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# Effects of Korean red ginseng on human gray matter volume and cognitive function: A voxel-based morphometry study

Eun Namgung[1] | Jungyoon Kim[1,2] | Hyeonseok Jeong[3] | Gahae Hong[1] | Myeongju Kim[1,2] | Rye Young Kim[1,4] | Shinhye Kim[1,2] | In Kyoon Lyoo[1,2,4,5,6]

[1]Ewha Brain Institute, Ewha Womans University, Seoul, South Korea

[2]Department of Brain and Cognitive Sciences, Ewha Womans University, Seoul, South Korea

[3]Department of Radiology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

[4]Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, South Korea

[5]The Brain Institute, University of Utah, Salt Lake City, Utah, USA

[6]Department of Psychiatry, University of Utah, Salt Lake City, Utah, USA

**Correspondence**

In Kyoon Lyoo, Ewha Brain Institute and Department of Brain and Cognitive Sciences, Ewha Womans University, Seoul, South Korea.
Email: inkylyoo@ewha.ac.kr

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## ABSTRACT

**Objective:** We aimed to investigate the effects of Korean red ginseng (KRG) supplementation on gray matter volume of the human brain which could be related to cognitive enhancing effects of KRG.

**Methods:** In this randomized, double-blind, placebo-controlled study, 51 healthy individuals were assigned to receive either KRG (1000 mg/day, $n = 26$) or placebo ($n = 25$) for 8 weeks. Gray matter volume of the whole brain was measured using voxel-based morphometry based on high-resolution T1-weighted magnetic resonance images acquired at baseline and week 8. The standardized composite cognitive scores of executive function, attention, and memory were also evaluated at baseline and week 8. Changes in gray matter volume as well as the composite cognitive scores were compared between the KRG and placebo groups.

**Results:** Following 8 weeks of KRG supplementation, the gray matter volume of the left parahippocampal gyrus increased significantly in the KRG group, relative to the placebo group ($p$ for interaction $< 0.001$). The KRG group also showed greater magnitude of enhancement in the composite cognitive scores relative to the placebo group ($p$ for interaction $= 0.03$).

**Conclusions:** Gray matter volume increase in the parahippocampus may be a key neural change as induced by KRG supplementation, which could be associated with cognitive enhancement.

**KEYWORDS**

brain magnetic resonance imaging, cognition, gray matter, Korean red ginseng, voxel-based morphometry

## 1 | INTRODUCTION

Korean red ginseng (KRG), also known as *Panax ginseng*, is a medicinal plant that has been used as a safe dietary supplement (Choi, 2008). Having ginsenosides as the major active ingredients, KRG has been reported to be potentially beneficial to a wide range of symptoms including physical, psychological, and cognitive dysfunctions (H. S. Kim, Hwang, & Oh, 2000; Kennedy, Scholey, & Wesnes et al., 2001a; Ye, Zhao, & Liu, 2013).

Previous studies have reported that KRG might have nootropic effects, which refer to the cognitive enhancement in healthy individuals (D. Kennedy et al., 2001a; D. Kennedy, Reay, & Scholey,

Eun Namgung and Jungyoon Kim contributed equally.

  

2007; D. O. Kennedy, Scholey, & Wesnes, 2001b, 2002; Reay, Scholey, & Kennedy, 2010). Potential mechanisms by which KRG enhances cognitive function in humans have not been clearly demonstrated. However, animal studies have reported that KRG might induce a series of processes associated with neuroprotection, including reduced oxidative stress, apoptosis, and inflammation, as well as increased neurogenesis (Kim et al., 2016, 2018; Nam et al., 2018; Wan et al., 2017).

Neuroprotection in the human brain may be manifested as gray matter volume increase reflecting new synapse formation, neural proliferation, and differentiation (Ban et al., 2018; Jeon et al., 2016; Woo et al., 2018). As such, we aimed to investigate the mechanisms of the KRG-induced cognitive enhancement in the human brain by measuring gray matter volume before and after 8 weeks of KRG supplementation. Implementing a randomized, double-blind, placebo-controlled design, we also tested cognitive enhancing or nootropic effects of KRG in executive function, attention, and memory, relative to the placebo group.

