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Original Article

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Ginko biloba: Constituent and Activity in the Treatment of Different Diseases

Adarsh Mishra[1], Lokesh Kumar[1], Deepak Gupta[1], Munna Vishwakarma[1], Himanshu Sharma[1], Navneet Kumar Verma[2]

[1] Students of B.Pharm, Buddha Institute of Pharmacy, GIDA Gorakhpur, UP, India-273209
[2] Associate Professor, Buddha Institute of Pharmacy, GIDA Gorakhpur, UP, India-273209

ABSTRACT

Ginkgobiloba is an ancient plant species that is thought to provide a variety of health benefits to living organisms and contains plenty of bioactive components, making it a chemically diversified plant. *G. biloba* has been shown to have a variety of medicinal and pharmacological properties, including anticancer, antidementia, antidiabetic,antiobesity, antilipidemic, antimicrobial, antioxidant, antilipid peroxidation, antiplatelet, anti-inflammatory, hepatoprotective, antidepressant, antiaging, immunomodulatory, antihypertensive, and neuroprotective effects and is frequently used to treat neurological, cardiovascular, and respiratorydiseases, such as tardive dyskinesia. So this review is all about to describe the therapeutic action and potency of Ginkgo biloba. A 2012 meta-analysis did not find support for the use of *Ginkgo biloba* in enhancing cognitive function in healthy adults. EGb has been shown to reduce the oxidative stress of cardiomyocytes in animal models of myocardial injury , atherosclerosis , hypertension by kidney damage , as well as in animals and human subjects with metabolic syndrome. The cardiovascular response to Ginkgo biloba is practically irrelevant in normotensive animals, confirming ex vivo studies. A treatment course of Ginkgo biloba 120 or 240 mg daily for 3 months, resulted in a significant decrease in diastolic blood pressure in the low-dose group.

Key Words: *Ginko biloba, Health Benefits, Bioactive Components*

***Corresponding Author**
Navneet Kumar Verma
Associate Professor, Buddha Institute of Pharmacy, GIDA Gorakhpur, UP, India-273209

INTRODUCTION

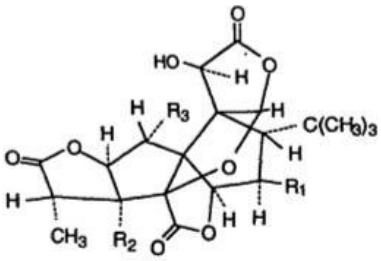
Plant-based phytochemicals have been utilized for over 1000 years and serve as a major platform for novel drug discovery. Ginkgo biloba L. (family: Ginkgoaceae; English name: Maidenhair tree) is a key source of novel herbal medications containing many bioactive constituents with therapeutic efficacy. [1-3] This plant species is ancient, deciduous, tall, and strong, with fan-shaped, irregularly lobed leaves, growing to heights of up to 40 meters. The genus name "biloba" refers to the tree's two separate lobes, and the genus name Ginkgo is a phonetic translation of the tree's Japanese name. G. biloba is clearly classified within the plant kingdom, and this plant is often termed a "living fossil" because, evolutionarily, it is one of the oldest seed plants. After the atomic bomb detonation in Hiroshima, Japan, in 1946, G. biloba was the first plant to germinate. Microorganisms, chemical pollutants, insects, and environmental factors have a little effect on species survival.[4-6]

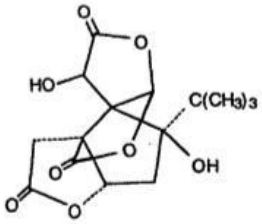
Chemical Constituents

Several chemical compounds have been derived from *G. biloba* with a wide range of therapeutic activities. Terpenoids and lignans, have been identified in *G. biloba* , described as-

- **Terpenoids**

Ten diterpenoid lactones have been discovered, known as ginkgolides Q, P, N, M, L, K, J, C, B, and A. Until recently, bilobalide was thought to be the only sesquiterpene lactone in *G. biloba*, but Dong et al. announced a new bilobalide isomer in 2020. *G.biloba* also contains nor-terpenoids, including three nor-sesquiterpenoids discovered by Shu et al. in *G. biloba* L.[7-11].



