



## NATURAL MEDICINAL CHEMISTRY : CURES FROM A “LIVING FOSSIL”

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**ABSTRACT:** Ginkgo (*Ginkgo biloba* L.), is one of the oldest living tree species and its leaves are among the most extensively studied herbs in use today. Nicknamed as “living fossil” by Charles Darwin, *Ginkgo* is over 150 million years old and was thought to be extinct until it was found growing in China in 17<sup>th</sup> Century. In western world, *Ginkgo* supplements are among the best-selling herbal medications. *Ginkgo* leaves contain two types of chemicals (flavonoids and terpenoids) believed to have potent antioxidant properties. *Ginkgo* has been used in Chinese traditional medicine to treat blood disorders and enhance memory. Scientific studies throughout the years have found evidence that supports these claims. Although not all studies agree, *Ginkgo* may help treat dementia (including Alzheimer’s disease) and intermittent claudication, or poor circulation in the legs. It also shows promise for enhancing memory in older adults.

**Keywords :** *Ginkgo biloba*, CNS, Alzheimer disease, EGb 761.

The *Ginkgo* tree (*Ginkgo biloba* L.), is the only surviving member of a family Ginkgoaceae, of trees, that appeared more 150 million years ago, and it is often called a “living fossil (Major, 8). It is distinct from all other living plants and is often categorized in its own division, Ginkgophyta. *G. biloba* is dioecious, on which, the male and female structures exist on separate trees. *Ginkgo* trees can grow over 35 m high, with the main stem up to 10 m in girth and can reach ages in excess of 1000 years. The tree is characterized by fan-shaped leaves split in the middle, which served as inspiration for the name “biloba” meaning two-lobed (Stromgaard, 14).

Although *G. biloba* and other species of the genus were once widespread throughout the world, their range shrank until by two million years ago to a small area of China. For centuries it was thought to be extinct in the wild, but is now known to grow in at least two small areas in Zhejiang province in Eastern China, in the Tian Mu Shan Reserve. However, recent studies indicate high genetic uniformity among *Ginkgo* trees from these areas, arguing against a natural origin of these populations and suggesting that the *Ginkgo* trees in these areas may have been planted and preserved by Chinese

monks over a period of about 1,000 years (Shen *et al.*, 13).

*Ginkgos* adapt well to the urban environment, tolerating pollution and confined soil spaces. They rarely suffer disease problems, even in urban conditions, and are attacked by few insects. For this reason, and for their general beauty, *Ginkgos* are excellent urban and shade trees, and are widely planted along many streets (Bombardelli *et al.*, 1).

Extreme examples of the *Ginkgo*’s tenacity may be seen in Hiroshima, Japan, where six trees growing between 1–2 km from the 1945 atom bomb explosion were among the few living things in the area to survive the blast. While almost all other plants (and animals) in the area were destroyed, the *Ginkgos*, though charred, survived and were soon healthy again. The trees are alive to this day (<http://kwanten.home.xs4all.nl/hiroshima.htm>).

*Ginkgo* leaf is the symbol of the Urasenke school of Japanese tea ceremony. The tree is the national tree of China. *Ginkgos* are also popular subjects for growing as penjing and bonsai; they can be kept artificially small and tended over centuries. Furthermore, the trees are easy to propagate from seed.

## Medicinal Value

The earliest records on the use of *G. biloba* as medicine dates back to 1505 AD, where *G. biloba* treated aging members of the royal court for senility (Dementia when seen in the elderly was called senile dementia or senility) (Drieu and Jaggy, 4). Around 1965, leaf preparations of *G. biloba* were introduced to the Western world by Dr. Willmar Schwabe, and together with Beaufour-Ipsen (now Ipsen), a standardized *G. biloba* extract called EGb 761 was developed (McKenna *et al.*, 9). Many *G. biloba* products have entered the market, and *G. biloba* extract is now among the best-selling herbal medications worldwide. Today over 50 million *G. biloba* trees are grown, particularly in China, France, and South Carolina in the United States, producing approximately 8000 tons of dried leaves each year. In India, *G. biloba* is seen at high altitude in Kumaun Himalaya (Sati and Joshi, 12). Since 2000, according to the current ATC-classification, *G. biloba* special extract is listed in the group of anti-dementia drugs together with cholinesterase inhibitors and memantine (Weinmann *et al.*, 15).

EGb 761 is standardized with respect to the content of terpene trilactones (6%) and flavonoids (24%). The terpene trilactones are the five ginkgolides (ginkgolide A, B, C, J and M) and bilobalide, whereas the flavonoids are mainly flavonol-O-glycosides. EGb 761 contains many other components, including proanthocyanidins (prodelphinidins) and organic acids, particularly ginkgolic acids (anarcadic acids), which have allergenic properties; hence, the content in EGb 761 is limited to 5 ppm (McKenna *et al.*, 9). The ginkgolides are diterpenes with a cage skeleton consisting of six five-membered rings, including three lactones, a tetrahydrofuran ring, and a spiro [4.4] nonane skeleton, and a characteristic tert-butyl group. The ginkgolides vary only in the number and positions of their hydroxyl groups. Bilobalide is also a terpene trilactones with a structure similar to the ginkgolides and is the major single component in EGb 761, comprising about 3% of the total extract, whereas the five ginkgolides

take up another 3% (Stromgaard, 14). The structural studies by Nakanishi (10) led to the discovery of the structures of ginkgolides rank among the greatest achievements in natural products research.

