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SHORT COMMUNICATION

An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease

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Background and purpose: Ginseng is one of the most popular herbs worldwide. Ginseng has various medical applications, and it seems to have significant effects as a cognition-enhancing drug. In this study, we examined the efficacy of Korean red ginseng (KRG) as an adjuvant therapy to conventional anti-dementia medications in patients with Alzheimer's disease. *Methods:* The trial was designed as a 12-week randomized study. Sixty-one patients (24 males and 37 females) with Alzheimer's disease 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 Alzheimer's Disease Assessment Scale (ADAS), Korean version of the Mini-Mental Status Examination (K-MMSE) and Clinical Dementia Rating (CDR) scale were used to assess the change in cognitive and functional performance at the end of the 12-week study period. *Results:* The patients in the high-dose KRG group showed significant improvement on the ADAS and CDR after 12 weeks of KRG therapy when compared with those in the control group ($P = 0.032$ and 0.006 respectively). The KRG treatment groups showed improvement from baseline MMSE when compared with the control group (1.42 vs. −0.48), but this improvement was not statistically significant. *Conclusions:* KRG showed good efficacy for the treatment of Alzheimer's disease; however, further studies with larger samples of patients and a longer efficacy trial should be conducted to confirm the efficacy of KRG.

Introduction

Ginseng root has been used for over 2000 years in many Asian countries. Although many studies have attested to the cognition-enhancing effects of ginseng in animals and healthy individuals, there is no direct evidence that ginseng therapy can improve cognitive function in patients with Alzheimer's disease. In the present study, we analysed the effects of Korean red ginseng (KRG) on cognitive function in patients with Alzheimer's disease.

Methods

The diagnostic criteria for probable Alzheimer's disease were consistent with the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) [1]. The inclusion criteria were age older than 50 years and baseline Mini-Mental State Examination score of ≥10 and ≤26. Patients were excluded if they had a history of psychiatric disorder, seizure disorder, or a medical condition that would limit the completeness of the study. Patients were also excluded if they had cognitive impairment because of stroke, hypoxic brain damage, cerebral neoplasia, infection, and medications such as antidepressants or psychoactive drugs. Sixty-one patients, aged 50–80 years, were diagnosed with probable Alzheimer's disease according to the NINDS-ADRDA criteria and enrolled in the present study. All participants had been treated with either donepezil (5–10 mg/day), galantamine (16–24 mg/day), memantine (20 mg/day) or rivastigmine (6–12 mg/day) at least for 6 months before randomization. The patients were enrolled in three treatment groups: low-dose KRG (4.5 g/day), high-dose KRG (9 g/day), and control, with the use of a 1:1:2 randomization ratio. KRG (total powder capsule, 6-year-old root, Korea Ginseng Corporation, Korea) was administered at a dose of 4.5 g/day ($n = 15$) or 9 g/day ($n = 15$) as adjunctive therapy for 12 weeks [2]. Ginsenosides, which are composed of Rb1 (1.96%), Rb2 (2.18%), Rc (1.47%), Rd (0.72%), Re (1.11%), Rf (0.24%), Rg1 (0.49%), Rg2 (0.13%), Rg3 (0.12%), Rh1 (0.12%) and Rh2 (0.003%), are the active constituent of KRG and account for 8.54% of the herb [3]. The 31 subjects who

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did not receive KRG were compared with those in the KRG groups. Cognitive functioning was assessed using the Alzheimer's Disease Assessment Scale (ADAS), the Korean version of the Mini-Mental Status Examination (K-MMSE) and Clinical Dementia Rating (CDR) scale before and 12 weeks after the administration of KRG.

All subjects provided written informed consent to participation in this study. The study was approved by the Institutional Review Board of Seoul National University Hospital. The data are expressed as mean ± SD or as numbers (percentages). The changes from baseline on the ADAS and MMSE showed a normal distribution. Inter-group comparisons of changes in ADAS and MMSE Scores were performed using the Student's *t*-test, and the test was not specified in these cases. The frequencies of side effects and withdrawal from the study were compared using Fisher's exact test. All *P*-values are two-tailed, and statistical significance was accepted for *P*-values < 0.05.

Results

There was no difference in baseline characteristics, including age ($P = 0.804$), gender ($P = 0.390$), ADAS-cog ($P = 0.561$), ADAS-non-cog ($P = 0.060$), MMSE ($P = 0.925$), CDR ($P = 0.450$) scores and composition of conventional anti-dementia drugs ($P = 0.308$), between the three treatment groups. Anti-dementic medications used before randomization were continued during the 12 week follow-up period. The patients in the KRG groups showed trends towards improvement on the ADAS-cog ($P = 0.057$) and CDR ($P = 0.037$) when compared with those in the control group. The improvements were significant in the patients treated with 9 g of KRG (Table 1). There was a significant difference in the mean change in ADAS-cog score between the patients treated with 9 g of KRG (−4.02 ± 12.27) and those in the control group (−0.43 ± 5.92). Similarly, there was also a significant difference in the mean change in CDR Score between the patients treated with 9 g of KRG (−0.69 ± 0.90) and those in the control group (−0.07 ± 0.49; $P = 0.0007$ and 0.006 respectively). There was no significant difference in ADAS-non-cog and MMSE Score between the two KRG groups and the controls.

No significant difference in adverse events was found between the three treatment groups ($P = 0.912$). Two patients in the low-dose KRS group complained of feeling feverish and two patients in the high-dose KRS group complained of nausea. Three participants in the control group reported symptoms of nausea, diarrhoea and headache respectively. All the subjects who reported adverse effects withdrew from the study.

