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Mind Games: Can Ginko Biloba Improve Your Memory?

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Introduction

It's the night before your first big exam. Before you lies a thick pile of notes which you haven't looked at since the first week of classes and which you must master before 8am tomorrow. Are you afraid? Not a bit. This is the night that you will cash in on your ingenious investment of \$29.95 for your bottle of Ginkgo biloba extract. You've been taking a pill daily for the last six weeks and are sure that already you have become the smartest person in the class. Tonight you will glide through the mass of notes, soaking every bit information into the knowledge sponge that your brain has become. Stay tuned.

Perhaps you have seen the television ads showing college students and business executives on the move, telling you how you can "get an edge on the competition" by taking their product. Ginkoba® a leading retailer and advertiser of Ginkgo biloba extract markets its product as "the thinking persons supplement". The makers of Ginkoba® claim that their product improves memory and concentration and that it enhances mental focus (1). An internet search for 'Ginkgo biloba' the more popular search engines will yield a long lists of herbal product retailers expounding the many mental enhancing abilities of Ginkgo biloba.

What is Ginkgo Biloba?

Extracts from the leaves of Ginkgo biloba tree (aka maidenhair tree) have been used medicinally for centuries (2). As one of the oldest surviving species of tree on earth, Charles Darwin called it a "living fossil"(3). It is claimed that a solitary Ginkgo tree was the only tree to survive the atomic blast in Hiroshima- a claim which ginkgo retailers like to cite frequently. In China, tea is made from parts of the ginkgo tree for the treatment of asthma and bronchitis. In Germany and France, because of reports that ginkgo biloba may increase blood flow in both systemic and cerebral vessels (3,4), ginkgo extracts are currently used to treat peripheral vascular disease and for a number of CNS symptoms such as intermittent claudication or cerebral insufficiency. In the United States, the relatively recent increase in the use of Ginkgo began with its popularity among proponents of "smart drugs," due to ginkgo's purported ability to improve mental alertness and overall brain function (5).

In the United States ginkgo extract is most commonly available in 40–60 mg tablets, although it can also be purchased in liquid form. Extracts of Ginkgo biloba are made from dried leaves in a multistep procedure where unwanted substances are removed and the active compounds are enriched. The final liquid extract is then dried to yield 1 part extract from 50 parts of raw material. The standardized extract of Ginkgo biloba, EGb 761, is a mixture consisting of 24 percent Ginkgo-flavonoid glycosides and 6 percent terpene lactones from green leaves (6). It contains three major flavonoids (quercetin, kaempferol, isorhamnetin), proanthocyanidins, diterpene ginkgolides (ginkgolides A, B and C), sesquiterpene bilobilade, and organic acids (7). The exact composition may vary somewhat between different manufacturers due to differences in extraction processes. Such extracts are amongst the most commonly prescribed drugs in Germany and France (7). Last year alone ginkgo sales in Germany topped \$163 million (3).

Mechanisms of Action

Several physiological mechanisms of action of ginkgo biloba extract have been reported. The specific physiologic effects of ginkgo may be caused by single active ingredients or by the combined action of the many active agents found in the extracts.

In 1987, Chung et al showed that Ginkgo extract, specifically ginkgolide B, is a powerful antagonist of platelet activating factor (PAF) (8). The double-blind, placebo-controlled, crossover study showed that two hours after administration of 80 mg and 120 mg doses of ginkgolide to six human subjects significantly inhibited PAF-induced platelet aggregation in platelet rich plasma ($p < 0.001$). Recent studies by Stucker et al (9) and Smith et al (10) further substantiate these initial findings.

Intermittent claudication (aka Charcot's syndrome or myasthenia angiosclerotica) is a condition caused by ischemia of the muscles which is characterized by attacks of lameness and pain in the calf muscles brought on by walking (11). A clinical trial by Thomas et al (12) for the use of Ginkgo biloba extract in the treatment of intermittent claudication concluded that Ginkgo significantly improved walking distance and reduced pain severity, suggesting the action of Ginkgo in promoting blood flow. Paick and Lee, (13) have implicated the non-ginkgolide non-flavonoid (NGF) fractions of ginkgo biloba extract as having potent relaxing effects on vascular smooth muscle. Recently, Chen et al (14) demonstrated that ginkgo biloba extracts exert cerebral vasorelaxation effects via a nitric oxide pathway. Other Western Europe studies implicating Ginkgo biloba in enhanced vascular blood flow include its use for the treatment of cochlear deafness, senile macular degeneration, diabetic retinopathy, and peripheral arterial insufficiency (2).

Many studies have also shown Ginkgo biloba extract to have powerful antioxidant properties. In 1996, White et al, explored the effect of Ginkgo leaf extracts on monoamine oxidase (MAO). In an assay utilizing rat brain mitochondrial extract, the author showed that commercial Ginkgo preparations produced reversible inhibition of MAO (both A and B, equally). Because MAO has a role in regulation of brain serotonin levels, this finding implicates a possible role for Ginkgo as an antidepressant (15). Oyama et al (16) showed that pretreatment of rat cerebral neurons with Ginkgo biloba extract greatly delayed a time dependent increase in the number of dead neurons during exposure to hydrogen peroxide. This protective effect against oxidative stress is consistent with an in vitro study by Princemail et al (17) showing that Ginkgo biloba extract has both scavenging effects on superoxide anions and a superoxide dismutase activity. These antioxidant properties have important implications for a role of Ginkgo

in cognition because evidence suggests that free radical oxidation reactions are part of the aging process and a normal contributor to it (18). Taken as a whole, there is strong evidence to suggest that Ginkgo biloba extracts are worthy of further investigation as potential neuroprotective agents.

