GINKGO BILOBA: A Cognitive Enhancer?

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Summary—Ginkgo biloba *is an herb often used as an alternative treatment to improve cognitive functions. Like most herbal treatments, the use of ginkgo is poorly regulated by government agencies, on the basis of either its efficacy or its health risks. This article reviews the experimental evidence available regarding efficacy, neurobiological actions, and health risks. Findings obtained in studies of humans often include demonstrations of rather mild cognitive enhancement. Interpretation of these findings is complicated by somewhat inconsistent findings, by experimental designs that do not permit identification of cognitive functions susceptible to the influence of ginkgo, and by the paucity of direct comparisons with other treatments. The number of peer-reviewed reports of studies in nonhuman animals is surprisingly small. In this small set, the findings reveal mild behavioral effects that might be attributable to actions on cognitive functions. However, these experiments in rodents, like those in humans, do not involve the use of designs to assess ginkgo's effects on particular cognitive attributes, and generally do not include direct comparisons with other treatments. Interpretation of the findings is further complicated by evidence, obtained in studies of both humans and rats, showing that a single administration of the treatment enhances performance on cognitive measures.*

If ginkgo has effects on cognition, there should be effects evident on biological processes as well. Neurobiological studies have largely examined the effects of chronic ginkgo administration, mirroring the most common design in behavioral studies. However, the addition of findings that single administration of ginkgo may influence behavior directs biological investigations to short-term actions of the treatment. Biological effects of ginkgo include vasodilation, protection of neurons from oxidative stress, and actions mediated by effects via neurotransmitters. Adverse reactions to ginkgo consumption have been observed but are relatively rare.

Collectively, the behavioral literature reviewed cannot be used conclusively to document or to refute the efficacy of ginkgo in improving cognitive functions. At best, the effects seem quite modest. In particular, it is questionable whether effects of ginkgo, if present, are equal to those obtained by administration of acetylcholinesterase inhibitors, hearing an arousing story, or ingesting glucose.

Much as there seems today to be a gene for every disease, and for every psychological construct, there appears to be an herb for every ailment. The use of dietary supplements and natural products to improve psychological functions is widespread throughout the world. In most cases, the use of dietary supplements to treat psychological disorders, or to augment normal functions, is based far more on folklore than on experimental findings. In the United States, it is easy to use such treatments because the federal government regulates them relatively weakly, compared with pharmaceuticals. Advertisement and labeling claims are monitored, but there remain many sources that promote using herbal treatments for a wide range of maladies. The widespread consumer use of dietary supplements to address psychological and other concerns warrants more attention to the efficacy of these treatments and to their possible health risks. Even if they do not cause medical problems, they have real costs—money, time, and avoiding other sources of treatment. It is in this context that the present report examines the experimental bases for the use of ginkgo as a treatment to improve cognitive functions.

The use of ginkgo for biological and psychological purposes, including to improve alertness, can be traced back for centuries in traditional Chinese medicine. Today, ginkgo is perhaps the most widely used herbal treatment selected specifically to augment cognitive functions. The use of ginkgo as a cognitive enhancer is especially prevalent in Europe. In recent years, ginkgo leaf extracts have been given the approval of the German Bundesgesundheit Association for treating dementia. In the United States, the National Institute on Aging is currently supporting a clinical trial to evaluate the efficacy of ginkgo in treating the symptoms of Alzheimer's disease. Although the findings of the clinical trials will likely provide the best data from which to determine whether ginkgo affects cognitive decline in dementia, the purpose of the present report is to evaluate the evidence for and against the usefulness of

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ginkgo in enhancing cognitive and other brain functions in healthy, as well as impaired, populations.

PHYTOBIOLOGY

The ginkgo tree (*Ginkgo biloba*), also known as the maidenhair or kew tree, is the only living member of the Ginkgoaceae family. Fossils of the trees have been dated back as far as 250 million years. The ginkgo tree may be the longest living extant tree, and was referred to by Darwin as "a living fossil" (Major, 1967). It appears to have curiously strong resistance to a wide range of insect pests and fungi, a fact that likely contributes to its longevity.

The ginkgo tree is indigenous to Korea, China, and Japan. It is popular for lining streets and for parks, although its seeds are reported to give off a foul odor when ripe. The tree may grow to 40 m in height and may live for more than 1,000 years. It flowers for the first time when it is about 25 years old. The seeds, often incorrectly referred to as fruit, become fleshy and plumlike, with a light green or yellow color. These seeds are usually about 3 cm in diameter and contain a two-edged edible nut. A wide variety of compounds is extracted from the seeds, leaves, and bark. The leaves are fan shaped, with bifurcated ribs, and glabrous.

Ginkgo biloba extract is a concentrate obtained from dried or fresh leaves in an acetone-water solution. A typical daily dose, and one used in many of the experiments described in this report (e.g., van Dongen, van Rossum, Kessels, Sielhorst, & Knipschild, 2000), is 120 mg of dried extract in two or three oral doses. The extract, which is sensitive to light, contains a series of flavonoids. Flavonoids include a very large group of natural plant products that are characterized by a specific chemical structure containing a series of carbon rings. The following flavonoids are found in the ginkgo extract: isorhamnetin, D-glucaric acid, anacardic acid, and kaempterol-3. Flavonoids appear to be well absorbed following ingestion, with half-lives (i.e., the time at which 50% of the chemical remains in the body) of 3 to 10 hr (Fourtillan et al., 1995). Ginkgo also includes a set of biflavonoids, a group of compounds that includes amentoflavone, ginkgetin, isoginketine, and bilobetin. The ginkgo extract also contains terpenes. Terpenes are a class of naturally occurring compounds that also include the active ingredients in catnip and marijuana plants. The ginkgo extract contains two different types of terpenes, the diterpenes, such as ginkgolide A, ginkgolide B, and ginkgolide C, and the sesquiterpene bilobalide.

WHAT ARE THE FINDINGS REGARDING GINKGO'S COGNITIVE EFFECTS IN HUMANS?

To date, there have been dozens of reported investigations of the cognitive effects of ginkgo in humans, as well as several reviews on the effects of ginkgo and other dietary supplements on psychological functions (e.g., Cupp, 1999; Defeudis, Bonnot, & Hörr, 1999; Fugh-Berman & Cott, 1999). Many of the primary research reports are in non-English language journals or journals with very restricted distribution, making assessment of the findings difficult. However, considering all the available evidence, one can fairly conclude that the drug can produce mild beneficial effects on various aspects of cognitive functioning, at least in some populations. The majority of studies have involved subjects with cognitive impairment, typically a diagnosis of early Alzheimer's disease. In addition, a few studies have examined the cognitive effects of ginkgo in healthy subjects. Most of the evidence suggesting cognitive-enhancing capabilities of ginkgo involves a specific, standardized extract referred to as EGb 761, developed by Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany (Oken, Storzbach, & Kaye, 1998).

