COMMENTARY

Can Ginkgo Biloba Combat Diseases?

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Herbal remedies have been widely used in many countries for centuries, and the products enjoyed a surge in popularity in the USA during the late '90s. During the past 20 years, an estimated 2 billion daily doses (120 mg) of Ginkgo biloba (GB) have been sold. French and German agencies consider it to be effective for the treatment of several diseases, and the immense amount of clinical studies concerning GB makes it worth revising the existing literature about this notable plant. Also, the National Institutes of Health (NIH) supports research on alternative therapies that include examining the effects of GB. With the rapid expansion of herbal medicine use in the United States, it is clear that our understanding of herb-herb, drug-herb and food-herb interactions should increase.

Key words: Herbal medicine, Dietary supplements, Flavonoids

Dietary supplements are a timely topic today in the research, legislative, business, and consumer arenas. The NIH have created an Office of Dietary Supplements to gather information on these substances (1). The dietary supplement industry has grown rapidly. Total sales of dietary supplements in 1998 increased to $13.9 billion, from approximately $8.6 billion in 1994 (2); and, in 2002, it reached $18.7 billion (3). The Dietary Supplement Health and Education Act (DSHEA; Public Law 103-417) of November 1994 broadened the regulatory definition of dietary supplements beyond essential vitamins, minerals, and amino acids, and even beyond other constituents proposed to optimize nutrition. According to this source, a dietary supplement must meet all of the following conditions:

- A product (other than tobacco) intended to supplement the diet, which contains one or more of the following: vitamins; minerals; herbs or other botanicals; amino acids; other plant-derived substances, and concentrates, metabolites, constituents, and extracts of these substances, or any combination of the above ingredients.
- Intended to take in tablet, capsule, powder, soft gel, gel cap, or liquid form.
- Not represented for use as a conventional food or as a sole item of a meal or the diet.
- Labeled as being a dietary supplement (4).

Herbal remedies have been widely used in many countries for centuries, and the products enjoyed a surge in popularity in the USA during the late '90s. Sales of herbal supplements tallied $4.18 billion in 2001, up from $4.12 billion in 2000, according to Hellmich (5), jumped 70% from 1994 to 1997, and reached $3.3 billion in 1999 (6). Health Canada, Natural Health Products Directorate estimates that over 50 percent of Canadians consume natural health products: herbs, vitamins and minerals, and homeopathic products (7).

A survey of university student athletes conducted to determine supplement use and perceived efficacy of supplements, showed that 21.7% (n=236) of these athletes used herbal supplementation. Two point one percent (2.1%) of the athletes perceived benefits of sport performance and 1.91% perceived benefits of healing process (using 5-point Likert scale: 5=strong agreement and 1=strong disagreement) although the specific name of the herbal remedy was not provided (8).

An herbal medicine is a type of dietary supplement (also called botanical) and is defined as a plant-derived product used for medicinal and health purposes for its scent, flavor, and/or therapeutic properties that contain herbs, either singly or in mixtures. Humans have been using plant products for medicinal purposes since the Neanderthal period, i.e. 60,000 years ago (9).

Ginkgo biloba (GB) products are one of the top ten botanical dietary supplements in the USA (10-12) with a retail sale of US $151 million in 1998 (13), and accounting for 4.3% of all single herb sales in 2001 (14). The use of GB for biological and psychological purposes, including improving alertness, can be traced back to centuries in traditional Chinese medicine (15-16). In the Ayurvedic tradition, Ginkgo is associated with long life and is used in longevity elixirs (17). During the past 20 years, an estimated two billion daily doses (120 mg) of Ginkgo have been sold (11). A report that describes a correlation of herbal and specialty supplement use in a large cohort study

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of older US adults (age 50-76) in western Washington state puts GB in fourth place with a prevalence use of 6.5% and 7.9% in men and women, respectively (6). In a national survey among members of a large group model health plan, including those with selected health conditions, GB occupied second place with 10.9% (n=15,985) as most frequently used (18).

Ginkgo biloba is registered for the treatment of several diseases and disorders in Europe. Ginkgo extract, which entered the market in Germany in 1982, is now used by more than 10 million Europeans annually, is government approved, and is covered by insurance and the German national health care system (17). The French and German agencies consider it to be effective for the treatment of several diseases and the immense amount of clinical studies concerning GB makes it worth revising the existing literature about this notable plant (19). Also, NIH supports research on alternative therapies that include examining the effects of GB (1, 20). This growing evidence about the benefits of GB, encouraged the author to review the literature about the particular characteristics, uses, and safety rules of this herbal medicine.

Phytobiology and chemistry

The ginkgo tree (Ginkgo biloba), also known as the maidenhair, kew, duck foot, or silver apricot tree; Latin name: Gingko biloba L. (15, 21) is the only living member of the Ginkgoaceae family. Fossils of the trees have been dated back as far as 250 million years. The ginkgo tree may be the longest living extant tree, and was referred to by Darwin as "a living fossil" (15, 17).

