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Improvement of Cognitive Function by Combining a Food Containing Fermented Rice Bran with Light Exercise
- A Randomized, Placebo-controlled, Double-blind, Parallel-group Study -

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This study aimed to verify the impact of consuming food containing fermented rice bran with 3-(4-hydroxy-3-methoxyphenyl) propionic acid (HMPA) combined with light exercise on cognitive function and muscle mass. This randomized, placebo-controlled, double-blind, parallel-group study involved healthy men and women aged 65-79. Participants consumed either rice bran fermented food containing HMPA or a placebo, in combination with light exercise, for 24 weeks. The primary outcome measures were Cognitrax and muscle mass. Secondary outcomes included body composition, Mini-Mental State Examination (MMSE), Self-rating Depression Scale (SDS), Apathy Scale, and biochemical tests (pentosidine and homocysteine). Analysis of the per-protocol set (n=67) revealed a significant improvement in change of Cognitrax reaction time (subject score) in the active food group after 24 weeks compared to the placebo group. No significant difference in muscle mass was observed between the two groups. Subgroup analysis of individuals without exercise habits also showed no significant difference in muscle mass between the active food and placebo groups. However, significant improvements in the active food group compared to the placebo group were noted in the following: change in Cognitrax Neurocognition Index (NCI) (standardized score, % score) after 24 weeks, composite memory (subject score, standardized score, % score) after 24 weeks, verbal memory (subject score) after 12 and 24 weeks, and reaction time (% score) after 24 weeks. The results of this study confirmed that consuming foods containing fermented rice bran with HMPA combined with light exercise improved reaction time, a part of cognitive function. Additionally, for individuals without exercise habits, this combination improved NCI, composite memory, verbal memory, and reaction time, a part of cognitive function (UMIN000050287).

Keywords: HMPA / Cognitive function / Randomized controlled study / Rice bran fermented product

Introduction

Since the World Health Organization (WHO) introduced the concept of a "healthy lifespan" in 2000, interest has increased in how to extend the period during which individuals can live healthily. In Japan, the Ministry of Health, Labour and Welfare developed "Health Japan 21 (Third Term)," which highlights extending a healthy lifespan as a primary objective (Ministry of Health, Labour and Welfare, 2023). Factors that hinder a healthy lifespan include metabolic syndrome, locomotive syndrome, and cognitive decline (Shibata, 2021), and it is suggested that daily exercise and diet can prevent and improve each of these conditions.

Polyphenols, known for their bioregulatory functions, are found in vegetables and fruits. Despite their numerous physiological benefits, their extremely low bioavailability is referred to as the "polyphenol paradox" (Osakabe, 2016). One explanation for this involves intestinal bacteria, which metabolize various polyphenols into lower molecular weight metabolites that are then absorbed and exert their functions (Mitsui et al., 2022). Polyphenols like curcumin, γ-oryzanol, hesperidin, and chlorogenic acid commonly produce 3-(4-hydroxy-3-methoxyphenyl) propionic acid (HMPA) as a metabolic product (Tan et al., 2015; Fujiwara

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et al., 1983; Roowi et al., 2009; Stalmach et al., 2009). Focusing on HMPA, we developed a food material called "fermented rice bran" that contains HMPA and confirmed its effects in preventing and improving metabolic syndrome, including anti-obesity, blood sugar improvement, and cholesterol improvement effects (Yoshino et al., 2021; Yoshino et al., 2022a; Yoshino et al., 2022b; Yoshino et al., 2023). Studies on HMPA intake in an obese mouse model showed significant improvements in fat accumulation from a high-fat diet and in lipid-related parameters in the liver and blood (Ohue-Kitano et al., 2019). In that study, 4-hydroxy-3-methoxycinnamic acid reproduced the previously reported anti-obesity effect (Wang et al., 2015), which was found to result from its metabolism to HMPA in the mouse intestine, indicating that HMPA is the active molecular entity (Ohue-Kitano et al., 2019).

