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Clinical trial

A randomized, double-blind, placebo-controlled study on the memory-enhancing effect of lactobacillus fermented *Saccharina japonica* extract

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ABSTRACT

Introduction: Memory problems are more common with ageing and are related to the development of Alzheimer's disease. This study investigated whether the intake of lactobacillus fermented *Saccharina japonica* (FSJ) extract improved the cognitive function during working memory processing and whether biomarkers were associated with task performance.

Methods: Eligible participants were assigned to either a control group or an experimental group by computerized randomization. Participants were asked to take either 2 capsules, once a day for 4 weeks of lactobacillus FSJ for the experimental group or placebo control capsules for the control group. The cognitive function was determined using the Beck depression inventory (BDI), Korean Wechsler Adult Intelligence Scale (K-WAIS), operation-word span task and Raven's test-based quantitative EEG test. Levels of amyloid-β, superoxide dismutase (SOD) in the serum using the ELISA were also measured.

Results: There was no significant difference between these two groups in all cognitive function tests using the independent sample *t*-test. However, the experimental group showed a significant difference in the correct answer percentage, concentration and left and right brain activity of space perception as assessed by the Raven test-based quantitative EEG test by a paired-sample *t*-test. Biochemical measurements showed, a slightly decreasing trend in amyloid-β, whereas SOD level was not significantly different between groups ($P > 0.05$).

Conclusion: These results suggest that FSJ may have the potential to improve cognitive function as evaluated by the Raven's test via, regulation of SOD antioxidant system. Our findings provide preliminary evidence of the safety of FSJ and its potential to improve memory.

1. Introduction

Working memory can be defined as the systems that are essential for keeping information in the mind while performing complex tasks, e.g. reasoning, comprehension, and learning. People with mild cognitive impairment have an increased risk of developing Alzheimer's disease in the near future, especially when their main problem involves memory [1]. Recently, one study reported a selective age-related decrease in both the protein and mRNA levels of the most abundant gamma-aminobutyric acid $(GABA)_A$ receptor [2]. The deficits of GABAergic neurons seem to be at least partially responsible for the altered gamma band oscillations and working memory deficits of the illness.

GABA is a primary mediator of inhibitory neurotransmission in the central nervous system. GABA is biosynthesized by animals, plants, and microorganisms via the α-decarboxylation of glutamic acid by a glutamate decarboxylase [3]. It has since been reported that GABA participates in a wide number of physiological responses including the regulation of blood pressure, hormonal release, food intake, locomotion, sexual behavior, as well as in pathological states like epilepsy, anxiety, schizophrenia, Parkinson's disease, Stiff-man syndrome and Alzheimer's disease (AD) [4]. Considering GABA's physiological and biochemical functions, the development of functional foods containing

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Table 1
Ingredients and formulation of the test food and the placebo food.

	FSJ - Experimental	Placebo control
Common Name	Lactic acid fermentation kelp extract	Lactose
Ingredients & Contents (per 1 capsule)	Lactic acid fermentation kelp extract 1 g/day (Lactic acid fermentation kelp extract 50 mg/day)	Lactose 1 g/day (Lactose 500 mg)
Type	600 mg capsule	Same as left
Description	Reddish brown capsule	Same as left
Administration Method	Take 2 capsules once a day 30 minutes after a meal	Same as left
Packing Unit	56 capsules in 1 bottle	Same as left
Storage Method	Room temperature storage	Same as left
Expiration Period	1 year	Same as left

high concentration of GABA has been actively tried [5–9]. Also, many microorganisms have been reported to produce GABA [10].

Recent research reported that consumption of fermented foods may be associated with a range of health benefits including disease prevention [11–14]. Points of interest have focused on the utilization and mass production of GABA as a bioactive food component [5–7]. Some studies have reported that marine plants produce biological activities. For example, Wantana and Fuda et al reported that GABA from sea oyster might be useful in the prevention liver diseases [15]. Our previous study demonstrated that enriched GABA contents (5.56% dry weight) after being fermented by L.brevis had antioxidant activity [16]. Also, increase of GABAergic transmission and modifiability was shown to be associated with the improvement of learning and memory [17]. In addition, our previous study reported cognitive improvement of GABA-enriched fermented *Saccharina japonica* (FSJ) on the memory deficient rats [18].

