AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

COMPLEMENTARY THERAPY ASSESSMENT

GINKGO BILOBA EXTRACT AND OCULAR CONDITIONS

September 2002

SUMMARY

INTRODUCTION TO THE TOPIC

Ginkgo biloba extract (GBE), which is derived from the dried ginkgo leaf, has become a very popular herbal supplement for its potential benefit in alleviating symptoms associated with peripheral vascular disease, dementia, asthma, and tinnitus. The most frequently used standardized extract for clinical applications is EGb 761 (W. Schwabe Co., Karlsruhe, Germany), which is prepared to a 35:1 to 67:1 ratio of dried leaves to final extract containing approximately 24% ginkgo flavone glycosides, approximately 6% terpene lactones, and proanthocyanodines. In the United States, GBE is widely available as a nutritional supplement. It has several potential mechanisms of action that include increasing blood flow, inhibiting platelet-activating factor (PAF), and protecting against damage from free radicals and lipid peroxidation. Given the role of vascular pathogenesis and molecules involved as lipid mediators in eye disease, GBE may have a potential benefit in managing certain eye disorders such as age-related macular degeneration (AMD), glaucoma, and vascular and toxic disorders of the retina.

CONCLUSIONS

A Cochrane Library systematic review identified a single randomized controlled trial that examined the effect of ginkgo extract EGb761 treatment for six months on the progression of AMD in 20 subjects. Improvement in visual acuity and clinical findings was reported, but these results should be considered equivocal because the observers were not masked. There are no other prospective randomized clinical trials that examine the effect of GBE on the clinical course of glaucoma or other ocular conditions, and further research is needed.

BENEFITS

Ginkgo extract has been used for centuries in China primarily for asthma and bronchitis, and it is frequently prescribed in Germany for asthma, bronchitis, dementia syndromes, claudication, tinnitus and vertigo, sexual dysfunction, and altitude sickness. To date there is no published study that demonstrates a definite beneficial effect of GBE on AMD, glaucoma, or other ocular conditions.

RISKS

The adverse reactions and toxicity of GBE include gastrointestinal upset, headache, dizziness, palpitations, and allergic skin reactions. There are a few reported cases of bleeding (i.e., hyphema, subarachnoid hemorrhage, and subdural hematomas) associated with GBE when used in conjunction with antiplatelet drugs and anticoagulants. Since ginkgo extract decreases platelet aggregation by inhibiting PAF, concomitant use with antiplatelet drugs and anticoagulants is not advised. In addition, patients who undergo surgery should be advised to discontinue ginkgo products prior to surgery to minimize bleeding risks that are similar to those of antiplatelet drugs. The adverse effect of GBE over a long period is unknown.

There is some economic risk to the individual using GBE because the cost can be significant and is seldom covered by health insurance.

REPORT

DESCRIPTION OF GINKGO BILOBA EXTRACT

In the United States, ginkgo has gained considerable popularity, and it has a substantial market share in the sales of herb supplements.[1] In general, ginkgo refers to ginkgo leaf extract, which is distinct from the ginkgo seed and fruit. Fresh ginkgo seeds contain ginkgotoxin, which has caused death in children[2] and seizures,[2-4] and the ginkgo fruit is a potent contact allergen.[5] The term "ginkgo" is derived from *Yin-Kuo*, which means "silver apricot", and biloba describing the bi-lobed, fan shaped leaves.[6] This phytomedicine has the Latin name of *Ginkgo biloba l*., and is also known as*adiantifolia*, *bai guo ye* or pei go su, duck foot tree, fossil tree, gingko, ginkgo folium, ginkyo, Japanese silver apricot, kew tree, maidenhair tree, *saliburia*, and *yen xing* or yinhsing.[5,7] Ginkgo trees originated two hundred million years ago and are the oldest living tree species in the world; they can live up to one thousand years.[8]

