REVIEW ARTICLE

Ginkgo biloba Extract: Mechanisms and Clinical Indications

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ABSTRACT. Diamond BJ, Shiflett SC, Feiwel N, Matheis RJ, Noskin O, Richards JA, Schoenberger NE. *Ginkgo biloba* extract: mechanisms and clinical indications. Arch Phys Med Rehabil 2000;81:668-78.

Objective: *Ginkgo biloba* may have a role 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, vasoocclusive disorders, and aging. The purpose of this review is to provide a synthesis of the mechanisms of action, clinical indications, and safety of *Ginkgo biloba* extract.

Data Sources: Empirical studies, reviews, chapters, and conference proceedings were identified in the following databases: Medline, the Research Council for Complementary Medicine based on the British Library database, and PsychInfo. *Ginkgo biloba,* EGb 761, Tanakan, Tebonin, Rokan, and LI 1370 were the principal index terms.

Study Selection and Data Extraction: Controlled clinical studies with both positive and negative findings are included, in addition to animals studies illustrating mechanisms of activity.

Data Synthesis: Ginkgo has shown activity centrally and peripherally, affecting electrochemical, physiologic, neurologic, and vascular systems in animals and humans with few adverse side effects or drug interactions. Ginkgo shows promise in patients with dementia, normal aging, and cerebrovascular-related disorders. Clinical indications include memory, information processing, and ADL.

Conclusions: Ginkgo shows promise in treating some of the neurologic sequelae associated with Alzheimer's disease, TBI, stroke, normal aging, edema, tinnitus, and macular degeneration. Mechanisms of action may include antioxidant, neurotransmitter/receptor modulatory, and antiplatelet activating factor properties. While safe, caution is advised when recommending ginkgo to patients taking anticoagulants. Future studies should examine dose effects, component activity, mechanisms, and clinical applications.

Key Words: *Ginkgo biloba;* EGb 761; Traumatic brain injury; Stroke; Aging; Dementia; Rehabilitation.

HERBAL PRODUCTS account for a substantial portion of the current interest in alternative treatments and *Ginkgo biloba* (GB) figures prominently in this interest. Interest in GB, however, has a long history. Fossil records place its origins 150 to 250 million years ago.[1] *Ginkgo* (derived from the Chinese Yin-Kuo, meaning "silver apricot") *biloba* (refering to its two-lobed, fan-shaped leaves) is derived from the leaf of the Maidenhair tree, which is believed to live 2,000 to 4,000 years.[2] Interest in the medicinal properties of GB can be traced back some 5,000 years to ancient China, where the healer Chen Noung (2767 to 2687 BC) described the medicinal properties of the plant in the first known pharmacopoeia, called the Chen Noung Pen T'sao.[1] Indications included ailments of the heart and lungs with the notation that inhaling its steam and imbibing its tea were palliative for both asthma and bronchitis.[2]

While firmly rooted in antiquity, GB is today the most frequently prescribed herbal preparation in Germany[3] and one of the most commonly used over-the-counter (OTC) herbal preparations in the United States.[4] In 1964, a GB extract called EGb 761 was developed by a German pharmaceutical company, and since that time hundreds of studies have examined ginkgo's effects in human and animal models. The German Commission E[5] (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.

GB extract or one of its components has been extensively studied in terms of its effects on the cognitive, physiologic, and psychiatric sequelae associated with neurologic and vascular conditions. Specific functions and conditions include recall/recognition memory, reaction time, attention, concentration, psychomotor function, fatigue, mood, outcomes, and information processing speed. GB has also been used experimentally in treating impairments and symptoms in Alzheimer's and age-associated dementia, traumatic brain injury, stroke, multi-infarct dementia, cerebral atherosclerosis, cerebral insufficiency, cerebral edema, inflammation, glutamate toxicity, necrosis, apoptosis, tinnitus, sexual dysfunction, and macular degeneration. This review will provide a synthesis of the mechanisms of action, clinical indications, and safety of GB extract.

DATA SOURCES AND DEFINITIONS

This review consists of peer-reviewed articles, conference proceedings, and relevant book chapters including a number of articles translated from German. Sources were identified using various strategies: (1) computer searches of the National Library of Medicine's Medline database (1966 to 1998), PsychInfo, and the British Library's Research Council for Complementary Medicine's database; and (2) citation tracking of references in articles and textbooks. The search words and acronyms were *Ginkgo biloba,* EGb 761, Tanakan, Tebonin, Rokan, and LI 1370 (Kaveri), the latter being brand names of GB extract.

Dozens of GB extract products are currently available to consumers. Most of these products use a 50:1 ratio by weight (50 pounds of leaf for each pound of extract) and are standardized to include 24% to 26% ginkgo flavonol glycosides. Many of the OTC ginkgo products may not be standard-

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ized. EGb 761 is a standardized GB extract manufactured to pharmaceutical standards by Dr. Willmar Schwabe Company, GmbH, Germany.[6] Tebonin, Tanakan, and Rokan contain EGb 761. Standardized extracts of EGb 761 are administered intravenously, in liquid form, or through tablets. Kaveri (LI 1370) is standardized on the same ingredients and in comparable dosages as EGb 761. Cp 202 refers to a GB extract that is devoid of all terpenes, and BN 52063 is a ginkgo preparation devoid of flavonoids. Ginkgo is generally administered in tablet or capsule form and based on dose-response evidence a dosage of up to 240mg would more typically be called for. The cost per day to a person taking 120mg of ginkgo can range from US $0.31 to $1.17 depending on brand. The acronym GBE (*Ginkgo biloba* extract) will be used interchangeably with EGb 761.

