The Efficacy of Ginseng on the Cognitive Function

Jae-Hyeok Heo¹ and Manho Kim²*

¹Department of Neurology, Seoul Medical Center, Seoul, Korea
²Department of Neurology, Seoul National University Hospital, Seoul, Korea
(Received June 3, 2009; Revised September 4, 2009; Accepted September 11, 2009)

Abstract: Ginseng is one of the most popular herbs throughout the world. Ginsenosides, the active constituent of ginseng, have been suggested to have diverse effects on cardiovascular, immune, mood and endocrine systems as well as cognitive performance. Many studies have revealed the beneficial effect of ginseng on cognition in normal human subjects and in animals. Recently, a few studies showing effects of ginseng on the patients with Alzheimer’s disease have been reported. However, the underlying mechanism is not clear at this stage and it is still obscure whether ginseng is cognitive stimulant or disease modifying agent. More detailed studies exploring the relationship between clinical efficacy and pathophysiology are required.

Key words: ginseng, ginsenoside, cognition, Alzheimer’s disease

INTRODUCTION

In the industrialized world the elderly population is expanding most rapidly and the prevalence of neurodegenerative disorders has increased significantly accompanied by aging society for the last decade. It is suggested that the number of people with dementia will double every 20 years to 81.1 million by 2040.¹

Because of the limited anti-dementia effect of acetylcholinesterases and the increasing prevalence of Alzheimer’s disease, new disease-modifying or effective cognitive enhancing drug is needed.

Ginseng is one of the most widely used herbal medicines in the world. The ginsenosides are thought to have anti-neoplastic, anti-oxidant or anti-stress.² Moreover, pharmacological effects of ginseng have been reported in the central nervous system, cardiovascular, endocrine, and immune systems.

Now, we will review the characteristics of ginseng and its effect on cognitive function as well as suggested working mechanism.

ACTIVE CONSTITUENTS OF GINSENG

Ginseng used in most studies were Panax ginseng (Asian ginseng), Panax quinquefolius (American ginseng), and Panax japonicus (Japanese ginseng) among seven major species of ginseng distributed in East Asia, Central Asia, and North America.³ Ginsenosides have been regarded as the active constituent of ginseng and may be classified into three major groups, the panaxadiol (Rb₁, Rb₂, Rb₃, Rc, Rd, Rg₃, Rh₂, Rs₁), panaxatriol (Re, Rf, Rg₁, Rg₂, Rh₁), and oleanolic acid groups (Ro), on the basis of the chemical structures of their saponins.³,⁴ Ginseng has both stimulatory and inhibitory effects on the central nervous system and modulate neurotransmission.³ Among them, Rb₁ and Rg₁ play a major role in these effects and Rb₁ is often used to represent the panaxadiol ginsenosides, whereas Rg₁ represents the panaxatriol ginsenosides.² The different species of ginseng have different relative amounts of panaxadiols and panaxatriols. Panax quinquefolius has the smallest Rg₁/Rb₁ ratio and Panax ginseng has the largest one, which suggested the possibility of different effect between the species of ginseng.²

POSSIBLE MECHANISMS IN NOOTROPIC EFFECTS

Several hypothesis are regarded as mechanisms underlying the nootropic effects of ginseng.⁵

First, the cholinergic system in the central nervous system might be potentiated by ginsenoside. Both Rg₁ and Rb₁ enhanced cholinergic system’s function through increas-
ing density of central M-cholinergic receptors and increasing level of Ach in the CNS by enhancement on choline acetyltransferase activity and inhibition on acetylcholine esterase activity.\(^6\)

Second, Liu et al. found that Rg\(_1\) increased the expression of c-fos gene, a marker of neuronal activity, in both young and old rats and cyclic adenosine monophosphate (cAMP) level in rat hippocampus, which suggested that ginsenoside might interfere with immediate early genes.\(^7\)

Third, because apoptosis is essential in physiological processes such as development, differentiation, and aging, pharmacological manipulation of that is important to prevent or treat many illnesses. In vivo study, Rg\(_1\) have inhibitory effect on NOS activity which provide an explanation for its anti-apoptotic and anti-aging function.\(^8\)

