J. Ginseng Res.
Vol. 31, No. 1, 51-53 (2007)

Cognitive improvement by ginseng in Alzheimer's disease

Soon-Tae Lee, MD[a,b,c], Kon Chu, MD[a,b], Jeong-Min Kim, MD[a,b], Hyun-Jeong Park, BS[a] and Manho Kim, MD, PhD[a,b,#]

[a]*Department of Neurology, Clinical Research Institute, Seoul National University Hospital, Seoul, South Korea*
[b]*Program in Neuroscience, Seoul National University, Seoul, South Korea*
[c]*Center for Alcohol and Drug Addiction Research, Seoul National Hospital, Seoul, South Korea*
[#]*Department of Neurology, Seoul National University Hospital 28, Youngon-Dong, Chongno-gu, Seoul 110-744, South Korea*
(Received November 11, 2006; Accepted March 5, 2007)

Abstract : Ginseng shows protective and trophic effects in neurodegenerative diseases in experimental models, and showed cognitive improvement in normal population. To investigate the efficacy of ginseng in patients with Alzheimer's disease, patients, who met NINDS-ADRDA criteria for AD were studied Subjects were randomly assigned to ginseng group and control group, and ginseng group was treated with Korean white ginseng powder (4.5 g/day) for 12 weeks. Efficacy variables included changes in mini-mental status exam (MMSE) and cognitive subscales of Alzheimer's disease assessment scale (ADAS-cog) at 4 weeks and 12 weeks. Baseline MMSE and ADAS scores showed no difference between the two groups. Results showed that ginseng improved ADAS-cog compared to the control group at 12 weeks ($p<0.05$). MMSE was also increased by ginseng treatment compared to the control at 12 weeks ($p<0.01$). This study suggests the symptomatic efficacy of ginseng in patients with Alzheimer's disease.

Key words : Ginseng, Alzheimer's disease, mini-mental status exam (MMSE), Alzheimer's disease assessment scale (ADAS)

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia. AD shows a progressive decline of memory and intellectual abilities, which eventually becomes severe enough to interfere with functioning in daily living, the overall quality of life, and ultimately leads to death. Although pharmacologic treatments are currently approved for treating mild- to moderate AD using acetylcholinesterase inhibitors (ACEI) and one NMDA antagonist, memantine, for advanced AD, the therapeutic efficacies need to be further improved.

Ginseng has been used to treat a wide variety of medical conditions, including age-related memory impairment for a long time. Pharmacologic effects of ginseng and its component have been demonstrated in the CNS and in cardiovascular, endocrine and immune system.[1] Recent experimental evidences suggest protective and tropic effects of ginseng in AD and ginseng was suggested to be beneficial in relation to symptomatic treatment and neuroprotection in age-associated cognitive disorders.[2]

Thus, we investigated whether ginseng treatment can improve the cognitive function of AD patients.

METHODS

Subjects and methods.

Study was designed as randomized, prospective, and open-label study. Ninety seven consecutive patients (aged 47 to 83 years, mean=66.1±9.1), who met NINDS-ADRDA criteria for AD[3] were included. After subjects were randomly assigned to ginseng group and control group, ginseng group were additionally treated with Korean white ginseng powder (*Panax ginseng*; n=58). Both Ginseng group and control group continued the conventional therapy (control group, n=39) for 12 weeks. At 4 weeks, 91 patients (ginseng group=54, control group=37) were re-evaluated and included in the efficacy analysis. Efficacy variables included changes from baseline scores of mini-mental status exam (MMSE) and Alzheimer's disease assessment scale - cognitive subscale (ADAS-cog scored

[#] To whom correspondence should be addressed.
(Tel) +82 2 2072 2193; (Fax) +82 2 3672 7553
(E-mail) kimmanho@snu.ac.kr

0-70) at 4 weeks and 12 weeks.

All eligible patients (or a legal representative) and the caregiver provided written informed consent to participate in the study, which was approved by institutional review boards of Seoul National University Hospital.

Statistical analysis.

Efficacy analyses were done on an intention-to-treat (ITT) basis. Changes from baseline scores of ADAS and MMSE showed normal distribution. Inter-group comparisons for changes of ADAS and MMSE were performed using the Student-t test. *P* values are two-tailed and statistical significance was accepted for p values<0.05.

