

GINKGO BILOBA MONOGRAPH

SCIENTIFIC NAME¹:

Ginkgo biloba
Family: Ginkgoaceae

COMMON NAME^{1,2}:

- ◆ Ginkgo
- ◆ Ginkyo
- ◆ Maidenhair tree
- ◆ Ginkgo Folium
- ◆ Kew tree
- ◆ Yinhsing (Silver Apricot-Japanese)
- ◆ Fossil Tree
- ◆ Salisburia Adiantifolia

ACTIVE INGREDIENTS³:

- ◆ Flavonol and Flavone glycosides
- ◆ Catechin
- ◆ Ascorbic acid
- ◆ Sesquiterpenes
- ◆ Ginkgolides
- ◆ Diterpene lactones
- ◆ Iron-based superoxide dismutase
- ◆ P-hydroxybenzoic acid

The dried green leaves from the ginkgo tree are used to obtain the crude drug formulation of ginkgo. Further, an acetone-water mixture is used for extraction and concentration of active constituents and for the removal of ginkgolic acids and other toxic compounds. The major active ingredient of ginkgo extract is flavonoid glycosides.

MECHANISM OF ACTION^{1,3,4}:

Ginkgo exhibits anti-inflammatory effects by interfering with the release of inflammatory compounds by competitively inhibiting the platelet-activating factor (PAF). Ginkgo comprises ginkgolides A and B antagonists that competitively inhibit the binding of PAF to the membrane receptor that may exert neuroprotective and antithrombotic effects. In addition, flavonoid glycosides and ginkgolide B may inhibit the oxidation of lipoprotein formation, platelet aggregation, and platelet adherence that may reduce the events of atherosclerosis and vascular injury. Furthermore, PAF antagonism may prevent cyclosporin-induced nephrotoxicity, and decrease coronary blood flow and myocardial contractility. Additionally, this mechanism may provide beneficial effects in circulatory diseases, hypersensitivity reaction, and bronchospasm.

Flavonoid glycosides may exert antioxidant effects that may reduce endothelial cell injury due to free radical oxidation thus decrease the development of atherosclerosis. Ginkgo constituents are efficient free radical scavenger that may prevent lipid peroxidation offering protection of the vascular walls. The free radical scavenging actions on superoxide anions may increase the half-life of endothelium-based relaxing factors; hence, cause relaxation of blood vessels. Further, ginkgo extract may increase cerebral blood flow, and protect neural and retinal tissue from oxidative or hypoxic injury. In addition, the ginkgo extract may offer intestinal mucosa protection against ischemic injury by decreasing neutrophil infiltration and lipid peroxidation,

stimulate choline uptake and prevent decline of age-related muscarinic receptors, and decrease blood viscosity. Further, there is a potential inhibitory effect of ginkgo on monoamine oxidase activity; however, the mechanism of action is unclear.

CURRENT INDICATION AND EFFICACY:

◆ Anticoagulant⁴:

- Efficacy-may be effective in adult population however not enough documentations are available on the effectiveness of anticoagulatory effects of ginkgo.
- Ginkgo may increase bleeding time due to inhibition of platelet activating factors.

◆ Asthma⁴:

- Efficacy-may be effective in adults but there are poor documentation available for asthma effects of ginkgo.
- Ginkgolides may be effective in both the early and late phases of airway hyperactivity.

◆ Cerebral Insufficiency^{4,5}:

- Efficacy-possibly effective in adults. Good documentations are available for the effectiveness of ginkgo in treating cerebral insufficiency. However, many of these studies were written in a different language other than English.
- According to a clinical review article it was shown that most controlled trials on the efficacy of Ginkgo on cerebral insufficiency had at least partially positive outcome. Most clinical trials used Ginkgo 120-160mg a day for at least four to six weeks to observe any favorable outcomes. Such results can be seen in a multi-center trial conducted in Germany, involving 303 outpatients that included subjects with mean age of 69 years, diagnosed with cerebral insufficiency, with average duration of symptoms for 46 months. One hundred and ten out of two hundred and nine (94 patients excluded from the analysis after randomization) patients were randomly assigned to Ginkgo 150mg daily for 12 weeks and the remaining ninety-nine patients were assigned to placebo. After 12 weeks of therapy physician reported that 71% of the patients in the Ginkgo group had symptomatic improvements compared to 32% in placebo.

