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Therapeutic Use of Ginkgo Biloba

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ABSTRACT: Gingko biloba, one of the most popular herbs in the USA is known for its various therapeutic uses and is now well researched for its various active compounds. Although originally grown in Asia, the tree is distributed all over the world. Leaves, bark, roots all have therapeutic properties and are used for various illnesses like asthma, circulatory ailments and cognitive support or dysfunction.

History and medicinal use of Ginkgo

Ginkgo biloba, one of the world's oldest living deciduous trees (1), contains a diverse range of pharmacologically active compounds which has made it an important therapeutic agent of traditional medicine for thousands of years. The plant is a gymnosperm native to eastern China currently distributed throughout the world, primarily in northern temperate climates (2). Until the early 1700s the tree grew primarily in China and other part of Asia; hence Chinese medical traditions have made extensive use of ginkgo since 2800 BCE (3). Its leaves, fruits and roots contain medically useful components (4,5). The leaf and fruit-based formulations are the most commonly used Ginkgo preparations in Chinese herbal medicines. Therapeutic applications include, treatment of asthma and other respiratory problems; infectious diseases such as tuberculosis and gonorrhea; circulatory ailments; and a diverse range of other disorders. In China and other Asian cultures, including Ayurvedic medicine of India, medicinal use of *Ginkgo biloba* has continued since ancient times as a mainstay of accepted medical treatment (6). Conversely ginkgo-based formulations have been utilized in the United States and other Western nations since the 1960s after the development of a methodology for isolating and making commercially available the subcomponents of the plant (7). In the past decade the use of Ginkgo as a health supplement and alternative to prescription formulations has increased substantially among Americans (8). Generally it is sold as a standardized extract of dried leaves (EGb761), containing 24% ginkgo-flavonol glycosides and 6% terpene lactones in edible caplet form (9,10). Reasons for self-administration of this herb vary widely, depending on desired health-related outcomes. Three major areas of health that are reputed to be improved by Ginkgo, are broadly grouped into (i) Neurological (ii) Circulatory and (iii) Sexual effects.

Enhanced cognition and neuroprotective effects. Traditionally, Ginkgo is known to contribute to enhanced memory, ability to focus, attention, alertness, and overall improved mental acuity. In keeping with tradition, ginkgo-based products are currently marketed as enhancers of neurocognitive abilities, in addition to other aspects of general health. This claim has proven valid in a number of investigations. For example, cohorts of healthy individuals administered neuropsychological testing before and following treatment with EGb761 (ginkgo extract) exhibited superior speed of information processing, working memory and executive decision-making as a result of EGb761 ingestion (1). The therapeutic potential of ginkgo was further validated in clinical trials of EGb761 in patients with impaired central nervous system (CNS) due to disease or injury. In these studies the extract has been shown to significantly improve the cognitive function of disorders including age-associated deterioration of the brain (11); hypoxia-associated neurological injury (12); Alzheimer's disease (13); and cardiovascular accident (CVA)/stroke (14). The growing body of information on therapeutic application of *Ginkgo biloba* through clinical trials has consistently demonstrated significant improvements in CNS function (15). Collectively, results of these studies suggest that the extracts of this plant may become an important component in the management of CNS disorders. It is nevertheless known that the whole extract of the plant (EGb 761) induces changes such as reversal of age-related depletion in brain chemicals (alpha 1-adrenergic, 5-HT1A) and allows extended retention of the brain fiber (hippocampal mossy fiber system) (11). These outcomes, along with the general phenomenon of neuroprotection mediated by ginkgolides may be substantially due to antioxidant activities of the terpeneoid ginkgolides (Ginkgo subcomponents) (16). Other biochemical properties exhibited by ginkgolides (Table 1) may also contribute to neuroprotection.

Effects on atherosclerotic and ischemic disease: Common medicinal application to which ginkgo has been traditionally applied was in the treatment of poor circulation associated with a wide range of diseases. In the early 1980s, a picture of how extracts of the plant acted to improve circulatory function began to emerge. Also, it was discovered in animal studies that platelet aggregation leading to clot formation in the peripheral vasculature could be suppressed by pretreatment with ginkgolides (17). This effect was also validated in humans with the demonstration that patients suffering from arteriosclerotic disorders manifested lower collagen induced platelet-aggregation when treated with Ginkgo extract, than a mock-treated control cohort (18), raising the possibility that ginkgolides might be useful in prevention of peripheral arterial occlusive disease and related complications.