The phytomedicinal use of ginkgo was described as early as 2600 BC in the Chen Noung Pen T'sao pharmacopoeia.[6] Ginkgo biloba extract (GBE) has been developed as the proprietary extract, EGb 761, by the W. Schwabe Co. of Karlsruhe, Germany. The chemistry, pharmacology, and toxicology on EGb 761 has been studied.[9] It is prepared as a 35:1 to 67:1 ratio of dried leaves to final extract, and contains 24% ginkgo flavone glycosides, 6% terpene lactones, and proanthocyanodines. In Germany, ginkgo is the most frequently prescribed herbal medicine and is consumed to relieve symptoms associated with asthma, bronchitis, dementia syndromes, claudication, tinnitus and vertigo, sexual dysfunction, and altitude sickness. [6]

MECHANISM OF ACTION

The chemistry of GBE is complex, and it contains a variety of constituents.[1,9] The extract is characterized by 22% to 27% flavonol glycosides (i.e., quercetin, kaempferol, isorhamnetin), 5% to 7% terpene lactones (i.e., ginkgolides A, B, and C, and bilobalide), and ginkgolic acids.[1,7,9] The whole extract is thought to be more active than any single isolated constituent. The effects of GBE are related to the following three mechanisms of action:

- It increases blood flow by decreasing blood viscosity and increasing erythrocyte deformability[10]
- It inhibits platelet activating factor predominantly by ginkgolide B,[11,12] which results in inhibition of platelet aggregation,[13] thrombin activity, and fibrinolysis
- It acts as an antioxidant, scavenging free radicals and affecting the glutathione reductase, superoxide dismutase, and nitric oxide synthase pathways[14-20]

The following pharmacological effects have been examined experimentally in <u>animal models and in vitro systems</u>:

- Enhanced blood flow and favorable metabolic parameters in rodent models of ischemic stroke and hypoxia[21-26]
- Improved cardiac function and biochemical parameters in rodent models of ischemia-reperfusion injury[27-30]
- Favorable modulation of neurons,[31-33] vestibular function,[34] electrophysiology parameters,[35,36] and retinal damage[37,38]

- Attenuation of histopathological and electrophysiological changes in rodent models of light-induced retinal degeneration,[39] reduction in free radicals in ischemic/reperfused diabetic retina,[40-43] chloroquine retinopathy,[44] and alloxan-induced optic nerve dysfunction[45]

The following pharmacological effects have been examined in clinical studies:

- Symptomatic improvement from asthma[46]
- Improved cognitive function in dementia[47-51]
- Symptomatic improvement from tinnitus[52-54]
- Improvement of sexual dysfunction[55]
- Relief from claudication[56-58]
- Effect on ophthalmic artery blood flow in normal subjects[59]
- Improvement of AMD, diabetic retinopathy, hypertensive retinopathy, and glaucoma[60]

DEFINITION OF THE PROBLEM

In the United States, the leading causes of visual disability are AMD, glaucoma, diabetic retinopathy, and cataract[61,62] and researchers are investigating GBE for any potential benefit on these conditions. Age-related macular degeneration is a disorder of the macula that occurs most often in patients aged 50 or older and is characterized by one or more of the following findings: drusen formation, retinal pigment epithelial (RPE) abnormalities, geographic atrophy of the RPE and choriocapillaris, and neovascular maculopathy. Recently, the Age-Related Eye Disease Study supported the use of antioxidant vitamins and minerals in patients with intermediate-risk AMD in order to slow the rate of progression to advanced AMD.[63,64] As yet, there is no proven effective therapy for the early and advanced non-neovascular form of AMD, for the majority of patients with neovascular maculopathy, or for preventing the development of AMD.