## 2 | METHODS

### 2.1 | Participants

Healthy individuals aged between 18 and 65 were recruited to the current study. Those with any of the following conditions were excluded: medical conditions requiring active treatments; lifetime Axis 1 psychiatric disorders including psychotic disorders and bipolar disorders; lifetime personality disorders; a history of taking psychiatric medications, including antidepressants, anxiolytics, or sleep medications, within the past 2 months prior to enrollment; an intelligence quotient lower than 80 as assessed using the Wechsler Adult Intelligence Scale (Wechsler, 1955); a history of traumatic brain injury with loss of consciousness; contraindications to brain magnetic resonance imaging (MRI). The study protocol and consent form were approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1005-062-319). The study procedures were also in accordance with the institutional and national guidelines as well as with the Helsinki Declaration revised in 2008. All participants provided written informed consent prior to participation.

### 2.2 | Study design and intervention

Eligibility of the participants was screened using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (SCID-IV; First, 1997) as well as examinations including vital signs, electrocardiograms, and blood tests. Enrolled participants were randomly allocated to receive either KRG or placebo for 8 weeks. The dosage for the supplementation was 1000 mg daily (500 mg/capsule × 2 capsules). Brain MRI and cognitive examinations were performed at baseline and week 8 as outcome measures of the current study.

### 2.3 | MRI acquisition

Brain MRI was performed using a 3.0 Tesla Philips Achieva magnetic resonance scanner (Philips Medical System) equipped with an 8-channel head coil. High-resolution T1-weighted images were acquired using a three-dimensional T1-weighted magnetization-prepared rapid gradient echo imaging sequence with the following parameters: echo time, 3.4 ms; repetition time, 7.4 ms; flip angle, 8°; field of view, 220 × 220 $mm^2$; voxel size, 0.86 × 0.86 × 1 $mm^3$; 180 contiguous sagittal slices.

### 2.4 | Voxel-based morphometry

Voxel-wise analysis of gray matter volume was conducted using the optimized voxel-based morphometry (VBM) implemented in functional magnetic resonance imaging of the brain (FMRIB) Software Library (FSL-VBM; Douaud et al., 2007, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Following the removal of the nonbrain tissues from T1-weighted images, a probabilistic tissue segmentation was performed to classify the images into the gray matter, white matter, and cerebrospinal fluid, using FMRIB's Automated Segmentation Tool. An initial template was created using the partial volume images of the gray matter, through affine registration into the Montreal Neurological Institute (MNI) standard space and by averaging the registered images. The gray matter images in the native space were normalized to the initial template and then averaged to create a final study-specific template. Subsequently, normalization of each gray matter image into the study-specific template was performed. The normalized images were then resliced into a voxel size of 2 × 2 × 2 $mm^3$. All registered images were modulated to estimate gray matter volume at each voxel and were then smoothed with an isotropic Gaussian kernel (sigma = 3; Good et al., 2001).

Statistical analysis of VBM was performed on the data from the participants who completed the study ($n = 37$). A paired $t$-test was used to examine time effects on gray matter volume within the KRG group using threshold-free cluster enhancement with 5000 permutations (Nichols & Holmes, 2002). A statistical threshold was set at $p < 0.05$ corrected for Family-wise Error (FWE; Hennen, 2003). In order to compare changes in gray matter volume between the two groups, group-by-time interaction effects were examined for each significant cluster using a generalized estimating equation (Hennen, 2003). The group (KRG vs. placebo), time (baseline vs. week 8), and group-by-time interaction terms were included in the model as fixed effects, and the within-subjects factor was treated as a random effect.

### 2.5 | Cognitive measures

Cognitive function was assessed at baseline and week 8 in the domains of executive function, attention, and memory. Executive function was evaluated using the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Kay, & Curtiss, 1993) and Stroop

Color-Word Task (Stroop, 1935). Attention was assessed using the Grooved Pegboard for nondominant hands (Lezak et al., 1983), Trail Making Test (TMT) part A (Reitan, 1958), Stroop Color Task (Stroop, 1935), and Spatial Span Forward (Wechsler, 1997). Memory was evaluated using the California Verbal Learning Test (CVLT) (Delis et al., 1987). The details on the cognitive tests in each of the cognitive domains are indicated in Supporting Table 1.

