Ginkgo

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Scientific Name

Ginkgo biloba.

Family: Ginkgoaceae.

Background

According to secondary sources, *Ginkgo biloba* has been used medicinally for thousands of years and is one of the top-selling herbs in the United States.

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

- According to secondary sources, *Ginkgo biloba* extract is obtained from the *Ginkgo* tree, which is believed to be the oldest living tree, dating back more than 200 million years. *Ginkgo* has been used for thousands of years in Asia, traditionally for respiratory complaints, memory loss, and circulatory problems, as well as for the culinary usage of the seed. *Ginkgo* was reportedly introduced by Chen Noung in the first pharmacopoeia, *Chen Noung Pen T'sao*.
- According to secondary sources, the *Ginkgo* tree is now cultivated in Europe, Japan, Southeast Asia, and the United States. In the United States, it has been planted along city streets since the 1700s. It is resilient against infection and pollution.
- According to secondary sources, many of *Ginkgo*'s current uses originate from research and clinical observations during the 1950s in Europe. In 1994, a standardized extract of *Ginkgo biloba* was approved by the health authorities in Germany for treatment of dementia. In 1998, *Ginkgo* accounted for $140 million in sales in the United States (88064). Today, use of *Ginkgo* is widespread in the Americas, Europe, and Asia.

People Use This For

Orally, ginkgo 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, and peripheral arterial disease (PAD). Ginkgo leaf is also used for cognitive problems related to Lyme disease, sexual dysfunction, and for sexual dysfunction 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); thrombosis; heart disease; arteriosclerosis; angina pectoris; hypercholesterolemia; cardiac reperfusion injury; 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, regulating bacterial flora, 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, 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 for scabies and skin sores.

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

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

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

Safety

LIKELY SAFE ...when used orally and appropriately. Standardized ginkgo leaf extracts have been used safely in trials lasting from several weeks to 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, 87752, 87864, 87888, 87897, 87901, 87904).

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 50mg/kg in rats is estimated to be equivalent to a single dose of about 240 mg in humans (18272).

...when used intravenously. Ginkgo leaf extract EGb 761 given intravenously seems to be safe for short-term use 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). A specific ginkgo dried extract (Ginko-TD, Tolidaru, Iran), 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 in one study lasting 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 (EGb 761, Tanakan, Ipsen) 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 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 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, a specific combination of ginkgo and Panax ginseng (Gincosan) does not seem to improve mood or cognition compared to placebo in postmenopausal women (87767). Also, taking a specific product containing ginkgo and brahmi (Blackmores Ginkgo Brahmi) for 4 weeks does not seem to 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 a 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). 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).

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 to conventional drugs such as the cholinesterase inhibitors. However, in preliminary comparative studies, a specific ginkgo leaf extract (EGb 761, Tanakan, Ipsen) 160-240 mg daily seems to be comparable to donepezil 5 mg daily for mild to moderate Alzheimer's dementia after 22-24 weeks of treatment (14499, 87826). However, indirect comparisons suggest that ginkgo might be less effective than the conventional drugs donepezil (Aricept), tacrine (Cognex), and other cholinesterase inhibitors (6224, 6490, 11981).

Ginkgo has also been evaluated for the prevention of dementia. 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). 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).

Most of the clinical studies on the effectiveness of ginkgo leaf for dementia have used the standardized extracts EGb 761 (Tanakan, 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. 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 (EGb 761) 120 mg daily orally for six months can significantly improve measures of color vision in patients with early diabetic retinopathy (6175).

Glaucoma. Taking ginkgo leaf extract 120-160 mg daily orally seems to improve pre-existing damage and reduce progression of damage to the visual field in patients with normal tension glaucoma (10378, 87900).

Peripheral vascular disease (PVD). Some evidence shows that taking a specific ginkgo extract (EGb 761, Tanakan, 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 (EGb 761) 300 mg daily does not significantly improve maximum treadmill walking time in patients with peripheral arterial disease compared to placebo (16638).

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).

Schizophrenia. A pooled analysis of 6 clinical trials shows that taking Ginkgo biloba 120-360 mg daily 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 Ginkgo biloba 360 mg daily plus haloperidol seems to reduce adverse behavioral and nerve symptoms associated with haloperidol treatment (87708).

Tardive dyskinesia. Clinical research shows that taking a specific ginkgo extract (EGb 761) 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 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. Although 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), 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) 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).

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

Asthma. Clinical research shows that a specific combination product containing Ginkgo biloba 270 mg, ginger, Picrorrhiza kurroa, and apocynin (AKL1) taken twice daily for 12 weeks does not improve respiratory symptoms or quality of life compared to placebo in patients with asthma (87786).

Cocaine dependence. Clinical research suggests that taking Ginkgo biloba (EGb 761) 120 mg daily for 10 weeks does not help maintain abstinence from cocaine use compared to placebo in cocaine-dependent patients (87723).

Hypertension. Clinical research shows that Ginkgo biloba extract (EGb 761, Schwabe Pharmaceuticals, Karsruhe, Germany) 240 mg taken daily for up to 6 years does not reduce blood pressure in hypertensive patients aged 75 years or older when compared to placebo (87853).

Multiple sclerosis. Some clinical evidence shows that taking Ginkgo biloba 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).

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, 87752, 87754, 87901).

LIKELY INEFFECTIVE

Cardiovascular disease. A large-scale randomized trial shows that taking a specific ginkgo extract (EGb 761, Tanakan, Ipsen) 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).

Altitude sickness. The effects of Ginkgo biloba 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 (GK 501, Pharmaton, Switzerland) 120 mg twice daily for 1-2 days before the climb from an altitude of 4280 meters to 4928 meters, shows that ginkgo 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.

Attention deficit-hyperactivity disorder (ADHD). There is preliminary evidence that 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). Another specific ginkgo extract (Ginko-TD, Tolidaru, Iran) has also been studied. A clinical trial shows that taking this extract 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 of at least 40% in a teacher/parent ADHD rating scale was seen in only 8% of children taking this ginkgo extract compared with 64% in children taking methylphenidate (17112).

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

Dyslexia. Preliminary clinical research suggests that taking a specific product product containing Ginkgo biloba (EGb 761) 80 mg daily for an average of 34 days can help reduce dyslexia in children (87790).