The ginkgo tree is remarkable in many ways and it appears to curiously have strong resistance to a wide range of insect pests and fungi, a fact that likely contributes to its longevity. The tree has a gray-colored bark and can reach a height of up to 30 m, with a girth of 7 m. Young trees have a conical, conifer-like shape and exhibit an interesting branching dimorphism (22). The species is native to temperate forests of China, Korea, and Japan; and has now spread worldwide by introduction to many countries because of its beauty and great environment adaptability (15, 22-23). The leaves are harvested in the summer because this is the time when the highest level of active compound exists (17).

The active constituents of GB include flavonoids and terpene lactones. Generally, enriched gingko extracts for the preparation of gingko products are standardized to contain 24% flavonoids (22-27%) and 6% terpene lactones (10, 16, 24) and no more than 5 parts per million ginkgolic acids (11, 25). The flavonoids and terpene lactones content is one of the important parameters to assess the quality of gingko products (10). The flavonoids are the following phytoestrogens: kaempferol, quercetin, isorhamnetin (26), and rutin (27). The terpenoids are sesquiterpene bilobalide, trilactones ginkgolides A, B, and C (15, 27). In a review of chemical analysis of GB leaves and extracts, important constituents are present in the medicinally used leaves: terpene trilactones, i.e., ginkgolides A, B, C, J and sesquiterpene bilobalide, many flavonol glycosides, biflavones (bilobetin, ginkgetin, isoginkgetin, amentoflavone and sciadopitysin), proanthocyanidins, alkyphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols (15, 22). On other hand, in the commercially important gingko extracts, some of these compounds are no longer present (28). Other researchers have identified luteolin, D-glucaric acid, anacardic acid and tricetin as flavones, catechins and sterols (15, 21).

Most commercial gingko products sold as dietary supplements in the United States appear to be standardized to above parameters (i.e., concentrated 50-1, standardized to 6% terpenes and 24% flavonol glycosides), although it is possible that there may be differences in the biological activity of various brands (24). Pharmacopeia grade gingko leaf, for use in manufacturing the standardized extracts described in many scientific studies, consists of the dried leaf of GB. The raw material may contain no more than 3.0% stems and not more than 2.0% of other foreign organic matter. It must contain not less than 0.8% flavonol glycosides as determined by liquid chromatography test. Additionally, the British Herbal Pharmacopoeia requires that the dried leaf contain not less than 18% water-soluble extractive (21). Li and Fitzloff (10) examined nine commercial GB products and found that most of these products contained flavonoids and terpene lactones as claimed on the label. Another study compared samples of GB from different commercial suppliers and observed an apparent variation in antioxidant activity of the various products investigated due to the physical nature of the GB (i.e., dried leaf powder or standardized concentrated extract) used in tablet formulation (29).

EGb 761® is a standardized extract of GB leaves and has antioxidant properties as a free radical scavenger. This extract has been available in Europe as an herbal extract since the early 1990's. However, the US FDA (United States Food and Drug Administration) does not approve products containing EGb 761® for use. This is a well-defined product and contains the percent parameters for terpenes and flavonoids aforementioned. Ginkgolide B and bilobalide account for about 0.8% and 3% of the total extract, respectively. Other constituents include proanthocyanidins, glucose, rhamnose, organic acids, D-glucaric and ginkgolic acids (30). The pharmacokinetics of Egb 761® has been investigated both in animal

experiments and in trials involving humans. An absorption rate of 60% was found in rats for a radioactively labeled extract. In humans, after application of an extract specified above, absolute bioavailability was 98-100% for ginkgolide A, 79-93% for ginkgolide B, and at least 70% for bilobalide (21). Gulec, et al. (31) conducted a study which showed that GB protects against cisplastin-induced nephrotoxicity. The protective effect of GB in the study was due primarily to the scavenging of free radicals. Therefore, the authors suggest that GB is potentially useful for the prevention or cure of renal toxicity during cisplatin chemotherapy.

Smith and Luo (13) presented in their mini-review paper some major biochemical/pharmacological activities of EGb 761®. For example, as a free radical scavenger, EGb761® decreases tissue levels of reactive oxygen species, inhibits membrane lipid peroxidation and, with its anti-platelet-activating factor activity, contributes to improvements in cerebral insufficiency. These authors presented EGb neuronal plasticity enhancing activity, as well as inhibition of αβ aggregation in neuroblastoma cells. EGb is able to ameliorate liver injury and prevent rats from carbon tetrachloride induced liver fibrosis by suppressing oxidative stress (32).

Traditional uses

The fruits of GB have been used as food and medicine for thousands of years. The fruits are prepared by fermentation and cooking and are considered a delicacy during weddings and feasts. In traditional Chinese medicine, ginkgo nuts are used as a kidney "yang"' tonic to increase sexual energy, halt bed-wetting and frequent nocturnal emissions, restore hearing loss, and soothe bladder irritation (22).

Extracts of the leaves of the maindenhair tree have long been used in China as a traditional medicine for various health disorders. A standardized extract is widely prescribed in Germany and France for the treatment of a range of conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus, headache (33-34), macular degeneration (35-36), arterial occlusive disease; preventing and treating cardiovascular disease (CVD) particularly ischemic cardiac syndrome (37-38), intermittent claudication (38-39), sexual dysfunction, mountain sickness, asthma, hypoxia (11), and diabetic retinopathy (20, 40).

