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## The Promise of Ginseng

Ginseng is sold by a variety of different health food companies today, all of which claim ginseng can enhance memory and learning. A number of different scientific studies have been conducted to substantiate these claims. As Petkov et al eloquently write, "The search for drugs able to mobilize the intellectual resources of man is, today, a task of both medical and social importance...this explains the growing research interest in newly synthesized compounds and in natural products as possible cognition enhancers" (1).

Ginseng has long been recognized for its medicinal purposes, mentioned as early as 33 BC in Chinese literature as a potent curative agent. A deciduous perennial plant which belongs to the Araliaceae family, ginseng species include: *Panax ginseng*, which grows in Korea; *Panax quinquefolium*, which grows in North America; *Panax notoginseng*, which grows in China; *Panax trifolius*, which grows in Northeastern America; *Panax psuedoginseng*, which grows in Nepal and Eastern Himalayas; and *Panax japonicus*, which grows in Japan. Ginseng – which translates into "man-root" in Chinese – often resembles human figures. Older roots are more valuable than younger ones in part because the older a root is, the more human-like is its shape. "Panax" means "cure all". Thus *Panax ginseng* is literally the "cure-all man-root" (2).

Chinese herbal medicine has used ginseng as a tonic to enhance memory, among many other restorative functions, for several thousand years. Recent clinical trials have sought to validate ginseng's ability to improve memory and will be outlined below.

### Ginsenosides and Memory and Learning

Some of the first trials involving ginseng focused on the possible role of ginsenosides, the saponins and biologically active components of ginseng. The effects of the ginsenoside Rb1, extracted from the North American ginseng, on central cholinergic metabolism was studied on scopolamine-induced memory deficient rats by Benishin et al. Scopolamine is a drug that blocks central cholinergic activity, thus producing a memory impairment in animals and humans which mimics dementia. Research conducted by Benishin et al indicates that 5mg/kg/day Rb1 can partially attenuate the scopolamine-induced amnesia. The study involved a passive learning paradigm, in which rats were required to remember the source of an aversive stimulus, an electrical shock, such that rats shocked by a prod will avoid touching it at a later times. 24 h after introduction to the aversive stimulus, rats were observed and latency to retouch the prod what quantitated as an indicator of learning. With scopolamine, a learning deficit was manifested as a decreased latency in retouching the prod. Administering Rb1 increased the latency to retouch the prod, improving the biochemical cholinergic deficits induced by scopolamine. Thus the results of the study indicated that Rb1 is effective in reversing memory and learning deficits in laboratory animals (3).

The biochemical basis of this reversal was that Rb1 was found to facilitate the release of acetylcholine (Ach). The central cholinergic nervous systems are thought to play crucial roles in learning and memory. The increase of Ach release was associated with an increased uptake of choline into nerve endings (3). Further research by Benishin indicated that the ability of Rb1 to reverse memory deficits might be related to the ability of Rb1 to also increase cholinergic neurotransmission by increasing the maximum velocity of choline uptake. Benishin's results indicated that prolonged administration of the Rb1 ginsenoside increased the number of choline uptake sites in the hippocampus and, to a lesser extent, in the cortex, two regions associated with memory and learning functions. Thus as more choline is taken into the cell, more Ach can be made and more is therefore available for release, theoretically for use in learning and memory. Benishin thus established ginseng as a nootropic agent; nootropic drugs are defined as those that improve memory and learning (4).

These studies established that ginseng had the ability to improve memory and learning in memory deficient rats. This research highlights the potential use of ginseng in age related deficits in cognitive function in animals and humans, and can become a very important tool in the future practice of geriatric medicine. Further indication for ginseng use in geriatric practice is the multitude of effects of the ginseng root beyond its cognition enhancing activity, including evidence that: the ginsenoside Rb1 antagonizes lipid peroxidation and scavenges oxygen free radicals; ginsenosides improve lipid metabolism, exerting a

prophylactic effect against atherosclerosis; and that ginsenosides slow down blood coagulation, increase fibrinolysis and inhibit platelet functions. These activities could reduce the potential for cerebral vascular accidents. Petkov et al characterizes ginseng as a drug regulating the aging process in the brain based on these and other favorable effects of ginseng (1). However, more relevant to the young medical student such as myself is whether or not ginseng has the ability to improve learning and memory in normal subjects. An experiment by Petkov et al on young (aged 3 months) and old (aged 26 months) rats attempted to answer this question.

Petkov et al examined the effect of standardized extracts of *Panax ginseng* (G115 titrated on 4% ginsenosides) on retention of learned behavior in these young and old rats. The study used condition-reflex methods to characterize the behavioral changes in learning and memory. The behavioral responses differed in their physiologic characteristics, such as active motor reactions to a stimulus in one experiment and inhibition of motor activity by a stimulus in another. For example, young rats were tested in a two-way active avoidance experiment with negative reinforcement. A shuttle box was divided into two equal compartments; light was a conditioned stimulus and an electric shock was an unconditioned stimulus. The increased number of electroshock avoidances in the shuttle-box trained rats and the decreased number of their inadequate responses showed that the animals had learned to enter the safety compartment immediately after the light stimulus to escape the aversive electrical stimulation. The ginseng extracts increased the number of avoidances on the second training day of the young rats (with a significance of difference versus controls of  $p < 0.05$ ) and upon almost all retention testings ( $p < 0.01$ ). The most pronounced increases occurred at the highest doses of ginseng, 150mg/kg ( $p < 0.001$ ); this dose also greatly decreased the number of inadequate responses ( $p < 0.001$ ). In another experiment with the young rats, called the "step-through" task, the acquisition and retention of the task was achieved when the rat remained in an illuminated compartment despite the innate phobia of the rats to light. At 50 and 150 mg/kg, ginseng increased the percentage of young rats that exhibited the learned behavior, remaining in the illuminated compartment for 180 s. (1)