Fibromyalgia. Preliminary clinical research suggests that taking Ginkgo biloba tablets (Bio-Biloba, Pharma Nord) 200 mg/day in conjunction with coenzyme Q-10 capsules (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 (17716).

Gastric cancer. Preliminary evidence suggests that taking carbohydrates from the outer layer of Ginkgo biloba fruit 250 mg 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 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 biloba, 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 and women (44103, 44181, 87876).

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 (EGb 761, Tanakan, Ipsen) 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 Ginkgo biloba extract 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 specific ginkgo extract (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).

Raynaud's syndrome. Some research suggests that taking ginkgo leaf extract orally can decrease the number of painful attacks per week in patients with Raynaud's syndrome (11363). However, other research suggests that ginkgo is no different than placebo in decreasing the number of attacks in these patients (87888). Also, one study shows that Ginkgo biloba 120 mg daily is less effective than nifedipine SR 30 mg/day orally in decreasing Raynaud's syndrome flares (87818).

Seasonal allergic conjunctivitis. Preliminary evidence shows that adding Ginkgo biloba extract to hyaluronic acid eye drops 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).

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, some preliminary clinical research shows that a specific combination product containing ginkgo, ginseng, damiana, L-arginine, multivitamins, and minerals (ArginMax) 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 for improving recovery in patients with acute ischemic stroke. Some evidence from poor quality trials 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 (17718, 87728).

More evidence is needed to rate ginkgo for these uses.

Dosing & Administration

- **Adult**

  Oral:

  - **General**: Traditional recommendations include *Ginkgo* products containing 24% flavoglycosides (also called flavone glycosides or flavones) and 6% terpenes: 80-240mg of a 50:1 standardized leaf extract daily; or 3-6mL of a 40mg/mL liquid extract in 2-3 divided doses; or 30-40mg of extract in a tea bag, prepared as a tea, for at least 4-6 weeks. There is a lack of evidence in support of the clinical benefit of small concentrations of *Ginkgo* found in fortified foods.
  - **Note**: According to secondary sources, beneficial effects may take 4-6 weeks to appear. *Ginkgo* seeds are potentially toxic and should be avoided.
  - **Acute ischemic stroke**: 40mg of *Ginkgo* has been used four times daily for four weeks (87961).
  - **Age-associated memory impairment (AAMI)**: *Ginkgo* extract up to 240mg daily for 12 weeks has been studied, but significant effects were lacking (87726, 88012). No evidence of benefit was observed for 0.9-1.9mL of *Ginkgo* three times daily (88013). In other studies, positive effects of a single dose of EGb 761 320-600mg were noted (87782, 87953). 240mg of extract for 42 weeks has been used, with some evidence of benefit (16635). 120mg of *Ginkgo*bene has been used three times daily for 57 days (87940). One *Ginkgo* leaf extract capsule has been used three times daily for three months (87813). 120mg of *Ginkgo* extract has been used twice daily for an average duration of 6.1 years (87848).
  - **Altitude (mountain) sickness**: 160mg of *Ginkgo* (EGb 761) daily has alleviated subjective symptoms in one study (6230). 120mg of *Ginkgo* twice daily for 3-4 days or doses prior to climbing and continuing for the duration (1-2 days) until reaching the endpoint (total of 4-5 days) has been used (61000, 87827, 11766).
  - **Autism**: 100mg of *Ginkgo biloba* EGb 761 has been taken daily for four weeks (87822).
  - **Blood pressure control*:*** 120mg of *Ginkgo biloba* extract has been used for a 6.1-year median follow-up period (87853).
  - **Cancer prevention**: 120mg of *Ginkgo* extract (EGb 761) has been used twice daily for an average 6.1 years (87859).
  - **Cardiovascular disease**: 120mg of *Ginkgo biloba* extract (EGb 761, Schwabe Pharmaceuticals, Karlsruhe, Germany) has been used twice daily for a median duration of 6.1 years (17402).
  - **Cerebral insufficiency**: *Ginkgo* administration at doses of up to 160mg in up to three divided doses daily for up to 12 weeks has shown improved concentration and functional status, and also reduced headaches, dizziness, depression, and anxiety (88014, 88015, 88016, 88007, 88017, 88018, 88019, 88020, 87896, 87887, 87935, 87762, 6221, 88021, 88022, 88023, 6219, 87934, 88024, 88025, 88026, 88027, 88028, 88029, 88030, 88031, 88032, 88033, 88034, 6222, 87797).
  - **Chronic cochleovestibular disorders**: 160mg of *Ginkgo biloba* (EGb 761) supplements (Tanakan or Tebokan) has been taken as two tablets twice daily over six weeks (87745).
  - **Claudication**: 80-120mg of *Ginkgo* extract daily for up to six months has been studied (87963, 88035, 88036, 88037, 87936). One trial used a higher dose of *Ginkgo* extract EGb 761, at a dose of 320mg daily for four weeks (87951). Some evidence shows that 240mg daily is more beneficial than 120mg daily (3461). Also, there is evidence that 6mL of *Ginkgo* liquid daily is more efficacious than 3mL of liquid daily for intermittent claudication (3461). 240mg of *Ginkgo* has been used daily for 24 weeks (87793). 160mg of a *Ginkgo biloba* preparation has been used daily for six weeks (87938, 88011). Other studied doses are 80-320mg of *Ginkgo biloba* daily in 1-3 divided doses for 4-24 weeks (87858), 1-3 tablets containing 40-160mg 1-3 times daily (for a total daily dose of 120-320mg) for 4-24 weeks (87828), five tablets of 60mg of EGb 761 for four months (16638), and 160mg of *Ginkgo biloba* extract daily for 24 weeks (87895).
  - **Cocaine dependence**: 120mg of *Ginkgo biloba* has been used daily for 10 weeks (87723).
  - **Cognitive performance**: 120mg of *Ginkgo biloba* has been used twice daily for 12 weeks, with some evidence of benefit (87787, 87903, 87885). 40mg of a *Ginkgo biloba* tablet has been used in combination with aspirin three times daily for three months (87902). Three 2,000mg tablets of Blackmore's *Ginkgo biloba* Forte have been taken 90 minutes prior to completing memory testing (8587). In a systematic review, doses studied have included 80-240mg of *Ginkgo* daily for 1-8 months with one *Ginkgo* treatment containing 1.14mg of flavone glycosides plus 1.93mg of *Ginkgo*lides daily for 24 weeks, but specific information regarding the overall dose of *Ginkgo* was lacking in that study (87836); 120-600mg of *Ginkgo* in a single dose or daily for two days to 12 weeks; 4mg/kg of *Ginkgo* leaf extract daily for 13 weeks (87789); and one capsule of a *Ginkgo* leaf extract three times daily for three months (87813). Another systematic review reported EGb 761 (Tebonin, Tanakan, or Rökan) at daily doses of 120-300mg for 4-52 weeks or Kaveri at daily doses of 112-160mg for 6-12 weeks (87819).
  - **Decreased libido and erectile dysfunction (impotence)**: 240mg of *Ginkgo biloba* has been used daily for up to six months (14383, 88038, 88039). 60mg daily for 12-18 months was used (88040). 207mg daily for four weeks has been taken (3965). 300mg of *Ginkgo* extract was taken as a single dose or daily for eight weeks (35915, 16640). 120mg *Ginkgo biloba* daily was taken for two weeks, then 160mg daily for two weeks, and then 240mg daily for the remaining four weeks for up to two months has been used (10893).
  - **Dementia**: For dementia, doses of up to 600mg daily of *Ginkgo* (mainly as EGb 761) in up to three divided doses have been studied for up to six years (most common doses were 120-240mg for six to 12 months) (88041, 6225, 1514,

