Ginkgo Biloba

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Ginkgo biloba is commonly used in the treatment of early-stage Alzheimer's disease, vascular dementia, peripheral claudication, and tinnitus of vascular origin. Multiple trials investigating the efficacy of ginkgo for treating cerebrovascular disease and dementia have been performed, and systematic reviews suggest the herb can improve the symptoms of dementia. Ginkgo is generally well tolerated, but it can increase the risk of bleeding if used in combination with warfarin, antiplatelet agents, and certain other herbal medications. Clinical issues of safety, dosing, use in the perioperative period, and pharmacology are addressed in this review. (Am Fam Physician 2003;68:923-6. Copyright© 2003 American Academy of Family Physicians)

Ginkgo biloba leaf extract is the most widely sold phytomedicine in Europe, where it is used to treat the symptoms of early-stage Alzheimer's disease, vascular dementia, peripheral claudication, and tinnitus of vascular origin. It also is one of the 10 best-selling herbal medications in the United States.[1] There are over 120 published clinical studies on ginkgo, primarily from Europe. The standardized preparation of Ginkgo biloba extract is EGb 761. In the United States, ginkgo is classified as a dietary supplement; the American brands that are comparable with EGb 761 that have been subjected to clinical studies are Ginkgold, Ginkoba, and Ginkai.[2] Standardized preparations contain 24 percent ginkgo flavonoid glycosides, 6 percent terpene lactones, and no more than 5 parts per million ginkgolic acids.[1,2]

Pharmacology

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.[3-6] Other pharmacologic effects include the following: endothelium relaxation mediated by inhibition of 3',5'-cyclic GMP (guanosine monophosphate) phosphodiesterase[7,8]; inhibition of age-related loss of muscarinergic cholinoceptors and α-adrenoceptors; and stimulation of choline uptake in the hippocampus.[1,9] Ginkgo extract also has been shown to inhibit beta-amyloid deposition.[10]

Uses and Efficacy

CEREBROVASCULAR DISEASE, DEMENTIA, AND MEMORY ENHANCEMENT

A systematic review[11] of eight randomized, double-blind, placebo-controlled studies concluded that ginkgo had modest effects on improving the symptoms of dementia and cerebral insufficiency equivalent to pharmacologic therapy with ergoloid mesylates (Hydergine). A later meta-analysis surveyed 50 articles to examine the effect of ginkgo on objective measures of cognitive function in patients with Alzheimer's disease.[12] [Evidence level A, meta-analysis] Four of these studies met inclusion criteria for adequate clinical trial design.[13-16] In the 212 subjects in the placebo and ginkgo groups, a significant overall effect size was found that was comparable with the benefits of donepezil (Aricept).[17] Efficacy was measured using the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and other standardized measures of cognition.

A review[18] of studies of at least six months in duration demonstrated that ginkgo extract and second-generation cholinesterase inhibitors were equally effective in treating mild to moderate Alzheimer's dementia. A systematic review[19] of nine studies on ginkgo use showed a safe and positive effect beyond placebo, but the investigators remained tentative in recommending it for treatment of dementia until better studies are conducted. A Cochrane meta-analysis of 33 trials concluded that ginkgo appears to be safe, and showed promising evidence of improvement of cognition and function among patients who received the herb. However, the three modern trials showed inconsistent results, suggesting that a large trial with modern methodology is needed to answer questions about treatment effects.[20] [Evidence level A, meta-analysis]

One of the studies analyzed in the Cochrane review[20] was a Dutch study[21] of 214 patients over 24 weeks using a medium dosage of ginkgo (160 mg per day), a high dosage of ginkgo (240 mg per day), or placebo in a crossover design. This study failed to show improvement in age-associated memory impairment or mild or moderate dementia in several neuropsychologic and behavior outcome measures.[21]

However, this study included patients with age-associated memory impairment rather than just persons with dementia, which may have limited the statistical power of its conclusions about the role of ginkgo in dementia.[22]

A randomized, placebo-controlled trial[23] of the effects of ginkgo in healthy, noninstitutionalized adults without dementia or other known mental deficit found no benefit from six weeks of ginkgo therapy (120 mg per day) on several standardized neuropsychologic measures of memory and learning. However, a study[24] using a similar design with a higher dosage of ginkgo (180 mg per day) showed clinically significant cognitive benefits in healthy persons.

The National Institutes of Health and the National Center for Complementary and Alternative Medicine have sponsored a multi-center, six-year, randomized, two-arm, double-blind, placebo-controlled trial of 2,000 patients. The trial will evaluate the safety and efficacy of ginkgo in preventing dementia and age-related cognitive decline and is currently underway and headed by investigators at the University of Pittsburgh. Another phase III trial is underway at the Oregon Health Sciences Center, Portland, to study the effects of ginkgo on cognitively intact elderly patients older than 85 years, and the effect on their progression to mild cognitive impairment. This study will use volumetric quantitative magnetic resonance imaging measures of brain size and peripheral oxidative markers.

