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Review Article

A Review on Evidence Based Practice of *Ginkgo biloba* in Brain Health

AR. Mullaicharam

Professor, Department of Pharmacy, Oman Medical College, Muscat, Sultanate of Oman

ABSTRACT
The brain is the platform for our mental health. But there is a growing body of evidence, and a number of significant voices are championing the role of diet in the care and treatment of people with mental health problems. Ginkgo biloba leaf extract has shown beneficial effect in treating impairments in memory, cognitive speed, activities of daily living (ADL), edema, inflammation and free-radical toxicity associated with traumatic brain injury (TBI), Alzheimer's dementia, stroke, vaso-occlusive disorders, and aging. The purpose of this chapter is to provide the mechanisms of action, clinical indications, and safety of *Ginkgo biloba* extract (GBE).

Key words: *Ginkgo biloba,* Pharmacology, Memory impairment, Safety issues, Dosage forms.

1. INTRODUCTION

The ginkgo tree (Fig.1) is having apricot shaped mature, yellow color fruits[1] the name ginkgo comes from the Chinese words *sankyo* or *yin-kuo*, which means a hill apricot or silver fruit. So the name ginkgo comes from the Chinese words *sankyo* or *yin-kuo.*The family name of ginkgo tree is Ginkgoaceae, which is in the class of Ginkgoatae. Englbert Kaempfer, a German surgeon, first used the term "Ginkgo" in 1712, but it was Linnaeus who termed it *Ginkgo biloba* in 1771.[2]

Fig.1: *Ginkgo biloba*

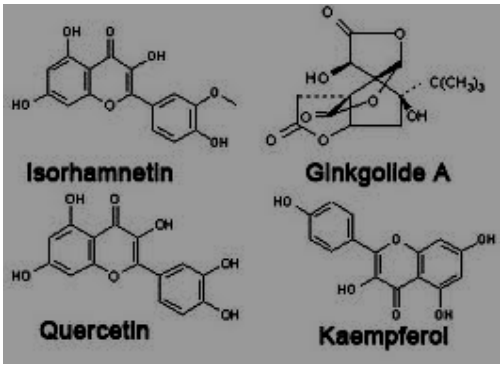
1.1 Botanical Information

Ginkgo biloba L. (Mantissa Plantarum Altera, 1771, Ginkgoceae) belongs to the botanical family of Ginkgoceae. The common names are Ginkgo,Kew tree,Ginkyo,Yinhsing (Silver Apricot-Japanese) ,Maidenhair tree ,Fossil Tree ,Ginkgo Folium, Salisburia Adiantifolia[3]
The synonyms are *Salisburia adiantifolia, Salisburia macrophylla,* and *Pterophylla salisburiensis*. Today, nearly 500 scientific papers now documenting Ginkgo's effects make it the well-researched botanical medicine available. With 10 million prescriptions written worldwide for *Ginkgo biloba* extract (GBE) in 1989 alone, and a 140% growth in the use of Ginkgo from 1997 to 1998, it is likely a plant medicine your patients are using or considering.[4,5]
While firmly rooted in antiquity, GB is today the most frequently prescribed herbal preparation in Germany and one of the most commonly used over-the-counter (OTC) herbal preparations in the United States[6].The German Commission Es (equivalent to the US Food and Drug Administration for botanicals) has approved GB for symptomatic treatment of deficits in memory, concentration, and depression from organic brain disease[7].

2. ACTIVE INGREDIENTS OF GINKGO BILOBA EXTRACT

Ginkgo biloba, like most plant medicines contains many active constituents, believed to have synergistic effects. Flavonoids including quercetin, kaempferol, and isorhamnetins; trilactonic diterpenes: Ginkgolide A, Ginkgolide B, Ginkgolide C; a trilactonic sesquiterpene: bilobalide; and proanthocyanidins are thought to afford Ginkgo it's medicinal effects.[5,8] Other constituents such as

glucose, rhamnose, hydroxykinurenic, kynurenic, protocatechic, vanillic, and shikimic acids, D-glucaric acid, ginkgolic acid, and related alkyphenols have also been isolated.[8]



The main active ingredients of ginkgo biloba extract (GbE) are :

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

The dried green leaves from the ginkgo tree are used to obtain the crude drug formulation of ginkgo.[9]

Flavonoids (including meletin, kaempferol and isorhamnetin) and laetones (including ginkgolides and bilobalide). GbE can remove free radicals, protect the endothelial cells of blood vessels, block platelet activating factors, and improve brain circulation[10, 11]. GbE has been widely used in the treatment of dementia, cognitive impairment, peripheral nerve problems, and vascular tinnitus[14]. However, clinical studies about the efficacy of GbE in the treatment of dementia have been inconclusive: some studies report beneficial effects on cognition and functioning.[15, 16] while others do not.[12, 15, 16].

