FAN-SHAPED LEAVES of the ginkgo tree are shown in this drawing from *Flora Japonica*, a book written by 19th-century Dutch physician Philipp Franz von Siebold. The extract obtained from the leaves (*inset on opposite page*) is one of the most widely used herbal treatments aimed at improving memory.

The Lowdown on Ginkgo Biloba

This popular herbal supplement may slightly improve your memory, but you can get the same effect by eating a candy bar

By Paul E. Gold, Larry Cahill and Gary L. Wenk

The ginkgo tree (*Ginkgo biloba*) is remarkable in many ways. Although indigenous to Korea, China and Japan, the tree can be found in parks and along city sidewalks around the world. It may grow as high as 40 meters and live for more than 1,000 years. Ginkgo fossils have been dated as far back as 250 million years ago, and Charles Darwin referred to the tree as "a living fossil." Nowadays, however, the ginkgo's primary claim to fame is the extract obtained from its fan-shaped leaves.

The use of ginkgo leaf extracts can be traced back for centuries in traditional Chinese medicine. Today ginkgo biloba is perhaps the most widely used herbal treatment aimed at augmenting cognitive functions—that is, improving memory, learning, alertness, mood and so on. Ginkgo is especially popular in Europe; officials in Germany recently approved the extract for treating dementia. In the U.S. 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.

But is there any evidence that ginkgo biloba can really improve cognitive functions? Information on most dietary supplements is based far more on folklore than on experimental findings. Because the U.S. Food and Drug Administration does not regulate herbal treatments, the manufacturers are not required to test the effectiveness or safety of their products. More attention to supplements such as ginkgo biloba is clearly warranted; even if the products do not cause medical problems, they can be costly and may prevent patients from seeking more pragmatic treatments. In an attempt to close the gap in our knowledge, we have reviewed the experimental evidence both for and against the usefulness of ginkgo biloba in enhancing brain functions.

Many Studies, Few Answers

THE TYPICAL DAILY DOSE of ginkgo biloba—and the one used in many of the experiments described in this article—is 120 milligrams of dried extract in two or three oral doses. The extract contains several flavonoids, a large group of natural plant products that are characterized by a specific chemical structure containing a series of carbon rings. Ginkgo extract also contains some biflavonoids, a related group of compounds, and two different types of terpenes, a class of naturally occurring chemicals that includes the active ingredients in catnip and marijuana.

FROM *Flora Japonica* BY SIEBOLD AND ZUCCARINI, LEIDEN 1835/42; IN THE LEIDEN UNIVERSITY BRANCH OF THE NATIONAL HERBARIUM OF THE NETHERLANDS; GETTY IMAGES

Ginkgo's Effects on the Brain

RESEARCHERS CANNOT SAY FOR CERTAIN WHETHER GINKGO BILOBA CAN IMPROVE COGNITIVE FUNCTIONS, BUT THEY HAVE FOUND THAT THE EXTRACT CAN AFFECT THE BRAIN IN SEVERAL WAYS

CIRCULATORY

- Stimulates widening of the blood vessels, which leads to increased blood flow to the brain and lowered blood pressure (perhaps reducing the risk of stroke).
- Reduces cholesterol levels in the blood (excessive cholesterol is correlated with an increased risk of Alzheimer's disease).
- Inhibits the aggregation of blood platelets and the formation of clots. This may lower the risk of an occlusive stroke (caused by a clot blocking a blood vessel in the brain) but raise the chance of a hemorrhagic stroke (caused by bleeding in the brain).

