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 17th 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 shrunk 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 (anarcardic 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 trilactone 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 IC50 values of 46.36 ± 2.43 µM, 10.27 ± 0.88 µM, and 14.93 ± 0.73 µM 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 µg/mL. A minimum inhibitory concentration (MIC) of 7.8 µg/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.

REFERENCES