Therefore, this present study was undertaken to evaluate the effect of FSJ on cognitive function in healthy participants and to elucidate the mechanism underlying these effects in human. The analyzed parameters for the mechanism included the expression of amyloid-β and antioxidants in the serum.

2. Materials & methods

2.1. Participants

All participants provided signed informed consent prior to the experiment. Participants' responses were treated confidentially and anonymously. Seventy two participants (age 18–65) participated in the study. Three participants were not included in the analysis due to either not completing the experiment or failure to follow instructions. The final group included in the analysis consisted of 69 participants (control group (n = 36) and experimental group (n = 33), Tables 2A–B and 3). This study was approved from the institutional review board of the Kyung Hee University (KHSIRB-13-004-1(RA)). Candidates were asked to complete the Beck Depression Inventory (BDI) at their first visit while waiting. Index score of ≤ 16 is considered to be within normal range.

2.2. Study design

2.2.1. Randomization and blinding

A double-blind, parallel-group, placebo-controlled trial was conducted. Eligible participants were assigned into the control group or experimental group by a computerized random allocation method. Eligible participants were assigned either to a control group or to an experimental group by a computerized random allocation method. Participants were randomly assigned subject numbers. Numbered packets were arranged to counterbalance the order of the nutritional supplements or placebo tablets allocated to participants; However, the participants and researchers were unaware which tablets individuals would receive (double blind design). The nutritional supplement and placebo tablets were similarly packaged in the nutritional supplement bottles. The coding files were kept confidential until the end of the study.

The first session pre-trial testing was completed (baseline) and the participants were given three weeks supply of capsules. Participants were contacted by telephone approximately 2–4 weeks into the trial period to encourage compliance. A second testing session was conducted approximately four weeks later, at which time the participants were instructed not to take any remaining capsules.

2.2.2. Ingredients and formulation of the nutritional supplement and the placebo

Trial nutritional supplement was fermented by *Lactobacillus brevis* BJ20 (KCTC 11377BP, Korea). Instructions were given to take the trial nutritional supplements 2 caps once a day, lactobacillus FSJ or control. The supplements consisted of either 500 mg capsules of standardized lactobacillus FSJ (Marine Bio, Busan, Korea) (experimental group) or cellulose, lactose, and magnesium stearate (placebo) (Table 1).

2.2.3. Efficacy measurements

All assessments were performed by an experienced Korean medicine doctor and the clinical research coordinators. The therapeutic responses were measured by using the scales as follows.

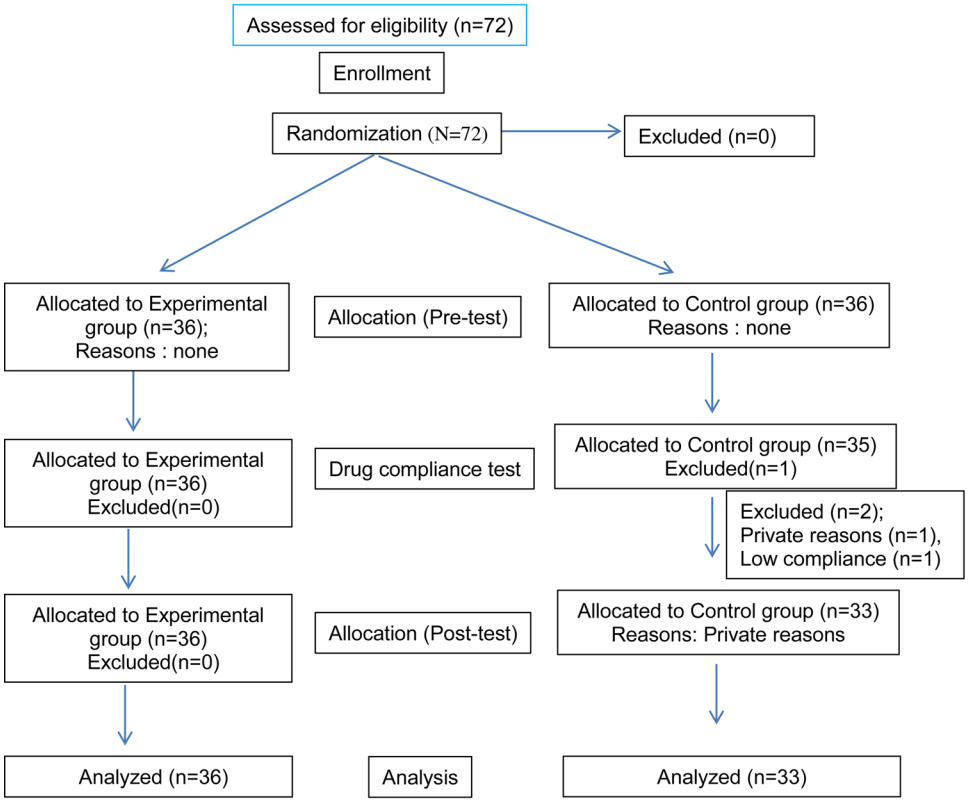
2.2.3.1. Korean Wechsler adult intelligence scale (K-WAIS). The three-subtests from the K-WAIS [19] composed of Digit Span, Digit Symbol Coding, and Block design was administered to estimate cognitive function. Digit Span measures working memory, short-term memory, and attention. Digit Symbol Coding measures speed of information processing, visual short-term memory, and set-shifting ability. Block design measures visual-motor coordination and perceptual organization.

