

Ginkgo Biloba

80 mg Tablets



Product Summary:

Ginkgo biloba is one of the oldest known therapeutic herbs. Studies have shown that ginkgo increases blood flow and circulation in the brain, helping to improve memory and cognitive function, as well as improve circulation throughout the body.

Properties/Uses:

The claim as approved by the *Natural Health Product Directorate* (NHPD): Helps enhance cognitive function and support peripheral circulation.



NERVOUS





Pharmacology:

Ginkgo biloba is one of the oldest and longest living tree species in the world. Traditionally, only ginkgo fruit was used medicinally and some of the first descriptions date back to 2600 BC for use in asthma and bronchitis.¹ However, today, ginkgo biloba leaf extract (EGb) is the favoured medicinal preparation. It is the most commonly prescribed herbal medicine in Germany¹ and the preferred choice for dementia.²

Ginkgo leaf and its extracts contain several active constituents including flavonoids, terpenoids, and organic acids. The majority of ginkgo leaf extracts are standardized to contain 24% to 25% flavone glycosides and 6% terpene lactones. Although many of ginkgo's constituents have intrinsic pharmacological effects individually, there is evidence that the constituents work synergistically to produce more potent pharmacological effects.^{3,4} Some of these effects have led to the predominant study of ginkgo as a treatment for age-related memory impairment, dementia, cognitive function, and peripheral vascular disease.

Early research demonstrated that taking EGb orally seems to improve cognitive function in some elderly people with mild to moderate age-related memory or cognitive impairment.^{5,6} In particular, clinical research has demonstrated improvement in measures of short-term visual memory, speed of cognitive processing⁶, learning rate and attention.⁷ However, EGb does not appear to improve memory in individuals over the age of 60, with normal mental function.^{7,8,9} It has also been suggested that EGb may not reduce the risk of developing age-related cognitive impairment in patients aged 85 years or older who have normal cognitive function. However, in this study, sub-group analysis indicated that lack of medication adherence was associated with cognitive decline, while consistent administration of EGb conferred benefit.¹⁰

EGb has also been evaluated for its potential role in both prevention of dementia and treatment of dementia-related symptoms. While epidemiological data indicates that EGb is not associated with a reduced risk of developing dementia in elderly patients with memory impairment¹¹, it has been found to moderately improve symptoms of Alzheimer's, vascular, or mixed dementias. Studies lasting from 3 months to a year show that EGb can stabilize or improve some measures of cognitive and social functioning in patients with multiple types of dementia.^{3,12-21} Although most clinical trials of EGb show benefit, there are some conflicting findings suggesting inconsistent and unpredictable potential benefit.¹⁹ However, a 2010 systematic review²² found that a specific ginkgo leaf extract (EGb761) yielded a statistically significant advantage compared to placebo in improving cognition for patients with Alzheimer's disease, vascular or mixed dementia. The authors concluded that EGb may be warranted as a symptomatic treatment for individuals with mild to moderate dementia, and that it may not be inferior to conventional treatments such as cholinesterase inhibitors. This has been corroborated in preliminary clinical research in which EGb761 at 160 mg per day was found to be comparable to donepezil 5 mg daily for mild to moderate Alzheimer's dementia after 24 weeks of treatment.²³





Furthermore, a prospective, community-based cohort study of 3,534 subjects aged 65 or older demonstrated a reduction in overall mortality with use of EGb.¹¹

Elderly individuals with cognitive impairment are not the only population who seem to benefit from EGb for cognitive enhancement. Healthy, young to middle-aged people have seen modestly improved memory and speed of cognitive processing, including increased speed of performance on factors assessing attention.^{7,24-27} Dosages of 120-240 mg have been suggested to be as effective as 600 mg daily.^{7,24,25} Additionally, some evidence suggests a synergistic effect with Panax Ginseng for memory enhancement that is superior to either herb alone.^{27,28}

Another hallmark of EGb is its ability to effectively address peripheral vascular insufficiency. The most common manifestation is intermittent claudication, a condition in which the lower leg muscles become severely fatigued and painful with cramping upon walking a short distance. The cause of peripheral vascular insufficiency is atherosclerosis, which impedes blood flow through the lower legs. A meta-analysis found that EGb was superior to placebo for the symptomatic treatment of intermittent claudication.²⁹ Additional evidence suggest that taking specific ginkgo extract EGb761 increases pain-free walking distance in patients with Fontaine's IIb peripheral arterial occlusive disease and intermittent claudication.^{30,31} It also might decrease overall PVD event incidence such as surgery and amputation in elderly patients.^{32,33} While most evidence is positive for PVD, one study, using EGb761, showed no benefit for maximal treadmill walking time in patients with peripheral arterial disease compared to placebo.³⁴

