

TOPIC:

GINKGO BILOBA

THE REVIEW OF

NATURAL PRODUCTS

DATE OF ISSUE:

AUGUST 2007

SCIENTIFIC NAME(S): *Ginkgo Biloba* L. Family: Ginkgoaceae

COMMON NAME(S): Ginkgo, maidenhair tree, kew tree, ginkyo, yinhsing (silver apricot-Japanese)

CLINICAL OVERVIEW– Ginkgo Biloba

Uses: Ginkgo has been studied extensively for its antioxidant and neuroprotective effects, as well as for treatment of cerebral insufficiency, cognitive impairment, dementia, peripheral vascular disease, premenstrual syndrome, schizophrenia, tinnitus, and vertigo. Limited studies also exist for its use in treating asthma, several forms of cancer, Raynaud disease, hyperlipidemia, radiation exposure, and drug-induced sexual dysfunction.

Dosing: Standardized ginkgo leaf extracts such as EGb 761 (*Tebonin forte*, Schwabe) have been used in clinical trials for cognitive and circulatory disorders at daily doses of 120 to 720 mg of extract. Extracts are usually standardized to 24% flavones and 6% terpeno lactones. Ginkgo is commercially available in several forms including teas, liquids, colas, capsules, extracts, tablets, sprays, and bars.

Contraindications: Individuals with known hypersensitivity reactions should avoid ginkgo use. Ginkgo may also interact with several medications. Because of the potential risk of increased bleeding or hemorrhage, ginkgo use should be avoided with antiplatelets (eg, aspirin) or anticoagulants (eg, warfarin), or if the patient has vitamin K deficiency. Patients with a history of, or a predisposition to, seizure activity should not take ginkgo.

Pregnancy/Lactation: Ginkgo should not be used during pregnancy and lactation. Animal studies indicate that ginkgo leaf has antiplatelet activity, as well as emmenagogue and hormonal properties.

Interactions: Ginkgo interacts with the human CYP-450 system and its isoenzymes, which may affect the metabolism of various drugs. It may also increase the risk of bleeding in individuals taking aspirin, ibuprofen, or warfarin and increase the risk of sedation in patients taking trazodone. Plasma concentrations of nifedipine may be elevated with ginkgo use, increasing therapeutic and adverse reactions. Conversely, *Ginkgo biloba* may reduce plasma concentrations of omeprazole and tolbutamide, decreasing the therapeutic effects. Caution patients receiving these agents against use of *Ginkgo biloba* without consulting their health care provider. *Ginkgo biloba* administration may increase the efficacy and decrease extrapyramidal adverse reactions of haloperidol, but only slightly decreases the area under the curve (AUC) of alprazolam.

Adverse Reactions: Severe adverse reactions are rare; possible reactions include headache, dizziness, heart palpitations, as well as GI and dermatologic reactions. Ginkgo pollen can be strongly allergenic. Contact with the fleshy fruit pulp may cause allergic dermatitis similar to poison ivy.

Toxicology: A toxic syndrome has been recognized in Asian children who have ingested ginkgo seeds.

BOTANY: The ginkgo is the world's oldest living tree species; it can be traced back more than 200 million years to fossils of the Permian geologic period and is the sole survivor of the family Ginkgoaceae. Individual trees may live as long as 1,000 years and grow to a height of about 38 m. Ginkgo has characteristic fan-shaped leaves. The species is dioecious; male trees more than 20 years old blossom in the spring. Adult female trees produce a plum-like, gray-tan fruit that falls in late autumn. Its fleshy pulp has a foul, offensive odor and can cause contact dermatitis. The edible inner seed resembles an almond and is sold in Asian markets.¹

HISTORY: The ginkgo species almost became extinct during the last ice age that began approximately 2 million years ago. The species survived in China where it was cultivated as a sacred tree and still decorates Buddhist temples throughout Asia. Ginkgo preparations have been used for medicinal purposes for more than a thousand years. Traditional Chinese physicians used ginkgo leaves to treat asthma and chilblains (ie, inflammation of the small blood vessels in the skin in response to cold, but above freezing, temperatures). Ancient Chinese and Japanese people ate roasted ginkgo seeds and considered them a digestive aid and preventive for drunken-

ness.² In the Western world, ginkgo has been used since the 1960s when technology made it possible to isolate its essential compounds. The flavonoids act as free radical scavengers, and the terpenes (ginkgolides) inhibit platelet activating factor.³ Ginkgo is one of the most commonly prescribed medications in Europe, but is not approved for medical use in the United States where it is sold only as a nutritional supplement.

CHEMISTRY: The main medicinal constituents are found in the ginkgo leaf.^{4,5} These include flavonoids and several terpene trilactones unique to ginkgo (ginkgolides and bilobalide). The 3 major flavonoids of ginkgo are quercetin, kaempferol, and isorhamnetine. About 40 minor flavonoids also have been identified and include catechins, dehydrocatechins (proanthocyanidins), and flavones (eg, ginkgetin, amentoflavone, bilobetin, sciadopitysin).⁶ The major terpene molecules unique to ginkgo are ginkgolides A, B, C, J, and M and bilobalide.^{6,7} Other medicinal constituents of ginkgo include shikimic, vanillic, ascorbic, and p-coumaric acids. Other leaf components include the steroids sitosterol and stigmasterol, polyprenols, benzoic acid derivatives, carbohydrates, straight chain hydrocarbons, alcohol, ketones, and 2-hexenol.⁶ There is a seasonal variation in the content of active compounds in leaves, with the highest amounts present in autumn.⁸

The seed portion of ginkgo contains carbohydrate (38%), protein (4%), and less than 2% fat. Ginkgotoxin, amino acids, cyanogenic glycosides, and long-chain phenols, including anacardic acid, bilobol, and cardanol, are also present.⁷ Ginkgolic acid and related alkylphenols from the lipid fraction of the fruit pods have been reviewed.⁹ The foul-smelling odor of the fleshy portion of the seeds is caused by high concentrations of butanoic and hexanoic acids. 4-O-methylpyridoxine has been isolated from the seeds.⁶

Biological standardization of ginkgo extracts has been reported.¹⁰

USES AND PHARMACOLOGY: There is an extensive history of clinical trials and pharmacological studies on ginkgo. It has been studied for its antioxidant and neuroprotective effects, as well as for treatment of cerebral insufficiency, cognitive impairment, dementia, peripheral vascular disease, premenstrual syndrome, schizophrenia, tinnitus, and vertigo. Limited studies exist for its use in treating asthma, several forms of cancer, Raynaud disease, hyperlipidemia, radiation exposure, and drug-induced sexual dysfunction. Pharmacokinetic testing of ginkgo in capsule, drop, and tablet forms has been performed in animals^{6,11} and humans.¹² The pharmacokinetics of ginkgo after intravenous (IV) and oral administration in humans have been documented.¹³ When administered orally while fasting, bioavailability is high; food did not change the AUC quantitatively but did increase the time to maximum plasma concentration (T_{max}).

Antioxidant – *Ginkgo biloba* extract (GBE) is known to have neuroprotective properties in diseases associated with free radical generation. The ginkgolides may contribute to these effects, and the flavonoid fraction contains free radical scavengers, both of which are important in conditions such as hypoxia, seizure activity, and peripheral nerve damage.¹⁴ Egb 761 induces phase 2 genes through a signaling pathway that is part of the antioxidant mechanism of EGB 761. Phase 2 enzymes play an important role in antioxidant activity by reducing electrophiles and reactive oxygen species.¹⁵

Animal data: In aged rats, GBE exerted a restorative effect caused by its protective action on the neuronal membrane¹⁶ and protected rat cerebellar neurons from oxidative stress induced by hydrogen peroxide.¹⁷ GBE is a potent inhibitor of nitric oxide production under tissue-damaging inflammatory conditions in murine macrophage cell lines.¹⁸ It was more effective than water-soluble antioxidants and as effective as lipid-soluble antioxidants in an in vitro model using human erythrocyte suspensions.¹⁹

Numerous other relevant reports exist, including effects of GBE on lipid peroxidation and cell necrosis in rat hepatocytes,²⁰ its effect as an oxygen radical scavenger and antioxidant,²¹ and its potent effects on copper-mediated low-density lipoproteins (LDL) oxidative modification.²²

Clinical data: GBE's antioxidant effects were studied in Chernobyl nuclear accident recovery workers with clastogenic factors (CF) evidenced as DNA fragmentation and damage. GBE was tested on the plasma of salvage personnel, and after 2 months of treatment at 40 mg 3 times a day, plasma CF regressed or completely disappeared.^{23,24}

Arteriosclerosis –

Animal data: Hypertensive arteriosclerosis was induced in rats with bilateral clamping of renal arteries. Over a 14-week period, the degree of arteriosclerosis and occurrence of stroke was more severe ($P < 0.05$) in untreated rats than in rats treated with a preparation of *Ginkgo biloba* known as *Tanakan*.²⁵

Clinical data: A German study examined the efficacy of ginkgo in 8 high-risk patients treated with an aortocoronary bypass. These patients received ginkgo 120 mg by mouth twice a day for 2 months with no other therapeutic regimen. Ellipsometric techniques indicated that ginkgo markedly slowed down the process of aggregational nanoplaque build-up and may have partially repaired endothelial dysfunction, which is responsible for the earliest stages of arteriosclerosis.²⁶

Asthma – Ginkgolides competitively inhibit the binding of platelet activating factor (PAF) to its membrane receptor.^{6,7} This effect is useful in treatment of allergic reaction and inflammation (asthma and bronchospasm) and also in circulatory diseases.