In studies of the pharmacological effects of *G. biloba*, particularly on effects in the central nervous system (CNS), EGb 761 has been widely used, and the effects include improvement of cognition, antioxidant effects, increased cerebral blood flow and circulation, modification of neurotransmission, and protection against apoptosis (Ponto *et al.*, 11).

The most extensive clinical studies with EGb 761 have focused on alleviation of Alzheimer's disease (AD). Several clinical studies for using EGb 761 for treatment of dementia and cognitive functions associated with AD, have concluded that EGb 761 have a small but significant effect on objective measures of cognitive function in AD, without significant adverse effects. However, in light of the current lack of treatment for AD patients, EGb 761 could prove useful as an alternative to the currently available treatments (Janssen *et al.*, 6).

Tinnitus is a symptom frequently encountered by ear, nose, and throat practitioners. A causal treatment is rarely possible, and drug and nondrug treatment options are limited. One of the frequently prescribed treatments is *G. biloba* extract. Therefore, randomized, placebo-controlled clinical trials of *G. biloba* extract preparations were searched for and reviewed systematically. There is evidence of efficacy for the standardized extract, EGb 761, in the treatment of tinnitus from three trials in patients in whom tinnitus was the primary complaint (von Boetticher *et al.*, 16).

Ginkgolide B (GKB) is an anti-inflammatory extract of *G. biloba* and has been used therapeutically. It is a known inhibitor of platelet activating factor (PAF), which is important in the pathogenesis of asthma. Histological studies demonstrated that GKB substantially inhibited OVA-induced eosinophilia in lung tissue and

mucus hyper-secretion by goblet cells in the airway. These results suggest that GKB may be useful for the treatment of asthma and its efficacy is related to suppression of extracellular regulating kinase/ MAPK pathway (Chu *et al.*, 3).

A study carried to investigate the anticancer effects of three analogues of EGb 761 samples on sarcoma 108 (S180)-bearing mice and leukemic 1210 (L1210) cell lines is reported. The study also evaluated the changes of endogeneous antioxidant scavenging enzymes, including superoxide dismutase (SOD), glutathione (GST), lipid peroxidation (LPx), and catalase (CAT), in the blood of the S180-bearing mice. The EGb 761, EGb 761-H (containing mainly flavonoid aglycones and terpene trilactones), and EGb 761-DT-H (containing mainly flavonoid aglycones) samples exhibited cytotoxicity and inhibitory activity with IC<sub>50</sub> values of  $46.36 \pm 2.43 \mu\text{M}$ ,  $10.27 \pm 0.88 \mu\text{M}$ , and  $14.93 \pm 0.73 \mu\text{M}$  in L1210 cell-based assays, respectively. This resulted in 41.74 %, 60.72 %, and 63.76 % reductions in tumor weight after 10 days of treatment, respectively. It was observed that anticancer activity of EGb 761 can be improved by increasing the concentration of the aglycone form of the flavonoid. Terpene trilactones cannot exert the anticancer effects of flavonoids *in vivo*. Raising the levels of the free radical scavenger enzymes GST, SOD and CAT may be one of the involved anticancer mechanisms (Feng *et al.*, 7).

Recently, the antibacterial activity of methanol, ethanol, chloroform, and hexane extracts of the leaves of Himalayan *G. biloba* was assessed against five animal and plant pathogenic strains (*Agrobacterium tumefaciens*, *Bacillus subtilis*, *Escherichia coli*, *Erwinia chrysanthemi*, and *Xanthomonas phaseoli*) employing disc-diffusion and broth-dilution assays. The methanol extract showed the highest activity (zone of inhibition of 15-21 mm) followed by ethanol (14-19 mm), chloroform (15-20 mm), and hexane (14-19 mm) extracts at 250  $\mu\text{g/mL}$ . A minimum inhibitory concentration (MIC) of 7.8  $\mu\text{g/mL}$  was found for

the methanol extract against most of the pathogens tested (Sati and Joshi, 12).

Other than these very specific medicinal uses, the Ginkgo leaf extract has been reported to have neuroprotective, cardioprotective, stress alleviating, and memory enhancing properties and possible effects on geriatric complaints and psychiatric disorders (like winter depression) (Boonkaew and Camper, 2). The extract scavenges excess free radicals and pretreatment with EGb 761 reduces damage by free radicals in patients undergoing coronary bypass surgery. The action of platelet activating factor is antagonized and platelet aggregation is reduced. Blood flow is increased. Release of prostacyclines and nitric oxide was shown to be stimulated (Dubey *et al.*, 5).

## Conclusion

The various medicinal uses of Ginkgo leaf extract where it is used either as an antioxidant, antiplatelet, antihypoxic, antiedemic, antibacterial, aphrodisiac, or even as regulator of microcirculatory actions, is believed due to its flavonoid and the terpenoid constituents. 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.

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