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INTERMITTENT CLAUDICATION

Another indication for ginkgo is intermittent claudication from peripheral vascular disease. A meta-analysis of eight studies concluded that the effects of ginkgo, though statistically significant and positive on increasing pain-free walking, were of modest effect size and questionable clinical relevance.[25] [Evidence level A, meta-analysis] A trial[26] that compared dosages of 120 mg and 240 mg of ginkgo demonstrated a substantial therapeutic benefit on pain-free walking distance with the higher dosage. Two placebo-controlled trials,[27,28] with a total of 190 patients, showed improved walking distance and decreased pain in patients with peripheral vascular disease.

TINNITUS

Another common indication for ginkgo is tinnitus. A recent study[29] of 1,121 subjects conducted using questionnaires and telephone interviews, without the use of standard audiometric testing as an outcome measure, failed to show a benefit of ginkgo in the treatment of tinnitus. Another randomized, placebo-controlled trial[30] of 103 patients showed 50 percent of patients with new-onset tinnitus had improvement or disappearance of symptoms in 70 days compared with 119 days to improvement in those receiving placebo. A review[31] of five heterogenous randomized controlled trials concluded that extracts of ginkgo biloba are moderately effective in treating tinnitus.

OTHER USES

Studies have shown positive results from the use of ginkgo for the following conditions: sexual dysfunction secondary to the use of selective serotonin reuptake inhibitors,[32] mountain sickness and decreasing vasoactivity in response to cold,[33] macular degeneration,[34] asthma,[35] and hypoxia.[36] The World Health Organization has recommended the use of ginkgo in Raynaud's disease, acrocyanosis, and post-phlebitic syndrome.[2,7]

Warnings, Interactions, Adverse Effects

During the past 20 years, an estimated 2 billion daily doses (120 mg) of ginkgo have been sold. The most important potential clinical problem with ginkgo is caused by its inhibition of the platelet-activating factor; this makes the use of ginkgo in conjunction with warfarin (Coumadin), aspirin, or other antiplatelet agents a matter of clinical judgment. A recent safety study[37] of the interaction of

TABLE 1.
Key Points About Ginkgo Biloba

Efficacy	Alzheimer's disease: effective Cerebrovascular disease: modest positive effects Dementia: modest positive effects Memory enhancement: ineffective in adults without dementia Intermittent claudication: modest positive effects Tinnitus: modest positive effects
Adverse effects	Rare: nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, weakness, skin rash
Interactions	Warfarin (Coumadin), aspirin, antiplatelet agents, herbal medications such as feverfew, garlic, ginseng, dong quai, red clover, and other natural coumarins
Dosage	120 to 240 mg per day, in 2 to 3 doses
Cost	$15 to $20 per month, depending on brand, for a dosage of 120 mg per day
Bottom line	Safe herbal medication; may be effective for treatment of symptoms of Alzheimer's disease, intermittent claudication, and tinnitus

ginkgo and warfarin showed no change in the international normalized ratio. Ginkgo should be discontinued between 36 hours and 14 days before surgery, based on either pharmacokinetics or consensus opinion.[38,39]

Herbal medications that may increase the risk of bleeding if used concurrently with ginkgo include the following: feverfew, garlic, ginseng, dong quai, red clover, and other natural coumarins. Several case reports of bleeding complications associated with ginkgo use include subdural hematoma,[40,41] subarachnoid hemorrhage,[42] intracerebral hemorrhage,[43] and hyphema[44]; the causality of these events has not been established. One case report[45] discussed an elderly patient who developed elevated blood pressure while taking a thiazide diuretic and ginkgo. The patient's blood pressure returned to normal when both substances were discontinued. This reaction is paradoxical in light of the known pharmacologic actions of these agents.[45]

The unprocessed ginkgo leaf contains ginkgolic acids that are toxic. Hypersensitivity to ginkgo preparations is a contraindication to use. Ginkgo is generally well tolerated, with side effects being rare, usually mild, and including nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, weakness, or skin rashes. Although no studies have been performed to support any restrictions on the use of ginkgo during pregnancy or lactation, it seems prudent not to administer ginkgo in the absence of any data.[1,2]

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 seen as early as four weeks.[13,46,47] The monthly cost for the usual daily dose of 120 mg is approximately $15 to $20.

Final Comment

With an aging population seeking solutions to troubling problems such as dementia and vasculopathy, ginkgo offers some benefit as a mild vasoactive and neuroprotective phytomedicine. It offers a relatively safe, inexpensive, and modestly effective treatment option when selected by patients or prescribing physicians for multi-infarct or Alzheimer's dementia. Evidence indicates that it is effective in slowing disease progression and ameliorating symptoms.

While some studies show no benefit in Alzheimer's disease, others show that it is comparable in its efficacy with the second-generation cholinesterase inhibitors. Ginkgo should be discontinued before surgery, but the time period has not been determined conclusively. Ginkgo also has demonstrated benefits in patients with peripheral vascular disease and tinnitus. Name brands using the same extract as those used in clinical research studies are to be recommended as the most reliable in the current herbal market in the United States. *Table 1* discusses the efficacy, safety, tolerability, and cost of ginkgo biloba.

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