In the last several decades, GB extracts have been widely used in Europe to treat age-related physical and cognitive disorders, including Alzheimer's disease (41) and improve alertness (15). A large multicentre, randomized, placebo-controlled trial of 2020 patients with dementia reported that ginkgo stabilized and improved cognitive performance (9). The results of a retrospective analysis to explore the treatment effect of GB in Alzheimer's disease indicated improvement in the group of patients with very mild to mild cognitive impairment (42). The National Institute on Aging supported a clinical trial (study started on April 2000 and completed on July 2005) to evaluate the efficacy of GB in treating the symptoms of Alzheimer's disease (43-44).

A survey of herbal use in children with attention-deficit-hyperactivity disorder or depression found GB as the herbal medicine given most frequently for behavioral condition. The survey also reported that 15% of children had taken herbal medicines during the previous year of the study recommended mostly (61%) by a friend or relative (45). Preliminary evidence suggests that the combination of GB and a tricyclic antidepressant may improve sleep continuity and non-REM sleep in depressed patients (46).

Treatment with GB extract significantly improves visual field damage in some patients with normal-tension glaucoma, although this deserves further investigation to evaluate not only visual fields, but ocular blood flow and optic nerve characteristics as well, said Luciano Quaranta, MD, at the annual meeting of the American Academy of Ophthalmology (47-48). One randomized controlled trial found improvement in visual acuity in age-related macular degeneration patients who supplemented with GB extract, although it has been suggested that these results should be treated with caution (36).

GB extract EGb 761® promotes vasodilatation and improves blood flow through arteries, veins and capillaries. It inhibits platelet aggregation and prolongs bleeding time. Although extracts are usually standardized to the flavonoid content, it is the terpenoid fraction that contains the platelet aggregation inhibitor (24). In the UK and other European countries, the cardioprotective effects of EGb 761® in myocardial ischaemia and reperfusion are being investigated in preclinical studies (30). GB improves both peripheral and cerebral blood flow; decreases blood viscosity and increases erythrocyte deformability. Patients with coronary heart disease, hypertension, hypercholesterolemia, and diabetes improved fibrinogen levels and plasma viscosity after treatment with GB. The extract inhibits both exogenously and endogenously induced arterial thrombus formations (48). GB extract produces effective electropharmacological actions in the cardiomyocytes and causes vasodilatation (27).

In a study of herbal product use and menopause symptom relief in primary care patients, the authors concluded that patients who are experiencing common menopausal symptoms are likely to use herbal products (phytoestrogens, St. John's wort, Ginkgo biloba, and ginseng) that are purported to provide menopause

symptom relief (49). Another study provides evidence of potential estrogenic activities of GB extract, which could be useful as an alternative for hormone replacement therapy (HRT), since GB phytoestrogens could be a part of selective estrogen receptor modulators (26). Also, Oh and Chung (50) concluded that EGb has a biphasic effect on estrogen, and can be considered a potential alternative to HRT with chemopreventive effects on breast cancer. GB caused modest cognitive improvements (memory and frontal lobe function) in a double-blind, placebo-controlled study with postmenopausal women (53-65 years old), randomly assigned to 7-day treatment with Ginkgo (120 mg/day, n=15) but also, the authors concluded, that these are unlikely to be secondary to major mood changes (51).

The World Health Organization has recommended the use of GB in Raynaud's disease (a common and painful condition characterized by episodic digital ischaemia produced by emotion and cold), acrocyanosis, and post-phlebitic syndrome (11). In the first double-blind placebo-controlled trial, (small pilot study) of GB phytosome (Seredrin) use in Raynaud's disease, the researchers concluded that this GB extract may be effective in reducing the number of Raynaud's attacks per week in patients suffering this disease (39, 52-53).

Ginkgo has also emerged as a new prophylactic agent for the prevention of acute mountain sickness (AMS) (54-55). Indirect evidence suggests that it may prevent hypoxic damage in tissues in part as a result of its antioxidant activity. In clinical trials its side effects profile was similar to placebo. In a randomized, double blind, placebo controlled trial comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers, findings suggested that prophylactic ginkgo may lead to a reduction in acute mountain sickness, with no recognizable side effects, indicating that it may be a viable alternative to acetazolamide (55). A study in thirty-six participants who reside at sea level and without high-altitude experience, supported the use of GB in the prevention of AMS, demonstrating that 24 hour pretreatment with GB and subsequent maintenance during exposure to high altitude are sufficient to reduce the incidence of AMS (54).

There has been conflicting evidence about the benefits of ginkgo. For example, the GB clinical trial published in August 2002 in JAMA (56) concluded that a leading ginkgo supplement did not produce measurable benefits for memory in healthy adults over 60, in addition, Pearson, et al. (57) indicated that regular use of GB during a long period of time does not enhance memory performance. Effects on performance, according these authors, were neither seen in episodic or in semantic memory tests. However, Birks, et al. (58), using the Cochrane Database System, the world's most respected scientific reviewer of clinical trials in medicine, concluded that published literature supports the safety and potential benefits of GB in treating memory loss and cognitive disorders associated with age-related dementia. Although their view is that there is a need for a large trial using modern methodology and permitting an intention-to-treat analysis to provide robust estimates of the size and mechanism of any treatment effects.

