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Research Article
Wheat Bran Improves Cognition in Older Adults with Memory Impairment: A Randomized Controlled Trial

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Abstract

Background and Objective: The neuroprotective effects of wheat (*Triticum aestivum* L.) water extract and its bran have been reported can make a hypothesis that wheat bran water extract(WBE) would offer benefits in elderly individuals with age-associated cognitive impairment. In this study, the efficacy and safety of WBE for improving cognitive function were investigated using a battery of neuropsychological assessments and clinical parameters. **Materials and Methods:** Seventy participants aged 50~80 years with subjective memory impairment were randomly assigned to receive either WBE (3 g per day) or placebo for 12 weeks. Neuropsychological assessments included the Computerized Neurocognitive Function test (CNT), Working Memory Test (WMT), Korean Mini-Mental State Examination, Brief Cognitive Rating Scale, Prospective and Retrospective Memory Questionnaire, Perceived Stress Scale, 36-item Short-Form Health Survey (SF-36). Serum brain-derived neurotrophic factor was also quantified. Assessments were administered before and after the intervention period. **Results:** Visual learning test (CNT)scores were higher in the WBE group compared to the placebo group. Additionally, participants in the WBE group showed decreased reaction times in the visual subtest of the WMT and increased SF-36 scores compared to those in the placebo group. There were no adverse events related to WBE consumption. **Conclusion:** These results suggested that WBE supplementation can improve cognitive function safely, especially visual memory, in older adults with subjective cognitive impairment.

Key words: *Triticum aestivum* L., wheat bran, age-associated cognitive impairment, neuropsychological assessment, working memory

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

An increasing elderly population poses a significant socioeconomic problem worldwide. The United Nations recently reported that the proportion aged 60 or over will increase steadily to 20~25% in developed countries and 6~17% in developing countries by 2030[1]. Cognitive impairment is an age-associated dysfunction that poses substantial socioeconomic burden. As a prodromal stage to dementia, the term mild cognitive impairment (MCI) was originally introduced to describe individuals who experience subjective memory impairment but exhibit normal general cognitive function (a Mini-Mental State Examination [MMSE] score $\geq$24)[2]. The estimated prevalence of MCI in individuals 60 years and older is 15-20%, with a 10% conversion rate to dementia per year[3]. Thus, the prevention or early treatment of age-related cognitive impairment in normal elderly individuals is important. Yet, efforts to identify substances with efficacy and safety for treating MCI have yielded disappointing results, except for the recent discovery of cholinesterase inhibitors[4,5]. To date, there are no pharmacological therapies approved by the United States Food and Drug Administration for the treatment of MCI[3].

Previous study showed that supplementation with wheat water extract (WB) and wheat bran water extract (WBE) improved visuospatial working memory in a rodent model of Alzheimer's disease (AD) by exerting neuroprotective effects and promoting the expression of neurotrophic factors[6,7]. Furthermore, WB and WBE had similar behavioral effects and reduced white matter injury in a rodent model of vascular dementia (VaD)[8,9]. These results suggested that WBE may have utility for supporting healthy cognitive function or for improving cognitive impairment in aging individuals. In the present study, a randomized controlled trial of WBE was performed to examine the safety and efficacy of WBE for the treatment of cognitive impairment in older adults with subjective memory impairment.

MATERIALS AND METHODS

Ethnic statements: This study was conducted at the Clinical Trial Center for Functional Foods at Chonbuk National University Hospital between December, 2013 and September 2014. The study protocol and informed consent form were approved by the Functional Foods Institutional Review Board of Chonbuk National University Hospital (FFIRB number, 2013-02-012). All subjects provided written informed consent prior to study participation. The protocol was registered at www.clinicaltrials.gov (NCT02489747).

Study design: The study was designed as a randomized double-blind placebo-controlled parallel trial. A total of 70 subjects who met the inclusion criteria were enrolled and randomly assigned to either an experimental group (n =35) or a placebo group (n = 35). All investigators, coordinators and participants were blinded to treatment assignments throughout the study.