ANTIOXIDANT

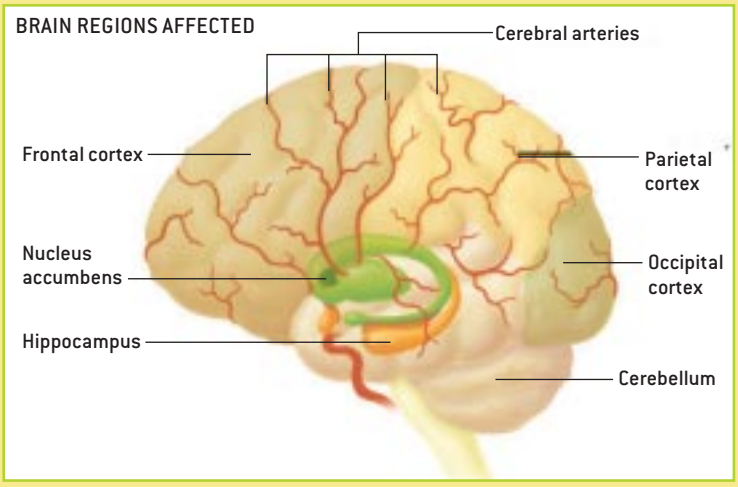
- Curbs the creation of free radicals, highly reactive oxygen molecules that may injure neurons and cause age-related changes in the brain.
- Alleviates the effects of cerebral ischemia—the loss of blood flow to the brain—by inhibiting the production of toxic free radicals after an ischemic episode.

GLUCOSE UTILIZATION

- Boosts the absorption of glucose, the body's primary fuel, in the frontal and parietal cortex, areas of the brain important for processing sensory information and for planning complex actions.
- Also increases glucose absorption in the nucleus accumbens and the cerebellum, brain regions involved in experiencing pleasure and controlling movement, respectively.

NEUROTRANSMITTER SYSTEMS

- Appears to help neurons in the forebrain absorb the nutrient choline from the blood. Choline is one of the components of acetylcholine, a brain chemical that transmits signals between certain neurons.
- Slows the attrition of neuron receptors that direct the response to serotonin, a neurotransmitter that reduces stress and anxiety.
- Enhances the release of gamma-amino butyric acid (GABA), another neurotransmitter that can relieve anxiety. Lowering stress may reduce the level of glucocorticoid hormones in the blood, which in turn may protect the hippocampus, a brain structure critical to normal learning.
- Raises the production of norepinephrine, yet another neurotransmitter. Enhanced activation of the norepinephrine system by certain antidepressants has been shown to reduce the symptoms of depression.



To date, dozens of investigations have examined the cognitive effects of ginkgo in humans, but many of the research reports are in non-English publications or in journals with very restricted distribution, making assessment of the findings difficult. The great majority of studies have involved subjects with mild to moderate mental impairment, usually a diagnosis of early Alzheimer's. Most of the experiments that show evidence of cognitive enhancement in Alzheimer's patients have used a standardized ginkgo extract known as EGb 761.

The ginkgo researchers have usually employed tests of learning and memory; less attention has been paid to other mental functions such as attention, motivation and anxiety. Moreover, because most of the investigators introduced the tests to the subjects after long-term use of ginkgo biloba (typically several months), it is hard to identify which cognitive abilities have been affected. For example, higher scores on the memory and learning tests might stem from the fact that subjects who used ginkgo paid better attention to the initial instructions. To get more specific data on ginkgo's effects, researchers need to administer the tests both before and after the subjects take the supplement.

Because the studies have varied so greatly in the numbers of subjects and the control over experimental conditions, it is useful to focus on only the most rigorous investigations. In 1998 Barry S. Oken of Oregon Health Sciences University and his colleagues considered more than 50 studies involving subjects with mental impairment and selected four that met a conservative set of criteria, including sufficient characterization of the Alzheimer's diagnosis, use of a standardized ginkgo extract, and a placebo-controlled, double-blind design (in which neither the subjects nor the investigators know until the end whether a given patient is receiving the extract or the placebo). Each of these studies showed that the Alzheimer's patients who received ginkgo performed better on various cognitive tests than did patients who received a placebo. Improvements were evident in standardized tests measuring attention, short-term memory and reaction time; the average extent of improvement resulting from ginkgo treatment was 10 to 20 percent.