◆ Dementia^{4,6}:

- Efficacy-possibly effective in adults. Good documentations available for the effectiveness of ginkgo in dementia.
- A 52 week, randomized double-blind, placebo-controlled, parallel-group, multicenter trial was conducted to assess the efficacy and safety of EGb 761 extract of Ginkgo biloba in patients with multi-infarct dementia (MID) and Alzheimer disease. The inclusion criteria for the study population included both men and women, 45 years of age or older, who was diagnosed with uncomplicated dementia per Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) and International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria. In addition, the study

subjects had mild to moderately severe dementia with a Mini-Mental State examination score of 9 to 26 and a Global Deterioration Scale score of 3 to 6. Further, the patients have no other major medical condition (i.e. cardiac disease, liver diseases, chronic renal insufficiency, insulin-dependent diabetes, or psychiatric disorder). Patients were excluded if they had a brain mass or intracranial hemorrhage. The primary outcome was to measure the cognitive impairment by assessing the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), daily living and social behavior by assessing the total score of the Geriatric Evaluation by Relative's Rating Instrument (GERRI), and lastly to measure the general psychopathology by assessing the Clinical Global Impression of Change (CGIC). 327 patients have been enrolled in the study where 251 patients had AD. 166 patients were randomly assigned to receive EGb 120mg QD for 52 weeks and 161 assigned to matching placebo. The EGb group was 1.4 points better on ADAS-Cog score compared to placebo ($p=0.4$), and improvement of GERRI score by 0.14 compared to placebo ($p=0.004$). In further analysis of the data it was shown that 27% of the patients treated with EGb had at least a 4 point improvement on the ADAS-Cog compared to 14% in the placebo group ($p=0.005$). Further, 37% of the patients on EGb improved on the GERRI compared to 23% of the patients on placebo ($p=0.003$). In the last outcome measured there was no statistical or clinical significance in the CGIC between EGb and placebo. The study concluded that EGb appears to be safe and effective in improving the cognitive performance and social functioning of patients with dementia.

◆ Inflammation⁴:

- Efficacy-may be effective however not enough sufficient documentation are available.
- May decrease inflammation via flare reduction, and inhibition of plasma aggregation in platelet-rich plasma and inhibition of PAF induced platelet aggregation.

◆ Memory Enhancement^{4, 7}:

- Efficacy-possibly effective in adults with fair amount of documentation.
- A six-week randomized, double-blinded, placebo-controlled, parallel-group trial was conducted to determine the effects of ginkgo in memory enhancement, and memory improvements in elderly population. The study included patients that were community dwelling volunteer men and women, older than 60 years of age, baseline Mini-Mental State Examination scores greater than 26, independent in instrumental activities of daily living (i.e. shopping, managing finances, and transportation). Patients who were taking antidepressant or other psychoactive medication in the past 60 days were excluded from the study. 230 patients were enrolled in the study where 115 patients were randomly assigned to receive ginkgo 40mg three times per day and the remaining 115 were assigned to a matching placebo. The outcome being measured were a standardized tests of learning, memory, attention, and concentration, mental status, and expressive language. Learning and memory skills were assessed using the California Verbal

Learning Test (CVLT), Wechsler Memory Scale-Revised (WMS-R). The mental status was assessed using the (WMS-R). In addition, attention and concentration was assessed using the Digit Symbol subscale of the Wechsler Adult intelligence Scale-Revised (WAIS-R), and Stroop Test. Expressive language was assessed by Controlled Category Fluency test, and Boston Naming Test. Memory questionnaire was completed for global evaluation of the patient. No significant differences were found between the ginkgo and placebo groups in the outcomes being measured (overall p=0.31). The study concluded that the 6-week trial with ginkgo did not enhance memory function.

◆ Ocular Disease⁴:

- Efficacy-may be effective in ocular disease. Poor documentation available.
- It was shown that patients with diabetic retinopathy had improvements in color vision and ischemia. Further, significant improvements were seen in long distance acuity in patients with macular degeneration treated with ginkgo extract compared to placebo.