87736, 1515, 87794, 16637, 88027, 16634, 88008, 87784, 6216, 87726, 5720, 88042, 16634, 87744, 87899, 87851, 87866, 87802, 87716, 16636, 87855, 17191, 87904, 87897, 87823, 87826, 88010, 6224, 87766, 17717). According to systematic or other reviews, participants were administered 120-240mg *Ginkgo biloba* in 1-3 divided doses daily for 3-12 months (87757) or 20-240mg of *Ginkgo* daily and followed-up after 22-26 weeks (87870). Another systematic review reported EGb 761 (Tebonin, Tanakan, or Rökan) at daily doses of 120-300mg for 4-52 weeks or Kaveri at daily doses of 112-160mg for 6-12 weeks (87819).

- **Depression and seasonal affective disorder (SAD)**: 240mg of *Ginkgo* has been used daily for up to 10 weeks (88043).
- **Gastric cancer**: 0.5g of *Ginkgo* has been used three times daily (87742).
- **Generalized anxiety disorder**: 240-480mg of *Ginkgo biloba* has been used daily in up to three divided doses for 4-8 weeks (57304, 15578, 57306).
- **Glaucoma**: 40mg of *Ginkgo* has been used three times daily for two weeks (10921). 160mg of *Ginkgo* has been used daily for four weeks, after which time the dose was decreased to 120mg daily (88044). *Ginkgo* extract LI 1370 100mg three times daily for six weeks has also been studied (88045). 80mg of *Ginkgo biloba* containing 19.2mg of flavonoid glycosides has been taken twice daily for four weeks (87886). 40mg of extract has been taken three times daily for four weeks (10378). In a retrospective study, patients who had been treated with 80mg of *Ginkgo biloba* extract twice daily over at least a four-year period were examined (87900).
- **Glucose tolerance**: 120mg of EGb 761 has been taken once daily for three months (14350).
- **Graves' disease (adjunct iodine/iodide)**: EGb 761 (120mg daily) has been used from three days prior to 30 days after ^{131}I (radioiodine) therapy (87795).
- **Hearing loss**: 120mg of *Ginkgo biloba* has been used twice daily (duration not known) (8543), and 40mg of *Ginkgo biloba* has been used three times daily over two different courses of 90 days (87834).
- **Macular degeneration**: *Ginkgo* (EGb 761) 160mg daily in two divided doses for six months has been studied (6227). *Ginkgo* extract LI 1370 (100mg three times daily) has also been used (88045). One study used *Ginkgo* 160mg daily for four weeks, after which time the dose was decreased to 120mg daily (88044). 60-240mg of *Ginkgo biloba* has been used twice daily for six months (11797).
- **Memory enhancement**: 120-360mg of *Ginkgo biloba* daily in single or 2-3 divided doses for up to six weeks has been studied (6214, 8236, 88046, 88047, 88048, 88049, 87741, 5718, 6214, 87879), as has 40mg of an aqueous extract twice daily (87758). Bio*Ginkgo* (LI 1370) 60mg has been used daily for five days (87706), and Ginkoba 40mg three times daily for six weeks has also been studied (8586, 87717, 87719, 87720, 87721, 87718). A single dose of 120mg of *Ginkgo biloba* extract was not effective in the absence of dosing with phosphatidylserine or phosphatidylcholine (87788). In a systematic review, participants in the included studies were administered 120mg of Blackmore's *Ginkgo*forte extract three times daily for 12 weeks, 160-240mg of EGb 761 2-3 times daily for six weeks to four months, 120mg of Li1370 extract once or twice daily for five days to 12 weeks, or 120mg of Ginkoba Gb extract three times daily for six weeks (87907).
- **Mental alertness(postprandial dip)**: *Ginkgo biloba* (mean dose: 184.5mg daily (range: 130-234mg daily)) for 13 weeks has been studied (87747).
- **Mood and cognition in postmenopausal women**: 120mg of *Ginkgo* has been used daily for seven days (87733) to six weeks (75491).
- **Multiple sclerosis (MS)**: 240mg of daily *Ginkgo*lide B or 360mg of *Ginkgo*lide B has been studied (87947).
- **Premenstrual syndrome (PMS)**: 80mg of *Ginkgo* extract EGb 761 has been used twice daily from day 16 of the first cycle to day 5 of the following cycle with the option to increase to 320mg daily after one month (6229, 39007). 40mg of *Ginkgo biloba* L. (Ginko T.D., Tolid-Daru Company, Tehran) has been used three times daily beginning on day 16 of the first cycle until day 5 of the next cycle for two cycles (87839). 120-160mg of *Ginkgo* has been used daily for two menstrual cycles (49185, 41492).
- **Pulmonary interstitial fibrosis**: 1g of *Ginkgo* extract has been used three times daily for three months (87772).
- **Quality of life**: 120mg of EGb 761 extract has been used daily for 4-10 months (87715, 87760).
- **Raynaud's**: 120mg of EGb 761 has been used twice daily for 10 weeks (87888). 360mg of extract has been taken daily for 10 weeks (32089). 40mg of *Ginkgo biloba* extract has been used three times daily for one week followed by 80mg three times daily for seven weeks (87818).
- **Retinopathy (type 2 diabetes)**: 80mg (2mL) of EGb 761 twice daily (duration unclear, although participants were assessed after 90 days and six months) (6175).
- **Schizophrenia**: 150mg of *Ginkgo biloba* extract has been used twice daily for eight weeks in addition to olanzapine (87778). Up to 360mg of *Ginkgo biloba*, in some trials in the form of EGb 761, has been used in up to three divided doses daily for up to 16 weeks, alone or in combination with antipsychotics (87864, 87844, 16639).
- **Smell disorders**: 80mg of *Ginkgo biloba* has been used three times daily for four weeks in addition to prednisolone and mometasone furoate (87845).
- **Tinnitus**: 150mg of LI 1370 in three divided doses daily for 12 weeks has been studied (221). 200mg of EGb 761 infusion has been used for 10 days, followed by a twice daily oral dose of 80mg for 12 weeks (9871). 40mg of *Ginkgo biloba* has been used daily for two treatment periods lasting three weeks each, with a two-week washout in between then and increased by 40mg every third day, up to a limit of 160mg daily in two divided doses (87901). 120-240mg of EGb 761 has been taken daily for 4-26 weeks (87883). 40mg of *Ginkgo biloba* has been used three times daily over two different courses of 90 days (87834). Doses reported in a systematic review were 150mg of LI1370 daily, 120mg of EGb 761 daily, and 120mg of *Ginkgo biloba* product daily, for 12 weeks (87752). In a systematic review, doses used were 2mL of EGb 761 (Tanakan) daily for three months, 14.6mg of EGb 761 (Seredrin, Farmaflor) daily for two weeks, 120mg of EGb 761 daily for 12 weeks, and 50mg of *Ginkgo biloba* extract three times daily for 12 weeks (88002).
- **Vertigo**: *Ginkgo* (EGb 761) 160mg daily has been well tolerated and effective for three months (6221).
- **Vitiligo**: 40mg of *Ginkgo* extract has been used three times daily for six months (87728, 87850). 60mg of standardized *G. biloba* has been taken twice daily for 12 weeks (17718).

