Ginkgo Biloba Extract: A Review

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Abstract

Extracts of the leaves of the Ginkgo biloba tree (ginkgo) have been used in China for medicinal purposes for hundreds of years. Research performed during the past fifteen years suggests that ginkgo may be of value in the treatment of age-related physical and mental deterioration, dementia, peripheral vascular disease, and organic impotence. Ginkgo may also reduce the severity of depression in individuals with cerebral dysfunction. Preliminary or uncontrolled studies suggest that ginkgo may benefit some patients suffering from tinnitus, vertigo, acute cochlear deafness, macular degeneration, cyclic edema, and asthma.
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The Ginkgo biloba tree (ginkgo) is the oldest tree on earth: more than 200 million years old.[1] Individual ginkgo trees sometimes live more than 1,000 years. For those of you who believe that nature is a metaphor, it should not be surprising that extracts of the leaves of the oldest tree on earth have been shown to exhibit what might be described as "anti-aging" effects. Even if you do not wish to grant Mother Nature that poetic license, there is a considerable amount of scientific research supporting the use of ginkgo as a treatment for age-related problems, as well as for other disorders.

Medicinal use of ginkgo leaves was mentioned as early as 1505 in a Chinese herbal text. In modern Chinese medicine, ginkgo is recommended to improve brain function and to relieve asthma. During the past fifteen years, ginkgo has been studied extensively by European scientists and has been found to be useful against a wide range of disorders, particularly conditions that are associated with aging. Annual sales in Europe, where ginkgo is approved as a prescription drug, amount to about $500 million. Standardized extracts of ginkgo were introduced into the United States in the mid 1980's; they are currently available without a prescription.

Ginkgo is said to be effective for a wide range of clinical conditions, many of which are seemingly unrelated in their etiology and pathogenesis. However, the broad therapeutic spectrum of ginkgo may be explainable in part by the fact that it influences two fundamental aspects of human physiology: 1) it improves blood flow to the brain and other tissues and 2) it enhances cellular metabolism. Because these functions are essential for good health, it is not unreasonable to consider the possibility that ginkgo might have a broad spectrum of clinical applications. Most of the illnesses relieved by ginkgo are associated with old age, a time of life when both blood flow and cellular metabolism deteriorate. Other disorders that may respond to ginkgo, including asthma, tinnitus, vertigo, and impotence, can also occur earlier in life.

Physiological Effects - Blood Flow and Cellular Metabolism

Ginkgo has been reported to enhance arterial and capillary blood flow and to increase cerebral glucose metabolism (independently of its effect on blood flow). For example, ginkgo increased coronary blood flow in a dose-dependent manner in isolated guinea pig heart preparations.[2] Ginkgo also protected against the effects of hypoxia in healthy volunteers, as determined by certain performance measurements and cardiorespiratory parameters under hypoxic conditions.[3] Ginkgo increased the functional activity of the brain in both humans and animals, as determined by signal-analysis electroencephalographic techniques.[4] Administration of ginkgo increased cerebral glucose consumption in rats subjected to cerebral ischemia.[5] Oral or intravenous administration of ginkgo normalized mitochondrial respiration, diminished cerebral edema, and preserved neurologic function in gerbils subjected to cerebral ischemia.[6] Administration of ginkgo also prolonged the survival time of mice exposed to lethal hypoxia.[7] Intravenous administration of ginkgo prevented mucosal damage associated with experimentally induced ischemia of the small intestine.[8] In a placebo-controlled trial with 10 apparently healthy individuals who had decreased blood fluidity, acute administration of ginkgo significantly increased blood flow in the nail fold capillaries and significantly reduced erythrocyte aggregation.[9]

Adequate blood flow and cellular metabolism are essential for good health, and a decline in these functions may explain in part the physical and mental deterioration that occur with aging. The research cited above indicates that ginkgo protects against ischemia and hypoxia by at least two different mechanisms. Ginkgo may therefore be of value for the prevention and treatment of various manifestations of aging, as well as conditions resulting from ischemia or hypoxia.

Other Effects

Ginkgo has been found to have antioxidant activity and to inhibit membrane lipid peroxidation.[10-12] These effects may play a role in the purported "anti-aging" action of ginkgo. The antioxidant action of ginkgo may explain its capacity to protect against myocardial injury in animal models of ischemia and reperfusion. [13,14] Chronic oral treatment with ginkgo also prevented the decline in apparent muscarinic (cholinergic) receptor density in the hippocampus of aged rats.[15] That observation may have implications for the prevention of cerebral aging and dementia, since receptor changes are thought to contribute to the age-related decline in brain cholinergic function.

