Ginkgo

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Scientific Name

Ginkgo biloba.

Family: Ginkgoaceae.

Background

Ginkgo biloba, which is the last remaining species of a primitive family of gymnosperms called ginkgoaceae, is a large tree with fan-shaped leaves that have radiating veins (89714). Although ginkgo is native to temperate Asia, including China, Japan, and Korea, it has been cultivated in Europe since around 1730 and in the United States since around 1784 (2660, 89715).

Also known as: Abricot Argenté Japonais, Adiantifolia, Arbe aux Écus, Arbe aux Quarante Écus, Arbe du Ciel, Arbre Fossile, Bai Guo Ye, Baiguo, Extrait de Feuille de Ginkgo, Extrait de Ginkgo, Fossil Tree, Ginkgo Biloba Leaf, Ginkgo Folium, Graine de Ginkgo, Herba Ginkgo Biloba, Japanese Silver Apricot, Kew Tree, Maidenhair Tree, Noyer du Japon, Pei Go Su Ye, Salisburia Adiantifolia, Yen Xing, Yinhsing.

CAUTION: See separate listing for Maidenhair Fern.

History

The ginkgo tree is thought to be one of the oldest living trees, dating back more than 200 million years (89715). Its seeds were used as part of traditional Chinese medicine about 2000 years ago, but more recent medicinal applications typically involve using leaf extracts (89714).

People Use This For

Orally, ginkgo leaf is used for dementia, including Alzheimer's, vascular, and mixed dementia. Ginkgo leaf is also used orally for conditions associated with cerebral vascular insufficiency, especially in the elderly, including memory loss, headache, tinnitus, vertigo, dizziness, difficulty concentrating, mood disturbances, and hearing disorders. It is also used orally for ischemic stroke, peripheral arterial disease (PAD), arteriosclerosis, angina pectoris, and cardiac reperfusion injury. Ginkgo leaf is also used for cognitive dysfunction related to chemotherapy or Lyme disease, as well as sexual dysfunction, including that caused by SSRI antidepressants. It is also used orally for cognitive disorders secondary to depression; eye problems, including macular degeneration and glaucoma; attention deficit-hyperactivity disorder (ADHD); autism; thrombosis; heart disease; hypercholesterolemia; premenstrual syndrome (PMS); dysentery and filariasis; and diabetic retinopathy. Ginkgo leaf is also used orally to improve cognitive behavior and sleep patterns in patients with depression, chronic fatigue syndrome (CFS), schizophrenia, and for the prevention of winter depression. Ginkgo leaf is also used orally for preventing acute mountain sickness and aging, regulating gastric acidity, improving liver and gallbladder function, controlling blood pressure, and treating Raynaud's disease. It is also used orally to treat asthma, allergies, bronchitis, and for various disorders of the central nervous system.

Ginkgo seed is used for cough, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), genitourinary complaints, to aid digestion, and to prevent drunkenness.

Topically, ginkgo leaf is used to wash chilblains, which are lesions on the fingers, toes, heels, ears, and nose caused by exposure to extreme cold. It is also used topically in wound dressings to improve circulation in the skin. Ginkgo seed is used topically for scabies and skin sores.

Intravenously, ginkgo leaf extract is used to increase cerebral blood flow, improve cognition, for psychiatric conditions in the elderly, and for metastatic colorectal cancer.

In foods, roasted ginkgo seed, which has the pulp removed, is an edible delicacy in Japan and China.

In manufacturing, ginkgo leaf extract has been used in cosmetics.

Safety

LIKELY SAFE ...when used orally and appropriately. Standardized ginkgo leaf extracts have been used safely in trials lasting for several weeks up to 6 years (1514, 1515, 3461, 5717, 5718, 6211, 6212, 6213, 6214, 6215)(6216, 6222, 6223, 6224, 6225, 6490, 14383, 14499, 16634, 16635)(16636, 16637, 17402, 17716, 17718, 87794, 87819, 87826, 87848, 87864)(87888, 87897, 87901, 87904, 89701, 89707). Also, a specific combination product (Memo, Pharco Pharmaceuticals, Alexandria, Egypt), which contains natural lyophilized royal jelly 750 mg, standardized ginkgo leaf extract 120 mg (containing 24% flavonoids glycosides and 6% terpenoids), and standardized Panax ginseng root extract 150 mg (containing 40% to 80% ginsenosides) has been used safely for up to 4 weeks (89712).

However, there is concern about toxic and carcinogenic effects seen in animals exposed to a ginkgo leaf extract containing 31.2% flavonoids, 15.4% terpenoids, and 10.45 ppm ginkgolic acid, in doses of 100 to 2000 mg/kg five times per week for 2 years. Hepatic, thyroid, gastric and nasal toxicities were seen, including thyroid and liver cancers, rates of which were increased in a dose-dependent manner (18272). However, the clinical relevance of this data for humans, using typical doses, is unclear. The content of the extract used is not identical to that commonly used in supplement products, and the doses studied are much higher than those typically used by humans. A single dose of 50 mg/kg in rats is estimated to be equivalent to a single dose of about 240 mg in humans (18272).

POSSIBLY SAFE ...when used intravenously, short-term. A standardized ginkgo leaf extract called EGb 761 ONC has been safely administered intravenously for up to 10 days (9871, 9872).

POSSIBLY UNSAFE ...when the roasted seed or crude ginkgo plant is used orally. Consuming more than 10 roasted seeds per day can cause difficulty breathing, weak pulse, seizures, loss of consciousness, and shock (8231, 8232). Crude ginkgo plant parts can exceed concentrations of 5 ppm of the toxic ginkgolic acid constituents and can cause severe allergic reactions (5714).

LIKELY UNSAFE ...when the fresh ginkgo seed is used orally. Fresh seeds are toxic and potentially deadly (11296).

There is insufficient reliable information available about the safety of ginkgo when used topically.

CHILDREN: POSSIBLY SAFE ...when used orally and appropriately, short-term (87790, 89708). A specific ginkgo dried extract (Ginko T.D., Tolidaru Pharmaceuticals), has been safely used in doses of 80-120 mg daily for 6 weeks in children aged 6-14 years (17112). Another specific combination product containing ginkgo leaf extract and American ginseng extract (AD-FX, CV Technologies, Canada) has also been safely used in children aged 3-17 years for up to 4 weeks (8235). LIKELY UNSAFE ...when ginkgo seed is used orally. The fresh seeds have caused seizures and death in children (8231, 11296).

PREGNANCY: POSSIBLY UNSAFE ...when used orally. There is concern that ginkgo might have labor-inducing and hormonal effects. There is also concern that the antiplatelet effects of ginkgo could prolong bleeding time if taken around the time of labor and delivery (15052). Theoretically, ginkgo might adversely affect pregnancy outcome; avoid using during pregnancy.

LACTATION: Insufficient reliable information available; avoid using.

Effectiveness

See detailed evidence summary

POSSIBLY EFFECTIVE

Anxiety. Clinical research shows that taking a specific ginkgo extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) for 4 weeks can reduce symptoms of anxiety in a greater percentage of adults with generalized anxiety disorder or adjustment disorder with anxious mood compared to placebo. After 4 weeks of treatment, a reduction in anxiety rating score of at least 50% was seen in 44% of patients treated with 480 mg/day, 39% of patients treated with 240 mg/day, and 22% of patients treated with placebo (15578).

Cognitive function. Although some clinical evidence suggests that taking ginkgo leaf extract 120-240 mg daily for up to 12 weeks for does not affect memory, executive function, or attention in healthy subjects (87788, 87907), most evidence suggests that ginkgo can modestly improve memory and speed of cognitive processing, including increasing speed of performance on factors assessing attention, in people with no complaints of memory impairment (6214, 6215, 8236, 8544, 8585, 8588, 9759, 87879). Lower doses of ginkgo 120-240 mg per day seem to be as effective as or more effective than higher doses up to 600 mg per day (6214, 8236, 8588).

Some evidence suggests that taking ginkgo in combination with Panax ginseng or codonopsis can enhance memory in healthy

young or middle-aged adults, and the combinations might be more effective than the individual products (8591, 9759, 87758). However, taking a specific combination product (Gincosan, Pharmaton Natural Health Products) containing a specific ginkgo leaf extract (GK501, Pharmaton Natural Health Products) 120 mg and a specific Panax ginseng extract (G115, Pharmaton Natural Health Products) 200 mg daily for 12 weeks does not improve mood or cognition compared to placebo in postmenopausal women (87767). Also, taking a specific combination product (Ginkgo Brahmi, Blackmore's Ltd.) containing ginkgo extract 120 mg and bacopa extract 300 mg for 4 weeks does not improve memory, problem solving, or executive function compared to placebo in healthy adults (87748).

Dementia. Some evidence shows that taking ginkgo leaf extract orally modestly improves symptoms of Alzheimer's, vascular, or mixed dementias. Studies lasting from 3 months to one year show that ginkgo leaf extract can stabilize or improve some measures of cognitive function and social functioning in patients with multiple types of dementia (1514, 1515, 2665, 2666, 6222, 6223, 6224, 6225, 6490, 11981)(16636, 17191, 17717, 87819, 87823, 87851, 87855, 87866, 87902, 89703)(89711, 89713). Higher doses of ginkgo (240 mg) seem to have a greater effect on cognitive function than lower doses (120 mg) (87855, 87866). However, due to poor study quality, there are concerns that some of the early ginkgo studies may not be reliable. Although most clinical trials show benefit, there are some conflicting findings suggesting inconsistent and unpredictable effects (5720, 16636, 16637, 87726, 87848, 88006, 89710).

There has been some debate about whether ginkgo is more effective in dementia patients who have neuropsychiatric symptoms. Most clinical research shows that ginkgo is not more effective in patients with neuropsychiatric symptoms compared to those without, and ginkgo does not seem to relieve the neuropsychiatric symptoms (17717, 87794, 87897).