2.2.3.2. Operation-word span task. The Operation - Word Span Task (Ospan) consists of simple maths problems and remembering words simultaneously, which was designed by Turner and Engle [20]. This task requires the simultaneous use of attentional and maintenance resources. It requires confirming the accuracy of a mathematical operation while remembering a word (e.g. $(4 \times 2) + 2 = 10$ *rose*). After a sequence of these operation word pairs the participant is asked to recall, in order, the words as they are presented.

2.2.3.3. Raven's test. The Raven's Progressive Matrices (RPM) test is a nonverbal intelligence test. Present study used the Fun Fun Brain (Laxtha, Inc, Korea, BES2000). Once a neurofeedback protocol is determined, such as 2 channel training, the specific location of

Table 2

A) Study Flow Chart



B) Experimental procedure

Step	Screening	Ttreatment	
No. of visit	1	2	3
Time	Baseline (0 day)	2 weeks (14 days)	4 weeks (28 days)
Written consent	O		
Preliminary test	O		
History taking (disease, drug)	O		
Beck depression inventory	O		
Inclusion/exclusion criteria	O		
Randomization	O		
K-WAIS	O		O
Operation-word span task	O		O
EEG test	O		O
Compliance check	O	O	O
Adverse reaction check	O	O	O

Table 3
Baseline demographic characteristics.

	Placebo (n = 32)	FSJ (n = 31)
Gender		
Male	15	13
Female	21	23
Age (years)	31.83 ± 16.32	32.86 ± 17.61
Medical history (Memory dysfunction)	none	none

electrodes are found on the patient's head. After test, the prefrontal lobe activity analyzed sensory motor rhythm (SMR) and M-Beta (middle beta)

Data = power of ratio of SMR + M-B / theta

2.2.3.4. Biochemical measurements. All participants had a fasting blood test at baseline prior to the start of the trial. Antioxidants and amyloid-β levels were measured at 4 weeks and after the start of the trial to explore the effect of the study nutritional supplement. Bloods were collected in a vacuum tube.

Human-specific amyloid-β enzyme-linked immunosorbent assay (ELISA) kit was purchased from Biovision (Milpitas, CA, USA). SOD was purchased from Biovision (Milpitas, CA, USA). The concentrations of amyloid-β and antioxidants in the serum were evaluated with ELISA kits in accordance with the manufacturer's recommendations. All data were analyzed using SoftMax Pro version 5 (Molecular Devices Corporation, CA).

2.3. Statistical analysis

All data analyzed intention to treat analysis (ITT) and last observation carried forward (LOCF). Demographics data were compared between the two groups using independent *t*-test or paired sample *t*-test. The statistical package for the Prism (Graphpad software, La Jolla, CA, USA) was used for the statistical analyses.