There is also contradictory evidence about the effectiveness of EGb for improving recovery in patients with acute ischemic stroke. A Cochrane Systematic Review³⁵ found that lower quality trials suggest that more patients have neurological improvement when treated with EGb, while one higher quality study found no benefit compared to placebo.

EGb has also demonstrated benefit in Raynaud's syndrome and vertigo. For those individuals with Raynaud's syndrome, EGb has been found to reduce the number of painful attacks per week.³⁶ Individuals with vertigo and equilibrium disorders experience improved symptoms with administration of EGb, which is superior to placebo.^{1,3,7}

Although the mechanism of action of EGb is only partially understood, there are several theories about how it might work in these varied conditions. The most prominently examined and proposed mechanism of action is ginkgo's ability to enhance cerebral and peripheral circulation, and reduce vascular permeability. It appears that EGb improves circulation by decreasing blood viscosity, affecting vascular smooth muscle and improving vasoregulation. Blood viscosity is likely reduced due to EGb's ability to competitively inhibit platelet activating factor (PAF) at the membrane receptors of several cells.³⁸ PAF inhibition decreases platelet aggregation⁵, phagocyte chemotaxis¹², smooth muscle contraction¹² and free-radical production.⁵ EGb also appears to inhibit formation of platelet thromboxane A2 and B2, further reducing platelet aggregation.³⁹ Interestingly, EGb appears to both relax spasmodic contracting vasculature and





contracts abnormally dilated vessels. It isn't entirely understood how it can achieve this contradictory effect, but it is suggested that EGb inhibits phosphodiesterase, resulting in increased cyclic AMP and release of catecholamines.⁴⁰ Furthermore, a recent study using dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSC-MRI) demonstrated improved global cerebral blood flow and left parietal-occipital white matter blood flow after EGb administration, providing supportive physical evidence of improved cerebral blood flow.⁴¹

One of the other prominent theories of EGb's action is its role as an antioxidant. Studies have demonstrated potent free radical scavenging abilities of both the flavonoids^{12,42} and proanthocyanidins.⁴³ The flavonoids seem to prevent or reduce cell membrane lipid peroxidation, leading to protection of neurons against oxidative damage.^{12,42} It is thought this might prevent progression of tissue degeneration in dementia.

Dementia may also be aided by EGb via inhibition of cell toxicity and death induced by beta-amyloid peptides.⁴ However, this has not yet been demonstrated in vivo. EGb might also influence certain neurotransmitter systems, such as the cholinergic system¹⁸, and seems to produce EEG changes similar to the acetylcholinesterase inhibitor, tacrine (Cognex).⁴⁴ Preliminary evidence also suggests effects on other neurotransmitter pathways, such as monoamine oxidase A and B, catechol-O-methyl transferase⁴⁵ and GABA.⁴⁶

EGb constituents ginkgolide A and B seem to decrease glucocorticoid biosynthesis, which might explain the proposed anti-stress and neuroprotective effects of EGb.²⁵ EGb761 has demonstrated reduction in stress-induced rises in adrenocorticotrophic hormone (ACTH), cortisol and blood pressure in animals and healthy volunteers.⁴⁷

Finally, some researchers speculate that EGb might decrease development of hyperinsulinemia associated with hypertension, which often precedes development of type 2 diabetes and atherosclerotic vascular disease.⁴⁸ This state is typically indicative of metabolic syndrome, which has been identified as an independent risk factor for Alzheimer's disease.⁴⁹ This may be fundamentally critical to the evolving understanding that Alzheimer's disease and dementia may be a result of insulin resistance within the brain (commonly referred to as Type 3 Diabetes)⁴⁹ and may signify a new mechanism of action for EGb's role in cognitive function.





Manufactured product information:

Manufacturer:

WN Pharmaceuticals® Ltd.