Components of *Ginkgo biloba* were found to have a potent capacity to antagonize the effects of platelet activating factor (PAF) (19), a mediator of inflammation, which causes vasoconstriction through its action on vascular endothelial cells, promoting inflammation-associated damage, ischemia/reperfusion injury and occlusive pathologies. The capacity of ginkgo extract to act as a PAF antagonist and inhibit clot formation, partly explains the beneficial effects the herb is known to have on circulatory function. As these aspects of Ginkgo's pharmacological properties became clearer, ginkgo became the subject of an increasing number of clinical trials to improve the outcome of vascular diseases. Many of these have met with a considerable degree

of success. These include indications that Ginkgo biloba extract may inhibit the progression of age-related macular degeneration (20); cardiac or peripheral ischemia (15), tinnitus (21); obstructive arteriosclerosis and ischemia-reperfusion injury (22); and inflammation associated with trauma or disease (14). Components of Ginkgo biloba have been shown to positively affect the outcome of organ transplant surgery. Significantly, J. Grino *et al* demonstrated in 1994 that this compound is capable of decreasing the incidence of post-transplant renal failure in patients receiving kidney transplants (23). The reduction in inflammation-associated mechanisms of graft rejection by ginkgolide B (23) suggests that extracts of the plant may become a valuable adjuvant therapy to currently used post-transplant immunosuppressive strategies.

Treatment of sexual dysfunction: Extracts of *Ginkgo biloba* have been proven effective in treatment of sexual dysfunction, particularly when the condition is induced by administration of anti-depressant medication (24). EGb761 administered orally to patients being treated with antidepressants resulted in improved libido, with a 4-6 week regimen of ginkgo necessary for reversal of depressant-induced sexual side effects (24,25). The sexual libido-enhancing effects of ginkgo have been validated in studies of other populations including pre- and postmenopausal women (26); and atherosclerotic males experiencing erectile dysfunction (27). The cellular and physiologic mechanisms responsible for these effects remain poorly defined at the time of this writing. It has been known that ginkgo-mediated effects include increased blood flow to the genitalia; (24,25).

Chemical and pharmacological properties of ginkgolides: Extracts of ginkgo may be used in a broad spectrum of clinical applications that could be neurological, hemodynamic, metabolic or immunological in nature. This extensive range of therapeutic utility is due to the diverse activity of individual subcomponents (ginkgolides) produced by the plant. 14 major pharmacologically active subcomponents of *Ginkgo biloba* have been identified (Table 1). These include 8 flavonoid compounds that are polyphenolic metabolites, widely distributed in vascular plants. They have analgesic properties and are also useful for treatment of inflammation. Two of these, bilobetin and ginkgetin, are shown to be potent anti-inflammatory (28) and therefore have potential for treatment of inflammatory diseases. *Ginkgo biloba* also contains 6 terpene lactones with antioxidant properties (29) which are potentially valuable as anti-inflammatory agents. The terpene lactone ginkgolides block PAF activity in a manner, which affects the same biological pathways that are sensitive to calcineurin-inhibitory drugs, such as Cyclosporin A and FK506 (30,31,32), offering possibilities for their use in post-transplant Immunosuppression. Ginkoloide terpines are also powerful antioxidants, which further contribute to control of inflammation by quenching reactive oxygen metabolites (33). The beneficial effects of ginkgo are thus attributable to mechanisms acting separately or in concert, as a result of the unique properties of each component. The biological activities of ginkgolides are summarized below (Table 1):

Limitations of Ginkgo as a therapeutic agent and potential for future use: The diverse range of pharmacological activities exhibited by components of *Ginkgo biloba* and the very promising results of human clinical trials both of the extract and individual ginkgolides, suggest that ginkgo-based pharmacotherapy has the potential to substantially augment current approaches to treatment of a number of serious and widespread diseases. This is particularly true for CNS-related disorders, inflammation and diseases of the microvasculature. Clinical advantages to application of this plant are further augmented by the known low incidence of toxicity and side effects associated with its use; even at high dosage (34,24). Despite these advantages, *Ginkgo biloba* suffers from a major drawback with respect to its broad application as a basis for therapeutic agents. Whereas both the extract and the individual ginkgolides have been shown to positively affect the outcome of many disease conditions, in no case is ginkgo alone sufficient to affect a cure. Nevertheless, recent studies have demonstrated that the most promising clinical application for this plant may be as an adjunct for traditional approaches to treatment of a number of diseases.

Ginkgo-augmented adjuvant therapy for neurocognitive disorders: Ginkgo extracts have been used to potentiate the effects of other herbal preparations. As an example it has been demonstrated that the therapeutic effectiveness of *Panax ginseng* extracts may be substantially improved by co-administration of this herb together with ginkgo extract. Extracts of ginseng root are known to improve neuropsychological measures in humans (35) and are commercially available for this purpose. The plant contains triterpene glycosides with known neuroprotective properties (36), which are believed to mediate its effects on memory and cognition (37). When a blend of ginseng and ginkgo were tested in animal models, it was found to be superior to either agent alone in enhancement of these attributes (38). Human clinical trials have confirmed this and show that combined therapy using extracts of both ginseng and ginkgo exhibit substantial memory-enhancing properties in healthy, middle-aged subjects (37). This demonstration of ginkgo-mediated augmentation of a clinical outcome by another agent (ginseng) underscores the utility of ginkgo extracts in adjuvant therapy. Whereas Ginkgo alone often may not be adequate to satisfactorily remediate a particular medical problem, its augmentative effect considerably boosts the action of other agents. It is in this arena that use of specific ginkgolides as adjuncts to conventional treatment hold enormous potential. An important case-in-point is Alzheimer's disease. Development of the disorder involves progressive loss of neurocognitive function, brought about by deposition of short amyloid peptides in the brain of afflicted individuals, which interact destructively with neurons. (39). Recently it has been shown that the non-steroidal anti-inflammatory drug (NSAID) ibuprophen and related NSAIDs