3. Results

3.1. Baseline demographic characteristics

As shown in Table 3, the control and experimental group were not significantly different in terms of gender and age distribution.

3.2. K-WAIS test and operation-word span task

The changes in the three subsets of K-WAIS and operation-word span task scores were presented in Fig. 1. The control and the experimental group had no significant difference in their Neuropsychological tests using the independent sample *t*-test ($P > 0.05$). However, pre-post comparison of the variables within each group showed a significant difference in all variables by paired the sample *t*-test ($P < 0.001$).

3.3. Raven's test

3.3.1. Changes in memory ability between the two groups

The results in memory ability test between the 2 groups at endpoint are shown in Fig. 2. The control and the experimental group had

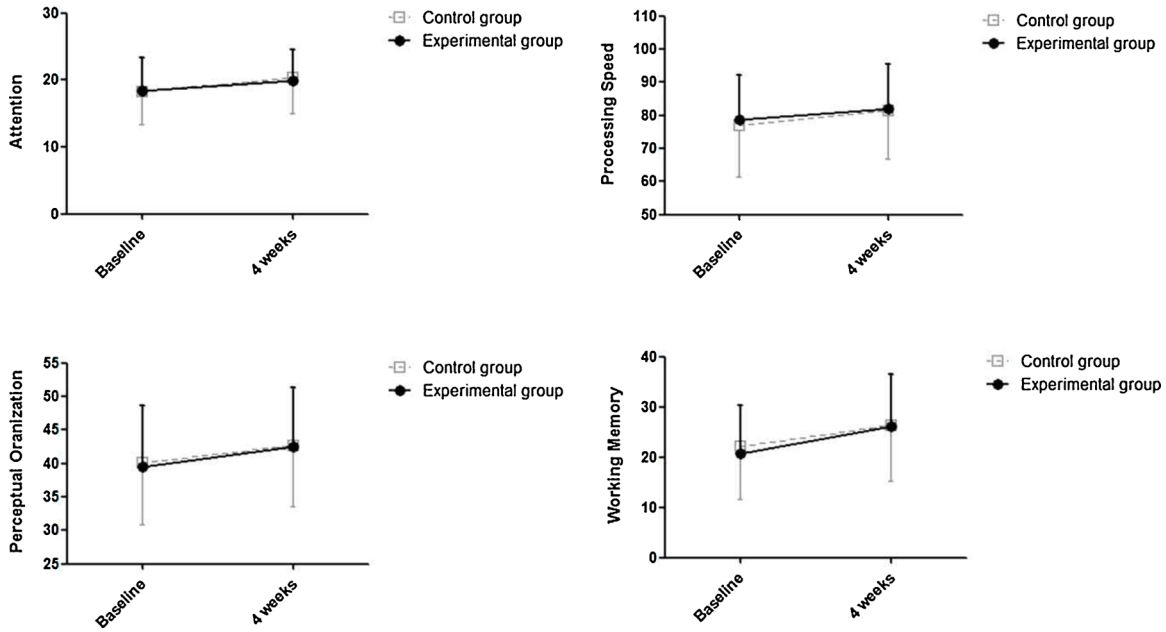


Fig. 1. Effects on cognitive functions measured by Korean Wechsler Adult Intelligence Scale (K-WAIS) and operation-word span task. Participants of the control group ($N = 36$) and the experimental group ($N = 36$) were evaluated with K-WAIS and operation-word span task, data shows the variables; attention, processing speed, perceptual organization, and working memory. Values are presented as mean ± S.D.