Oken and his colleagues reported that ginkgo's effect was comparable to that of the drug donepezil, which is currently the treatment of choice for Alzheimer's. Donepezil enhances brain

ALICE Y. CHEN

activity by inhibiting the breakdown of acetylcholine, a brain chemical that transmits signals between certain neurons. Despite these apparently encouraging findings, though, another recent, large and well-controlled trial of EGb 761 (sponsored by its manufacturer, Dr. Willmar Schwabe Pharmaceuticals in Karlsruhe, Germany) involving patients with a mild or moderate stage of dementia reported no "systematic and clinically meaningful effect of ginkgo" on any of the cognitive tests employed.

A critical question concerns whether the ginkgo treatment in studies showing positive effects actually improved cognitive abilities in Alzheimer's patients or merely slowed their deterioration. Two different answers to this key question have come from a 1997 investigation led by Pierre L. Le Bars of the New York Institute for Medical Research. In this study, which was one of the four analyzed by Oken, the results varied according to the cognitive test that was employed. Measured by the Alzheimer's Disease Assessment Scale Cognitive Subscale, the performance of the patients treated with the placebo slowly deteriorated over a year, whereas the performance of patients treated with ginkgo remained stable. But according to a second test—the Geriatric Evaluation by Relative's Rating Instrument—ginkgo-treated subjects improved by about the same amount that placebo-treated subjects deteriorated.

Furthermore, at least one study has reported positive effects on mentally impaired subjects after just a single treatment of ginkgo. Herve Allain of the University of Haute Bretagne in Rennes, France, gave one fairly high dose of ginkgo—320 or 600 milligrams—to a small group of elderly people with mild, age-related memory impairment. An hour after the treatment, Allain tested the subjects' memory by rapidly presenting short lists of words or drawings and then asking the patients to recall the lists immediately afterward. Their ability to recall the rapidly presented material increased significantly after ingestion of ginkgo. This finding raises the possibility that short-term, rather than long-term, biological actions provide the basis for ginkgo's reported effects on cognition.

It should be noted that ginkgo has also been shown to impair performance. For example, in a small study of elderly people with mild to moderate memory impairment, G. S. Rai of Whittington Hospital in London and his team found that after 24 weeks of treatment, patients who took ginkgo could not recall digits as well as patients who received a placebo.

Help for the Healthy?

UNFORTUNATELY, FAR FEWER studies have examined the cognitive effects of ginkgo biloba on healthy young adults. In one small study during the mid-1980s, I. Hindmarch of the University of Leeds in England administered a battery of tests to eight healthy subjects aged 25 to 40 after they took the ginkgo extract EGb 761. Hindmarch reported that the highest dose tested (600 milligrams) improved performance in only a short-term memory test. More recently, two reports from Cognitive Drug Research, a laboratory in Reading, England, provide minor support for the view that ginkgo may enhance cognitive functions in young people. One study reported that subjects who took a dose of ginkgo performed better on tasks assessing attention than did subjects who took a placebo. The other study showed an improvement in memory among middle-aged subjects (ages 38 to 66) who were treated with a combination of ginkgo and ginseng, another herbal remedy touted as a memory aid. The effects seen in the latter study, however, could not be attributed to ginkgo alone and did not increase with the dosage, which would be expected of a truly effective substance.

Information on most dietary supplements is based far more on folklore than on EXPERIMENTAL FINDINGS.

For most pharmaceuticals, researchers conduct a large number of studies with lab animals before they test the drugs in humans. Such experiments can be useful in determining a drug's safety and effectiveness. But because ginkgo is unregulated, its manufacturers have not been required to perform animal tests. As a result, there are relatively few research reports in refereed journals examining the efficacy of ginkgo in improving learning and memory in animals. Perhaps the most notable example is a 1991 study of young adult mice that were trained to press a lever to receive food. Mice treated with ginkgo for four to eight weeks learned the task slightly more quickly than did the control mice. As with humans, though, it is difficult to pin down whether ginkgo actually enhances the learning process or whether it has other effects that improve the animals' performance at a specific task. For instance, investigators have reported that repeated administration of ginkgo reduced stress in rats, and altered stress responses can themselves have a great influence on learning and memory.

