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Phytochemicals from *Ginkgo biloba*: Its Economic Significance, Pharmacological Benefits and Clinical Insights

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Abstract

It has been regarded as a valuable plant for humans and is regarded as a "living fossil" because of its strong therapeutic value and the high demand for its herbal products around the world. Ginkgol, alkyl phenols, flavonoids, and flavonoid glycosides are among the numerous constituents of *G. biloba*. Millions of *G. biloba* trees, mostly in USA, South Carolina, France and the China, to satisfy the commercial demand for *G. biloba* products, tons of dried leaves are produced annually. Its extract contains anti-inflammatory, anti-asthmatic, antioxidant, scavenging of radicals and neuroprotective properties. It also improves cognitive function in Alzheimer's patients. Ginkgo has been shown to improve a wide range of clinical criteria of assessment such as changes in the patient's subjective performance, cerebral insufficiency and patient attention in tasks requiring rapid orientation and readaptation.

Keywords: *Ginkgo biloba*, flavonoids, Terpenoids, Phenolic acids, Biginkgoside, anti-cancer, anti-inflammatory.

Introduction

Ginkgo biloba L. (common names: ginkgo, maidenhair-tree) has been valued by humans for almost 2000 years and regarded as "living fossil". The origin of *G. biloba* is thought to the natural forest, even though its native habitat is in China, Japan and Korea, hilly valleys in eastern China's Zhejiang province ^[1, 2]. China was the only country with knowledge of this botanical resource till 350 years ago. Since its nuts are utilized in worship more than 100 *G. biloba* plants that date back more than a millennium still stand near Chinese temples ^[2]. Although ginkgo's swimming sperm or spermatozoids, were only identified a century ago, the plant most likely evolved 200 million years ago ^[2].

There are currently no near relatives of *G. biloba* in the plant kingdom. Therefore, It is categorized under the Ginkgophyta, a distinct division. This taxon's reproductive architecture and multiflagellated sperm cells set it apart from the Coniferophyta (Conifers), while its vegetative anatomy sets it apart from the Cycadophyta (Cycads) ^[3]. According to molecular analysis of the genome Cycads and ginkgo are far more closely related than conifers ^[2]. The finding of fossils from the Jurassic period (180 million years ago) in China's Henan Province that have organs like ginkgo that contain ovules has lately cleared up the doubt ^[4].

Ginkgo leaves have been utilized as teas for medicinal

purposes throughout the history of the seeds and Chinese herbal medicine have been recognized for their medicinal properties.

Its effectiveness as a medication and dietary supplement for memory enhancement, as well as a treatment or prophylactic strategy for neurological conditions like Alzheimer's disease, has been proven by clinical research. Because of its immunomodulatory, anti-inflammatory, neuroprotective, and antioxidant qualities, it has also demonstrated potential as a treatment strategy for conditions linked to the cardiovascular system ^[5, 6, 7]. In Europe and America, ginkgo leaf extracts are currently offered in a variety of forms, such as injectable formulations, oral liquids, and film-coated capsules ^[8].

Herbal medicines, food and nutritional supplements and botanical and complementary therapies all commonly use these extracts.

Distribution of *G. biloba*

Around 1730 in the 18th century, *G. biloba* was brought to Europe. One of the earliest trees to reach Europe is the one that still stands at the Utrecht botanical park. Goethe linked the glory of this tree to a poem he composed at Heidelberg on September 27, 1815. According to information found in some publications ^[9], Liu Wen-Tai's book from 1505 A.D. ^[10] appears to be the first to show the proper *G. biloba* leaf

prescription for internal medicinal usage in China. The fruit (baigo) has been used for a very long time and the Republic of China's medical dictionary contains a note about its leaf extract. *G. biloba* belongs to the mixed mesophytic forest group that encircled hill area that borders China's Yangtze River Valley [11, 12]. According to reports, one of the last remaining wild *G. biloba* plants are discovered on the western peak of Tianmu Mountain (1506 m amsl) in Zhejiang Province, China. Introduced to Europe in 1730, ginkgo is extensively grown as a medicinal plant, especially in China, Germany, Korea, United States and the France, and attractive tree in parks and sidewalks. According to "Pen Ts'o Kang Mu," ginkgo seeds have therapeutic qualities [13].



