

*Ginkgo biloba*  
An Ancient Tree for an Aging Society



*Ginkgo biloba* belongs to the botanical family of *Ginkgoaceae* consisting of approximately 15 genera. The ginkgo tree, known to be among the oldest living species on this planet, has flourished in forests for more than 200 million years, hence it is called a “living fossil”. The modern-day *Ginkgo biloba* has a very distinct appearance characterized by its fan-shaped leaves. They also live a very, very long time. A single *Ginkgo biloba* tree might drop its distinct fan-shaped leaves every year for centuries, if not millennia. As a ginkgo ages, it does not just survive, it thrives. Though 600-year-old ginkgos grow thinner annual rings, they are likely to pump out just as much defensive and immune-supporting chemicals as their younger relatives.

This tree having survived millions of years has developed a unique adaptability to thrive in even extremely polluted environments. This attribute has made the male ginkgos very popular in air polluted cities. Its resistance, adaptability and regenerative strength, is unsurpassed in the plant kingdom and it imparts this adaptogen quality to its user. Thus, it is medicinally considered an adaptogen

remedy. It is a dioecious tree with the male and female reproductive organs on separate trees. The name ginkgo comes from the Chinese words *sankyō* or *yin-kuo*, which means a hill apricot or silver fruit, due to their apricot shaped mature fruits and yellow color.



### *Phytotherapeutic Properties and Uses*

Both the leaves and the nuts of this tree have been in use for the past several centuries in traditional Chinese medicine. In fact, the nuts are known to have a longer history of usage, being first mentioned in herbals in the Yuan dynasty [1280 to 1368 AD], published in 1350 AD.<sup>1</sup> Thus, for over 5000 years, the seeds (nuts) have been used to treat pulmonary disorders (like asthma, cough, and enuresis), and bladder inflammation, while the leaves have been mainly used to treat heart and lung dysfunctions and skin infections.<sup>2,3</sup> However, it was only in the last 30 to 50 years that the use of the ginkgo leaf and its standardized extracts have been used for cognitive ailments.<sup>4,5,6,7,8</sup>

According to The German Commission E (a scientific advisory board of the Federal Institute for Drugs and Medical Devices), *Ginkgo B.* has three primary uses or indications:

(1) For symptomatic treatment of disturbed performance in organic brain syndrome within the regimen of a therapeutic concept in cases of dementia syndromes with the following principal symptoms: memory deficits, disturbances in concentration, depressive emotional condition, dizziness, tinnitus, and headache. The primary target groups are dementia syndromes, including primary degenerative dementia, vascular dementia, and mixed forms of both.

(2) Improvement of pain-free walking distance in peripheral arterial occlusive disease in Stage II of Fontaine (intermittent claudication) and in a regimen of physical therapeutic measures, particularly walking.

(3) Vertigo and tinnitus (ringing in the ear) of vascular and involuntional origin.

Studies have also shown positive results from the use of ginkgo for the following conditions: sexual dysfunction secondary to the use of selective serotonin reuptake inhibitors<sup>9</sup>, mountain sickness and decreasing vasoactive response to cold<sup>10</sup>, macular degeneration<sup>11</sup>, asthma<sup>12</sup>, and hypoxia.<sup>13</sup>

The World Health Organization reiterated The Commission E approved uses noted above adding the following specific conditions to peripheral arterial occlusive disease: Raynaud's disease, acrocyanosis, and post phlebitis syndrome.<sup>14</sup>



### *Physiological Mechanisms*

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.<sup>15, 16, 17, 18</sup> 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 muscarinic cholinergic receptors and  $\alpha$ -adrenoceptors; and stimulation of choline uptake in the hippocampus.<sup>19</sup> Ginkgo extract also has been shown to inhibit beta-amyloid deposition, thus suggested in Alzheimer's disease.<sup>20, 21, 22, 23</sup>

### *Chemistry and Pharmacology of Ginkgo biloba leaf*

Since 2001 over 3000 papers on *Ginkgo biloba* have appeared, and about 400 of them pertain to chemical analysis. The 2 main pharmacologically active groups of compounds present in the Ginkgo leaf are the flavonoids and the terpenoids. Flavonoids are a group of low molecular weight substances that are widely spread in the plant kingdom. Flavonoids present in the Ginkgo leaf extract are flavones, flavonols, tannins, biflavones (amentoflavone, bilobetin, 5-methoxybilobetin, ginkgetin, isoginkgetin and sciadopitysin), and associated glycosides of quercetin and kaempferol attached to 3-rhamnosides, 3-rutinosides, or p-coumaric esters.<sup>24, 25, 26</sup>