Similarly, continuous intake of food containing 4-hydroxy-3-methoxycinnamic acid has been reported to improve cognitive function (Kudoh et al., 2020), suggesting that HMPA, an active molecular entity, also has this effect. Additionally, tests using central nervous system glial cells (astrocytes) showed that HMPA promotes the expression of aquaporin 4, which aids in brain waste removal, and TGF-β and IL-10, which are anti-inflammatory cytokines in the brain (Nishitani Y. JP Patent 6236185), indicating its potential to improve cognitive decline. HMPA has also been shown to be rapidly absorbed and retained in muscle tissue for up to six hours after administration in rats (Abe et al., 2023), suggesting its potential impact on muscles. A study using a rat model of disuse muscle atrophy confirmed that HMPA suppresses muscle mass loss and activates muscle metabolism-related factors such as Akt and AMPK (Kayaki et al, 2023). Therefore, HMPA may improve the three major factors impeding a healthy lifespan: metabolic syndrome, locomotive syndrome, and cognitive decline. However, no human studies have yet examined its effects on locomotive syndrome and cognitive decline.

Therefore, the purpose of this study was to verify the effects of continuous intake of fermented rice bran containing HMPA in combination with light exercise on cognitive function and muscle mass. Specifically, a placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy adult men and women aged between 65 years or older and less than 80 years old in which 100 mg/day of fermented rice bran containing HMPA was taken for 24 weeks in combination with light exercise.

Participants and Methods

1. Study implementation system

This study was conducted after receiving review and approval (approval date January 25, 2023, approval number 2022-10) from the Hokkaido Information University Bioethics Committee (IRB number 11000162), which consists of independent third parties not involved in the study. The study adhered to the Ethical Guidelines for Medical and Health Research Involving Human Subjects (March 10, 2022, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and Ministry of Economy, Trade and Industry Notification No. 1, partially revised). It complied with the principles outlined in the Declaration of Helsinki (revised at the World Medical Association General Assembly in Fortaleza, October 2013).

This study was conducted at the Hokkaido Information University Health Information Science Research Center from May 10, 2023 (the start date of the pre-observation period) to November 27, 2023 (the final examination date). There were no modifications to the study plan during the study. The study details were registered with UMIN-CTR before commencement and were managed by the Health Information Science Center of Hokkaido Information University (UMIN000050287).

2. Participants

A consent form was used to brief potential participants of the study's objectives, significance, inclusion and exclusion criteria, test foods, methodologies, procedures, management protocols, and other pertinent details, as well as the specific study timeline before the study commenced. Their voluntary written consent was obtained, and only those who consented were considered eligible as potential study participants. Preliminary assessments were conducted on consenting candidates, and eligibility was determined based on predefined inclusion and exclusion criteria. Selected by the principal investigator as suitable participants, a total of 70 participants were included in the study.

Selection criteria: (1) Participants who agree to participate in this study with a written informed consent., (2) Japanese healthy males and females aged 65-79 years old at the time of screening test, (3) Participants who are concerned about memory loss due to aging, or whose memory loss has been pointed out by others, (4) Participants whose relatively low the standardized score of composite memory measured by Cognitrax at the time of screening test, (5) Participants who can write diary and questionnaire, visit an inspection facility and receive examinations in designated days.