Most of the experiments have measured effects using tests of learning and memory; less attention has been paid to other cognitive domains, such as attention processes. Moreover, because most experiments have used chronic or single-dose administration of ginkgo prior to testing the efficacy of the drug in enhancing cognitive functions, it is difficult to identify the cognitive locus of any effects demonstrated. The use of a post-training design in which the treatment is administered after training, together with demonstrations of time-dependent effects on memory, would address this issue. When treatments are administered before training, in either chronic or single-treatment experiments, improvements on measures of learning and memory might reflect influences of ginkgo on sensorimotor, attention, or motivation functions rather than on memory storage per se. In addition, evidence we discuss later suggests that ginkgo may be a treatment that can reduce anxiety in rodents. Effects on functions such as anxiety are also likely to be reflected secondarily on measures of learning and memory. It seems evident that researchers need to pay more attention to selecting tests that tap different and relatively specific aspects of cognition, as well as use experimental designs such as post-training procedures to assess retrograde effects of ginkgo on memory.

Studies of Patients With Cognitive Impairment

The overwhelming majority of published reports of ginkgo's effects on cognition have involved patients classified as having mild to moderate cognitive impairment. In general, these studies have found mild, but statistically significant increases in performance on various standardized tests of cognitive function after chronic treatment with ginkgo compared with placebo. The published reports vary greatly in terms of critical issues such as statistical power and control over experimental conditions, though doses used have been similar.

Recently, Oken et al. (1998) provided a careful meta-analysis of this literature. They evaluated studies meeting a conservative set of criteria, including sufficient characterization of the Alzheimer's disease diagnosis, use of a standardized ginkgo

extract, and a placebo-controlled, double-blind design. Oken et al. performed a meta-analysis of effect size on the results of the 4 studies—of more than 50 studies considered—that met these criteria. This analysis revealed a highly significant overall effect of ginkgo compared with placebo. (Specifically, the analysis revealed that the average effect size from the 4 studies was equal to approximately half the standard deviation.) Each of these studies reported improved performance on various standardized cognitive tests among Alzheimer's patients who received ginkgo compared with those who received a placebo. Improvements were evident on tests involving various cognitive abilities, such as attention, short-term memory, and choice reaction time. Oken et al. further noted that the mean effect size for ginkgo determined by this analysis is comparable to that previously reported for the drug donepezil, which is currently the drug of choice for treating Alzheimer's disease. Donepezil acts by enhancing the function of acetylcholine neurons in the brain by inhibiting the catabolism of acetylcholine (i.e., it is an acetylcholinesterase inhibitor).

Despite these apparently encouraging findings, another recent, large, and well-controlled trial of EGb 761 (sponsored by its manufacturer) involving patients with a mild or moderate stage of dementia reported no "systematic and clinically meaningful effect of ginkgo" on any of the cognitive measures employed (van Dongen et al., 2000, p. 1188). Thus, beneficial cognitive effects of ginkgo on cognitive function in mildly demented patients remain possible, but unproven.

A critical question concerns whether ginkgo treatment actually improves cognitive abilities in Alzheimer's disease, or instead slows the deterioration of cognitive abilities. This question is important because it is not clear whether a drug that simply slows, and therefore prolongs, cognitive deterioration in diseases like Alzheimer's disease is helpful or harmful to a patient's quality of life. In addition, prolongation of deterioration is quite obviously an issue with significant social and economic consequences. Regarding ginkgo, different answers to this key question may come even from a single study. For example, in a large and well-controlled study by Le Bars et al. (1997; included in the meta-analysis of Oken et al., 1998), ginkgo treatment either slowed deterioration, improved cognitive performance, or indeed had no effect depending on the cognitive assessment used. According to one standardized cognitive assessment scale (the Alzheimer's Disease Assessment Scale–Cognitive Subscale; Fig. 1a), Alzheimer's patients treated with placebo slowly deteriorated over the course of the study, while performance of patients treated with ginkgo remained stable. According to a second assessment scale (the Geriatric Evaluation by Relative's Rating Instrument; Fig. 1b), ginkgo-treated subjects improved by about the same amount that placebo-treated subjects deteriorated.

Although to date most studies of ginkgo's effect on cognitively impaired subjects have employed chronic treatment (generally 120–240 mg/day over several months), at least one study reported effects of a single treatment with ginkgo. Allain

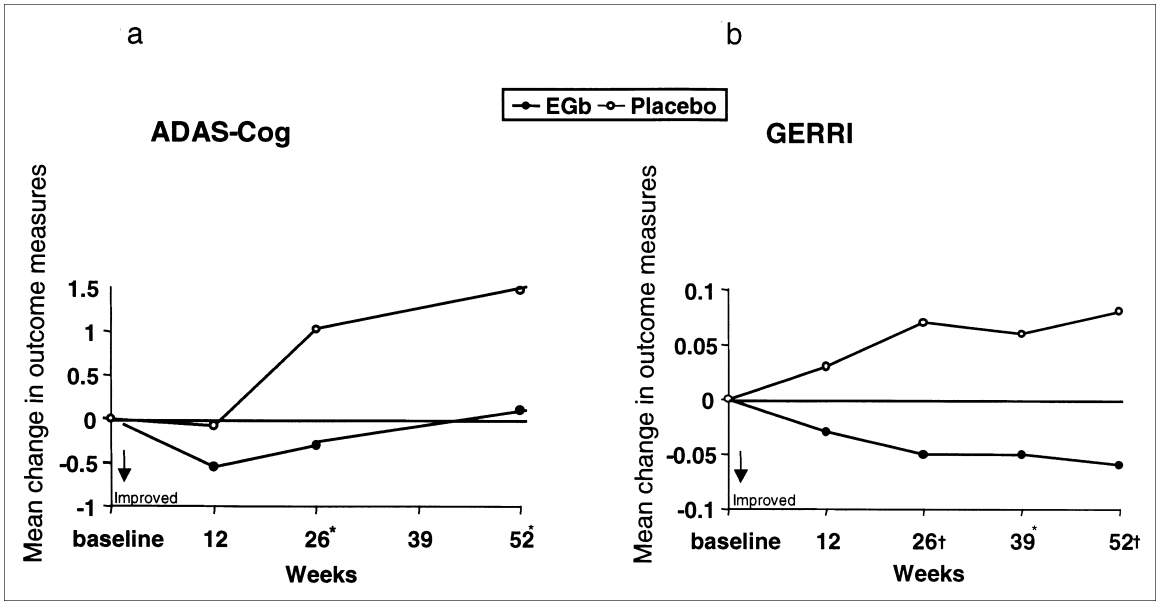

Fig. 1. Effects of ginkgo (EGb) on two cognitive measures in individuals with Alzheimer's disease. Changes in outcomes of individuals given EGb and placebo were compared using the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog; a) and the Geriatric Evaluation by Relative's Rating Instrument (GERRI; b). Note that lower numbers on the ordinate refer to better performance. Both measures show deterioration of performance in placebo-treated individuals. However, the ADAS-Cog assessment indicates EGb treatment resulted in stabilized scores during the 52-week test period, but the GERRI assessment indicates EGb treatment resulted in improved scores during the test period. (Adapted from Le Bars et al., 1997.)