In the WCST assessing cognitive flexibility of executive attention, participants were informed to precisely sort every response card with one of four stimulus cards by receiving feedback of being right or wrong for each trial according to the sorting rule, which switches from color, to number of figures, or form without participants being told (Heaton et al., 1993). The numbers of correct responses, incorrect responses, and perseverative responses were used as the outcome measures (Heaton et al., 1993). In the Stroop Color-Word Task evaluating response inhibition, participants were presented with the list of words printed in colors incongruent with the meaning and asked to quickly and precisely name color of the word instead of reading the word. The outcome measures included the number of correct responses and response time (Stroop, 1935).

The tests included in attention domain require visuospatial processing as well as precise and quick actions through hand-eye coordination or verbalization. The Grooved Pegboard test measured response time to complete in which participants were asked to sequentially and accurately insert pegs with a key along one side in 20 holes with randomly positioned slots (Lezak et al., 1983). The TMT part A asked participants to draw a continuous line between circles of 25 numbers in an ascending order as accurately and quickly as possible (Reitan, 1958). The number of incorrect responses was used as the outcome measure (Reitan, 1958). The Stroop Color task assessed response time to complete in which participants read a list of words printed in colors congruent with the meaning as precisely and quickly as possible, which requires quick and accurate verbal processing of visual input (Stroop, 1935). In the Spatial Span Forward, participants were asked to point a series of blocks in the same sequence as presented by the examiner before. The number of correct responses was used as the outcome measure (Wechsler, 1997).

The CVLT of memory domain required participants to learn, recall, and recognize items from a 16-item word list that were read aloud by an examiner (Delis et al., 1987). The CVLT measuring verbal memory is categorized into immediate recall, short-delay, and long-delay as well as free recall, cued recall, and retention (Delis et al., 1987). For cued recall which measures associative memory, participants were informed to recall items that correspond to each of four categories (Delis et al., 1987). The numbers of correct responses for short-delay and long-delay cued recall, as well as numbers of total incorrect and repetitive responses were used as the outcome measures for study (Delis et al., 1987).

Each test score was converted to standardized $z$ scores using the group mean scores and standard deviations of the baseline. If necessary, test scores were reversed to indicate better performance with positive $z$ scores. Composite $z$ scores for the combined cognitive function was calculated by averaging $z$ scores of all cognitive domains that included executive function, attention, and memory.

### 2.6 | Statistical analysis

All statistical analysis was performed on those who completed the study ($n = 37$). Between-group differences for demographic and clinical characteristics at baseline were assessed using Fisher's exact tests for categorical variables as well as independent $t$-tests or Mann–Whitney $U$ tests for continuous variables, respectively.

Changes in the composite cognitive scores were compared between the two groups by testing group-by-time interaction effects using a generalized estimating equation (Hennen, 2003). The group (KRG vs. placebo), time (baseline vs. week 8), and group-by-time interaction terms were included as fixed effects, as well as the within-subjects factor were included as a random effect. In addition, time effects were assessed to examine within-group changes in the composite cognitive scores using a generalized estimating equation (Hennen, 2003).

An alpha-level of 0.05 was considered to be statistically significant based on a two-tailed test. All data analyses were performed using Stata SE version 13.1 (StataCorp.).

## 3 | RESULTS

### 3.1 | Participant characteristics

Sixty volunteers were screened for study eligibility and a total of 51 healthy participants were enrolled to the study. Participants were randomly assigned to receive either KRG ($n = 26$) or placebo ($n = 25$) for 8 weeks (Figure 1). Of 26 individuals allocated in the KRG group, four individuals withdrew consent and four individuals were lost to follow up. Six out of 25 individuals in the placebo group discontinued participation during 8 weeks of treatment: consent withdrawal ($n = 1$); follow-up loss ($n = 5$). The final analysis included 18 and 19 participants who completed the study in the KRG and placebo groups, respectively (Figure 1). The completion rates did not significantly differ between the KRG (69.2%) and placebo (76%) groups ($p = 0.76$). No adverse events were reported during the study period.

