J. Ginseng Res.
Vol. 33, No. 3, 161-164 (2009)

Review

The Efficacy of Ginseng on the Cognitive Function

Jae-Hyeok Heo[1] and Manho Kim[2]*

[1]*Department of Neurology, Seoul Medical Center, Seoul, Korea*
[2]*Department 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-dementic 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 (Rb_1, Rb_2, Rb_3, Rc, Rd, Rg_3, Rh_2, Rs_1), panaxatriol (Re, Rf, Rg_1, Rg_2, Rh_1), 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, Rb_1 and Rg_1 play a major role in these effects and Rb_1 is often used to represent the panaxadiol ginsenosides, whereas Rg_1 represents the panaxatriol ginsenosides.[2)] The different species of ginseng have different relative amounts of panaxadiols and panaxatriols. Panax quinquefolius has the smallest Rg_1/Rb_1 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 Rg_1 and Rb_1 enhanced cholinergic system's function through increas-

* Corresponding author. E-mail: kimmanho@snu.ac.kr
Phone: +82-2-2072-2193, Fax: +82-2-3672-7553

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 monophosphophate (cAMP) level in rat hippocampus, which suggested that ginseoside might interfere wth 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, ginsenoisde 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 rodent.[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_1, 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_1 has axonal extension activity in degenerated neurons and synaptic loss induced by Aβ.

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 β 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 β-amyloid-induced amnesia in rats, found that chronically treating the rats with ginseng saponins resulted in a dose-related improvement against β-amyloid-induced amnesia; a significant reversion was observed at the hightest ginseng saponin dose (80 mg/kg/day).[19)]

The amyloid β-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 Aβ detected in the brains of these animals at 18 hours postdrug administration. These results, which suggested the capacity of ginseng on reducing Aβ 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.[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 ReproductionTest, the Rey-Ostreith 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.[23]

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).[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.[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.

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 Aß peptide at 1999.[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.[27] Actually, Galantamine, an alkaloid 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 Alzhiemer'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.

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).

REFERENCES

1. Ferri CP, Prince M, brayne, C, Brodaty H, Fratiglioni L, Ganguli M, Hal K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Alzheimer's Disease International.: Global prevalence of dementia: a Delphi consensus study. Lancet 366: 2112-2117 (2005)
2. Lian XY, Zhang Z, Stringer JL. Protective effects of ginseng components in a rodent model of neurodegeneration. Ann Neurol. 57: 642-648 (2005)
3. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 58: 1685-1693 (1999)
4. Tachikawa E, Kudo K, Harada K, Kashimoto T, Miyate Y,

Kakizaki A, Takahashi E. Effects of ginseng saponins on responses induced by various receptor stimuli. Eur J Pharmacol. 369: 23-32 (1999)
5. Cheng Y, Shen LH, Zhang JT. Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. Acta Pharmacol Sin. 26: 43-49 (2005)
6. Zhang JT, Liu Y, Qu ZW, Zhang XL, Xiao HL. Influence of ginsenoside Rb1 and Rg1 on some central neurotransmitter receptors and protein biosynthesis in mouse brain. Acta Pharm Sin. 23: 12-16 (1988)
7. Liu M, Zhang JT. Influence of ginsenoside Rb1 and Rg1 on some central neurotransmitter receptors and protein biosynthesis in mouse brain. Acta Pharmacol Sin. 17: 171-174 (1996)
8. Chen XC, Chen Y, Zhu YG, Fang F, Chen LM. Protective effect of ginsenoside Rg1 against MPTP-induced apoptosis in mouse substantia nigra neurons. Acta Pharamcol Sin. 23: 829-834 (2002)
9. Ying Y, Zhang JT, Shi CZ, Qu ZW, Liu Y. Study on the nootropic mechanism of gnsenoside Rb1 and Rg1 influence on mouse brain development. Acta Pharm Sin. 29: 241-245 (1994)
10. Shen LH, Zhang JT. Ginsenoside Rg1 promotes proliferation of hippocampal progenitor cells. Neurol Res. 26: 422-428 (2004)
11. Kim HJ, Woo DS, Lee G, Kim JJ. The relaxation effects of ginseng saponin in rabbit corporal smooth muscle: is it a nitric oxide donor? Br J Urol. 82: 744-748 (1998)
12. Liao B, Newmark H, Zhou R. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. Exp Neurol. 173: 224-234 (2002)
13. Huong NT, Matsumoto K, watanabe H. The antistress effect of majonoside-R2, a major saponin component of Vietanamese ginseng: neuronal mechanisms of action. Methods Find Exp Clin Pharrmacol. 20: 65-76 (1998)
14. Liu M, Zhang JT. Protective effects of ginsenoside Rb1 and Rg1 on cultured hippocampal neurons. Acta Pharm Sin. 30: 674 (1995)
15. Tohda C, Matsumoto N, Zou K, Meselhy MR, Komatsu K. Aß(25-35)-induced memory impairment, axonal atrophy, and synaptic loss are ameliorated by M1, a metabolite of protopananxadiol-type saponins. Neuropsychopharmacol. 29: 860-868 (2004)
16. Kurimoto H, Nishijo H, Uwano T, Yamaguchi H, Zhong YM, Kawanishi K, Ono T. Effects of nonsaponin fraction of red ginseng on learning deficits in aged rats. Physiol Behav. 82: 345-355 (2004)
17. Bao HY, Zhang J, Yeo SJ, Myung CS, Kim HM, Kim JM, Park JH, Cho J, Kang JS. Memory enhancing and neuroprotective effects of selected ginsenosides. Arch Pharm Res. 28: 335-342 (2005)
18. Kim S, Ahn K, Oh TH, Nah SY, Rhim H. Inhibitory effects of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem Biophys Res Commun. 296: 247-254 (2002)
19. Wang LC, Wang B, Ng SY, Lee TF. Effects of ginsengsaponins on beta-amyloid-induced amnesia in rats. J Ethnopharmacol. 103: 103-108 (2006)
20. Chen F, Eckman EA, Eckman CB. Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides. FASEB J. 20: 1269-1271 (2006)
21. D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E, Lecchini S, Frigo GM, Crema A. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. J Ethnopharmacol. 16: 15-22 (1986)
22. Sorensen H, sonne J. A double masked study of the effects of ginseng on cognitive functions. Curr Ther Res. 57: 959-968 (1996)
23. Reay JL, Kennedy DO, Scholey AB. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol. 20: 771-781 (2006)
24. Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzhimer Disease. Alzheimer Dis Assoc Disord. 22: 222-226 (2008)
25. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY, Kim M. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. Eur J Neurol. 15: 865-868 (2008)
26. Schenk D, barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Leiberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandevert C, Walker S, Wogulis M, Yednock T, Games D, Seubert P. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400: 173-177 (1999)
27. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Demen. 21: 113-118 (2006)