Intravenous/Intramuscular:

- **Cardiovascular disease**: Intravenous *Ginkgo* has been used (87.5mg of *Ginkgo biloba* extract) daily for two weeks (87791, 87806).
- **Claudication (peripheral vascular disease)**: The *Ginkgo* product Tanakan has been studied parenterally at a dose of 100mg in 500cc of normal saline, administered twice daily for eight days, for peripheral vascular disease (87912). Safety has not been established. A single intravenous injection of 35mg of *Ginkgo biloba* extract into the femoral vein has been used after maximum claudication pain was achieved (87926).
- **Dementia**: In a review, a single study administered infusions of *Ginkgo* (further details are lacking) (87802). Another systematic review reported infused EGb 761 at a daily dose of 200mg for four days weekly and Geriaforce at a daily dose of 2.85-5.7mL for 24 weeks (87819).

- **Diabetic nephropathy**: 20mL of *Ginkgo biloba* in 250mL of normal saline daily for four weeks has been used as an intravenous drip in combination with Western medicine (87775).
- **Tinnitus**: 200mg of EGb 761 infusion has been used for 10 days followed by a twice-daily oral dose of 80mg for 12 weeks (9871, 87883). In a systematic review, an injection with 200mg of *Ginkgo* was given daily for 10 days, followed by treatment with 80mg of *Ginkgo* by mouth daily for three months (88002).
- **Note**: According to secondary sources, the intravenous *Ginkgo* product Tebonin, which was available in Germany, was removed from the German market due to significant adverse effects.

Ocular:

- **Ocular allergy**: Two eyedrops containing a combination of *Ginkgo biloba* and hyaluronic acid were used in each eye (information regarding the composition of the drops was lacking) three times daily for one month (87829).

- **Children**

Oral:

- **Attention-deficit hyperactivity disorder (ADHD)**: Doses of 80-120mg have been used daily in three divided doses for six weeks; the dose was increased from 40mg daily in week 1 to 120mg daily in week 3 if the patient was over 30kg or to 80mg daily if the patient was under 30kg (59001, 17112).
- **Dyslexia**: A single dose of EGb 761® 80mg has been used daily for an average of 34.4 days (87790).