Most clinical studies have not compared ginkgo leaf extract to conventional drugs such as the cholinesterase inhibitors. Preliminary comparative studies show that taking a specific ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) 160-240 mg daily for 22-24 weeks seems to be comparable to donepezil (Aricept) 5 mg daily for mild to moderate Alzheimer's dementia (14499, 87826). However, indirect comparisons suggest that ginkgo leaf extract might be less effective than the conventional drugs donepezil (Aricept), tacrine (Cognex), and other cholinesterase inhibitors (6224, 6490, 11981, 89710).

Ginkgo has also been evaluated for the prevention of dementia. Epidemiologic research shows that taking ginkgo extract is not associated with a decreased risk of developing dementia in elderly patients with memory impairment. However, it might be associated with a decreased risk of overall mortality (14812). Also, three large-scale clinical trials also show that taking ginkgo extract 120 mg twice daily does not reduce the risk of developing all-cause dementia or Alzheimer's disease in elderly patients with normal cognitive function or in those with mild cognitive impairment (16634, 87848, 87904). In addition, evidence from a larger analysis suggests that, although taking ginkgo extract may improve cognition in patients with Alzheimer's disease, it does not prevent disease progression (89713).

Most of the clinical studies on the effectiveness of ginkgo leaf for dementia have used the standardized extracts EGb 761 (Dr. Willmar Schwabe Pharmaceuticals and Ipsen) and LI 1370 (Lichtwer Pharma). These two extracts are similar and prepared to contain approximately 24% to 25% flavone glycosides and 6% terpene lactones. Other products with similar ingredients include Ginkai (Lichtwer Pharma), Ginkgo 5 (Pharmline), Ginkgold and Ginkgo (Nature's Way), and Quanterra Mental Sharpness (Warner-Lambert).

Diabetic retinopathy. There is some evidence that taking a specific ginkgo leaf extract called EGb 761 120 mg/day orally for 6 months can significantly improve measures of color vision in patients with early diabetic retinopathy (6175).

Glaucoma. Taking ginkgo leaf extract 120-160 mg orally in two or three divided doses daily for up to 12.3 years seems to improve pre-existing damage and reduce the progression of damage to the visual field in patients with normal tension glaucoma (10378, 87900). However, some conflicting evidence exists. Taking a specific ginkgo extract (Ginaton, Dr. Willmar Schwabe Pharmaceuticals) 40 mg three times daily for 4 weeks does not appear to improve damage or progression of glaucoma in patients with newly diagnosed normal tension glaucoma (89707). Reasons for the discrepancies may be due to the duration of treatment, the formulation of ginkgo leaf extract used, or the severity of glaucoma at baseline.

Peripheral vascular disease (PVD). Some evidence shows that taking a specific ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals and Ipsen) orally increases pain-free walking distance in patients with Fontaine's IIb peripheral arterial occlusive disease and intermittent claudication and might decrease overall PVD event incidence such as surgery or amputation in elderly patients (3461, 6211, 6212, 6213, 17402). Significant benefit has been found with doses as low as 120-160 mg per day (6211). However, there is some evidence that a higher dose of 240 mg per day might be more beneficial in some patients (3461, 6212).

Although most research is positive, some research shows that taking a specific ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) 300 mg daily for 16 weeks does not significantly improve maximum treadmill walking time compared to placebo in patients with peripheral arterial disease (16638). A reason for this discrepancy may be due to the duration of treatment. An analysis of clinical evidence suggests that taking ginkgo leaf extract does not significantly improve maximum treadmill walking distance compared to placebo in patients with Fontaine stage II PVD and intermittent claudication when administered for 6-8 weeks or 12-16 weeks, but does increase maximum treadmill walking distance by about 85 meters when administered for at least 24 weeks (89440).

Premenstrual syndrome (PMS). Taking ginkgo leaf extract orally 80 mg twice daily or 40 mg three times daily seems to produce significant relief in breast tenderness and other physical and psychological symptoms associated with PMS when started during the 16th day of the menstrual cycle and continued until the 5th day of the following cycle for up to two cycles (6229, 87839). Specific ginkgo leaf extracts that have been assessed for this condition include Ginko T.D. (Tolidaru Pharmaceuticals) and EGb 761, which is an ingredient in several commercial products including Tebonin (Dr. Willmar Schwabe Pharmaceuticals), Tanakan (Ipsen), and Quanterra Mental Sharpness (Warner-Lambert).

Schizophrenia. A pooled analysis of six clinical trials shows that taking a standardized ginkgo leaf extract called EGb 761, 120-360 mg/day orally in addition to standard antipsychotic medications (such as olanzapine, clozapine, or haloperidol), can reduce total and negative symptoms of schizophrenia compared to treatment with antipsychotic medications alone (87844). Also, treatment with a standardized ginkgo leaf extract called EGb 761, 360 mg daily in combination with haloperidol 0.25 mg/kg daily for 12 weeks, seems to reduce adverse behavioral and nerve symptoms associated with haloperidol treatment (87708).

Tardive dyskinesia. Clinical research shows that taking a specific ginkgo extract called EGb 761 (Yi Kang Ning, Yang Zi Jiang Pharmaceuticals Ltd., Jiangsu, China) 80 mg three times daily for 12 weeks can reduce the severity of tardive dyskinesia by at least 30% compared to placebo in schizophrenic patients being treated with antipsychotic medications (87864).

Vertigo. Taking ginkgo leaf extract 160 mg/day orally seems to improve symptoms of vertigo and equilibrium disorders (5721, 6220, 6221). There is evidence from two clinical studies that ginkgo leaf extract is significantly more effective than placebo (6220) and possibly as effective as betahistine for improving vertigo and dizziness caused by vascular vestibular disorders and vestibular disorders of unknown origin (6220, 6221).

POSSIBLY INEFFECTIVE

Age-related memory impairment. Some early clinical evidence suggests that ginkgo leaf extract might result in small improvements in memory and cognitive function in non-demented patients with age-related memory impairment (5717, 6216). Also, taking a specific combination product (Memo, Pharco Pharmaceuticals), which contains natural lyophilized royal jelly 750 mg, standardized ginkgo leaf extract 120 mg (containing 24% flavonoid glycosides and 6% terpenoids), and standardized Panax ginseng root extract 150 mg (containing 40% to 80% ginsenosides), orally for 4 weeks improves memory in elderly patients with mild cognitive impairment when compared with placebo (89712).

However, most clinical evidence shows that taking ginkgo leaf extract orally does not improve memory or attention in elderly individuals with normal mental function (5718, 8586, 8587, 8588), those with mild cognitive impairment (87848), or those with dementia and age-associated memory impairment (87726).

Clinical research also shows that taking a standardized ginkgo leaf extract (Thorne Research Inc., Sandpoint, ID) 240 mg daily does not reduce the risk of developing age-related cognitive impairment in elderly patients aged 85 years and older who have normal cognitive function (16635).

Ginkgo has also been evaluated for prevention of dementia in patients with existing age-related cognitive impairment. Epidemiologic research shows that taking ginkgo is not associated with a decreased risk of developing dementia in elderly patients with memory impairment; however, it might be associated with a decreased risk of overall mortality (14812). A large-scale clinical trial also shows that taking ginkgo extract 120 mg twice daily does not reduce the risk of developing all-cause dementia or Alzheimer's disease in elderly patients with mild cognitive impairment (16634).

Antidepressant-induced sexual dysfunction. Although some preliminary clinical research suggests taking ginkgo leaf extract orally might help sexual dysfunction caused by antidepressant therapy (3965, 3967), subsequent research indicates that it is probably ineffective (207, 3966, 3969, 10893, 14383).

Chemotherapy-related complications. Clinical research shows taking a specific ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) 60 mg twice daily starting prior to the second cycle of chemotherapy and continuing until one month after chemotherapy completion does not prevent chemotherapy-related cognitive dysfunction compared to placebo in chemotherapy naïve breast cancer patients (89701).

Hypertension. Clinical research shows that taking a standardized ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) 240 mg daily for up to 6 years does not reduce blood pressure compared to placebo in hypertensive patients aged 75 years or older (87853).

Multiple sclerosis (MS). Most clinical evidence shows that taking ginkgo leaf extract or ginkgolide B, a constituent of ginkgo leaf extract, does not improve cognition or disability in patients with multiple sclerosis (87739, 87787, 87903, 87947). However, a single preliminary clinical study suggests that taking a standardized ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) may improve processing speed compared with placebo in patients with multiple sclerosis (89705).

Seasonal affective disorder (SAD). Taking ginkgo leaf extract orally does not seem to prevent winter depression symptoms in patients with SAD (8233).

Tinnitus. Taking ginkgo leaf extract orally does not seem to improve symptoms of tinnitus. Although some studies have shown benefit, the majority of evidence indicates that ginkgo leaf extract is not consistently effective for patients with tinnitus (221, 910, 5721, 6218, 6219, 9871, 87754, 87901).

LIKELY INEFFECTIVE

Cardiovascular disease. A large-scale randomized trial shows that taking a specific ginkgo leaf extract called EGb 761 (Dr. Willmar Schwabe Pharmaceuticals) 240 mg/day orally does not significantly reduce the risk of myocardial infarction, angina, stroke, cardiovascular disease-related hospitalization, or mortality in elderly patients (17402).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Age-related macular degeneration (AMD). Preliminary clinical research suggests that taking ginkgo leaf extract 60-240 mg orally twice daily for up to 6 months might improve symptoms of AMD (6227, 6228, 11797). There is limited evidence that ginkgo leaf extract might significantly improve distance vision in patients with AMD (6227).