In this review, a number of studies refer to a geriatric condition known as "cerebral insufficiency." In Germany, this is a frequently cited clinical indication for ginkgo. While this diagnostic category is not universally recognized, it is characterized by 12 primary symptoms: confusion, memory impairments, absentmindedness, dizziness, tinnitus, headache, low energy levels, depressed mood, poor concentration, fatigue, anxiety, and decreased physical activity.[1]

A total of 188 sources covering human, animal, and in vitro studies were initially retrieved. Table 1 provides a summary of 24 controlled trials (ie, randomized, or double-blinded, placebo controlled trials) that meet at least four out of five of the following criteria[6]: (1) patient descriptions; (2) randomized or double-blinded, placebo controlled; (3) intervention described (ie, dose and duration); (4) statistical analysis; and (5) standardized outcome measures. Studies are listed alphabetically by author with information on experimental design, outcome measures, and results. Table 2 presents a summary of dosages and ranges, durations, and indications/symptoms for studies reporting data on treatment effects and adverse events. The animal and in vitro studies cited in this review are laboratory-based and use rigorous and well-established techniques.

EFFECTS IN HUMANS

Healthy Subjects

The studies cited in this section provide evidence for GBE's general and, in some cases, selective effects on cerebral activity.

Electroencephalogram (EEG) power and event-related potential (ERP) activity. In a study using EEG measures, greater alpha wave power was demonstrated in a dose-dependent manner after administration of 240 versus 120mg of EGb 761 per day.[7] Following a dose of 600mg, increased alpha power was observed in the frontal and occipital regions bilaterally, accompanied by increased alertness. In another study, EGb 761 administered in single daily doses of 80 and 160mg to 15 young subjects resulted in increases in the absolute and relative power of both the alpha and beta components and a concomitant decrease in the relative power of the theta band.[8] In addition, the P300 cortical ERP showed a significant decrease in latency.

Memory and information processing. In a double-blind, cross-over research design, psychometric tests were used to evaluate information processing and other cognitive functions in response to a range of oral doses of GBE acutely administered to healthy volunteers.[9] One hour after a single dose of 600mg of GBE, increases in memory scanning speed were reported. Different effects were reported on tests of visual-perceptual and reaction-time, arguing against a generalized effect.

Retinomuscular reflex. In evaluating the effect of GB on the retinomuscular reflex, subjects exposed to hypoxic conditions were administered computer tasks to verify that the polysynaptic retinomuscular reflex time was impaired.[10] It was reported that the reflex times and respiratory rate were significantly reduced after EGb 761 administration, further supporting the role of EGb 761 in oxygen regulation. Taken together, these findings suggest that GBE administered both acutely and chronically to healthy subjects is associated with improvements in cognition, shortening of the retinomuscular reflex time, and in the reduction of P300 latencies. These findings support the role of GB as a cerebral activator. GBE-induced changes in P300 latency may be associated with enhanced processing efficiency and memory updating. In addition, increases in the power of the higher frequency EEG components is often associated with enhanced cognitive performance. Thus, these studies provide support for the idea of using GB as an adjunctive pharmacologic therapy and provide some insight into its possible mechanisms of action (ie, alteration of ERP latencies).

Clinical Trials

The studies cited in this section examine GBE's neuroprotective and cognitive enhancing properties in treating dementing conditions including age-associated pathologic degenerative processes, vascular insufficiency (multi-infarct dementia), dementia of the Alzheimer's type, and "cerebral insufficiency."[3,11-13]

Cerebrovascular insufficiency, vascular and Alzheimer's dementia. *EEG activity: memory and vigilance.* A double-blind, placebo-controlled trial examined the effects of EGb 761 on neurophysiologic and psychometric parameters in 36 patients with cerebrovascular insufficiency.[14] Half of the subjects received EGb 761 at a dosage of 120mg per day for 8 weeks. After 4 to 8 weeks of treatment, the relative power of the EEG alpha component was increased in the EGb 761–treated patients. In another study, 120mg of GBE were administered for 12 or 24 weeks to 31 patients, 50 years or older, with mild to moderate memory impairments. Memory improved and the power and amplitude of low frequency components (1 to 3Hz) was reduced.[15] The 24-week group demonstrated greater reductions than the 12-week group. Changes in EEG correlated with improvements in cognition and memory.

These results, however, were not confirmed in another double-blind study of patients with cerebral insufficiency who were matched on age, education, and severity and who were assigned to three experimental groups.[16] The study lasted 12 weeks with EEG and psychometric assessments performed at 4, 8, and 12 weeks. No significant advantage of GBE over the two reference substances was noted on EEG. However, measures of vigilance in a more impaired subgroup of subjects did improve in those taking GBE. In an uncontrolled study involving patients with possible or probable Alzheimer's disease, the magnitude of effects associated with a single 240-mg dose of ginkgo (standardized dry extract of *Ginkgo biloba* leaf) and a single 40-mg oral dose of tacrine (tetrahydroaminocrine), a so-called "cognitive activator," was examined using quantitative pharmaco-electroencephalographic techniques. Ginkgo was slightly more effective than tacrine in inducing changes in EEG profiles. That is, both substances induced a pre-post relative increase in alpha activity (ie, 7.5 to 13Hz) and a decrease in slow wave activity (ie, delta and theta of 1.3 to 7.5Hz) similar to that seen in healthy younger subjects.[17] Overall, these studies suggest that consistent with previous findings in healthy subjects, ginkgo appears to exert an activating effect on EEG power in clinical populations as well.