et al. (1993) examined the effects of fairly high (320 or 600 mg), single doses of ginkgo on performance in a task involving briefly presented stimuli and rapid information processing. The task consisted of repeated, increasingly rapid presentations of short lists of words or drawings, with an immediate free-recall test given after each list. In a within-subjects design, the performance of 18 healthy elderly subjects described as having mild, age-related memory impairment was examined 1 hr after placebo or ginkgo treatment. The subjects' ability to recall rapidly presented material immediately after the material was presented was significantly increased after ingestion of ginkgo. The ability of a single dose of ginkgo to improve performance on this task opens the possibility that it is short-term, rather than long-term, biological actions that provide the bases for any effects ginkgo has on cognition. This issue is very important for understanding the mechanisms by which ginkgo might act on cognitive functions and is also very important in defining the conditions under which ginkgo might be effective. The effects of single treatments with ginkgo deserve much more attention than they have received.

It should be noted that ginkgo has also been reported to impair performance. For example, in a small (31 patients), placebo-controlled study, Rai, Shovlin, and Wesnes (1991) found that after 24 weeks of treatment, patients who received ginkgo were impaired in a digit-recall task compared with patients who received a placebo. Negative results for ginkgo, as for other treatments, are likely underrepresented in the literature. Reports such as the one by Rai et al. underscore the need for caution when assessing the cognitive effects of any drug, in particular one, such as ginkgo, for which beneficial effects may be desired by patients or investigators a priori.

Effects of Ginkgo on Cognition in Younger, Healthy Subjects

One small study (8 subjects) assessed the effects of several doses of the ginkgo extract EGb 761 on performance on a battery of tests, including a test of the ability to hold information in short-term memory. Hindmarch (1986) reported that the highest dose tested (600 mg) improved performance only in the Sternberg short-term memory test, leading the author to suggest that ginkgo's effects are specific for memory processes. Also, C. Stough (personal communication, May 10, 2000) conducted two investigations involving approximately 80 subjects receiving chronic ginkgo treatment. Although these studies have not yet been reported in peer-reviewed journals, the treatment apparently produced significantly improved performance on a few of the tests of cognitive function examined.

Two recent reports from one laboratory (Kennedy, Scholey, & Wesnes, 2000; Wesnes, Ward, McGinty, & Petrini, 2000) provide minor support for the view that ginkgo may have beneficial cognitive effects in younger individuals. Kennedy et al. used a cross-over design involving 20 subjects and three doses of a standardized ginkgo extract (GK501) and reported enhancing effects of the drug on an index of attention. Wesnes et al. studied "middle-aged" subjects (ages 38–66) treated with a combination of ginkgo and ginseng. They reported a significant effect of the drug combination on some indices of memory; however, the effects were not dose dependent, and of course cannot be attributed to ginkgo itself. Clearly, although there are some indications of potential beneficial effects of ginkgo on cognitive processes in healthy subjects, the available data do not as yet allow that conclusion to be made with certainty.

Finally, it should be noted that none of the potential effects of ginkgo on memory in humans reported to date are clearly attributable to direct effects of the drug on memory processes. In each case, indirect effects of the drug on memory via direct effects on other processes (such as arousal and attention) are possible, if not likely.

ANIMAL MODELS

The evidence showing effects of ginkgo on measures of brain function, particularly when coupled with effects, though modest, on human cognition, suggests that there would be a wealth of information about ginkgo's effects on cognitive functions, particularly learning and memory, in nonhuman animals. Typically, a large number of studies with laboratory animals is conducted before many tests are performed in humans. Apparently, however, the reverse is true in the case of ginkgo; there are very few research reports in refereed journals examining the efficacy of ginkgo in improving learning and memory in nonhuman animals.

The high ratio of human to nonhuman studies may reflect two things—that ginkgo has been used to improve cognition in humans for centuries and that ginkgo is a relatively safe treatment. As indicated by the few experiments available for review here, there is a clear need for basic science experiments in animals other than humans to clarify the efficacy of ginkgo in enhancing cognitive functions.

There are obvious advantages of improved experimental control and design features that can be implemented in studies of rodents rather than humans. Unfortunately, however, even within the small literature on ginkgo's effects on learning and memory in rodents, adequate designs are rare. Also, many of the reports showing enhancement of learning and memory in rodents appear in book chapters (e.g., Christen, Costentin, & Lacour, 1992), where there is often insufficient information about experimental procedures to evaluate the findings presented adequately.

An early study showed improvement of learning and memory in young adult mice trained to press a lever to receive food (E. Winter, 1991). The ginkgo extract EGb 761 was dissolved in drinking water at a concentration that resulted in a daily dose of 100 mg/kg; no other doses were tested. The findings showed that mice pretreated with ginkgo for 4 to 8 weeks learned the task slightly more quickly than did control mice. Although there were no treatment-related differences in food intake dur-

ing the pretreatment period, weight change was not noted, and possible differential responses to food restriction imposed prior to training were not tested. Thus, it is difficult to determine whether changes in motivation, or in sensorimotor functions, might have contributed to the effects on acquisition of the task. Although a clear interpretation of the bases for these findings is not possible, this remains one of the best demonstrations of ginkgo's effects on learning and memory and offers the strongest basis for additional experimentation.

In an experiment with aged rats (J.C. Winter, 1998) that was subject to many of the same concerns, EGb 761 failed to enhance significantly performance on one variant of an eight-arm radial-arm maze task in which the rats underwent continuous training with different numbers of baited arms, but did enhance performance on a second variant of training in an eight-arm radial maze in which rats were required to make delayed nonmatching-to-sample responses. In the latter task, four arms of the maze were open and baited and the other four arms were closed during the first phase of each daily session. Then, after a 30-min delay, all arms were open, and only the previously closed arms were baited. Thus, for best performance, rats would enter only those arms not visited during the first phase of training on that day and would enter each newly opened arm only once. Rats treated with EGb 761 showed fewer retroactive (entries into arms open in the first phase) and proactive (second entries into now-open arms) errors.