Ginkgo has been shown to exert specific effects on the noradrenergic system and on beta-receptors,[16] and to enhance the regeneration of motor nerves in rats subjected to traumatic nerve injury. [17] Ginkgo also inhibited the activity of platelet-activating factor in vitro, in laboratory animals, and in human volunteers.[18] Since platelet-activating factor has been implicated in allergic inflammation, anaphylactic shock and asthma, ginkgo may have value in the prevention and treatment of these disorders. Ginkgo also appears to modulate some enzyme systems and ionic pumps. The originality of the pharmacologic actions of ginkgo lies in the preferential focusing of its effects on ischemic areas.[19]

Clinical Studies - Age-Related Decline

Most of the clinical research on ginkgo has been done using a Ginkgo biloba extract standardized to contain 24% ginkgoheterosides. Unless specified otherwise, "ginkgo" will refer to that extract. In one study, 40 volunteers (aged 57-77 years) received 40 mg of ginkgo three times a day or a placebo, for 12 weeks. Among individuals with initially

low values for measures of vigilance and reaction time, there were significant improvements in these parameters in the ginkgo group relative to the placebo group. However, among individuals with initially normal values, administration of ginkgo had no significant effect. These results suggest that ginkgo has a positive effect in elderly individuals with impaired mental performance and vigilance.[20]

In a double-blind study of 166 geriatric patients, ginkgo was found to be an effective treatment of age-related cerebral disorders (as determined by a specially designed geriatric clinical evaluation scale). The difference between treatment and placebo groups became statistically significant after three months and the difference between groups increased further during subsequent months.[21]

In an open trial, 112 patients (mean age, 71 years) with numerous symptoms attributed to "chronic cerebral insufficiency" received ginkgo (40 mg three times a day) for one year. During that time, there were significant improvements in short-term memory, alertness, mood disturbances, vertigo, headaches, and tinnitus. There were no side effects and no interactions with commonly used heart and diabetes medications. The effects of ginkgo were usually apparent after three months of treatment and became more pronounced with time.[22] In a double-blind study of 90 outpatients with cerebral insufficiency, ginkgo was significantly more effective than placebo, as determined by various tests of cognitive function.[23]

In a double-blind trial, 31 patients over age 50 years showing mild to moderate memory impairment were randomly assigned to receive ginkgo (40 mg three times a day) or a placebo for six months. At the end of the treatment period, ginkgo was significantly superior to placebo, as determined by objective tests of memory.[24]

Dementia

Some 216 patients with mild-to-moderate dementia of the Alzheimer's type or multi-infarct dementia were randomly assigned to receive ginkgo (120 mg twice daily) or a placebo for 24 weeks, in a double-blind trial. Of the 156 patients who completed the trial, significantly more patients receiving ginkgo (28%) showed an improvement in psychological tests, compared to patients receiving placebo (10%). Beneficial effects were slightly greater in the patients with Alzheimer's disease than in those with multi-infarct dementia.[25] In another study, 36 patients with organic brain syndrome received ginkgo (40 mg three times a day) or a placebo, in an eight-week double-blind trial. Objective tests of cerebral function demonstrated a highly significant improvement in the ginkgo group, compared to the placebo group.[26] Kleijnen and Knipschild reviewed 40 clinical trials on the effect of ginkgo on cerebral insufficiency. Although only eight of the trials were judged to be well performed, virtually all of the trials reported positive results. In most trials the dosage was 120 mg per day, given for at least 4-6 weeks.[27]

Depression

Forty patients (aged 51-78 years) with mild-to-moderate cerebral dysfunction combined with episodes of depression that had shown insufficient response to antidepressant medications were studied. These medications were continued and the patients were randomly assigned to receive ginkgo (80 mg three times a day) or a placebo for eight weeks, in double-blind fashion. In the ginkgo group, there was a 50% reduction in the severity of depression (as determined by the Hamilton Depression Scale) after four weeks, and a 68% reduction after eight weeks. In contrast, the improvement in the placebo group was less than 10% at both four and eight weeks ($p < 0.01$ for ginkgo vs. placebo).[28]

Cardiovascular Disease

Seventy-nine patients with intermittent claudication due to peripheral atherosclerosis received ginkgo (40 mg three times a day) or a placebo for six months. Pain reduction was four times greater in the ginkgo group than in the placebo group ($p < 0.001$). Total walking distance also improved to a significantly greater degree in the ginkgo group than in the placebo group. Plethysmographic studies showed a significant increase in blood flow on the affected side in patients receiving ginkgo, compared to a slight decrease in blood flow in the placebo group.[29] In another study, 20 patients with intermittent claudication received 160 mg of ginkgo twice daily or a placebo for four weeks, in a double-blind fashion. An objective test of arterial perfusion indicated that the area of ischemia after exercise decreased by 38% in the ginkgo group but was unchanged in the placebo group ($p = 0.04$).[30] These results suggest that ginkgo is of value in the treatment of peripheral occlusive vascular disease.

In animal studies, administration of ginkgo protected against electrocardiographic abnormalities and arrhythmias induced by myocardial ischemia. Treatment with ginkgo also decreased the intensity of ventricular fibrillation during reperfusion.[31] These findings suggest that ginkgo may be beneficial in the treatment of ischemic heart disease and myocardial infarction; clinical studies in these areas would be worthwhile.