The flavonoid content in the Ginkgo leaf is known to vary between seasons, with greater amounts found in fall than in spring. These compounds are known to act mainly as antioxidants/free radical scavengers and enzyme inhibitors, and cation chelators.<sup>27, 28, 29</sup> In general, the bioavailability of flavonoids is relatively low due to limited absorption and rapid elimination.<sup>30</sup>

Flavonoids in the glycosidic form are poorly absorbed in the intestine; only in the aglycone form can they 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.<sup>31, 32</sup>

Two types of terpenoids are present in Ginkgo as lactones (nonsaponifiable lipids present as cyclic esters): 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.<sup>33</sup>

### *Psychoemotional Signature*

In traditional phytotherapy, all plants have both a physiological effect and psychoemotional effect. Ginkgo's vitality regenerates the efficiency of the central nervous system and organs, while balancing 'polar forces.' Ginkgo's signature represents unity and equilibrium of nature's polarities. The mind-body is made up of two poles, described in traditional Chinese medicine as yin and yang, and these interact dynamically to maintain health, balance and harmony. The two brain hemispheres and the autonomic nervous system with its sympathetic and parasympathetic branches are balanced within this natural polarity. However, polarity may become imbalanced, i.e. left brain dominant or sympathetic dominant, with resulting loss of dynamism and vitality. Within unity and equilibrium vitality is strongest.

In western culture causal-analytic thinking causes the brain's left hemisphere to become over-stimulated, whereby, similar-synthetic thinking of the right brain hemisphere becomes neglected and diminishes. Over time this imbalance adversely affects the brain's cognitive and sensory faculties, and results in overall loss of vitality and synthesis of consciousness. Ginkgo restores mind-body balance and harmony.



### Dosage

For patients who have memory problems and dementia, the dosage of ginkgo is 120 to 240 mg daily, taken in two to three doses. 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. An initial period of six to 12 weeks is recommended to assess the effectiveness of ginkgo, although results have been early as four weeks.<sup>34, 35, 36</sup>

The monthly cost for the usual daily dose of 120 mg is approximately \$15 to \$20.

### Quality

The ginkgo flavonglycosides (ginkgo flavone glycosides) of *Ginkgo biloba*, comprising quercetin, kaempferol and isorhamnetin are the phytochemicals most often referred to as indicators of quality and efficacy. However, these compounds are mainly marker compounds which are used to identify the extract. The clinically active ingredients are believed to be terpenoids that include the ginkgolides and bilobalide, which cannot be tested by normal HPLC methods. They require more sophisticated methods of detection such as Refractive Index (RI), Evaporative Light Scattering Detectors (ELSD) or Mass Spectrometry (MS). The other important group of phytochemicals from Ginkgo are the ginkgolic acids. Interestingly, these compounds have been identified as contact allergens. The maximum level of ginkgolic acids in *Ginkgo biloba* extracts has been set by the European authorities at 5 ppm. Many poor-quality extracts contain levels of ginkgolic acids which are many orders of magnitude higher than this recommended maximum. Thus, all commercial preparations of Ginkgo leaf extract must contain 5 ppm or less of ginkgolic acids to minimize these adverse reactions.

### Warnings, Interactions, Adverse Effects

During the past 20 years, an estimated 2 billion daily doses (120 mg) of ginkgo have been sold. Studies show that a relatively low risk is associated with the consumption of Ginkgo leaf products. The most important potential clinical problem with ginkgo is caused by its inhibition of the platelet-activating factor.

Thus, it is important to use the best clinical judgement when using ginkgo in conjunction with warfarin (Coumadin), aspirin, or other antiplatelet agents. A 2001 safety study of the interaction of ginkgo and warfarin showed no change in the international normalized ratio.<sup>37</sup> Generally, ginkgo should be discontinued between 36 hours and one week before surgery, based on either pharmacokinetics or consensus opinion.<sup>38</sup>

German authorities report no side effects on pregnant and lactating women; however, data with respect to effects on fertility, lactation, and pregnancy, particularly near labor, are inadequate to be conclusive.

### **Summary Physiological Actions**

Increases blood flow, tissue oxygenation and tissue nutrition; platelet activating factor (PAF) antagonism; antioxidant - prevention of membrane damage caused by free radicals; enhances memory and cognitive function, especially in the elderly.

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