Pharmacological profile

The metabolism of flavonoids in humans is an important aspect that must be taken into account when discussing their biological activities. Some work has indicated that flavonoids and their glycosides have a low bioavailability in general, and, more importantly, has stressed the importance for absorption on the type of glycosidic bound and sugar moiety present. Some studies have suggested that different metabolic routes compete for flavonoid metabolism, including methylation, sulphation, glucuronidation and oxidative degradation pathways; glucuronide conjugation seems to be a major reaction in the metabolism of polyphenols. The mechanism of action of ginkgo is believed to be produced by its functions as neuroprotective agent, antioxidant, free-radical scavenger, membrane stabilizer, and inhibitor of platelet activating factor via the terpene ginkgolide B.

In a study conducted by Oliveira and others (59) plasma samples from human volunteers were taken after consumption of GB capsules, and analyzed by liquid chromatography coupled with electrospray mass spectrometry, for the presence of flavonoid glucuronides and flavonoid glycosides; evidencing the presence of flavonoid glycosides in samples of plasma. The results of this study suggested that glucuronidation is the main pathway for the metabolism of flavonoids and the authors support the view that flavonoid glycosides can be absorbed without hydrolysis.

Platelet activating factor (PAF) is thought to mediate symptoms of asthma by binding to receptors on neutrophils, eosinophils, and macrophages, which are involved in airway inflammation. In animal models, ginkgolide B inhibits PAF-induced eosinophil and neutrophil chemotaxis, bronchoconstriction, and pulmonary anaphylaxis. According to Ritch (48), BN 52063 (a combination of 40% ginkgolide A, 40% B, and 20% C) antagonizes bronchoconstriction in young patients with atopic asthma. Beckert, et al. (60) investigated the effect on platelet function of five commercially available herbal agents including GB, and concluded that GB did not affect platelet function in vivo.

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 muscarinergic cholinoceptors and α-adrenoceptors; and stimulation of choline uptake in the hippocampus. In addition to the action of several components of the extract, Birks and Van Dongen (33) include increasing blood supply by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, notably the catecholamines (61) and reducing the density of oxygen free radicals as a mechanism of action.

The psychological and physiological benefits of ginkgo are said to be based on its primary action of regulating neurotransmitters and exerting neuroprotective effects in the brain, protecting against or retarding nerve cell degeneration. Ginkgo also benefits vascular microcirculation by improving blood flow in small vessels and antioxidant activity (30). The anti-oxidative and anti-peroxidative properties of its flavonoid component and the anti-inflammatory activity of its terpenoid component are thought to be the basis for the purported efficacy of GB in Alzheimer's disease (AD) (41). Alzheimer's disease is characterized by a cognitive decline and deposition of β-amyloid (Aβ) plaque in the cortex and hippocampus. Ginkgo extract also has been shown to inhibit beta-amyloid deposition (11). The data in a transgenic mouse model of AD (Tg2576) indicated that chronic GB treatment (70 mg/kg/day in water) can block an age-dependent decline in spatial cognition without altering Aβ levels and without suppressing protein oxidation (62). Several trials with individuals aged 18-59 years have documented enhanced working memory following administration of 120mg/day of GB for 14-30 days (16).

Diet supplementation with plant extracts such as GB (EGb761®) for health and prevention of degenerative diseases is popular. However, it is often difficult to analyze the biological activities of plant extract due to their complex nature and the possible synergistic and/or antagonistic effects of their components (63). Although GB has been reported to enhance cognitive function in patients with selected neural disorders, a study conducted by Mattes and Kate (16) revealed no beneficial effects of chronic GB use at a mean level of 185mg/d on the post-lunch dip in alertness or on chemosensory function in healthy adults.

To date, no studies have shown a positive association between antioxidant intake and reduced glaucoma risk, but GB has been shown to possess antioxidant properties that help increase blood circulation of the optic nerve, and reduce vasospasm and serum viscosity. A recent randomized, placebo-controlled trial of 27 patients with normal tension glaucoma reported an improvement in pre-existing visual field damage in some ginkgo-treated patients (3).

According to Bryan (61), while there is some support for the efficacy of ginkgo in clinical populations, studies employing more objective measures of cognitive performance and non-clinical populations have not demonstrated a reliable beneficial effect of ginkgo.

However, although some studies demonstrate a positive effect of ginkgo, studies using more objective measures of cognitive performance have produced mixed support for its efficacy.

Dosage

For patients who have memory problems and dementia, the recommended dosage of ginkgo is 120 to 240 mg daily taken in two to three doses. This is usually available in the form of 40-mg tablets or in liquid form at a concentration of 40 mg/mL (46). The dosage in patients with tinnitus and peripheral vascular disease is no more than 160 mg per day, taken in two or three doses. Doses as high as 320 mg/day have also been studied (46). An initial period of six to 12 weeks is recommended to assess the effectiveness of ginkgo, although results have been as early as four weeks. On the other hand, the German Commission E recommends administration for a period of not less than 8 weeks in the treatment of chronic conditions and review of benefits before exceeding 3 months (22). The monthly cost for the usual daily dose of 120 mg is approximately $15 to $20 (11). Use of crude, dried leaf preparations or extemporaneous preparation of the leaves as a tea is not recommended because of insufficient quantity of active ingredients (46).