Allergic rhinitis (hayfever). Preliminary evidence shows that applying specific eye drops (Trium, SOOFT) containing

ginkgo extract 0.05% and hyaluronic acid 0.15%, three times daily for one month can decrease redness by 80%, discharge by 40%, and swelling by 10% compared to using eye drops with hyaluronic acid only in patients with seasonal allergic conjunctivitis (87829). Altitude sickness. The effects of ginkgo extract on altitude sickness are conflicting. Some research suggests that taking ginkgo extract 80-120 mg twice daily for 4 days before the ascent to an altitude of 4300-5400 meters significantly reduces the occurrence of symptoms of acute altitude sickness, including headache, fatigue, dyspnea, nausea, and vomiting, compared to placebo (6230, 87827). However, a large-scale trial using a different ginkgo extract (GK501, Pharmaton Natural Health Products) 120 mg twice daily for 1-2 days before the climb from an altitude of 4280 meters to 4928 meters, shows that ginkgo extract has no effect on preventing altitude sickness (11766). Also, another small study suggests that taking ginkgo extract 120 mg twice daily for 3 days before an ascent does not reduce altitude sickness compared to placebo (87827). The conflicting results may be due to differences in starting baseline altitudes before ascent, duration of pretreatment period, or the source of the ginkgo product.

Asthma. Clinical research shows that a taking two capsules of a specific combination product (AKL1, AKL International Ltd.) containing ginkgo extract 130 mg/capsule, ginger 100 mg/capsule, and Picrorhiza kurroa 270 mg/capsule twice daily for 12 weeks does not improve lung function, respiratory symptoms, or quality of life compared to placebo in adult patients with asthma (87786).

Attention deficit-hyperactivity disorder (ADHD). There is preliminary evidence that taking a specific combination product (AD-fX, CV Technologies, Canada) containing ginkgo leaf extract, in combination with American ginseng (Panax quinquefolius), might significantly improve ADHD symptoms such as anxiety, hyperactivity, and impulsivity in children aged 3-17 years (8235). However, other clinical research shows that taking a different standardized ginkgo extract (Ginko T.D., Tolidaru Pharmaceuticals) 80-120 mg daily for 6 weeks is not as effective as methylphenidate 20-30 mg/day in children aged 6-14 years with newly-diagnosed ADHD. An improvement in a teacher/parent ADHD rating scale of at least 40% was seen in only 8% of children taking this ginkgo extract compared with 64% in children taking methylphenidate (17112).

Autism. Clinical research shows that taking a specific ginkgo extract (Ginko T.D., Tolidaru Pharmaceuticals) 80-120 mg/day for 10 weeks along with risperidone 1-3 mg/day does not improve symptoms of autism compared to risperidone alone in autistic children aged 4-12 years (89708).

Chronic obstructive pulmonary disease (COPD). Clinical research shows that taking two capsules of a specific combination product (AKL1, AKL International Ltd.) containing ginkgo extract, ginger, and Picrorhiza kurroa twice daily for 8 weeks does not improve respiratory symptoms compared to placebo in patients with COPD (89702).

Cocaine dependence. Clinical research suggests that taking a standardized ginkgo leaf extract called EGb 761 120 mg twice daily for 10 weeks does not help maintain abstinence from cocaine use compared to placebo in cocaine-dependent patients (87723).

Colorectal cancer. Preliminary clinical research suggests that intravenous ginkgo extract (EGb 761 ONC), in combination with 5-fluorouracil, might be useful for metastatic colorectal cancer (9872).

Dyslexia. Preliminary clinical research suggests that taking a standardized ginkgo leaf extract called EGb 761 80 mg daily for an average of 34 days can help reduce dyslexia compared to baseline in children aged 5-16 years (87790).

Fibromyalgia. Preliminary clinical research suggests that taking tablets containing ginkgo extract (Bio-Biloba, Pharma Nord) 200 mg/day in conjunction with capsules containing coenzyme Q10 (Bio Quinone Q10, Pharma Nord) 200 mg/day orally for 84 days improves patient's quality of life, such as physical fitness levels, emotional feelings, social activities, overall health, and pain, compared to baseline (17716).

Gastric cancer. Preliminary evidence suggests that taking carbohydrates from the outer layer of ginkgo fruit 250 mg orally twice daily for 30 days may reduce tumor size in patients with gastric cancer compared to pretreatment (87742).

Hearing loss. There is preliminary evidence that ginkgo leaf extract 120 mg orally twice daily might help short-term idiopathic hearing loss (8543). However, because many of these patients recover spontaneously, evaluating its effectiveness for this use is difficult.

Hemorrhoids. Preliminary clinical evidence suggests that taking a combination of ginkgo extract, troxerutin, and heptaminol for one week may decrease some symptoms of hemorrhoids, including bleeding, pain, feelings of incomplete defecation, and discharge (87751).

Migraine headache. Preliminary clinical evidence shows that ginkgolide B, a constituent of ginkgo biloba extract, may help prevent migraines in children (44181, 87876). Also, a specific product (Migrasoll, Pharmaval Srl) containing ginkgolide B 60 mg, coenzyme Q10 11 mg, and vitamin B2 8.7 mg, taken twice daily for 4 months, may help prevent migraines in women (44103).

Ovarian cancer. Epidemiological evidence suggests that use of ginkgo extract for 6 months is associated with a decreased risk for developing ovarian cancer (14813).

Pancreatic cancer. Preliminary clinical research suggests that a specific intravenous ginkgo extract called EGb 761 ONC, given with 5-fluorouracil, might slow the progression of pancreatic cancer in some patients (87699). However, since the study did not include a control group, it is unclear if the effects of treatment were greater than the effects of 5-fluorouracil alone.

Quality of life. Preliminary clinical evidence suggests that taking a standardized ginkgo leaf extract called LI 1370 (Lichtwer Pharma) 120 mg daily for up to 6 months may improve quality of life measures such as activities of daily living, mood, sleep, and alertness in elderly individuals (87715, 87760).

Radiation exposure. Preliminary clinical research suggests that taking a standardized gingko leaf extract called EGb 761 (Tanakan, Ipsen) 120 mg daily for 2 months might reduce clastogenic factors in the blood of patients who had previously been irradiated. The reduction in clastogenic factors was observed for at least 7 months after initiation of ginkgo in most patients (17719).

Radiation-induced skin toxicity. Preliminary clinical research suggests that topically applying a specific cream product (Radioskin 2, Herbalab di Perazza Massimiliano Company), which contains ginkgo extract, Aloe vera, and metal esculetina, along with another specific cream product (Radioskin 1, Herbalab di Perazza Massimiliano Company), which contains alga atlantica and ethylbisiminomethylguaicolo manganese cloruro, may improve skin hydration and reduce skin toxicity associated with radiation therapy in patients with breast cancer (89727). The creams were applied topically two to three times daily at least 3 hours before and after radiation treatment from 15 days prior to radiation until one month after completion.

Raynaud's syndrome. Some research suggests that taking a standardized ginkgo extract (Seredrin, Health Perception Ltd.) 120 mg orally three times daily for 10 weeks can decrease the number of painful attacks per week in patients with Raynaud's syndrome (11363). However, other research suggests that ginkgo extract is no different than placebo in decreasing the number of attacks in these patients (87888). Also, another study shows that taking ginkgo extract 120 mg daily is less effective than nifedipine SR 30 mg/day orally in decreasing Raynaud's syndrome flares (87818).

Sexual dysfunction. Some clinical research shows that taking a ginkgo leaf extract 300 mg daily for 8 weeks does not significantly improve sexual function in women with sexual arousal disorder (16640). However, other preliminary clinical research shows that taking a specific combination product (ArginMax for Women, Daily Wellness Company) containing ginkgo leaf extract, Panax ginseng root extract, damiana leaf extract, L-arginine, multivitamins, and minerals for 4 weeks can improve sexual satisfaction compared to placebo in women who are self-reported to have sexual dysfunction (46933).

Stroke. There is contradictory evidence about the effectiveness of ginkgo extract for improving recovery in patients with acute ischemic stroke. Some evidence from poor quality research suggests that more patients have neurological improvement when treated with ginkgo. However, a higher quality trial found no neurological improvement in patients treated with ginkgo compared to placebo (14435).

Vitiligo. Preliminary clinical research suggests that taking a specific ginkgo extract (Ginkgo Plus, Seroyal) 120 mg daily reduces the progression of vitiligo vulgaris and size of the lesions compared to baseline (17718, 87728).

More evidence is needed to rate ginkgo for these uses.

Dosing & Administration

- Adult

  Oral:

  Age-related macular degeneration: A standardized ginkgo leaf extract called EGb 761, 60-240 mg orally in two or three divided doses daily for 6 months, has been used (6227, 11797). This extract is standardized to contain 5% to 7% terpene lactones and 22% to 27% ginkgo flavone glycosides. It is an ingredient of several commercial products, including Tanakan (Ipsen) and Tebonin forte (Schwabe).

  Altitude sickness: A standardized ginkgo leaf extract called EGb 761, 160 mg in two divided doses daily has been used (6230). A different standardized ginkgo extract, 120 mg twice daily for 3-4 days prior to climbing and continuing for 1-2 days until reaching target altitude, has been used (87827).

  Anxiety: A standardized ginkgo extract called EGb 761, 80 or 160 mg three times daily for 4 weeks, has been used (15578).

  Cognitive function: Single doses of ginkgo extract 240-600 mg have been used (6215, 8236). A standardized ginkgo extract called EGb 761, 120-240 mg taken once daily or in two or three divided doses daily for 4 weeks to 4 months, has been used (8585, 8588, 87879). Another specific ginkgo extract called LI 1370 (Lichtwer Pharma), 120-300 mg daily in three divided doses for 2 days has been used (6214). A specific combination product (Ginkoba M/E, Pharmaton SA) containing ginkgo extract (GK501, Pharmaton SA) 100-600 mg and Panax ginseng (G115, Pharmaton SA) 60-360 mg, taken as a single dose or once daily for 12 weeks, has been used (8591, 9759). Also, two capsules of a product containing ginkgo extract 40 mg/capsule and Codonopsis 75 mg/capsule, have been used daily (87758).

  Dementia: A standardized ginkgo extract called EGb 761 120-240 mg, taken once daily or in two or three divided doses daily for up to 7.3 years, has been used (1514, 2665, 2666, 5720, 6225, 6490, 14499, 16637, 17191, 17717)(87726, 87794, 87823, 87826, 87848, 87897, 87902, 89710). A similar standardized ginkgo extract called LI 1370 (Lichtwer Pharma) has also been used.