Size/UPC:

90's 7 77747 10260 0

NPN:

80031239

Expiry Date:

36 months from date of manufacture

Active Ingredient:

Each tablet contains:

Ginkgo Biloba 55:1 Extract (leaf) (24% flavone glycosides, 6% terpenes lactones) . . . 80 mg (equivalent to 4400 mg of dried leaves).

Non-Medicinal Ingredients (in descending order):

Dibasic calcium phosphate dihydrate, microcrystalline cellulose, magnesium stearate

Appearance:

Brown speckled caplet.

Packaging:

175 cc white round bottle with safety seal under a 38 mm white induction sealed cap with vented interior seal and a label applied to the bottle. Lot number and expiry date are printed on label applied to exterior of bottle.

Storage:

Store in a tightly closed container in a cool, dry place.





Dose:

Oral dosages typically range from 60 mg to 240 mg, as found in the literature. Higher dosages should be administered in divided doses two to three times daily. For all indications, it is advisable to begin at lower doses of about 120 mg per day to avoid adverse gastrointestinal effects. Titrate to higher doses as indicated.

Condition-specific Dosing:

Dementia/age-related memory impairment: 120-240 mg per day; divided into 2-3 doses.^{3,12}

Cognitive function (healthy young persons): 120-600 mg per day in divided doses; 120-240 mg may be as effective as 600 mg per day.^{24,25}

Peripheral vascular disease: 120-240 mg per day; divided into 2-3 doses; higher doses may be more effective.³⁰

Vertigo: 120-160 mg per day divided into 2-3 doses.⁵⁰

Reynaud's Disease: 360 mg per day, divided into 3 doses has been used.³⁶

Directions:

(Adults): 1 tablet, 2 times daily or as recommended by a physician. Consult a physician for use beyond 6 weeks.

Caution:

The caution as approved by the *Natural Health Product Directorate* (NHPD): KEEP OUT OF THE REACH OF CHILDREN. Consult a physician prior to use if you are taking medications for diabetes, high blood pressure, or seizures, or if you are pregnant or breastfeeding. Do not use if you are taking health products that affect blood coagulation (e.g., blood thinners, clotting factor replacements, acetylsalicylic acid, ibuprofen, fish oils, vitamin E) as these products may increase the risk of spontaneous bleeding. STORE AT ROOM TEMPERATURE IN A DARK, DRY PLACE. DO NOT USE IF SEAL UNDER CAP IS BROKEN OR MISSING.



Deficiency Symptoms:

N/A.

Drug Interactions /Contraindications:

Anticoagulant/antiplatelet drugs or supplements: Caution should be exercised in patients taking antiplatelet or anticoagulant medications (e.g. acetylsalicylic acid, clopidogrel, dalteparin, enoxaparin, heparin, indomethacin, ticlopidine, warfarin, ibuprofen), as well as other herbs or supplements that may reduce coagulation (omega-3 fish oils, garlic, ginger, Vitamin E) due to concern regarding ginkgo's potential ability to reduce platelet aggregation and blood clotting.^{5,38,39} Concomitant use could increase the risk of spontaneous bleeding. See *Adverse Reactions* for further information.

Anticonvulsants: Theoretically, taking ginkgo might reduce the effectiveness of anticonvulsants. See *Adverse Reactions* for further information

Antidiabetes drugs: Ginkgo leaf extract seems to alter insulin secretion and metabolism and might affect blood glucose levels in type 2 diabetics.^{48,51} Individuals using oral hypoglycemic agents may experience decreased insulin levels and increased blood glucose.⁵¹ However, in patients with pancreatic exhaustion, taking ginkgo appears to stimulate pancreatic beta-cells resulting in increased insulin and C-peptide levels.⁵² Ginkgo does not seem to significantly affect the pharmacokinetics of metformin.⁵² Diabetic patients should use ginkgo cautiously and monitor blood glucose levels closely.