Fig 1: *G. biloba* seeds **Fig 2:** *G. biloba* leaves **Fig 3:** *G. biloba* tree

Phytochemicals from *G. biloba*

The primary components of *G. biloba* include flavonoids, flavonoid glycosides, biginkgosides A–I, terpenoids, ginkgol, proanthocyanidins, carboxylic acids, alkylphenols and alkylphenolic acids, isoginkgetin, bilobanone, ginkgotoxin, and polyprenols. The most significant bioactive substances in *G. biloba* are bilobalides (about 6%), which belong to the diterpenoid category of secondary metabolites and ginkgolides (Table 1). In the next paths, the key important elements of *G. biloba* are discussed.

Flavonoids and its Categories:-

Studies reveal that approximately hundreds of flavonoid Glycosides and flavonoids have been found in *G. biloba* [14]. It is possible to divide the reported flavonoids into seven main categories: Flavonols and their derivatives isoflavones and isoflavone glycosides, flavone glycoside and flavones, biflavonoids, biginkgosides, flavan-3-ols, flavanone glycosides and flavanones all fall under this category. However, flavonols—which include myricetin, laricitrin, patuletin, isorhamnetin, syringetin, quercetin, kaempferol and myricetin 3',4'-dimethyl ether are the primary flavonoid components [15]. The most significant benefits of ginkgo flavonoids are antibacterial, anti-inflammatory, anti-oxidation, anti-cancer antiviral and neuroprotective properties. For example, research indicates that the sides of biginkgo contain neuroprotective and anti-neuroinflammatory properties. Ginkgo bioflavonoids are said to possess anti-inflammatory, antiviral, antifungal, antibacterial and anticancer properties. Additionally, they have shown encouraging effects against metabolic, cardiovascular and neurodegenerative disorders. There are now about 13 biflavonoids known to exist in ginkgo, including amenoflavone, bilobetin, sciadopitysin, ginkgetin, and isoginkgetin [16].

Terpenoids, Phenolic Acids, Alkylphenols and Alkylphenolic Acids-

The other most significant components of *G. biloba* are

terpenoids, which include sesquiterpenoids and diterpenoids. The primary sesquiterpenoids from ginkgo are bilobalide and its derivatives, whereas the primary diterpenoids are ginkgolides A–Q (Table 1) [17]. Ginkgolides' bioactivities for treating epilepsy, enhancing memory and learning, managing metabolic illnesses and addressing cardiovascular issues have been documented in a number of research [18]. Ginkgolic acids are one of the five major families of alkylphenols that are found in *G. biloba*, together with cardanols, α -hydroxycardanols, cardols, urushiols and isourushiols [19]. Several research suggest that *G. biloba*'s alkylphenols may be poisonous and allergic. But in certain cancer cell lines, they have also demonstrated strong cytotoxic effects [2]. Vanillic acid, protocatechuic acid isovanillic acids, p-hydroxybenzoic acid, caffeic acid, ferulic acid, p-coumaric acid gallic acid, sinapic acid, and m-hydroxybenzoic acid are among the phenolic acids found in *G. biloba* [15].

Table 1: Phytochemicals from *G. biloba*.

Compd. in Leaves	Ref.
6-Hydroxy-2-(10-hydroxy-11-pentadecenyl) benzoic acid	[20]
6-Hydroxy-2-(11-hydroxy-9-pentadecenyl) benzoic acid	[20]
6-Hydroxy-2-(12-hydroxy-13-heptadecenyl) benzoic acid	[20,21]
6-Hydroxy-2-(13-hydroxy-11-heptadecenyl) benzoic acid	[20,21]
8-(5-Carboxy-2-methoxyphenyl)-5,7-dihydroxy-4'-methoxyflavone	[22]
Biginkgoside A, R1= -H, R2= -H	[23]
Biginkgoside B, R1= -OH, R2= -OH	[23]
Biginkgoside C, R1= -H, R2= -H	[23]
Biginkgoside D, R1= -H, R2= -H	[23]
Biginkgoside E, R1= -OH, R2= -OH	[23]
Biginkgoside F, R1= -H, R2= -OH	[23]
Biginkgoside G, R1= -H, R2= -H	[23]
Biginkgoside H, R1= -H, R2= -H	[23]
Biginkgoside I, R1= -OH, R2= -OH	[23]
Bilobanone	[24]
Bilobalide A	[25]
Di-Me ether (3,3'), 1,2-Bis(3,4-dihydroxyphenyl)ethylene	[26]
Ginkgetin 7"-glucoside	[27]
Isoginkgetin 7-glucoside	[28]
Isoginkgetin	[28]
Isorhamnetin 3-O-[4-Hydroxy-E-cinnamoyl-($\rightarrow$ 6)- β -Dglucopyranosyl-(1 $\rightarrow$ 2)- α -L-rhamnopyranoside]	[29]
Shikimic acid	[30]
Tridecylphenol	[31]
Compd. in Seeds	
Dihydrophaseic acid	[32]
Ginkgotoxin	[33,34]
Hydroginkgolic acid	[20]
Compd. in Fruits	
Dihydro (3,4)-8-hydroxy-3-tridecyl-1H-2-benzopyran-1-one	[35]
Ginkgol	[36]
Compd. in Roots	
Ginkgool	[37]