- **Standardization & Formulation**

- *Ginkgo* is available in leaf, leaf extract, and seed formulations. *Ginkgo* leaf extract is the most commonly used form.
- Products that utilize standardized extracts referred to as EGb 761 should contain 22-27% *Ginkgo* flavone glycosides (primarily quercetin, kaempferol, and isorhamnetin) and 5-7% terpenoids (2.8-3.4% *Ginkgo*lides A, B, and C, and 2.6-3.2% bilobalide). *Ginkgo*lide B and bilobalide account for 0.8% and 3% of the total extract, respectively (<5ppm). Other constituents include proanthocyanidins, glucose, rhamnose, organic acids, and D-glucaric and *Ginkgo*lic acids (PM:12757407). The drug:extract ratio has been suggested as being 35-67:1 (15578, 14350, 16640). Clinical trials known to have used EGb 761 have been reported (87828, 87802, 16636, 87794, 87904, 87897, 87823, 87826, 88006, 88010, 87879, 87901, 87844, 57304, 87883, 15578, 14350, 16640, 87848, 87853, 17717, 6224, 87782, 16638, 6213, 87951, 87888, 6175), and have included the commercial products Rökan and Tanakan (87828, 87797, 88011). Kaveri was reported to contain 25% glycosides and the terpene lactones, *Ginkgo*lides, and bilobalide (16636). The Rökan used in one study contained 40mg or 20mg of *Ginkgo biloba* (EGb 761) leaf extract, standardized to 9.6mg of flavone glycosides (87797).
- Ginko T.D., produced from *Ginkgo* leaf extracts (drug:extract ratio of 4:1), was standardized to contain 24% flavonoid glycoside and 6% terpene lactone (87839). One Ginko T.D. tablet contained 40mg of *Ginkgo biloba* dried extract (17112).
- The standardized *Ginkgo* extract, GK 501, used in one study contained at least 24% *Ginkgo*flavone glycosides and 6% terpenes (11766).
- According to secondary sources, products that utilize standardized extracts referred to as LI 1370 should contain 25% *Ginkgo* flavone glycosides and 6% terpenoids.
- Standardized extracts used in clinical trials have contained 22-27% *Ginkgo* flavonoids and 5-7% terpene lactones, consisting of 2.6-3.4% *Ginkgo*lides A, B, and C, as well as 2.6-3.2% bilobalide, with <5ppm of *Ginkgo*lic acids (87855, 87851, 87789). Other standardized products have included 24.66% *Ginkgo*flavones and 6.54% terpene lactones, including *Ginkgo*lides A, B, and C (2.07%) and bilobalide (1.65%), with <2ppm of arsenic and 26.1% *Ginkgo*flavones, including quercetin (5.28%), kaempferol (4.0%), isorhamnetin (0.84%), and total aglycones (10.12%); and 6.61% terpene lactones, including *Ginkgo*lides A, B, and C (6.055%) and bilobalide (0.555%), with 1ppm of arsenic and <20ppm of heavy metals (87827). A 120mg dose contained 7.2mg of terpene lactones and 28.8mg of *Ginkgo biloba* flavone glycosides (17402). In another study, each 120mg *Ginkgo* tablet contained 29.7mg of flavoglycosides and 7.3mg of terpene lactones (87903). An 80mg extract contained 19.2mg of flavonoid glycosides (87886). An extract made from the leaf was standardized to contain 6% terpene lactones and 24% flavonoid glycosides (41492, 35915). A dried extract of *G. biloba* containing 9.6mg of *Ginkgo* flavonglycosides (produced by Ginkocer Ranbaxy, India) was used (87728). *Ginkgo biloba* extracts contained 24-31% flavonol-glycosides and 4.5-6.7% terpene lactones (87836, 87858, 10378, 41492). 2,000mg of *Ginkgo* tablets each contained 40mg of active *Ginkgo*, which was standardized to contain 10.7mg of *Ginkgo* flavonglycosides and 2.7mg of *Ginkgo*lides and bilobalide (8587). A *Ginkgo* leaf capsule contained 9.6g of flavonoids (87813). In healthy subjects, a single dose of *Ginkgo biloba* was standardized to a minimum of 24% *Ginkgo* flavonglycosides and 6% terpene lactones (87877).
- According to secondary sources, *Ginkgo biloba* extract was associated with three batch failures, resulting in the presence of pesticides. *Ginkgo biloba* was since removed from the formulation due to lack of confidence in the supplier's ability to test for pesticides using validated procedures.

Adverse Effects

Report an Adverse Reaction to Ginkgo

General: *Ginkgo* appears to be well tolerated at suggested doses in most healthy adults for up to six months. In several reviews and clinical trials, *Ginkgo* use was associated with similar or lower rates of adverse effects as placebo (1515, 6211, 88008, 87697, 87716, 87802, 16636, 87794, 17191, 87897, 75491, 87879, 87826, 87864, 87848, 87752, 17717, 10378, 87888), or evidence of harm was lacking, according to information from clinical trials (87866). Hypersensitivity was reported in a clinical trial (88006). Postmarket surveillance of >10,000 subjects found a 1.69% incidence of minor symptoms, including headache, nausea, and gastrointestinal complaints (88007). The most concerning potential complication is bleeding, which has been life threatening in a small number of case reports. *Ginkgo* in the form of fresh seeds has been associated with toxicity in anecdotal reports, and regulations in some countries do not allow *Ginkgo* seeds in foods.

⊞ **Cardiovascular**

⊞ **Dermatologic**

⊞ **Endocrine**

⊞ Gastrointestinal

⊞ Genitourinary

⊞ Hematologic

⊞ Musculoskeletal

⊞ Neurologic/CNS

⊞ Ocular/Otic

⊞ Psychiatric

⊞ Other

Toxicology

- In human research, significant differences between groups in the incidence of death, hemorrhagic events (in gastrointestinal, vascular, and nervous systems), stroke, cardiac failure, angina, and myocardial infarction were lacking vs. placebo (87904, 17402, 87848). However, adverse events such as death, stroke, and subdural hematoma have been reported in clinical trials (88010), and stroke occurred at higher levels than in the placebo group (16635). Also, in a case report, a fatal brain hemorrhage occurred in a patient in treatment with *Ginkgo biloba* (87873). Major adverse events that have occurred in high-risk patients using *Ginkgo* in clinical trials included one death due to cardiac arrest, one death due to stroke, and one transient ischemic attack (87897); and one heart attack and one hospitalization due to depression (87903). The role of *Ginkgo* is unclear in these studies.
- In humans, ingestion of *Ginkgo* seeds has produced tonic-clonic seizure activity and loss of consciousness, potentially leading to death (8231). This adverse effect (sometimes referred to as "gin-nan food poisoning") has been documented in as many as 70 case reports between 1930 and 1970, with the worst outcomes seen in infants. Seizure activity has been attributed to 4-metoxypyridoxine (4-*O*-methlypyridoxine), also known as "*Ginkgo*toxin," which is present in much higher doses in *Ginkgo* seeds than in commercial *Ginkgo* products (88003). There are examples of case reports reporting seizure following ingestion of *Ginkgo* nuts (8232, 12183). In several reviews of *Ginkgo* at suggested doses, there was no seizure activity (1515, 6211, 88008, 87697), although there are published case reports of patients with a well-controlled seizure disorder who presented with seizures following commencement of *Ginkgo* therapy; in one case, they subsided with cessation of *Ginkgo*, whereas in the other, the seizures were fatal (7090, 14281).
- According to a technical report from the National Toxicology Program of the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH), rats and mice received tube feedings of *Ginkgo biloba* extract in corn oil at doses of 100, 300, or 1,000mg/kg (rats) and 200, 600, or 2,000mg/kg (mice) five times weekly for two years. The authors concluded that *Ginkgo biloba* extract led to cancer of the thyroid gland in both male and female rats as well as male mice. Cancers of the liver were observed in male and female mice. All intervention animals experienced increased rates of lesions in the liver, thyroid gland, and nose, and lesions of the forestomach were noted in mice. The effect of *Ginkgo biloba* in humans is unclear from this study. In animal research, the oral LD_{50} in mice was 7,725mg (6223, 87967).
- Colchicine has been isolated in commercial preparations of *Ginkgo biloba* (8541). Use of herbal supplements was linked with higher blood levels of lead in women in the United States; however, the specific effects of *Ginkgo biloba* are unclear (35893).
- Chronic energy drink consumption was associated with excessive inoperative bleeding and other toxicity (87880, 77197, 35752); specific details related to *Ginkgo* are 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 adidtion, 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 or platelet aggregation (17111). 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.