Cognition, motor activity, mood, and neurologic function. In a double-blind study, 50 patients suffering from chronic cerebral insufficiency of vascular origin were administered

Table 1: Overview of Clinical Studies

Authors	Symptoms	Design	Outcome Measures	Dose/Duration	Outcome
Allain et al[28]	Memory impairment	n = 18; RPC, DB Mean age: 69.3	Dual-coding task (information processing)	320 or 600 mg, 1h prior to testing	Dual-coding task (information processing): Treatment = 960ms, placebo = 1,920ms (F = 16.3, p = .00001); no dose effects
Arrigo and Cattaneo[22]	Cerebrovascular insufficiency	n = 80; DB, PC Mean age: 26	Wechsler Adult Intelligence Scale (WAIS), block design, word recognition; Rey's complex figure, memory; Spielberg State-Trait Anxiety Inventory	120mg/d for 45 days	WAIS: Treatment = +0.8, placebo = +0.2; word recognition: treatment = 16.3, placebo = 2.6; Rey's complex figure: treatment = 2.9, placebo = 1.4; memory: treatment = +16.7, placebo = +6.7; anxiety: treatment = −5.6, placebo = −2.5
Brüchert et al[35]	Aging, cerebral insufficiency	n = 303; R, DB	Figure connection test	50 mg TID for 12 weeks	Figure connection test: improvements after 6 weeks
Deberdt[105]	Cognitive impairment	n = 80; Mean age: 68	Memory	160mg/d one time	Memory: treatment = +2.03, placebo = −.09
Eckmann[19]	Cerebral insufficiency	n = 60; PC Mean age: 54	Concentration, fatigue, cerebral function	160mg/d for 6 weeks	Concentration, fatigue, cerebral function: treatment = reduction over placebo (p < .001)
Eckmann et al[18]	Cerebrovascular insufficiency	n = 50; PC Mean age: 59.5	Dizziness, motor activity, speech comprehension/production, depression	Tebonin forte drops, 60/d for 30 days	Dizziness: treatment = improvement over placebo (p = .068)
Gessner[104]	Cerebrovascular insufficiency	n = 60; RPC, DB Mean age: 67	EEG, behavioral, psychometric tests Three groups: GBE, nicergoline, or placebo	12wks for EEG; 4, 8, 12wks behavioral	No significant changes found between groups
Gerhardt et al[26]	Aging, cerebrovascular	n = 80; R	Cerebrovascular function	N/A	Cerebrovascular function: dihydroergotoxine exhibited greater effects than GBE
Halama et al[84]	Cerebrovascular insufficiency	n = 40; RPC Mean age: 55	Sandoz Clinical Assessment-Geriatric (SCAG)	120mg/d for 12wks	SCAG: Treatment = −9.0, placebo = no change
Hamann[32]	Vestibular disorder	RPC, DB	Vertigo, body sway amplitude	4 drops twice/d	Vertigo: no change; Body sway amplitude: treatment = −22.2 mm, placebo = −10.3mm
Hartmann and Frick[27]	Vascular dementia	n = 52; RPC, DB	Psychometric tests	20mL TID solution 3mo	Psychometric tests: GBE group no different from placebo
Hofferberth[29]	Senile dementia	n = 40; PC; Mean age: 62.5	Memory, attention, psychomotor, physiology	80mg TID	Memory & attention: treatment = −5, placebo = +2
Kanowski et al[13]	Alzheimer's and multi-infarct dementia	n = 156; multicenter; RPC, DB	Syndrome short test (SKT): attention and memory; Nurem geriatric observation (NAB): activities of daily living; clinical global impressions (CGI) (Item 2): Psychopathology	EGb 761 & placebo: 240mg/d BID	CGI: change to "much improved" or "very much improved" (32% vs 17%); SKT: a decrease in total score of at least 4 point (38% vs 18%); NAB: a decrease in total score of at least 2 point (33% vs 23%)
Le Bars et al[24]	Alzheimer's disease, multi-infarct dementia	n = 309; RPC, DB, parallel study	Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative Rating Instrument (GERRI)	120 mg/d for 52 weeks	ADAS-Cog: treatment = 27% of patients experienced 4-point improvement, placebo = 14% improved (p = .005); GERRI: treatment = 37% improved, placebo = 23% (p = .003).
Luthringer et al[8]	Healthy volunteers	n = 15; single & DB, partial PC Mean age: 29	Absolute and relative power of alpha, beta, theta waves	80 or 160mg/d, 5 days	Alpha and beta: increased until 5 days posttreatment; theta: power decreased; P300 latency: decreased (pre: 309ms; post: 294ms)
Maier-Hauff[31]	Subarachnoid hemorrhage, cerebral insufficiency	n = 50; R, DB Mean age: 48	Reaction time, attention, short-term memory, accuracy, recurring figures (Zimmermann test battery)	150mg/d LI 1370 for 12 weeks	Accuracy, reaction time, short-term memory: increased

Table 1: Overview of Clinical Studies (Cont'd)