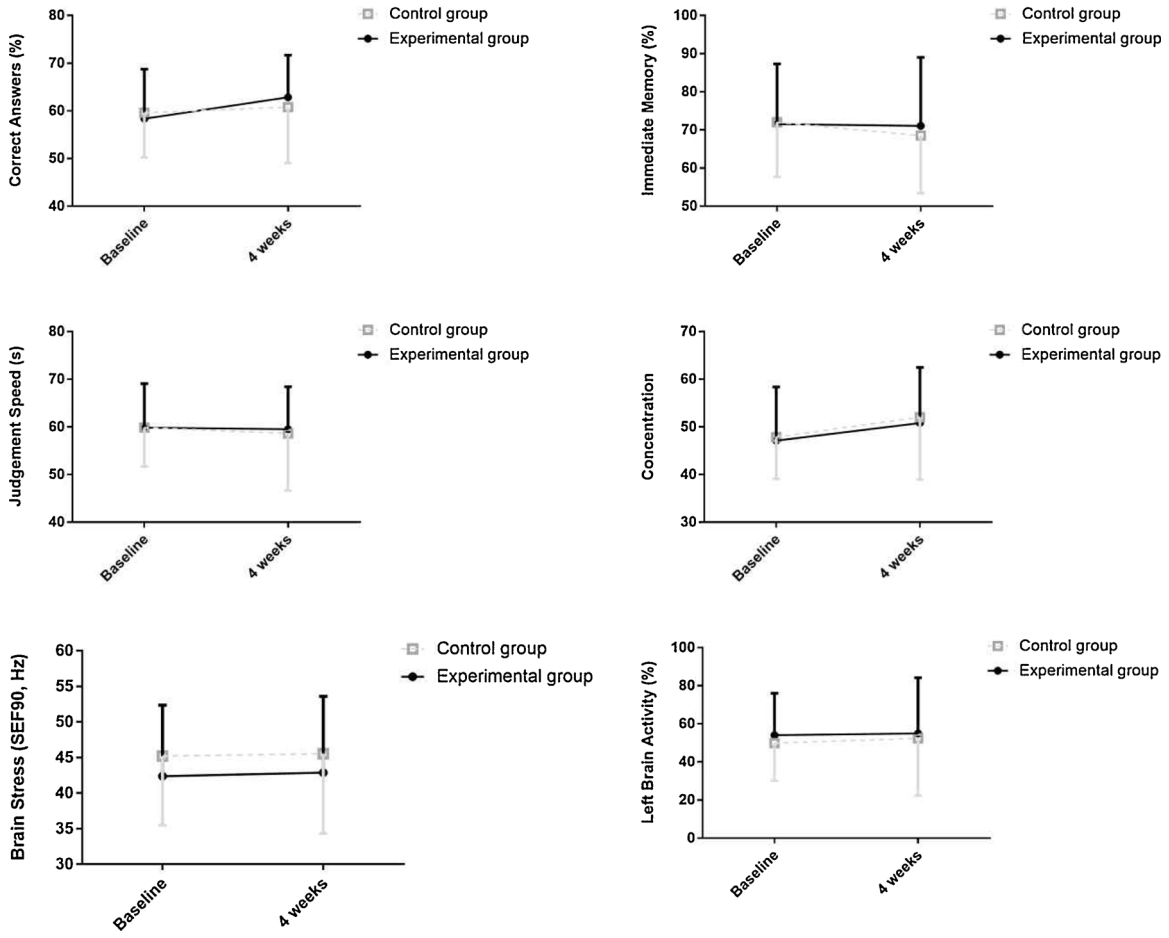


Fig. 2. Effects on memory-related cognitive functions measured by the Raven test-based quantitative EEG. Values are presented as mean ± S.D.

no significant difference in memory ability using the independent sample *t*-test ($P > 0.05$). However, pre-post comparison of the variables within each group showed a significant difference in correct answers (%) but only in the experimental group ($P < 0.05$) by paired sample *t*-test).

3.3.2. Changes in numerical ability between the two groups

The results in numerical ability test between the 2 groups at the study end-point are shown in Fig. 3. Test variables showed no difference between the control and the experimental group using the independent sample *t*-test ($P > 0.05$). Pre-post comparison of the variables within each group showed no significant difference either ($P > 0.05$ by paired sample *t*-test).

3.3.3. Changes in space perception ability between the two groups

The results in space perception ability test between the 2 groups at the end-point are shown in Fig. 4. There was no statistical difference in brain stress, judgement speed and left/right brain activity of the 2 groups. Test variables showed no difference between the control and the experimental group by the independent sample *t*-test ($P > 0.05$). However, pre-post comparison of the variables within each group showed a significant difference in correct answers (%) ($P < 0.05$), concentration ($P < 0.001$), and left brain activity ($P < 0.05$) only in the experimental group using a paired sample *t*-test.