Glaucoma is a disorder of the optic nerve characterized by acquired loss of retinal ganglion cells and atrophy of the optic disc, and there is an associated variable degree of psychophysical dysfunction that is assessed primarily by visual field testing. While clinical research has identified some risk factors for glaucomatous optic neuropathy, hypothetical risk factors such as excitotoxicity and oxidative stress are currently being studied. The mainstay of current glaucoma therapy is to lower intraocular pressure (IOP) with drugs, laser surgery, and filtration surgery.[65] New approaches for glaucoma treatment are theoretical and speculative; they are based on enhancing ocular blood flow,[66,67] neuroprotection,[68,69] and potentially using ginkgo biloba.[70]

Diabetic retinopathy is characterized as a microvascular disease of the retina that may manifest with ischemic, hemorrhagic, or exudative findings. While numerous prospective randomized controlled clinical trials have examined the treatment outcome of laser and vitreous surgery on various forms of diabetic retinopathy,[71-73] complementary approaches in treating diabetic mellitus are being investigated based on nutritional and herbal supplements.[74]

Cataract is characterized by a degradation of the optical quality of the crystalline lens through loss of clarity or change in color, and the presence of cataract leads to a variety of symptoms, such as impaired visual acuity, glare, and altered color perception. Complementary and alternative therapies to change the natural history of cataract formation are based primarily on vitamin supplementation, antioxidants, and herbal remedies.[75-77]

FDA STATUS/LEGAL STATUS

According to the National Institutes of Health Office of Dietary Supplements, the Dietary Supplement Health and Education Act of 1994 defined dietary supplements as a product (other than tobacco) intended to supplement the diet that bears or contains one of more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. Any of these must be intended for ingestion in the form of a capsule, powder, softgel, liquid, or gel cap, and must not be represented as a conventional food or as a sole item of a meal or the diet.

Dietary supplements are widely available through many commercial sources including health food stores, grocery stores, and pharmacies, and by mail and on the Internet. Historically in the United States the most prevalent type of dietary supplement was a multivitamin/mineral tablet or capsule that was available in pharmacies by prescription or over the counter. Supplements containing strictly herbal preparations were less widely available. Currently in the United States a wide array of supplement products are available, including vitamins, minerals, and other nutrients; botanical supplements; and ingredients and extracts of animal and plant origin, but producers of supplements are not allowed to attribute any potential health benefit to their product.

The Dietary Supplement Health and Education Act of 1994 limits the authority of the Food and Drug Administration (FDA) over these products since they are not classified as drugs. The FDA requirement for premarket review of dietary supplements is less than it is for other products it regulates, such as drugs and many additives used in conventional foods. The FDA oversees safety, manufacturing, and product information such as claims in a product's labeling, package inserts, and accompanying literature. The Federal Trade Commission, which oversees advertising, has issued advertising guidelines and has taken a number of enforcement actions against companies whose advertisements contained false and misleading information.

SUMMARY OF EVIDENCE

Search Methods and Study Selection

In November 2001, MEDLINE, EMBASE, and the Cochrane Library were searched using the keyword ginkgo (with variant spellings and names) and the MeSH terms eye diseases, diabetes mellitus, macular degeneration, glaucoma, and cataract. The Cochrane Library had one systematic review of GBE and AMD, which identified one randomized clinical trial. The MEDLINE and EMBASE searches did not identify additional randomized clinical trials for ginkgo biloba and any other ocular condition after the date of the Cochrane systematic review. A search of MEDLINE and EMBASE for additional articles other than this single published trial was undertaken using the same keywords.

Statistical Issues and Study Design

According to the Cochrane Library systematic review[78] last updated in the third quarter of 2001, there has been one published randomized trial by Lebuisson et al[79] in which administration of GBE for AMD was compared with a control group. In this trial, the treatment group (n=10) received 80 mg of ginkgo extract EGb 761 twice daily and the placebo group (n=10) received a substance identical in appearance, taste, and smell. Treatment lasted for 6 months. Outcomes assessed were distance and near visual acuity, visual field, and clinical assessment of disease progression. Assessment of the outcome was not masked.

Merte and Merkel conducted a German observational study to examine the effect GBE in 46 patients who had glaucoma (n=27), AMD (n=6), diabetic retinopathy (n=9), or hypertensive retinopathy (n=4).[60]

In this study Rökan® 40 mg was given four times daily for one week, then 40 mg three times daily for an average of 15 months. Visual acuity, perimetry, ophthalmoscopy, fundus photography, fluoroscein angiography, ophthalmodynamometry, IOP, blood pressure, and pulse rate were evaluated monthly.