Authors	Symptoms	Design	Outcome Measures	Dose/Duration	Outcome
Mancini et al[37]	Psychoorganic senile dementia	*n* = 80; RPC Mean age: 74	SCAG scale, Toulouse-Pieron cancellation	80mg ID for 6wks	SCAG: treatment = −15.4, placebo = −0.7; Toulouse-Pieron cancellation: treatment = −.3 errors, placebo = +.7 errors
Meyer[89]	Tinnitus	*n* = 259; R, multicenter	Tinnitus rating	4mL/d	Rating: treatment = 1.00, placebo = .67, (p = .08)
Rai et al[15]	Memory impairment	*n* = 27; RPC, DB; Mean age: 50	Kendrick Digit Copying & Learning (KDC & KDL) task; digit recall task, P300 latency	40mg TID for 12-24wks	KDC: treatment = 26.8s, placebo = 24.3s; KDL: treatment = 106.6s, placebo = 94.53s; Digit recall task: treatment = 47.92 errors, placebo = 32.73 errors; P300 latency: treatment = 426.2ms, placebo = 392.7ms
Schaffler and Reeh[10]	Hypoxia	*n* = 8; SB, PC, cross-over trial Mean age: 26	Retinomuscular reflex time; respiratory rate	4 mL/d Tebonin for 14 days	Retinomuscular reflex time: treatment = decreased ($p < .05$); respiratory rate: treatment = decreased ($p < .05$)
Schubert and Halana[20]	Cerebral insufficiency, depression	*n* = 40; PC Mean age: 58	Hamilton Depression Scale (HDS), Short test of general intelligence	240mg/d for 8wks	HDS: treatment = −7.0 (day 28), −9.5 (day 56), placebo = −1.0 (overall); short test of general intelligence: treatment = +15.0, placebo = −1.0 point (p = .02)
Schwerdtfeger[33]	Vestibular disorder	*n* = 50; RPC, DB Mean age: 42.7	Electronystagmograph (ENG) with calorimetry and the rotary chair examination	120mg/d & 60mg/d for 2mo	ENG: treatment = over 50% evaluated as "very good" or "good," placebo = 47% condition deteriorated
Subhan and Hindmarch[9]	Healthy	DB, cross-over	Sternberg memory test	600mg acutely	Memory span: increased; reaction time: no change
Wesnes et al[23]	Idiopathic cognitive impairment	*n* = 54; RPC Mean age: 73.5	Recall, reaction time, recognition. Crichton geriatric rating scale	Tanakan: 120mg/d for 12 weeks	Recall: treatment = 6.1, placebo = 5.5; reaction time: treatment = 562ms, placebo = 570ms; recognition: treatment = 1,109ms, placebo = 1,342ms

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.

either 120mg per day of GBE or placebo for 1 month prior to assessment.[18] Within the ginkgo group, improvements were noted in motor activity, speech comprehension and production, and mood, as well as a reduction in dizziness. In a placebo-controlled, double-blind trial examining 60 patients with cerebral insufficiency, GBE was administered at a dosage of 160mg per day for 6 weeks.[19] Improvements in concentration and reduction in fatigue were reported.

Patients with moderate cerebral insufficiency diagnosed with depression were administered 240mg of GBE in a placebo-controlled study.[20] All patients were concurrently taking antidepressive medication (ie, tricyclics or tetracyclics) at the same dosage and frequency throughout the trial. Statistically significant improvements were recorded on the Hamilton Depression Scale (ie, a decrease of 9.5 points for the treatment group)[20] and the Short Test of General Intelligence (ie, an improvement of 15 points) in patients taking ginkgo. These changes are also clinically significant and suggest that ginkgo can play a role in treating depression and that GBE combined with antidepressants can be clinically more effective than either substance in isolation in patients with cerebral insufficiency.

In a double-blind, placebo-controlled study of 40 outpatients diagnosed with mild to moderate cerebrovascular insufficiency, patients receiving 120mg per day of GBE for 12 weeks showed improvement on clinical assessment and on self-rating scales monitoring changes in dizziness, tinnitus, headaches, and hearing loss.[21] Statistically significant improvements were noted in 18 of 20 patients including improvements in tinnitus, dizziness, and in the frequency and severity of headaches. The authors concluded that GBE has therapeutic value in the treatment of cerebrovascular insufficiency. Eighty patients with cerebrovascular insufficiency were tested in a double-blind, placebo-controlled, crossover study.[22] Group A received GBE for the first 45 days and placebo for the remainder of the trial, and Group B initially received placebo followed by GBE. Patients in the GBE versus placebo treatment blocks showed significant improvement on the Wechsler Adult Intelligence Scale (WAIS)[22] block design and on a visual-spatial contruction task providing support for GBE's beneficial effects in treating some of the symptoms of cerebrovascular insufficiency. It should be noted, however, that an improvement of 0.7 points on the block design subtest of the WAIS, while being statistically significant, is unlikely to represent a clinically meaningful change.

Fifty-four elderly patients with idiopathic cognitive impairment were administered ginkgo or placebo over a 3-month period in a randomized, placebo-controlled (RPC), double-blind study.[23] Although both the treatment and placebo groups showed improvement, the improvement in recall and reaction time scores in the GBE treatment condition was significantly

Table 2: Dosage and Duration Classified by Etiology/Symptom and Adverse Events

	Dosage	Duration
Indications/Symptoms		
Cerebral	≤400mg/d; 3.5mg/mL	3wks to 13mo
Cerebrovascular	101-200mg/d; 0-60 drops/d	3wks to 3mo
Information processing	≤600mg/d	3mo to 6mo
Dementia	≤200mg/d	5wks to 3mo
Hypoxia	1-10mL/d	2wks
Ischemia	≤100mg/d; 0-150g/mL/d	7 to 9wks
Metabolic	≤1,000g/mL/d	≤24h
Tinnitus	101-200mg/d; 1-10mL/d	3mo
Vestibular	101-200mg/d; ≤60 drops/d; ≤100ng/mL/d	3 to 9wks
Subarachnoid hemorrhage	101-200mg/d	3mo
EEG	≤600mg/d	N/A
Memory	150mg/d to 320mg/d	≤24h to 24wks
Adverse events		
Spontaneous hyphemia, 325mg[39]	40mg twice daily	1wk
Subdural hematoma headache, nausea, diplopia, vomiting[40]	60mg twice daily	2yrs
Memory impairment, dizziness[41]	50mg three times daily	6mo
Gastrointestinal upset[24]	40mg twice daily	1yr

greater than the placebo condition. Improvements in cognition were accompanied by increased motivation and interest in activities of daily living.