The baseline demographic and clinical characteristics of the study completers are shown in Table 1. There were no significant differences in age ($z = 0.55$, $p = 0.58$), sex ($p = 0.27$), years of education completed ($z = 0.16$, $p = 0.87$), handedness ($p = 1.00$), and marital status ($p = 0.62$) between the study completers in the KRG and placebo groups (Table 1). The intelligence quotient ($t = 0.82$, $p = 0.42$) as well as the standardized $z$ scores of the combined cognitive function ($z = 0.55$, $p = 0.58$), executive function ($z = 0.79$, $p = 0.43$), attention ($z = 0.30$, $p = 0.76$), and memory ($z = 1.22$, $p = 0.22$) also did not differ between the KRG and placebo groups (Table 1).

**TABLE 1** Demographic and clinical characteristics of study completers

| | Korean red ginseng ($n = 18$) | Placebo ($n = 19$) | $p$ |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, years | 38.6 (15.3) | 40.6 (14.9) | 0.58 |
| Women, number (%) | 12 (66.7) | 16 (84.2) | 0.27 |
| Education, years | 14.9 (2.2) | 14.8 (2.0) | 0.87 |
| Right handedness, number (%) | 17 (94.4) | 18 (94.7) | 1.00 |
| Marital status, number (%) | | | 0.62 |
| Married | 9 (50.0) | 11 (57.9) | |
| Never married | 9 (50.0) | 7 (36.8) | |
| Separated/widowed/divorced | 0 (0.0) | 1 (5.3) | |
| Clinical characteristics | | | |
| Intelligence quotient | 114 (14.0) | 117 (13.3) | 0.42 |
| Combined cognitive function | −0.09 (0.62) | 0.08 (0.42) | 0.58 |
| Executive function | −0.13 (0.79) | 0.12 (0.41) | 0.43 |
| Attention | −0.04 (0.70) | 0.04 (0.55) | 0.76 |
| Memory | −0.10 (0.74) | 0.10 (0.82) | 0.22 |

*Notes*: Data are indicated in mean (standard deviation) and number (%). Continuous variables were compared using independent *t*-test or Mann–Whitney *U* tests. Categorical variables were compared using Fisher's exact tests. Cognitive domain composite scores are presented as standardized *z* scores.

### 3.2 | Changes in gray matter volume

Following 8 weeks of the KRG supplementation, significant increases in gray matter volume were found in the cluster in the left parahippocampal gyrus ($t = 8.38$, FWE-corrected $p = 0.005$, cluster size = 49 voxels [392 $mm^3$], peak MNI coordinates [x, y, z] = [−34, −12, −24]; Figure 2a). A post-hoc analysis showed a significant group (KRG vs. placebo)-by-time interaction within this cluster ($z = 3.94$, $p$ for interaction < 0.001; Figure 2b).

### 3.3 | Changes in cognitive function

The composite score of combined cognitive function significantly increased in the KRG group after 8 weeks of the supplementation, with a greater degree as compared to the placebo group ($z = 2.20$, $p$ for interaction = 0.03). The improvement in the composite score of combined cognitive function was significant in the KRG group ($z = 5.23$, $p < 0.001$), but not in the placebo group ($z = 1.90$, $p = 0.06$).

For each composite score of specific cognitive domains, the KRG group showed significant increase in the scores of executive function ($z = 2.39$, $p = 0.02$), attention ($z = 2.35$, $p = 0.02$), and memory ($z = 3.62$, $p < 0.001$). In contrast, the placebo group did not show increase in the cognitive scores of executive function ($z = 1.55$, $p = 0.12$), attention ($z = 0.81$, $p = 0.42$), and memory ($z = 1.22$, $p = 0.22$; Table 2).

## 4 | DISCUSSION

The current study results suggest that 8 weeks of KRG supplementation may increase the left parahippocampal gray matter volume, while enhancing the general cognitive function in healthy individuals. To the best of our knowledge, this study is the first randomized, double-blind, placebo-controlled study to investigate KRG-induced structural changes of the human brain regarding the cognitive enhancing effects. It is noteworthy that a series of neural changes including new synapse formation as well as neural proliferation and differentiation might have increased the gray matter volume as accompanied by the cognitive enhancement (Ban et al., 2018; Jeon et al., 2016; Woo et al., 2018). As such, we speculate that the gray matter volume increase observed in the current study is likely to reflect the neuroprotective and subsequent cognitive enhancing effects of KRG in the human brain.