Exclusion criteria were defined as follows: (1) Participants whose MMSE score is ≦ 23 points, (2) Participants who are under medication for dementia, Alzheimer's disease, psychiatric disorder and cerebrovascular disease, (3) Participants who have a history or are suspected patient of cranial nerve disease and psychiatric disorders, (4) Participants with musculoskeletal disorders or injuries that limit physical activity, (5) Participants who receiving exercise therapy, or who have been restricted from exercising by a physician, (6) Participants with implantable electronic medical devices, (7) Participants who are under treatment or have a history of serious diseases, or who affected with infectious diseases requiring reports to the authorities, (8) Participants with major surgical history relevant to the digestive system, (9) Participants with significant abnormalities on clinical and physical examination, (10) Participants with severe anemia (11) Participants with dysphagia, (12) Participants who have performed a cognitive test similar to this study within 3 mos. prior to this study, (13) Participants who are difficult to perform cognitive tests, (14) Participants who are unable to perform the specified exercise program, (15) Participants who may develop allergies related to the study, (16) Participants who regularly take medicine, functional foods which would affect cognitive function or muscle mass, (17) Heavy smokers, alcohol addicts or participants with disordered lifestyle, (18) Participants who habitually engage in strenuous physical activities, (19) Participants who are engaged in physical labor, (20) Participants who donated either 400 ml whole blood within 16 wks. (women), 12 wks. (men), 200 ml whole blood within 4 wks., or blood components within 2 wks., prior to this study, (21) Participants who feel bad mood by blood collection, (22) Participants who currently participate in other clinical trials, or participated within the last 4 wks. prior to this study (23) Participants whose lifestyle is expected to change during the study period, (24) Participants who are ineligible due to physician's judgment.

3. Test food

Two types of test foods were used in the study: active food and placebo food. The active food was a hard capsule containing 100 mg of fermented rice bran containing 23 mg of HMPA (brand name: ACTIBODY® RB, manufactured by Maruzen Pharmaceuticals Co., Ltd.) per tablet. The placebo food had the fermented rice bran substituted with dextrin and was identical in appearance and flavor to the active food. Participants were instructed to consume one tablet of the test food daily with water or hot water for 24 weeks. The dosage of fermented rice bran with HMPA for this study was determined according to that used in a previous clinical study confirming its impact on postprandial blood glucose, which is closely associated with cognitive function (Yoshino et al., 2022a).

4. Light exercise load

The light exercise load consisted of leg-raising exercises with knee joint extension in a seated position. One set consisted of lifting each leg 10 times, with two sets per day, in the morning and evening. The light exercise was designed with reference to the exercise program presented in the Ministry of Health, Labour and Welfare's "National Health Promotion Movement in the 21st Century (Healthy Japan 21)" as exercises to maintain and improve mobility, which declines with age, and was set as exercises to train the quadriceps, which are closely related to the stability of walking and standing movements, taking into consideration continuity and safety, such as the strain on the knees and the risk of falling.

5. Rationale for the number of enrolled participants

No studies to date have investigated the effects of consuming fermented rice bran for 24 weeks in humans, combined with light exercise, on cognitive function and muscle mass. Consequently, the sample size was not determined based on statistical power calculations but rather on feasibility, drawing from typical exploratory studies. The target enrollment was set at 35 participants per group, accounting for potential discontinuations, dropouts, and exclusions from analysis during the study period.

6. Study methods

This study was conducted as a randomized, placebo-controlled, double-blind, parallel-group study. A total of 69 participants were randomly assigned to either the active food group or the placebo group by an allocation manager not directly involved in the study. The randomization was performed using a stratified permuted block method with gender, age, Neurocognition Index (NCI) standardized score, and muscle mass as stratification factors. The allocation manager generated an allocation list detailing the assignment results, which was securely stored on a password-protected electronic medium. This allocation list remained undisclosed to all study personnel until the analysis participants and analysis methods were finalized, ensuring the blinding protocol was maintained throughout

the study.

On each test day, the following assessments were conducted: interviews, anthropometric measurements (including body weight, body fat percentage, BMI, muscle mass, lean mass, skeletal muscle mass, and skeletal muscle index (SMI)), vital signs (systolic blood pressure, diastolic blood pressure, pulse), blood tests (including WBC, RBC, Hb, Ht, Plt, AST, ALT, γ-GTP, ALP, LDH, FIB-4 index, BUN, CRE, UA, TC, LDL-C, HDL-C, TG, fasting blood glucose, and HbA1c), Cognitrax tests (Verbal Memory Test (VBM), Visual Memory Test (VIM), Finger Tapping Test (FTT), Symbol Digit Coding (SDC), Stroop Test (ST), Shifting Attention Test (SAT), Continuous Performance Test (CPT)), Self-Rating Depression Scale (SDS), Apathy Scale, Brief Job Stress Questionnaire area B, and brief-type self-administered diet history questionnaire (BDHQ). Additionally, biochemical tests (pentosidine and homocysteine) were conducted on the test days before and after the 24-week intake period. The Mini-Mental State Examination (MMSE) was performed 24 weeks after intake, using screening test scores as a baseline for comparison.