Recently, in a large clinical trial the efficacy and safety of EGb 761 was evaluated in patients with Alzheimer's disease and multi-infarct dementia. Le Bars and colleagues[24] conducted a 52-week, double-blind, RPC, parallel-group, multicenter study of EGb 761 consisting of 309 patients. Patients were administered EGb (120mg/d) or placebo. At the 52-week end-point analysis, evaluable data were obtained from 202 of the original 309 patients. Using the literature-based cutoff score of ±4 as an indicator of change, 27% of participants who received EGb showed positive changes on the cognitive subscale of the Alzheimer's Disease Assessment Scale compared with 14% of the people in the placebo group. EGb 761 stabilized, and in some cases, improved cognitive performance and functional activities. Effect size appeared to be independent of age or severity of symptoms at baseline. However, no differences were detected on a global rating of clinical symptoms. This lack of effect of EGb is in contrast to the findings of a meta-analysis of controlled trials that evaluated the effects of tacrine on the symptoms of Alzheimer's disease. It was reported that tacrine produced a small but beneficial effect on the clinician's Global Impression of Change score. The odds of improving on this scale when taking tacrine improved by about 50%.[25]

In addition, when the efficacy of GBE was compared with dihydroergotoxine in the treatment of cerebrovascular-related symptoms in a 6-week, randomized trial of 80 elderly patients,[26] improvements were found more frequently in the dihydroergotoxine group than the GBE group. The effect of GB has also been examined in vascular dementia. GBE (150mg/d) was evaluated in 52 ambulatory patients[27] over a period of 3 months. A strong placebo effect was observed and the treatment was not superior to the placebo in improving psychometric performance.

Overall, these findings suggest that ginkgo was effective in improving neurologic functions (eg, cognitive, mood, motoric, headache, and motivational) across a diverse etiological spectrum (eg, cerebral insufficiency, Alzheimer's disease, multi-infarct dementia, and idiopathic cognitive impairment). In two trials involving patients with cerebrovascular-related symptoms and vascular dementia, ginkgo improved functioning but was not superior to dihydroergotoxine or placebo, and in one trial EGb was more effective for symptoms responsive to tacrine.

Normal aging: information processing and EEG activity. In a double-blind, RPC cross-over study, 18 men and women suffering from moderate, age-related memory impairments were administered GBE at doses of 320 or 600mg an hour before performing a dual-coding test that measured the speed of information processing.[28] Following administration of GBE, subjects displayed faster processing speeds for both verbal and visual information. Given the previously documented effects of ginkgo on EEG activity and the fact that aging is often accompanied by an increase in slow wave EEG activity with a concomitant decrease in alpha activity,[29,30] it is plausible that ginkgo's cognitive enhancing effects may have been mediated by changes in cerebral activation and EEG activity.

Stroke. In a clinical trial of 50 patients (mean age of 48) who had suffered aneurysmal subarachnoid hemorrhages,[31] subjects participated in the trial between 7 and 42 months after surgery. Half the patients received 150mg per day of GBE (LI 1370) and half received placebo. At 12 weeks, the GBE-treated group displayed significantly faster reaction times, improved accuracy, and short-term memory compared with pretherapy results and the results of placebo controls.

Vestibular disorders. GB has been evaluated in patients suffering from Ménière's syndrome, neuropathia vestibularis, and posttraumatic vertigo in a double-blind, RPC study.[32] Patients had at least one of three major symptoms of vestibular disorders (vertigo, nystagmus, or dysequilibrium) for 3 or 4 years. All patients received vestibular training and 17 of the 35 patients received 4 drops of GBE, twice daily (160mg GBE) for 4 weeks. GBE and vestibular training together were significantly more effective than training alone.

Similarly a double-blind, placebo-controlled study involving 50 people concluded that GBE (120mg three times a day for 4 months) was effective in treating vertigo of vascular origin as well as vertigo resulting from cervical curve syndrome (a peripheral insufficiency of the inner ear), a finding that was independent of age and duration of symptoms.[33] Eighty-six percent of the patients on GBE improved. The placebo group showed improvement, but not as dramatically, nor was it maintained.

Taken together these finding indicate that GB can exert ameliorative effects on cognition, mood, and vestibular function in stroke, dementia, aging, and various neurologic disorders, in addition to modulating cerebral blood flow and brain wave activity. Interestingly, several studies have demonstrated that GB can exert its effects within a short period of time (ie, within 1 to 3 hours). Future work should more closely examine these short-term effects and their mechanisms of action.

SAFETY

Ginkgo has generally been safe and has displayed no verified adverse drug interactions.[3,24,34-36] It should be noted, however, that because ginkgo exhibits monoamine oxidase (MAO) inhibitor properties, it could exert a synergistic effect when combined with other MAO-inhibitor drugs. In addition, be-

cause ginkgo acts as an antiplatelet activating factor, caution should be used when it is administered with anticoagulants.