3.4. Biochemical measurements

The results in the blood tests between the 2 groups at the end-point are shown in Fig. 5. After 4 weeks, there were no statistically significant differences between two groups. The present study showed that the serum level of Aβ was reduced by 32.0% and the serum level of SOD was increased by 20.0% for FSJ group.

4. Discussion

This present study investigated whether FSJ improved memory using concentration and perception tests. In particular, we explored by applying an operation-word span task and Raven's test data whether FSJ altered the brain activity and cognitive discrimination. The main findings are that FSJ treated group significantly increased the percentage of correct answers and concentration for space perception for memory ability and space perception ability. Biochemical measurements, there were no significant differences between two groups. A previous study has already reported the relationship between Alzheimer's disease and reactive oxygen species (ROS) [21]. Another

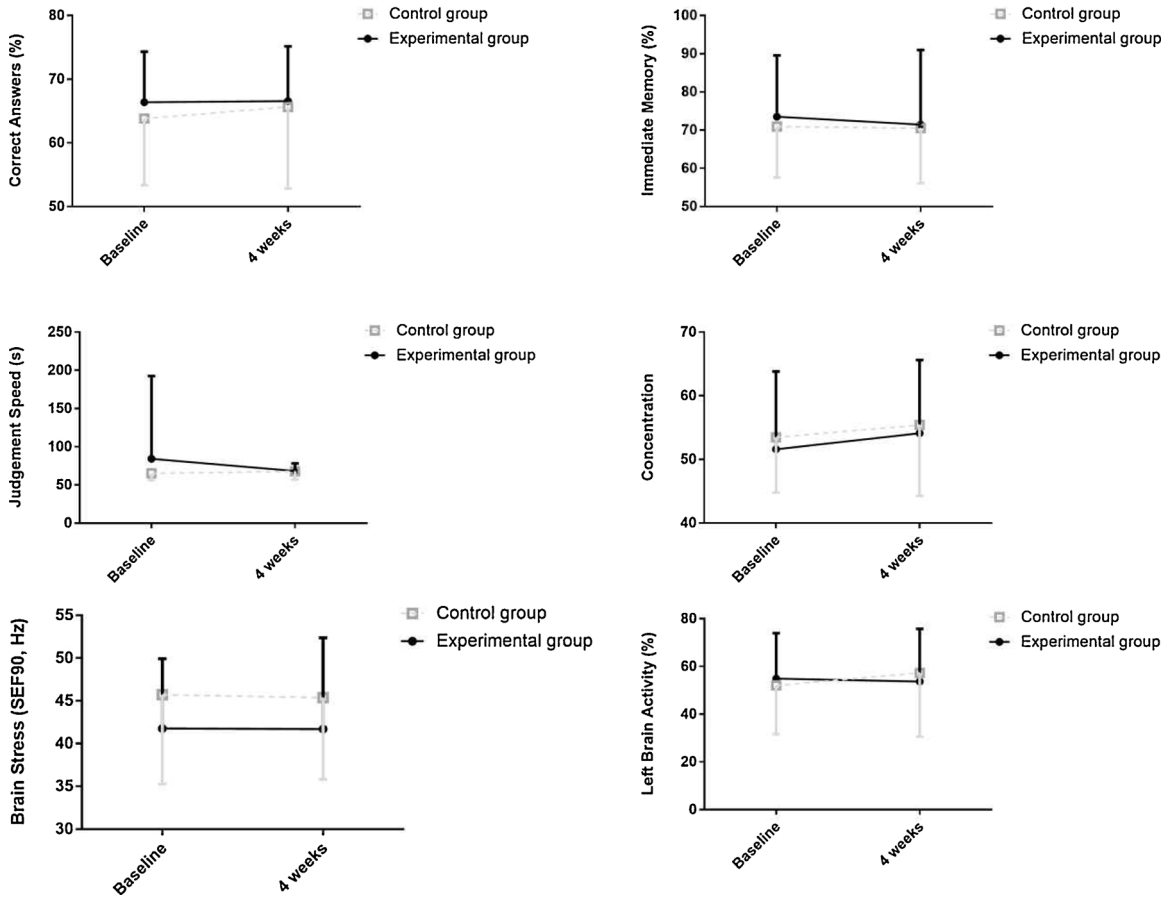


Fig. 3. Effects on number-related cognitive functions measured by the Raven test-based quantitative EEG. Values are presented as mean ± S.D.