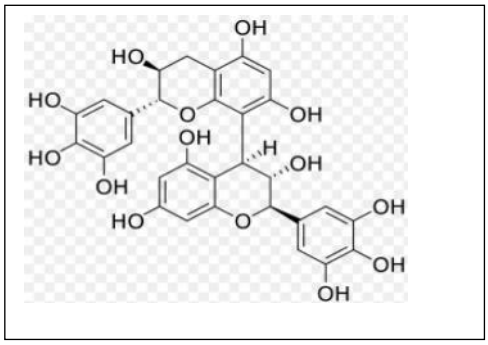


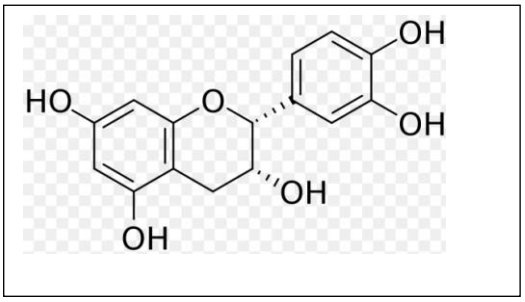
(40) Bilobalide

		R_1	R_2	R_3
(35)	Ginkgolide A	H	OH	H
(36)	Ginkgolide B	H	OH	OH
(37)	Ginkgolide C	OH	OH	OH
(38)	Ginkgolide J	OH	OH	H
(39)	Ginkgolide M	OH	H	OH

- **Proanthocyanidins**

Prodelphinidin and procyanidin are two proanthocyanidins that have been identified in *G. biloba* at a ratio of 85 : 15. Prodelphinidin is an epigallocatechin polymer, whereas procyanidin is comprised of epicatechin.





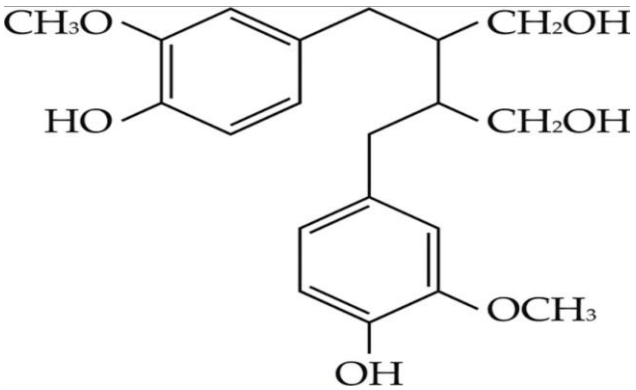
- **Polyprenols**

Polyprenols, which are active ingredients identified in *G. biloba*, comprised of long chains of 14–24 isopentenyl units and have a similar structure as S-polyterpene alcohol (dolichols), which can be found in mammals, including people.