For That, by which we See all colors, Taste all flavors, Smell all fragrances, Hear all sounds, And feel the touch of our beloved. That is the Self...

...Katha Upanishad

have the potential to inhibit and perhaps prevent onset of Alzheimer's in susceptible individuals (40). It is also known that Ginkgo biloba alleviates neurocognitive symptoms of the disease; in fact placebo-controlled clinical trials of Ginkgo extract demonstrate a therapeutic effect similar to prescription drugs such as tacrine or donepezil, with very low associated toxicity or side effects to patients (6). It is thus possible that combined treatment with both agents may act synergistically to prevent its onset or decrease its severity. It has been shown that the calcineurin-inhibitory immunosuppressive drugs FK506 and Cyclosporin-A were capable of inhibiting graft rejections in transplantation. The toxicity of these drugs makes it difficult to use them for long-term. Recently, it was demonstrated (in animal model) that extract of Ginkgo biloba, EGb761, decreased cardiac arrhythmias and improved cardiac function when used together with FK506 (30). These observations are now being explored in our (Dr. Guha's) laboratory.

Table 1. SUBCOMPONENTS OF GINKGO BILOBA: 14 pharmacologically active ginkgolides characterized with respect to their physical, chemical and biological properties

COMPOUND	CHEMICAL SPECIES	MAJOR PHARMACOLOGICAL PROPERTIES
GA, ginkgolide A, BN52020, CAS 15291-75-5	terpene lactone	PAFR antagonist, but no apparent antioxidant properties
GB, ginkgolide B, BN52021, CAS 15291-77-7	terpene lactone	PAFR antagonist, with antioxidant properties
GC, ginkgolide C	terpene lactone	PAFR antagonist, with antioxidant properties
GJ, ginkgolideJ	terpene lactone	PAFR antagonist, with antioxidant properties
GM, ginkgolideM	terpene lactone	PAFR antagonist, with antioxidant properties
Bilobalide	sesquiterpene	Primarily an antioxidant, poor PAFR properties
Amentoflavone	flavonoid	Inhibits cyclooxygenase without affecting lipoxygenase. Will inhibit PLA-2, strong inhibitor of cAMP-phosphodiesterase
Bilobetin	flavonoid	Inhibits PLA-2, in turn inhibiting the production to TNF-a, iNOS and inducible cyclooxyganase (COX-2), moderate inhibitor of cAMP phosphodiesterase
Sequoiaflavone	flavonoid	Moderate inhibitor of cAMPphosphodiesterase
Ginkgetin	flavonoid	Inhibits PLA-2, in turn inhibiting the production of TNF-a, iNOS and inducible cyclooxygenase (COX-2). Inhibits pathogenesis of arthritis
Isoginkgetin	flavonoid	Weak inhibitor of cAMP-phyosphodi-esterase irreversible inhibitor of lymphocyte proliferation
Sciadopitysin	flavonoid	Irreversible inhibitors of lymphocyte proliferation
Rutin	flavonoid	Inhibitor of lymphocyte proliferation.
Quercetin	flavonoid	Inhibitor of lymphocyte proliferation, PLA-2 inhibitor, Moderate inhibitor of camp-phosphdiesterase

Toxicity: Ginko biloba extracts are known to be safe. However, gastrointestinal discomforts, headaches and dizziness have been reported. Ginko leaf extracts are well tolerated as opposed to Ginko fruit derived supplements.

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Program at a Glance

Time	September 23	September 24	September 25
8:30 am-2 pm	*Opening with Havan*	*Keynote address*	*Keynote Address*
	Session-1 **Cancer, Pain and Palliative Care**	*Session-3* **Women's Health Inflammation & Immunity**	*Session-5* **Herbs, Diet and Nutrition, Mind Body Relation**
12:-2 pm	*Lunch Break*	*Lunch Break*	*Lunch Break*
2-5 pm	*Session-2* **Metabolic Syndrome**	*Session-4* **Basic concepts & Holistic Approach of Ayurveda**	*Keynote address* *Closing ceremony*
5-6 pm	*Inauguration & Keynote address*	*Keynote address*	*ISAH Board Meeting*
6-8 pm	**Cultural Program & Dinner**	**Ganga Arti and Kirtan Boat ride and Dinner**	
9 am-5 pm	**Poster session & commercial exhibition**		