7. Endpoints

The following items were set as primary and secondary endpoints.

1) Primary endpoints

Cognitrax, muscle mass

2) Secondary endpoints

MMSE, emotional function assessment (SDS, Apathy Scale), body composition (weight, body fat percentage, BMI, lean mass, skeletal muscle mass, SMI), biochemical test (pentosidine, homocysteine)

8. Statistical analysis

The results are expressed as mean ± standard deviation. Background information on the participants was analyzed using two independent sample t-tests, the Mann-Whitney U test or Fisher's exact test. Comparisons between the active food group and the placebo group were conducted at each test using two independent sample t-tests. An additional analysis was performed on participants who responded "no" to the question "Do you usually consciously move your body or exercise?" in the lifestyle questionnaire administered during the screening test. Statistical analysis was performed using SPSS (version 25, IBM, Tokyo) without adjustment for multiplicity, and a significance level of 5% was applied for two-sided tests.

Results

1. Study participant's background

The study flow chart is shown in Figure 1.

Among 181 potential study participants who provided consent, 70 participants were selected in this study. One participant withdrew from the study before pre-intake test due to starting medication that met exclusion criteria, leaving 69 participants allocated to the study. Subsequently,

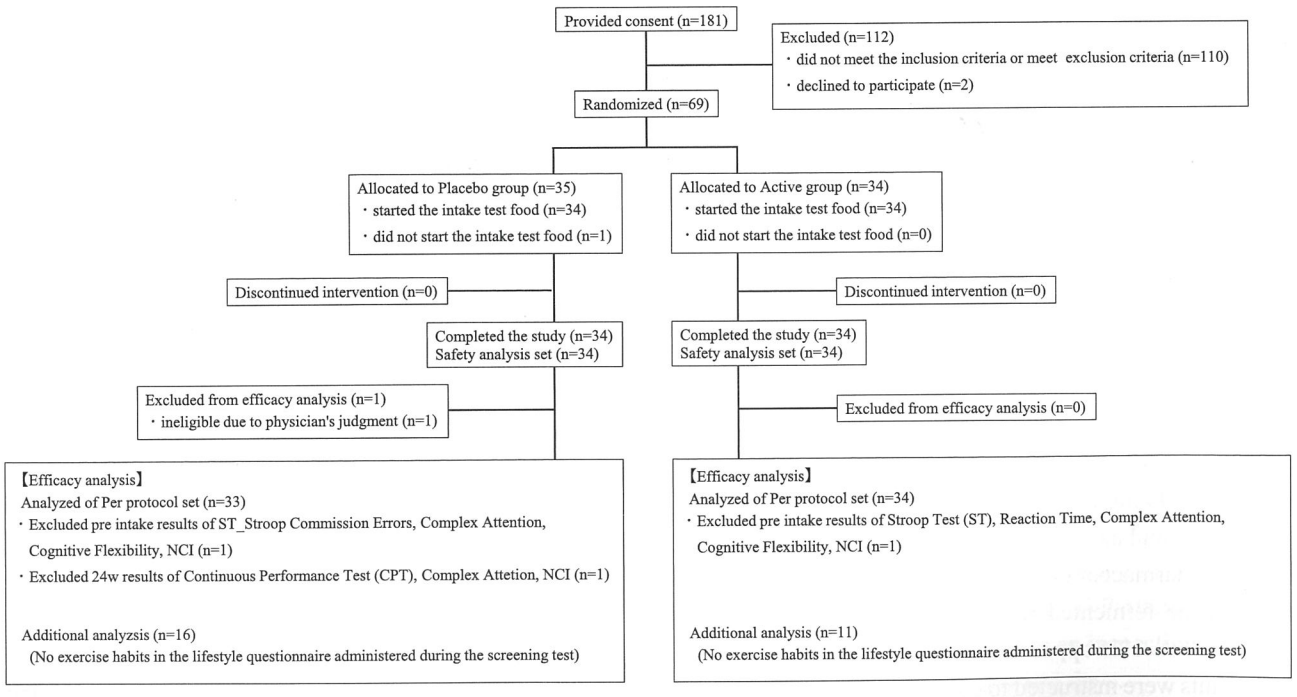

Fig.1. Flow chart showing the number of participants in the active and placebo groups at each stage of the study