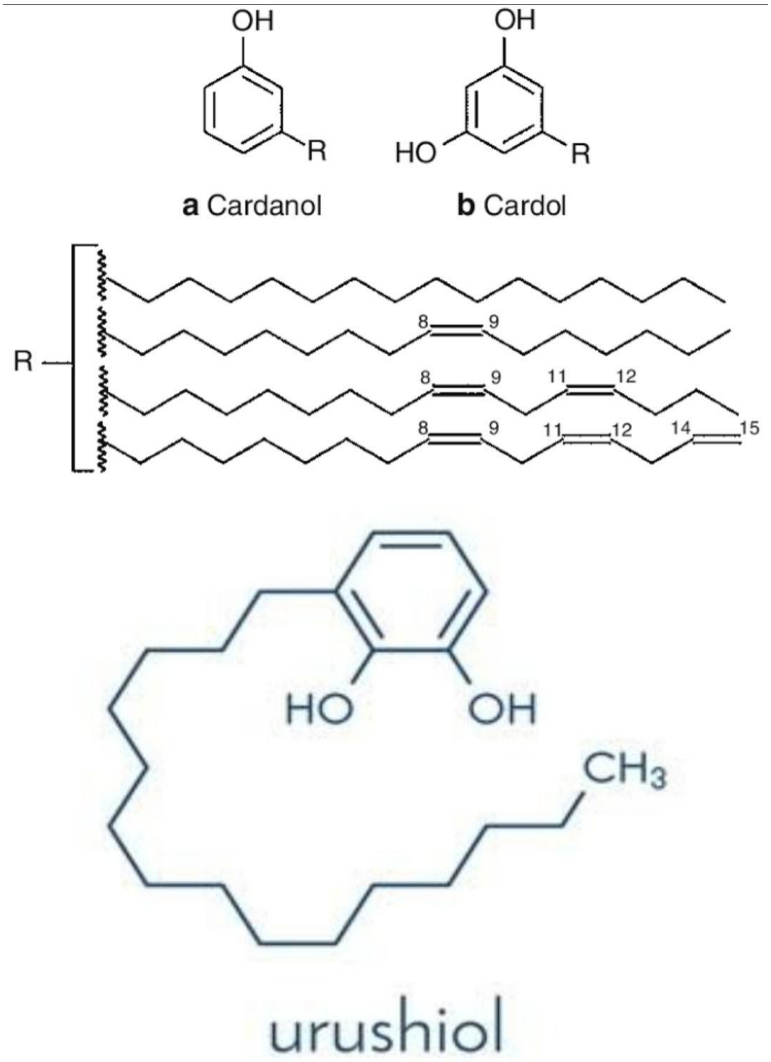
- **Lignans**

Lignans were identified in *G. biloba* roots in 2015 and in *G. biloba* seeds in 2018. Lignans obtained from *G. biloba* show antioxidant properties [12]. In 2018, lignans were also discovered in GBE. Pinoresinol contains 0.012–0.020 mg/mL diglucoside and 1.05–1.87 mg/mL total lignan glycosides. Five lignans were isolated from *G. biloba* by Shu et al.

- **Alkylphenols and Alkylphenolic Acids**



Alkylphenols can be divided into five groups: cardols, cardanols, *α*-hydroxycardanols, urushiols, isourushiols, and alkylphenolic acids. Although ginkgolic acids are known to be toxic, they have also been reported to display potential pharmacological effects.[13-16]



PHARMACOLOGICAL ACTION OF GINKGO BILOBA

- **Dementia/ Cognitive Impairment**

In terms of treatment for existing dementia, data has been contradictory regarding the efficacy of *Ginkgo biloba* extract (EGb). A 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of 309 patients in 1997 concluded that EGb was safe and though modestly, it appeared to stabilize and improve the cognitive performance as well as social functioning of dementia patients for six months to 1year.Similarly, another 24-week randomized controlled trial with 410 outpatients found that treatment with EGb 761 using a once-daily dose of 240 mg was safe and demonstrated a statistically significant improvement in cognition, psychopathology, functional status and quality of life of patients and caregivers. On the other hand, a randomized control trial of 513 outpatients with mild to moderate dementia of the Alzheimer type did not support the efficacy of ginkgo extract. A systematic review of 36 trials in 2009 and another review of 38 trials in 2018, though demonstrated that *Ginkgo biloba* was relatively safe, but did not support its clinical benefit for patients with cognitive impairment anddementia. Conversely, a 2015 systematic review of 9 trials concluded that EGb761 at 240 mg/day was able to decelerate decline in cognition, function, behavior, and global change at 22 to 26 weeks in patients with dementia, especially for those with neuropsychiatric symptoms. A 2017 study of 12 systematic reviews also suggested that at doses greater than 200mg/day for at least five months, EGb had potentially beneficial effects for patients with dementia. In terms of preventing dementia, there is also insufficient evidence to support the use of ginkgo. The (GEM) Ginkgo Evaluation of Memory study showed that *Ginkgo biloba* at 120 mg twice a day was not effective in reducing both all-cause dementia incidence and Alzheimer dementia incidence in elderly patients with normal cognition or with mild cognitive impairment. Similarly, the Guid Age clinical trial conducted in patients aged 70 years or older who spontaneously reported memory complaints to their primary care physician in France. This trial randomized patients with either 120 mg standardized *Ginkgo biloba* extract or matching placebo and did not support the benefit of long-term use of standardized EGb in reducing the risk of progression to Alzheimer disease throughout five years. A meta-analysis of two trials involving 5889 participants showed no significant difference in the rate of developing dementia between *Ginkgo biloba* and the placebo in late-life.A 2012 meta-analysis did not find support for the use of *Ginkgo biloba* in enhancing cognitive function in healthy adults.[18-23]