If ginkgo can really enhance mental processes, how does it work? Studies of humans and lab animals have indicated several classes of biological effects that might contribute to ginkgo's putative improvement of cognitive functions [*see box on opposite page*]. Whatever its effects, ginkgo appears to pose few health

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MONICA STEVENSON *Food Pix*

The Other "Brain Boosters"

By Mark A. McDaniel, Steven F. Maier and Gilles O. Einstein

OLDER ADULTS HAVE shown a strong interest in over-the-counter "brain boosters," many of which are marketed with grand claims touting their benefits. There are sound biochemical reasons for expecting some of these nutrients to be effective. In a review of published research, we found studies showing that some of these substances had robustly enhanced memory in lab animals and occasionally produced impressive improvements in humans as well. Nevertheless, there are numerous questions about the sample sizes in the studies, the generality of the results across different memory tests and populations, and other aspects of the procedures and data. These problems, in conjunction with a general lack of research demonstrating that the results can be replicated, dampen enthusiasm for the effectiveness of these nutrients in substantially arresting or reversing memory loss. Here is an abbreviated summary of the findings for six kinds of nonprescription compounds that are claimed to be memory enhancers and treatments for age-related memory decline.

PHOSPHATIDYLSERINE (PS)

A naturally occurring lipid, PS has been shown to reduce many consequences of aging on the neurons in older rats and mice and to restore their normal memory in a variety of tasks. Research on the impact in humans is limited, though. For older adults with moderate cognitive impairment, PS has produced modest increases in recall of word lists. Positive effects have not been as consistently reported for other memory tests.

CHOLINE COMPOUNDS

Phosphatidylcholine, which is typically administered as lecithin, has not proved effective for improving memory in patients with probable Alzheimer's disease. Research on citicoline is practically nonexistent, but one study reported a robust improvement in story recall for a small sample of normally aging older adults.

PIRACETAM

Developed in 1967, Piracetam has not been approved by the U.S. Food and Drug Administration, but it is sold in Europe and Mexico under several names (including Nootropil and Pirroxil). Animal studies suggest that the drug may improve neural transmission and synaptic activity and also combat age-related deterioration of neuronal membranes. But there is no clear sign of any cognitive benefits in patients with probable Alzheimer's or adults with age-associated memory impairment.

VINPOCETINE

An alkaloid derived from the periwinkle plant, vinpocetine increases blood circulation in the brain. In three studies of older adults with memory problems associated with poor brain circulation or dementia-related disease, vinpocetine produced improvements in performance on cognitive tests measuring attention, concentration and memory.

Acetyl-L-carnitine (ALC)

An amino acid included in some "brain power" supplements sold in health food stores, ALC participates in cellular energy production, a process especially important to neurons. Animal studies show that ALC reverses age-related decline in the number of receptor molecules on neuronal membranes. But studies of patients with probable Alzheimer's have reported only nominal advantages for ALC in a range of memory tests.

ANTIOXIDANTS

Antioxidants such as vitamins E and C help to neutralize tissue-damaging free radicals, which become more prevalent with age. But studies have found that vitamin E does not offer significant memory benefits for patients with Alzheimer's or early Parkinson's disease. A combination of vitamins E and C did not improve college students' performance on several cognitive tasks.

A more detailed version of this article appeared as "Brain-Specific Nutrients: A Memory Cure?" by Mark A. McDaniel, Steven F. Maier and Gilles O. Einstein in Psychological Science in the Public Interest *(May 2002). (Available at www.psychologicalscience.org/journals/pspi/3_1.html) McDaniel is chair of the department of psychology at the University of New Mexico. Maier is director of the Center for Neuroscience at the University of Colorado at Boulder. Einstein is chair of the department of psychology at Furman University.*

BUYERS BEWARE: Dietary supplements have not proved effective for enhancing memory.