one participant in the placebo group withdrew from the study before starting the test food intake due to cataract surgery, as determined by the principal investigator. These withdrawals resulted in 68 participants initiating the test food intake. No participants discontinued or dropped out during the intake period, and all 68 completed the study as planned. During a case review before case fixation, one participant who had started antihypertensive and insomnia medications after beginning the test food intake and had been on these medications for an extended period was excluded from the efficacy analysis by the principal investigator. Therefore, 67 participants were included in the efficacy analysis. Additionally, for Cognitrax assessments, if a participant did not respond correctly, resulting in a % score of 0, or if the principal investigator deemed the results invalid due to a misunderstanding of test rules, the relevant test items and derived scores were excluded from the analysis.

Table 1 presents the background information of the efficacy analysis participants. The average test food intake rate was 98.61% in the placebo group (minimum 80.36%) and 99.35% in the active food group (minimum 83.33%). The average participation rate in light exercise was 99.58% in the placebo group (minimum 97.62%) and 99.55% in the active food group (minimum 94.05%). Statistical analysis showed no significant differences between the active food and placebo groups in terms of background information, test food intake rate, or participation rate in light exercise.

Table 1. Baseline characteristics of participants in the PPS

Item	Placebo (n=33)	Active (n=34)
Sex (Male/Female)	14/19	13/21
Age (years)	69.27 ± 3.35	69.91 ± 3.84
Height (cm)	159.17 ± 7.81	158.30 ± 7.92
Weight (kg)	53.72 ± 7.00	54.17 ± 10.22
Body fat percentage (%)	25.79 ± 7.77	25.69 ± 7.88
BMI (kg/m^2)	21.18 ± 2.12	21.55 ± 3.36
NCI_standardized score	101.58 ± 9.31	101.15 ± 8.99
Muscle mass (kg)	37.64 ± 6.44	37.72 ± 6.93

Mean ± standard deviation.
No significant difference between the groups.

2. Cognitrax

Table 2 (Part 1-3) illustrates the progression of Cognitrax scores. The active food group exhibited a significant improvement in reaction time (subject score) change after 24 weeks of intake compared to the placebo group. Significant differences in the percentage scores for simple attention and motor speed were observed between the active food and placebo groups after 12 weeks of intake. However, no significant differences were noted between the groups after 24 weeks of intake in these categories.

3. Body composition

Table 3 presents the changes in body composition over time. No significant differences were observed between the active food group and the placebo group in terms of muscle mass and other body composition measures.

4. MMSE, emotional function assessment (SDS score, Apathy Scale), biochemical test (pentosidine, homocysteine)

Table 4 displays the trends in MMSE scores, emotional function assessments (SDS score, Apathy Scale), and biochemical tests (pentosidine, homocysteine). No significant differences were observed between the active food group and the placebo group in these measures.

5. Additional analyses

An additional analysis was performed on participants who responded "no" to the question "Do you usually consciously move your body or exercise?" in the lifestyle questionnaire administered during the screening test. There were 16 participants in the placebo group and 11 participants in the active food group who met this criterion.

Background information for the additional analysis participants is detailed in Table 5. No statistically significant differences were found between the active food group and the placebo group across all measured parameters.

Table 6 (Part 1-3) illustrates the progress of Cognitrax for the additional analysis participants. Significant improvements were observed in the active food group compared to the placebo group in NCI (standardized score, % score) after 24 weeks of intake, composite memory (subject score, standardized score, % score) after 24 weeks of intake, verbal memory (subject score) after 12 and 24 weeks of intake, and reaction time (% score) after 24 weeks of intake. Furthermore, a notable difference was noted between the active food group and the placebo group in the change in motor speed (subject score, standardized score, % score) after 12 weeks of intake. However, this difference was not significant after 24 weeks of intake.