Safety issues

There is little research examining the safety of herbal medicines, particularly when taken in conjunction with conventional drug therapies (i.e. prescription and over-the-counter), despite the evidence suggesting that they are commonly used simultaneously (64). According to Jamison (65), almost one-third of current users of herbal medicines are at risk of an herb-drug interaction. The median lethal dose of GB extract is 15.3g per kilogram of body weight. Several recent review articles and herbal medicine textbooks have noted that ginkgo may increase the risk of bleeding (14).

The most common potential herb-drug interaction is between ginkgo and aspirin and/or non steroidal anti-inflammatory drugs (NSAID's). This finding has important potential implications because both of these products are regularly used by older people and are over-the-counter products that can be purchased directly by

the patient without awareness of a health professional. Although the risk of bleeding with ginkgo may be linked to its antiplatelet effects, there are few published data on the relative risk for such events given the millions of people who have used this herb (41). In a 4-week, randomized, double-blind, placebo-controlled, parallel design trial, Gardner, et al. (66) concluded that in older adults with peripheral artery disease or cardiovascular disease risk, a relative high dose of GB (300 mg/day) combined with 325 mg/day aspirin did not have a clinically or statistically detectable impact on indices of coagulation examined over 4 weeks, compared with the effect of aspirin alone. Spontaneous bleeding has been reported in patients taking acetaminophen with caffeine-ergotamine, as well as with ginkgo alone (65). For this reason, it is advisable to exert caution when combining GB with warfarin, heparin, aspirin, or any other drugs with anticoagulant or antiplatelet effects such as ticlopidine –Ticlid®-, clopidogrel –Plavix®-, and dipyridamole –Persantine® (7, 25, 51-52, 67). Although less frequent, combinations of ginkgo and the antidepressant trazodone -Desyrel®- may increase the risk of coma.(46, 65) Other reported drug interactions with central nervous system (CNS) drugs include GB affecting their therapeutic effectiveness. For example, if taken with GB, alprazolam's effect could be slightly decreased and Haldol's effect could be increased with a decrease in its extrapyramidal side effects (51, 68).

Different case reports have been published in the literature related to the safe use of GB tablets. In a case report published by Smolinske (24) of a 70-year-old man who had been taking 325 mg aspirin daily for 3 years, findings revealed that he developed a spontaneous hyphema one week after beginning therapy with GB tablets 40 mg twice daily. The bleeding resolved after discontinuation of the GB despite continued use of aspirin (24). Another case was reported by Sierpina and others (11), with subarachnoid hemorrhage associated with GB in an elderly patient. Although the patient developed elevated blood pressure while taking a thiazide diuretic and ginkgo, the blood pressure returned to normal when both substances were discontinued (11). Intracerebral hemorrhage associated with warfarin combined with ginkgo has also been reported, and the combination of warfarin and ginkgo should therefore be avoided (9). In another case report, a 33-year-old woman with no history of concomitant warfarin or antiplatelet medications developed a spontaneous bilateral subdural hematoma after taking 60mg of GB extract twice a day for two years. Bleeding times were prolonged while she continued taking GB and returned to normal when the herb was discontinued (24, 48).

Ginkgo biloba products are contraindicated in individuals with hypersensitivity to the plant or its products (22). It is not recommended in people with seizure disorders because it may reduce the effects of seizure medication; it is also not recommended in people hypersensitive to poison ivy, cashews, or mangoes (20). The unprocessed ginkgo leaf contains acids that are toxic (11). The crude Ginkgo plant parts can exceed concentrations of 5 parts per million of the toxic ginkgolic acid constituents and have caused severe allergic reactions. Individuals should therefore avoid the crude plant pills (17). Ginkgo seeds (nuts) appear to be considerably more toxic than the extract of the leaves, but in a study conducted by Philp (67), patients with controlled, preexisting epilepsy developed recurrent seizures within 2 weeks of beginning to take commercial extract. In the study, the seizures stopped when the herb was discontinued.

Ginkgo has also been identified as possibly interacting with garlic (Allium sativum), phosphatidylserine (also used for improving mental function), policosanol (also used for intermittent claudication), high-dose vitamin E or oils containing omega 3 fatty acids, and other natural products with relatively mild anticoagulant effects (7, 25, 67). Other herbal medications that may increase the risk of bleeding if used concurrently with GB include the following: feverfew, ginseng, don quai, red clover, and other natural coumarins (11). Some reports suggest that GB may reduce the effects of seizure medications (20).

Ginkgo may interfere with the management of diabetes because the metabolic clearance of insulin (17, 64) and oral hypoglycemic agents (46, 69) may increase. In traditional Chinese medicine, use of GB is contraindicated in "excess" conditions in which there is acute infection with fever (22). Large doses may lead to orthostatic hypotension, a condition of low blood pressure sometimes seen following abrupt postural changes, such as standing up after being seated. This effect may be related to ginkgo's actions upon cardiovascular function and blood pressure (15). On the other hand, thiazide diuretics interactions increase blood pressure when combined with GB (46). Among potentially safe herbs studied for circulatory disturbances and dementia, GB was included (70).