study showed that SOD modulates synaptic plasticity, learning and memory [22]. Zhan et al reported that the regulating metabolism of free radicals in the brain tissue can improve learning and memory ability [23]. Furthermore, it has been shown that extracellular superoxide dismutase overexpression protects against aging-induced cognitive impairment in mice [24]. Taken together, FSJ has the potential to improve memory improvement and brain function.

Saccharina japonica extract mainly consists of sugar protein, amino acids, minerals, polyphenols, and dietary fiber [25] and shows some biological activities, such as anti-mutagenic activity, antibacterial activity, and antioxidant activity [26]. Glutamic acid (6.29% (w/w)) and GABA among SJ were not detected before fermentation. However, during fermentation with L. brevis. GABA content was markedly increased. Many food products have been used successfully with lactic acid bacteria to increase the content of GABA, these have included: brown rice, kimchi, many milk products, (e.g.cheese), and the Asian adzuki bean. These foods have been developed to treat disease or with the purpose of providing specific health benefits and are called functional foods. These results were in agreement with our previous report [27].

Raven's test was developed as a "pure" measure of Spearman's concept of general intelligence. It is widely used as a measure of working memory. Raven's test showed that judgement speed for numerical ability, percentage of concentration for memory ability and concentration for space perception ability was significantly different between the two groups. A previous study showed that fucoidan, one of constituents from brown algae is a complex sulfated polysaccharide [28] and could ameliorate the learning and memory ability in Aβ-induced AD rats [29]. Another study reported that GABA by lactobacillus buchneri isolated from kimchi was found to have a neuroprotective effect on neuronal cells [30,31]. These results showed that use of FSJ demonstrated improved memory in the Raven's test. Thus, FSJ may be a good food candidate as a neuroprotective agents for learning and memory impairment.

Oxidative stress plays an important role in the development and progression of AD in clinical [32]. It has been shown that Aβ induced oxidative stress, including increased production of hydrogen peroxide and lipid peroxides in neurons [33]. Furthermore, Hirano et al. (2011) reported that reactive oxygen species cause memory defects when activity of the anti-ROS system is decreased [34]. Consistent with these results, the present study showed that the serum levels of Aβ was reduced by 32.0%, compared with that of the control group. However, control group also reduced the serum levels of Aβ. The serum levels of SOD were increased by 20.0% for FSJ group. The long-term efficacy of this nutritional supplement is not known. However, the present study proved it was potent in increasing the serum antioxidant.