There are two main pharmacologically active groups of compounds present in the Ginkgo leaf extract.They are are the flavonoids and the terpenoids[17].

Flavonoids, also called phenylbenzopyrones or phenylchromones, are a group of low molecular weight substances that are widely spread in the plant kingdom. Flavonoids present in the Ginkgo leaf extract are flavones, flavonols, tannins, biflavones (amentoflavone, bilobetol, 5-methoxybilobetol, ginkgetin, isoginkgetin and sciadopitysin), and associated glycosides of quercitin and kaempferol attached to 3-rhamnosides, 3-rutinosides, or p-coumaric esters[1.] These compounds are known to actmainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators[18.]

In general, the bioavailability of flavonoids is relatively low due to limited absorption and rapid elimination[19]. Flavonoids in the glycosidic form are poorly absorbed in the intestine; only in the aglycone form can they be absorbed directly[19]. Once absorbed, flavonoids reach the liver where they are metabolized to conjugated derivatives[21] .It is known that the biological activities of flavonoid metabolites are not always the same as those of the parent compound.[20]. There are no adequate studies determining the dose of Ginkgo extract needed to achieve beneficial effects, although the recommended dose of standardized extract, EGb 761, is 40 to 60 mg, 3 to 4 times daily based on clinical trials [24].

3. PHARMACOLOGICAL EFFECTS OF GINKGO BILOBA

Ginkgo leaf extract is having multifaceted pharmacological activities. The Ginkgo leaf extract may work through various mechanisms of action. Following are the suggested mechanisms of the Ginkgo leaf extract proved by various studies[22].

- Antioxidant effect, anti-platelet activating factor (Anti-PAF) activity for cardio and cerebral vascular diseases,
- Inhibition of beta amyloid peptide (Aβ) aggregation to reduce Alzheimer's progression,
- Decreased expression of peripheral benzodiazepine receptor (PBR) for stress Alleviation,
- Stimulation of endothelium derived relaxing factor to improve blood circulation[23, 24, 18, 17].

A.

Ginkgolides A, B, and C, and bilobalide have been shown to increase circulatory perfusion, antagonize platelet activating factor (PAF), have neuroprotective effects, and serve as cognitive activators. The flavone glycosides possess antioxidant and mild platelet aggregation inhibiting activities[25,26,33].

GBE stimulates choline uptake in the hippocampus, improves hypoxic tolerance, and glucose utilization[28]. It also has membrane stabilizing and blood viscosity lowering effects[29].

Absorption of *Ginkgo biloba* in animal studies using radiolabeled extract showed a 60% absorptive efficiency following oral administration with peak serum levels at 1.5 hours supporting an upper GI absorption site[31]. The flavonoids were found to accumulate in the aorta, eyes, skin, and lungs; the heart muscle retained twice the activity of a comparative volume of skeletal muscle, and adrenal glands were also a site of accumulation[31]. Seventy two hours post administration, the hippocampus and

striated bodies showed 5 times greater uptake than the blood,[27,30] while T1/2 for Ginkgolide A, B, and bilobalide were 4.50, 10.57, and 3.21 hours respectively, supporting the need for TID dosage[31].

3.1 Mechanism of Actions

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 oxidization 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[9,32,33].

Flavonoid glycosides may exert antioxidant effects that may reduce endothelial cell injury due to free radical oxidation thus decrease the development of atherosclerosis. 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 declination of age-related muscarinic receptors, and decrease blood viscosity[9,32,33]. Further, there is a potential inhibitory effect of ginkgo on monoamine oxidase activity; however, the mechanism of action is unclear.

3.2 Clinical Applications

3.2.1 Cerebrovascular Insufficiency

Quite a lot of studies have tested the efficacy of GBE for improving status in those with cerebrovascular insufficiency. In a double blind trial of 90 patients conducted by Vesper and Hansgen over a twelve-week course[28].

Ginkgo was found to improve several clinical parameters of measure including:

1) Patient attention in tasks requiring quick orientation and readaptation, 2) for cerebral insufficiency, 3) Changes in the patient's subjective performance, and 4) Changes in the patient's objective behavior as observed by others.

The results of previous studies proved that GBE has significantly superior effect than placebo in all parameters measured.

The multicenter study carried out by Taillandier et al with longitudinal design, performed under strict methodological conditions, found GBE was effective against cerebral disorders associated with aging in166 patients. Results became statistically significant at 3 months, increased during the following months, and were congruent with the overall clinical assessment by the specialist in charge[34].

Another study carried out by Grassel for 24-week duration with 72 patients with cerebral insufficiency.The results showed statistically significant improvements in short term memory after 6 weeks, and learning rate (as measured by psychometric testing) after 24 weeks[35].