Self-medication with GB is not recommended among patients with cardiovascular disease (CVD) who are taking anticoagulants and antiplatelet drugs. Although GB extracts look promising for preventing and treating CVD, Mahady (38) recommends well-controlled clinical trials before clinical recommendations can be made. A case of frequent ventricular arrhythmias probably due to GB was presented in a patient that complained of palpitations twice in a month and on both occasions, symptom and electrocardiographic evidence of ventricular arrhythmias

resolved with discontinuation of GB (71). GB should be discontinued before surgery, but the time period has not been determined conclusively (11) although some authors indicate patients should stop taking ginkgo 36 hours before the procedure (22).

Ginkgo is generally well tolerated, with side effects being rare, usually mild, and including nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, weakness, and skin rashes (11, 20, 52), burning eyes, breathlessness (17), increased salivation, decreased appetite and tinnitus (15). Also, in a study that explored the incidence and severity of potential interactions between prescription medications and dietary supplements, the most common products included GB, among others; the results showed that most potential drug-dietary supplement interactions found were not serious (72). Although no studies have been conducted to support any restrictions on the use of ginkgo during pregnancy or lactation, Sierpina, et al. (11) recommend not administering ginkgo in the absence of any data. However, Mahady (40) suggests that the use of GB during pregnancy or nursing is contraindicated due to a lack of safety information. Convulsions have been reported in children following consumption of large numbers of seeds. 67 Fifty ginkgo seeds can induce tonic/clonic seizures and loss of consciousness. Seventy reports have shown 27% lethality attributed only to ginkgotoxin found in the seeds (51).

Other evidence related to GB-drug interactions is reported by Coxeter, et al. (68). According to these authors, GB enhanced drug efficacy in animal studies with amikacin and ticlopidine, where ginkgo potentiated ototoxicity of aminoglycosides and enhanced antithrombotic effects, respectively. On the other hand, the plasma concentrations and the therapeutic effect of omeprazole may be reduced with GB (51).

Herbal medicine is a traditional form of healing in many cultures. Some herbal medicines, such as GB have shown enough promise to warrant large-scale clinical studies involving supplements. However, consumers should carefully evaluate claims and evidence of dietary supplements.

Conclusions

According to the data shown above, Ginkgo provides health benefits in the following ways:

- Tissue effects include membrane stabilization, as well as antioxidant and free radical-scavenging actions.
- Use of oxygen and glucose is improved; most especially, it clears toxic metabolites that accumulate during ischemia.
- Nerve cells, including brain cells, are protected.
- Vascular effects exerted on the lining of the arteries, capillaries, and veins are the regulation of blood vessel tone and vasodilatation and increased blood flow.
- Platelet aggregation, platelet adhesion, and degranulation are inhibited (i.e., allergic and inflammatory components are released). Specifically, the platelet-activating factor (PAF) is potently inhibited.
- Neuron-metabolism and neurotransmitter disturbances are beneficially influenced.

With the rapid expansion of the use of herbal medicine in the United States, it is clear that our understanding of herb-herb, drug-herb and food-herb interactions will increase. Physicians, pharmacists, dietitians, nurses and other healthcare providers should be aware of these potential interactions and monitor and inform their patients accordingly.

Resumen

Los remedios botánicos han sido utilizados extensamente por siglos en muchos países. Sus productos o derivados han aumentado en popularidad en los Estados Unidos a finales de los años 1900. Durante los últimos 20 años, se estima que se han vendido 2 mil millones de dosis diarias (120mg) de Ginkgo biloba (GB). En Francia y Alemania, el GB se considera efectivo para el tratamiento de algunas enfermedades. La cantidad significativa de estudios clínicos sobre esta hierba es digna de atención para revisar la literatura existente sobre esta planta. Además, los Institutos Nacionales de la Salud ofrecen apoyo en la investigación en terapias alternativas que incluyen examinar los efectos del GB. Con la rápida expansión del uso de la medicina botánica en los Estados Unidos, es necesario aumentar nuestro conocimiento en las interacciones hierba-hierba, droga-hierba y alimento-hierba.

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References

1. National Institutes of Health. Clinical Trials. Available at: URL: http://clinicaltrials.gov/ct/show/NCT00010803?order=1.
2. Position of the American Dietetic Association: Food fortification and dietary supplements. J Am Diet Assoc 2001;101:115-125.
3. Springer RJ. Can nutritional supplements benefit ocular health? Rev Ophthalmology 2004;11:57-60.