Evidence for Ginkgo Biloba in Memory Enhancement

Ginkgo biloba is one of the most widely prescribed drugs in Western Europe where it has been used to treat peripheral vascular diseases such as intermittent claudication and cerebral insufficiency (7). Cerebral insufficiency is an imprecise term describing a collection of twelve symptoms: difficulties in concentration and memory, absent mindedness, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus (ringing in the ears), and headache (19). The symptoms of cerebral insufficiency have been associated with impaired cerebral circulation and are thought to be early signs of degenerative or multi-infarct dementia.

Although a fair amount of research in Western Europe substantiates the use of Ginkgo biloba for the treatment of these conditions, much of the research quality has been poor. In 1992, a critical review by Kleijnen and Knipschild (19) assessed the efficacy of ginkgo biloba extracts on cerebral insufficiency. Of the 40 Western European research trials that they studied, all but one showed positive effects of Ginkgo extract compared with placebo on improving symptoms of cerebral insufficiency. However, using an index of predefined criteria for good methodology, the authors found that only eight of the 40 research trials were well performed. Shortcomings of the invalidated studies included inadequacies in the number of patients included, randomization procedures, patient characteristics, measuring techniques, and data presentation. Nonetheless, all eight of the valid trails reported positive results for the use of Ginkgo in cerebral insufficiency. Increased vascular blood flow was thought to be the primary effect responsible for these improvements.

In the United States, research on a role for Ginkgo biloba in cognition has been virtually non-existent with regards to human trials. Until relatively recently, no mention of Ginkgo biloba had even appeared in the Journal of the American Medical Association. The October, 1997, issue described the first empirical clinical trial of Ginkgo extract to have been conducted on human subjects in the United States (20). The study objective was to assess the safety and efficacy of ginkgo biloba extract (EGb761) in Alzheimer's disease and multi-infarct dementia. This elaborately executed 52-week, randomized double-blind, placebo controlled, parallel-group, multicenter study concluded that EGb appears able to stabilize and, in a substantial number of cases, improve the cognitive performance of demented patients for six months to one year. Although the duration of improvement is modest, the changes induced by EGb were of a significant magnitude to be recognized by caregivers as measured by a rating instrument assessing daily living and social behavior. With regards to safety, adverse events associated with EGb were found to be no different from those associated with the placebo.

There has been very little research on the effects of Ginkgo biloba extract on cognitive function in healthy young adults, both in Europe and the United States. This fact is well illustrated by the fact that even among the 17 trials listed by the makers of Ginkoba® to legitimize the claims for their product, only one of the trials was performed on healthy subjects (1). Interestingly, the results of this randomized, double-blind crossover study were inconclusive, showing no statistically significant changes from the placebo for two

of the three psychological tests employed for memory assessment (21). A similar study by Subhan using healthy subjects was also inconclusive (22). However, it must be noted that in both of these trials the test sessions took place only 1 hour post-dosing using a single 600 mg extract dose (see below). The remaining trials cited by Ginkoba® involved cognitive enhancements in subjects suffering from the age related cerebral disorders previously described.

Adverse Effects

In Germany and France, the generally recommended dosage of Ginkgo extract for most indications (i.e. intermittent claudication) is 120 – 160 mg per day (40 – 60 mg tid). For its use in cerebral insufficiency or other peripheral vascular disorders treatment must last four to six continuous weeks before positive effects can be expected (1,19).). Despite the fact that ginkgo is used in patients who are often taking many other drugs, there are no known drug interactions (1,20). No serious side effects have been noted in any trial and, if present, side effects were no different from those in patients treated with placebo (19,20). Rare and generally mild adverse reactions are headaches, mild gastrointestinal disturbances and mild allergic skin rashes (1). There have, however, been two isolated cases reported which implicate the use of Ginkgo in spontaneous bleeding from the iris and development of bilateral subdural hematomas, respectively (23,24).

The Bottom Line

Among those retailers who market Ginkgo biloba as a "smart drug", there are many mechanisms by which Ginkgo biloba is purported to confer its memory enhancing properties. The most frequent and consistently cited mechanism of action in enhanced cognitive function is the ability of Ginkgo extract to increase vascular blood flow to the brain, increasing cerebral oxygen supply, and thus maximizing mental function. Also cited frequently are Ginkgo's powerful antioxidant properties which act to protect the brain from free-radical damage. Retailers also like to cite Ginkgo's PAF antagonist properties, which are said to protect the brain by hindering the processes that lead to stroke. As we have seen, there is some degree of evidence in support of all of these claims. However, the common denominator in all the studies described is the age of the experimental subjects. If you suffer from cerebral insufficiency, multi-infarct dementia, Alzheimer's Disease or any combination of such diseases, evidence suggests that Ginkgo biloba may indeed improve your mental function. However, if you are a young and healthy person simply trying to enhance the function of your mind and perhaps attain a higher state of consciousness with Ginkgo biloba, you may be in for a disappointment. At present, there simply is no adequate data to support any such claims. Much more research on healthy subjects is needed before definitive conclusions can be drawn.

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