- ***Diabetic Nephropathy***

Diabetic Nephropathy (DN), the most common microvascular complication of diabetes, is characterized by persistent microalbuminuria, renal tubular, and interstitial fibrosis, which is also the most common etiology of end-stage renal disease. The incidence of DN ranges from 25% to 40% in type 1 diabetic patients to 5% to 40% in type 2 diabetic patients. DN is a progressive process. Its early clinical manifestations are glomerular hyperfiltration and increased urinary albumin excretion rate. Its pathological features are glomerular basement membrane thickening, mesangial dilatation, and tuberous sclerosis. With the development of DN, the number of damaged glomeruli increases and the glomerular filtration rate decreases significantly. The clinical manifestations of this stage are massive proteinuria and glomerular and tubulointerstitial fibrosis. According to Mogensen stage, DN can be divided into 5 stages. Due to the imperceptible symptoms of stage I and II, most patients of DN were not diagnosed until stage III or after stage III. Once DN enters its end stage (stage V), treatment will be more difficult than other kidney diseases. Thus, it becomes particularly important to find interventions that can delay the progression of DN in the early stage. At present, the key to the treatment of DN is to strengthen blood glucose control, so new anti-diabetic drugs with specific renal protective effects are widely used in clinical practice. There is evidence that G biloba may have potential therapeutic effects on a variety of diseases, such as diabetic cardiomyopathy, neurodegenerative diseases, neurodegenerative retinal diseases, myocardial lesion, hippocampus neuronal lesions, cancer, obesity, and liver damage. Modern pharmacological studies have revealed that it has antioxidant, anti-inflammatory, and anti-platelet aggregation effects. Flavonol glycosides and terpene trilactones are the main components to exert biological activities. G biloba can reverse the increase of fasting blood glucose, 24 hours urinary protein, blood urea nitrogen, and creatinine and improve the change of renal ultrastructure in DN rats. [24-26]

According to the results of a metabolomic study, oleic acid and glutamate may be the potential biomarkers for G biloba against kidney injury. In a randomized, double-blind, multi-center, controlled trial, researchers found that G biloba could attenuate deterioration of albuminuria in type 2 diabetes patients, which indicating that G biloba could be a promising option of renoprotective agents for the early stage of DN. Cardiovascular activity of Ginkgo biloba and it's main compound.[27-28]

- **Sexual Dysfunction**

Many small studies have explored the role of EGb in treating sexual dysfunction. A triple-blind, placebo-controlled trial of 24 patients with sexual dysfunction due to antidepressant drugs showed no statistically significant differences in responses and side-effect profiles between the EGb group and the placebo group. A randomized control trial of 108 patients showed that a nutritional supplement containing L-arginine, ginseng, ginkgo, damiana, multivitamins, and minerals, helped increase the level of sexual desire in premenopausal, perimenopausal, and postmenopausal women compared to placebo.[29-31]