RESULTS

A total of 82 patients (50 ginseng, 32 control) completed all 12 weeks of treatment. Baseline characteristics including sex and mean age, as well as the baseline ADAS-cog and MMSE score were not different between ginseng and control groups (Baseline ADAS-cog: 20.8± 8.5 in the control group, 21.9±9.3 in the ginseng group; Baseline MMSE: 22.0±3.9 in the control group, 21.5±3.8 in the ginseng group). The proportion of patients withdrawn did not differ significantly for control group (17.9%) versus ginseng group (13.9%) (p=0.581, Chi-square test). No treatment emergent condition and no treatment-related death were reported.

Efficacy analysis showed that ginseng group improved ADAS-cog score compared to control group at 4 weeks (Changes from baseline, Control = +1.1±3.9, Ginseng group = -4.2±4.1, p=0.012), and at 12 weeks (control = -0.45±6.0, Ginseng group= -3.3±5.3, p= 0.029)

MMSE also showed improvement in ginseng group. Baseline MMSE of were 22.0±3.9 in control group, and 21.5±3.7 in ginseng group (p=0.435). At 4 weeks, ginseng group showed an improvement of MMSE by 1.0±2.4 points from baseline, while control group changed by -0.58±2.4 (p=0.033). At 12 weeks, ginseng group improved by 1.8±2.8 points, while control group changed by -0.03±3.1 (p=0.009).

DISCUSSIONS

In this study, we investigated the effect of ginseng treatment on the cognitive function of AD, and found that administration of ginseng to AD patients can further improve the cognitive function scales including ADAS-cog and MMSE.

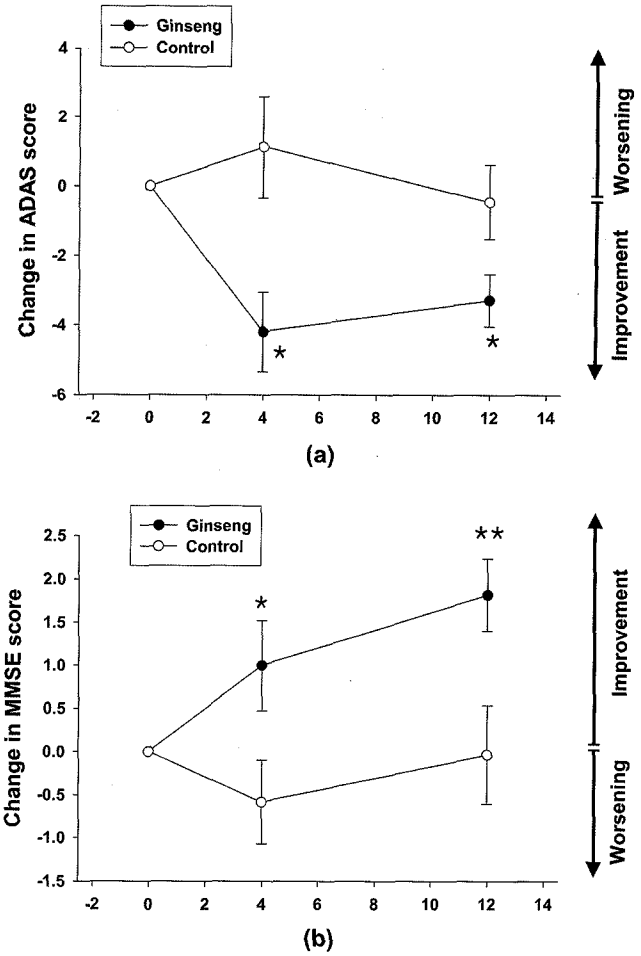

Fig. 1. Changes in outcome variables. During 12 weeks of ginseng treatment, ginseng improved ADAS-cog (A) and MMSE scores (B). *p<0.05, **p<0.01 vs control group.

The major active constituents of the *Panax* genus are also thought to be saponins, in this case species-specific triterpenoid glycosides known as ginsenosides, of which over 30 individual examples have been identified.[4] Among the variable ginsenosides, Rb1 is often used to represent the panaxadiol ginsenosides, whereas Rg1 represents the panaxatriol ginsenosides.[5] The different species of ginseng have been shown to have different relative amounts of panaxadiols and panaxatriols.[1,5] American ginseng has the smaller ratio of Rg1/Rb1, and Asian ginseng has the larger ratio of Rg1/Rb1.[5] We used Asian ginseng, because Rg1 is reported to be a neuronal stimulant[6] and Some evidence shows that ginsenosides can stimulate the cognitive function. Ginsenosides have the ability to intercalate into the plasma membrane due to their amphiphilic in nature, can alter membrane function

and secondarily alter membrane receptor function.[1,5] Ginseng has high agonistic affinity for the nicotinic receptor.[2]

