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File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ EGb 761®
■ Psychiatric Disorders

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RE: Review of EGb 761® Ginkgo Extract in the Treatment of Psychiatric Disorders

Montes P, Ruiz-Sánchez E, Rojas C, Rojas P. *Ginkgo biloba* extract 761: A review of basic studies and potential clinical use in psychiatric disorders. *CNS Neurol Disord Drug Targets*. 2015;14(1):132-149.

There are many ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extracts marketed to treat central nervous system disorders; however, most pre-clinical and clinical research studies have analyzed a specific standardized ginkgo extract named EGb 761® (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany). The authors assert that "EGb 761 has the ability to produce neuroprotection due to its chemical composition and the synergy of its components." This review provides an overview of EGb 761 for the treatment of psychiatric disorders such as anxiety and depression.

EGb 761 is a well-characterized preparation, derived from a water-acetone extract of dried green ginkgo leaves, which is processed using a standardized method to remove lipophilic compounds and concentrate the active components as follows: 24% flavonoid glycosides (primarily of quercetin, kaempferol, and isorhamnetin), 6% terpenoid trilactones (3.1% ginkgolides A, B, C, J, and M; 2.9% bilobalides), and 5-10% organic acids (kynurenic, hydroxykinurenic, and vanillic acids). [Note: The concentration of these compounds is substantially higher in the extract than in the raw leaf.] Although the pharmacological effects of EGb 761 have been associated with numerous constituents, researchers have primarily focused on these three classes of compounds which are well absorbed, extensively metabolized, and have half-lives ranging from two to six hours. Clinical studies indicate that the optimal therapeutic dose of EGb 761 is 120-240 mg/day.

The most commonly reported adverse events are nausea (0.9%), headache (0.9%), gastrointestinal disturbances (2.6%), sleep disturbances/dizziness (0.4%), and skin reactions (0.3%). There have been four case reports of cerebral hematomas (bleeding) associated with the consumption of ginkgo extracts (but not EGb 761) taken alone or in conjunction with other therapies; however, systematic reviews of randomized controlled trials (RCTs) have not detected any increased risk of bleeding in ginkgo-treated patients or in patients taking ginkgo plus anticoagulants. Although there is no conclusive

evidence that ginkgo is associated with an increased risk of bleeding, the authors err on the side of caution in recommending that additional studies should be conducted to definitively resolve the controversy regarding this potential adverse effect. No other adverse effects have been reported.

Pharmacokinetic studies indicate that EGb 761 does not significantly alter cytochrome P450 (CYP) drug metabolism, although effects from other ginkgo products have been reported. In an animal model, EGb 761 enhanced the effect of diazepam, and there has been a case report that EGb 761 augmented the sedative effect of trazodone in a patient with Alzheimer's disease (AD). However, the results of a human pharmacokinetic study refute the clinical relevance of these findings. Evidence from RCTs suggests that EGb 761 may increase the efficacy and decrease the adverse effects of other antipsychotic drugs.

The authors review the evidence supporting four mechanisms that may account for the neuroprotective effects of EGb 761; namely, antioxidant effects, modulation of neurotransmission, hormonal regulation of the hypothalamic-pituitary-adrenal axis, and upregulation of neurotrophic factors.

Stress is a major pathogenic factor triggering psychiatric disorders, particularly depression and anxiety. The results of nine experimental studies evaluating the antidepressant and anxiolytic effects of EGb 761 are summarized. In RCTs, EGb 761 significantly reduced anxiety parameters in patients with generalized anxiety disorder (n=80) or adjustment disorder with anxious mood (n=25) in a dose-dependent manner. A single dose of EGb 761 significantly reduced blood pressure (without affecting heart rate) in healthy subjects (n=70) exposed to stressful stimuli, and in another study, salivary cortisol levels were significantly reduced. Based on this evidence, the authors conclude that EGb 761 regulates the stress-induced activation of the hypothalamic-pituitary-adrenal axis which is associated with anxiety and depression.

Although ginkgo is used to treat a variety of psychiatric conditions, the authors assert that "there are more studies and a better data base for mechanisms and clinical effects of EGb 761 related to dementia than for any other phytopharmaceutical medicine." The authors describe nine RCTs that included a total of 2101 patients with AD, vascular dementia, or AD plus cerebrovascular disease. Eight trials compared a placebo to 120-240 mg/day EGb 761, while the ninth study compared EGb 761 (240 mg/day) plus donepezil (10 mg/day) to donepezil (10 mg/day) alone. Treatment duration ranged from 12-52 weeks, and all of the studies measured cognitive function.

In six of the studies, EGb 761 supplementation produced a significant improvement (P values not reported) in cognitive function compared to placebo. Two dose-ranging trials (120-240 mg/day) revealed no significant improvement in the EGb 761 groups. No significant difference between groups was found in the study comparing the efficacy of EGb 761 plus donepezil to donepezil alone; however, the incidence of adverse effects was lower in the EGb 761 plus donepezil group compared to donepezil alone.

Systematic reviews of the neuroprotective effects of ginkgo have produced variable results. The authors point out that the negative 2009 Cochrane review included all ginkgo products, while reviews restricted to EGb 761 reported positive effects in the treatment of cognitive impairment/dementia. They summarize the results of four relatively large clinical trials (n=400-512 in each trial) which found that EGb 761 was

more effective than placebo in treating neuropsychiatric symptoms such as anxiety, apathy/indifference, depression/dysphoria, irritability/mood, and sleep/nighttime behavior. The authors conclude that EGb 761 ameliorates neuropsychiatric symptoms and thus promotes clinical improvements in cognitive performance, activities of daily living, and quality of life.

To summarize, EGb 761 is a well-characterized, standardized ginkgo extract with good tolerability and a low incidence of adverse effects that ameliorates psychiatric disorders. "EGb 761 has demonstrated effectiveness in the treatment of cognitive impairment and non-cognitive symptoms associated with dementia," and it is "particularly useful when dementia is accompanied by neuropsychiatric symptoms such as anxiety and depression/dysphoria." The few trials assessing the efficacy of EGb 761 in reducing the incidence of dementia have produced variable results. The authors point out that a number of factors (e.g., age, disease state, preparation form and dose, environmental variables, and ethnicity) may influence the therapeutic effect of EGb 761. They also briefly review the positive results of RCTs that evaluated the efficacy of EGb 761 in the treatment of schizophrenia (two trials) and attention deficit disorder (one trial).

The authors conclude that even though the safety, tolerability, and efficacy of EGb 761 has been demonstrated in RCTs cumulatively involving thousands of patients, additional research is still needed to determine whether EGb 761 is more effective alone or when combined with pharmaceutical treatments.

—Heather S. Oliff, PhD

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