- **Antioxidant Activity:-**

Several studies have shown that EGb exhibits significant antioxidant activity in vitro in a wide range of tissues from animal models and human subjects. This antioxidant activity has been attributed to both terpenoids ginkgolides and bilobalide, as well as to flavonoids . Overall, EGb is known to increase the levels of glutathione, to increase the activity of superoxide dismutase, and to decrease the expression and activity of NADPH oxidase, whereas decreasing the levels of malondialdehyde. More recently it has also become apparent that the antioxidant activity of EGb can also be attributed to the activation of the Akt/Nrf2 signal pathway, which is in part responsible for the regulation of the cellular resistance to oxidative stress . These activities lead to a decrease in the levels of reactive oxygen and nitrogen species, thus preventing lipid and protein peroxidation, respectively, thereby decreasing cellular damage. With regards to cardiovascular disease, EGb has been shown to reduce the oxidative stress of cardiomyocytes in animal models of myocardial injury , atherosclerosis , hypertension by kidney damage , as well as in animals and human subjects with metabolic syndrome.[31-34]

- **Cardiac Activity In Vitro and Ex Vivo**:-

Ginkgo biloba is known to modulate the activity of several ion channels on cardiomyocytes in vitro. For example, EGb decreases the maximum voltage of the ventricular action potential and shortens its duration. These actions are attributed to the inhibition of calcium channels, delayed rectifier potassium channels, and of inward rectifier potassium channels. In contrast, bilobalide also decreases maximum voltage, but shortens the action potential duration and enhances the calcium and delayed rectifier potassium currents. In addition, another study has demonstrated that EGb inhibits hyperpolarization-activated cyclic nucleotide-gated channels 2 and 4, being more potent in the latter, present in the sinoatrial node and ventricles. These results suggest that multiple bioactive compounds of Ginkgo biloba are able to differently modulate cardiomyocyte ion channels, therefore exerting different effects on cardiac electrophysiological properties. In a rat model of D-galactose-mediated ventricular ageing, treatment with EGb significantly reduced intracellular calcium concentration during diastole and increased its reuptake by means of sarcoplasmic endoplasmic receptor calcium ATPase, therefore improving diastolic dysfunction [85]. In an electrocardiography (ECG) study of guinea pig hearts, EGb and ginkgolide A increased the PR interval, indicating a calcium channel-blocking activity. In contrast, the PR interval was reduced by ginkgolide B. In addition, both ginkgolides A and B and bilobalide reduced the

QT interval, suggesting the activation of potassium channels, whereas EGb resulted in an increased QT interval. Both EGb and ginkgolide B reduced the heart rate. The atrioventricular block was observed with EGb, ginkgolide A, and bilobalide, which suggests an arrhythmogenic potential that should be better characterized.[35-36]