Table 7 displays the changes in body composition over time. No statistically significant differences were observed between the active food group and the placebo group in terms of muscle mass and other body composition measures.

Table 2. Scores for each cognitive function domain in Cognitrax (PPS) (Part 1)

Item				pre-intake	12w	24w
NCI	Standardized score	Placebo	Score	101.44 ± 9.42	104.44 ± 8.44	103.91 ± 6.98
			Δ		2.97 ± 4.17	2.16 ± 4.55
		Active	Score	101.06 ± 9.12	104.03 ± 8.68	104.21 ± 6.88
			Δ		2.85 ± 4.40	3.50 ± 4.62
	% score	Placebo	Score	54.56 ± 20.32	60.91 ± 19.47	59.78 ± 17.24
			Δ		6.19 ± 9.08	4.35 ± 8.26
		Active	Score	53.12 ± 21.34	60.24 ± 19.11	60.42 ± 16.70
			Δ		6.82 ± 10.09	8.13 ± 10.86
Composite Memory	Subject score	Placebo	Score	93.97 ± 8.67	95.69 ± 7.53	94.21 ± 7.38
			Δ		1.41 ± 6.68	0.24 ± 6.42
		Active	Score	92.74 ± 9.30	94.59 ± 8.89	94.79 ± 8.38
			Δ		1.85 ± 7.64	2.36 ± 7.71
	Standardized score	Placebo	Score	101.64 ± 14.93	104.84 ± 13.38	102.18 ± 12.91
			Δ		2.75 ± 12.57	0.55 ± 11.61
		Active	Score	99.76 ± 16.13	103.09 ± 14.72	103.45 ± 13.93
			Δ		3.32 ± 13.64	4.12 ± 13.83
	% score	Placebo	Score	55.73 ± 28.92	59.94 ± 26.12	55.61 ± 27.41
			Δ		3.06 ± 25.37	-0.12 ± 21.55
		Active	Score	52.26 ± 29.69	57.44 ± 29.85	57.85 ± 27.92
			Δ		5.18 ± 28.01	6.48 ± 28.29
Verbal Memory	Subject score	Placebo	Score	51.24 ± 6.36	51.97 ± 5.24	52.03 ± 5.32
			Δ		0.41 ± 4.76	0.79 ± 5.06
		Active	Score	50.68 ± 5.91	52.38 ± 5.96	52.76 ± 4.98
			Δ		1.71 ± 4.62	2.30 ± 5.11
	Standardized score	Placebo	Score	105.33 ± 18.93	107.53 ± 15.37	107.79 ± 15.65
			Δ		1.38 ± 14.28	2.45 ± 15.32
		Active	Score	104.09 ± 16.66	109.15 ± 16.31	110.18 ± 14.03
			Δ		5.06 ± 13.31	6.70 ± 14.71
	% score	Placebo	Score	63.18 ± 32.67	65.34 ± 29.72	67.30 ± 28.58
			Δ		0.44 ± 28.08	4.12 ± 23.10
		Active	Score	59.74 ± 29.52	67.82 ± 30.97	70.48 ± 26.40
			Δ		8.09 ± 27.90	11.82 ± 29.34
Visual Memory	Subject score	Placebo	Score	42.73 ± 4.56	43.72 ± 4.11	42.18 ± 4.35
			Δ		1.00 ± 5.07	-0.55 ± 4.58
		Active	Score	42.06 ± 5.64	42.21 ± 5.48	42.03 ± 5.21
			Δ		0.15 ± 5.71	0.06 ± 6.06
	Standardized score	Placebo	Score	97.52 ± 13.13	101.00 ± 12.94	96.27 ± 13.66
			Δ		3.63 ± 15.83	-1.24 ± 13.86
		Active	Score	96.00 ± 17.24	96.24 ± 16.79	95.88 ± 15.27
			Δ		0.24 ± 17.67	0.03 ± 18.74
	% score	Placebo	Score	46.55 ± 25.35	52.53 ± 28.04	43.52 ± 27.49
			Δ		6.25 ± 32.72	-3.03 ± 30.64
		Active	Score	43.38 ± 30.62	44.00 ± 30.98	42.70 ± 30.17
			Δ		0.62 ± 31.65	-0.39 ± 32.75
Psychomotor Speed	Subject score	Placebo	Score	151.27 ± 15.75	155.00 ± 15.60	152.36 ± 14.65
			Δ		3.31 ± 6.68	1.09 ± 9.98
		Active	Score	154.65 ± 18.72	156.65 ± 20.07	157.06 ± 18.05
			Δ		2.00 ± 7.47	2.82 ± 7.86
	Standardized score	Placebo	Score	105.61 ± 11.75	108.38 ± 12.04	106.88 ± 12.25
			Δ		2.69 ± 5.21	1.27 ± 6.70
		Active	Score	108.09 ± 10.40	109.41 ± 11.26	109.91 ± 9.21
			Δ		1.32 ± 5.44	1.88 ± 5.80
	% score	Placebo	Score	61.58 ± 25.24	66.50 ± 23.17	63.85 ± 25.50
			Δ		4.81 ± 10.33	2.27 ± 14.88
		Active	Score	67.88 ± 22.20	69.35 ± 21.74	71.52 ± 18.28
			Δ		1.47 ± 10.92	3.85 ± 11.55