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, in other clinical research, taking ginkgo biloba 120 mg twice daily for 12 days had 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 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 biloba. 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).

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.

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). 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).

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.

INFERTILITY: Some evidence suggests that Ginkgo biloba 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

- **Constituents**: Flavonoids (glycosides) and terpenoids (*Ginkgo*lide, bilobalide) are considered to be *Ginkgo*'s primary active components (87735, 87722, 6208, 87955, 87771, 88053). Other constituents include 6-hydroxykynurenic acid (87785). Most studies have been conducted with the standardized *Ginkgo* preparation EGb 761® (24% *Ginkgo* flavone glycosides, 6% terpenoids), or LI 1370 (25% *Ginkgo* flavone glycosides, 6% terpenoids).
- The pharmaceutical quality of different *Ginkgo biloba* brands has been investigated (8584). It was determined that many available brands do not have levels of certain constituents equivalent to those stated in the German Commission E *Ginkgo* monograph (for example, flavone glycosides, terpene lactones, and *Ginkgo*lides).
- **Analgesic effects**: In animal research, EGb 761® inhibited inflammation and hyperalgesia when given locally and centrally (87872). In animal research, *Ginkgo biloba* extract (GBE) attenuated hyperalgesia in a peripheral neuropathy model (87908).
- **Anticancer effects**: *In vitro* and epidemiological evidence support the use of *Ginkgo biloba* for ovarian cancer (14813). Epidemiological evidence suggests that risk of ovarian cancer was less in users of *Ginkgo*, and *in vitro* evidence suggests that in ovarian cancer cells, *Ginkgo*lides block cell cycle at G0/G1.
- In human research, GBE prevented the iodine-131-induced increase in lymphocyte micronuclei and clastogenic factors, suggesting a prevention of genotoxic damage (87892). In human research, *Ginkgo biloba* exocarp polysaccharides (GBEP) induced apoptosis and differentiation of tumor cells (87742). *In vitro* research suggested that the mechanism of action involved the altered expression of c-myc, bcl-2, and c-fos genes.
- *In vitro*, *Ginkgo*lide B proteins in BRCA1 mutant ovarian epithelial cells, which were involved in cancer mechanisms, were consistently up- or downregulated (87882). Tompkins determined that a novel xenobiotic responsive element regulated by aryl hydrocarbon receptor is involved in breast cancer resistance protein (BCRP)/ABCG2 induction in LS174T cells *in vitro* (87863). EGb 761® was found to induce the BCRP promoter.
- **Antioxidant/anti-inflammatory effects**: In human research, use of an antioxidant product containing *Ginkgo* reduced levels of oxidative stress, as well as homocysteine levels (44162). In patients undergoing hypothermic cardiopulmonary bypass, GBE had antioxidant effects in erythrocytes, protecting against lipid peroxidation (87860). In human research, GBE increased glutathione levels (87890).
- *Ginkgo* significantly reduced the amount of platelet MDA-thiobarbituric acid reacting substances, in supplemented humans (14455). Flavonoids serve as free-radical scavengers and have been shown to reduce oxidative stress in human models (88054, 87966, 88055, 87980, 88001, 87750, 87946, 87948, 87911). This mechanism is hypothesized to reduce oxidative cellular damage in Alzheimer's disease and has prompted theories that *Ginkgo* may have favorable effects on reperfusion injury (87968, 87941, 88056, 87945, 87929, 87832, 87957). *Ginkgo*lides inhibited receptor binding of platelet activating factor (PAF), which may mediate beneficial clinical effects (87927, 88057, 87921, 88058, 87916, 87915, 88059, 87891, 87906, 87950, 87923, 87928, 87959). PAF is proinflammatory, induces platelet aggregation, and contracts bronchial smooth muscle (88060). *Ginkgo* has been found to increase corticosteroid secretion in rats (5723).
- In animal research, EGb 761® inhibited inflammation and hyperalgesia when given locally and centrally (87872).
- *In vitro*, in human vascular endothelial cells, *Ginkgo*lide B reduced the expression of Nox 4, as well as the generation of reactive oxygen species (87871). *Ginkgo*lide B also inhibited the expression of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule 1 (IAM-1). Although the inhibition of NF-kappaB p65 (NF-kB) likely played a role in the inhibition of MCP-1 and IAM-1, other mechanisms played a role in the reduced expression of Nox 4.
- In human research, *Ginkgo* use resulted in a decrease in IL-6, IL-8, and TNF-alpha (87772).
- **Blood pressure effects**: The role of *Ginkgo biloba* in blood pressure regulation has been discussed; however, further details are lacking (88061).
- **Cardiovascular effects**: In human research, GBE induced the production of VEGF (perhaps involved in myocardial protection) (87825).
- In animal research, an ethanol extract of *Ginkgo biloba* leaves reduced the heart rate and contractility, as well as the coronary flow (87894). The effects were dose dependent, as lower doses lacked these effects. Antiarrhythmic effects of *Ginkgo*lide B were shown in isolated rat hearts (87914). In animal research and in isolated hearts, *Ginkgo* protected against myocardial ischemia (87917).
- *In vitro*, *Ginkgo*lide B improved the contractile function of rat hearts treated by ischemia-reperfusion (87833). The function of left ventricle was partially protected from injury and had a decreased infarct size and release of lactate dehydrogenase.

Mechanisms of action involved an increased cardiomyocyte shortening amplitude and expression of protein Bcl-2, and decreased the ratio of Bax to Bcl-2.