Subjects visited the clinical trial center4 times during the 12-week intervention period, including a screening visit (visit 0), a registration day visit (visit 1), a mid-study visit at 6 weeks (visit 2) and an end-of-study visit at 12 weeks (visit 3). At screening, participants were subjected to a comprehensive physical examination, medical history, electrocardiography, blood and urine laboratory testing, anthropometric measurements and administration of the Korean Mini-Mental State Examination(K-MMSE)[10]. During the study, safety was assessed by monitoring vital signs, physical status and adverse events at every visit and by evaluating electrocardiography and laboratory test findings at visits 0 and 3. Participants were also asked to report any adverse events, recent illnesses, medical treatments or changes in lifestyle during the course of the study. Outcome measurements were performed at visits 0 or 1 as a baseline and at visit 3 as a post-intervention time point.

Participants: Eligible subjects were men and women between the ages of 50 and 80 years with subjective memory impairment and a K-MMSE score $\geq$24 points. The exclusion criteria were as follows: (1) Had an active or previous history (within 5 years) of any mental disorder, (2) Was taking any other medication or supplement for cognitive problems, (3) Had any ongoing medical illness or history of chronic diseases (within 3 years), (4) Alcohol or drug abuse, (5) Had difficulty with normal communication, (6) Was unable to read or write or had an uncorrected visual impairment, (7) Was unable to write due to motor disability affecting the hands or upper limbs, (8) Was allergic or hypersensitive to the test extract, (9) Had participated in another clinical trial within the past 2 months, (10) Had a condition that might have interfered with successful participation in the study or risked the subject's safety in the opinion of the investigators.

Interventions: Subjects assigned to the experimental group (WBE group)and control group (placebo group) consumed 3,000 mg of WBE or placebo daily for 12 weeks (3 capsules, 3 times a day), respectively. WBE and placebo capsules were supplied by DongA One Corp. (Seoul, Republic of Korea).

WBE for use in capsules was produced by a standardized manufacturing process with 3 main steps (destarching,

extraction and drying) as described previously[9]. Briefly, starch in and attached to wheat bran was removed by successive sieving, stirring, sieving and decanting. In the extraction step, active components such as arabinoxylan were extracted with hot water and the supernatant was obtained through filtration. Finally, the supernatant was spray-dried to yield WBE. Each WBE capsule contained 333.3 mg of WBE. Each placebo capsule contained starches and dyes to match the capsules for size, color, opacity and odor.

During the study, subjects were prohibited from taking any medications or dietary supplements with the purpose of improving cognitive function. Medications that were taken for 4 or more weeks prior to participation in the study and were supposed not to affect the reliability of the study were permitted under a physician's control. All participants were asked to maintain their usual lifestyle (e.g., diet, physical activity, work and sleep habits) throughout the trial. Detailed dietary assessments were performed using the 3-day record method at visits 1 and 3.

Measurements

CNT: Neuropsychological function was assessed using the CNT (RAPAEL ComCog®, NEOFECT Co., Seoul Korea), including memory tests (visual learning test, verbal learning test, digit span test and visual span test), attention tests (visual continuous performance test/visual CPT, auditory continuous performance test/auditory CPT, visual controlled continuous performance test/visual controlled CPT and auditory controlled continuous performance test/auditory controlled CPT) and the trail-making test.

WMT: Subjects completed the visuospatial and verbal WMT subtests using SuperLab Pro 2.0 Software (Cedrus Co, San Pedro, California, USA). For the visuospatial WMT, a computer display was used to present subjects with a 4×4 matrix (total 16 boxes) containing 4 randomly scattered spots as the cue stimulus for 1 sec. Subjects were required to remember the positions of the spots. After the cue stimulus disappeared, another matrix containing 2 randomly scattered spots was presented as an interference stimulus for 1.5 sec. Finally, a test spot was presented and subjects were instructed to press a keyboard space bar as quickly as possible if the spot was located in 1 of the 4 cue stimulus positions.