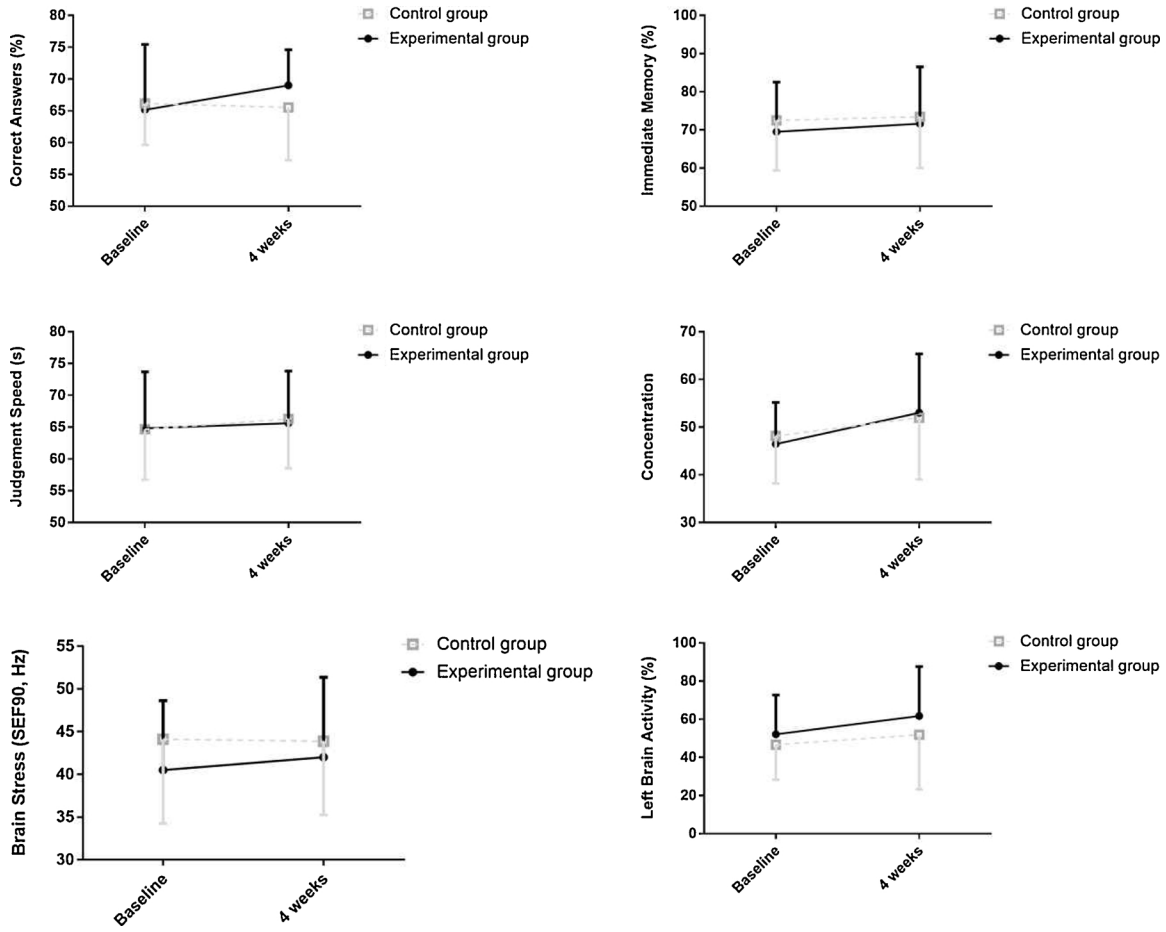


Fig. 4. Effects on spatial perception-related cognitive functions measured by the Raven test-based quantitative EEG. Values are presented as mean ± S.D.

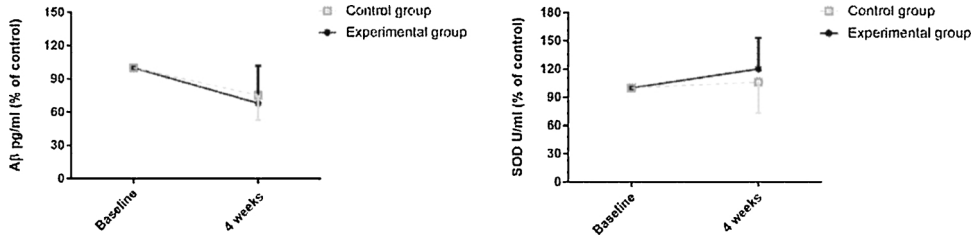


Fig. 5. The changes in the activity of amyloid-β and antioxidant enzymes (SOD). Values are presented as mean ± S.D.

5. Limitations of this study

This study showed that all participants showed an improvement in cognitive function. This may have been because the cognitive tests were completed over a short period of time and they may have shown a practice or learning effect. Participants were not asked which treatment they thought they had been given, which would have confirmed the success of blinding. Further studies will be needed over a longer time to confirm these effects and whether they are sustainable.

6. Conclusion

Taken together, our findings provide preliminary evidence for the putative beneficial effect of FSJ on neurocognitive function by suggesting changes in concentration and perception ability via regulation of antioxidant activity.

Author contributors

All research done by the authors. HJ, HS, GR, KH, JM, Mira conducted the experiment and analyzed the data. IS, HJ, HS, JH, BJ, YM, CP and CS participated in preparation of the manuscript and design of the study. All the authors approved and read the final version manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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