- **Coagulation and antiplatelet effects**: Bleeding, hemorrhage, and hematomas, possibly or likely associated with *Ginkgo* use, have been reported in clinical trials, meta-analyses, systematic reviews, and clinical trials (13135, 87828, 35915, 87965, 578, 8581, 13002, 14456, 87977, 244, 87868, 579, 87974, 87855, 13194, 14315, 88000, 13179, 87888, 87813, 10450); however, other studies have suggested a lack of effect on bleeding rates (17402). Some, but not all, studies have suggested inhibitory effects of *Ginkgo* on platelet function or coagulation parameters in healthy volunteers (87732, 87768, 12114, 51394, 87727, 52880, 14450, 9760).
- *Ginkgo biloba* extract decreased plasma D-dimer concentration, a marker of intravascular coagulation, in chronic peritoneal dialysis patients (87773). Significant changes in blood levels of fibrinogen, von Willebrand factor, hs-CRP, albumin, and liver enzymes were lacking. Bleeding episodes were lacking. A controlled clinical trial found that dry extract of *Ginkgo biloba* reduced blood viscosity more than *Allium sativum* (garlic) (51394). In a study in male subjects, *Ginkgo* use lacked an effect on the international normalized ratio of prothrombin time or platelet aggregation (12881). In combination with warfarin, *Ginkgo* at suggested doses lacked significant effects on clotting status, or the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects.
- *Ginkgo* supplementation inhibited platelet aggregation from platelets isolated from healthy volunteers and patients with type 2 diabetes, and inhibited urinary 11-dehydro thromboxane (Tx) B2, 2,3-dinor-6-keto-prostaglandin (PG) F1alpha, and 6-keto-PGF1alpha production in healthy volunteers (14450, 9760). An inhibition of collagen-induced platelet aggregation and Tx A2 synthesis was shown by the same authors (details are lacking) (88062).
- **CYP450 effects**: Although *Ginkgo* and its constituents were found to affect CYP activity *in vitro* (87817, 14337, 87861), in human research, *Ginkgo* altered levels of only some, but not all, CYP450-metabolized agents in the blood, and many studies suggest a lack of effect on CYP activity (87800, 87805, 87893, 11029, 14337, 48628, 17111, 87846, 14451, 87824, 87830, 13108).
- **Gastrointestinal effects**: In animal research, GBE increased the neural profile area of the of the colon (87810).
- **Lipid-lowering effects**: *In vitro* in hepatocytes, GBE decreased the total cholesterol content and cholesterol influx (87840). The activity of HMG-CoA reductase was inhibited, and there were increases in the expression of cholesterogenic genes and genes involved in cholesterol metabolism (including SREBF2). Other genes, such as INSIG2, LDLR, LRP1, and LRP10, were also regulated by the extract. Based on similar experiments using lovastatin, the authors concluded that GBE modulates cholesterol metabolism through a different mechanism than lovastatin.
- **MAOI effects**: Monoamine oxidase (MAO) inhibition by *Ginkgo* has been reported in animals (6233), but confirmation in subsequent animal research was lacking (6232). In limited human research, significant changes in human brain MAO A or B were lacking, measured by positron emission tomography after one month of 120mg of *Ginkgo* daily in a small human sample (88009).
- **Neuroprotective effects**: In human research, *Ginkgo biloba* resulted in cognitive activator profiles based on recordings of computer-analyzed EEGs (6067).
- In animal research, GBE protected against glutamate-induced neurotoxicity of retinal cells (88051). In an animal neuropathic pain model, GBE had antiallodynic effects, resulting in the reduction of paw withdrawal thresholds to mechanical frequencies and the withdrawal frequencies to cold stimuli (87831). In animal research, GBE increased the neural profile area of the myenteric plexus of the colon (87810).
- *In vitro*, EGb 761® protected against neurodegenerative induced by antimycin A1 plus 2-deoxy-D-glucose (87874). Mechanisms of action included reduced ATP-levels, oxidized redox state, lipid peroxidation damage, and oxidative damage of mitochondrial DNA.
- Logani et al. wrote a review on the actions of *Ginkgo biloba* in the treatment of conditions involving cerebral hypoxia (2660). The authors concluded that although the mechanism of action is unclear, flavonoid and terpenoid components likely play a role, possibly in the antagonism of platelet activating factor (PAF), via antioxidant and metabolic actions, or via effects on neurotransmitters.
- **Neurotransmitter effects**: Neuroprotective properties have been attributed to inhibition of age-related decline of adrenergic and cholinergic receptors (88063, 87737, 87949, 87975). *Ginkgo* increased serotonin levels, muscarinic binding sites, and serum levels of acetylcholine and norepinephrine (87969). *In vitro*, *Ginkgo*lide B and bilobalide blocked the pore of the 5-HT3 receptor (87865). The location at which this occurred overlapped the picrotoxin binding site.
- According to a review, mechanism of action of *Ginkgo biloba* related to dementia may include prevention of Abeta aggregation, insulin resistance, mitochondrial dysfunction, and hypoperfusion (87837).
- **Ocular effects**: Although improved vision was observed in a case report (87792), no effect of *Ginkgo* on ocular blood flow was observed in clinical research (87783). In human research, a *Ginkgo biloba* in combination with hyaluronic acid ophthalmic solution (GB-HA) resulted in reduced ocular inflammation, as well as allergy symptoms (87829).
- **Vascular effects**: *Ginkgo* has been found to have vasodilatory effects, which have been attributed to stimulation of endothelium-derived relaxing factor (EDRF) and prostacyclin release. Studies have suggested that *Ginkgo* inhibits nitric oxide, causing vascular relaxation (87971, 87698, 88052, 87749, 87806). In a controlled single-blind study of 10 healthy human subjects (87910) and a controlled crossover study of patients with known claudication (87926), *Ginkgo* significantly increased blood capillary flow and decreased erythrocyte aggregation. In healthy adult males, a single dose of *Ginkgo biloba* reduced the peripheral augmentation index vs. baseline (the difference vs. the control group was lacking) and significantly increased vascular function measured by the stiffness index after two hours (87877). Significant changes in blood pressure and heart rate were lacking. In human research, *Ginkgo* treatment resulted in improvement in blood flow velocity of the middle cerebral artery and the anterior cerebral artery; however, statistically significant changes in blood flow velocity of the posterior cerebral artery, vertebral artery, and basilar artery were lacking (87902). In patients with diabetic nephropathy, GBE increased the brachial arterial endothelium function and the level of NO, and decreased the level of vWf (87821). In human research, GBE decreased erythrocyte stiffness, relaxation time blood plasma viscosity, and plasma fibrinogen (6212).
- **Other effects**: An *in vitro* study demonstrated that *Ginkgo* promoted proliferation of human skin fibroblasts (87976). *Ginkgo biloba* extract promoted endothelial progenitor cell (EPC) proliferative, migratory, adhesive, and *in vitro* vasculogenesis capacity, therefore promoting EPC augmentation and enhancing its functional activity (87763).