Mancini and colleagues[37] reported good tolerability using measures of renal function and blood crasis. In rare cases, patients have shown skin reactions, headache, and mild gastrointestinal (GI) upset.[6,13] In a meta-analysis of 25 controlled studies involving 739 patients, 4.4% of the patients experienced adverse events: 2.6% GI, 0.9% headaches, 0.4% sleep disturbance/dizziness, and 0.3% skin eruptions.[38] In a recent study older subjects were administered 120mg/d of EGb 761 or placebo,[24] and the incidence of GI upset was slightly higher in the EGb 761 group. However, there were no significant differences in either the incidence or in the severity of adverse events reported in the two groups.

A handful of case studies have reported adverse events in individuals taking GB; however, there is no definitive evidence linking it as a causal factor in these reports. For example, a 70-year-old man on concurrent aspirin therapy developed a case of spontaneous hyphema[39] and the symptoms disappeared after withdrawing the OTC extract. A woman who suffered a spontaneous bilateral subdural hematoma had been treating herself with ginkgo extract for 2 years, in addition to taking ergotamine and caffeine.[40] A 72-year-old woman with no history of head trauma but computed tomography evidence of a left subdural hematoma complained of memory impairments and dizziness while taking GBE.[41] Recently, it was also reported that a subarachnoid hemorrhage occurred in an individual taking ginkgo.[42]

Although ginkgo has not been causally linked to these adverse symptoms, these reports would suggest that physicians should exercise caution when prescribing GBE to individuals who are also taking anticoagulants.[43] It should be noted that some constituents from GB leaves (eg, ginkgolic acids) are not present in GBE but may be present in some nonstandardized OTC ginkgo products. These anacardic acid–like allergenic constituents could potentially cause side effects and future research should examine this issue.[44] Overall, given the long history of use and the number of studies that have administered GB variants in differing dosages and durations to patients of differing etiologies and ages, GBE has a notable history of safety.

BIOLOGIC MECHANISMS OF ACTION

This section reviews possible mechanisms mediating GB's clinical effects. The research is derived from both animal and clinical studies on GB's peripheral and central effects, including its vasomodulatory, metabolic, antiplatelet, antioxidant, and receptor/transmitter modulating properties.

Constituents

EGb 761, which figures prominently in most of the controlled studies, is standardized to 24% ginkgo-flavone glycosides and 6% terpenoids.[2,45,46] The major constituents of EGb 761 (>0.1%) are: flavonol monoglycosides (eg, quercetin-3-0-glucoside, quercetin-3-0-rhamnoside, and 3'-0-methylmyricetin-3-0-glucoside), flavonol diglycosides, flavonol triglycosides, coumaric esters of flavonol diglycosides, flavonoidic compound, terpenes (eg, bilobalide, ginkgolides A, B, C, and J), organic acids, and steroids. Table 3 provides information on isolated GB components and their activity.

Table 3: Investigator, Isolated Component, and Activity

Investigator	Isolated Component	Function
Barth et al (1991)[57]	Flavone	Inhibits lipid peroxidation
Ramassamy et al (1992)[79]	Flavone	Mediates 5-HT uptake
Gryglewski et al (1987)[66]	Flavone	Inhibits platelet aggregation
Coeffler (1998)[60]	Ginkgolide B	Anti-platelet activating factor properties
Janssens et al (1995)[59]	Bilobalide	Delays onset of hypoxic glycolysis
Amri et al (1996)[83]	Bilobalide, Ginkgolide A, Ginkgolide B	Induces PBR downregulation; increases ACTH concentration

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

Pharmacokinetics: Absorption, Distribution, and Excretion

A number of studies have addressed the issues of absorption, duration of effects, and excretion of GBE. For example, in examining the effects of an orally administered dose of ginkgo in a rat model, expired orally administered and radiolabeled ^{14}C-CO_2 extract represented 16% of the administered dose excreted in the first 3 hours after dosing out of a total of 38% after 72 hours. Twenty-one percent of the administered dose was excreted in the urine and 29% was excreted in the feces. Absorption reached at least 60%. Based on blood-specific activity data, the pharmacokinetics of GB were characteristic of a two-compartment model consisting of a first-order phase and a biologic half life of approximately 4.5 hours. With respect to distribution, radioactivity was primarily associated with the plasma, through a gradual uptake after 48 hours. Specific activity in the erythrocytes matched that of the plasma findings. Activity levels peaked at 1.5 hours, and it was speculated that the upper GI tract was also an absorption site, in addition to neuronal, glandular tissue, and occular tissue.[47] In a study involving two healthy volunteers, flavonol glycosides (50, 100, and 300mg LI 1370) were absorbed in the small intestine with peak plasma concentrations reached within 2 to 3 hours. The half life of the flavonol glycosides was between 2 and 4 hours. Within 24 hours, plasma concentration values had returned to baseline levels.[48] In a study involving possible or probable Alzheimer's patients, an orally administered dose of standardized extract of dry GB leaves induced EEG changes within 3 hours, suggesting that it was adequately absorbed, metabolized, and crossed the blood-brain barrier.[17] Generally, GB whole extract or its constituents have exhibited half lives ranging from 2 to 4 hours and activity levels that peak at 1.5 to 3 hours in animal and human models.