Animal data: Research reveals no animal data regarding the use of ginkgo for asthma.

Clinical data: Ginkgolides were effective in early and late phases of airway hyperactivity in one double-blind, randomized, crossover study in asthma patients.⁷

Cancer – The standardized extract of *Ginkgo biloba* leaves has been examined for treating several forms of cancer.²⁷ Numerous mechanisms of action have been proposed.^{24,28} The peripheral benzodiazepine receptor (PBR) is involved in several cell functions, including cell proliferation and apoptosis.²⁸ PBR is overexpressed in certain types of malignant human tumors and cancer cell lines. Treatment with EGb 761 may be useful in preventing or treating metastatic and invasive forms of cancers by decreasing PBR mRNA levels and inhibition of the proliferation of breast, glioma, and hepatocarcinoma cell lines. Other mechanisms of action²⁴ include the following:

- 1.) Promotion of apoptosis (programmed cell death) of cancer cells;
- 2.) An anticlastogenic (clastogenesis is the gain or loss of pieces of chromosome) effect on chromosomes by repairing and reconstituting broken and damaged chromosomes;
- 3.) A powerful therapeutic effect on the treatment of fibrosis-related cancer;
- 4.) A therapeutic effect on free radical-induced cancer;
- 5.) A therapeutic effect on the treatment of cancer incident to the result of numerous carcinogens;
- 6.) A therapeutic effect on preventing free radical-induced cancer;
- 7.) An enhancing effect on radiation therapy in the treatment of cancer; and
- 8.) A significant therapeutic effect on reducing the size of cancer tumors.

Animal data: Caspase-3 is a key mediator of apoptosis in mammalian cells. EGb 761-induced apoptotic cancer cell death by activating caspase-3 in oral cavity cancer cells in rats.²⁹

EGb 761 may reduce the risk of stomach cancer by dose-dependent inhibition of gastric mucosal lesions.^{30,31}

Clinical data: Thirty patients with gastric cancer were treated with 2 oral *Ginkgo biloba* exocarp polysaccharides (GBEP) capsules twice a day for over 1 month. An electron gastroscope was used to measure the area of tumors before and after treatment. Inhibitory and effective rates were then calculated. Results show that GBEP capsules reduced the area of tumors by an effective rate of 73%.³²

In one clinical trial, 32 patients with progressive advanced colorectal cancer were treated with ginkgo extract (EGb 761) 350 mg following conventional 5-fluorouracil (5-FU) therapy. Ginkgo improved the efficacy of 5-FU in colorectal cancer patients. Progression of the cancer occurred in 22 patients,

there was no change in 8 patients, and partial responses were seen in 2 patients for an overall response rate of 6.3%. Results of the combined treatment of EGb 761 and 5-FU suggest a favorable benefit-risk ratio and an increased median survival time of 9.5 months, which is similar to other second-line combination treatments.³³

One epidemiologic study claims that ginkgolide A and B may be associated with chemoprevention of certain forms of ovarian cancer.³⁴

Cerebral insufficiency – Cerebral insufficiency may cause anxiety and stress, as well as memory, concentration, and mood impairment and hearing disorders, all of which may benefit from ginkgo therapy.

Animal data: Ginkgo leaf improves cerebral metabolism and protects against hypoxic damage in animals with cerebral ischemia.⁷

Clinical data: IV injection of GBE produced an age-related increase in cerebral blood flow in about 70% of the patients evaluated. Patients between 30 and 50 years of age had a 20% increase from baseline, compared with 70% in those 50 to 70 years of age. The time to reach peak blood flow was shorter in elderly patients.³⁵ Cerebral insufficiency in 112 patients (average age, 70.5 years) treated with ginkgo leaf extract 120 mg for 1 year, reduced symptoms such as headache, dizziness, short-term memory, vigilance, and disturbance.⁷ Electroencephalographic effects of different GBE preparations have been investigated.³⁶

A review of 40 clinical trials was performed, most of which evaluated GBE 120 mg daily for 4 to 6 weeks and reported positive results in treating cerebral insufficiency. However, only 8 studies did not have major methodological flaws; therefore, the results from these studies were difficult to interpret. Results suggest that long-term treatment (longer than 6 weeks) is required and that any effect is similar to that observed following treatment with ergoloids.³⁷ A meta-analysis of 11 placebo-controlled, randomized, double-blind studies, concluded that GBE 150 mg daily was superior to placebo in patients with cerebrovascular insufficiency.³⁸

Diabetes – Ginkgo-induced reduction of blood glucose may involve several mechanisms of action. One hypothesis involves ginkgo improving pancreatic beta cell function by stimulating insulin secretory activity. Similar to other insulin secretagogues, ginkgo's effect was dependent on calcium influx and activation of kinases (2 in particular, CaMK II and PKA). Protein kinases may help improve calcium efficacy during glucose-stimulated insulin secretion.³⁹

Animal data: EGb 761 and bilobalide were assessed over 15 days in normal rats and in rats with type 2 diabetes induced by streptozotocin injection. Overall, treatment with EGb 761 or

bilobalide increased glucose uptake and glycogen synthesis as evidenced by increased concentrations in liver and skeletal muscle.⁴⁰ Ginkgo reduced the elevation of rat plasma glucose levels after oral administration of various saccharinity agents by inhibiting alpha-amylase and glucosidase.⁴¹ Evidence also exists for nephro-,⁴² cardio-,⁴³ and hepatoprotective⁴⁴ effects of EGb 761 against diabetes.

Clinical data: Twenty healthy subjects with normal glucose tolerance blood levels were administered a glucose tolerance test before and after 3 months of therapy with *Ginkgo biloba* 120 mg at bedtime. After 3 months, a significant ($P < 0.001$) increase in fasting plasma levels of insulin and C-peptide and C-peptide AUC was found when measured after 2 hours of 75 g glucose tolerance test. No changes in glucose tolerance were observed. EGb 761 was hypothesized to increase the rate of insulin metabolic clearance.⁴⁵ In a follow-up study, EGb 761 increased pancreatic beta cell function in type 2 diabetes patients on oral hypoglycemic agents in response to glucose tolerance testing.⁴⁶ The pharmacokinetic properties of metformin 500 mg once daily were not affected with coingestion of 120 mg of EGb 761 over 3 months.⁴⁷ Ingestion of 120 mg of EGb 761 for 3 months did not produce insulin resistance in the non- and prediabetic populations, nor did it exacerbate the disease in the type 2 diabetic subjects.⁴⁸

Memory improvement – Animal experiments found ginkgo to be associated primarily with cholinergic effects and secondarily with a histaminergic mechanism.⁴⁹

Animal data: Oral administration of GBE alone or in combination with *Panax ginseng* improved retention of learned behavior using conditioned-reflex methods (punishment or positive reinforcement) in young and old rats.⁵⁰ GBE can improve behavioral adaptation despite adverse environmental events, as shown in rats taught reward versus punishment (stress) testing to obtain drinking water. This supports clinical use of ginkgo to treat cognitive impairment in the elderly population.⁵¹

Clinical data: In elderly men with slight age-related memory loss, ginkgo supplementation reduced the time required to process visual information.⁵² Effects of GBE on event-related potentials in 48 patients with age-associated memory impairment have been studied.⁵³ Improvement in memory, as measured by a series of psychological tests, in 8 patients (average age, 32 years) was found 1 hour after administration of GBE 600 mg versus placebo, again confirming the plant's effectiveness.⁷

Mental disorders caused by dementia – Clinical application of *Ginkgo biloba* in dementia syndromes has been reported, and therapeutic efficacy has been demonstrated.^{54,55} One report supports early GBE therapy in dementia, especially because the lack of adverse reactions as compared with other dementia

drugs.⁵⁶ EGb 761 is the focus of two phase 3 clinical trials, the GEM (Ginkgo Evaluation of Memory) study in the United States and the GuidAge study in France. Primary outcome measures of the GEM study include decreased incidence of dementia due to all causes following EGb 761 administration, while secondary outcome measures include rate of cognitive and functional decline, incidence of cardiovascular and cerebrovascular events, and mortality. The primary outcome measure of the GuidAGE study is the prevention of Alzheimer disease. Results for each study should be available around 2010, and each study includes more than 3,000 subjects older than 70 years of age.⁵⁷⁻⁶⁰

Animal data: There is no animal data regarding the use of ginkgo for dementias.