- **Vasorelaxant Activity Ex Vivo**

Ginkgo biloba and some of its compounds have shown significant vasorelaxant activities in humans and in different animal species, namely rats, pigs and rabbit the probable vasorelaxation mechanisms of the extracts of Ginkgo biloba (EGb). An endothelial cell is represented on top and a vascular smooth muscle cell at the bottom (cGMP-cyclic guanosine monophosphate; NO -nitric oxide; NOS-nitric oxide synthase; PNs- prostanoids; ROS-reactive oxygen species; VGCC-voltage-gated calcium channel).Results of the vasorelaxant activity of Ginkgo biloba ex vivo (5-HT-serotonin; DA- dopamine; EGb-extract of Ginkgo biloba; GKA -Ginkgolide A; L-NAME-NW-nitro-L-arginine methyl ester; KC-potassium chloride; L-NMMA -NG-methyl-L-arginine; m.o.-months old NE -norepinephrine; PE-phenylephrine; SHRS- spontaneously hypertensive rats; SNP-sodium nitroprusside; TEA-tetraethyla Results of the vasorelaxant activity of Ginkgo biloba ex vivo (5-HT-serotonin; DA- dopamine; EGb-extract of Ginkgo biloba; GKA -Ginkgolide A; L-NAME-NW-nitro-L-arginine methyl ester; KC-potassium chloride; L-NMMA -NG-methyl-L-arginine; m.o.-months old NE -norepinephrine; PE-phenylephrine; SHRS- spontaneously hypertensive rats; SNP-sodium nitroprusside; TEA-tetraethylammonium; TTX- tetrodotoxin; WKYRS-Wistar-Kyoto rats; w.o.- weeks old). EGb evoked a concentration-dependent relaxation of norepinephrine (NE)-precontracted aortae of Wistar rats. This response was reported to have been significantly inhibited by L- nitro-methyl-arginine (NMMA, i.e., nitric oxide synthase inhibitor) but not by tetraethylammonium (TEA, i.e., voltage-gated potassium channel blocker), suggesting that NO is an important mediator, whereas the potassium efflux-mediated hyperpolarization of vascular smooth muscle (VSM) was not considered relevant . Later, the same authors identified that EGb-mediated vasorelaxation is age-dependent, with a lower response intensity being observed in the aortae of older animals, although this finding was not statistically significant.[37-38]

- **Vasoconstrictor Activity Ex Vivo**

In a minor subset of studies, EGb has been shown to evoke vasoconstriction ex vivo. EGb potentiated the NE-induced aortic contraction of New Zealand rabbits, suggesting a potential stimulatory action on the release of catecholamines or an inhibitory activity over monoamine oxidase (MAO) enzymes. Effectively, Ginkgo biloba has been shown to inhibit MAO enzymes in rats due to the presence of kaempferol. A subsequent study showed similar vasoconstrictor activity in the rabbit vena cava, which was partly blocked by phenoxybenzamine (i.e., alpha-1 adrenoreceptor blocker), suggesting an antagonistic action on alpha-1 receptors. Taken together, ex vivo studies revealed that the vasoactive effects of EGb are species- and strain-dependent.[39]

Anti-Hypertensive Activity of EGb in Vivo animal model

Several studies have been published so far on the effects of Ginkgo biloba on the blood pressure profile of normotensive animals, as well as in different hypertensive animal species and strains, such as L-NAME-mediated hypertension rats, deoxycorticosterone acetate (DOCA)-salt hypertensive rats, SHRS , and SHRSP/Izm rats. Results of the anti-hypertensive activity of Ginkgo biloba in vivo (DOCA- deoxycorticosterone acetate; EGb-extract of Ginkgo biloba; i.v. intravenous; L-NAME-NW- nitro-L-arginine methyl ester; SHRS- spontaneously hypertensive rats; SHRSP/Izm- SHRS spontaneously hypertensive stroke- prone rats; WKYRS-Wistar-Kyoto rats). That activity is age- and strain-dependent. In normotensive Sprague- Dawley rats, the intravenous administration of EGb reduced blood pressure over a period of 5 min, and was attenuated by pretreatment with L-NAME, again suggesting the prominent role of NO in this cardiovascular response. Similar results from the oral administration of EGb in WKYRS have been reported. One study reported that a 20-day administration failed to change blood pressure, although it lowered heart rate. Another reported that the 30-day oral administration of EGb failed to change blood pressure in young normotensive WKYRS. This suggests that the cardiovascular response to Ginkgo biloba is practically irrelevant in normotensive animals, confirming ex vivo studies, probably due to the fact that these animals do not demonstrate a decrease in NO release.[39]

Effects of Ginkgo biloba on Blood Pressure and Heart Rate in Healthy Subjects—In Vivo Studies

