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RE: A Review of Phytochemicals that Enhance Human Brain Function

Kennedy DO, Wightman EL. Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. *Adv Nutr*. January 2011;2(1):32-50.

There is a limited number of drugs that can help people slow the cognitive decline associated with aging, and these drugs have undesirable side effects. Many people turn to herbal products to help preserve memory and cognitive abilities. Plants have many chemicals that influence brain function, yet few have been thoroughly tested in humans. The purpose of this article was to review current knowledge about plant extracts and phytochemicals which have been tested in humans and assess their effectiveness in improving brain function.

Many secondary metabolites affect the central nervous system in insects and animals. Secondary metabolites that have central nervous system effects and that have been studied in humans include alkaloids, terpenes, and phenolic compounds.

Alkaloids
Humans have used alkaloid-containing plants medicinally for thousands of years. Medicinal and social alkaloids include atropine, ephedrine, cocaine, morphine, nicotine, and caffeine.

Caffeine is the most widely consumed psychoactive substance in the world. It is an antagonist of the inhibitory adenosine A1 and A2 receptors, which is responsible for the stimulation, and also causes constriction of blood vessels in the brain. Caffeine also increases activity in dopamine neuronal systems. At low doses, caffeine increases alertness and improves performance on tests of attention. At high doses, caffeine can cause anxiety, insomnia, rapid heart beat, and agitation.

Nicotine is found in tobacco (*Nicotiana tabacum*). Nicotine binds to acetylcholine receptors and increases the release of acetylcholine, serotonin, and other neurotransmitters. It increases dopamine activity, which is associated with its addictive effect. Clinical trials in smokers and non-smokers show that nicotine improves performance on tests of memory and attention.

Terpenes

Terpenes are a diverse group of lipid-soluble compounds. Some terpenes are non-toxic and are common in foods and spices; others are toxic.

Ginkgo (*Ginkgo biloba*) leaves contain a number of terpenes, including bilobalide and ginkgolides A, B, C, and J. Effects of ginkgo leaf extracts in the central nervous system include modulation of several neurotransmitter systems, enhanced blood flow in the brain, and scavenging of free radicals. Ginkgo is one of the most popular herbal products, and it is used to improve cognitive performance. More than 30 clinical trials have tested the effects of ginkgo on cognitive function in people with dementia or age-related cognitive impairment. One meta-analysis concluded that the evidence for cognitive improvement with ginkgo supplementation is inconsistent, while another meta-analysis concluded that ginkgo improves attention, executive function, and long-term memory.

Lemon balm (*Melissa officinalis*) contains a variety of monoterpenoids and sesquiterpenes. Effects of lemon balm on the central nervous system include binding to specific cholinergic receptors, increased activity of the neurotransmitter gamma-aminobutyric acid (GABA), and antioxidant activity. Limited clinical trials have shown that lemon balm has anti-anxiety effects, improves agitation and quality of life in people with severe dementia, but has inconsistent effects on memory.

Asian ginseng (*Panax ginseng*) roots contain 40 or more triterpene saponins known as ginsenosides. Ginseng root extracts have neuroprotective effects, modulate the neuroendocrine system and the synthesis of nitric oxide, which relaxes blood vessels and influences many cellular activities. Clinical trials have shown that ginseng improves accuracy on memory tests and improves the speed of performing attention tasks. The impact of ginseng on mood has been inconsistent in clinical trials to date.

Sage (*Salvia officinalis*) contains a range of monoterpenes. Effects on the central nervous system include anti-inflammatory activity and decreased breakdown of the acetylcholine neurotransmitter. Clinical trials have demonstrated improved memory, attention, and alertness in healthy people after single doses of sage extract and improved cognitive function in people with Alzheimer's disease after 16 weeks of an alcoholic tincture of sage.

Valerian (*Valeriana officinalis*) root contains a variety of terpenes, including the valepotriates and valerenic acid. Valerian compounds modulate serotonin receptor subtypes, GABA, and adenosine receptors and have anxiolytic activity. Some clinical trials suggest that valerian improves sleep quality; others were not conclusive.

Phenolics

Phenolics are ubiquitous in plants and they are important components in the human diet. They range from simple, low molecular weight compounds to complex, large structures such as flavonoids, tannins, and anthocyanins.

Curcumin is a polyphenol from turmeric (*Curcuma longa*). Curcumin prevented cognitive deficits and improved learning and memory in mouse models of Alzheimer's disease. Curcumin also reversed amnesia in rats. Many small pilot studies have been conducted in humans, but there are few controlled clinical trials to support a benefit of curcumin in brain function.

Epigallocatechin-3-gallate (EGCG) and related polyphenols are present in tea (*Camellia sinensis*). In vitro and animal studies suggest that EGCG may have protective effects in Alzheimer's disease and Parkinson's disease. EGCG improved cognitive performance and

increased antioxidant capacity in rats. In epidemiological studies, greater consumption of green tea is associated with reduced risk of cognitive impairment and neurodegenerative disorders.

St. John's wort (SJW; *Hypericum perforatum*) extract contains a variety of phenolic compounds that have an impact on brain function, including phenolic acids, flavonoids, hyperforin, and hypericin. SJW extracts have been reported to inhibit reuptake of serotonin, dopamine, and GABA, but this finding is highly doubtful. Other reports include increased neurotransmitter sensitivity and altered receptor binding. Clinical trials have established that SJW is an effective treatment in people with mild to moderate depression.

Resveratrol is found in the skin of red grapes (*Vitis vinifera*) and in some other edible plants. Resveratrol preserved behavior and cognitive performance in older rats with brain injuries. In healthy humans, single doses of resveratrol increased blood flow and oxygen uptake in the frontal cortex of the brain, suggesting it may have benefits in Alzheimer's disease and other neurological disorders.

Soy (*Glycine max*) extract contains isoflavones such as genistein, daidzein, and glycetin that have very weak estrogen-like effects. Several clinical trials have shown that soy isoflavones modestly improve neurocognitive function and mood in postmenopausal women, but other clinical trials showed no improvement. Compared to a diet with no soy isoflavones, a diet rich in soy isoflavones was associated with improved short-term and long-term memory in men and women.

Conclusion

The authors conclude that the literature describing the effectiveness of herbal extracts for improving brain function is "somewhat equivocal." Research on caffeine and nicotine has been hampered by the addictive nature and serious adverse effects attributed to these alkaloids. Research is progressing among plants containing terpenes, particularly ginkgo and valerian. However, the methodological quality of some of the clinical trials has been poor, and results have been inconsistent. Interest in the potential cognitive benefits of curcumin, EGCG, resveratrol, and soy isoflavones is relatively recent, and human clinical trials are still in the early stages.

The authors describe challenges in developing plant-based products to prevent or reverse age-related cognitive decline. Challenges include identifying the active components, understanding the synergism among the active components, defining the environmental stressors and growing conditions under which plants produce increased amounts of secondary metabolites, and standardizing plant products to provide beneficial amounts of active compounds.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.