Peripheral Effects

Vasomodulatory effects. GBE has been shown to exert constrictive or dilatory effects on blood vessels in a state-dependent manner (ie, depending on whether the vasculature was initially in a constricted or dilated state) in a rabbit model.[49-51] GBE potentiates the concentration of norepinephrine and causes the Ca^{2+}-dependent constriction of isolated aorta and vena cava. In addition to augmented sympathetic stimulation, the constrictor effect may also involve diminished catechol-O-methyltransferase (COMT) activity, or partial reuptake inhibition.[52] In contrast to constrictive mechanisms, the dilatory effects appear to be endothelium-dependent. Alternative mechanisms may involve MAO inhibition,[53] prostacyclin (PGI_2) release,[54] beta-adrenoceptor agonism, increased intracellular Ca^{2+} sequestration,[55] increased nitric oxide synthase activity,[2] decreased nitric oxide (NO) synthase activity,[56] or decreased lipid peroxidation.[57] In a study using a rabbit model of cerebral vasospasm, GBE has reduced vasospasm,[51] which

could extend its clinical application to the treatment of stroke, cerebral and systemic atherosclerosis, idiopathic hypertensive episodes, cardiogenic and endotoxic shock, anaphylaxis, migraine, and intermittant claudication. Seemingly contradictory mechanisms of action may, in fact, be attributable to ginkgo's differential response to state dependent effects.

Metabolic effects. GBE has caused increases in glucose uptake and glycogen synthesis in smooth muscle cells in a concentration-dependent manner.[58] Studies on hypoxic endothelial cells indicate that GBE and bilobalide (a terpene fraction) (table 3) can delay the onset of hypoxic glycolysis by prolonging adenosine triphosphate (ATP) generation.[59] The underlying mechanisms, however, remain unclear.

Antiplatelet activating factor activity. GBE appears to inhibit platelet aggregation by increasing concentrations of endothelium-derived thrombolytics (eg, NO and prostacyclin). Ginkgolide B (a component of the terpene fraction) shows antiplatelet activating factor (PAF) properties.[60] Moreover, even after preincubating PAF with platelets, ginkgolide B produces an almost complete dissociation of bound PAF.[61,62] This finding is important due to the role played by PAF in the pathophysiology of edema, inflammation, and hypercoagulable states.

Antioxidant properties. GBE has been shown to induce the destruction of various radical species, including OH, O^{2-}, the diphenylpicrylhydrazyl radical, and the adriamycyl radical.[56,63] It can scavenge NOs and reduce nitrate levels in a dose-dependent manner,[56,63] providing further support for its role as broad-spectrum scavenger.[64] In vitro and in vivo studies demonstrate that the flavone component of GBE can inhibit lipid peroxidation[57,65] and platelet aggregation.[66] The flavone component may mediate ginkgo's ability to protect physiologic systems from reactive oxygen species. This may be useful in treating the effects of blood lipoprotein oxidation that result in the deposition and aggregation of atherosclerotic plaques following hypoperfusion-reperfusion and hypoxic states. Decreases in oxidation-induced carbonylation of apolipoprotein B at all concentrations of GBE and a concentration-dependent decrease in low density lipoprotein (LDL) lipid peroxidation have also been reported.[67] The fact that GBE inhibits Cu^{2+}-mediated LDL oxidation may have important medical implications for heart disease.

GBE is associated with increased prostacyclin synthesis[68] and inhibition of the radicals produced via the arachidonic acid cascade.[69] GB has inhibited the cascade of events leading to programmed cell death in cultured rat cerebellar neurons.[70] Overall, GBE appears to exert a protective effect on rat cerebellar neurons under oxidative stress.

Central Effects

GBE exerts transmitter/receptor effects that are likely mediated via radical scavenging/inhibition, hemodynamic/metabolic modulation, PAF antagonism, MAO and COMT inhibition, alpha-agonist, receptor density modulation, and NO synthase inhibition. Evidence indicates that GB can alter and restore a variety of central states and conditions (table 4).

Cerebral blood flow. In an uncontrolled study, regional cerebral blood flow (rCBF) and 123-iodo-amphetamine binding were measured in six patients with unilateral middle cerebral artery infarcts who were administered GBE during the first month postinfarct.[71] Three out of six patients exhibited decreases in rCBF and delayed 123-iodo-amphetamine binding. While these results contradict other evidence that GBE promotes increases in cerebral blood flow,[72-74] two of the three patients who did not show decreases in rCBF and who received GBE immediately after the vascular event, showed significant clinical recovery.

Table 4: Central Effects: Alterations and Restorations

Cerebral hemodynamics[103]
Hypoxia-induced cerebral blood flow dysregulation[72]
Hypoperfusion[113]
Survival[114,115]
Necrosis (ie, rat hippocampal cells)[74]
Stroke index and respiratory control ratio[62]
Free fatty acid concentration[116]
Calcium influx[117]
Ionic state[118]
Glucose consumption[119]
Edema and inflammation[61]
Dopaminergic synaptosome peroxidation[79]
EEG alpha (ie, increases) and theta power (ie, decreases)[34]
Restorative effects on hypoxic blood-brain barrier[120]

Transmitter/receptor effects. In this section, GBE-associated changes in cerebral transmitter, receptor, and enzyme activity are described. GBE has induced increases in norepinephrine turnover in rats,[75] alpha-2–receptor density,[76] muscarinic acetycholine (mACh) and serotonin (5-HT) receptor density, and decreases in beta-adrenoceptor density.[77] Whether increased norepinephrine turnover is solely the result of GBE-induced, COMT inhibition, or associated increase in synthesis and utilization is not clear. GBE also nonspecifically inhibits MAO[53] and COMT activity.[52] These are among the many effects that may mediate GBE's purported activity in reversing age-associated cognitive decline.

GBE is believed to exert effects on the alpha-2–adrenoceptor and in reversing the age-associated decrease in maximal binding (β_{max}) of rauwolscine, an alpha-2–agonist[76,78] particularly evident in cortex and hippocampus of older versus younger rats. EGb 761 and Cp 202 (a GB extract devoid of terpenes) have induced increased synaptosomal uptake of 5-HT in mouse cortex (an effect inhibited by clomipramine). BN 52063 (devoid of flavonoids) and quercetin (a flavonoid constituent of GBE), did not increase synaptosomal uptake.[79] Overall, the flavonoid component appears to mediate 5-HT uptake.[79] This could result in increasing the bioavailability of serotonin in the central nervous system.