  Diabetic retinopathy: A standardized ginkgo leaf extract called EGb 761 120 mg daily for 6 months has been used (6175).

  Fibromyalgia: Ginkgo extract (Bio-Biloba, Pharma Nord) 200 mg daily in conjunction with coenzyme Q10 (Bio Quinone Q10, Pharma Nord) 200 mg daily for 84 days has been used (17716).

  Gastric cancer: Carbohydrates from the outer layer of ginkgo fruit 250 mg twice daily for 30 days has been used

(87742).

Glaucoma: Ginkgo leaf extract 120-160 mg, taken in two or three divided doses daily for up to 12.3 years, has been used (10378, 87900).

Hearing loss: Ginkgo leaf extract 120 mg twice daily for 8 weeks has been used (8543).

Migraine headache: A specific product (Migrasoll, Pharmaval Srl, Italy) containing ginkgolide B 60 mg, coenzyme Q10 11 mg, and vitamin B2 8.7 mg, twice daily for 4 months, has been used (44103).

Peripheral vascular disease (PVD): A standardized ginkgo extract called EGb 761 120-240 mg, taken once daily or in two divided doses daily for up to 6.1 years, has been used (3461, 6212, 6213, 17402).

Premenstrual syndrome (PMS): A specific ginkgo leaf extract (Ginko T.D., Tolidaru Pharmaceuticals), 40 mg three times daily beginning on the 16th day of a menstrual cycle and continuing until the 5th day of the next cycle, has been used (87839). Another standardized ginkgo extract called EGb 761, 80 mg twice daily beginning on the 16th day of a menstrual cycle and continuing until the 5th day of the next cycle for two cycles, has been used (6229).

Quality of life: A standardized ginkgo extract called LI 1370, 120 mg daily for 4-10 months, has been used (87715, 87760).

Radiation exposure: A standardized gingko extract called EGb 761 (Tanakan, Ipsen) 120 mg daily for 2 months has been used (17719).

Raynaud's syndrome: A standardized ginkgo extract (Seredrin, Health Perception Ltd.) 120 mg three times daily for 10 weeks has been used (11363).

Schizophrenia: A standardized ginkgo leaf extract called EGb 761 (Yi Kang Ning, Yang Zi Jiang Pharmaceuticals Ltd., Jiangsu, China), 120-360 mg daily for 8-16 weeks, has been used (87708, 87844).

Sexual dysfunction: A specific combination product (ArginMax for Women, The Daily Wellness Company) containing ginkgo leaf extract, Panax ginseng root extract, damiana leaf extract, L-arginine, multivitamins, and minerals, taken daily for 4 weeks, has been used (46933).

Tardive dyskinesia: A standardized ginkgo leaf extract called EGb 761, 80 mg three times daily for 12 weeks, has been used (87864).

Vertigo: A standardized ginkgo leaf extract called EGb 761, 160 mg taken once daily or in two divided doses daily for 3 months, has been used (6220, 6221).

Vitiligo: A standardized ginkgo extract (Ginkgo Plus, Seroyal) 120 mg in two divided doses daily for up to 6 months has been used (17718, 87728).

Intravenous/Intramuscular:

Colorectal cancer: A standardized ginkgo extract called EGb 761 ONC, 350 mg administered intravenously over 30 minutes on days 1-6 of every 3-week cycle in combination with 5-fluorouracil 500 mg/m2 administered intravenously 30 minutes daily on days 2-6 of every 3-week cycle for 4 courses of treatment, has been used (9872).

Pancreatic cancer: A standardized ginkgo extract called EGb 761 ONC, 350 mg administered intravenously over 30 minutes on days 1-6 of every 3-week cycle in combination with 5-fluorouracil 500 mg/m2 administered intravenously 30 minutes daily on days 2-6 of every 3-week cycle until disease progression, has been used (87699).

Topical:

Allergic rhinitis (hayfever) : Two drops of a specific eye drop product (Trium, SOOFT, Italy) containing a combination of ginkgo extract 0.05% and hyaluronic acid 0.15%, applied to each eye three times daily for one month, has been used (87829).

Radiation-induced skin toxicity: A specific cream product (Radioskin 2), which contains ginkgo extract, Aloe vera, and metal esculetina, along with another specific cream product (Radioskin 1), which contains alga atlantica and ethylbisiminomethylguaicolo manganese cloruro, applied two to three times daily at least 3 hours before and after radiation treatment, beginning 15 days prior to radiation and continuing until one month after completion, has been used (89727).

- Children

Oral:

Attention deficit- hyperactivity disorder (ADHD): A specific combination product (AD-fX, Afexa Life Sciences, Canada) containing American ginseng extract 200 mg plus ginkgo extract 50 mg twice daily for 4 weeks has been used in children ages 3 to 17 years (8235).

Dyslexia: A standardized ginkgo leaf extract called EGb 761 80 mg daily for an average of 34 days, has been used in

children aged 5-16 years (87790).

Migraine headache: Combination formulations containing ginkgolide B (BN52021), a constituent of ginkgo extract, along with coenzyme Q10, riboflavin, and magnesium, administered twice daily for 3 months, have been used in school-aged children (44181, 87876).

- Standardization & Formulation

In general, ginkgo extracts are standardized to flavone glycoside and terpene lactone content. One standardized ginkgo extract called EGb 761, which has been used in a number of clinical trials, is standardized to contain 22% to 27% flavone glycosides and 5% to 7% terpene lactones, which include 2.8% to 3.4% ginkgolides A, B, and C and 2.6% to 3.2% bilobalide (6175, 6224, 15578, 16638, 16640, 17402, 87794, 87823, 87826, 87848)(87855, 87879, 87897, 87901, 87904, 88006, 89705). Another standardized ginkgo extract called LI 1370 has been standardized to contain 25% flavone glycosides, 3% ginkgolides, and 5% bilobalide (221). Some ginkgo leaf extract products, including Ginko T.D. (Tolidaru Pharmaceuticals) and GK501 (Pharmaton), are standardized to contain 24% flavonoid glycoside and 6% terpene lactone (10378, 11766, 87839).

A specific combination product (Memo, Pharco Pharmaceuticals) containing natural lyophilized royal jelly 750 mg, standardized ginkgo leaf extract 120 mg (containing 24% flavonoid glycosides and 6% terpenoids), and standardized Panax ginseng root extract 150 mg (containing 40% to 80% ginsenosides) has been used in clinical research (89712).

Some crude extracts from ginkgo leaves contain the constituent ginkgolic acid. This constituent can have strong allergenic properties and might have possible mutagenic and carcinogenic properties. Standardized ginkgo leaf extracts such as EGb 761 contain no greater than 5 ppm in concentration of ginkgolic acids (5714, 8584). In isolated cases, ginkgo has been contaminated with colchicine (8541). However, follow-up studies have indicated that this contamination is not widespread (8542).

Adverse Effects

Report an Adverse Reaction to Ginkgo

General: Orally, ginkgo leaf extract is well tolerated in typical doses (11981). It can cause mild gastrointestinal (GI) upset, headache, dizziness, palpitations, constipation, and allergic skin reactions (5719, 5721, 6220). Large doses can cause restlessness, diarrhea, nausea, vomiting, lack of muscle tone, and weakness. Spontaneous bleeding is one of the most concerning potential side effects associated with ginkgo (13135), although several large-scale clinical trials and a meta-analysis show that the incidence of bleeding in patients taking ginkgo is not significantly higher than in those taking placebo (16634, 16635, 17179, 17402).

Topically, ginkgo fruit and pulp can cause severe allergic skin reactions and irritation of mucous membranes and the gastrointestinal tract. Cross-reactivity is possible with ginkgo fruit in individuals allergic to poison ivy, poison oak, poison sumac, mango rind, and cashew shell oil (380).

Tell patients to avoid crude ginkgo plant parts; which can exceed concentrations of 5 ppm of the toxic ginkgolic acid constituents, and can cause severe allergic reactions (5714).

Cardiovascular

Frequent nocturnal episodes of paroxysmal atrial fibrillation have been reported for a 35 year-old women taking ginkgo extract 240 mg/day orally for 2 months. Following discontinuation of ginkgo, arrhythmias ceased (87884). In one clinical trial, the rate of ischemic stroke and transient ischemic attacks was significantly higher in patients taking ginkgo extract orally compared to placebo (16635).

Dermatologic

Orally, ginkgo leaf extract can cause allergic skin reactions in some patients (14449, 15578). In one case, a patient developed acute generalized exanthematous pustulosis 48 hours after taking a single-ingredient gingko product. The rash resolved within 10 days after discontinuing ginkgo (14449). There is also a case of Stevens-Johnson syndrome following a second administration of a preparation containing ginkgo leaf extract, choline, vitamin B6, and vitamin B12 (208).

Topically, ginkgo fruit and pulp can cause severe allergic skin reactions and irritation of mucous membranes. Cross-reactivity is possible with ginkgo fruit in individuals allergic to poison ivy, poison oak, poison sumac, mango rind, and cashew shell oil (380).

Gastrointestinal

Orally, ginkgo extract may cause mild gastrointestinal discomfort or pain (3965, 8543, 17112, 87818, 87858), nausea and vomiting (8543, 17112, 87728, 87844, 87858), diarrhea (87844), dry mouth (17112), and constipation (5719, 87787). However, post-market surveillance suggests that the incidence of these events is relatively low, occurring in <2% of patients (88007).

Orally, fresh ginkgo seeds can cause stomachache, nausea, vomiting, or diarrhea. Ingesting roasted seeds in amounts larger than the normal food amounts of 8-10 seeds per day, or long-term, can also cause these same adverse reactions (8231, 8232).

Genitourinary

Blood in the urine has been reported for one patient taking ginkgo extract orally (87858).