Table 1 Change from baseline in neuropsychological testing for the 0–12 weeks

	Control ($n = 31$)			4.5 g/day ($n = 15$)			9 g/day ($n = 15$)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	Baseline	12 weeks	Change
M:F	10:21			6:9			8:7		
Age	66.68 ± 7.53			66.07 ± 6.7			67.73 ± 11.83		
ADAS	27.25 ± 12.55	24.55 ± 11.09	−2.70 ± 8.22	23.59 ± 8.44	20.96 ± 10.06	−2.9 ± 9.09	27.1 ± 9.43	23.33 ± 16.05	−4.85 ± 15.11*
Cog	20.51 ± 9.05	20.08 ± 8.91	−0.43 ± 5.92	19.72 ± 6.77	17.87 ± 8.62	−1.9 ± 6.19	23.03 ± 8.67	19.74 ± 14.11	−4.02 ± 12.27**
Non-cog	6.74 ± 5.14	4.45 ± 3.41	−2.29 ± 5.11	3.87 ± 2.59	3.09 ± 3.30	−1 ± 3.90	4.07 ± 3.32	3.58 ± 2.81	−0.83 ± 4.17
MMSE	21.45 ± 4.43	20.84 ± 4.15	−0.48 ± 2.93	22.07 ± 3.99	23.55 ± 3.75	1.27 ± 3.26	21.43 ± 6.63	23 ± 7.16	1.54 ± 3.64
CDR	1.05 ± 0.28	0.98 ± 0.37	−0.07 ± 0.49	0.97 ± 0.48	0.95 ± 0.61	0 ± 0.55	1.43 ± 1.11	0.77 ± 0.63	−0.69 ± 0.90**

CDR, Clinical Dementia Rating; MMSE, Mini-Mental Status Examination; ADAS, Alzheimer's Disease Assessment Scale; M, male; F, female.
*$P < 0.05$ for comparing mean change with control group; **$P < 0.01$ for comparing mean change with control group.

Discussion

We performed an open-label pilot study to evaluate the adjunctive effect of KRG in Alzheimer's disease and found that additional treatment with KRG improved cognitive performance in patients with Alzheimer's disease. Ginseng extracts exert a wide range of effects on psychomotor performance, including attention, processing and auditory reaction time, in healthy individuals [4]. Red ginseng is produced by steaming raw ginseng. Red ginseng is reported to be more pharmacologically active, and the various biological activities of red ginseng may result from the production of different chemical constituents (Rh4 and Rf2) during the steaming process [5]. The underlying mechanism by which ginseng improves cognitive functioning in patients with Alzheimer's disease is not clearly understood. Several animal studies have shown that ginsenosides, such as Rb1 and Rg1, prevent scopolamine-induced memory deficits [6]. A previous study reported that Rb1 appeared to increase the uptake of choline in central cholinergic nerve endings as well as the release of acetylcholine from hippocampal slices [6]. Both Rb 1 and Rg1 were shown to increase choline acetyltransferase levels, which in turn reduced scopolamine-induced memory deficits. Moreover, several studies have investigated the effectiveness of ginseng on beta-amyloid-induced neurotoxic effects. Ginsenoside Rb 1 and M1 were shown to improve amyloid-induced amnesia in mice [7]. After Rb1 or M1 treatment, there was significant recovery of amyloid-induced axonal atrophy and synaptic loss, which suggested that ginsenoside may aid in the repair of damaged neuronal networks [7]. A recently published study reported that ginseng and ginsenosides are capable of reducing the levels of the Alzheimer's amyloid β peptide in both cell-based assays and in an *in vivo* mouse model of Aβ accumulation after a single administration of ginsenoside compounds [8].

The KRG treatment had significant effects on the global assessment of dementia symptoms, as demonstrated by marked improvement in the ADAS-cognitive subscale. There were no differences in the non-cognitive subscale between the KRG and control groups. There was no difference in MMSE Score between the KRG and control groups in this study, which is probably attributable to the demerits of the MMSE, left hemispheric preponderance and a deficiency in the evaluation of frontal lobe function. The patients who were treated with a high dose of KRG showed significant improvement on the ADAS-cog and CDR when compared with the patients in the control group. Consequently, the clinically relevant and statistically significant improvement in cognitive function with a high dose of KRG suggested that the proper dose of KRG for Alzheimer's disease was around 9 g/day, which was relatively higher than the doses used in other healthy volunteer studies [4]. KRG was well tolerated in patients treated with both the 4.5 g/day and 9 g/day doses of KRG throughout the course of this 12-week study. The overall incidences of adverse effects and withdrawal were small and tolerable.

Our study had several limitations. First, the number of study subjects was small, and the study duration was too short to allow for any conclusions regarding the clinical availability of KRG. Secondly, because this study was not blinded, the possibility of a placebo effect cannot be excluded. Thirdly, because we did not use a detailed neuropsychological test to assess specific brain regions, such as the frontal lobe or temporal lobe, the exact cerebral locations affected by ginseng remain unknown. Fourthly, further studies measuring biological markers are needed to elucidate the links between neuropsychological improvement and pathophysiological alteration.

Nevertheless, our finding that KRG has positive effects on cognitive improvement in Alzheimer's disease warrants further large-scale, long-term studies to confirm the clinical efficacy of adjuvant KRG therapy.

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