GINKGO

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.

Scientific Name:

Ginkgo biloba.
Family: Ginkgoaceae.

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).

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. 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:

POSSIBLY EFFECTIVE

Age-related memory impairment. Taking ginkgo leaf extract orally seems to improve cognitive function in some elderly people with mild to moderate age-related memory or cognitive impairment. Ginkgo leaf extract might modestly improve some measures of cognitive function, particularly short-term visual memory and possibly speed of cognitive processing, in non-demented patients with age-related memory impairment (5717,6216). But taking ginkgo leaf extract does not improve memory in people over the age of 60 with normal mental function (5718,8586,8587,8588).

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).

Cognitive function. Taking ginkgo leaf extract orally seems to improve some measures of cognitive function in healthy young to middle-aged people. Ginkgo might 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 (6214,6215,8236,8544,8588,9759). Lower doses of 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 a combination of Panax ginseng and ginkgo is effective for enhancing memory and that the combination might be more effective than either product alone (8591,9759).

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 (15 14,1515,2665,2666,6222,6223,6224,6225,6490,11981,1663 6) (17191,17717). 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 potential benefits (5720,16636,16637).

There has been some debate about whether ginkgo is more effective in dementia patients who have neuropsychiatric symptoms. Clinical research shows that ginkgo is not more effective in patients with neuropsychiatric symptoms compared to those without (17717).

Most clinical studies have not compared ginkgo to conventional drugs such as the cholinesterase inhibitors. However, in a preliminary comparative trial, a specific ginkgo leaf extract (EGb 761, Tanakan, Ipsen) 160 mg daily seems to be comparable to donepezil 5 mg daily for mild to moderate Alzheimer's dementia after 24 weeks of treatment (14499). Indirect comparisons suggest that ginkgo might be less effective than the conventional drugs donepezil (Aricept), tacrine (Cognex), and other cholinesterase inhibitors (6224,6490,11981).

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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 ginkgo leaf extract orally for six months can significantly improve measures of color vision in patients with early diabetic retinopathy (6175).

Glaucoma. Taking ginkgo leaf extract orally seems to improve pre-existing damage to the visual field in patients with normal tension glaucoma (10378).

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 seems to produce significant relief in breast tenderness and neuropsychological symptoms associated with PMS when started during the 16th day of the menstrual cycle and continued until the 5th day of the following cycle (6229).

Raynaud's syndrome. Taking ginkgo leaf extract orally seems to decrease the number of painful attacks per week in patients with Raynaud's syndrome (11363).

Vertigo. Taking ginkgo leaf 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

Altitude sickness. A small preliminary study suggested that a specific ginkgo extract (EGb 761, Tanakan, Ipsen) 80 mg twice daily significantly reduced the occurrence of symptoms of acute altitude sickness including headache, fatigue, dyspnea, nausea, and vomiting in climbers to an altitude of 5400 meters (6230). But a large-scale trial using a different ginkgo extract (GK 501, Pharmaton, Switzerland) 120 mg twice daily shows that ginkgo has no effect on preventing altitude sickness in climbers to an altitude of 4928 meters (11766).

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 doesn't seem to prevent winter depression symptoms in patients with SAD (8233).

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).

Tinnitus. Taking ginkgo leaf extract orally doesn't seem to improve symptoms of tinnitus. Some studies have shown benefit, but the majority of evidence indicates that ginkgo leaf extract is not consistently effective for patients with tinnitus (221,910,5721,6218,6219,9871).

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 orally 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).

Anxiety. Preliminary clinical research shows that a specific ginkgo extract (EGb 761, Tanakan, Ipsen) can reduce symptoms of anxiety in adults with generalized anxiety disorder or adjustment disorder with anxious mood. After 4 weeks of treatment, a 50% or greater reduction in anxiety rating score was seen in 44% treated with 480 mg/day and 39% treated with 240 mg/day (15578).

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 the intravenous ginkgo extract (EGb 761, Tanakan, Ipsen) in combination with 5-fluorouracil might be useful for metastatic colorectal cancer (9872).

Fibromyalgia. Preliminary clinical research suggests that taking Ginkgo biloba tablets (Bio-Biloba, Pharma Nord) 200 mg in conjunction with coenzyme Q-10 capsules (Bio Quinone Q10, Pharma Nord) 200 mg orally daily for 84 days improves patient's quality of life such as physical fitness levels, emotional feelings, social activities, overall health, and pain (17716).