4. United States Food and Drug Administration. Dietary supplement health and education act of 1994. Center for food safety and applied nutrition. Available at: URL: www.vm.cfsan.fda.gov/~dms/dietsupp.html.
5. Hellmich N. A botanical debate infuses herb industry. USA Today. 2003.
6. Gunther S, Patterson, RE, Kristal, AR, Stratton, KL, et al. Demographic and health- related correlates of herbal and specialty supplement use. J Am Diet Assoc 2004;104:27-34.
7. Insel P, Turner RE, Ross D. Nutrition. Jones and Bartlett Publishers, Inc., 2004;76:82-83.
8. Burns RD, Schiller MR, Merrick MA, Wolf KN. Intercollegiate student athlete use of nutritional supplements and the role of athletic trainers and dietitians in nutrition counseling. J Am Diet Assoc 2004;104:246-249.
9. Hodges PJ, Kam PCA. The peri-operative implications of herbal medicines. Anaesthesia 2002;57:889-899.
10. Li W, Fitzloff JF. HPLC determination of flavonoids and terpene lactones in commercial Ginkgo biloba products. Journal of Liquid Chromatography and Related Technologies 2002;25:2501-2514.
11. Sierpina VS, Wollschlaeger B, Blumenthal M. Ginkgo biloba. Am Fam Physician 2003;68:923-926.
12. Top-Selling Medicinal Herbs in the US, 1998-2002. World Almanac and Book Facts, 2004: p. 97-105.
13. Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol 2004;64:465-472.
14. Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with ginkgo biloba a case report and systematic review of the literature. J Gen Intern Med 2005;20:657-661.
15. Gold PE, Cahill L, Wenk GL. Ginkgo Biloba: A cognitive enhancer? Psychol Sci Publ Interest 2002;3:2-11.
16. Mattes RD, Pawlik MK.Effects of Ginkgo biloba on alertness and chemosensory function in healthy adults. Hum Psychopharmacol Clin Exp 2004;19:81-90.
17. Freeman L. Mosby's Complementary and Alternative Medicine. A Research-Based Approach. Mosby, Inc., 2004: p. 455-460.
18. Schaffer DM, Gordon NP, Jensen CD, Avins AL. Nonvitamin, nonmineral supplement use over a 12-month period by adult members of a large health maintenance organization. J Am Diet Assoc 2003;103:1500-1505.
19. Zimmermann M, Colciaghi F, Cattabeni F, Di Luca M. Ginkgo biloba extract: from molecular mechanisms to the treatment of Alzheimer's disease. Cell Mol Biol 2002;48:613-623.
20. US General Accounting office. Report to chairman, special committee on aging, US senate. Health products for seniors. "Anti-Aging" products for physical and economic harm. 2001;9:16, 30.
21. American Botanical Council. Ginkgo biloba leaf extract. Herbalgram.org. Available at: URL: www.herbalgram.org/default.asp?c=he040.
22. Mckenna DJ, Jones K, Hughes K. Efficacy, safety, and use of Ginkgo biloba in clinical and preclinical applications. Altern Ther Health Med 2001;7:70-90.
23. Son Y. Effects of nitrogen fertilization on foliar nutrient dynamics in ginkgo seedlings. J Plant Nutr 2002;25:93-102.
24. Smolinske SC. Dietary supplement-drug interactions. JAMWA 1999;54:191-192,195.
25. Bratman S, Girman AM. Mosby's handbook of herbs and supplements and their therapeutic Uses. Mosby, Inc., 2003: p. 593-601.
26. Oh SM, Chung KH. Estrogenic activities of Ginkgo biloba extracts. Life Sciences 2004;74:1325-1335.
27. Satoh H, Nishida S. Electropharmacological actions of Ginkgo biloba extract on vascular smooth and heart muscles. Clin Chim Acta 2004;342:13-22.
28. Van Beek TA. Chemical analysis of Ginkgo biloba leaves and extracts. J Chromatogr A 2002;967:21-55.
29. Mantle D, Wilkins RM, Gok MA. Comparison of antioxidant activity in commercial Ginkgo biloba preparations. J Altern Complement Med 2003;9:625-629.
30. ADIS R&D Profile. Egb 761 Ginkor biloba extract, Ginkor. Drugs in R&D 2003;4:188-193.
31. Gulec M, Mustafa I, Ramazan Y, Huseying O, et al. The effects of ginkgo biloba extract on tissue adenosine deaminase, xanthine oxidase, myeloperoxidase, malondialhedehyde, and nitric oxide in cisplatin-induced nephrotoxicity. Toxicol Ind Health 2006;22:125-130.
32. Liu S-Q, Yu J-P, Chen H-L, Luo H-S, et al. Therapeutic effects and molecular mechanisms of ginkgo biloba extract on liver fibrosis in rats. Am J Chin Med 2006;34:99-114.
33. Birks J, Grimley EV, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2002;CD003120.
34. Stevinson EE. Ginkgo biloba may help tinnitus but needs further investigation. BMJ 2003;327:630-633.
35. J.-Gertz, H, Kiefer M. Review about Ginkgo biloba special extract Egb 761 (Ginkgo). Curr Pharm Design 2004;10:261-264.
36. Bartlett H, Eperjesi F. Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements. Ophthal Physiol Opt 2005;25:179-194.
37. Le Bars PL. Magnitude of effect and special approach to Ginkgo biloba Extract Egb 761® in cognitive disorders. Pharmacopsychiatry 2003;36:44-49.
38. Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. J Cardiovasc Nurs 2002;16:21-32.
39. Muir AH, Robb R, McLaren M, Daly F, et al. The use of Ginkgo biloba in Raynaud's disease: a doubleblind placebo-controlled trial. Vascular Medicine 2002;7:265-267.
40. Mahady GB. Ginkgo Biloba: A Review of Quality, Safety, and Efficacy. Nutr Clin Care 2001;4:140-147.
41. Doraiswamy PM. Non- cholinergic strategies for treating and preventing Alzheimer's Disease. CNS Drugs 2002;16:811-824.
42. Le Bars PL, Velasco FM, Ferguson JM, Dessain EC, et al. Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract Egb[Sup®] in Alzheimer's Disease. Neuropsychobiology 2002;45:19-27.
43. Hodes RJ. Statement on Alzheimer's disease to senate. Appropriations committee, subcommittee on labor, health and human services and education. National Institute of Aging. Available at: URL: www.nia.nih.gov/AboutNIA/BudgetRequests/AD2001April3.htm.
44. National Institutes of Health. Office of Dietary Supplements. Available at: URL: http://dietary-supplements.info.nih.gov/.
45. Cala S, Baumgarther J, Crismon ML. A survey of herbal use in children with attention-deficit-hyperactivity disorder or depression. Pharmacotherapy 2003;23:222-230.
46. Fetrow CW, Avila JR. Professional's Handbook of Complementary & Alternative Medicines. Lippincott Williams & Wilkins, 2004: p. 358-365.
47. Guttman C, Quaranta L. Visual field damage may improve with Ginkgo biloba. Ophthalmol Times 2001;26:18.
48. Ritch R. How Ginkgo biloba extract has value in medicinal use. Ophthalmol Times 2000;25:14-15.
49. Dailey RK, Neale AV, Northrup J, West P, et al. Herbal product use and menopause symptom relief in primary care patients; A Metro-Net study. J Womens Health 2003;12:633-641.
50. Oh SM, Chung KH. Antiestrogenic activities of Ginkgo biloba extracts. J Steroid Biochem Mol Biol 2006;100:167-176.
51. Hartley DE, Heinze L, Elsabagh S, File SE. Effects on cognition and mood in postmenopausal women of 1- week treatment with Ginkgo biloba. Pharmacol Biochem Behav 2003;75;711-720.
52. Bressler R. Herb-drug interactions, Interactions between Ginkgo biloba and prescription medications. Geriatrics 2005;60:30-33.