The commonly used 2-back verbal WMT was used to assess verbal working memory. Subjects were presented with a random set of 90 Korean letters. Letters were shown consecutively, each letter was displayed on the computer display for 900 ms followed by a blank screen for 100 ms and then the next letter. Participants were required to remember the letter character displayed on the computer screen and to press a keyboard spacebar if the letter was the same as that presented in the previous 2 stimuli. Accuracy (the number of correct responses/the total number of targets) and response time (interval between target presentation and pressing the space bar) were measured.

Other examinations: The K-MMSE, Brief Cognitive Rating Scale (BCRS) and Prospective and Retrospective Memory Questionnaire(PRMQ) were used to measure cognitive function and the 36-item Short-Form Health Survey (SF-36) and Perceived Stress Scale (PSS) were used to evaluate quality of life. Additionally, laboratory tests were conducted for safety assessments including urinalysis, complete blood counts and quantification of serum total protein, albumin, alkaline phosphatase, γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, glucose, creatine kinase, total cholesterol, triglyceride and urinalysis. Venous blood samples were also collected for the quantification of serum Brain-derived neurotrophic factor (BDNF).

Statistical analysis: To determine the sample size required to verify superiority of the test group compared to the placebo group after the 12-week intervention, a mean between-group difference inchange in CNT visual learning test score of 0.83±1.56 was used. Assuming 80% power, a2-tailed α of 0.05, 20% attrition and equal sample sizes for both groups, a total of 70 subjects (35 subjects in each group) was required. End point analyses were performed on the intention-to-treat (ITT) population and safety analyses were performed on the safety population using SAS® version 9.2 software (SAS Institute, USA). Data were presented as the Mean±Standard deviation for all continuous variables.

The primary and secondary efficacy variables were the change scores from the baseline to 12 weeks measures. Differences among baseline, week 6 and 12 within a group as well as differences between two groups after 12 weeks treatment were analyzed. Linear mixed-effects models were used to analyze both differences among continuously measured data within a group and repeatedly measured data between groups. Treatment group, treatment visit and the interaction term (treatment group×treatment visit) were included as fixed effects. Baseline demographic characteristics were compared between groups using independent t-tests for the continuous variables and Chi-square test for the frequencies of categorized variables. Differences were considered to be statistically significant when $p<0.05$.

RESULTS

Subject characteristics: During the study, 4 subjects (2 in the WBE group and 2 in the placebo group) withdrew from the study. Among 66 subjects who completed the study, 2violated the study protocol (pill compliance below 70%). No subjects were excluded from the efficacy analysis in accordance with the protocol plan determining the ITT population. A study flow diagram is shown in Fig. 1.

There were no significant between-group differences in baseline characteristics except for height of the anthropometric parameter (p = 0.091, Table 1). It was determined that anthropometric height did not influence the efficacy or safety of the study, so no adjustments were made.

Safety: There were no significant between-group differences in changes in any of the safety parameters from baseline to end-of-study. All laboratory test values were within normal reference ranges. A total of 5 adverse events were documented in 5 individuals (3 in the WBE group [1 gingival pain, 1 tooth extraction and 1 knee joint pain] and 2 cases in the placebo group[1 indigestion, 1 dyspnea]). None of the adverse events were attributable to the ingestion of WBE in the WBE group.

Efficacy

CNT scores: visual learning test: The 16 different figures were presented, at one-second intervals, in fixed order, over five learning trials (T1~T5), the participants were asked to

Table 1: Baseline characteristics of participants by assignment

Demographic parameters	WBE (n = 35)	Placebo (n = 35)	Total (n = 70)	p-value
Sex (Male/female)	16/19	13/22	29/41	0.467
Age (year)	63.37±3.40	66.14±4.36	65.76±3.90	0.412
Height (cm)	161.74±8.91	158.31±7.76	160.03±8.47	0.091
Weight (kg)	63.31±9.42	60.50±9.45	61.90±9.47	0.217
BMI (kg m^{-2})	24.16±2.60	24.08±2.79	24.12±2.68	0.902
Alcohol consumption (persons)	10 (28.5%)	12 (34.2%)	22 (31.4%)	0.607
Smoker (persons)	2 (5.7%)	0 (0%)	2 (2.8%)	0.493
Education (year)	10.00±3.79	10.46±3.7	10.23±3.72	0.611
K-MMSE score	27.29±1.34	27.14±1.52		0.703