In a recent study using a promising approach to the issue of ginkgo's effects on learning and memory, Wirth, Stemmeline, Will, Christen, and Di Scala (2000) found that ginkgo enhanced performance in young adult rats tested on an olfactory discrimination task. Either chronic (30 days) or acute (10 min before training) administration of ginkgo improved short-term recognition of a novel versus familiar odor. Similar, though more modest, effects were also seen in aged rats. These effects appear to be quite reliable, and further research extending this approach is warranted. For example, as the authors noted, the experiment does not permit attribution of the effects to either learning and memory or attention. Similarly, the possibility that ginkgo altered the rats' motivation to explore novel stimuli or altered olfactory sensitivity needs to be assessed. The comparable efficacy of chronic and acute administration of ginkgo in this test of short-term memory is analogous to that reported in humans by Allain et al. (1993). Confirmation that the effects of ginkgo can be attributed to acute actions will have important implications for treatment, as well as for understanding the underlying biological bases of these effects.

Another experiment examined the effects of a ginkgo extract, a ginseng extract, or their combination (Gincosan®) on memory for several aversive tasks (Petkov et al., 1993). The extracts, each at three doses, were administered orally for 7 days, ending 1 hr before training. The results can best be described as robustly erratic. The effects on shuttlebox learning were large for the low and high doses in young rats. None of the doses, however, enhanced young rats' learning in either a step-through or a step-down inhibitory avoidance task or in a unique swim task. In single-treatment experiments with aged rats, with different doses used in different conditions, enhancement was seen at only one dose of each drug. Similarly, when combinations of drugs were tested, only a single dose and drug combination was effective in aged rats. Moreover, Petkov et al. did not report basic measures of how the treatments affected the rats' shock thresholds and activity levels, so it is difficult to interpret the findings.

Ginkgo was also reported to enhance memory for passive avoidance learning in aged mice (Stoll, Scheuer, Pohl, & Muller, 1996). However, the only effect was to increase the latency to return to a shock compartment when tested 60 s after training, a result more likely reflecting postshock freezing than memory. No effects were evident on memory tests administered 24 hr after training. Pretraining injections of ginkgo also partially reversed scopolamine-induced amnesia for inhibitory avoidance training (Chopin & Briley, 1992), but again the authors offered no information about possible alterations of shock thresholds or locomotor activity. Interestingly, the report of this experiment includes broad dose-response curves from which it is possible to compare directly the positive effects of ginkgo with those obtained with two cholinesterase inhibitors, tacrine and galanthamine, and the nootropic agent piracetam. The effect of ginkgo at its optimal dose was less than 50% of the effect of the cholinesterase inhibitors and about the same as that of piracetam. Thus, even if additional controls support the interpretation that ginkgo acts to attenuate amnesia, the effect is very small and substantially smaller than that obtained with other treatments.

Another experiment tested the effects of ginkgo on learning and memory in young and old mice, including an outbred strain, Swiss, and two inbred strains, C57BL/6J and DBA/2J (Cohen-Salmon et al., 1997). Swiss mice received injections of ginkgo (EGb 761; 40 mg/kg) or saline for 10 or 24 days; training began after the 7th or 21st day of injection and continued thereafter. Analyses of errors made by the Swiss mice during learning in a shock-motivated visual discrimination Y-maze revealed fewer errors in the ginkgo-treated mice than in the saline-treated mice during initial training. However, these effects—after pooling across treatment duration and restricting analyses to the first 3 days of training—were very small in both young mice (approximately 13.2 vs. 12.5 errors in ginkgo vs. control conditions) and old mice (approximately 14.8 vs. 13.5 errors in ginkgo vs. control conditions). In similar experiments with the inbred mice, ginkgo apparently impaired learning in young C57BL/6J mice and improved learning in DBA/2J mice. Thus, there appears to be no clear and consistent pattern of results evident within or across the strains and ages. Moreover, whether the small effects reflected differences in sensorimotor functions that might have contributed to apparent differences in learning and memory was untested.

A recent experiment (Gajewski & Hensch, 1999) examined effects of ginkgo on maze training in only 5 mice, each tested on four different mazes. Whether or not the mice showed im-

provement under ginkgo cannot be distinguished because of possible differences in the maze versions and acquisition of general learning abilities (i.e., learning set) across tasks.

There are other behavioral actions reported for ginkgo that may have relevance for interpreting its effects on learning and memory. Ginkgo appears to reduce stress in rats, a property that is certainly important to consider in evaluating the acute and chronic effects of ginkgo on the acquisition of avoidance tasks. For example, several investigators, using several different models, have reported that repeated administration of ginkgo reduced stress in rats (Chermat, Brochet, DeFeudis, & Drieu, 1997; Hasenöhrl et al., 1996, 1998; Porsolt, Martin, Lenegre, Fromage, & Drieu, 1990; Rodriguez de Turco, Droy-Lefaix, & Bazan, 1993; Satyan, Jaiswal, Ghosal, & Bhattacharya, 1998). Interestingly, some of these studies showed that ginkgo had no effect on learning in some tasks, for example, inhibitory avoidance learning (Porsolt et al., 1990) and cued and place versions of a swim task (Hasenöhrl et al., 1998), findings that contrast with the results of some experiments described earlier. Altered stress responses at the time of training can themselves have very large effects on learning and memory, generally enhancing performance at moderate levels and impairing performance at high levels, in an inverted-U dose-response manner. For example, stress responses such as increases in circulating levels of epinephrine, glucocorticoids, and glucose have a very well characterized influence on memory in rodents, and similar results have often been observed in humans also (cf. Cahill, 1999; Cahill & McGaugh, 1996, 1998; Gold, 2001; Korol & Gold, 1998). In particular, manipulations of stress responses can often enhance cognitive functions in aged rodents and humans (Gold, 2001; Korol & Gold, 1998).

Collectively, the set of findings regarding ginkgo's effects on cognition in nonhuman animals is perplexing in terms of both the paucity and the overall quality of the information available. Clear evidence for or against the possibility that ginkgo enhances learning and memory in rats and mice is not available at this time.

BIOLOGICAL ACTIONS

If ginkgo has effects on cognition, there should be effects evident on biological processes as well. There are several classes of such effects that might contribute to ginkgo's putative enhancement of cognitive functions. Considering the findings by Wirth et al. (2000) that chronic and acute treatments with ginkgo have comparable actions on rats' performance in an olfactory recognition task, and the findings by Allain et al. (1993) that acute treatment with ginkgo can enhance some cognitive functions, the issue of whether chronic or acute biological actions of ginkgo are important remains unclear.

Physiology

In the cardiovascular system, ginkgo extract can stimulate vasodilation that leads to increased blood flow and lowered blood pressure (Shen & Zhou, 1995). Consumption of the extract may also be able to reduce plasma cholesterol levels. The ginkgolide B terpene is a potent antagonist against platelet activity factor (Smith, MacLennan, & Darlington, 1996) and inhibits platelet aggregation, thrombin activity, and fibrinolysis. The effects of the extract on bleeding and clotting, as well as its other actions on the cardiovascular system, could have both beneficial and detrimental effects on function of the central nervous system, for example, through differential consequences for development of occlusive or hemorrhagic strokes.