GBE produced improvement in parameters including: single symptoms, total score of clinical symptoms, and global effectiveness[36].

3.2.2 Memory Impairment

While in a crossover study of 18 elderly men and women (mean age 69.3 years), orally administered GBE was found to significantly improve the speed of information processing in dual-coding tests, a study of eight healthy females found differences between GBE and placebo in only one of three methods of evaluation.[37,38]

3.2.3. Alzheimer's disease and Multi-infarct Dementia

Several studies suggest that GBE may be helpful in treating Alzheimer's disease and multiinfarct dementia, with few if any side effects[31].

A 1996 multicenter double-blind, placebo controlled prospective study by Kanowski et al. evaluated 156 patients with presenile and senile primary degenerative dementia of the Alzheimer's type (DAT), and multi-infarct dementia (MID) who used either GBE 120mg bid or placebo for 24 weeks. A multidimensional evaluation approach using objective variables of Clinical Global Impressions (CGI) for psychopathological assessment, Syndrome-Kurztest(SKT) for assessment of attention and memory, and Nurnberger Alters-Beobachtungsskala (NAB) for assessment of activities of daily life were used. Efficacy was defined as response in at least two of the three variables. Within a conservatively defined response criterion, 28% of the GBE group responded vs. 10% in the placebo group. Similar effects were noted with GBE in both types of dementia with a slightly better response for those with DAT. Five patients reported minor side effects of skin reactions, gastrointestinal complaints, and headache.[40]

GBE also ranked superior in self-rated activities of daily living, improvement of the most prominent symptom, and decrease in depression, demonstrating GBE efficacy on behavioral, psychopathologic, and psychometric planes[41].

3.2.4. Prevention of Neurodegenerative Diseases

Alzheimer's disease is a form of dementia that progressively deteriorates intellectual

capacity of various domains of the brain, particularly with aging[42] . Alzheimer's disease affects about 4% of the population over 65 and 20% of those over 80.[43] Research

has now found links between Alzheimer's disease and deposition of amyloid beta peptide (Aβ)[44, 45, 46]. Aβ is a polypeptide with 39 to 43 amino acid residues and a major component of senile plaques and vascular amyloid deposits of the brains of patients suffering from Alzheimer's disease. Ginkgo leaf extract is known to inhibit the formation of Aβ from β-amyloid precursor protein (APP), a crucial process in the pathogenesis of Alzheimer's disease[46]. Formation of amyloid precursor protein has been indirectly linked to high cholesterol levels [47,48,49]. It has been postulated that the inhibition of Aβ is through the Ginkgo leaf extract's ability to compete with free cholesterol for interaction with Aβ and thereby decrease their aggregation[46]. Alternatively, the Ginkgo leaf extract inhibits ROS accumulation induced by Aβ (particularly flavonol quercitin) and also reduces neuron apoptosis, where apoptosis is considered to be one of the main causes for neurodegenerative diseases[44, 45, 50, 51] and thus help to relieve Alzheimer's disease. Ginkgolide B and bilobalide are reported to inhibit apoptosis induced by staurosporine (alkaloid anticancer drug) and serum deprivation[50]. Bilobalide also prevented DNA fragmentation due to hydroxyl radical β-amyloid and hydrogen peroxide[50].

3.2.5. Resistant Depression

In the GBE group, the median Hamilton Depression Scale scores dropped from 14 to a remarkable 7 in four weeks, then to 4.5 by week eight. Only a one-point drop occurred in the placebo group. Overall cognitive function was improved, and no side effects were reported showing potential therapeutic benefit of GBE in resistant depression[28].

Table 1 shows overview of various clinical studies carried out by using Ginkgo extract[7].