Values are presented as Mean±SD, p-values are comparisons between the two groups using independent t-tests, WBE: Wheat bran water extract, BMD: Body mass index, K-MMSE: Korean mini-mental state examination

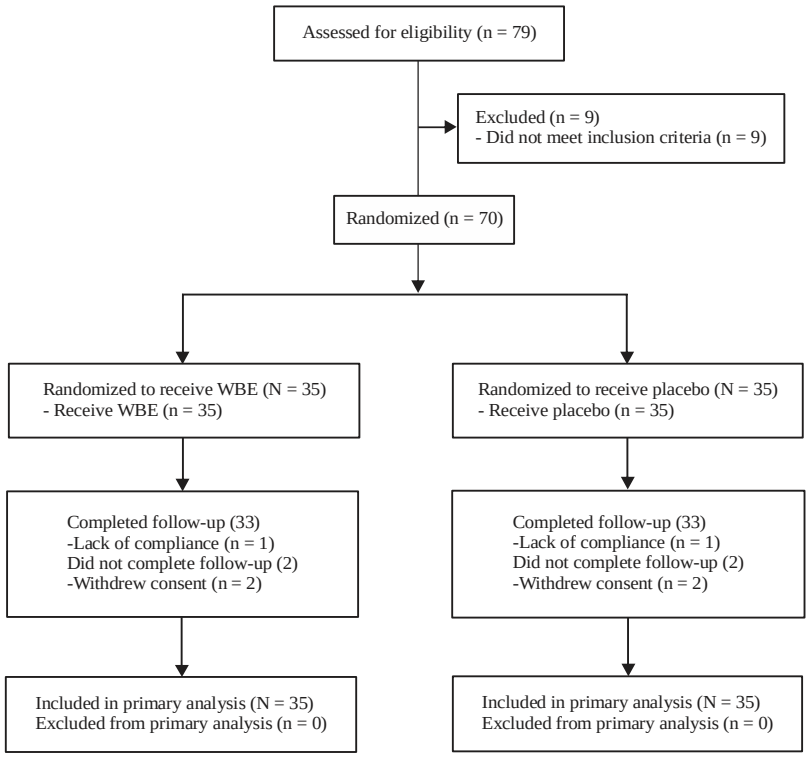

Fig. 1: Flow of participants through the study

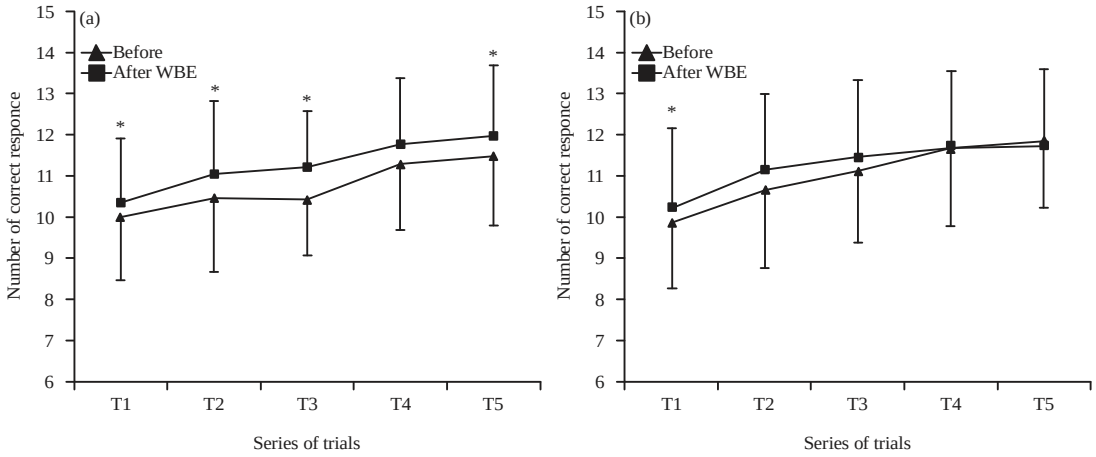

Fig. 2(a-b): Learning curves of visual learning test, (a) After administration of WBE, the number of correct response was increased significantly than before at four points of trails (T1, T2, T3 and T5) and (b) In the placebo group, the number of correct response was increased at T1 only. WBE: Wheat bran water extract, *p<0.05 analyzed by linear mixed model