CHUCK SAVAGE *Corbis*

risks, particularly at the typical doses of 120 to 240 milligrams a day. Some complications have been noted, though, including subdural hematomas (clots between the skull and brain) and gastrointestinal problems. As is the case with most plant extracts and medications, ingestion of ginkgo is at times associated with nausea and vomiting. In addition, some users experience increased salivation, decreased appetite, headaches, dizziness, tinnitus (ringing in the ears) and skin rash. Large doses may lead to orthostatic hypotension, a condition of low blood pressure sometimes seen after abrupt postural changes, such as standing up after being seated. Still, the general impression is that the incidence of serious adverse consequences 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.

Because of the differences in experimental designs used to test ginkgo and other treatments, it is difficult to make direct comparisons of efficacy. For instance, on a test involving memory of a brief story, glucose enhanced performance in young adult and healthy elderly subjects by about 30 to 40 percent. In people with Alzheimer's, the improvement on a similar memory test approached 100 percent, with smaller enhancements seen on other measures. The extent of improvement in these experiments is much larger than the 10 to 20 percent gain shown with ginkgo. But most of the experiments testing the effects of glucose have used short-term treatments and compared performance before and afterward, whereas most of the experiments testing ginkgo have used long-term treatments and compared ginkgo-treated subjects with a control group.

Does ginkgo biloba in fact enhance cognitive function? The proof for even a MILD BENEFIT is weak.

But to return to our original question, does ginkgo biloba in fact enhance cognitive function? In general, the reported effects are rather small. The number of experiments is also small, and they are of mixed quality, so the proof for even a mild benefit is weak. In humans, ginkgo may slow cognitive decline during dementia. It is possible that ginkgo's main effects on memory kick in after one dose and are relatively short-lived, but the research literature is so limited that significant issues such as this one cannot be adequately evaluated at this time.

The Bottom Line

GIVEN THE AVAILABLE EVIDENCE, is ginkgo biloba the best therapy for improving memory? Other supplements have been found to influence cognitive function in humans and lab animals [*see box on opposite page*]. Pharmaceuticals such as donepezil can strongly enhance learning and memory in rodents and induce modest though significant improvements in humans. But relatively simple interventions can produce some of the same results. For example, hearing an exciting story apparently releases epinephrine from the adrenal glands into the circulation, thereby enhancing one's memory without any drugs at all. One mechanism by which epinephrine might enhance memory is by liberating glucose from stores in the liver, thereby increasing the circulating glucose available to the brain.

Eating a simple sugar can also improve one's memory. Considerable evidence indicates that glucose administered systemically (to humans by ingestion and to rodents by injection) enhances cognitive performance in young and elderly rats, mice and humans, including people with Alzheimer's. Like most treatments that improve memory, glucose's effects follow a dose-response curve in the shape of an inverted U. Only intermediate doses improve memory; low doses are ineffective, and high doses may actually impair memory.

Establishing direct comparisons of efficacy is vital to identifying which treatments improve cognition the most. This is one of many instances in which further studies of rodents would be useful because of the researchers' ability to control all the variables in the experiment. Only one study has directly compared the effects of ginkgo with those of other treatments. This study showed that the peak enhancement observed with ginkgo was about half of that seen with other drugs. More direct comparisons, in both humans and lab animals, are clearly needed.

We began our survey of the research 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, under some conditions. Our overriding impression, however, is that we do not have enough information to say conclusively whether ginkgo does or does not improve cognition. There are too few experiments on which to base clear recommendations, and most of the studies showing benefits have involved too few subjects.

But there are enough positive findings, perhaps just enough, to sustain our interest in conducting further research on ginkgo. 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 in larger numbers of subjects from diverse populations. So the true test of ginkgo's efficacy lies ahead. SA

MORE TO EXPLORE

A more detailed version of this article appeared as **"Ginkgo Biloba: A Cognitive Enhancer?"** by Paul E. Gold, Larry Cahill and Gary L. Wenk in *Psychological Science in the Public Interest*, Vol. 3, No. 1, pages 2–11; May 2002. Available at www.psychologicalscience.org/journals/pspi/3_1.html

More information about ginkgo biloba and other dietary supplements can be found on the Web at **dietary-supplements.info.nih.gov/** and **www.cfsan.fda.gov/~dms/supplmnt.html**

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