Antioxidant Properties

There is considerable evidence relating cell damage caused by free oxygen radicals to the aging process, a relationship often associated with the neuropathology underlying Alzheimer's disease (e.g., see Friedlich & Butcher, 1994). Like substances found in many other plants, components of the ginkgo extract have antioxidant properties (Seif-El-Nasr & El-Fattah, 1995). Components of the extract can inhibit the activity of superoxide dismutase and monoamine oxidase, two widespread enzymes that contribute to the production of free radicals in the brain and body (Gsell, Reichert, Youdim, & Riederer, 1995). These antioxidant substances can scavenge free radicals that might injure neurons and thereby retard age-related changes in brain and other functions. These positive and often subtle protective effects of *Ginkgo biloba* extract on brain function and cellular health are not unique to ginkgo. Many different plants have been found to contain a large variety of flavonoids that exhibit antioxidant or anti-inflammatory properties. Recently, researchers have demonstrated that the flavonoids in red wine and chocolate can offer significant protection for both the brain and the cardiovascular system.

Ginkgo extract may also protect neurons from consequences of oxidative stress such as apoptosis (i.e., programmed cell death; Oyama, Chikahisaa, Uehaa, Kanemaruc, & Nodac, 1996). The extract can attenuate the toxic effects of cerebral ischemia, or loss of blood flow to the brain, by rescuing neurons from the harmful effects of free radicals and by enhancing the function of important energy-producing systems. Treatment with ginkgo extract has also been shown to reduce the production of arachidonic acid, a particularly toxic by-product of lipid metabolism that appears in the brain following an ischemic episode. Impaired blood flow in the brain may underlie aspects of the memory impairment associated with normal aging. These actions may underlie the modest neuroprotective and cognitive-enhancing effects that have been attributed to this plant extract.

The diterpenes and sesquiterpenes, rather than the flavonoids or biflavonoids, appear to be the main component of the ginkgo extract that is responsible for protection of brain tissue against brain injury due to reduced oxygen or blood flow (Oberpichler, Beck, Abdel-Rahman, Bielenberg, & Krieglstein, 1988). Although the flavonoids and biflavonoids found in ginkgo extract do have antioxidative properties *in vitro* (Chen et al., 1999;

Joyeux, Lobstein, Anton, & Mortier, 1995), they are not able to pass through the blood-brain barrier in sufficient quantity to reach an effective concentration to reproduce these effects within the brain. Therefore, the diterpenes and sesquiterpenes are probably responsible for any clinical effects. In particular, ginkgolide B and bilobalide may provide the neuroprotective and anti-apoptotic effects attributed to ginkgo extracts (Ahlemeyer, Möwes, & Krieglstein, 1999; Krieglstein et al., 1995; Rapin, Zaibi, & Drieu, 1998; Zhou et al., 2000).

Brain Biochemistry

Compounds contained within ginkgo extract have been shown to have many effects on brain function. Particular attention has been given to the actions of ginkgo and its constituents on the function of the forebrain's acetylcholine system. The extensive degeneration of this neurotransmitter system in patients with Alzheimer's disease may underlie their cognitive deficits (Whitehouse, Price, Clark, Coyle, & DeLong, 1981). For this reason, numerous drug therapies have targeted this particular neural system. In order to function normally, acetylcholine neurons in the brain must obtain two nutrients—choline and acetyl—from the diet. The choline component of this transmitter is obtained from numerous dietary sources, such as lecithin, and the acetyl molecule is produced in the cell from glucose or other sugars. Acetylcholine-containing neurons absorb choline from the body via energy-dependent transport processes. The activity of this transporting system can be enhanced by treatment with ginkgo extract (Kristofikova, 1997). Although ginkgo might be able to enhance the function of acetylcholine neurons by increasing the amount of acetylcholine that is produced, it is also possible that if these neurons produce more acetylcholine, they do not necessarily release more. This situation might be analogous to having gasoline in one's car without ever driving it anywhere. Thus, the functional consequence of increased acetylcholine formation is unclear.

Consumption of *Ginkgo biloba* extract can increase glucose utilization in the frontal and parietal cortex, areas of the brain that are important for processing sensory information and for planning complex actions. Glucose utilization is also enhanced in the nucleus accumbens and the cerebellum (Rapin & Le Poncin Lafitte, 1986), brain regions involved in experiencing pleasure and controlling movement, respectively. Enhanced neural activity in these areas might underlie some of the cognitive changes reported by people who use this extract, such as enhanced vigilance, or its alleged antidepressant-like effects. Surprisingly, although ginkgo elevates brain glucose utilization and has positive effects on acetylcholine production in the forebrain, the effects of ginkgo are not associated with a significant increase in EEG (electroencephalogram) power, an indicator of general brain activity (Kuenkel, 1993).

Ginkgo biloba extract may also have indirect actions upon brain systems involved in stress, particularly upon the function of the neurotransmitter serotonin (e.g., Ramassamy, Christen, Clostre, & Costentin, 1992). Recently, therapeutic drugs have been designed to act upon a specific type of serotonin receptor known as 5HT-1A in order to reduce stress and anxiety, suggesting a potential neural action for ginkgo. Long-term stress has been found to reduce the number of these receptors in the brain. Chronic treatment with *Ginkgo biloba* extract attenuates this reduction; surprisingly, this effect is greatest in aged rats (Bolanos-Jimenez et al., 1995; Huguet, Drieu, & Piriou, 1994). The flavonoid components of *Ginkgo biloba* extract may have a greater effect on the function of the serotonin neurotransmitter system than do the terpenes.

The anti-anxiety actions of ginkgo may also have an indirect effect on aging and the brain. Stress is associated with an elevation in the level of glucocorticoids in the blood. Some scientists believe that long-term elevation of glucocorticoids may underlie degeneration of the hippocampus, a brain structure that is critical for normal learning to occur. *Ginkgo biloba* extract may be able to reduce the stress-induced elevation in glucocorticoid levels (Trovero, Brochet, Tassin, & Drieu, 1999).

The anti-anxiety actions of *Ginkgo biloba* extract may be due to its ability to enhance release of the neurotransmitter GABA, or gamma-amino butyric acid (Sasaki, Hatta, Haga, & Ohshika, 1999). GABA is an important inhibitory neurotransmitter that is distributed throughout the brain. The activation of this system has long been a target of the pharmaceutical industry for the treatment of chronic anxiety. The widely used benzodiazepine drugs, including valium, librium, xanax, restoril, and many others, share a similar mechanism of action: They all enhance the function of GABA in the brain. *Ginkgo biloba* may act in a similar fashion.