It is noteworthy that the 8-week KRG supplementation improved general cognitive function encompassing the tests in the three domains of executive function, attention, and memory that were within normal range, as well as increased the left parahippocampal gray matter volume, in healthy individuals. The tests included in the current study assessed executive function requiring cognitive flexibility (Heaton et al., 1993) and response inhibition (Stroop, 1935), attention which needs visuospatial processing and hand-eye coordination (Lezak et al., 1983; Reitan, 1958; Stroop, 1935; Wechsler, 1997), as well as associative and verbal memory

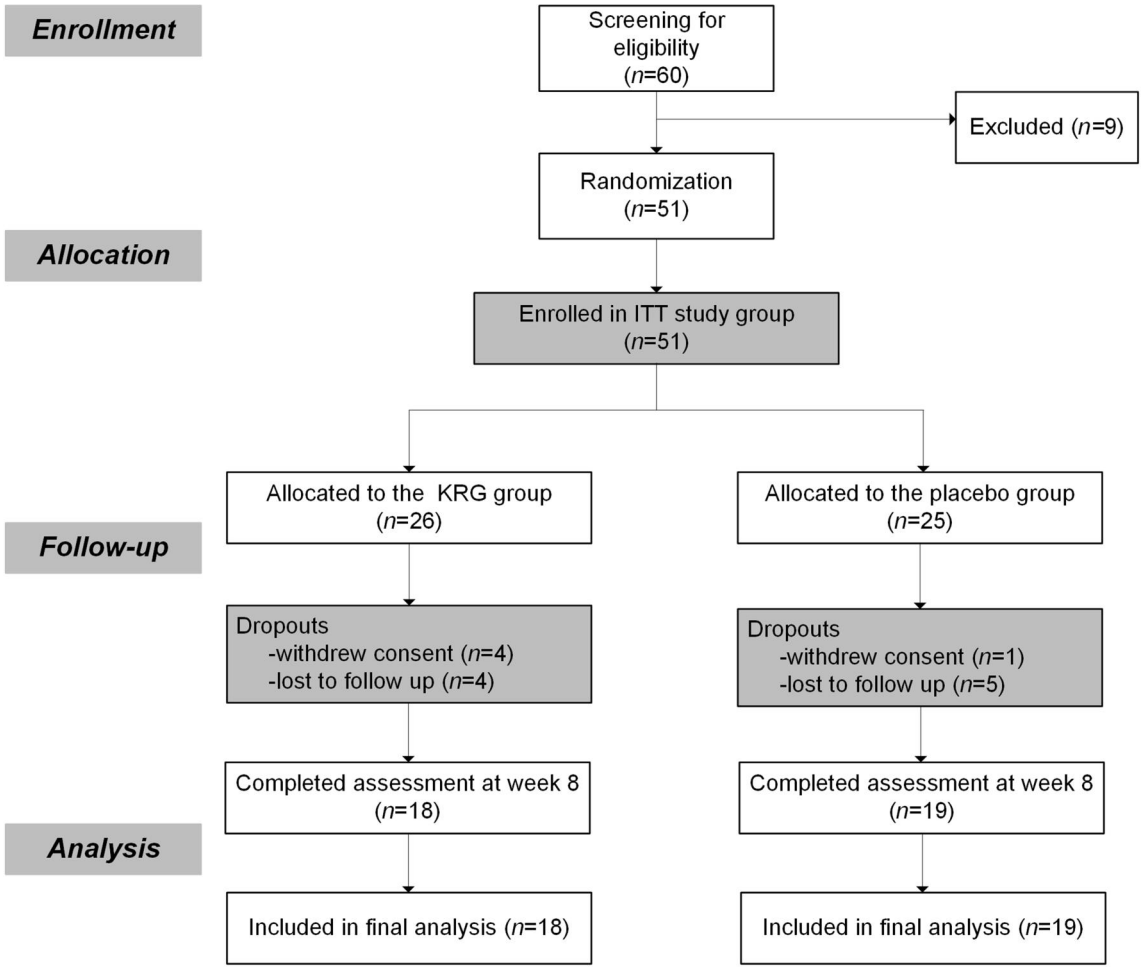


**FIGURE 1** The flow diagram of the current study; ITT, intent-to-treat; KRG, Korean red ginseng

(Delis et al., 1987). As these tests require capability to understand context through visuospatial processing and take precise and quick actions by verbalizing or using hands (Wechsler, 1997), the KRG-induced cognitive enhancement may be attributed to KRG-induced increase in gray matter of the left parahippocampus which lies in the left inferior temporo-occipital cortex and is part of the left limbic system surrounding the hippocampus (Aminoff, Kveraga, & Bar, 2013).

It is notable that the parahippocampus has been associated with a wide variety of cognitive functions (Aminoff, Kveraga, & Bar, 2013), since it is highly interconnected with other brain regions including the frontal, temporal, and parietal cortices, as a component of the default mode node network (Baldassano, Beck, & Fei-Fei, 2013; Suzuki, 2009). With respect to the memory and attention domains that were