Clinical data: Effects of GBE 240 mg daily in approximately 200 patients with dementia of the Alzheimer type and multi-infarcton dementia have been investigated in a randomized, double-blind, placebo-controlled, multicenter study. Parameters such as psychopathological assessment, attention, memory, and behavior were monitored, resulting in clinical efficacy of the extract in dementia of both types.⁶¹ In another set of patients with moderate dementia (of Alzheimer, vascular, or mixed types), short-term IV infusion therapy with GBE also had positive results, improving psychopathology and cognitive performance.⁶² In a 52-week, randomized, double-blind, placebo-controlled, multicenter study, mild to severe Alzheimer or multi-infarction dementia patients received GBE 120 mg daily versus placebo. Results of this report again confirm improved cognitive performance and social functioning in those patients who have mild to moderately severe dementia.⁶³

One 52-week randomized, double-blind, placebo-controlled, parallel-group, multicenter trial examined the effect of EGb 761 administered at a lower dose of 40 mg 3 times a day on cognitive performance and social functioning. Primary outcome measures included results from the Alzheimer Disease Assessment Scale (ADAS-cog), which has gained acceptance as the best primary criterion of efficacy. Scores range from 0 to 70, with the lower number indicating best outcome. Patients were placed in several strata based on severity of condition. Results documented that EGb 761 improved mild to moderate dementia and slowed the deterioration of severe dementia.⁶⁴

EGb 761 was approved for the treatment of dementia in Germany,⁵⁷ partly based on evidence from a case-control study known as the EPIDOS (Epidemiology of Osteoporosis) study in a cohort of 1,462 elderly women older than 75 years of age. Sixty-nine women with Alzheimer-type dementia were compared with 345 paired women whose cognitive function remained normal. The cognitive function was evaluated at baseline and over a 7-year follow-up period. Results documented fewer women developing Alzheimer dementia after being prescribed EGb 761 for 2 years.^{57,65}

Controversy persists on the clinical efficacy of EGb 761 versus cholinesterase inhibitors. A meta-analysis on the efficacies of ginkgo, donepezil, rivastigmine, and galantamine on changes in cognitive function in patients with dementia was examined. Outcomes were assessed after 6 months of treatment and primarily included patient tolerability. According to the results of the meta-analysis, patient compliance was more effective with cholinesterase inhibitors than with ginkgo.⁶⁶ One 24-week randomized, placebo-controlled, double-blind trial found no difference in efficacy of EGb 761 (160 mg by mouth once a day) versus donepezil (5 mg by mouth once a day) in treating mild to moderate Alzheimer dementia.⁶⁷ A review article documents a more favorable adverse reaction profile for EGb 761, with up to 90% of patients developing nausea and vomiting during therapy with cholinesterase inhibitors. Also the efficacy of cholinesterase inhibitors rapidly diminishes after ending administration when compared with EGb 761. Finally, adverse drug reactions are over 10 times more common and treatment costs 5 times higher with cholinesterase inhibitors than with EGb 761.⁶⁸

Mental disorders caused by schizophrenia –

Animal data: There is no animal data supporting the use of ginkgo for schizophrenia.

Clinical data: Concurrent use of *Ginkgo biloba* and haloperidol may increase the efficacy and decrease extrapyramidal adverse reactions of haloperidol. In a double-blind, placebo-controlled study, 56 patients with chronic, treatment-resistant schizophrenia were randomly assigned to receive *Ginkgo biloba* extract 360 mg daily plus haloperidol 0.25 mg/kg/day, while 53 patients received placebo plus haloperidol for 12 weeks. Coadministration of *Ginkgo biloba* and haloperidol was clinically superior to placebo plus haloperidol in treating positive and negative symptoms in these patients. As a mechanism, it is suspected that *Ginkgo biloba* may scavenge free radicals produced by hyperdopaminergic activity.⁶⁹ In a single-blind study over an 8-week period, 29 patients diagnosed with schizophrenia were randomized to receive olanzapine with *Ginkgo biloba* extract or olanzapine alone. Often antioxidant enzymes like superoxide dismutase and catalase are elevated in patients with chronic schizophrenia, and patients administered the extract had greater decreases in mean levels of these antioxidant enzymes compared with patients who did not receive the extract. Patients also reported greater improvements on the Scale for the Assessment of Positive Symptoms than patients receiving olanzapine therapy alone.⁷⁰ In a 12-week randomized, blind, controlled study, EGb 761 and haloperidol were more effective than placebo and haloperidol in treating symptoms in patients with chronic refractory schizophrenia.⁷¹

One study examined the potential immunostimulatory properties of EGb 761 and its therapeutic actions on schizophrenia, who often have decreased immune function. One hundred nine

schizophrenic inpatients were randomly assigned to 12 weeks of treatment with either EGb 761 plus haloperidol or placebo plus haloperidol. The results document a potential relationship between decreased immune function and increased free radical production in schizophrenia. The addition of EGb 761 improved decreased peripheral immune function in schizophrenia, particularly in several T-cell subpopulations.⁷²

Peripheral vascular disease –

Animal data: There is no animal data regarding the use of ginkgo for peripheral vascular disease.

Clinical data: A meta-analysis evaluating GBE in peripheral arterial disease found a large therapeutic effect of the plant.⁷³ Numerous studies of GBE and circulatory disorders have been conducted, including GBE's ability to protect against cardiac ischemia reperfusion injury,⁷⁴ to adjust fibrinolytic activity,⁷⁵ and, in combination with aspirin, to treat thrombosis.⁷⁶ It appears useful in management of peripheral vascular disorders such as Raynaud disease, acrocyanosis, and postphlebitis syndrome.⁷⁷ In humans, IV administration of ginkgo extract 50 to 200 mg caused a dose-dependent increase in microcirculation and blood viscoelasticity in patients with pathologic blood flow disorders.⁷⁸

A 6-month, double-blind trial suggested some efficacy in treating obliterative arterial disease of the lower limbs. Patients who received the extract showed a clinically and statistically significant improvement in pain-free walking distance, maximum walking distance, and plethysmographic recordings of peripheral blood flow.⁷⁹ GBE improved walking performance in 60 patients with intermittent claudication, with good tolerance of the treatment.⁸⁰ However, another report concluded that GBE 120 mg daily had no effect on walking distance or leg pain in intermittent claudication patients but did improve other cognitive functions.⁸¹ A review of 10 controlled trials evaluating treatment with the plant for this condition reported poor methodological quality but noted that all studies showed clinical efficacy of GBE in treating intermittent claudication.⁸² In another study in which GBE extract was given, peripheral blood flow increased 40% to 45%, compared with an increase of 35% after administration of nicotinic acid.⁸³

Sexual dysfunction caused by antidepressant drugs –

Animal data: There is no animal data regarding the use of ginkgo for sexual dysfunction caused by antidepressant drugs.

Clinical data: Twenty-two patients were treated with *Ginkgo biloba* 300 mg 3 times a day for sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRI). Three women (13.6%) experienced some improvement in sexual function. SSRI-induced sexual dysfunction was defined as a decrease in sexual desire, arousal, or orgasm within 1 month of starting treatment with an SSRI. No statistical data was provided.⁸⁴

One review article reported no improvement with ginkgo versus placebo in a 2-month randomized, placebo-controlled, double-blind study of 37 patients with SSRI-induced sexual dysfunction. Patients received placebo or ginkgo 120 mg daily, which was increased to 240 mg daily by the end of the study. Outcomes were assessed by questionnaire and found a substantial placebo effect with improvement in sexual function.⁸⁵

In a small 6-week prospective pilot study, 12 patients with antidepressant-induced sexual dysfunction were treated with oral *Ginkgo biloba* 240 mg every day. Outcome measures included results from Hamilton Anxiety, Hamilton Depression, and Wheatley Stress and Sex Profile questionnaires. Results from patient responses documented a significant ($P < 0.01$) improvement in sexual function during supplementation with ginkgo. Minor adverse reactions (eg, gastric irritation) were recorded during the study.⁸⁶ A 12-week, triple-blind, placebo-controlled study that involved 21 patients and investigated comparable outcome measures documented similar results.⁸⁷

Stress and anxiety – In rats, an assay of monoamine oxidase (MAO) inhibition produced by ginkgo extracts (dried and fresh leaves) was performed, suggesting a mechanism by which the plant may exert its antistress actions.⁸⁸ Ginkgo leaf extract inhibited MAO-A and MAO-B in the rat brain. The neuroprotective properties of ginkgo are primarily caused by kaempferol.⁸⁹ Glucocorticoid synthesis, regulated by adrenocorticotrophic hormone (ACTH), which accelerates cholesterol transport, can lead to neurotoxicity. Ginkgolides A and B decrease cholesterol transport, reducing corticosteroid synthesis. The antistress and neuroprotective effects of GBE may also be mediated by this mechanism of action.⁹⁰

Animal data: GBE in combination with *Zingiber officinale*, was compared with diazepam in a study of anxiolytic effects in animals. Results showed these effects to be comparable to those of diazepam, but in high doses the combination may have anxiolytic properties.⁹¹ Social behavior in animals has been evaluated using GBE, diazepam, and ethyl beta-carboline-3-carboxylate.⁹²

Clinical data: In a randomized, placebo-controlled, double-blind study, 107 patients diagnosed with generalized anxiety disorder or adjustment disorder with anxious mood received either 480 mg of EGb 761, 240 mg of EGb 761, or placebo once daily for 4 weeks. Primary outcome measures included results from the Hamilton Anxiety Scale. Secondary outcome measures included results from a series of psychological exams. EGb 761 was superior to placebo in high- and low-dose EGb 761 treatment groups on all secondary outcome measures.⁹³

Tinnitus hearing disorder therapy – Because of the diverse etiology of tinnitus and lack of objective methods to measure its symptoms, results using GBE for treatment of this syndrome of hearing disorder are contradictory. GBE may have positive effects in some individuals.⁹⁴

Animal data: In animals with salicylate-induced tinnitus, GBE resulted in a statistically significant decrease of behavioral manifestations.⁹⁵

Clinical data: In patients with hearing disorders secondary to vascular insufficiency of the ear, about 40% of those treated orally with a leaf extract for 2 to 6 months showed improvement in auditory measurements. The extract also was extremely effective in relieving vertigo associated with vestibular dysfunction.⁷⁷

Other pharmacological activity –

Analgesic activity: In one animal study in rats, EGb 761 blocked thermal hyperalgesia and had significant ($P < 0.01$) analgesic activity.⁹⁶