In comparing the effects of ginseng on young and old rats, a step-down experiment was conducted such that rats were trained to remain on a plastic mobile platform to escape an electric footshock. Learned behavior was exhibited as remaining on the platform for as long as possible. Results indicated no significant difference in the step down latency and in the percentage of rats exhibiting learned behavior between the control young and old rats. At low doses, ginseng extracts significantly prolonged the step down latency and increased the percentage of old rats reaching the learned criterion; no such significant results were obtained for the young rats. At a higher dose of 50mg/kg, significant results were obtained for the younger rats at the last training day for step down latency and at 24-hour retention testing ( $p < 0.001$ ). However, at a higher dose of 150 mg/kg, no significant results were obtained. Thus this experiment demonstrated two important points: first, that ginseng had a greater effect at lower doses on the older rats versus the younger rats; and second that there is a possible "bellshaped dose-effect dependency" in drugs with cognition-enhancing results, and these values are important in defining their "therapeutic window". According to the authors, the real values for ginseng used for facilitation of learning and improvement of memory are still being debated. (1)

#### Other Cognition-Enhancers in Ginseng?

The favorable effect of ginsenosides on learning and memory in rats has therefore been established through various experimental methods. It has recently been discovered that a polysaccharide fraction of ginseng root may also improve learning and memory in rats. Lyubimov et al observed the latency of development of a conditioned active escape response (CAER) to determine the effects of a polysaccharide fraction (PSF) of *Panax ginseng* on rats in a shuttle box with a one-sided escape route subjected to a constantly varying gradient of aversive stimuli (electrical shock). Two regimes of presentation were used: easy (unconditioned stimulus immediately follows conditioned stimulus), and hard (conditioned stimulus followed by interval and then by unconditioned stimulus). In the easy regime, a dose of 10mg/animal of PSF produced significant ( $p < 0.05$ ) improvement in mean escape times compared to the controls. In the hard regime, the greatest improvement in escape time was seen with a dosage of 5mg/animal of PSF, although this value does not appear to be statistically significant. (5)

Another interesting result from this study was that rats given PSF demonstrated the presence of hyperalgesia (excessive sensitivity to pain). Thus the authors assert that one reason for the accelerated-learning effect in animals administered PSF may be due to CAER's dependence on pain reinforcement (5). In contrast, the study by Petkov et al mentioned earlier studied the effects of ginsenosides on a variety of behavioral methods, differing in their physiological characteristics; the same results (increased learning and memory) obtained from these differing methods allowed the authors to exclude the possibility that non-specific factors (such as responses to painful stimuli) were responsible for the accelerated learning (1). Since the same experiments have not been done with PSF, it cannot be conclusively stated that PSF has a beneficial affect on learning and memory; in this instance, the results may better be explained by an increased sensitivity to painful stimulation. Further experimentation is therefore warranted.

## Conclusions

All of the experiments cited in this paper have been studies done on rats. These studies have established the mechanism of action of ginseng on the brain, as well as provided some proof of the cognition-enhancing effects of ginsenosides and total ginseng extracts on learning and memory in rats. Ideally, these same results would accurately extrapolate to humans. However, I could not find any human trials done to assay the efficacy of ginseng on learning and memory. HerbTech, a health food distributor, claims on its Internet website that its "Remember-FX" capsule, containing ginseng extracts, has proven beneficial effect on humans, both in normal students and older adults. They claim an increase in "memory index" (determined from a series of memory tests) from 3.7 to 13.7 in young students and from -5.6 to 10.5 in an older age group with the administration of Remember-FX (6). The study, though, lacked scientific validity, and there is no scientific proof, published in journals, supporting this claim. Nonetheless, one incontrovertible human trial has passed the test of time: for thousands of years, Chinese medicine has prescribed ginseng to treat the effects of aging on the brain and on memory. The job of science is to isolate the chemical that is exerting this beneficial effect.

Science has already validated that ginseng acts at the central cholinergic centers of the brain as a nootropic agent in memory deficient rats. More recent evidence extends this benefit to normal young as well as older rats. Now, the focus of ginseng has turned to its synergistic effects with other Chinese herbs in traditional Chinese medicinal prescriptions (such as DX-9386, containing ginseng, polygala, acorus and hoelen) as well as novel herbal prescriptions (such as S-113m, containing *Biota orientalis*, *Panax ginseng* and *Schisandra*). Both of these herbal prescriptions increase learning and memory in learning impaired mice. DX-9386 has a direct action on the hippocampus (7). S-113m has a beneficial effect through some direct action on the learning and memory processes (8,9). Efforts are being made to determine the mechanism of action of the prescriptions. These prescriptions might be useful for treating physiological aging and age-related memory deficits in humans. Thus, I believe it is only a matter of time before science confirms ginseng's beneficial effect on humans, young and old.

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