53. Ho LJ, Lai JH. Chinese herbs as immunomodulators and potential disease-modifying antirheumatic drugs in autoimmune disorders. Curr Drug Metabol 2004;5:181-192.
54. Moraga FA, Flores A, Serra J, Esnaola C, et al. Ginkgo biloba decreases acute mountain sickness in people ascending to hih altitute at Ollagüe (3696m) in northern Chile. Wilderness Environ Med 2007;18:251-257.
55. Gertsch JH, Basnyat B, Johnson EW, Oropa J, et al. Randomized, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ 2004;328:797.
56. Solomon PR, Adams F, Silver A, Zimmer J, et al. Ginkgo for memory enhancement: A randomized controlled trial. JAMA 2002;288: 835-840.
57. Pearson J, Bringlöv N, Lars G, Nyberg L. The memory-enhancing effects of Ginseng and Ginkgo biloba in healthy volunteers. Psychopharmacology 2004;172:430-434.
58. Birks J, Grimley EV, Van DM. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2007; CD003120.
59. Oliveira EJ, Watson DG. Grant MH. Metabolism of quercetin and Kaempferol by rat hepatocytes and the identification of flavonoid glycosides in human plasma. Xenobiotica 2002;32:279-287.
60. Beckert BW, Concannon MJ, Henry SL, Smith DS, et. al. The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature. Plast Reconstr Surg 2007;120:2044-2050.
61. Bryan J. Mechanisms and evidence for the role of nutrition in cognitive ageing. Ageing Int 2004;29:28-45.
62. Stackman RW, Eckenstein F, Frei B, Kulhanek D, et al. Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. Exp Neurol 2003;184:510-520.
63. Rimbach G. Effect of Ginkgo biloba (EGB 761®) on differential gene expression. Pharmacopsychiatry 2003;36:95-99.
64. Dergal JM, Gold JL, Laxer DA, Lee MSW, et al. Potential interactions between herbal medicines and conventional drug therapies used by older adults attending a memory clinic. Drugs Aging 2002; 19:879-886.
65. Jamison J. Clinical guide to nutrition and dietary supplements in disease management. Churchill Livingstone (an Elsevier Science Company), 2003: p. 551-555.
66. Gardner CD, Zehnder JL, Rigby AJ, Nicholus JR, et al. Effect of Ginkgo biloba (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: a randomized clinical trial. Blood Coagul Fibrinolysis 2007;18:787-793.
67. Philp RB. Herbal-Drug Interactions and Adverse Effects (an evidence-based quick reference guide). McGraw-Hill. Medical Publishing Division, 2004: p. 120-122.
68. Coxeter PD, McLachlan AJ, Duke CC, Roufogalis BD. Herb-drug interactions: an evidence based approach. Curr Medi Chem 2004; 11:1513-1525.
69. Triggiani V, Resta F, Guastamacchia E, Sabbà C, et al. Role of antioxidants, essential fatty acids, carnitine, vitamins, phytochemicals and trace elements in the treatment of Diabetes mellitus and its chronic complications. Endocrine, Metabolic & Immune Disorders-Drug Targets 2006;6:77-93.
70. Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. Am J Health Syst Pharm 1999;56:125-38.
71. Cianfrocca C, Pelliccia F, Auriti A, Santini M. Ginkgo biloba- induced frequent ventricular arrhythmia. Ital Heart J 2002;3:689-691.
72. Peng CC, Glassman, PA, Trilli LE, Hayes-Hunter J, et al. Incidence and severity of potential drug- dietary supplement interaction in primary care patients: An exploratory study of 2 outpatient practices. Arch Intern Med 2004;164:630-636.