The effects of *Ginkgo biloba* extract on mood may also be related to its actions upon the norepinephrine neurotransmitter system. Enhanced activation of this system by standard tricyclic antidepressants has been shown to reduce the symptoms of depression, and long-term oral treatment with *Ginkgo biloba* extract has produced similar changes in norepinephrine receptor function (Huguet & Tarrade, 1992). Once again, this effect appears to be more pronounced in aged than young animals.

Adverse Effects

Whatever its beneficial effects on cognition, ginkgo appears to pose few health risks, particularly at the doses typically used (generally 120–240 mg/day). However, some complications have been noted. These include subdural hematomas (Oken et al., 1998) and gastrointestinal problems (Le Bars et al., 1997). For example, as is the case with most plant extracts or medications, ingestion of ginkgo extract is sometimes associated with nausea and vomiting. In addition, some users experience increased salivation, decreased appetite, headaches, dizziness, tinnitus, and a skin rash. Large doses may lead to orthostatic hypotension, a condition of low blood pressure sometimes seen following abrupt postural changes, such as standing up after being seated; this effect may be related to ginkgo's actions

upon cardiovascular function and blood pressure. Still, the general impression is that the incidence of serious adverse effects after use of ginkgo is quite low. Also, this incidence may be reduced further if and when optimal individual dose regimens for ginkgo are established.

CONCLUSIONS

Does Ginkgo Enhance Cognitive Functions?

This is the key question for which we hoped to find an answer. In general, the effects reported for ginkgo are rather small, the number of experiments is small, and the experiments are of uneven quality.

In humans, ginkgo may slow cognitive decline during dementia. This would be consistent with purported actions of ginkgo as an antioxidant and as an alleviator of some consequences of chronic stress. Interestingly, however, the two tests of acute effects of ginkgo on memory, one in humans and one in rats, suggest that this treatment may, like many other treatments, act on ongoing cognitive processes and not on chronic problems. If future research confirms that the main effects on cognition can be seen after acute treatment, and do not require chronic treatment, theories about the underlying biological bases of ginkgo's effects will have to be constrained by this evidence. Unfortunately, the literature is so small that significant issues such as this one cannot be adequately evaluated at this time.

Is Ginkgo Better Than Other Drugs or Better Than an Exciting Story or Glucose-Sweetened Lemonade?

There are several treatments known to enhance cognitive function in humans and other animals. For most treatments, the demonstrations also include findings of enhancement in individuals with dementia. For example, donepezil and other acetylcholinesterase inhibitors have robust effects on learning and memory in rodents and modest though significant effects in humans; several acetylcholinesterase inhibitors have been approved for treatment of Alzheimer's disease. In an attempt to compare directly the efficacy of ginkgo with acetylcholinesterase inhibitors, a meta-analysis performed by Oken et al. (1998) showed that the mean extent of improvement resulting from ginkgo treatment was 10 to 20%, a value roughly comparable to the magnitude of improvement often seen in clinical trials with acetylcholinesterase inhibitors. In rodents, the one experiment with a direct comparison of ginkgo versus acetylcholinesterase inhibitors showed clearly greater efficacy of the latter treatment (Chopin & Briley, 1992).

The findings obtained with ginkgo, and with other treatments as well, should also be viewed in the context of other experiments showing enhancement of cognition by relatively simple treatments. For example, learning an arousing story can enhance memory, apparently by activating endogenous stress-related hormones such as epinephrine (Cahill & McGaugh, 1998). In addition, epinephrine administered soon after learning enhances memory formation in humans and other animals (Cahill & Alkire, 2000; Gold, 2001). One mechanism by which epinephrine might enhance memory is by liberating glucose from hepatic stores, thereby increasing circulating glucose levels and increasing glucose available to the brain (McNay, Fries, & Gold, 2000). And glucose administered systemically to both humans and rodents has large effects on memory, including enhancement of cognitive performance on several measures in individuals with Alzheimer's disease (Korol & Gold, 1998). Thus, like ginkgo, a simple sugar can enhance memory.

Because of the differences in experimental designs used to test the effects of ginkgo and other treatments, it is difficult to make direct comparisons of efficacy. For example, on a verbal declarative memory test, glucose enhanced performance in young adult and healthy aged subjects by about 30 to 40% (for review, see Korol & Gold, 1998). In individuals with Alzheimer's disease, the improvement on tests of verbal declarative memory approached 100%, with smaller effects seen on other measures (Manning, Ragozzino, & Gold, 1993). The extent of improvement in these experiments is much larger than that shown with ginkgo. However, most experiments testing the effects of glucose on cognition in humans have used acute treatments and within-subjects comparisons, whereas most experiments testing ginkgo have used chronic treatments and across-subjects designs. Therefore, it is not possible to compare directly the efficacy of glucose and ginkgo. Establishing these comparisons is important in identifying not only which treatments improve cognition, but also which do so the best. This is one of many instances in which the heightened experimental control available in studies of rodents would be an asset to determine which treatments are most effective in improving cognitive functions. There is only one experiment, using rats, in which a direct comparison of ginkgo with other treatments was made (Chopin & Briley, 1992). More direct comparisons, in both humans and other animals, of ginkgo with other treatments are needed.

Recommendations

We began our survey of the literature with healthy skepticism but with a commitment to avoid prejudging the findings. We found evidence supporting the view that ginkgo enhances cognitive functions, albeit rather weakly and with considerable variability, under some conditions. However, our overriding impression after seeing the available studies is that there is not enough information to say that ginkgo does or does not improve cognition. There are enough positive findings, perhaps just enough, to sustain our interest in finding out whether ginkgo does improve cognition. In addition to there being too few experiments on which to base clear recommendations, most of the initial studies of the benefits of *Ginkgo biloba* have

involved too few subjects. Many years of experience with investigations of new drugs have demonstrated that the initial positive results from studies involving a small number of subjects tend to disappear when the drugs are tested on larger numbers of subjects from diverse populations.

REFERENCES

Ahlemeyer, B., Möwes, A., & Krieglstein, J. (1999). Inhibition of serum deprivation- and staurosporine-induced neuronal apoptosis by Ginkgo biloba extract and some of its constituents. *European Journal of Pharmacology*, *367*, 423–430.

Allain, H., Raoul, P., Lieury, A., LeCoz, F., Gandon, J.-M., & d'Arbigny, P. (1993). Effect of two doses of Ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. *Clinical Therapeutics: The International Journal of Drug Therapy*, *19*, 549–558.

Bolanos-Jimenez, F., Manhaes de Castro, R., Sarhan, H., Prudhomme, N., Drieu, K., & Fillion, G. (1995). Stress-induced 5-HT1A receptor desensitization: Protective effects of Ginkgo biloba extract (EGb 761). *Fundamental & Clinical Pharmacology*, *9*, 169–174.

Cahill, L. (1999). A neurobiological perspective on emotionally influenced, long-term memory. *Seminars in Clinical Neuropsychiatry*, *4*, 266–273.