Hematologic

Spontaneous bleeding is one of the most concerning potential side effects associated with ginkgo. There are several published case reports linking ginkgo to episodes of minor to severe bleeding; however, not all case reports clearly establish ginkgo as the cause of bleeding. In most cases, other bleeding risk factors were also present including taking other medications, old age, liver cirrhosis, recent surgery, and other conditions. In most cases, bleeding occurred after several weeks or months of taking ginkgo (13135). Large-scale clinical trials and a meta-analysis evaluating standardized ginkgo leaf extracts show that the incidence of bleeding in patients taking ginkgo is not significantly higher than in those taking placebo (16634, 16635, 17179, 17402).

There are several case reports of intracerebral bleeding. Some of these cases resulted in permanent neurological damage and one case resulted in death (244, 578, 8581, 13135, 13179, 14456, 87868, 87977).

There are at least 4 cases of ocular bleeding including spontaneous hyphema (bleeding from the iris into the anterior part of the eye) and retrobulbar hemorrhage associated with ginkgo use (579, 10450, 13135).

There are also cases of surgical and post-surgical complications in patients using ginkgo. Retrobulbar hemorrhage (bleeding behind the eye) during cataract surgery has been associated with ginkgo use (10450). Excessive postoperative bleeding requiring transfusion has also occurred following laparoscopic surgery in a patient who had been taking ginkgo leaf extract (887). There have also been two cases of excessive bleeding during surgery and post-surgical hematoma in patients undergoing rhytidoplasty and blepharoplasty (13002). In another case, an elderly woman taking ginkgo experienced excessive postoperative bleeding following total hip arthroplasty (13194). In another case, use of ginkgo following liver transplantation surgery was associated with subphrenic hematoma requiring evacuation by laparotomy. The patient also subsequently experienced vitreous hemorrhage (14315). In another case, an elderly woman who had taken ginkgo chronically experienced excessive post-operative bleeding following an ambulatory surgical procedure (14453).

In another case, an elderly man experienced nose bleeds and ecchymosis following use of ginkgo. These instances of bleeding stopped when ginkgo was discontinued, and recurred when the patient started taking ginkgo again (13135).

Persistent bleeding has also occurred following dental surgery (87862) and laparoscopic cholecystectomy (88000). Nosebleed has also been reported as an adverse effect in a clinical trial (87813).

Musculoskeletal

Edema has been reported for three patients treated with ginkgo extract 40 mg orally three times daily (87818).

Neurologic/CNS

Orally, ginkgo extract may cause headache (6220, 8543, 87818), dizziness (5719, 87818), increased desire to sleep (87839), and sedation (10893) in some patients.

Orally, fresh or roasted ginkgo seeds in amounts larger than the normal food amounts of 8-10 seeds per day, or long-term, can cause restlessness, seizure, loss of consciousness, or shock (8231, 8232, 12183). The fresh seeds contain large amounts of ginkgotoxin, which can cause seizures and death. Ginkgo leaf and ginkgo leaf extract contain small amounts of ginkgotoxin, which is unlikely to cause these more serious effects (11296). However, there are anecdotal reports of seizure occurring after use of ginkgo leaf preparations both in patients without a history seizure disorder and in those with previously well-controlled epilepsy (7030, 7090, 14281).

Ocular/Otic

Orally, ginkgo extract may cause tinnitus is some patients, although the incidence is rare (8543).

Topically, eye drops containing ginkgo extract and hyaluronic acid may cause stinging sensations in some people (87829).

Toxicology

There is some concern about toxic and carcinogenic effects seen in rats and mice exposed to a ginkgo leaf extract containing 31.2% flavonoids, 15.4% terpenoids, and 10.45 ppm ginkgolic acid, in doses of 100 to 2000 mg/kg five times per week for 2 years. There were dose-dependent increases in rates of liver problems including cancer, hypertrophy, hyperplasia, hepatocyte fatty changes, and bile duct hyperplasia. There were also dose-dependent increases in thyroid problems such as cancer and hypertrophy, nasal hyperplasia and epithelial atrophy, and gastric problems including inflammation, hyperplasia, hyperkeratosis, and ulcers. However, the doses studied are much higher than those typically used by humans, since a single dose of 50 mg/kg in rats is estimated to be equivalent to a single dose of about 240 mg in humans (18272). Therefore, the clinical relevance for these adverse effects in humans is unclear.

Interactions with Drugs

ALPRAZOLAM (Xanax)

Interaction Rating = Moderate Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = B

Ginkgo might decrease the effectiveness of alprazolam in some patients. Ginkgo extract 120 mg twice daily (Ginkgold), seems to decrease alprazolam levels by about 17%. However, ginkgo does not appear to decrease the elimination half-life of alprazolam. This suggests that ginkgo is more likely to decrease absorption of alprazolam rather than induce hepatic metabolism of alprazolam (11029).

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = A

Several pharmacodynamic studies suggest that ginkgo inhibits platelet aggregation. It is thought that the ginkgo constituent, ginkgolide B, displaces platelet-activating factor (PAF) from its binding sites, decreasing blood coagulation (6048, 9760). Several case reports have also documented serious bleeding events in patients taking ginkgo (244, 578, 579, 8581, 13002, 13135, 13179, 13194, 14456, 87868). However, some evidence suggests that short-term use of ginkgo leaf might not significantly reduce platelet aggregation and blood clotting (87732). One study shows that healthy men who took a specific ginkgo leaf extract (EGb 761) 160 mg twice daily for 7 days did not have reduced prothrombin time (12114). Also, a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80-480 mg daily for up to 32 weeks, did not find a significant effect on platelet aggregation, fibrinogen concentration, or PT/aPTT (17179). In addition, a single dose of ginkgo plus clopidogrel (Plavix) does not seem to significantly increase bleeding time (14811). Similarly, a single dose of ginkgo extract 80 mg plus ticlopidine (Ticlid) 250 mg does not seem to significantly affect bleeding time, platelet aggregation, or pharmacokinetics of ticlopidine (17111, 87846). It has been suggested that ginkgo has to be taken for at least 2-3 weeks to have a significant effect on platelet aggregation (14811). Until more is known, use higher doses of ginkgo cautiously patients who are taking antiplatelet or anticoagulant drugs.

Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.

ANTICONVULSANTS

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = D

Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves (8232). Ginkgo leaf extract contains trace amounts of ginkgotoxin. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems unlikely to cause toxicity (11296). However, there are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history of seizure disorder and in those with previously well-controlled epilepsy (7030, 7090). Theoretically, taking ginkgo might reduce the effectiveness of anticonvulsants for preventing seizure. Some anti-epileptic drugs include phenobarbital, primidone (Mysoline), valproic acid (Depakene), gabapentin (Neurontin), carbamazepine (Tegretol), phenytoin (Dilantin), and others.

ANTIDEPRESSANT DRUGS

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = D

In vitro and ex vivo evidence suggests that ginkgo may increase synaptosomal reuptake of serotonin (24638). Theoretically, taking serotonergic antidepressants with ginkgo might decrease their efficacy. These drugs include the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and others; and tricyclic and atypical antidepressants such as amitriptyline (Elavil), clomipramine (Anafranil), imipramine (Tofranil), and others.

ANTIDIABETES DRUGS

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = B

Ginkgo leaf extract seems to alter insulin secretion and metabolism, and might affect blood glucose levels in people with type 2 diabetes (5719, 14448). The effect of ginkgo seems to differ depending on the insulin and treatment status of the patient. In diet-controlled diabetes patients with hyperinsulinemia, taking ginkgo does not seem to significantly affect insulin or blood glucose levels. In patients with hyperinsulinemia who are treated with oral hypoglycemic agents, taking ginkgo seems to decrease insulin levels and increase blood glucose following an oral glucose tolerance test. Researchers speculate that this could be due to ginkgo-enhanced hepatic metabolism of insulin. In patients with pancreatic exhaustion, taking ginkgo seems to stimulate pancreatic beta-cells resulting in increased insulin and C-peptide levels, but no significant change in blood glucose levels in response to an oral glucose tolerance test (14448). Theoretically, taking ginkgo might alter the response to antidiabetes drugs. Advise patients with type 2 diabetes to use ginkgo cautiously. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

ATORVASTATIN (Lipitor)

Interaction Rating = Moderate Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = B

In humans, intake of ginkgo extract appears to increase atorvastatin clearance, reducing the area under the curve of atorvastatin by 10% to 14% and the maximum concentration by 29%. However, this interaction does not appear to affects cholesterol synthesis and absorption (89706). Until more is known, advise patients to use ginkgo cautiously if they take atorvastatin.

BUSPIRONE (BuSpar)

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Unlikely • Level of Evidence = D

Ginkgo in combination with fluoxetine (Prozac), St. John's wort, melatonin, and buspirone (BuSpar) might cause hypomania in patients with depression (8582). Whether ginkgo alone or in combination with buspirone can cause hypomania is unknown.

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = B

There is preliminary evidence that ginkgo leaf extract can mildly inhibit cytochrome P450 1A2 (CYP1A2) enzymes (1303, 6423, 6450). However, clinical research suggests ginkgo might not affect CYP1A2 (10847). Until more is known, use ginkgo cautiously in patients taking drugs metabolized by these enzymes. Some drugs metabolized by CYP1A2 include acetaminophen (Tylenol), amitriptyline (Elavil), clopidogrel (Plavix), clozapine (Clozaril), diazepam (Valium), estradiol, olanzapine (Zyprexa), ondansetron (Zofran), propranolol (Inderal), ropinirole (Requip), tacrine (Cognex), theophylline, verapamil (Calan, Covera-HS, Isoptin, Verelan), warfarin (Coumadin), and others.

CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = B

There is some evidence that a specific ginkgo leaf extract (Remembrance, Herbs Product LTD, Hong Kong) 140 mg twice daily can induce CYP2C19 enzymes and potentially decrease levels of drugs metabolized by these enzymes (13108). However, other clinical research shows that taking ginkgo biloba 120 mg twice daily for 12 days has no effect on levels of drugs metabolized by CYP2C19 (87824). Until more is known, advise patients to use ginkgo cautiously if they take any CYP2C19 substrate. Some drugs metabolized by CYP2C19 include amitriptyline (Elavil), carisoprodol (Soma), citalopram (Celexa), diazepam (Valium), lansoprazole (Prevacid), omeprazole (Prilosec), phenytoin (Dilantin), voriconazole, warfarin, and many others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = D

There is preliminary evidence that a specific standardized extract of ginkgo leaf (EGb 761) can significantly inhibit CYP2C9 in vitro (11026, 12061, 14337). The terpenoid (ginkgolides) and flavonoid (quercetin, kaempferol, etc.) constituents seem to be responsible for the enzyme inhibition. Most ginkgo extracts contain some amount of these constituents. Therefore, other ginkgo leaf extracts might also inhibit the CYP2C9 enzyme in vitro. However, clinical research suggests that ginkgo might not have a significant effect on CYP2C9 in humans. Ginkgo does not seem to significantly affect the pharmacokinetics of CYP2C9 substrates diclofenac or tolbutamide. Until more is known, advise patients to use ginkgo cautiously if they take any CYP2C9 substrate. Some of these drugs include include amitriptyline (Elavil), diazepam (Valium), zileuton (Zyflo), celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), warfarin (Coumadin), and others.warfarin (Coumadin), glyburide, glipizide, amitriptyline valdecoxib (Bextra), phenytoin (Dilantin), and many others.

CYTOCHROME P450 2D6 (CYP2D6) SUBSTRATES

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = B

There is preliminary evidence that ginkgo leaf extract can modestly inhibit CYP2D6 enzymes by about 9% (1303, 6423, 6450). This might not result in clinical significant changes in levels of drug metabolized by CYP2D6 (11029). Preliminary clinical research also suggests that ginkgo does not significantly affect levels of donepezil, a CYP2D6 substrate (11027). Other clinical research also suggests ginkgo does not inhibit CYP2D6 (10847). Until more is known, use ginkgo cautiously in patients taking CYP2D6 substrates. Some drugs metabolized by CYP2D6 include amitriptyline (Elavil), clozapine (Clozaril), codeine, desipramine (Norpramin), donepezil (Aricept), fentanyl (Duragesic), flecainide (Tambocor), fluoxetine (Prozac), meperidine (Demerol), methadone (Dolophine), metoprolol (Lopressor, Toprol XL), olanzapine (Zyprexa), ondansetron (Zofran), tramadol (Ultram), trazodone (Desyrel), and others.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = B

There is conflicting evidence about whether ginkgo induces or inhibits CYP3A4 (1303, 6423, 6450, 11026, 87800, 87805). Ginkgo does not appear to affect hepatic CYP3A4 (11029). However, it is not known if ginkgo affects intestinal CYP3A4. Preliminary clinical research suggests that taking ginkgo does not significantly affect levels of donepezil, a CYP3A4 substrate (11027). Other clinical research also suggests ginkgo might not significantly inhibit CYP3A4 (10847). Until more is known, use ginkgo cautiously in patients taking drugs metabolized by CYP3A4. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), diltiazem (Cardizem), estrogens, indinavir (Crixivan), triazolam (Halcion), and others.

EFAVIRENZ (Sustiva)

Interaction Rating = Major Do not take this combination.
Severity = High • Occurrence = Probable • Level of Evidence = D

There are two case reports of decreased efavirenz concentrations and increased viral load in patients taking ginkgo. An HIV-positive male experienced over a 50% decrease in efavirenz levels over the course of 14 months while taking ginkgo extract. HIV-1 RNA copies also increased substantially, from less than 50, to more than 1500. It is suspected that terpenoids from the

ginkgo extract reduced drug levels by inducing cytochrome P450 3A4 (CYP3A4) or p-glycoprotein (16821). Another patient stable on antiviral therapy including efavirenz for 10 years, had an increase in viral load from <50 copies/mL to 1350 copies/mL after 2 months of taking a combination of supplements including ginkgo. After stopping ginkgo, the viral load was again controlled with the same antiviral therapy regimen (25464). Advise patients to avoid taking ginkgo with efavirenz.

FLUOXETINE (Prozac)

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Unlikely • Level of Evidence = D

Ginkgo in combination with buspirone (BuSpar), St. John's wort, melatonin, and fluoxetine might cause hypomania in patients with depression (8582). Whether ginkgo alone or in combination with fluoxetine can cause hypomania is unknown.

HYDROCHLOROTHIAZIDE

Interaction Rating = Minor Be watchful with this combination.
Severity = Mild • Occurrence = Unlikely • Level of Evidence = D

There is a single case report of a patient experiencing hypertension after taking ginkgo along with hydrochlorothiazide (14806). Monitor patient using this combination for potential hypertensive exacerbations.

IBUPROFEN

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = D

Ginkgo might have antiplatelet effects and has been associated with several case reports of spontaneous bleeding. Theoretically, combining ginkgo with ibuprofen might have additive antiplatelet effects and increase the risk of bleeding. In one case, a 71-year-old man had taken a specific ginkgo extract (Gingium, Biocur, Germany) 40 mg twice daily for 2.5 years. About 4 weeks after starting ibuprofen 600 mg daily he experienced a fatal intracerebral hemorrhage (13179). However, the antiplatelet effects of ginkgo have been questioned. A meta-analysis and other studies have not found a significant antiplatelet effect with standardized ginkgo extracts, 80 mg to 480 mg taken daily for up to 32 weeks (17179).

NIFEDIPINE

Interaction Rating = Minor Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = B

Animal research and some clinical evidence suggests that taking ginkgo leaf extract orally in combination with oral nifedipine might increase nifedipine levels and cause increased side effects, such as headaches, dizziness, and hot flushes (87764, 87765). However, taking ginkgo orally does not seem to affect the pharmacokinetics of intravenously administered nifedipine (87765).

OMEPRAZOLE (Prilosec)

Interaction Rating = Minor Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = B

A specific ginkgo leaf extract (Remembrance, Herbs Product LTD, Hong Kong) 140 mg twice daily can induce CYP2C19 enzymes and decrease levels of omeprazole by about 27% to 42% (13108).

RISPERIDONE (Risperdal)

Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = D

A single case of priapism has bene reported for a 26 year-old schizophrenic man who used risperidone 3 mg/day along with ginkgo extract 160 mg/day (87796). Risperidone is metabolized by cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A4 (CYP3A4). These enzymes are inhibited by ginkgo. Theoretically, ginkgo may inhibit the metabolism of risperidone and increase the risk of adverse effects.

SEIZURE THRESHOLD LOWERING DRUGS

Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = D

Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves (8232). Ginkgo leaf extract contains trace amounts of ginkgotoxin. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems unlikely to cause toxicity (11296). However, there are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history of seizure disorder and in those with previously well-controlled epilepsy (7030, 7090, 14281). Advise patients taking these drugs to avoid ginkgo leaf products. Some drugs that lower the seizure threshold include anesthetics (propofol, others), antiarrhythmics (mexiletine), antibiotics (amphotericin, penicillin, cephalosporins, imipenem), antidepressants (bupropion, others), antihistamines (cyproheptadine, others), immunosuppressants (cyclosporine), narcotics (fentanyl, others), stimulants (methylphenidate), theophylline, and others.

SIMVASTATIN (Zocor)

Interaction Rating = Moderate Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = B

Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves (8232). Ginkgo leaf extract contains trace amounts of ginkgotoxin. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems

unlikely to cause toxicity (11296). However, there are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history of seizure disorder and in those with previously well-controlled epilepsy (7030, 7090, 14281). Advise patients taking these drugs to avoid ginkgo leaf products. Some drugs that lower the seizure threshold include anesthetics (propofol, others), antiarrhythmics (mexiletine), antibiotics (amphotericin, penicillin, cephalosporins, imipenem), antidepressants (bupropion, others), antihistamines (cyproheptadine, others), immunosuppressants (cyclosporine), narcotics (fentanyl, others), stimulants (methylphenidate), theophylline, and others.

TALINOLOL
Interaction Rating = Major Do not take this combination.
Severity = High • Occurrence = Probable • Level of Evidence = B

There is some evidence that using ginkgo leaf extract 120 mg orally three times daily for 14 days can increase levels of talinolol by 36% in healthy male individuals. However, single doses of ginkgo do not seem to affect talinolol pharmacokinetics (87830).

TRAZODONE (Desyrel)
Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = D

Use of ginkgo leaf extract with trazodone has been associated with coma. In one case, an Alzheimer's patient taking trazodone 20 mg twice daily and ginkgo leaf extract 80 mg twice daily for four doses became comatose. The coma was reversed by administration of flumazenil (Romazicon). Coma might have been induced by excessive GABA-ergic activity. Ginkgo flavonoids are thought to have GABA-ergic activity and act directly on benzodiazepine receptors. Ginkgo might also increase metabolism of trazodone to active GABA-ergic metabolites, possibly by inducing cytochrome P450 3A4 (CYP3A4) metabolism (6423).

WARFARIN (Coumadin)
Interaction Rating = Moderate Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = D

Ginkgo leaf might increase the anticoagulant effects of warfarin and risk of bleeding (576). Ginkgo is thought to have antiplatelet effects and might have additive effects when used with warfarin. There is also some evidence that ginkgo leaf extract can inhibit cytochrome P450 2C9, an enzyme that metabolizes warfarin. This could result in increased warfarin levels (12061). However, research in healthy people suggests that ginkgo has no effect on INR, or the pharmacokinetics or pharmacodynamics of warfarin (12881, 15176, 87727, 87889). Also, a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80 mg to 480 mg daily for up to 32 weeks, did not find a significant effect on platelet aggregation, fibrinogen concentration, or PT/aPTT (17179). There is also some preliminary clinical research that suggests ginkgo might not significantly increase the effects of warfarin in patients that have a stable INR (11905); however, these contradictory findings are in small-scale, short-term studies that may not have the power to detect a small or moderate effect on bleeding risk. Until more is known, monitor INRs closely in patients taking ginkgo.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Theoretically, concomitant use of ginkgo with other herbs and supplements that affect platelet aggregation could increase the risk of bleeding. However, the extent of ginkgo's antiplatelet effects is questionable. There is conflicting evidence about whether gingko inhibits platelet aggregation. Several pharmacodynamic studies suggest that ginkgo inhibits platelet aggregation. Several case reports have also documented serious bleeding events in patients taking ginkgo (244, 578, 579, 8581, 13002, 13135, 13179, 13194, 14456, 87868). However, clinical trials and a meta-analysis evaluating standardized ginkgo leaf extracts show that the incidence of bleeding in patients taking ginkgo is not significantly higher than in those taking placebo (16634, 16635, 17179, 17402). Until more is known, advise patients to use ginkgo cautiously if they take other herbs and supplements that affect platelet aggregation.