Several studies have recorded data on the short-term effects of Ginkgo biloba on the blood pressure of healthy subjects For example, a group of young healthy subjects enrolled in a study to assess the effects of Ginkgo biloba on ocular vessels. The results showed no change in blood pressure 3 h after taking 240 mg EGb 761 extract when compared to a placebo. In a different study the oral administration of 360 mg EGb 761 did not change heart rate, blood pressure, or arterial pulse characteristics over a period of 6 h when compared with a placebo. Thirdly, a group of healthy subjects took 120 mg EGb for 2 days. No significant changes in blood pressure or heart rate were noted against the placebo. In a fourth study, a group of young healthy subjects received 120 mg EGb daily for 5 days. On day 5 of the experiment, both heart rate and systolic blood pressure were lower than on previous days. In another group of young healthy subjects, 240 mg of EGb was given for 7 days, and no change in blood pressure, heart rate, or electrocardiographic parameters were noted when compared with the placebo. Finally, a group of healthy subjects was examined before and after a 3 month treatment course with Ginkgo biloba 120 mg/day, and a significant decrease in systolic and diastolic blood pressure was reported. The hemodynamic effects of Ginkgo biloba are both dose- and time- dependent. However, the variability between these

studies can also be attributed to differences in their design, namely imbalances in terms of the male-to- female ratio and the probable variability in terms of the menstrual cycle, a known variable that influences hemodynamics . These studies were carried out in the absence of challenge tests. In a different study, a group of young healthy subjects received EGb 761Ⓡor the placebo orally. Both groups were subjected to stress tests (mental stress and handgrip static exercise) before and after taking the extract. Results showed that Ginkgo biloba significantly prevented the rise in blood pressure evoked by stress tests when compared to a placebo. In addition, the extract also prevented the increase in blood cortisol in males. Although these results are interesting and suggest that Ginkgo biloba may also suppress the hypothalamus- hypophysis - adrenal axis, they may also lack reproducibility. According to the authors, this study was carried out during a regular university course and not in an experimental environment, which may affect the results. Finally, in a group of 60 elderly subjects with mild-to-moderate cognitive impairment, a treatment course of Ginkgo biloba 120 or 240 mg daily for 3 months, resulted in a significant decrease in diastolic blood pressure in the low-dose group.[38-40]

CONCLUSION

The ginkgo leaf medicines containing the dry extract can be used to improve the age-related cognitive impairment (worsening of mental abilities) and quality of life of adults with mild dementia. We found a statistically significant advantage of Ginkgo biloba compared to placebo in improving cognition for the whole group of patients with Alzheimer's disease, vascular or mixed dementia. Regarding activities of daily living, there was no significant difference for the whole dementia group. Ginkgo biloba displays a modulatory effect on cardiac function by acting in different ion channels on cardiomyocytes. It also displays vasorelaxant activity, attributed to the potentiation of the endothelial release of nitric oxide and prostanoids, in addition to the blockage of calcium channels on vascular smooth muscle. In healthy humans, Ginkgo biloba increases perfusion in different vascular beds, namely the ocular, cochlear, cutaneous, cerebral, and coronary, without significantly affecting blood pressure. Collectively, Ginkgo biloba is considered to be generally safe, with a low frequency of adverse reactions. Ginkgo biloba extract (GBE) facilitates blood flow, influences nitric oxide systems, and has a relaxant effect on smooth muscle tissue. These processes are important to the sexual response in women and, hence, it is feasible that GBE may have a therapeutic effect. The present study was the first to provide an empirical examination of the effects of both short- and long-term GBE administration on subjective and physiological (vaginal photoplethysmography) measures of sexual function in women with Sexual Arousal Disorder. A single dose of 300 mg GBE had a small but significant facilitatory effect on physiological, but not subjective, sexual arousal compared to placebo in 99 sexually dysfunctional women. The long-term effects of GBE on sexual function were assessed in 68 sexually dysfunctional women who were randomly assigned to 8 weeks treatment of either GBE (300 mg/daily), placebo, sex therapy which focused on training women to attend to genital sensations, or sex therapy plus GBE. When combined with sex therapy, but not alone, long-term GBE treatment significantly increased sexual desire and contentment beyond placebo.

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