Cahill, L., & Alkire, M. (2000). Epinephrine enhancement of human memory consolidation. *Society for Neuroscience Abstracts*, *26*, 707.

Cahill, L., & McGaugh, J.L. (1996). Modulation of memory storage. *Current Opinion in Neurobiology*, *6*, 237–242.

Cahill, L., & McGaugh, J.L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience*, *21*, 294–299.

Chen, C., Wei, T.T., Gao, Z.H., Zhao, B.L., Hou, J.W., Xu, H.B., Xin, W.J., & Packer, L. (1999). Different effects of the constituents of EGb 761 on apoptosis in rat cerebellar granule cells induced by hydroxyl radicals. *Biochemistry and Molecular Biology International*, *47*, 397–405.

Chermat, R., Brochet, D., DeFeudis, F.V., & Drieu, K. (1997). Interactions of Ginkgo biloba extract (EGb 761), diazepam and ethyl beta-carboline-3-carboxylate on social behavior of the rat. *Pharmacology, Biochemistry & Behavior*, *56*, 333–339.

Chopin, P., & Briley, M. (1992). Effects of four non-cholinergic enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats. *Psychopharmacology*, *106*, 26–30.

Christen, Y., Costentin, J., & Lacour, M. (Eds.). (1992). *Effects of Ginkgo biloba extract (Egb 761) on the central nervous system*. Paris: Elsevier.

Cohen-Salmon, C., Venault, P., Martin, B., Raffalli-Sebille, M.J., Barkats, M., Clostre, F., Pardon, M.C., Christen, Y., & Chapouthier, G. (1997). Effects of Ginkgo biloba (EGb 761) on learning and possible actions on aging. *Journal of Physiology*, *91*, 291–300.

Cupp, M.J. (1999). Herbal remedies: Adverse effects and drug interactions. *American Family Physician*, *59*, 1239–1245.

Defeudis, F., Bonnot, D., & Hörr, R. (1999). Ginkgo biloba extract (EGb 761) rationale for use as a treatment for Alzheimer's Disease. In B. Vellas & L.J. Fitten (Eds.), *Research and practice in Alzheimer's Disease* (Vol. 2, pp. 288–298). New York: Springer.

Fourtillan, J.B., Brisson, A.M., Girault, J., Ingrand, I., Decourt, J.P., Drieu, K., Jouenne, P., & Biber, A. (1995). Proprietes pharmacocinetiques du Bilobalide et des Ginkgolides A et B chez le sujet sain apres administrations intraveineuses et orales d'extrait de Ginkgo biloba (EGb 761) [Pharmacokinetic properties of bilobalide and ginkgolides A and B in healthy subjects after intravenous and oral administration of *Ginkgo biloba* extract]. *Therapie*, *50*, 137–144.

Friedlich, A.L., & Butcher, L.L. (1994). Involvement of free oxygen radicals in B-Amyloidosis: An hypothesis. *Neurobiology of Aging*, *15*, 443–455.

Fugh-Berman, A., & Cott, J.M. (1999). Dietary supplements and natural products as psychotherapeutic agents. *Psychosomatic Medicine*, *61*, 712–728.

Gajewski, A., & Hensch, S.A. (1999). Ginkgo biloba and memory for a maze. *Psychological Reports*, *84*, 481–484.

Gold, P.E. (2001). Drug enhancement of memory in aged rodents and humans. In M.E. Carroll & J.B. Overmier (Eds.), *Animal research and human health: Advancing human welfare through behavioral science* (pp. 293–304). Washington, DC: American Psychological Association.

Gsell, W., Reichert, N., Youdim, M.B., & Riederer, P. (1995). Interaction of neuroprotective substances with human brain superoxide dismutase: An in vitro study. *Journal of Neural Transmission. Supplementum*, *45*, 271–279.

Hasenöhrl, R.U., Nichau, Ch., Frisch, Ch., De Souza Silva, M.A., Huston, J.P., Mattern, C.M., & Haecker, R. (1996). Anxiolytic-like effects of combined extracts of Zingiber officinale and Ginkgo biloba in the elevated plus maze. *Pharmacology, Biochemistry & Behavior*, *53*, 271–275.

Hasenöhrl, R.U., Topic, B., Frisch, Ch., Haecker, R., Mattern, C.M., & Huston, J.P. (1998). Dissociation between anxiolytic and hypomnestic effects for combined extracts of zingiber officinale and Ginkgo biloba as opposed to diazepam. *Pharmacology, Biochemistry & Behavior*, *59*, 527–535.

Hindmarch, I. (1986). Activite de l'extrait de Ginkgo biloba sur la memoire a court terme [Activity of *Ginkgo biloba* extract on short-term memory]. *Presse Medicale*, *15*, 1592–1594.

Huguet, F., Drieu, K., & Piriou, A. (1994). Decreased cerebral 5–HT1A receptors during ageing: Reversal by Ginkgo biloba extract (EGb761). *Journal of Pharmacy & Pharmacology*, *46*, 316–318.

Huguet, F., & Tarrade, T. (1992). Alpha 2-adrenoceptor changes during cerebral aging: The effect of Ginkgo biloba extract. *Journal of Pharmacy & Pharmacology*, *44*, 24–27.

Joyeux, M., Lobstein, A., Anton, R., & Mortier, F. (1995). Comparative antilipid peroxidant, antinecrotic and scavenging properties of terpenes and biflavones from Ginkgo biloba. *Planta Medica*, *61*, 126–129.

Kennedy, D.O., Scholey, A.B., & Wesnes, K.A. (2000). The dose-dependent cognitive effects of acute administration of Ginkgo biloba to healthy young volunteers. *Psychopharmacology*, *151*, 416–423.

Korol, D.L., & Gold, P.E. (1998). Glucose, memory and aging. *The American Journal of Clinical Nutrition*, *67*, 764S–771S.

Krieglstein, J., Ausmeier, F., El-Abhar, H., Lippert, K., Welsch, M., Rupalla, K., & Henrich-Noack, P. (1995). Neuroprotective effects of Ginkgo biloba constituents. *European Journal of Pharmaceutical Sciences*, *3*, 39–48.

Kristofikova, Z. (1997). In vitro effect of Ginkgo biloba extract (Egb761) on the activity of presynaptic cholinergic nerve terminals in rat hippocampus. *Dementia & Geriatric Cognitive Disorders*, *8*, 43–48.

Kuenkel, H. (1993). EEG profile of three different extractions of Ginkgo biloba. *Neuropsychobiology*, *27*, 40–45.

Le Bars, P.L., Katz, M.M., Berman, N., Itil, T.M., Freedman, A.M., & Schatzberg, A.F. (1997). A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia: North American EGb study group. *Journal of the American Medical Association*, *278*, 1327–1332.