Table 1: Overview of Clinical Studies

Authors	Symptoms	Outcome Measures	Dose/Duration
Allain et al	Memory impairment	Dual-coding task (information processing)	320 or 600 mg. 1 h prior to testing
Arrigo and Cattaneo	Cerebrovascular insufficiency	Wechsler Adult Intelligence Scale (WAIS), block design, word recognition; Rey's complex figure, memory; Spielberg State-Trait Anxiety Inventory	120 mg/d for 45 days
Bruchen et al	Aging, cerebral insufficiency	Figure connection test	50 mg TID for 12 weeks
Deberdt	Cognitive impairment	Memory	160mg/d one time
Eckmann	Cerebral insufficiency	Concentration, fatigue, cerebral function	160mg/d for 6 weeks
Eckmann et al	Cerebrovascular insufficiency	Dizziness, motor activity, speech comprehension / pro duction, depression	Tebonin forte drops, 60/d for 30 days
Hamann	Vestibular disorder	Vertigo, body sway amplitude	4 drops mice/d
Hartmann and Frick	Vascular dementia	Psychometric tests	20mL TID solution 3month
Hofferberth	Senile dementia	Memory, attention, psychomotor, physiology	80mg TID
Kanowski et al	Alzheimer's and multi-infarct dementia	Syndrome short test, attention and memory	EGb761 and placebo: 24Omg / d BID
Le Bars et al	Alzheimer 's disease, multi-infarct dementia	Alzheimer 's disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative Rating Instrument (GERRI)	120 mg/d for 52 weeks
Maier-Hauff	Subarachnoid hemorrhage, cerebral insufficiency	Reaction time, attention, short term memory, accuracy	150mg / d LI 1370 for 12 weeks.
Mancini et al	Psychoorganic senile dementia	SCAG scale. Toulouse-Pieron cancellation	80 mg ID for 6weeks
Rai et al	Memory impairment	Kendrick Digit Copying and Learning (KDC and KDL) task; digit recall task, P300 latency	40 mg TID for 12 - 24weeks
Wesnes et al	Idiopathic cognitive impairment	Recall, reaction time, recognition. Crichton geriatric rating scale	Tanakan: 120 mg /d for 12 weeks

Abbreviations: R, randomized; DB, double-blind; SB, single-blind; RPC, randomized placebo-controlled; PC, placebo-controlled; TID, three times a day; BID, twice a day.

Table 2 shows Dosage of Ginkgo extract and duration of administration required by Etiology/ Symptom and Adverse events[7].

Table 2 : Dosage and duration classified by Etiology/ Symptom and Adverse events.

Indications/Symptoms	Dosage	Duration
Cerebral	400 mg / d; 3.5mg / mL	3 weeks to 13 month
Cerebrovascular	101- 200 mg/d; O-60 drops/d	3weeks to 3month
Information processing	600 mg / d	3 months to 6 months
Dementia	200 mg / d	5 weeks to 3 months
Hypoxia	1-10 ml / d	2 weeks
Ischemia	100 mg / d: 0 -150g/ml/d	7-9 weeks
Vestibular	101-200 mg / d	3 weeks to 9 weeks
Subarachnoid Hemorrhage	101-200 mg / d	3 months
Memory	150 mg/d to 320 mg/ d	24 hours to 24 weeks
Memory impairment	50 mg three times daily	6 months

Table 3: Investigator, Isolated Component, and Activity[7]

Investigator	Isolated Component	Function
Barth et al (1991)	Flavone	Inhibits lipid peroxidation
Ramassamy et al (1992)	Flavone	Mediates 5-HT uptake
Gryglewski et al (1987)	Flavone	Inhibits platelet aggre gation
Coeffler (1998)	Ginkgolide B	Anti-platelet activating factor properties
Janssens et al (1995)	Bilobalide	Delays onset of hypoxic glycolysis
Amri et al (1996)	Bilobalide, Ginkgolide A, Ginkgolide B	Induces PBR downregulation; increases ACTH concentration.

Abbreviations: 5-HT. serotonin; PBR, peripheral benzodiazepere-type receptor; ACTH, adrenocorticotropic hormone.

4. SAFETY ISSUES

Based on previous studies[33], it was proved that Ginkgo Biloba is relatively safe. There have been very few reported cases of adverse effects, which included stomach complaints, dyspepsia, and nausea. It is likely to be unsafe to use gingko 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. 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.

5. CONCLUSION

Ginkgo biloba extract (GBE) is used for effective brain function. Various research studied were carried out to find its phytomedicines and its efficacy under many conditions. Many research reports regarding the use of GBE in cerebrovascular insufficiency, memory impairment in the elderly, Alzheimer's disease, multi-infarct dementia, resistant depression, peripheral artery insufficiency, venous insufficiency, and asthma is well supported by multiple studies. GBE for tinnitus, schizophrenia, psychotic organic brain syndrome, vertigo of undetermined origin, and PMS, although less supported, still deserves serious consideration because of GBE's high tolerability, and the limited or complete lack of efficacy with conventional treatments for these conditions.[28] Specifically, further research is needed in the following areas: (1) dose-response characteristics;(2) quantification of bioavailability, washout periods, and long-term effects; (3) determination of optimal timing for treatment interventions; (4) examination of ways that GB can be used most effectively as an adjunctive therapy, so that treatment effects are optimized [20]; (5) clearer delineation of the conditions for which GB is most (and least) useful; and (6) examination of possible drug interactions[7]. Before making informed clinical decisions, physicians should be clear about the mechanisms, indications, dose/duration ranges, and safety history of GB in conjunction with the patient's medical history and current medications, which will provide very effective beneficial effects.

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