Pharmacokinetics

- **Bioavailability**: The oral bioavailabilities of the terpene lactones *Ginkgo*lide A, *Ginkgo*lide B, and bilobalide are 98-100%, 79-93%, and 70%, respectively. Absorption has been found to occur principally via the small intestine. One study showed that after the oral administration of GBE 160mg to healthy volunteers, the plasma concentrations of *Ginkgo*lides A and B and bilobalide were 41.8, 5.6, and 37.6ng/mL, respectively (87771).

- In human research, the median maximum concentrations of bilobalide and *Ginkgo*lide A and B after administration of various *Ginkgo* products were 3.53-26.85ng/mL, 3.62-16.44ng/mL, and 1.38-9.99ng/mL, respectively, with the highest plasma levels of all three following use of EGb 761® (87849).
- **Elimination/half-life**: The half-lives of *Ginkgo*lides A and B and bilobalide have been found to be 4.5, 10.6, and 3.2 hours, respectively, with peak plasma levels at 2-3 hours. Approximately 70% of *Ginkgo*lide A, 50% of *Ginkgo*lide B, and 30% of bilobalide are excreted unchanged in urine, with seven other metabolites detectable in the urine but undetectable in serum. Duration of action has been reported as seven hours. Ten adult volunteers with an average age of 28 years were given a single oral dose of six tablets of *Ginkgo biloba* extract. Quercetin and kaempferol in human urine were determined by using reverse-phase high-performance liquid chromatography (RP-HPLC) (87740, 70321). The results showed that the elimination rate constant (k) and the absorption rate constant (ka) of quercetin were slightly more than those of kaempferol, and the absorption half-life (t1/2a), the elimination half-life (t1/2), and t_{max} of quercetin were less than those of kaempferol; the differences were, however, not statistically significant. The mean values of ka for quercetin and kaempferol, respectively were 0.61/hr and 0.55/hr, those of t1/2a were 1.51 hours and 1.56 hours, those of k were 0.37/hr and 0.30/hr, those of t1/2 were 2.17 hours and 2.76 hours, and those of t_{max} were 2.30 hours and 2.68 hours; mean absorption and elimination of quercetin and kaempferol were 0.17% and 0.22%, respectively. Quercetin and kaempferol were excreted in human urine mainly as glucuronides.
- **Other**: In an open-label study, significant decreases in midazolam concentrations following *Ginkgo biloba* extract administration suggested that GBE may induce CYP3A metabolism (87800, 87805). Significant effects on lopinavir, ritonavir, and fexofenadine exposures were lacking. However, in healthy volunteers, it was determined that *Ginkgo biloba* lacked relevant clinical effects on CYP enzymes (87893), and various studies in humans suggested that there was a lack of effect of *Ginkgo biloba* on CYP2D6 or CYP3A4 (11029) or on CYP2C9, based on diclofenac or tolbutamide metabolism (14337). The lack of clinically relevant effects of *Ginkgo biloba* on CYP activity was also mentioned in a review (48628). *Ginkgo* reduced clearance of omeprazole in human research (13108).
- In hepatocytes *in vitro*, EGb 761®, as well as *Ginkgo*lides A and B induced CYP2B6, CYP3A4, UGT1A1, MDR1, and MRP2 (87817). Effects of other constituents, such as bilobalide, or the flavonoids quercetin, kaempferol, and tamarixetin were lacking. The *Ginkgo*lides were also activators of pregnane receptor X, whereas quercetin and kaempferol activated pregnane receptor X, constitutive androstane receptor, and aryl hydrocarbon receptor. The expression of UGT1A1 and CYP1A2 in HepG2 cells was induced by the flavonoids. *In vitro*, *Ginkgo biloba* inhibited CYP2C9 (14337).
- *In vitro*, the *Ginkgo* flavonoids apigenin, kaempferol, and quercetin modified the activity of organic anion transporting polypeptides 1A2 and 2B1 (87861). All three resulted in a decrease of the OATP1A2-mediated fexofenadine transport and the OATP1A2- and OATP2B1-mediated transport of atorvastatin.
- In human research, *Ginkgo biloba* extract lacked effect on ticlopidine pharmacokinetic parameters in healthy individuals also taking ticlopine (17111, 87846, 14451), as well as on voriconazole pharmacokinetics in Chinese volunteers identified as CYP2C19 poor and extensive metabolizers (87824) or metformin in patients with diabetes (14454), and it had no or limited effects on the pharmacokinetics of warfarin (15176, 87889). In human research, *Ginkgo biloba* extract increased the maximum plasma concentrations of talinolol as well as the area under the concentration-time curve (0-24 and 0-infinity) (87830). Changes in the elimination half-life and the time to C_{max}, and effects of a single dose of *Ginkgo biloba* were lacking.
- The effects of *Ginkgo biloba* leaf extract (GBE) on the pharmacokinetics and pharmacodynamics of nifedipine (NFP), a calcium-channel blocker, were studied using eight healthy volunteers (87765, 87764). Simultaneous oral ingestion of GBE (240mg) did not significantly affect any of the mean pharmacokinetic parameters of either NFP or dehydronifedipine, a major metabolite of NFP, after oral administration of NFP (10mg); however, the maximal plasma NFP concentrations in two subjects were approximately doubled by GBE.
- According to a review, *Ginkgo* decreased the plasma concentrations of omeprazole, ritonavir and tolbutamide (48603). In a case report of a patient with HIV using efavirenz, use of *Ginkgo* was suggested as being responsible for the decreased plasma concentrations of the drug and resulting virological failure (16821).

Evidence Table / Discussion

See detailed Evidence Summary

References

See Monograph References

This monograph was last reviewed on 3/20/2015 and last updated on 4/22/2015. 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.