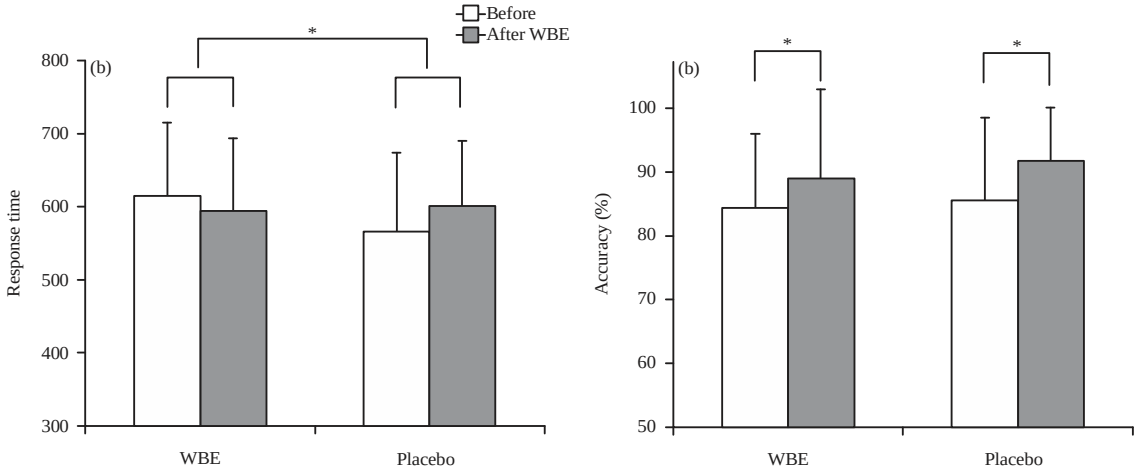

Fig. 3(a-b): Result of Visual working memory task (WMT), (a) The reaction time of visual WMT was significantly shorter than before in the WBE group but not in the placebo group and (b)The accuracy of visual WMT was improved in both groups. WBE: Wheat bran water extract, *p<0.05analyzed by linear mixed model

recall as many figures as they can in any order. Participants were performed this test twice, before and after administration of WBE (WBE group) or placebo (placebo group). In the WBE group, T1, T2, T3 and T5 scores were significantly increased after administration of WBE to the scores of 10.36±1.54, 11.03±1.79, 11.21±1.36 and 11.97±1.70 from 10.00±1.33, 10.46±1.54, 10.43±1.54 and11.49±1.70, respectively ($p<0.05$, Fig. 2). However, only T1 score was increased compared to before in the placebo group.

Visual WMT scores: Visual WMT, like as visual learning test, was performed twice, before and after administration of WBE (WBE group) or placebo (placebo group). In the WBE group, the reaction time was significantly faster than before from 615.24±98.95 msec to 594.38±98.29 msec after administration of WBE ($p = 0.042$) but not in the placebo group (Fig. 3a). The accuracy was improved in both groups (Fig. 3b).

SF-36 scores: In the WBE group, SF-36 scores increased from 70.30±16.76 at baseline to 75.43±12.82 at end-of-study ($p = 0.032$). In contrast, there was no change in SF-36 scores between baseline and end-of-study in the placebo group. Accordingly, there was a statistically significant difference in change in SF-36 score between groups ($p = 0.047$).

Other assessments: There were no significant between-group differences in changes in K-MMSE score, BCRS score, PRMQ score, PSS score or serum BDNF level from baseline to end-of-study.

DISCUSSION

In a double-blind randomized controlled trialof WBE in older adults with subjective memory impairment, WBE intake (3 g/day for 12 weeks) improved vision-related cognition including visual memory and visuospatial working memory as well as quality of life in the absence of any serious adverse effects.