Antifibrotic activity: EGb 761 was effective in arresting fibrosis development in 86 patients with chronic hepatitis.⁹⁷ *Ginkgo biloba* had potent antifibrotic activity against bleomycin-induced lung fibrosis in rats.⁹⁸

Chemotherapeutic activity: *Ginkgo biloba* has in vitro and in vivo activity against *Pneumocystis carinii*⁹⁹ and has been studied in animals with diabetes,^{100,101} as well as in human diabetic patients. Seed extracts of the plant possess antibacterial and antifungal activity.⁶ Ginkgetin, from *Ginkgo biloba*, inhibited the influenza virus sialidase, which facilitates release of virus particles from the infected cell.¹⁰²

Hyperlipidemia: *Ginkgo biloba* helped prevent the deterioration of lipid profiles when subjects were challenged with high-cholesterol meals over an extended holiday season.¹⁰³

Ocular effects: Some studies have reviewed GBE's numerous mechanisms that may be beneficial in treating ophthalmic disorders,⁶ including its therapeutic value in ocular blood flow, antioxidant activity, platelet activating factor inhibitory activity, nitric oxide inhibition, and neuroprotective activity in certain forms of glaucoma.^{104,105}

Premenstrual syndrome: A multicenter, double-blind, placebo-controlled study of 143 women (18 to 45 years of age) administered a ginkgo extract 160 mg daily (EGb 761) or placebo documented improvement in the symptoms of premenstrual syndrome, particularly breast-related symptoms, with ginkgo supplementation.¹⁰⁶ GBEs exhibited estrogenic and antiestrogenic activity and had a biphasic effect on estrogen.¹⁰⁷

Multiple sclerosis: A 4-week, double-blind, placebo-controlled study examined the efficacy of 240 mg daily of EGb 761 in 22 patients with multiple sclerosis. Outcome measures included depression, anxiety, fatigue, symptom severity, and functional performance, with ginkgo-treated patients showing greater improvement in measures of fatigue, symptom severity, and functionality. No adverse reactions were reported.¹⁰⁸

Stroke: *Ginkgo biloba* extract is widely used in China to treat acute ischemic stroke.^{109,110} However, a systematic review that included 10 trials with a total of 792 patients and assessed the

efficacy of ginkgo found no convincing evidence to support the use of ginkgo for recovery after stroke or improvement in neurological deficit at the end of treatment.¹¹⁰ Some animal studies document a neuroprotective effect of bilobalide, a constituent of *Ginkgo biloba*, in treating brain edema secondary to stroke or traumatic brain injury.^{111,112} Another animal study documented similar efficacy with the use of EGb 761 and *Losartan* (an angiotensin II receptor antagonist) in reducing expression of pro-apoptotic genes. Reduction of the immunoreactivity of these genes may have a therapeutic effect for stroke treatment.¹¹³

Ulcerative colitis: Results of macroscopic, histological, and biochemical data document that *Ginkgo biloba* reduced inflammation and acute colonic damage induced by acetic acid dose-dependently in rats. The authors demonstrate that *Ginkgo biloba* may be effective in certain forms of inflammatory bowel disease involving cytokines or free radicals.¹¹⁴

DOSING: Standardized ginkgo leaf extracts such as EGb 761 (*Tebonin forte*, Schwabe) have been used in clinical trials for cognitive and circulatory disorders at daily doses of 120 to 720 mg of extract. Extracts are usually standardized to 24% flavones and 6% terpene lactones.^{80,115-121} Ginkgo is available commercially in several dosage forms, including teas, liquids, colas, capsules, extracts, tablets, sprays, and bars.

PREGNANCY/LACTATION: Ginkgo should not be used during pregnancy and lactation. A systematic review of 7 electronic databases found evidence from animal studies that ginkgo leaf has antiplatelet activity,¹²² as well as emmenagogue and hormonal properties. The review article also refers to a report of ginkgo products being adulterated with colchicine, which can arrest cell division, thus affecting fetal growth; however, the accuracy of this report has been challenged. An animal study in pregnant rats treated with 7 to 14 mg/kg/day of ginkgo resulted in significant reduction in fetal body weights.¹²³

INTERACTIONS: Ginkgo interacts with the human CYP-450 system and its isoenzymes, which may affect the metabolism of various drugs.¹²⁴⁻¹²⁷

Anticoagulants (eg, warfarin) – Intracerebral hemorrhage occurred in a woman 78 years of age receiving warfarin and *Ginkgo biloba*.¹²⁸ The patient had been taking warfarin for 5 years, with her daughter reporting that she had been giving her mother *Ginkgo biloba* for 2 months. During that time, she developed severe apraxia, a marked change in her mild to moderate cognitive deficits, and an inability to feed herself; a computer tomography scan revealed a left parietal hemorrhage. The interaction was attributed to additive or synergistic anticoagulant effects between *Ginkgo biloba* and warfarin. Bleeding disorders have also been reported in at least 2 patients

receiving *Ginkgo biloba* in the absence of warfarin.^{128,129} In a placebo-controlled, double-blind, crossover study in patients on stable, long-term warfarin therapy, *Ginkgo biloba* 100 mg daily did not influence the anticoagulant response of warfarin measured by the international normalized ratio.¹³⁰

Anticonvulsants (eg, phenytoin, valproic acid and derivatives) – A case report exists of a 55-year-old man who suffered from a fatal breakthrough seizure.¹³¹ Evidence documented subtherapeutic serum levels for both of his anticonvulsants *Depakote* and *Dilantin*. The man was also self-medicating with *Ginkgo biloba*. Both *Depakote* and *Dilantin* are metabolized by CYP2C9, so induction of this enzyme by ginkgo may explain their subtherapeutic levels. Ginkgo also has been found to protect against the hepatotoxicity in *Depakote*-treated patients; the mechanism of action involves ginkgo reducing the overproduction of reactive oxygen species caused by *Depakote*.^{132,133}

Antihypertensives (eg, nifedipine, propranolol) – *Ginkgo biloba* may inhibit the metabolism of nifedipine, elevating nifedipine plasma concentrations and increasing the pharmacologic and adverse reactions. Compared with giving nifedipine alone, administration of nifedipine 10 mg after 18 days of *Ginkgo biloba* 120 mg/day to 21 healthy volunteers increased nifedipine plasma levels 29% when measured 0.5 hours after nifedipine administration.¹³⁴ An animal study documented that pretreatment with EGb 761 decreased plasma concentrations of propranolol by inducing several CYP enzymes.¹³⁵

Antiplatelet medications (eg, aspirin) – Spontaneous hemorrhaging into the anterior chamber of the right eye occurred in a man 70 years of age while taking aspirin and *Ginkgo biloba* tablets (containing 40 mg of extract).¹³⁶ The patient had been taking aspirin 325 mg daily for 3 years and started *Ginkgo biloba* 1 week before the bleeding episode. The interaction may have resulted from an additive or synergistic inhibitory effect on platelet aggregation caused by at least one of the GBE components.¹³⁷

Benzodiazepines (eg, alprazolam, midazolam) – *Ginkgo biloba* may slightly decrease alprazolam plasma concentrations. In 12 healthy volunteers, 14 days of pretreatment with GBE 60 mg twice daily decreased the AUC of alprazolam 17% when administered as a single oral 2 mg dose.¹³⁸ The clearance of midazolam was decreased 26% in an experiment in 10 healthy volunteers who were also administered GBE 360 mg daily for 28 days.¹³⁹

Cyclosporin – Results of an animal study documented decreased oral bioavailability of cyclosporin (62%) and reduced clearance (51%) with ginkgo.¹⁴⁰

Digoxin – An open-label, randomized, crossover study in 8 healthy volunteers who were administered ginkgo 240 mg daily for 2 weeks documented a 21.9% increase in the AUC of digoxin at a dosage of 0.5 mg.¹⁴¹

Haloperidol – Concurrent use of *Ginkgo biloba* and haloperidol may increase the efficacy and decrease extrapyramidal adverse reactions of haloperidol as documented in a double-blind, placebo-controlled study of 56 patients with chronic, treatment-resistant schizophrenia.⁶⁹

Nonsteroidal anti-inflammatory drugs (eg, ibuprofen) – Fatal intracerebral mass bleeding occurred in a man 71 years of age taking concurrent *Ginkgo biloba* and ibuprofen.¹⁴² He had been taking GBE 40 mg twice daily for at least 30 months before his death, which occurred 4 weeks after starting ibuprofen 600 mg daily. –

Proton-pump inhibitors (eg, omeprazole) – *Ginkgo biloba* may increase the metabolism of omeprazole, reducing its plasma concentrations and decreasing therapeutic effect. In 12 healthy subjects, administration of omeprazole 40 mg after 12 days of pretreatment with GBE 140 mg twice daily decreased the ratio of the omeprazole AUC to the 5-hydroxyomeprazole metabolite 68%, compared with taking omeprazole alone.¹⁴³ In addition, urinary recovery of the metabolite was reduced.

SSRIs (eg, fluoxetine) – *Ginkgo* may increase the risk of serotonin syndrome when taken with SSRIs. A case report documents a hypomanic episode after the addition of *Ginkgo biloba* and St. John's wort to a regimen of buspirone and fluoxetine.¹⁴⁴

Sulfonylureas (eg, tolbutamide) – In a study in 10 healthy men taking tolbutamide 125 mg alone and after receiving *Ginkgo biloba* extract 120 mg 3 times daily for 28 days, pretreatment with *Ginkgo biloba* reduced tolbutamide AUC 16% and attenuated the blood-glucose lowering effect of tolbutamide.¹⁴⁵ *Ginkgo biloba* may increase the metabolism (CYP2C9) of tolbutamide.