improved by KRG supplementation, the parahippocampus was involved in encoding and retrieval of associative memory (Davachi, Mitchell, & Wagner, 2003; Diana, Yonelinas, & Ranganath, 2010; Zola-Morgan, Squire, Amaral, & Suzuki, 1989) as well as in visuospatial processing (Kravitz, Peng, & Baker, 2011; Mullally & Maguire, 2011; Park, Brady, Greene, & Oliva, 2011). Previous findings where the parahippocampal cortex was primarily associated with contextualizing and coordination of verbal, visual, and spatial inputs (Aminoff, Kveraga, & Bar, 2013) also support the involvement of the left parahippocampal gyrus in cognitive enhancement observed in the current study, including cognitive flexibility and response inhibition as executive function.

Since there have been sparse studies in human brain changes induced by KRG, potential action mechanisms of KRG with regard to neuroprotection and cognitive enhancement could be inferred from previous animal studies. First of all, ginseng may have neuroprotective effects by modulating long-term potentiation, upregulating brain-derived neurotrophic factor levels, and regulating several molecules involved in neuronal metabolism (Kim et al., 2016, 2018). Other plausible action mechanisms of KRG in the brain could be antioxidant and anti-inflammatory effects as indicated by decreased levels of inflammatory cytokines and oxidative damage (Tian, Ren, Wang, Zhang, & Zhou, 2018; Wan et al., 2017; Wang et al., 2018).

Considering the relatively small sample size and high inclusion rates of women in the current study, future larger studies are needed to validate the generalizability of these findings. The dose-dependent