Chung et al examined the effect of GBE on ophthalmic artery blood flow in 11 normal subjects.[59] The study was designed as a randomized double-masked crossover trial using Ginkoba® (Pharmaton, Ridgefield, CT) 40 mg three times a day for 2 days and fructose as the placebo. Clinical end points of IOP; heart rate; arterial blood pressure; and color doppler imaging of the ophthalmic, central retinal, and short posterior ciliary arteries were measured at baseline, after 2 days of treatment, again at baseline after a 2-week washout, and after the crossover treatment of 2 days.

There were no published studies found on GBE in relation to diabetic retinopathy and cataract.

Specification of Level of Evidence

A Level I rating is assigned to properly conducted, well-designed randomized clinical trials; a Level II rating is assigned to well-designed cohort and case-control studies; and a Level III rating is assigned to case series.

The study[79] cited in the Cochrane Review was a randomized controlled trial, and while rated as Level I evidence, the trial was small (n = 20) and the assessment of outcome was not masked, so its findings must be viewed cautiously. The German observational study[60] on glaucoma is rated as Level III evidence, and the small ocular blood flow study[59] in normal subjects is rated as Level II evidence.

REPORTED BENEFITS

The Lebuisson et al study on AMD[79] cited in the Cochrane Library review showed improved distance visual acuity in both treated and control groups during the 6 months of treatment, but it showed a greater improvement in the ginkgo-treated group (Level I evidence). Tests of association for near vision and visual field were stated to be not statistically significant. Clinical observation of disease progression suggested that nine out of ten patients in the treatment group improved compared to two in the control group. Although improvement in visual acuity and clinical findings were reported, these results should be considered equivocal because the observers were not masked.

The Merté and Merkle study[60] found that ginkgo treatment during a period of 14 to 17 months was well tolerated by the patients. One subject reported improvement in severity of claudication and hearing impairment. However, there was no clear beneficial effect of ginkgo with respect to glaucoma, AMD, diabetic retinopathy, and hypertensive retinopathy over the course of 14 to 17 months of treatment (Level III evidence).

The Chung study[59] found a statistically significant increase in end diastolic velocity in the ophthalmic artery following 2 days of GBE treatment, although a large standard error was reported (Level II evidence). The clinical significance of this change in a small number of normal subjects is unknown. It is also important to recognize that the short posterior ciliary arteries perfuse the optic nerve at the level of the optic disc, and not the ophthalmic artery. Caution is advised in interpreting their findings in light of the growing interest in neuroprotection strategies for glaucoma management. Proof of concept for neuroprotection applied to glaucoma has not been validated in prospective randomized clinical trials, but the current research efforts in this field hold promise for the development of new glaucoma treatments.

RISKS

The adverse reactions and toxicity of GBE include gastrointestinal upset, headache, dizziness, palpitations, and allergic skin reactions.[5,80] There is a report of ginkgo precipitating seizures in two patients with well-controlled epilepsy.[81] There are a few reported cases of bleeding (i.e., hyphema,[82] subarachnoid hemorrhage,[83] and subdural hematomas[84]) associated with GBE when used in conjunction with antiplatelet drugs and anticoagulants. Since ginkgo extract decreases platelet aggregation by inhibiting PAF, concomitant use with antiplatelet drugs and anticoagulants is not advised. In addition, patients who undergo surgery should be advised to discontinue ginkgo products prior to surgery to minimize bleeding risks that are similar to those of antiplatelet drugs.[85] The adverse effect of GBE over a long period is unknown.

There is some economic risk to the individual using GBE because the cost can be significant and is seldom covered by health insurance.[86]

QUESTIONS FOR SCIENTIFIC INQUIRY

To understand the role of GBE in the treatment of AMD, glaucoma, and vascular disorders and toxicities of the retina, the following questions should be answered.