Major, R.T. (1967). The ginkgo, the most ancient living tree: The resistance of Ginkgo biloba L. to pests accounts in part for the longevity of this species. *Science*, *157*, 1270–1273.

Manning, C.A., Ragozzino, M., & Gold, P.E. (1993). Glucose enhancement of memory in patients with Alzheimer's disease. *Neurobiology of Aging*, *14*, 523–528.

McNay, E.C., Fries, T.M., & Gold, P.E. (2000). Decreases in rat extracellular hippocampal glucose concentration associated with cognitive demand during a spatial task. *Proceedings of the National Academy of Sciences, USA*, *97*, 2881–2885.

Oberpichler, H., Beck, T., Abdel-Rahman, M.M., Bielenberg, G.W., & Krieglstein, J. (1988). Effects of Ginkgo biloba constituents related to protection against brain damage caused by hypoxia. *Pharmacological Research Communications*, *20*, 349–368.

Oken, B.S., Storzbach, D.M., & Kaye, J.A. (1998). The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Archives of Neurology*, *55*, 1409–1415.

Oyama, Y., Chikahisaa, L., Uehaa, T., Kanemaruc, K., & Nodac, K. (1996). Ginkgo biloba extract protects brain neurons against oxidative stress induced by hydrogen peroxide. *Brain Research*, *712*, 349–352.

Petkov, V.D., Kehayov, R., Belcheva, S., Konstantinova, E., Petkov, V.V., Getova, D., & Marovska, V. (1993). Memory effects of standardized extracts of Panax ginseng (G115), Ginkgo biloba (GK 501) and their combination Gincosan (PHL-00701). *Planta Medica*, *59*, 106–114.

Porsolt, R.D., Martin, P., Lenegre, A., Fromage, S., & Drieu, K. (1990). Effects of an extract of Ginkgo biloba (EGB 761) on "learned helplessness" and other models of stress in rodents. *Pharmacology, Biochemistry & Behavior*, *36*, 963–971.

Rai, G.S., Shovlin, C., & Wesnes, K.A. (1991). A double-blind placebo controlled study of Ginkgo biloba extract ("tanakan") in elderly outpatients

with mild to moderate memory impairment. *Current Medical Research Opinions*, *12*, 350–355.

Ramassamy, C., Christen, Y., Clostre, F., & Costentin, J. (1992). The Ginkgo biloba extract, Egb761, increases synaptosomal uptake of 5-hydroxytryptamine: In vitro and ex vivo studies. *Journal of Pharmacy & Pharmacology*, *44*, 943–945.

Rapin, J.R., & Le Poncin Lafitte, M. (1986). Consommation cerebrale du glucose. Effet de l'extrait de Ginkgo biloba [Cerebral glucose consumption: The effect of *Ginkgo biloba* extract]. *Presse Medicale*, *15*, 1494–1497.

Rapin, J.R., Zaibi, M., & Drieu, K. (1998). In vitro and in vivo effects of an extract of Ginkgo biloba (EGb 761), ginkgolide B, and bilobalide on apoptosis in primary cultures of rat hippocampal neurons. *Drug Development Research*, *45*, 23–29.

Rodriguez de Turco, E.B., Droy-Lefaix, M.T., & Bazan, N.G. (1993). Decreased electroconvulsive shock-induced diacylglycerols and free fatty acid accumulation in the rat brain by Ginkgo biloba extract (EGb 761): Selective effect in hippocampus as compared with cerebral cortex. *Journal of Neurochemistry*, *61*, 1438–1444.

Sasaki, K., Hatta, S., Haga, M., & Ohshika, H. (1999). Effects of bilobalide on gamma-aminobutyric acid levels and glutamic acid decarboxylase in mouse brain. *European Journal of Pharmacology*, *367*, 165–173.

Satyan, K.S., Jaiswal, A.K., Ghosal, S., & Bhattacharya, S.K. (1998). Anxiolytic activity of ginkgolic acid conjugates from Indian Ginkgo biloba. *Psychopharmacology*, *136*, 148–152.

Seif-El-Nasr, M., & El-Fattah, A.A. (1995). Lipid peroxide, phospholipids, glutathione levels and superoxide dismutase activity in rat brain after ischaemia: Effect of ginkgo biloba extract. *Pharmacological Research*, *32*, 273–278.

Shen, J.G., & Zhou, D.Y. (1995). Efficiency of Ginkgo biloba extract (EGb 761) in antioxidant protection against myocardial ischemia and reperfusion injury. *Biochemistry & Molecular Biology International*, *35*, 125–134.

Smith, P.F., MacLennan, K., & Darlington, C.L. (1996). The neuroprotective properties of the Ginkgo biloba leaf: A review of the possible relationship to platelet-activating factor (PAF). *Journal of Ethnopharmacology*, *50*, 131–139.

Stoll, S., Scheuer, K., Pohl, O., & Muller, W.E. (1996). Gingko biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. *Pharmacopsychiatry*, *29*, 144–149.

Trovero, F., Brochet, D., Tassin, J.P., & Drieu, K. (1999). Ginko biloba extract Egb761 reduces the development of amphetamine-induced behavioral sensitization: Effects on hippocampal type II corticosteroid receptors. *Brain Research*, *818*, 135–139.

van Dongen, M.J., van Rossum, E., Kessels, A., Sielhorst, H., & Knipschild, P. (2000). The efficacy of Ginkgo for elderly people with dementia and age-associated memory impairment: New results of a randomized clinical trial. *Journal of the American Geriatrics Society*, *48*, 1183–1194.

Wesnes, K.A., Ward, T., McGinty, A., & Petrini, O. (2000). The memory enhancing effects of a Gingko biloba/Panax ginseng combination in healthy middle-aged volunteers. *Psychopharmacology*, *152*, 353–361.

Whitehouse, P.J., Price, D.L., Clark, A.W., Coyle, J.T., & DeLong, M.R. (1981). Alzheimer Disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of Neurology*, *10*, 122–126.

Winter, E. (1991). Effects of an extract of Ginkgo biloba (EGb 761) on learning and memory in mice. *Pharmacology, Biochemistry & Behavior*, *38*, 109–114.

Winter, J.C. (1998). The effects of an extract of Ginkgo biloba, EGb 761, on cognitive behavior and longevity in the rat. *Physiology & Behavior*, *63*, 425–433.

Wirth, S., Stemmeline, J., Will, B., Christen, Y., & Di Scala, G. (2000). Facilitative effects of EGb 761 on olfactory recognition in young and aged rats. *Pharmacology, Biochemistry & Behavior*, *65*, 321–326.

Zhou, L.J., Song, W., Zhu, X.Z., Chen, Z.L., Yin, M.L., & Cheng, X.F. (2000). Protective effect of bilobalide on amyloid beta-peptide 25-35-induced PC12 cell cytotoxicity. *Acta Pharmacologica Sinica*, *21*, 75–79.