Alprazolam: Ginkgo might decrease the effectiveness of alprazolam via decreased absorption.⁵³

CYP 450 Substrates: various cytochrome P450 enzymes have demonstrated inhibition (increase drug levels in the body) or induction (reduce drug levels in the body) via ginkgo in vitro and in animal models.^{46,54-59} Therefore, medication metabolized through these pathways may be affected. However, most evidence is preliminary and thus effects may not be significant. Until more is known, caution is advised in patients taking any of the associated medications:

- CYP1A2 inhibition: Tylenol, amitriptyline, clopidogrel, clozapine, diazepam, estradiol, olanzapine, ondansetron, propranolol, ropinirole, tacrine, theophylline, verapamil, warfarin.
- CYP2C19 induction: amitriptyline, carisoprodol, citalopram, diazepam, lansoprazole, omeprazole, phenytoin, warfarin.
- CYP2C9 inhibition: warfarin, glyburide, glipizide, amitriptyline, valdecoxib, phenytoin





- CYP2D6 inhibition: amitriptyline, clozapine, codeine, despramine, donepezil, fentanyl, flecainid, fluoxetine, meperidine, methadone, metoprolol, olanzapine, ondansetron, tramadol, trazadone.
- CYP3A4: there is conflicting evidence whether ginkgo induces or inhibits CYP3A4. Ginkgo does not appear to affect hepatic CYP3A4, but it is not known whether it affects intestinal CYP3A4. Thus ginkgo should be used cautiously in any patient using drugs metabolized by this enzyme. Such drugs include: lovastatin, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, triazolam. HIV drug, efavirenz may also be affected, reducing efficacy of the drug to manage viral load.

Toxicity/Adverse Reactions:

Orally, ginkgo biloba leaf extract is well tolerated at typical doses.^{17,22} The most commonly reported adverse effect is mild gastrointestinal upset. It rarely causes headache, dizziness, palpitation, constipation, and allergic skin reactions.

Spontaneous bleeding is one of the most concerning potential side effects associated with ginkgo. Several published case reports link ginkgo to episodes of minor to severe bleeding. However, not all case reports clearly established ginkgo as the cause of bleeding. In most cases, other bleeding risk factors were also present. Furthermore, a 2011 systematic review and meta-analysis of 18 randomized trials demonstrated no increased risk of bleeding with use of standardized ginkgo biloba extract.⁶⁰

Ginkgo seeds contain ginkgotoxin, however it is only present in leaves in trace amounts. The amount of ginkgotoxin in ginkgo leaf and leaf extract is unlikely to cause toxicity.⁶¹ However, ginkgotoxin may cause seizures. Anecdotal reports of seizure occurring after use of ginkgo leaf both in patients with and without history of seizure disorder exist.^{62,63} Thus, individuals who suffer from seizure disorders may be at risk of lower seizure threshold with use of ginkgo biloba and should exercise caution.



Allergen Content/Ingredient Sensitivity:

NO	YES
Artificial Colors	
Artificial Flavors	
Artificial Sweeteners	
Corn Products	
Egg Products	
Fish	
Gluten	
Hydrolyzed Plant Protein	
Lecithin	
Milk Products	
Peanuts	
Preservatives	
Sesame Products	
Shellfish	
Soy Products	
Starch/Modified Starch	
Sulphites (<10 ppm)	
Tartrazine	
Tree Nuts	
Wheat Products	
Yeast	

ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTION:

Free of animal products

NOT ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTION:

Kosher





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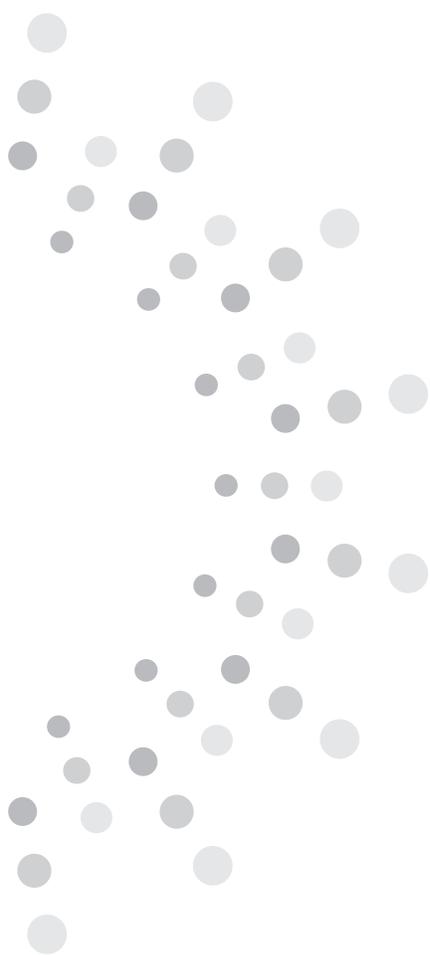


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Revision #00