Macular Degeneration

Loss of vision occurs frequently with advancing age. Age-related macular degeneration, the most common cause of visual loss in the elderly, is thought to result in part from oxidative damage to the retina. In one study, administration of gingko diminished the decline in retinal function in rats with alloxan-induced diabetes. The effect of ginkgo appeared to be due to a reduction in free-radical damage to the retina.[32] Ginkgo has also been tested in a small, double-blind trial on 10 patients with senile macular degeneration. Ginkgo was found to be significantly more effective than placebo, as assessed by improvement in long-distance visual acuity.[33]

Tinnitus

Tinnitus is a persistent problem that affects millions of Americans and is often refractory to conventional medical treatment. In a double-blind study, 103 patients with tinnitus received either gingko or a placebo. Marked improvement occurred in 40% of patients receiving ginkgo, compared to 24.4% of those receiving placebo. The improvement in tinnitus was significantly greater in the ginkgo group than in the placebo group.[34] In an uncontrolled trial, 21 patients with tinnitus (usually of greater than three years' duration) received ginkgo (40 mg three times a day) for 12 weeks. A few patients reported slight improvement, but the treatment was considered ineffective in most cases.[35] In another study, 20 individuals with tinnitus who had reported improvement after receiving ginkgo participated in a double-blind crossover trial. The patients were given 14.6 mg of an extract of ginkgo twice daily for two weeks, and a placebo for another two weeks, with a one-week washout period between treatments. Ginkgo was found to be no more effective than placebo in relieving tinnitus.[36] In my clinical experience with six patients, half believed that ginkgo was helpful; the improvement was usually noticeable within two weeks. Additional controlled studies are needed to determine whether ginkgo is effective against tinnitus and to identify the optimal dose and duration of treatment.

Vertigo

Seventy patients with recent-onset idiopathic vertigo received ginkgo or a placebo for three months. Ginkgo was significantly more effective than placebo, as measured by intensity, frequency and duration of symptoms. After three months, 47% of patients receiving ginkgo were asymptomatic, compared to 18% of those given placebo.[37]

Acute Cochlear Deafness

Acute cochlear deafness is believed to be due to metabolic derangements that result from ischemia. The prognosis of acute cochlear deafness is dependent on rapid initiation of effective treatment. Because of its antiischemic effects, ginkgo has been tested as a treatment for acute cochlear deafness. In a double-blind trial, significant recovery occurred in patients treated with either ginkgo or the alpha-blocker nicergoline, but the improvement was distinctly better in the ginkgo group than in the nicergoline group.[38]

Cyclic Edema

Cyclic edema in women is thought to be result from increased capillary permeability. Flavonoids, which are components of ginkgo extracts, are capable of normalizing excessive capillary permeability. In one study, administration of ginkgo to ten women with cyclic edema corrected the abnormal capillary permeability in all cases. Of the ten women treated with ginkgo, three showed complete elimination of edema and six others improved.[39] In a double-blind study, ginkgo was also effective against the "congestive" symptoms of premenstrual syndrome, particularly breast symptoms.[40]

Impotence

Sixty patients with impotence were studied. In all cases, impaired penile arterial blood flow had been demonstrated by objective tests and all of the patients had failed to respond to papaverine injections. Each patient received 60 mg/day of ginkgo for 12-18 months. Improvements in penile arterial blood flow, documented by duplex sonography, were evident after six to eight weeks of treatment. After six months, 50% of the patients had regained potency and, in another 20%, a new trial of papaverine was then successful.[41] This study suggests that ginkgo is an effective treatment for about half of patients with impotence that is associated with impaired blood flow. However, because there is a significant psychological component to sexual function, a double-blind study is needed before this treatment can be considered proven.

Asthma

Platelet-activating factor, a compound that occurs naturally in the body, is believed to be a trigger for asthma. Ginkgo is a strong inhibitor of platelet-activating factor and might therefore have some value in the prevention or treatment of asthma. Preliminary studies have suggested a beneficial effect,[42] but larger controlled studies are needed before ginkgo can be considered an effective treatment for asthma.

Radiation Damage

Clastogenic factors (compounds that damage chromosomes) can be found in the plasma of some individuals who have been exposed to large amounts of radiation. Ginkgo at a concentration of 100 mcg/ml inhibited the clastogenic activity of blood obtained from individuals who had been exposed to the Chernobyl nuclear accident. Nine such individuals received ginkgo (40 mg three times a day) by mouth for two months. After treatment, there was a significant reduction in clastogenic activity in plasma.[43] However, since there was no control group, it is difficult to determine whether this improvement was spontaneous or a result of ginkgo treatment.

Dosage and Administration

In most of the studies discussed previously, the dosage of ginkgo was 120 mg/day (40 mg, three times a day) of an extract standardized to contain 24% ginkgoheterosides (one of the presumed active ingredients). In a few studies, larger doses (up to 320 mg/day) were used. Products made from the whole leaf of the ginkgo tree are probably not as effective as the standardized extract. The beneficial effects of ginkgo are sometimes seen as early as one or two weeks after starting treatment. However, in many cases, ginkgo must be taken for three months or longer before results are evident.

Toxicity and Interactions

Ginkgo is considered nontoxic and only rarely causes minor side effects, such as headache or abdominal pain. Ginkgo has not been reported to interact or interfere with any nutrients or medications. It is not known whether ginkgo is safe for pregnant and nursing women.

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