Economic Importance

According to a report by a management firm located in London, *G. biloba* is a species that urgently needs to be

conserved due to its use in herbal remedies. Every year, the global demand for *G. biloba* rises from 26% to 32%. Therefore, it is imperative that *G. biloba* be cultivated on a wide scale (Masood, 1997) [38]. Because it has a significant impact on the cardiovascular system of humans, particularly on cerebral vascular function, *G. biloba* has seen a sharp increase in Western medical interest since the 1980s. Every year, more than \$6.5-7 billion is spent on botanical remedies, with ginkgo being the most popular herbal remedy [39]. 50 million *G. biloba* trees, mostly in USA, South Carolina, France and the China, produce 8,000 tons of dried leaves a year to meet the commercial demand for *G. biloba* products [40]. In 2001, between 4.5 and 5.1 million pounds of dried leaves were consumed annually, making ginkgo one of the most widely used medicinal plants [41]. In open global commercial market, Consumption of *G. biloba* has been rising quickly, at 25% a year.

The share of the global commercial market held by Germany, Switzerland and France is 31%, 8% and 5% respectively. Right now, there are currently over 142 *G. biloba* products available worldwide and their use is predicted to triple over the next five years. *G. biloba* is purchased by the pharmaceutical and herbal sectors as tincture, powder extract, and leaf extract [42].

Pharmacological Benefits

Ginkgo leaf extract has a variety of pharmacological properties. The extract from ginkgo leaves may function via a number of different methods. These are the hypothesized mechanisms of ginkgo leaf extract that have been demonstrated by numerous investigations [43] such as anti-platelet activating factor (anti-PAF) activity and antioxidant effect for cerebral vascular and cardiovascular disorders. Inhibition of the aggregation of beta amyloid peptide (A β) to slow the progression of Alzheimer's disease. Reduced peripheral benzodiazepine receptor (PBR) expression in order to reduce stress. To increase blood circulation, endothelium-derived relaxing factor is stimulated [44, 45, 46, 47].

Despite its remarkable life, the ginkgo tree is being investigated more and more for possible uses in meals, vitamins and health care. Seeds and leaves that have been stripped of their fleshy outer layer, either fresh or dried are therapeutic portions of the ginkgo tree. It has many active ingredients, but the two most significant ones are

terpene trilactones and flavanol glycosides. For these two elements, ginkgo leaf extract is standardized. The active components in ginkgo extract fortify capillary walls, increase blood flow, inhibit clot formation, and protect nerve cells from harm during low oxygen levels. The leaves' extracts are used to treat dementia symptoms including concentration problems and amnesia. Additionally, the extract has anti-inflammatory [40], anti-asthmatic [48], scavenge radicals [49], wound-healing [50], antioxidant [41] and neuroprotective qualities. It also enhances cognitive abilities in Alzheimer's patients [39, 51].

Clinical Studies

Clinical trials are human experimentation used to evaluate the safety and effectiveness of bioactive substances like those in *G. biloba*. The highest dosage of 400 mg sorafenib and 240 mg EGb was found to be both effective and well-tolerated for patients with advanced hepatocellular carcinoma by Cai *et al.* in a clinical trial assessing the safety and efficacy of combined treatment [52]. According to clinical research, giving dementia patients 240 mg of EGb 761 daily can either stabilize or slow the decline of mental performance, particularly in those who have neuropsychiatric symptoms [53]. Numerous research have examined GBE's effectiveness in improving the condition of people with cerebrovascular insufficiency. Vesper and Hansgen carried out a twelve-week, double-blind study with 90 patients [54]. Numerous clinical parameters of measure, including cerebral insufficiency, changes in the patient's subjective performance, changes in the patient's objective behaviour as observed by others, and patient attention in activities requiring quick orientation and readaptation, were shown to improve with ginkgo. Single symptoms, the overall score of clinical symptoms, and global efficacy were among the metrics that improved with GBE [55]. Although oral GBE significantly accelerated information processing in dual-coding tests, Memory Impairment crossover research involving 18 senior men and women (mean age 69.3 years) found that GBE and placebo differed in only one of three evaluation techniques in a study of eight healthy females [56, 57]. An overview of several clinical research employing ginkgo extract is provided in Table 2 [58].