Trazodone – The risk of sedation with trazodone may increase with concurrent ingestion of *Ginkgo biloba*.¹⁴⁶ A woman 80 years of age with Alzheimer disease went into a coma during coadministration of trazodone 20 mg twice daily and *Ginkgo biloba* 80 mg twice daily. The patient was taken to the hospital and immediately regained consciousness following the administration of flumazenil to antagonize the effects of trazodone. The mechanism for this possible interaction is not known.

ADVERSE REACTIONS: Severe adverse reactions are rare; possible effects include headache, dizziness, heart palpitations, as well as GI and dermatologic reactions. *Ginkgo* pollen can be strongly allergenic. Contact with the fleshy fruit pulp can cause allergic dermatitis similar to poison ivy.

Adverse reactions from clinical trials using doses of up to 160 mg/day for 4 to 6 weeks did not differ from placebo

groups. Injectable forms of ginkgo may cause circulatory disturbances, skin allergy, or phlebitis. A parenteral ginkgo product (*Tebonin*) has been withdrawn from the market because of the possible severity of adverse reactions.⁶

Cardiovascular effects – In one case report, a patient developed heart palpitations after taking *Ginkgo biloba*,¹⁴⁷ which resolved with discontinuation. Another study documented reductions in systolic and diastolic blood pressure with ginkgo extract 120 mg daily for 3 months.⁴⁵

In one report, spontaneous bilateral subdural hematomas were associated with ingestion of the plant.¹²⁸

Dermatological effects – The fleshy fruit pulp has been known since ancient times as a skin irritant. Constituents alkylbenzoic acid and alkylphenol derivatives cause reactions of this type. Allergic dermatitis (eg, erythema, edema, blisters, itching) have all been reported,⁶ with the existence of cross-allergenicity between ginkgo fruit pulp and poison ivy. Ginkgolic acid and bilobin are structurally similar to the allergens of poison ivy, mango rind, and cashew nut shell oil. Contact with the fruit pulp may cause erythema and edema, with the rapid formation of vesicles accompanied by severe itching and symptoms lasting 7 to 10 days. Ingestion of as little as 2 pieces of pulp has been reported to cause perioral erythema, rectal burning, and tenesmus (painful spasms of the anal sphincter).¹

A 45-year-old man developed acute generalized exanthematous pustulosis during treatment for tinnitus with ginkgo. Within 2 days, the rash spread to his limbs and face but resolved within 10 days after discontinuation of the ginkgo supplement.¹⁴⁸

GI effects – Allergens ginkgol and ginkgolic acid can cause contact reactions of mucous membranes resulting in cheilitis and GI irritation. Oral ingestion of ginkgo preparations, however, does not produce this effect.^{6,7} *Ginkgo* pollen can also be strongly allergenic.¹⁴⁹

TOXICOLOGY: Individuals with known hypersensitivity reactions should avoid ginkgo use. *Ginkgo* may also interact with several medications. Because of the potential risk of increased bleeding or hemorrhage, ginkgo use should be avoided with antiplatelets (eg, aspirin) or anticoagulants (eg, warfarin), or if the patient has vitamin K deficiency.^{150,151} Patients with a history of, or a predisposition to, seizure activity should not take ginkgo.¹⁵²

A toxic syndrome (“Gin-nan” food poisoning) has been recognized in children who have ingested ginkgo seeds. Approximately 50 seeds have produced tonic-clonic seizures and loss of consciousness.^{153,154,155} Seventy reports (between 1930 and

1960) found 27% lethality, with infants being most vulnerable. Ginkgotoxin (4-O-methylpyridoxine), found only in the seeds, was considered responsible for this toxicity.^{6,7} In animal experimentation with GBE, no mutagenic or teratogenic effects

were found. Oral administration of up to 1,600 mg/kg/day to rats did not produce teratogenic effects. Other animal toxicity data are available including lethal dosing and other studies performed in mice, rats, guinea pigs, rabbits, and dogs.⁶

