CNI607 4/98 Rev. 7/99
JOURNAL OF APPLIED NUTRITIONAL SCIENCE

Vol.6, No.7

Ginkgo biloba: Mind, Mood, and Memory

BY JAMES ROUSE, N.D.

Ginkgo biloba, termed a living fossil and the oldest living tree species, has survived for 200 million years.[1] The leaves and seeds of ginkgo, first cited as a medicinal agent almost 5000 years ago in the traditional Chinese pharmacopoeia, have historically been used to relieve symptoms of asthma and cough, and to treat bronchitis and incontinence.[2] Over the past 20 years, European phytochemists have discovered that a highly concentrated ginkgo leaf extract can dramatically improve vascular circulation. Ginkgo has become an increasingly well-known medicinal plant worldwide and is now among the best-selling phytomedicines in Europe, where it is prescribed as a treatment for peripheral vascular disorders, particularly cerebral insufficiency, including general dementia and Alzheimer's disease.[1,3]

CLINICAL USES OF GINKGO

Clinical studies indicate use of the standardized extract of ginkgo in the treatment of poor circulation, impotence, heart disease, eye disease, tinnitus, chronic cerebral insufficiency, short-term memory loss, brain trauma, depression, dementia, and conditions associated with senility.[1] Ginkgo's primary clinical application has been in the treatment of peripheral vascular disease such as cerebral insufficiency.

Symptoms in the elderly that may be considered in diagnosing cerebral insufficiency include: difficulties of concentration and memory; absent mindedness; confusion; lack of energy; tiredness; depressive mood; anxiety; dizziness; tinnitus; and headache.[4] These symptoms have been associated with impaired cerebral circulation and may be early indications of dementia. While the loss and/or damage of cerebral substance can hardly be compensated for in patients with severe dementia, there are compensatory possibilities for those suffering from only mild to moderate dementia. These could be used to improve the patients' quality of life and/or to postpone the loss of independence and the necessity for full-time care as long as possible.

The therapeutic effects of ginkgo are attributed to a synergism of its components rather than a single biologically active compound.[1] The most important substances are flavonoids (ginkgo flavone glycosides) and terpenoids (ginkgolides and bilobalide).[4] Virtually all of the clinical research published on *Ginkgo biloba* in the last 15 years has utilized a specific standardized extract developed in Germany containing 24% ginkgo flavone glycosides and 6% terpenoids, designated EGb 761, at a dose of 40 mg three times a day.[4] However, some studies have used a slightly higher dosage of 80 mg three times a day. Treatment must be for 4-6 weeks before positive effects can be expected.[4]

GINKGO AND ITS EFFECTS ON THE BRAIN

Brain functions require large amounts of energy in the form of a constant supply of glucose and oxygen. In dementia due to degeneration with neuronal loss and impaired neurotransmission, decline of intellectual function is associated with disturbances in the supply of oxygen and glucose.[4] Release of free radicals and lipid peroxidation may occur in these circumstances with harmful consequences. Because brain cells contain a high percentage of unsaturated fatty acids in their membranes, they are extremely susceptible to free radical damage. The oxidation of unsaturated fatty acids in membranes leads to a decrease in membrane fluidity and disruption of membrane structure and function.[5] This cellular damage may be a major mechanism of age-related functional decline.[6,7] The brain cell is also extremely susceptible to hypoxia. Thus, diminished circulation to the brain sets off a chain reaction that disrupts membrane function and energy production and ultimately leads to cellular death.

The various compounds found in ginkgo may play a protective role in different stages of the decline of intellectual function via several mechanisms of action: vasoregulating activity of arteries, capillaries, and veins (increased blood flow); platelet activating factor (PAF) antagonism; homeostasis of inflammation and oxidative stress; prevention of cell membrane damage caused by free radicals; and neurotransmission modulation.[3,4]

• Increase in Cerebral Blood Flow

The action of ginkgo extract in promoting cerebral blood flow has been demonstrated in several animal and human pharmacological studies.[7-10] These studies have shown that ginkgo extracts improve vasoregulating activity, decrease blood viscosity, and antagonize platelet activating factor (PAF), thereby improving blood flow. In addition, ginkgo has been shown to prevent metabolic disturbances in experimental models of insufficient blood supply to the brain.[10,11] It accomplishes this by enhancing oxygen utilization and increasing cellular uptake of glucose, thus restoring energy production, as well as reducing the formation of reactive oxygen species.[3,9-11]

• Antioxidant Properties

The mechanism of action of ginkgo in the central nervous system is only partially understood, but the main effects seem to be related to its antioxidant properties.[6] The compounds in ginkgo act to varying degrees as scavengers for free radicals, which have been considered the mediators of the excessive lipid peroxidation, decline of membrane fluidity, and cell damage

observed in Alzheimer's disease.[6,7] Pharmacological effects of the extract related to its free-radical scavenging properties include inhibition of lipid peroxidation, helping to maintain integrity and permeability of cell walls,[1,3,4,7,11] and protection of brain neurons against oxidative stress and post-ischemic injury induced by free radical production.[11,12]

• Effects on Neuronal Tissues

Numerous in vitro studies, primarily in rats, have been conducted to establish the function of ginkgo in neuronal tissues and to determine actions on various receptor sites.[3,7,13] Prolonged treatment with the ginkgo extract is correlated with an increase in density of cerebral muscarinic and serotonin receptors and the thyrotropin-releasing hormone receptors.[3,8,13] Inhibition of brain lipid peroxidation may explain the restorative effect of ginkgo on the age-related decreases in the receptor density of different neurotransmitter systems.[13] In addition, the extract has been shown to increase acetylcholine synthesis,[3,7] increase the turnover of norepinephrine,[13] and may influence dopaminergic neurons.[3]

HUMAN CLINICAL TRIALS

The aforementioned mechanisms of action may explain the positive results of many clinical trials that indicate ginkgo's effectiveness in the treatment of cerebral insufficiency. In a review of 40 published trials on the general clinical efficacy of ginkgo extracts for dementia-related symptoms, the methodological quality was assessed and 8 of the trials were deemed well-designed.[14] The results of the analysis indicate that ginkgo is effective in reducing symptoms of cerebral insufficiency, although further studies are needed for a more detailed assessment of the efficacy of ginkgo.