Some other herbs and supplements that affect platelet aggregation include angelica, clove, danshen, garlic, ginger, glucosamine, Panax ginseng, and others.

SEIZURE THRESHOLD LOWERING HERBS AND SUPPLEMENTS: Ginkgo seeds contain ginkgotoxin, which can cause seizures in high doses (11296). Theoretically, patients taking supplements that also lower the seizure threshold might be at greater risk. There are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history seizure disorder and in those with previously well-controlled epilepsy (7030, 7090). Advise patients taking these supplements to avoid ginkgo products. Some of these supplements include butanediol (BD), cedar leaf, Chinese club moss, EDTA, folic acid, gamma butyrolactone (GBL), gamma hydroxybutyrate (GHB), glutamine, huperzine A, hydrazine sulfate, hyssop oil, juniper, L-carnitine, melatonin, rosemary, sage, wormwood, and others.

ST. JOHN'S WORT: Ginkgo in combination with buspirone (BuSpar), fluoxetine (Prozac), melatonin, and St. John's wort might cause hypomania in patients with depression (8582). Whether ginkgo alone, or in combination with St. John's wort, can cause hypomania is unknown.

Interactions with Foods

None known.

Interactions with Lab Tests

None known.

Interactions with Diseases

BLEEDING DISORDERS: Ginkgo leaf might decrease platelet aggregation by inhibiting platelet-activating factor (PAF), and thereby exacerbate bleeding disorders (6048, 9760). However, a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80 mg to 480 mg daily for up to 32 weeks, did not find a significant effect on bleeding risk, as measured by platelet aggregation, fibrinogen concentration, or PT/aPTT (17179). Until more is known, use ginkgo with caution in people with bleeding disorders.

DIABETES: Ginkgo leaf extract seems to alter insulin secretion and metabolism, and might affect blood glucose levels in people with type 2 diabetes (5719, 14448). The effect of ginkgo seems to differ depending on the insulin and treatment status of the patient. In diet-controlled diabetes patients with hyperinsulinemia, taking ginkgo does not seem to significantly affect insulin or blood glucose levels. In patients with hyperinsulinemia who are treated with oral hypoglycemic agents, taking ginkgo seems to decrease insulin levels and increased blood glucose following an oral glucose tolerance test. Researchers speculate that this could be due to ginkgo-enhanced hepatic metabolism of insulin. In patients with pancreatic exhaustion, taking ginkgo seems to stimulate pancreatic beta-cells resulting in increased insulin and C-peptide levels, but no significant change in blood glucose levels in response to an oral glucose tolerance test (14448). Theoretically, ginkgo might interfere with the management of diabetes. Monitor blood glucose levels closely.

EPILEPSY: Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves (8232). Ginkgo leaf and ginkgo leaf extract contain trace amounts of ginkgotoxin, which can cause seizures in high doses. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems unlikely to cause toxicity (11296). However, there are several anecdotal reports of seizure occurring in patients taking combination products containing ginkgo and single ingredient ginkgo products. However, there is not yet enough evidence to prove that ginkgo can actually cause seizure in certain patients (7030). Until more is known, use cautiously or avoid in epileptic patients or patients prone to seizure.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY: A case of acute hemolytic anemia has been reported for a female patient with G6PD deficiency who received an injection of ginkgo extract 17.5 mg for dementia prophylaxis (89709). The patient recovered following intravenous fluid treatment and cessation of ginkgo. Until more is known, use cautiously or avoid in patients with G6PD deficiency.

INFERTILITY: Some evidence suggests that ginkgo extract might inhibit oocyte fertilization and should be avoided in couples attempting to conceive (4239, 4240). This effect has not yet been demonstrated in humans; however, until more is known, use with caution in couples attempting to conceive and avoid use in couples having difficulty conceiving.

SURGERY: Ginkgo leaf extract has antiplatelet effects and can cause excessive bleeding if used prior to surgery (887, 13002, 14453). Tell patients to discontinue ginkgo at least 2 weeks before elective surgical procedures.

Mechanism of Action

General: The applicable parts of ginkgo are the leaf and the seed. Ginkgo leaf is the most commonly used form of ginkgo, usually as an extract.

Ginkgo leaf and its extracts contain several active constituents including flavonoids, terpenoids, and organic acids (87722, 87735, 87771, 87785, 87955, 88053). Many ginkgo leaf extracts are standardized to contain about 24% to 25% flavonoid glycosides and 6% terpenoids. The major flavonoids are primarily derived from the flavonol rutin and include isorhamnetin, quercetin, kaempferol, and proanthocyanidins. The primary terpenoids are ginkgolides A, B, C, M, and J, and bilobalide (1515). Other constituents of ginkgo leaf extracts include biflavones, proanthocyanidins, alkylphenols, phenolic acids, and polyprenols (18272).

Although many of ginkgo's constituents have intrinsic pharmacological effects individually, there is evidence that the constituents work synergistically to produce more potent pharmacological effects than any individual constituent (1514, 6494).

Anticancer effects: Some clinical or epidemiological evidence suggests that ginkgo may be helpful in the prevention or treatment of colorectal cancer (9872), gastric cancer (87742), ovarian cancer (14813), and pancreatic cancer (87699). The exact anticarcinogenic mechanism of action of ginkgo extract is not clear. In humans, ginkgo extract appears to prevent the iodine-131-induced increase in lymphocyte micronuclei and clastogenic factors, which suggests that ginkgo extract may prevent genotoxic damage (87892). In vitro evidence suggests that ginkgo extract and the constituents quercetin and ginkgolides A and B inhibit ovarian cancer cell proliferation by blocking the G0/G1 to S phase of the cell cycle (14813). Additional in vitro research shows that ginkgolide B, a constituent of ginkgo extract, can up- and down-regulate various proteins involved in proliferation, tumor suppression, and DNA damage repair in breast cancer gene 1 (BRCA1)-mutant ovarian epithelial cells (87882). Other in vitro evidence suggests that exocarp polysaccharides from ginkgo extract can induce apoptosis and differentiation of gastric cancer cells, possibly by altering the expression of c-myc, bcl-2, and c-fos genes (87742).

Anticoagulant/antiplatelet effects: Ginkgolides in the leaf competitively inhibit platelet activating factor (PAF) binding at the membrane receptors of numerous cells (5719, 9760, 87871). PAF inhibition decreases platelet aggregation (5717). Also, preliminary research suggests that ginkgo leaf extract can inhibit formation of platelet thromboxane A2 and thromboxane B2, which reduces platelet aggregation (8583).

However, in humans, there is evidence that ginkgo leaf may not reduce platelet aggregation and blood clotting with short-term use. In one study, healthy men who took the specific ginkgo leaf extract (EGb 761) 160 mg twice daily for 7 days did not have reduced prothrombin times (12114). It has been suggested that ginkgo has to be taken for at least 2-3 weeks to have a significant effect on platelet aggregation (14811). However, a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80-480 mg daily for up to 32 weeks, did not find a significant effect on platelet aggregation, fibrinogen concentration, or PT/aPTT (17179).

Antidiabetic effects: Ginkgo might affect insulin secretion. In healthy volunteers, ginkgo leaf extract (EGb 761) seems to increase pancreatic beta-cell function in response to glucose loading and modestly reduce blood pressure. Some researchers speculate that ginkgo might decrease development of hyperinsulinemia associated with hypertension, which often precedes development of type 2 diabetes and atherosclerotic cardiovascular disease (5719).

In patients with type 2 diabetes, the effect of ginkgo on insulin appears to be dependent on the insulin-producing status of the patient. In diet-controlled diabetes patients with hyperinsulinemia, taking ginkgo does not seem to significantly affect insulin or blood glucose levels following an oral glucose tolerance test. In those patients with hyperinsulinemia who are treated with oral hypoglycemic agents, taking ginkgo seems to result in decreased insulin levels and increased blood glucose following an oral glucose tolerance test. Researchers speculate that this could be due to ginkgo-enhanced hepatic metabolism of insulin or of diabetes drugs (14448); however, ginkgo does not seem to significantly affect the pharmacokinetics of metformin (14454).

In patients with pancreatic exhaustion, taking ginkgo seems to stimulate pancreatic beta-cells resulting in increased insulin levels and increase C-peptide levels in response to an oral glucose tolerance test (14448).

Ginkgo does not appear to affect insulin resistance or glucose disposal in patients with or without type 2 diabetes (14350).

Anti-inflammatory effects: Central nervous system (CNS) disorders, such as dementia, and other conditions including peripheral arterial disease, hypersensitivity disorders, allergies, asthma, and bronchitis might benefit from ginkgo's anti-inflammatory effects. Preliminary clinical evidence shows that ginkgo extract 1 gram three times daily for 3 months reduces levels of interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha (TNF-alpha) in patients with pulmonary interstitial fibrosis, leading to improvements in symptoms and lung function (87772). In animals, the standardized ginkgo extract called EGb 761 has been showed to inhibit carrageenan-induced inflammation (87872).

Antimicrobial effects: Ginkgo leaf might have some antimicrobial activity, including activity against Pneumocystis carinii and possibly some gram-positive bacteria and yeast (6069).

Ginkgo seeds seem to have antibacterial and antifungal effects (11701, 11702).