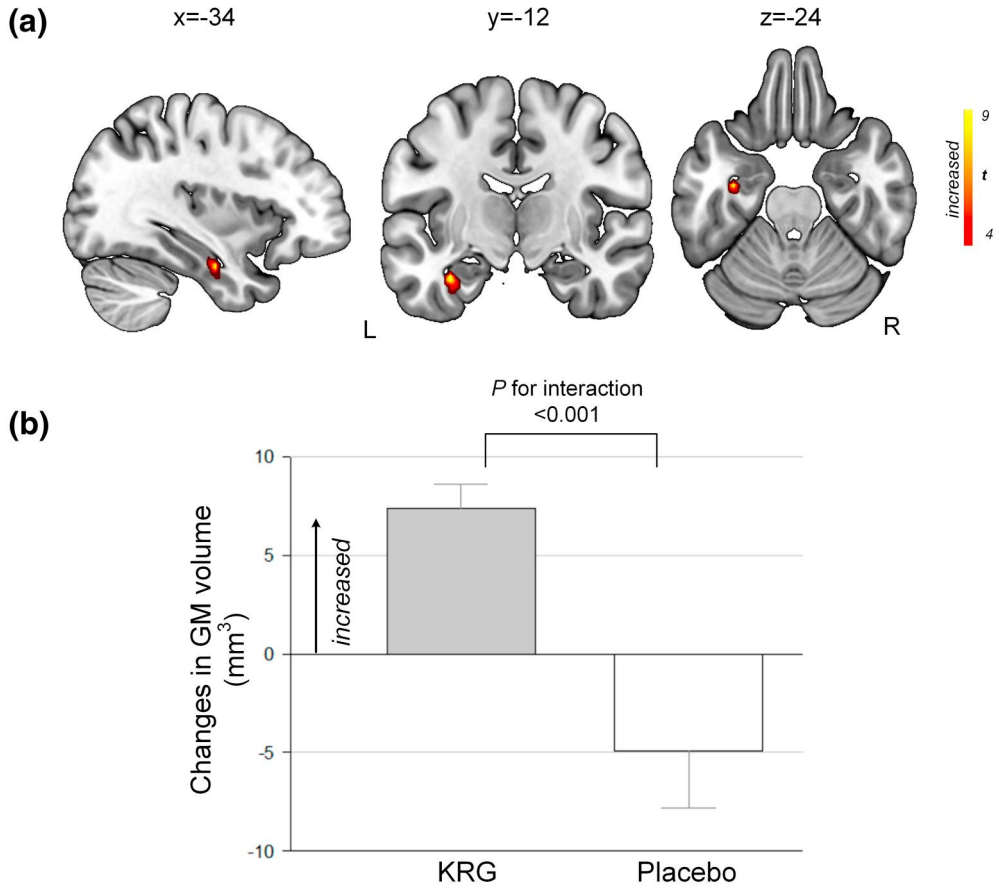


**FIGURE 2** Changes in gray matter volume after 8 weeks of the KRG supplementation. (a) A brain cluster with significant increase in the gray matter volume after 8 weeks of the KRG supplementation is indicated: left parahippocampal gyrus. The color bar represents voxel-level *t* values and the numbers above the brain slices indicate MNI coordinates. (b) A post-hoc analysis within the brain cluster showed a significant group (KRG vs. placebo)-by-time interaction in the gray matter volume ($mm^3$); GM, gray matter; KRG, Korean red ginseng; L, left; MNI, Montreal Neurological Institute; R, right

**TABLE 2** Changes in cognitive function after 8 weeks of the KRG supplementation

| | Korean red ginseng ($n = 18$) | | | Placebo ($n = 19$) | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Week 8 | *p* | Baseline | Week 8 | *p* | *p* for interaction |
| Combined cognitive function | −0.09 (0.62) | 0.22 (0.45) | <0.001 | 0.08 (0.42) | 0.20 (0.39) | 0.06 | 0.03 |
| Executive function | −0.13 (0.79) | 0.23 (0.51) | 0.02 | 0.12 (0.41) | 0.24 (0.30) | 0.12 | 0.15 |
| Attention | −0.04 (0.70) | 0.24 (0.44) | 0.02 | 0.04 (0.55) | 0.13 (0.60) | 0.42 | 0.28 |
| Memory | −0.10 (0.74) | 0.21 (0.75) | <0.001 | 0.10 (0.82) | 0.24 (0.78) | 0.22 | 0.29 |

*Notes*: Cognitive domain composite scores are presented as mean of the standardized *z* score (standard deviation). Composite *z* scores for the combined cognitive function were calculated by averaging *z* scores of the three cognitive domains (executive function, attention, and memory). The tests included in the three cognitive domains are represented in Table S1.

Abbreviation: KRG, Korean red ginseng.

effects as well as clinical implications of KRG supplementation were not assessed in this study as we focused on the gray matter and cognitive changes in healthy individuals. The clinical implications underlying gray matter volume increases and cognitive enhancement as induced by KRG supplementation remain yet to be clarified in the future studies in individuals with neurological or psychiatric conditions such as mood disorders or cognitive deficits.

## 5 | CONCLUSION

This study demonstrates KRG-induced gray matter increases in the parahippocampus of the human brain accompanied by enhancement of general cognitive functions. Considering that neuroprotective process may have induced increases in gray matter volume, the current study findings may add a new insight into the neurobiological

mechanisms of KRG-induced cognitive enhancement in the human brain.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*In Kyoon Lyoo* https://orcid.org/0000-0002-9717-1935

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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