- What are the effects of biochemical oxidation on the eye?
- What is the role of PAF in the healthy eye and in the diseased eye?
- Is GBE supplementation beneficial, and, if so, in what amount and in what formulation? At what stage or age would supplementation be beneficial in particular eye disorders? How long would supplementation need to take place to remain effective?
- Which groups of people derive benefit from supplementation? Can we use objective testing to preselect these favorable responders?

INFORMATION FOR PATIENTS

The following useful information is from "An FDA Guide to Dietary Supplements," http://vm.cfsan.fda.gov/~dms/supplmnt.html.

- Consumers who use dietary supplements should always read product labels, follow directions, and heed all warnings.
- To help protect themselves, consumers should look for ingredients in products with the U.S.P. notation that indicates that the manufacturer followed standards established by the United States Pharmacopoeia. Consumers should also realize that the word “natural” on the label doesn’t guarantee that a product is safe.
- Supplement users who suffer a serious harmful effect or illness that they think is related to supplement use should call a doctor or other health care provider.
- If shoppers find dietary supplements with labels stating or implying the product can help diagnose, treat, cure, or prevent a disease, they should realize the product is being marketed inappropriately as a drug and as such has not been evaluated for safety or effectiveness.

- The majority of supplement manufacturers are responsible and careful, but as with all products on the market, consumers need to be discriminating. The FDA and industry have important roles to play, and consumers also must take responsibility.

CONCLUSIONS

The role of GBE in slowing the progression of AMD has not been adequately answered in randomized controlled trials. A Cochrane Library systematic review identified a single randomized controlled trial that examined the effect of ginkgo extract EGb761 treatment for 6 months on the progression of AMD in 20 subjects. Improvement in visual acuity and clinical findings were reported, but the observers were not masked and these results should be considered equivocal. There are no other published clinical trials that examine the effect of GBE on the clinical course of glaucoma or other ocular conditions. Further research is needed to evaluate the potential role of GBE for the treatment of ocular conditions.

DEVELOPMENT OF COMPLEMENTARY THERAPY ASSESSMENTS

Complementary, or alternative, therapies are a growing part of health care in America. Americans spend an estimated $14 billion a year on alternative treatments. Mainstream medicine is recognizing a need to learn more about alternative therapies and determine their true value. Many U.S. medical schools are beginning to devote a small part of training to alternative therapies. The editors of *The Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. More scrutiny and scientific objectivity is being applied to determine whether evidence exists to support their effectiveness.

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate complementary therapies in eye care and develop an opinion on their safety and effectiveness, based on available scientific evidence, in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologist and patients evaluate the research and make more rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated in the same way that traditional medicine is evaluated; that is, evidence of safety, efficacy, and effectiveness should be demonstrated.[87] Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved, it is important that data and scientific information be used to form a basis for all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.[88]

Ideally, a study of efficacy compares a treatment to a placebo or another treatment, using a double-masked controlled trial and well-defined protocol. Reports should describe enrollment procedures, eligibility criteria, clinical characteristics of the patients, methods for diagnosis, randomization method, definition of treatment, control conditions, and length of treatment. They should also use standardized outcomes and appropriate statistical analyses.

The goal of these assessments is to provide objective information of complementary therapies and provide a scientific basis for physicians to advise their patients, when asked.

To accomplish these goals, the assessments are intended to do the following in general:

- Describe the scientific rationale or mechanisms of action for the complementary therapy
- Describe the methods and basis for collective evidence
- Describe the relevant evidence
- Summarize the benefits and risks of the complementary therapy
- Pose questions for future research inquiry
- Summarize the evidence on safety and effectiveness

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Additional Resources

NIH Office of Dietary Supplements available at http://odp.od.nih.gov/ods

FDA Consumer: *An FDA Guide to Dietary Supplements.* Available at http://www.cfsan.fda.gov/~dms/fdsupp.html

Federal Trade Commission available at http://www.ftc.gov

Prepared by the American Academy of Ophthalmology Complementary Therapy Task Force

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