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

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

Radiation exposure. Preliminary clinical research suggests taking a specific gingko extract (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).

Schizophrenia. Preliminary clinical research suggests that taking a specific ginkgo leaf extract (EGb 761, Tanakan, Ipsen) 120 mg daily in combination with clozapine significantly improves negative symptoms in schizophrenia patients who are refractory to clozapine alone (16639).

Stroke. There is contradictory evidence about theeffectiveness 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) 60 mg twice daily 10 minutes before breakfast and dinner reduces the progression of vitiligo vulgaris and size of the lesions (17718).

More evidence is needed to rate ginkgo for these uses.

Mechanism of Action:

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. Many ginkgo leaf extracts are standardized to contain 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).

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. One theory is that ginkgo leaf might work by protecting tissues from oxidative damage. Ginkgo leaf flavonoids have antioxidant and free radical scavenging properties (2660,5715,5717,5719,14455). 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). Protecting neurons and other tissues from oxidative damage might prevent progression of tissue degeneration in patients with dementia and other conditions. 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.

Ginkgolides in the leaf competitively inhibit platelet activating factor (PAF) binding at the membrane receptors of numerous cells (5719,9760). 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. Preliminary research also suggests that ginkgo leaf extract can inhibit formation of platelet thromboxane A2 and thromboxane B2, further reducing platelet aggregation (8583). 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).

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).

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

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).

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).

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

Ginkgo seeds contain the neurotoxin ginkgotoxin (4'-O-methylpyridoxine). Ginkgotoxin can cause seizures, paralysis, and death when taken in high doses. Ginkgotoxin antagonizes the activity of pyridoxine, possibly by inhibiting enzymes such as pyridoxal kinase or glutamate decarboxylase in the brain. GABA is synthesized from glutamate by glutamate decarboxylase. By inhibiting glutamate decarboxylase, ginkgotoxin indirectly inhibits GABA (12183,13423). Boiling ginkgo seeds seems to reduce 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 (6048,9760).

A 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. 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).

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).

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 90mg/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 gingko 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).

Adverse Reactions:

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. 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).

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).

In one clinical trial, the rate of ischemic stroke and transient ischemic attacks was significantly higher in patients taking ginkgo compared to placebo (16635). Ginkgo leaf extract can cause allergic skin reactions in some patients. 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).

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 50mg/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.

Fresh ginkgo seeds can cause stomachache, nausea, vomiting, diarrhea, restlessness, difficulty breathing, weak pulse, seizures, loss of consciousness, and shock. 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). The fresh seeds contain large amounts of ginkgotoxin, which can cause seizures and death. The antidote for ginkgotoxin poisoning is pyridoxine (11296). Ginkgo leaf and ginkgo leaf extract contain small amounts of ginkgotoxin.

The small amount of ginkgotoxin in the leaves and leaf

extract seems unlikely to cause toxicity (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). There is not enough evidence to prove that ginkgo leaf is the sole cause of seizure in these patients. Until more is known, advise patients with seizure disorders and those taking drugs that lower the seizure threshold to avoid ginkgo leaf products.

There is some in vitro evidence that suggests high concentrations of ginkgo might reduce male and female fertility (4239,4240); however, this has not been demonstrated in humans.

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).

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 are 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 (244,578,8581, 13135,13179,14456). 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 Drugs:

ALPRAZOLAM (Xanax) <<interacts with>>GINKGO

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 doesn't appear to decrease the elimination half-life of alprazolam. This suggests ginkgo is more likely to decrease absorption of alprazolam rather than induce hepatic metabolism of alprazolam (11029).

ANTICOAGULANT/ANTIPLATELET DRUGS <<interacts with>> GINKGO

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 (244,578,8581,13135,13179,14456). Some evidence suggests that short-term use of ginkgo leaf might not significantly reduce platelet aggregation and blood clotting. 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). However, single doses of ginkgo plus cilostazol (Pletal) do seem to prolong bleeding time. 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). But a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80-480 mg daily in studies lasting up to 32 weeks, did not find a significant effect on platelet aggregation, fibrinogen concentration, or PT/aPTT (17179). Also, 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). Until more is known, use 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 <<interacts with>> GINKGO

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.