It has also been demonstrated that after 4 weeks of GBE treatment, a marked increase occurred in the number of mACh receptors in 24-month old rats. However, in 3-month-old rats, increases in mACh receptors and decreases in kainic acid-glutamate receptors did not reach statistical significance.[80] Increased survival and brain dopamine synthesis following bilateral carotid ligation has been found in rats given EGb 761.[81] Using a mouse model, Ramassamy and colleagues[82] examined GBE's effects on the neurotoxicity of N-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), which serves as a model for Parkinson's disease. Untreated animals showed a decrease in synaptosomal uptake, as well as a 25% reduction in striatal dopaminergic nerve endings. Uptake inhibition, membrane stabilization, or inhibition of MPTP conversion by MAO likely mediated GBE's effects. In animal models (ie, rats), GBE has exerted regulatory effects on the peripheral benzodiazepine-type receptor (PBR).[83] EGb 761 (ie, bilobalide, ginkgolide A and/or ginkgolide B) has induced down regulation of PBR in rats. In addition, decreased serum corticosterone levels and increased serum adrenocorticotropic hormone concentrations were also observed.[83]

CONCLUSION

Ginkgo's reported neuroprotective and cognitive enhancing properties suggest a clinical role in treating a variety of medical[13,14,29,36,37,60,67,84-94] and neurologic and physiologic symptoms.[14,20,27,35,61,79,88,95-99] Ginkgo has also exerted effects on cognitive performance in healthy younger subjects[9] and in age-associated cognitive deterioration.[100,101]

For practicing clinicians who want guidelines regarding dosages and durations, studies reporting positive findings (ie, significant improvement on one or more outcome measures) generally had dosages between 120 to 300mg/d, administered for durations of 3 to 12 weeks (table 2). Generally, treatments lasting 4 to 6 weeks are needed before positive effects can be expected[1] when GB is being taken for the purpose of affecting memory, mood, or other physiologic functions. It should be noted that the *Physician's Desk Reference (PDR) for Herbal Medicines*[102] states that when using GB as a dietary supplement, the average daily recommended dose is 120mg of dry extract in divided doses.

In studies reporting adverse events (most of which were case reports), dosages ranged from 80 to 150mg/d for durations of 1 week to 1 year. These patients generally had multiple comorbid conditions and were taking other medications, in addition to GB.

GB appears to exert its effects through its antioxidant and anti-PAF activity, in addition to its modulatory effects on cerebrovasculature tone, receptor/transmitter activity, glucose metabolism, and electroencephalographic activity. Dose-dependent effects have been reported in the following conditions: cognitive impairment,[23,28,29,37,78,86] cerebrovascular insufficiency,[14,19-22,26,31,35,71,103-109] tinnitus,[89,110] hypoxia,[10] vestibular disorders,[32,37] and aging.[26,35,111,112] Five components of GBE (table 3) appear to exhibit concentration dependent antioxidant,[57,60,66] metabolic,[59] and neurotransmitter[79,83] regulatory effects. The literature does not currently support a general statement regarding the efficacy of various ginkgo preparations across multiple studies given the different methods, measures, and analysis techniques that were employed. Moreover, most of the controlled studies have used the standardized extract EGb 761, so differences across studies would likely not be attributed to differences in ginkgo preparations.

While the majority of published studies support GB's efficacy and safety in healthy and clinical populations,[38] a handful of studies find no effects, selective effects, or effects that are counter to predicted outcomes. For example, GBE was no more effective than either nicergoline[104] or dihydroergotoxine[26] in treating cerebrovascular disease. In addition, two studies found that GBE was not effective in treating the symptoms of vascular dementia[27] and vertigo.[32]

With respect to the magnitude of treatment effects, GB has been associated with improvements in a variety of measures that reflect cognitive and functional status as well as mood. Determining the clinical significance of these changes is complex due to differences in outcome measures, scale sensitivity, and lack of standardization across studies. In some cases, statistically significant outcomes may translate into limited clinical significance. Thus, the statistically significant 0.7 point increase reported on the Block Design subtest of the WAIS[22] is unlikely to represent a clinically meaningful change. However, statistically significant changes observed on instruments such as the Hamilton Depression Rating Scale[20] (ie, 9.5 point decrease) and the Sandoz Clinical Assessment Geriatric assessment (ie, 9 point decrease)[37,84] also represented clinically significant changes as well. Interpretation of clinically nonsignificant results can become complex. That is, GB may slow down disease progression (ie, in Alzheimer's), and so, compared with a healthy control group and previous baseline performance, a treatment group may show no statistically significant improvement, masking the fact that cognitive decline has been slowed. As a whole, these findings suggest that despite the complexity inherent in interpreting results, clinically meaningful, albeit subtle, improvements have been observed in a number of studies supporting the usefulness of GB in various clinical indications.

The quality of clinical and animal research examining GB is generally good, with many controlled clinical trials and rigorous laboratory-based studies. However, future research should use more sensitive and standardized outcome measures, measures with validated interrater and intrarater and test-retest reliability, parallel test forms, better descriptions of patients and diagnoses, and more controlled trials. Specifically, 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.

In making informed clinical decisions, physicians should be apprised of the mechanisms, indications, dose/duration ranges, and safety history of GB in conjunction with the patient's medical history and current medications.

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