While many European studies have reported positive results of ginkgo (EGb 761) in the treatment of diverse neurological disorders,[8] the first clinical trial conducted in the United States to assess the efficacy and safety of EGb in Alzheimer's and multi-infarct dementia was recently published in the *Journal of the American Medical Association*.[6] In this randomized, double-blind, placebo-controlled, multicenter study, patients received 120 mg/day EGb or placebo for 1 year. The results of the study indicated that EGb was safe and appeared capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients.

Given the results of the many studies conducted over the last 15 years as well as the long history of its use, the safety of ginkgo seems well established.[1] No serious side effects have been noted in any trial, only mild gastric disturbances; very rare side effects include headache and dizziness.[1,4] While there are no known drug interactions,[4] the use of ginkgo may be contraindicated in those patients taking anti-coagulant (blood thinning) agents.

COMPLEMENTARY HERBS

Because cell damage caused by free radicals has been implicated in the etiology of Alzheimer's, herbs in addition to ginkgo that possess strong antioxidant properties may also prove beneficial in improving brain function. Rosemary leaves (*Rosmarinus officinalis*) contain numerous antioxidant compounds, most notably carnosol and carnosic acid, which have been shown to be powerful inhibitors of lipid peroxidation.[5,15] Perhaps not coincidentally, rosemary has a long history of use as a memory-enhancing herb, and is known as the "herb of remembrance."[16] In addition, rosemary contains compounds such as carvacrol and limonene that inhibit acetylcholinesterase, an enzyme involved in the breakdown of acetylcholine. Acetylcholine is a neurotransmitter that plays a key role in cognition and reasoning, a deficit of which may play a role in memory loss associated with Alzheimer's. Like rosemary, sage (*Salvia officinalis*) is an herb that possesses powerful antioxidant properties as well as acetylcholinesterase-inhibiting compounds.[16]

While ginkgo is an excellent herb for improving general peripheral circulation, other herbs are useful for improving specific organ, sensory, or glandular tissue circulation. For example, hawthorn (*Crataegus oxyacantha*) improves the blood supply to the heart by dilating the coronary vessels and is useful for early-stage heart disease, while bilberry (*Vaccinium myrtillus*) contains anthocyanosides which are potent antioxidants that help strengthen capillaries and improve capillary and venous blood flow. Bilberry extracts are now used in the treatment of many eye disorders including cataracts, macular degeneration, and diabetic retinopathy. Horse chestnut seed (*Aesculus glabra*) is an herb that improves circulation to the lower extremities and is useful for the treatment of varicose veins.[16]

REFERENCES

1. Foster S. Ginkgo, *Ginkgo biloba*. Botanical Series No. 304. Austin: American Botanical Council; 1996.
2. Bensky D, Gamble A. Chinese Herbal Medicine, Materia Medica. Washington: Eastland Press; 1993.
3. Turan I, Martorano D. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Pharmacol Bull* 1995;31:147-58.
4. Kleijnen J, Knipschild P. *Ginkgo biloba. Lancet* 1992;340:1136-9.
5. Haraguchi H, Saito T, Okamura N, et al. Inhibition of lipid peroxidation and superoxide generation by diterpenoids from *Rosmarinus officinalis. Planta Med* 1995;61:333-6.
6. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA* 1997;278:1327-32.
7. Stoll S, Scheuer K, Pohl O, et al. *Ginkgo biloba* extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. *Pharmacopsychiat* 1996;29:144-9.
8. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the *Ginkgo biloba* special extract Egb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiat* 1996;29:47-56.
9. Krieglstein J, Beck T, Seibert A. Influence of an extract of *Ginkgo biloba* on cerebral blood flow and metabolism. *Life Sci* 1986;39:2327-34.
10. Oberpichler H, Beck T, Abdel-Rahman MM, et al. Effects of *Ginkgo biloba* constituents related to protection against brain damage caused by hypoxia. *Pharmacol Res Commun* 1988;20:349-68.
11. Seif-el-Nasr M, El-Fattah AA. Lipid peroxide, phospholipids, glutathione levels and superoxide dismutase activity in rat brain after ischaemia: effect of *Ginkgo biloba* extract. *Pharmacol Res* 1995;32:273-8.
12. Oyama Y, Chikahisa L, Ueha T, et al. *Ginkgo biloba* extract protects brain neurons against oxidative stress induced by hydrogen peroxide. *Brain Res* 1996;712:349-52.
13. Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT_{1A} receptors during ageing: reversal by *Ginkgo biloba* extract (EGb 761). *J Pharm Pharmacol* 1994;46:316-8.
14. Kleijnen J, Knipschild P. *Ginkgo biloba* for cerebral insufficiency. *Br J Clin Pharmac* 1992;34:352-8.
15. Aruoma OI, Halliwell B, Aeschbach, et al. Antioxidant and pro-oxidant properties of active rosemary constituents: carnosol and carnosic acid. *Xenobiotica* 1992;22:257-68.
16. Duke J. The Green Pharmacy. Rodale Press; 1997.