Antioxidant effects: Although the mechanism of action of ginkgo leaf is only partially understood, there are several theories about how it might work for various disease states. Ginkgo leaf flavonoids have antioxidant and free radical scavenging properties (2660, 5715, 5717, 5719, 14455, 87871, 87945). In elderly patients, intake of ginkgo extract has been shown to increase levels of the radical scavenger glutathione in the liver of elderly patients and reduce platelet malondialdehyde levels in patients with type 2 diabetes (14455, 87890). The flavonoids seem to prevent or reduce cell membrane lipid peroxidation (1515, 14455), and decrease oxidative damage to erythrocytes (5717). Ginkgo's flavonoids also protect neurons and retinal tissue from oxidative stress (1515, 5719), and injury following ischemic episodes (1515, 2660, 87832, 87929, 87941, 87957, 87968). Ginkgo terpene lactones, such as ginkgolide B, Protecting neurons and other tissues from oxidative damage might prevent progression of tissue degeneration in patients with dementia and other conditions.

Cardiovascular effects: Ginkgolides in the leaf competitively inhibit platelet activating factor (PAF) binding at the membrane receptors of numerous cells (5719, 9760, 87871). PAF inhibition decreases platelet aggregation (5717), decreases phagocyte chemotaxis and smooth muscle contraction (1515), prevents degranulation of neutrophils, decreases free radical production (5716, 5717), decreases damaging glycine production after brain injury, and reduces excitatory amino acid receptor function (2660). Inhibition of PAF might increase cardiac contractility and coronary blood flow.

Ginkgo leaf products might benefit CNS and vascular conditions by improving circulation. Ginkgo leaf seems to improve blood flow to capillaries throughout the body including in the CNS, eyes, ears, extremities, and other tissues. Ginkgo leaf likely improves circulation by both decreasing blood viscosity and affecting vascular smooth muscle. Ginkgo leaf seems to restore the balance between prostacyclin and thromboxane A2, resulting in improved vasoregulation. Therefore, ginkgo leaf relaxes spasmodic contracting vasculature and contracts abnormally dilated vessels. It is not clear exactly how ginkgo causes vascular contraction and improves venous tone, but these effects might be due to phosphodiesterase inhibition, resulting in increased cAMP levels and release of catecholamines (6492). Some ginkgo constituents may also have a potent relaxing effect on vascular smooth muscle and improve blood flow to the corpus cavernosum; which is thought to be helpful for erectile dysfunction (213). Overall, ginkgo leaf seems to increase cerebral and peripheral blood flow microcirculation, and reduce vascular permeability (5721, 6492).

In addition to decreasing platelet aggregation and improving circulation, some evidence shows that ginkgo extract may also have cardioprotective effects. When administered to patients as part of the cardioplegia perfusion during cardiac surgery, ginkgo extract appears to induce the production of plasma vascular endothelial growth factor (VEGF) (87825). Also, evidence from animal research shows that ginkgo extract or its constituent ginkgolide B may attenuate ischemia- and reperfusion-induced arrhythmia and other injury (87833, 87894, 87914, 87917).

Drug metabolizing effects: Ginkgo appears to affect several cytochrome P450 enzymes in vitro and in animal models; however, in humans, ginkgo does not seem to significantly affect most of these enzymes (14452). There is preliminary evidence that ginkgo leaf extract is a weak inhibitor of cytochrome P450 1A2 (CYP1A2), decreasing activity by approximately 13% (1303); however, contradictory clinical research suggests that ginkgo leaf extract does not significantly affect the activity of CYP1A2 (10847).

The effects of ginkgo leaf extract on CYP3A4 are unclear. There is some in vitro evidence that ginkgo leaf extract might inhibit CYP3A4 (6450, 11026); however, in vivo, ginkgo leaf extract does not seem to inhibit CYP3A4 (1303, 10847, 11029). In addition, there is anecdotal evidence that suggests ginkgo leaf extract might actually induce CYP3A4 (6423, 16821), but this effect has not yet been verified.

The ginkgo leaf extract EGb 761 (Ginkgold, others), which is the most common extract used in clinical studies, seems to strongly inhibit CYP2C9 in vitro (11026, 12061, 14337).

Different constituents in ginkgo seem to have different effects on hepatic enzymes. The terpenoidic fraction (ginkgolides) seems to inhibit just CYP2C9 in vitro and possibly p-glycoprotein in vivo (16821). The flavonoidic fraction (quercetin, kaempferol, myricetin, etc.) seems to inhibit CYP2C9, CYP1A2, CYP3A4, and CYP2E1 in vitro (11026, 11028, 12061).

However, clinical research suggests that ginkgo leaf extract does not significantly affect the activity of CYP1A2, CYP2C9, or CYP2D6 (10847, 14337), while inhibition of CYP2C19 occurred in one study in humans (13108).

Ginkgo extract appears to mildly inhibit CYP2D6 enzymes, by about 9% (1303, 6423, 6450, 11026, 12061); however, this effect might be too small to be clinically significant (11029). Some clinical research suggests that ginkgo leaf extract does not significantly affect the activity CYP2D6 (10847). Additional clinical research suggests that taking ginkgo 90 mg/day for 30 days does not affect donepezil levels (11027). Donepezil is a substrate of both CYP2D6 and CYP3A4.

In vitro, ginkgo seems to inhibit organic anion transporting polypeptide (OATP) uptake of estrone-3-sulfate. But ginkgo might not cause clinically significant interactions through this mechanism. In healthy volunteers, ginkgo does not seem to significantly alter the pharmacokinetics of the OATP substrate ticlopidine (14451, 17111).

Lipid-lowering effects: In vitro evidence suggests that ginkgo extract decreases total cholesterol content, inhibits HMG-CoA reductase activity, and decreases cholesterol influx in cultured hepatocytes (87840). However, it is unclear if ginkgo extract has lipid-lowering effects in animals or humans.

Neurologic/CNS effects: Ginkgo leaf extract might be helpful for Alzheimer's disease due to effects on beta-amyloid proteins. There is preliminary evidence that ginkgo leaf extract can inhibit toxicity and cell death induced by beta-amyloid peptides (6494). However, this has not yet been demonstrated in vivo. Ginkgo might also influence certain neurotransmitter systems, such as the cholinergic system (6490), and seems to produce EEG changes similar to the acetylcholinesterase inhibitor tacrine (Cognex) (6067). There has been some speculation that ginkgo leaf inhibits monoamine oxidase A and B (5721), but so far studies have found conflicting results (6231, 6232, 6233). It is suggested that ginkgo leaf inhibits catechol-O-methyl transferase (COMT, an enzyme which breaks down adrenergic transmitters) and increases the number of alpha-adrenoreceptors in the brain; which would help reverse the decline in brain alpha-adrenoceptor activity that occurs with aging (2660).

There is some evidence that ginkgo flavonoids have GABA-ergic effects and might directly affect benzodiazepine receptors (6423). However, the clinical significance of this effect is not known.

Ginkgo leaf extract might have effects on neurotransmitters. Animal model studies have shown that ginkgo leaf extract significantly reduces uptake of dopamine and norepinephrine (17297, 17298). However, this effect is not seen after a single 100 mg/kg dose, but was found after 14 days of therapy (17298).

The ginkgolides A and B seem to decrease glucocorticoid biosynthesis, which might also play a role in ginkgo's proposed anti-stress and neuroprotective effects (5723, 5724, 8236). Some evidence shows that a specific ginkgo extract (EGb 761, Tanakan) reduces stress-induced rises in adrenocorticotrophic hormone (ACTH), cortisol, and blood pressure in animals and in healthy volunteers (15578).

Ginkgo extract may also protect against neurotoxicity induced by other drugs. Animal research shows that ginkgo extract protects retinal cells against glutamate-induced neurotoxicity (88051). Also, in vitro evidence suggests that standardized ginkgo extract called EGb 761 protects against neurodegeneration induced by verapamil or antimycin A1 plus 2-deoxy-D-glucose (87874, 87975).

Seizure threshold-lowering effects: Ginkgo seeds contain the neurotoxin ginkgotoxin (4'-O-methylpyridoxine), which can cause seizures, paralysis, and death when taken in high doses (8231, 8232, 12183). Ginkgotoxin antagonizes the activity of pyridoxine, possibly by inhibiting enzymes such as pyridoxal kinase or glutamate decarboxylase in the brain. Therefore, since GABA is synthesized from glutamate by glutamate decarboxylase, by inhibiting glutamate decarboxylase, ginkgotoxin indirectly inhibits GABA (13423). Boiling ginkgo seeds reduces the ginkgotoxin content to safe levels (11296).

Ginkgo leaves and ginkgo leaf extracts can also contain the ginkgotoxin; however, ginkgotoxin is present in much higher amounts in ginkgo seeds than leaves. It is unclear whether it is present in ginkgo leaf extracts in high enough concentrations to cause toxicity (11296). However, seizures have been reported in people taking ginkgo leaf preparations (6048, 7030, 7090, 9760, 14281).

Pharmacokinetics

Absorption: One pharmacokinetic study found that administration of various ginkgo extracts resulted in median maximum concentrations of bilobalide, ginkgolide A, and ginkgolide B of 3.53-26.85 ng/mL, 3.62-16.44 ng/mL, and 1.38-9.99 ng/mL, respectively (87849). Another pharmacokinetic study using the specific ginkgo leaf extract EGb 761 found that the bioavailability of ginkgolides A and B was greater than 80%, that of bilobalide was 70%, while that of ginkgolide C was very low (18272).

Elimination: In humans, the elimination rate constant for the ginkgo constituents quercetin and kaempferol are 0.37/hr and 0.30/hr, respectively. Quercetin and kaempferol were excreted in the urine mainly as glucuronides (87740). A pharmacokinetic study using the specific ginkgo leaf extract EGb 761 found that the half-lives of ginkgolides A and B and bilobalide were 4, 6, and 3 hours, respectively, and the amounts of each excreted unchanged in the urine were approximately 70%, 50%, and 30%, respectively (18272).

Evidence Table / Discussion

See detailed Evidence Summary

References

See Monograph References

This monograph was last reviewed on 3/20/2015 and last updated on 1/20/2016. Monographs are reviewed at least once per year. If you have comments or suggestions on something that should be reviewed or included, please tell the editors. For details about our evidence-based approach, see our Editorial Principles and Process.