In addition, neuroprotective and neuro-regenerative property of ginsenosides are also well investigated. Gingseng showed efficacy in reduction of Aâ level[7,8], and the associated memory loss.[9,10,11] Ginsenosides have antioxidant properties and the ability to scavenge free radicals.[12,13,5] Ginsenosides can increase proliferation and differentiation of neural progenitor cells in dentate gyrus of hippocampus of normal adult mice.[14] Increase of expression of brain derived neurotrophic factor, Bcl-2 and antioxidant enzyme, enhanced new synapse formation, inhibition of apoptosis and calcium overload are also important neuron protective factors induced by ginsenosides.[14,15]

The present study, however, presents little about the mechanistic aspect. In addition, further studies are warranted because of the following reasons. First, dose-response effect should be analyzed. Second, more long-term efficacy of ginseng or the symptom change with ginseng withdrawn should be verified. In addition, given the systemic effect of ginseng, appropriate blood test will increase the safety profile of ginseng.

In summary, ginseng treatment was safe and effective in AD patients. Although it needs further placebo-controlled trials to conclude the efficacy, ginseng may be the additional option for AD treatment.

REFERENCES

1. Attele, A.S., Wu, J.A. and Yuan, C-S.: Ginseng pharmacology: multiple constituents and multiple actions. *Biochem Pharmacol* **58**, 1685-1693 (1999).
2. Lewis, R., Wake, G., Court, G., Court, J.A., Pickering, A.T., Kim, Y.C. and Perry, E.K.: Non-ginsenoside nicotinic activity in ginseng species. *Phytother Res.* **13**, 59-64 (1999).
3. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E.M.: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*; **34**, 939-944 (1984).
4. Tachikawa, E., Kudo, K., Harada, K., Kashimoto, T., Miyate, Y., Kakizaki, A. and Takahashi, E.: Effects of ginseng saponins on responses induced by various receptor stimuli. *Eur J Pharmacol.* **369**, 23-32 (1999).
5. Lian, X.Y., Zhang, Z. and Stringer, J.L.: Protective effects of ginseng components in a rodent model of neurodegeneration. *Ann Neurol.* **57**, 642-648 (2005).
6. Li, W. and Fitzloff, J.F.: HPLC determination of ginsenosides content in ginseng dietary supplements using ultraviolet detection. *J Liq Chromatogr Relat Technol* **25**, 2485-2500 (2002).
7. Chen, F., Eckman, E.A. and Eckman, C.B.: Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides. *FASEB J.* **20**, 1269-1271 (2006).
8. Joo, S.S. and Lee, do I.: Potential effects of microglial activation induced by ginsenoside Rg3 in rat pri ary culture: enhancement of type A Macrophage Scavenger Receptor expression. *Arch Pharm Res.* **28**, 1164-1169 (2005).
9. Tohda, C., Matsumoto, N., Zou, K., Meselhy, M.R. and Komatsu, K.: Abeta(25-35)-induced memory impairment, axonal atrophy, and synaptic loss are ameliorated by M1, A metabolite of protopanaxadiol-type saponins. *Neuropsychopharmacology.* **29**, 860-868 (2004).
10. Tohda, C., Kuboyama, T. and Komatsu, K.: Search for natural products related to regeneration of the neuronal network. *Neurosignals.* **14**, 34-45 (2005).
11. Wang, L.C., Wang, B., Ng, S.Y. and Lee, T.F.: Effects of ginseng saponins on beta-amyloid-induced amnesia in rats. *J Ethnopharmacol.* **103**, 103-108 (2006).
12. Lim, J.H., Wen, T.C., Matsuda, S. *et al.*: Protection of ischemic hippocampal neurons by ginsenoside Rb1, a main ingredient of ginseng root. *Neurosci Res* **28**, 191-200 (1997).
13. Kitts, D.D., Wijewickreme, A.N. and Hu, C.: Antioxidant properties of a North American ginseng extract. *Mol Cell Biochem* **203**, 1-10 (2000).
14. Cheng, Y., Shen, L.H. and Zhang, J.T.: Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. *Acta Pharmacol Sin.* **26**, 143-149 (2005).
15. Salim, K.N., McEwen, B.S. and Chao, H.M.: Ginsenoside Rb1 regulates ChAT, NGF and trkA mRNA expression in the rat brain. *Brain Res Mol Brain Res.* **47**, 177-182 (1997).