-2, and TNF- α) and inflammatory stress markers (p53 and p53-phospho-serine 15). Also the numbers of T cells (CD4+/CD25-/FOXP3) were reduced during this treatment.

Cardioprotective activity:

G. biloba extract also showed cardioprotective activity on a cardiac necrosis model of rats. G. Biloba and phytosome (GBP) formulation was administered orally for 21 days at 100 and 200 mg/kg per day. Diabetic cardiomyopathy is one factor which is induced by diabetic oxidative stress resulting in an opening of MPTP, leading to disfunctioning myocardium. G. biloba extract attenuates the oxidative stress and improves antioxidant enzyme levels, acting as a blocker of MPTP in animal models. When coadministered with atractyloside (an mPTP opener), the preventive effect is reversed.

Anti cancer:

The extract was found effective as an antitumor agent by inhibiting aromatase activity in MCF-7 cells. In addition, CYP19 mRNA and CYP19 promoter 1.3 and PII expression was decreased in the treated cell model. G. biloba extract was also found effective at preventing gastric cancer cell proliferation and at inducing apoptosis with a significant increase in caspase 3 and P53 and a decrease in antiapoptotic Bcl-2 levels biloba flavanoid compound, kaempferol, was also tested for cell proliferative and apoptosis activity against pancreatic cancer cells. This flavonoid, at 70 μ M concentration for 4 days, was found to significantly inhibit the proliferation of cancer cells. When co administered with the anticancer drug, 5-fluorouracil, a synergistic effect was recorded with increased apoptic cell concentrations. The role of NO in cancer cell proliferation is also downregulated because of alteration of the NO synthase enzyme expression by G. biloba extract. G. biloba also overcomes the toxic side effects of anticancer drugs. As such, when G. biloba extract is co administered with cisplatin (an anticancer drug), no significant auditory brainstem response (ABR) threshold shift is recorded. Similarly, endocochlear potentials (EPs) decreased less than 20% for G. biloba coadministration compared to 50% using cisplatin alone. Hair cells in both groups remained intact in rats treated with G.

biloba extract in combination with cisplatin as compared to hair loss in rats treated with cisplatin alone.

Other effects:

G. biloba has also been used to treat brain function impairment and inner ear disorders such as hearing loss, vertigo, and tinnitus. Diabetic cataracts are one of the earliest secondary complications of diabetes, eventually leading to loss of vision. The pharmacological effects of G. biloba extract (EGb 761) for prevention of diabetic-induced cataract conditions in rat lenses, cultured in high-glucose conditions, have been reported. It also was found to suppress transforming growth factor β 2 or Smad pathway activation, increase E-cadherin, and decreases α smooth muscle actin expression, all of which makes G. biloba an potential drug candidate for the prevention of diabetes-induced cataracts.

Caution:

While generally considered safe for most people when used as directed, ginkgo biloba may interact with certain medications, so it's important to consult with a healthcare professional before using it, especially for individuals on blood thinners or anti-seizure medications.

Forms of Consumption:

Ginkgo biloba supplements are commonly available in the form of capsules, tablets, or liquid extracts. The standardized extract is often used in research and clinical studies.

Side effects:

Ginkgo biloba is a herb that has antioxidant, anti-inflammatory and analgesic properties. It is used to manage a variety of diseases. However, like any other medication, it can cause side effects in some people. Some of the common side effects of Ginkgo biloba include: Palpitations, Bleeding disorder, Dizziness

, Gastrointestinal discomfort, Headache Hypersensitivity. If you experience any of these symptoms, it is recommended to stop using Ginkgo biloba and consult your doctor. It is important to note that Ginkgo biloba may interact with certain medications such as Astemizole, Azelastine, Benazepril, and Buclizine. Therefore, it is advisable to consult your doctor before taking Ginkgo biloba if you are on any medication. If you miss a dose of Ginkgo biloba, skip it and continue with your normal schedule. Do not double the dose.

Ginkgo biloba available dosage forms or medicine:

1. Immunotron capsule (G.biloba extract)

2. Ginkgo biloba (support cognitive function) Dietary supplement
3. ginkgo biloba drop (ayurvedic preparation) Amalsir
4. Butterfly express Tincture Ginkgo
5. pure ginkgo root oil (cold pressed)
6. ginksoft softgel capsule
7. Nutrabiome Ginkgo biloba syrup (helpful in management of tinnitus & vertigo memory, mental performance & blood circulation)
8. ginkgo biloba (standardized extract) Supports healthy brain function & circulation. (Herbal supplement)
9. *GB-Plus* by Entrust Healthcare Pvt Ltd.
10. *Gogo* by Zeelab Pharmacy Pvt Ltd.
11. *Cel-GB* by Celosia Pharmaceutical Pvt Ltd.
12. *Gkoba* by Sigmund Promedica.
13. *Ginkosyn* by Syndicate Life Sciences Pvt Ltd.
14. *Ginkonex* by Nexus India.

Dosage and Safety:

Recommended doses of Ginkgo biloba supplements vary, but a common range is 120-240 mg per day, divided into two or three doses. While generally considered safe for most individuals, caution is advised, especially for those on blood thinners or anti-seizure medications.

Research Status:

While some studies suggest potential benefits, the overall scientific evidence on the effectiveness of ginkgo biloba is mixed, and further research is ongoing to establish its precise therapeutic effects.

Ongoing Research and Challenges:

Due to its popularity, the scientific community continues to explore the full extent of Ginkgo biloba's therapeutic effects. Some studies indicate positive outcomes, but the overall evidence is mixed. Challenges in research include variability in study designs, populations, and Ginkgo biloba preparations used.

Conclusion:

Ginkgo biloba stands as a fascinating botanical specimen with a rich history and potential health benefits. While research continues to uncover its therapeutic properties, individuals considering its use should approach it with awareness, seeking guidance from healthcare professionals. The maidenhair tree remains a subject of exploration and admiration, intertwining the threads of nature, medicine, and cultural symbolism.

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