REFERENCES

- 1 Becker LE, Skipworth GB. Ginkgo-tree dermatitis, stomatitis, and proctitis. *JAMA* 1975;231:1162-1163.
- 2 Castleman M. *The Herb Quarterly*. 1990 Spring:26.
- 3 Z'Brun A. Ginkgo—myth and reality [in German]. *Schweiz Rundschr Med Prax*. 1995;84:1-6.
- 4 van Beek TA, Bombardelli E, Morazzoni P, Peterlongo F. *Ginkgo biloba* L. *Fitoterapia*. 1998;LXIX:195-244.
- 5 van Beek TA, Lelyveld GP. Concentration of Ginkgolides and bilobalide in *Ginkgo biloba* leaves in relation to the time of year. *Planta Med*. 1992;58:413-416.
- 6 *Ginkgo biloba*. In: De Smet PA, et al, eds. *Adverse Effects of Herbal Drugs*. New York, NY: Springer-Verlag; 1997:51-66.
- 7 Newall CA, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Health-Care Professionals*. London, England: Pharmaceutical Press; 1996:138-140.
- 8 Briancon-Scheid F, Lobstein-Guth A, Anton R. HPLC separation and quantitative determination of biflavones in leaves from *Ginkgo biloba*. *J Med Plant Res*. 1983;49:204-207.
- 9 Jaggy H, Koch E. Chemistry and biology of alkylphenols from *Ginkgo biloba* L. *Pharmazie*. 1997;52:735-738.
- 10 Steinke B, Muller B, Wagner H. Biological standardization of Ginkgo extracts [in German]. *Planta Med*. 1993;59:155-160.
- 11 Pietta PG, Gardana C, Mauri PL, Maffei-Facino R, Carini M. Identification of flavonoid metabolites after oral administration to rats of a *Ginkgo biloba* extract. *J Chromatogr B Biomed Appl*. 1995;673:75-80.
- 12 Wojcicki J, Gawronska-Szklarz B, Bieganski W, et al. Comparative pharmacokinetics and bioavailability of flavonoid glycosides of *Ginkgo biloba* after a single oral administration of three formulations to healthy volunteers. *Mater Med Pol*. 1995;27:141-146.
- 13 Fourtillan J, Brisson AM, Girault J, et al. Pharmacokinetic properties of Bilobalide and Ginkgolides A and B in healthy subjects after intravenous and oral administration of *Ginkgo biloba* extract (EGb 761) [in French]. *Therapie*. 1995;50:137-144.
- 14 Smith PE, MacLennan K, Darlington CL. The neuroprotective properties of the *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor (PAF). *J Ethnopharmacol*. 1996;50:131-139.
- 15 Liu XP, Goldring CE, Coppole IM, et al. Extract of *Ginkgo biloba* induces phase 2 genes through Keap1-Nrf2-ARE signaling pathway. *Life Sciences*. 2007; In Press, Accepted Manuscript.
- 16 Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT_{1A} receptors during ageing: reversal by *Ginkgo biloba* extract (EGb 761). *J Pharm Pharmacol*. 1994;46:316-318.
- 17 Oyama Y, Chikahisa L, Ueha T, Kanemaru K, Noda K. *Ginkgo biloba* extract protects brain neurons against oxidative stress induced by hydrogen peroxide. *Brain Res*. 1996;712:349-352.
- 18 Kobuchi H, Droy-Lefaix MT, Christen Y, Packer L. *Ginkgo biloba* extract (EGb 761): inhibitory effect on nitric oxide production in the macrophage cell line RAW 264.7. *Biochem Pharmacol*. 1997;53:897-903.
- 19 Kose K, Dogan P. Lipoperoxidation induced by hydrogen peroxide in human erythrocyte membranes. 2. Comparison of the antioxidant effect of *Ginkgo biloba* extract (EGb 761) with those of water-soluble and lipid-soluble antioxidants. *J Int Med Res*. 1995;23:9-18.
- 20 Joyeux M, Lobstein A, Anton R, Mortier F. Comparative antilipoperoxidant, antineurotic and scavenging properties of terpenes and biflavones from Ginkgo and some flavonoids. *Planta Med*. 1995;61:126-129.
- 21 Maitra I, Marcocci L, Droy-Lefaix MT, Packer L. Peroxyl radical scavenging activity of *Ginkgo biloba* extract EGb 761. *Biochem Pharmacol*. 1995;49:1649-1655.
- 22 Yan L, Droy-Lefaix MT, Packer L. *Ginkgo biloba* extract (EGb 761) protects human low density lipoproteins against oxidative modification mediated by copper. *Biochem Biophys Res Commun*. 1995;212:360-366.
- 23 Emerit I, Oganessian N, Sarkisian T, et al. Clastogenic factors in the plasma of Chernobyl accident recovery workers: anticlastogenic effect of *Ginkgo biloba* extract. *Radiat Res*. 1995;144:198-205.
- 24 Eli R, Fasciano JA. An adjunctive preventive treatment for cancer: ultraviolet light and *Ginkgo biloba*, together with other antioxidants, are a safe and powerful, but largely ignored, treatment option for the prevention of cancer. *Med Hypotheses*. 2006;66:1152-1156.
- 25 Fang Y, Huang R, Zhang Y, Lin J, Li J. A preliminary investigation of Tanakan in the treatment of hypertensive arteriosclerosis and stroke in rats. *Chin Med J* [in English]. 2000;113:425-428.
- 26 Schäfer P, Rodríguez M, Just S, et al. The effect of *Ginkgo biloba* (EGb 761) on arteriosclerotic nodule formation and size in a long-term clinical trial. *Desalinat*. 2006;191:426-431.
- 27 Li W, Pretner E, Shen L, Drieu K, Papadopoulos V. Common gene targets of *Ginkgo biloba* extract (EGb 761) in human tumor cells: relation to cell growth. *Cell Mol Biol*. 2002;48:655-662.
- 28 Pretner E, Amri H, Li W, et al. Cancer-related overexpression of the peripheral-type benzodiazepine receptor and cytostatic anticancer effects of *Ginkgo biloba* extract (EGb 761). *Anticancer Res*. 2006;26(1A):9-22.
- 29 Kim KS, Rhee KH, Yoon JH, Lee JG, Lee JH, Yoo JB. *Ginkgo biloba* extract (EGb 761) induces apoptosis by the activation of caspase-3 in oral cavity cancer cells. *Oral Oncol*. 2005;41:383-389.
- 30 Wang Q, Zhao WZ, Ma CG. Protective effects of *Ginkgo biloba* extract on gastric mucosa. *Acta Pharmacol Sin*. 2000;21:1153-1156.
- 31 Chen SH, Liang YC, Chao JC, et al. Protective effects of *Ginkgo biloba* extract on the ethanol-induced gastric ulcer in rats. *World J Gastroenterol*. 2005;11:3746-3750.
- 32 Xu AH, Chen HS, Sun BC, et al. Therapeutic mechanism of *Ginkgo biloba* exocarp polysaccharides on gastric cancer. *World J Gastroenterol*. 2003;9:2424-2427.
- 33 Hauns B, Haring B, Kohler S, Mross K, Unger C. Phase II study of combined 5-fluorouracil/*Ginkgo biloba* extract (GBE 761 ONC) therapy in 5-fluorouracil pre-treated patients with advanced colorectal cancer. *Phytother Res*. 2001;15:34-38.
- 34 Ye B, Aponte M, Dai Y, et al. *Ginkgo biloba* and ovarian cancer prevention: Epidemiological and biological evidence. *Cancer Lett*. 2006 Dec 26; [Epub ahead of print].
- 35 Agnoli A, Fiorani P, Pistolesse GR. Preliminary results in the modifications of cerebral blood flow using xenon-133 during administration of *Ginkgo biloba* [in Italian]. *Minerva Med*. 1973;64(suppl 79):4166-4173.
- 36 Kunkel H. EEG profile of three different extractions of *Ginkgo biloba*. *Neuropsychobiology*. 1993;27:40-45.
- 37 Kleijnen J, Knipschild P. *Ginkgo biloba* for cerebral insufficiency. *Br J Clin Pharmacol*. 1992;34:352-358.
- 38 Hopfenmuller W. Evidence for a therapeutic effect of *Ginkgo biloba* special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age [in German]. *Arzneimittelforschung*. 1994;44:1005-1013.
- 39 Choi SE, Shin HC, Kim HE, et al. Involvement of Ca²⁺, CaMK II and PKA in EGb 761-induced insulin secretion in INS-1 cells. *J Ethnopharmacol*. 2007;110:49-55.
- 40 Rapin J, Yoa R, Bouvier C, Drieu K. Effects of repeated treatments with an extract of *Ginkgo biloba* (EGb 761) and bilobalide on liver and muscle glycogen contents in the non-insulin-dependent diabetic rat. *Drug Development Research*. 1997;40:68-74.
- 41 Tanaka S, Han LK, Zheng YN, Okuda H. Effects of the flavonoid fraction from *Ginkgo biloba* extract on the postprandial blood glucose elevation in rats [in Japanese]. *Yakugaku Zasshi*. 2004;124:605-611.
- 42 Welt K, Weiss J, Martin R, Hermsdorf T, Drews S, Fitzl G. *Ginkgo biloba* extract protects rat kidney from diabetic and hypoxic damage. *Phytomedicine*. 2006 Jun 15; [Epub ahead of print].
- 43 Niu YH, Yang XY, Bao WS. Protective effects of *Ginkgo biloba* extract on cultured rat cardiomyocytes damaged by H₂O₂. *Zhongguo Yao Li Xue Bao*. 1999;20:635-638.
- 44 Welt K, Weiss J, Martin R, et al. Ultrastructural, immunohistochemical and biochemical investigations of the rat liver exposed to experimental diabetes and acute hypoxia with and without application of Ginkgo extract. *Exp Toxicol Pathol*. 2004;55:331-345.
- 45 Kudolo GB. The effect of 3-month ingestion of *Ginkgo biloba* extract on pancreatic beta-cell function in response to glucose loading in normal glucose tolerant individuals. *J Clin Pharmacol*. 2000;40:647-654.
- 46 Kudolo GB. The effect of 3-month ingestion of *Ginkgo biloba* extract (EGb 761) on pancreatic beta-cell function in response to glucose loading in individuals with non-insulin-dependent diabetes mellitus. *J Clin Pharmacol*. 2001;41:600-611.
- 47 Kudolo GB, Wang W, Javors M, Blodgett J. The effect of the ingestion of *Ginkgo biloba* extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects: a double blind placebo-controlled, crossover study. *Clin Nutr*. 2006;25:606-616.
- 48 Kudolo GB, Wang W, Elrod R, Barrientos J, Haase A, Blodgett J. Short-term ingestion of *Ginkgo biloba* extract does not alter whole body insulin sensitivity in non-diabetic, pre-diabetic or type 2 diabetic subjects: a randomized double-blind placebo-controlled crossover study. *Clin Nutr*. 2006;25:123-134.
- 49 Yamamoto Y, Adachi Y, Fujii Y, Kamei C. *Ginkgo biloba* extract improves spatial memory in rats mainly but not exclusively via a histaminergic mechanism. *Brain Res*. 2007;1129:161-165.
- 50 Petkov VD, Kehayov R, Belcheva S, et al. Memory effects of standardized extracts of *Panax ginseng* (G115), *Ginkgo biloba* (GK 501) and their combination *Gincocan* (PHL-00701). *Planta Med*. 1993;59:106-114.
- 51 Rapin JR, Lamproglou I, Drieu K, Defeudis FV. Demonstration of the "anti-stress" activity of an extract of *Ginkgo biloba* (EGb 761) using a discrimination learning task. *Gen Pharmacol*. 1994;25:1009-1016.
- 52 Allain H, Raoul P, Lieury A, LeCoz F, Gandon JM, d'Arbigny P. Effect of two doses of *Ginkgo biloba* extract (EGb 761) on the dual-coding test in elderly subjects. *Clin Ther*. 1993;15:549-558.