◆ Intermittent Claudication⁸:

- Effective in adult population.
- Meta-analysis of randomized trials found a significant difference in improvements in pain-free walking distance in patients taking Ginkgo compared to placebo with 95% Confidence Intervals, and weighted mean difference of 34 meters. The average dosing range of ginkgo extract used in the analysis was between 120mg to 160mg for 24 weeks. The studies concluded that Ginkgo biloba are relatively safe to use and may be effective in increasing the distance of pain free walking in patients with intermittent claudication.

DOSAGE FORMS, RECOMMENDED DOSES, DURATION^{1, 4-6}:

◆ Ginkgo is available in the following form capsule, tablet, powder, extract, and tea.

◆ Recommended dose:

- Oral-Extract
 - General use of extract-standardized to contain 6% terpene lactones and 24% ginkgo flavonglycosides (40 to 80mg TID) for six to eight weeks.
 - Intermittent Claudication: 120 to 160mg QD for 24 weeks.
 - Asthma: 40mg TID for six to eight weeks
 - Cerebrovascular disease: 120 to 160mg QD for twelve weeks need to treat for at least 4 to 6 weeks to observe favorable outcome.
 - Dementia: 120mg to 240mg BID-TID for at least eight weeks and follow up with physician for cognitive assessment after three months of therapy.
 - Poor documentation available for Ginkgo dosing.

DRUG INTERACTIONS AND DRUG-DISEASE INTERACTIONS^{1,4}:

◆ Anticoagulants:

- Major drug interaction exists between ginkgo and anticoagulants. Concurrent use of the two drug products may increase risk of bleeding complications. Ginkgolide B may inhibit platelet aggregation or blood coagulation that can lead to serious bleeding conditions. If both agents are necessary need to monitor bleeding time, signs and symptoms of excessive bleeding.

◆ Anticonvulsants

- Moderate drug interaction exists between ginkgo and anticonvulsants. Patients who are on anticonvulsant for seizure disorders are at risk for neurotoxicity due to 4'-O-methylpyridoxine found as a contaminant in ginkgo products. Ginkgo may provoke seizures and decrease the effectiveness of anticonvulsant.

◆ Antiplatelet Agents:

- Moderate drug interaction exists between ginkgo and antiplatelet agents. Concomitant use of the two drugs may increase the risk of bleeding disorders due to inhibition of platelet aggregation. If concurrent use of ginkgo and antiplatelet agent is necessary monitor bleeding time and signs and symptoms of excessive bleeding.

◆ Selective Serotonin Reuptake Inhibitors (SSRIs):

- Moderate drug interaction exists between ginkgo and SSRIs. Concurrent use of the two drug products may increase risk of serotonin syndrome, which is a condition of serotonergic hyperstimulation that can manifest as restlessness, myoclonus, changes in mental status, tremor, diaphoresis, and shivering. Monitor patients for symptoms of serotonin syndrome when given in combination.

◆ Thiazide Diuretics:

- Moderate drug interaction exists between ginkgo and thiazide diuretics. Concurrent use of the two products may increase blood pressure. In concomitant use is necessary monitor blood pressure frequently.

◆ Trazodone:

- Major drug interaction exists between ginkgo and trazodone. Concurrent use of the two products may cause excessive sedation and potential coma. If therapy with both drugs is necessary, use low dose trazodone and monitor patient carefully for signs of excessive sedation.

◆ Ginkgo Allergy:

- Do not use ginkgo in patients with allergies to this product

SAFETY ISSUES^{4,9}:

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Ginkgo Biloba is relatively safe there has been very few reported cases of adverse effects, which included stomach complaints, dyspepsia, and nausea. It is likely to be unsafe to use ginkgo intravenously due to severe adverse effects and has been withdrawn from the market. Due to inhibiting effects of ginkgo on platelet activating factors it raises great concerns during perioperative stage. Four cases of spontaneous bleeding, one spontaneous hyphema, and one incident of postoperative bleeding followed by laparoscopic cholecystectomy have been reported in patients taking ginkgo. In addition, terpenoids which is a ginkgo extract are highly bioavailable when given orally with an elimination half life of 3 to 10 hours thus it is highly recommended to discontinue ginkgo at least 36 hours prior to surgery. Further, safety in pregnancy and lactation is unclear due to lack of reliable information; thus, it may be better to avoid using this product completely. The use of ginkgo is relatively safe however it is not commonly prescribed by providers due to unregulated sales of herbal products that may have been exposed to adulterants, variable dosing, and heavy metal toxicity.

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