Wheat is primarily composed of starch, proteins and dietary fibers including arabinoxylan and β-glucan[11,12]. Arabinoxylan is a polymer wherein arabinose and xylose are linked at the β-1,4 position in the form of xylopyranosyl residue[12]. Previous animal studies have shown that arabinoxylan supplementation increases the brain expression of choline acetyltransferase, an enzyme that catalyzes generation of acetylcholine from acetyl CoA and choline and muscarinic acetylcholine receptors in a manner associated with improved visuospatial working memory in rats after scopolamine-induced amnesia[13]. Taken together, it can be hypothesized that WBE supplementation enhances cognitive function by promoting cholinergic neurotransmission. Thus, the actions of WBE may be similar to those of cholinesterase inhibitors such as donepezil.

WB and WBE have also been reported to attenuate Aβ-mediated cell death by decreasing oxidative stress and subsequent apoptosis *in vitro*[6,7]. *In vivo*, WB and WBE supplementation improved visuospatial working memory in rodents with memory impairment resultant from Aβ infusion or Aβ overexpression[6,7]. Furthermore, arabinoxylan supplementation up-regulated the expression of neurotrophic BDNF after scopolamine-induced amnesia in rats[13]. Similarly, butyrate, the fermentation product of arabinoxylan and β-glucan in the large intestine, was found to improve memory function in rodents by inhibiting his tone deacetylase activity[14]. Although we did not observe any effects of WBE intake on serum BDNF in the present study, it can be suggested that WBE supplementation improves cognition by preventing neuronal cell death and enhancing trophic support to neurons. To this end, WBE may have particular utility in the context of AD.

With regard to VaD, previous animal studies have shown that WB and WBE improve water maze escape latencies and attenuates myelin degradation in a rat model of bilateral common carotid artery occlusion[8,9]. β-glucan was also reported to prevent ischemic damage via an antioxidant mechanism, whereas arabinoxylan and arabinose were found to inhibit astrocytic activation and prevent loss of the myelin sheath[8,15-17]. VaD is attributed to reduced blood supply to the brain caused by blood vessel damage, ultimately resulting in subcortical white matter lesions and cognitive impairment[18-20]. Therefore, the myelin-protective effects of WBE may promote cognitive function in individuals with diffuse white matter lesions related to VaD.

It is notable that in the present study, visual memory but not verbal memory, was improved by WBE supplementation. Visual memory is processed and conveyed via a long neural pathway from the visual cortex to the prefrontal area via the parietal and temporal lobes[21]. Therefore, it can be hypothesized that visual-related memory is particularly vulnerable to damage associated with MCI and VaD. As per the abovementioned studies, WBE intake may have exerted neuroprotective effects in both gray and white matter to improve neurotransmission related to visual memory in individuals with age-related cognitive decline in the present study.

Finally, quality of life was evaluated using the SF-36 and the scores were significantly improved after 12 weeks of WBE supplementation in the experimental group. This result suggested that better quality of life was related to improvements in cognitive function, although additional studies are needed to examine the possible direct effects of WBE on emotional processing and mood regulation.

Future studies are required to identify the specific actions of distinct *Triticum aestivum* L. components and to determine the exact mechanisms by which WBE promotes cognitive function in humans. This knowledge will ultimately facilitate the use of WBE in dietary interventions and the development of related therapeutics for the treatment of age-related cognitive decline.

CONCLUSION

In the present study, 12 weeks WBE supplementation significantly increased visual cognition and quality of life in older adults with subjective cognitive impairment as assessed using the CNT, WMT and SF-36. In addition, WBE supplementation up to 3 g/day did not produce any adverse events in humans.

SIGNIFICANCE STATEMENT

This study discovers the effects of WBE that can be beneficial for people who are suffered from age-related

cognitive decline. It is the first human study about the cognitive enhancing effects of WBE based on previous animal studies. This study will help the researcher to uncover the critical areas of cognitive disorders such dementia that many researcher were not able to explore. Thus the results of this study on development of novel therapeutic agent for cognitive disorders may be arrived at.

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