ANTIDIABETES DRUGS <<interacts with>> GINKGO

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 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, 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) <<interacts with>> GINKGO

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 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 <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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). Some drugs metabolized by CYP2C19 include amitriptyline (Elavil), carisoprodol (Soma), citalopram (Celexa), diazepam (Valium), lansoprazole (Prevacid), omeprazole (Prilosec), phenytoin (Dilantin), warfarin, and many others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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). 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) <<interacts with>> GINKGO

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

There is a single case report of decreased efavirenz concentrations and increased viral load in a patient 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). Monitor patients using this combination for therapeutic response and changes in viral load.

FLUOXETINE (Prozac) <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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

Gingko 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).

OMEPRAZOLE (Prilosec) <<interacts with>> GINKGO

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 <<interacts with>> GINKGO

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.

TRAZODONE (Desyrel) <<interacts with>> GINKGO

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) <<interacts with>> GINKGO

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 Foods:

None known.

Interactions with Lab Tests:

None known.

Interactions with Diseases or Conditions:

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.

Dosage/Administration:

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ORAL: For dementia syndromes, a dosage of 120-240 mg per day of ginkgo leaf extract, divided in two or three doses, has been used (1514,1515). A 240 mg once-daily formulation of ginkgo extract (EGb 761) has also been used (17191). 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).

For peripheral vascular disease (PVD), a dosage of 120-240 mg per day of ginkgo leaf extract (EGb 761, Tanakan, Ipsen), divided into two or three doses, has been used; however, the higher dose may be more effective (3461,17402).

For reversing sexual dysfunction due to SSRIs, the typical starting dose is 60 mg twice daily of ginkgo leaf extract. This dose can be titrated up to 240 mg twice daily (212).

For cognitive function improvement in healthy young people, dosages of 120-600 mg per day have been used (6214,6215,8236).

For vertigo or tinnitus, dosages of 120-160 mg per day of ginkgo leaf extract, divided into two or three doses, have been used (221).

For prevention of altitude sickness, 80 mg of ginkgo leaf extract twice daily has been used (6230).

For premenstrual syndrome (PMS), 80 mg twice daily, starting on the sixteenth day of the menstrual cycle until the fifth day of the next cycle has been used (6229).

For the treatment of attention deficit-hyperactivity disorder (ADHD), a specific combination product (AD-fX, CV Technologies, Canada) containing ginkgo leaf extract 50 combined with American ginseng extract 200 mg twice daily has been used (8235).

For the treatment of normal tension glaucoma, ginkgo leaf extract 40 mg 3 times daily has been used for up to four weeks (10378).

For Raynaud's disease, a dosage of 360 mg per day of ginkgo leaf extract, divided into three doses, has been used (11363).

For fibromyalgia, ginkgo (Bio-Biloba, Pharma Nord) 200 mg daily in conjunction with coenzyme Q-10 (Bio Quinone Q10, Pharma Nord) 200 mg for 84 days has been used (17716).

For radiation exposure, a specific gingko extract (Tanakan, Ipsen) 120 mg daily for 2-months has been used (17719).

For vitiligo, a specific ginkgo extract (Ginkgo Plus, Seroyal) 60 mg twice daily 10 minutes before breakfast and dinner for 12 weeks has been used (17718).

For all indications, start at a lower dose of not more 120 mg per day to avoid adverse gastrointestinal (GI) effects. Titrate to higher doses as needed. Dosing may vary depending on the specific formulation used. Most trials used specific standardized Ginkgo biloba leaf extracts. Some people take 0.5 mL of a standard 1:5 tincture of the crude ginkgo leaf three times daily (5011). 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).

Editor's Comments:

When people talk about Ginkgo biloba, they usually mean ginkgo leaf extract. However, traditionally only Ginkgo biloba fruit was used. "Ginkgo biloba" comes from the Chinese term Yin-Kuo, meaning "silver apricot," and biloba also describes its two-lobed, fan shaped leaves (5721). Ginkgo biloba is one of the longest living tree species in the world. Ginkgo trees can live as long as a thousand years. Using ginkgo for asthma and bronchitis was described in the first pharmacopoeia, Chen Noung Pen T'sao, dating to 2600 BC (5721). Ginkgo is the most frequently prescribed herbal medicine in Germany (5721) and is the preferred treatment for dementia (6491).
The National Center for Complementary and Alternative Medicine (NCCAM) is conducting a 5-year study of 3000 people aged 75 and older to determine if ginkgo, 240 mg daily, prevents dementia or Alzheimer's disease (6226).
In isolated cases ginkgo has been contaminated with colchicine (8541). However, follow-up studies indicate that this contamination is not widespread (8542).