- ⁵³ Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry*. 1995;28:134-142.
- ⁵⁴ Herrschaft H. The clinical application of *Ginkgo biloba* in dementia syndromes (restoration of brain performance in vascular or degenerative CNS disease) [in German]. *Pharm Unserer Zeit*. 1992;21:266-275.
- ⁵⁵ Itil T, Martorano D. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharmacol Bull*. 1995;31:147-158.
- ⁵⁶ Reisecker F. Therapy approaches in cerebral cognitive deficits—neuropsychiatric aspects [in German]. *Wien Med Wochenschr*. 1996;146:546-548.
- ⁵⁷ Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. *Eur J Pharmacol*. 2006;545:51-64.
- ⁵⁸ DeKosky ST, Fitzpatrick A, Ives DG, et al; GEMS Investigators. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of *Ginkgo biloba* extract in prevention of dementia. *Contemp Clin Trials*. 2006;27:238-253.
- ⁵⁹ Fitzpatrick AL, Fried LP, Williamson J, et al; GEM Study Investigators. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience. *Contemp Clin Trials*. 2006;27:541-553.
- ⁶⁰ Vellas B, Andrieu S, Ousset PJ, Ouzid M, Mathieux-Fortunet H. The GuidAge study: Methodological issues. A 5-year double-blind randomized trial of the efficacy of EGb 761(R) for prevention of Alzheimer disease in patients over 70 with a memory complaint. *Neurology*. 2006;67(9 Suppl 3):S6-S11.
- ⁶¹ Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type of multi-infarct dementia. *Pharmacopsychiatry*. 1996;29:47-56.
- ⁶² Haase J, Halama P, Hörr R. Effectiveness of brief infusions with *Ginkgo biloba* Special Extract EGb 761 in dementia of the vascular and Alzheimer type [in German]. *Z Gerontol Geriatr*. 1996;29:302-309.
- ⁶³ Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb Study Group. *JAMA*. 1997;278:1327-1332.
- ⁶⁴ Le Bars PL, Velasco FM, Ferguson JM, Dessain EC, Kieser M, Hoerr R. Influence of the severity of cognitive impairment on the effect of the *Ginkgo biloba* extract EGb 761 in Alzheimer's disease. *Neuropsychobiology*. 2002;45:19-26.
- ⁶⁵ Andrieu S, Gillette S, Amouyal K, et al. Association of Alzheimer's disease onset with *Ginkgo biloba* and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study. *J Gerontol A Biol Sci Med Sci*. 2003;58:372-377.
- ⁶⁶ Kurz A, Van Baelen B. *Ginkgo biloba* compared with cholinesterase inhibitors in the treatment of dementia: a review based on meta-analyses by the cochrane collaboration. *Dement Geriatr Cogn Disord*. 2004;18:217-226.
- ⁶⁷ Mazza M, Capuano A, Bria P, Mazza S. *Ginkgo biloba* and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol*. 2006;13:981-985.
- ⁶⁸ Schulz V. Ginkgo extract or cholinesterase inhibitors in patients with dementia: what clinical trials and guidelines fail to consider. *Phytomedicine*. 2003;10(suppl 4):74-79.
- ⁶⁹ Zhang XY, et al. A double-blind, placebo-controlled trial of extract of *Ginkgo biloba* added to haloperidol in treatment-resistant patients with schizophrenia. *J Clin Psychiatry*. 2001;62:878-883.
- ⁷⁰ Atmaca M, Tezcan E, Kuloglu M, Ustundag B, Kirtas O. The effect of extract of *Ginkgo biloba* addition to olanzapine on therapeutic effect and antioxidant enzyme levels in patients with schizophrenia. *Psychiatry Clin Neurosci*. 2005;59:652-656.
- ⁷¹ Knable MB. Extract of *Ginkgo biloba* added to haloperidol was effective for positive symptoms in refractory schizophrenia. *Evid Based Ment Health*. 2002;5:90.
- ⁷² Zhang XY, Zhou DF, Cao LY, Wu GY. The effects of *Ginkgo biloba* extract added to haloperidol on peripheral T cell subsets in drug-free schizophrenia: a double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*. 2006;188:112-117.
- ⁷³ Schneider B. *Ginkgo biloba* extract in peripheral arterial diseases. Meta-analysis of controlled clinical studies. *Arzneimittelforschung*. 1992;42:428-436.
- ⁷⁴ Haramaki N, Aggarwal S, Kawabata T, Droy-Lefaix MT, Packer L. Effects of natural antioxidant *Ginkgo biloba* extract (EGb 761) on myocardial ischemia-reperfusion injury. *Free Radic Biol Med*. 1994;16:789-794.
- ⁷⁵ Shen JG, Zhou DY. Efficiency of *Ginkgo biloba* extract (EGb 761) in antioxidant protection against myocardial ischemia and reperfusion injury. *Biochem Mol Biol Int*. 1995;35:125-134.
- ⁷⁶ Belougne E, Aguejof O, Imbault P, et al. Experimental thrombosis model induced by laser beam. Application of aspirin and an extract of *Ginkgo biloba*: EGb 761. *Thromb Res*. 1996;82:453-458.
- ⁷⁷ Nazzaro P, Di Carlo A. Treatment of angiostrophic skin diseases with *Ginkgo biloba* [in Italian]. *Minerva Med*. 1973;64(suppl 79):198-200.
- ⁷⁸ Koltringer P, Langsteger W, Klima G, Reisecker F, Eber O. Hemorheologic effects of *Ginkgo biloba* extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood [in German]. *Fortschr Med*. 1993;111:170-172.
- ⁷⁹ Bauer U. 6-month double-blind randomised clinical trial of *Ginkgo biloba* extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittelforschung*. 1984;34:716-720.
- ⁸⁰ Blume J, Kieser M, Holscher U. Placebo-controlled double-blind study of the effectiveness of *Ginkgo biloba* special extract EGb 761 in trained patients with intermittent claudication [in German]. *Vasa*. 1996;25:265-274.
- ⁸¹ Draback H, Petersen JR, Winberg N, Hansen KF, Mehlsen J. The effect of *Ginkgo biloba* extract in patients with intermittent claudication [in Danish]. *Ugeskr Laeger*. 1996;158:3928-3931.
- ⁸² Ernst E. *Ginkgo biloba* in treatment of intermittent claudication. A systemic research based on controlled studies in the literature [in German]. *Fortschr Med*. 1996;114:85-87.
- ⁸³ Bartolo M. Clinical results in therapy of peripheral vascular diseases with *Ginkgo biloba* [in Italian]. *Minerva Med*. 1973;64(suppl 79):4187-4193.
- ⁸⁴ Ashton AK, Ahrens K, Gupta S, Masand PS. Antidepressant-induced sexual dysfunction and *Ginkgo biloba*. *Am J Psychiatry*. 2000;157:836-837.
- ⁸⁵ Boone SA, Shields KM. Dietary supplements for female sexual dysfunction. *Am J Health-Syst Pharm*. 2005;62:577-580.
- ⁸⁶ Wheatley D. *Ginkgo Biloba* relieves sexual dysfunction due to antidepressant drugs. *European Neuropsychopharmacology*. 1999;9(suppl 5):253-254.
- ⁸⁷ Wheatley D. Triple-blind, placebo-controlled trial of *Ginkgo biloba* in sexual dysfunction due to antidepressant drugs. *Hum Psychopharmacol*. 2004;19:545-548.
- ⁸⁸ White H, Scates PW, Cooper BR. Extracts of *Ginkgo biloba* leaves inhibit monoamine oxidase. *Life Sci*. 1996;58:1315-1321.
- ⁸⁹ Sloley BD, Urchick LJ, Morley P, et al. Identification of kaempferol as a monoamine oxidase inhibitor and potential neuroprotectant in extracts of *Ginkgo biloba* leaves. *J Pharm Pharmacol*. 2000;52:451-459.
- ⁹⁰ Amri H, Ogwegu SO, Boujrad N, Driou K, Papadopoulos V. In vivo regulation of peripheral-type benzodiazepine receptor and glucocorticoid synthesis by *Ginkgo biloba* extract EGb 761 and isolated ginkgolides. *Endocrinology*. 1996;137:5707-5718.
- ⁹¹ Hasenohrl R, Nichau CH, Frisch CH, et al. Anxiolytic-like effect of combined extracts of *Zingiber officinale* and *Ginkgo biloba* in the elevated plus-maze. *Pharmacol Biochem Behav*. 1996;53:271-275.
- ⁹² Chermat R, Brochet D, DeFeudis FV, Driou K. Interactions of *Ginkgo biloba* extract (EGb 761), diazepam and ethyl betacarboline-3-carboxylate on social behavior of the rat. *Pharmacol Biochem Behav*. 1997;56:333-339.
- ⁹³ Woelk H, Arnoldt KH, Kieser M, Hoerr R. *Ginkgo biloba* special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: A randomized, double-blind, placebo-controlled trial. *J Psychiatr Res*. 2006; [Epub ahead of print].
- ⁹⁴ Holgers KM, Axelsson A, Pringle I. *Ginkgo biloba* extract for the treatment of tinnitus. *Audiology*. 1994;33:85-92.
- ⁹⁵ Jastreboff PJ, Zhou S, Jastreboff MM, Kwapisz U, Gryczynska U. Attenuation of salicylate-induced tinnitus by *Ginkgo biloba* extract in rats. *Audiol Neurootol*. 1997;2:197-212.
- ⁹⁶ Biddlestone L, Dolan S. The medicinal herb ginkgo reverses thermal hyperalgesia in a model of post-surgical pain. *Eur J Pain*. 2006;10(suppl 1):S84.
- ⁹⁷ Li W, Dai QT, Liu ZE. Preliminary study on early fibrosis of chronic hepatitis B treated with *Ginkgo biloba* Composita [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 1995;15:593-595.
- ⁹⁸ Iraz M, Erdogan H, Kotuk M, et al. *Ginkgo biloba* inhibits bleomycin-induced lung fibrosis in rats. *Pharmacol Res*. 2006;53:310-316.
- ⁹⁹ Atzori C, Bruno A, Chichino G, Bombardelli E, Scaglia M, Ghione M. Activity of bilobalide, a sesquiterpene from *Ginkgo biloba*, on *Pneumocystis carinii*. *Antimicrob Agents Chemother*. 1993;37:1492-1496.
- ¹⁰⁰ Agar A, Yargicoglu P, Apaydin KC, Oguz Y. The effect of *Ginkgo biloba* extract on EEG spectra in experimental diabetes: no relation to lipid peroxidation. *Int J Neurosci*. 1994;76:259-266.
- ¹⁰¹ Punkt K, Adams V, Linke A, Welt K. The correlation of cytophotometrically and biochemically measured enzyme activities: changes in the myocardium of diabetic and hypoxic diabetic rats, with and without *Ginkgo biloba* extract treatment. *Acta Histochem*. 1997;99:291-299.
- ¹⁰² Miki K, Nagai T, Suzuki K, et al. Anti-influenza virus activity of biflavonoids. *Bioorg Med Chem Lett*. 2007;17:772-775.
- ¹⁰³ Kenzelmann R, Kade F. Limitation of the deterioration of lipid parameters by a standardized garlic-ginkgo combination product. A multicenter placebo-controlled double-blind study. *Arzneimittelforschung*. 1993;43:978-981.
- ¹⁰⁴ Hirooka K, Tokuda M, Miyamoto O, Itano T, Baba T, Shiraga F. The *Ginkgo biloba* extract (EGb 761) provides a neuroprotective effect on retinal ganglion cells in a rat model of chronic glaucoma. *Curr Eye Res*. 2004;28:153-157.
- ¹⁰⁵ Ritch R. Complementary therapy for the treatment of glaucoma: a perspective. *Ophthalmol Clin North Am*. 2005;18:597-609.
- ¹⁰⁶ Tamborini A, Taurelle R. Value of standardized *Ginkgo biloba* extract (EGb 761) in the management of congestive symptoms of premenstrual syndrome [in French]. *Ref Fr Gynecol Obstet*. 1993;88:447-457.
- ¹⁰⁷ Oh S, Chung K. Antiestrogenic activities of *Ginkgo biloba* extracts. *J Steroid Biochem Mol Biol*. 2006;100:167-176.
- ¹⁰⁸ Johnson SK, Diamond BJ, Rausch S, Kaufman M, Shiflett SC, Graves L. The effect of *Ginkgo biloba* on functional measures in multiple sclerosis: a pilot randomized controlled trial. *Explore (NY)*. 2006;2:19-24.
- ¹⁰⁹ EGb 761: *Ginkgo biloba* extract, Ginkor. *Drugs R D*. 2003;4:188-193.
- ¹¹⁰ Zeng X, Liu M, Yang Y, Li Y, Asplund K. *Ginkgo biloba* for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2005;(4):CD003691.