Table 2: Overview of Clinical Studies

Authors	Symptoms	Outcome Measures	Dose/Duration
Allain <i>et al</i>	Memory impairment	Dual-coding task (information processing)	320 or 600 mg. 1 h prior to testing
Arrigo and Cattaneo	Cerebrovascular insufficiency	Wechsler Adult Intelligence Scale (WAIS), block design, word recognition; Rey's complex figure, memory; Spielberg State-Trait Anxiety Inventory	120 mg/d for 45 days
Bruchen <i>et al</i>	Aging, cerebral insufficiency	Figure connection test	50 mg TID for 12 weeks
Deberdt	Cognitive impairment	Memory	160mg/d one time
Eckmann	Cerebral insufficiency	Concentration, fatigue, cerebral function	160mg/d for 6 weeks
Eckmann <i>et al</i>	Cerebrovascular insufficiency	Dizziness, motor activity, speech comprehension/pro duction, depression	Tebonin forte drops, 60/d for 30 days
Hamann	Vestibular disorder	Vertigo, body sway amplitude	4 drops mice/d
Hartmann and Frick	Vascular dementia	Psychometric test	20mL TID solution 3month
Hofferberth	Senile dementia	Memory, attention, psychomotor, physiology	80mg TID
Kanowski <i>et al</i>	Alzheimer's and multi-infarct dementia	Syndrome short test, attention and memory	EGb761 and placebo: 240mg/d BID
Le Bars <i>et al</i>	Alzheimer 's disease, multi-infarct dementia	Alzheimer 's disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative Rating Instrument (GERRI)	120 mg/d for 52 weeks
Maier-Hauff	Subarachnoid hemorrhage, cerebral insufficiency	Reaction time, attention, short term memory, accuracy	150mg/d LI 1370 for 12 weeks
Mancini <i>et al</i>	Psychoorganic senile dementia	SCAG scale. Toulouse-Pieron cancellation	80 mg ID for 6weeks
Rai <i>et al</i>	Memory impairment	Kendrick Digit Copying and Learning (KDC and KDL) task; digit recall task, P300 latency	40 mg TID for 12-24 weeks
Wesnes <i>et al</i>	Idiopathic cognitive impairment	Recall, reaction time, recognition. Crichton geriatric rating scale	Tanakan: 120 mg/d for 12 weeks

Abbreviations: R, randomized; DB, double-blind; SB, single-blind; RPC, randomized placebo-controlled; PC, placebo-controlled; TID, three times a day; BID, twice a day^[58].

Conclusion

Since nuts are used in worship, the current study highlights the significance of *G. biloba* in many ways. As a result, hundreds of *G. biloba* plants that are over a thousand years old still exist in Tibetan and Chinese temples. Since the 1980s, *G. biloba* has witnessed a dramatic rise in attention in Western medicine. The pharmacological characteristics of ginkgo leaf extract are diverse. The extract may work in a variety of ways, including halting the accumulation of beta amyloid peptide (A β) to delay the development of Alzheimer's disease, antioxidant impact for cardiovascular and cerebral vascular illnesses, to improve blood flow, as well as in food, supplements and medical treatments. Flavanol glycosides and terpene trilactones are the two most significant. These two elements are standardized in the ginkgo leaf extract. Active compounds in the leaf extracts strengthen capillary walls, increase blood circulation and inhibit the formation of clots. They are also used in treating dementia symptoms such as amnesia and difficulties concentrating. The extract possesses wound-healing, anti-asthmatic, antioxidant and neuroprotective properties. Additionally, it improves Alzheimer's sufferers' cognitive capacities. According to clinical research, EGb 761 can either maintain or postpone the decline of mental ability in dementia patients, particularly in those who have neuropsychiatric symptoms. Numerous clinical criteria of assessment, including, changes in the patient's subjective performance, cerebral insufficiency and patient attention in the tasks requiring quick orientation and readaptation, have been reported to improve with ginkgo.

Declaration of Competing Interest

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