Fourth, ginsenoside has been suggested to modulate synaptic plasticity, which is regarded as one of the most essential mechanisms in the process of learning and memory. Yang et al. found that administration of Rg\(_1\) and Rb\(_1\) in weaning mice significantly increased the thickness of cortex and density of synapses in the hippocampal CA3 region.\(^9\)

Fifth, Shen et al. reported that ginsenoside Rg\(_1\) enhanced the proliferation of hippocampal progenitor cells in rodents.\(^10\) In the study, incubation of NPCs with ginsenoside Rg\(_1\) resulted in significant increase in absorbency value, \(^3\)H-thymidine incorporation and the number of proliferating progenitor cell spheres. Moreover, two weeks of Rg\(_1\) administration led to marked enhancement of the number of dividing cells in the hippocampus of adult mice.

In addition, a neuroprotective mechanisms, including a defence against overproduction of NO, glutamate and kainic acid-induced excitotoxicity, free radical-mediated lipid peroxidation, and a blockade of calcium overinflux into neurons, has also been reported.\(^11\)-\(^14\)

**ANIMAL STUDIES**

To evaluate the efficacy of ginsenosides on various memory-impairment animal models have been used.

Tohda C et al. revealed that M\(_4\), a metabolite from ppd-type saponins, and Rb\(_1\) improve memory disorder in a mouse model of Alzheimer’s disease.\(^15\) They also suggested that M\(_4\) has axonal extension activity in degenerated neurons and synaptic loss induced by A\(_\beta\).

In aged rats, the non-saponin fraction of red ginseng has been suggested to have the effects on learning deficits.\(^16\) In the study, performance of the aged rats was significantly impaired in the place-learning task (PLT) compared to young rats and treatment with non-saponin significantly ameliorated deficits in place-navigation learning in the aged rats in the PLT. They proposed that improvement of spatial learning in aged rats might be attributed partly to augmentation of long-term potentiation (LTP) in the CA3 subfield by the non-saponin fraction.

Rg\(_3\) and Rg\(_5\)/Rk\(_1\) has been regarded to have an enhancing effects on psychomotor activity in a mouse model of amyloid \(\beta\) accumulation (Tg2576 mice) and neuroprotective effects inhibiting the excitotoxic neuronal damage induced by glutamate or NMDA.\(^17\) This theory is supported by previous study, which reported that influx of NMDA or glutamate-induced Ca\(^{2+}\) was inhibited by ginsenosides.\(^18\)

Similarly, Wang et al., in an investigation into the effects of ginseng saponins on \(\beta\)-amyloid-induced amnesia in rats, found that chronically treating the rats with ginseng saponins resulted in a dose-related improvement against \(\beta\)-amyloid-induced amnesia; a significant reversion was observed at the highest ginseng saponin dose (80 mg/kg/day).\(^19\)

The amyloid \(\beta\)-reducing capacity of ginsenosides have been reported in cell-based assays and in vivo in a mouse model.\(^20\) In the study, even a single, orally administered dose of ginsenoside Re, Rg\(_1\) or Rg\(_3\), results in a significant reduction of the amount of A\(_\beta\) detected in the brains of these animals at 18 hours postdrug administration. These results, which suggested the capacity of ginseng on reducing A\(_\beta\) levels, are in line with the many positive reports on learning and memory in animal models.