- ¹¹¹ Mdzinarishvili A, Kiewert C, Kumar V, Hillert M, Klein J. Bilobalide prevents ischemia-induced edema formation in vitro and in vivo. *Neuroscience*. 2007;144:217-222.
- ¹¹² Kiewert C, Kumar V, Hildmann O, et al. Role of GABAergic antagonism in the neuroprotective effects of bilobalide. *Brain Res*. 2007;1128:70-78.
- ¹¹³ Loh KP, Low LS, Wong WH, et al. A comparison study of cerebral protection using *Ginkgo biloba* extract and Losartan on stroked rats. *Neurosci Lett*. 2006;398:28-33.
- ¹¹⁴ Mustafa A, El-Medany A, Hagar HH, El-Medany G. *Ginkgo biloba* attenuates mucosal damage in a rat model of ulcerative colitis. *Pharmacol Res*. 2006;53:324-330.
- ¹¹⁵ Peters H, Kieser M, Holscher U. Demonstration of the efficacy of *Ginkgo biloba* special extract EGb 761 on intermittent claudication placebo-controlled, double-blind multicenter trial. *Vasa*. 1998;27:106-110.
- ¹¹⁶ Kanowski S, Hermann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Phytomed*. 1997;4:3-13.
- ¹¹⁷ Wettstein A. Cholinesterase inhibitor and ginkgo extracts in therapy of dementia. A comparison of effectiveness based on controlled studies [in German]. *Fortschr Med*. 1999;117:48-49.
- ¹¹⁸ Hofferberth B. The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *Human Psychopharmacol*. 1994;9:215-222.
- ¹¹⁹ Hofferberth B. The effect of *Ginkgo biloba* on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome. A double-blind study against placebo [in German]. *Arzneimittelforschung*. 1989;39:918-922.
- ¹²⁰ Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of *Ginkgo biloba* extract and nicergoline [in French]. *Presse Med*. 1986;15:1559-1561.
- ¹²¹ Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb Study Group. *JAMA*. 1997;278:1327-1332.
- ¹²² Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of ginkgo (*Ginkgo biloba*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2006;13:e277-284.
- ¹²³ Pinto RM, Fernandes ES, Reis JE, Peters VM, Guerra MD. Intra-uterine growth retardation after prenatal administration of *Ginkgo biloba* to rats. *Reprod Toxicol*. 2007 Jan 14; [Epub ahead of print].
- ¹²⁴ von Moltke LL, Weemhoff JL, Bedir E, et al. Inhibition of human cytochromes P450 by components of *Ginkgo biloba*. *J Pharm Pharmacol*. 2004;56:1039-1044.
- ¹²⁵ Chang TK, Chen J, Yeung EY. Effect of *Ginkgo biloba* extract on procarcinogen-bioactivating human CYP1 enzymes: identification of isorhamnetin, kaempferol, and quercetin as potent inhibitors of CYP1B1. *Toxicol Appl Pharmacol*. 2006;213:18-26.
- ¹²⁶ Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: a literature review. *Drugs*. 2005;65:1239-1282.
- ¹²⁷ Chavez ML, Jordan MA, Chavez PI. Evidence-based drug-herbal interactions. *Life Sci*. 2006;78:2146-2157.
- ¹²⁸ Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology*. 1996;46:1175-1176.
- ¹²⁹ Gilbert GJ. *Ginkgo biloba*. *Neurology*. 1997;48:1137.
- ¹³⁰ Engelsen J, Nielsen JD, Winther K. Effect of coenzyme Q10 and *Ginkgo biloba* on warfarin dosage in stable, long-term warfarin treated outpatients. A randomized, double blind, placebo-crossover trial. *Thromb Haemost*. 2002;87:1075-1076.
- ¹³¹ Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with *Ginkgo biloba*. *J Anal Toxicol*. 2005;29:755-758.
- ¹³² Foroughinia F, Sabayan B. *Ginkgo biloba* extract: As a novel agent in prevention of valproic acid hepatotoxicity. *Medical Hypotheses*. 2007;68:918-919.
- ¹³³ Ilhan A, Iraz M, Kamisli S, Yigitoglu R. Pentylene-tetrazol-induced kindling seizure attenuated by *Ginkgo biloba* extract (EGb 761) in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:1504-1510.
- ¹³⁴ Smith M, et al. An open trial of nifedipine-herb interactions: nifedipine with St. John's wort, ginseng or *Ginkgo biloba*. *Clin Pharmacol Ther*. 2001;69:P86.
- ¹³⁵ Zhao LZ, Huang M, Chen J, et al. Induction of propranolol metabolism by *Ginkgo biloba* extract EGb 761 in rats. *Curr Drug Metab*. 2006;7:577-587.
- ¹³⁶ Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. *N Engl J Med*. 1997;336:1108.
- ¹³⁷ Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ. Effect of ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man. *Lancet*. 1987;1:248-250.
- ¹³⁸ Markowitz JS, Donovan JL, Lindsay DeVane C, Sipkes L, Chavin KD. Multiple-dose administration of *Ginkgo biloba* did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. *J Clin Psychopharmacol*. 2003;23:576-581.
- ¹³⁹ Uchida S, Yamada H, Li XD, et al. Effects of *Ginkgo biloba* extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. *J Clin Pharmacol*. 2006;46:1290-1298.
- ¹⁴⁰ Yang CY, Chao PD, Hou YC, Tsai SY, Wen KC, Hsiu SL. Marked decrease of cyclosporin bioavailability caused by coadministration of ginkgo and onion in rats. *Food Chem Toxicol*. 2006;44:1572-1578.
- ¹⁴¹ Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, Erhardt PW. Impact of *ginkgo biloba* on the pharmacokinetics of digoxin. *Am J Ther*. 2003;10:247-251.
- ¹⁴² Meisel C, John A, Roots I. Fatal intracerebral mass bleeding associated with *Ginkgo biloba* and ibuprofen. *Atherosclerosis*. 2003;167:367.
- ¹⁴³ Yin OQ, et al. Prediction and mechanism of herb-drug interaction: effect of *Ginkgo biloba* on omeprazole in Chinese subjects. *Clin Pharmacol Ther*. 2003;73:P94.
- ¹⁴⁴ Spinella M, Eaton LA. Hypomania induced by herbal and pharmaceutical psychotropic medicines following mild traumatic brain injury. *Brain Inj*. 2002;16:359-367.
- ¹⁴⁵ Galluzzi S, Zanetti O, Binetti G, Trabucchi M, Frisoni GB. Coma in a patient with Alzheimer's disease taking low dose trazodone and *Ginkgo biloba*. *J Neurol Neurosurg Psychiatry*. 2000;68:679-680.
- ¹⁴⁶ Cianfrocca C, Pelliccia F, Auriti A, Santini M. *Ginkgo biloba*-induced frequent ventricular arrhythmia. *Ital Heart J*. 2002;3:689-691.
- ¹⁴⁷ Pennisi RS. Acute generalised exanthematous pustulosis induced by the herbal remedy *Ginkgo biloba*. *Med J Aust*. 2006;184:583-584.
- ¹⁴⁸ Long R, Yin R, Zhen Y. Partial purification and analysis of allergenicity, immunogenicity of *Ginkgo biloba* L. pollen [in Chinese]. *Hua Xi Yi Ka Da Xue Xue Bao*. 1992;23:429-432.
- ¹⁴⁹ Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with *Ginkgo biloba*: a case report and systematic review of the literature: a case report and systematic review of the literature. *J Gen Intern Med*. 2005;20:657-661.
- ¹⁵⁰ Schneider C, Bord C, Misse P, Arnaud B, Schmitt-Bernard CF. Spontaneous hyphema caused by *Ginkgo biloba* extract. *J Fr Ophtalmol*. 2002;25:731-732.
- ¹⁵¹ Granger AS. *Ginkgo biloba* precipitating epileptic seizures. *Age Ageing*. 2001;30:523-525.
- ¹⁵² Yagi M, Wada K, Sakata M, Kokubo M, Haga M. Studies on the constituents of edible and medicinal plants. IV. Determination of 4-O-methylpyridoxine in serum of the patient with gin-nan food poisoning [in Japanese]. *Yakugaku Zasshi*. 1993;113:596-599.
- ¹⁵³ Hasegawa S, Oda Y, Ichiyama T, Hori Y, Furukawa S. *Ginkgo* nut intoxication in a 2-year-old male. *Pediatr Neurol*. 2006;35:275-276.
- ¹⁵⁴ Miwa H, Iijima M, Tanaka S, Mizuno Y. Generalized convulsions after consuming a large amount of ginkgo nuts. *Epilepsia*. 2001;42:280-281.
- ¹⁵⁵ Uchida S, Yamada H, Li XD, et al. Effects of *Ginkgo biloba* extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. *J Clin Pharmacol*. 2006;46:1290-1298.