**HUMAN STUDIES**

**Normal human subjects**

Several studies addressed the effects of ginseng in healthy populations. These include a study by D’Angelo et al. who attempted to assess the effect of ginseng on motor performance, auditory and visual simple reaction times, choice reaction times, attention, mental arithmetic performance, and logical deduction performance.\(^21\) The study involved 32 healthy young subjects who received either standardized preparation of Korean ginseng (G115; 100 mg) twice a day for 12 weeks or placebo capsules. There was a favorable effect of G115 relative to baseline performance in attention (cancellation test), processing auditory reaction time, which implied the effects of ginseng on certain psychomotor functions in healthy sub-
jects. Another study was by Sorensen et al. and included 112 healthy subjects over 40 years who were given either 400 mg of ginseng extract or placebo daily for 8-9 weeks.\textsuperscript{22} Tests included the finger tapping test, auditory and visual simple reaction time tests, a 5-min letter and symbol cancellation test, a verbal fluency test, a Logical Memory and Reproduction Test, the Rey-Ostreich Complex Figure Test, and a computerized Wisconsin Card Sort Test. The ginseng group showed significant performance improvements in the fastest trials of the auditory simple reaction time test, and on the Wisconsin Card Sort Test, a putative test of ‘executive’ function. Recently, Reay et al. demonstrated that Panax ginseng possess glucoregulatory properties and can enhance cognitive performance with the study involving 27 healthy young adults, who completed a 10 minute ‘cognitive demand’ test battery at baseline, consumed capsules containing either ginseng (extract G115) or a placebo and 30 minutes later a drink containing glucose or placebo.\textsuperscript{23}

\section*{Patients with Alzheimer’s disease}

Though many studies have investigated the effects of ginseng on cognitive function in animals and healthy individuals, only a few studies have reported its clinical effects in patients with Alzheimer’s disease.

The first study, by Lee et al. involved 97 patients with Alzheimer’s disease who were randomly assigned to the ginseng (n=58) or the control group (n=39).\textsuperscript{24} In the study, ginseng treatment improved the cognitive subscale of Alzheimer disease assessment scale (ADAS) and mini-mental status examination (MMSE), and discontinuing ginseng declined the improved ADAS and MMSE scores of ginseng group to the levels of the control group.

The second study was by Heo et al. and involved 61 patients with Alzheimer’s disease who were given either Korean red ginseng or not.\textsuperscript{25} In this study subjects were randomly assigned to one of the following treatment groups: low-dose KRG (4.5 g/day, n=15), high-dose KRG (9 g/day, n=15), or control (n=31). The patients in the high-dose KRG group showed significant improvement on the ADAS and Clinical Dementia Rating (CDR) after 12 week study period compared to control group.

\section*{CONCLUSIONS}

Although AD had already been described about 100 years ago and enormous research efforts had been given, only a few symptomatic treatment options exist at present. Current medications such as several acetylcholinesterase inhibitor and NMDA receptor antagonist do not prevent or reverse the disease cascade, and provide only modest symptomatic benefits. The amyloid beta reduction was reported in AD model transgenic mice with active vaccination with Aβ peptide at 1999.\textsuperscript{26} However, the clinical trials of active vaccination treatment for AD were halted due to the development of meningoencephalitis in some treated patients.

Clinical trials suggested to modify the disease process are also under investigation, and there is a place for herbal medicine. Currently some materials derived from a particular plant, such as ‘curcumin’ from ‘Curcuma longa Linn’ and ‘Huperzine A’ from ‘Huperzia serrata’, are actively investigated.\textsuperscript{27} Actually, Galantamine, an alkylidene cholinesterase inhibitor approved by FDA and commercially used, is originally derived from European ‘daffodils’ or common ‘snowdrops’.

Ginseng has positive effect on cognitive improvement in healthy persons and Alzheimer’s patients, which is supported by the various in vitro and in vivo experimental studies. Moreover, there are no known major adverse effects associated with Ginseng or ginsenosides. These warrant further large-scale, long-term rigorous studies to confirm the clinical effect of ginseng on cognitively impaired disorders, such as Alzheimer’s disease and other neurodegenerative disease.

\section*{ACKNOWLEDGEMENT}

This work was supported by grants from the Korean Society of Ginseng, Korea Health 21 R&D Project, Ministry of Health & Welfare (A080448), FPR08K1301-02210, WCU-Neurocytomics program (800-20080848) and the Interdisciplinary Research Initiatives Program by College of Medicine, Seoul National University (2008).

\section*{REFERENCES}

4. Tachikawa E, Kudo K, Harada K, Kashimoto T, Miyate Y.