Placebo group：excluded pre-intake results of ST_Stroop Commission Errors, Complex Attention, Cognitive Flexibility, NCI (n=1). excluded 24w results of Continuous Performance Test (CPT), Complex Attention, NCI (n=1).

Active group：excluded pre intake results of Stroop Test (ST), Reaction Time , Complex Attention, Cognitive Flexibility, NCI (n=1)

Mean ± standard deviation.

Δ：change compared to baseline.

*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 2. Scores for each cognitive function domain in Cognitrax (PPS) (Part 2)

Item				pre-intake	12w	24w	
Reaction Time	Subject score	Placebo	Score	784.42 ± 144.03	786.22 ± 126.09	785.52 ± 106.60	
			Δ		2.50 ± 107.30	1.09 ± 91.13	
		Active	Score	807.67 ± 153.51	776.88 ± 146.20	771.42 ± 122.52	
			Δ		-33.06 ± 65.37	-41.53 ± 78.21	*
	Standardized score	Placebo	Score	94.24 ± 16.86	94.34 ± 13.98	94.55 ± 12.31	
			Δ		0.16 ± 11.71	0.30 ± 9.92	
		Active	Score	92.39 ± 15.25	95.82 ± 14.66	96.45 ± 11.96	
			Δ		3.55 ± 7.20	4.41 ± 8.64	#
	% score	Placebo	Score	39.94 ± 25.07	41.41 ± 24.23	40.76 ± 22.42	
			Δ		1.47 ± 17.31	0.82 ± 14.94	
		Active	Score	38.36 ± 21.97	44.65 ± 25.69	44.36 ± 22.92	
			Δ		6.73 ± 13.21	6.75 ± 13.55	#
Complex Attention	Subject score	Placebo	Score	7.03 ± 5.89	5.25 ± 4.10	5.28 ± 3.37	
			Δ		-1.84 ± 4.39	-1.71 ± 4.46	
		Active	Score	8.91 ± 7.66	6.94 ± 5.89	7.24 ± 6.01	
			Δ		-2.00 ± 4.32	-2.00 ± 4.41	
	Standardized score	Placebo	Score	107.94 ± 11.21	111.13 ± 7.29	111.19 ± 6.54	
			Δ		3.29 ± 8.13	3.23 ± 7.90	
		Active	Score	105.64 ± 12.21	108.88 ± 9.27	108.52 ± 9.01	
			Δ		3.27 ± 7.06	3.38 ± 7.33	
	% score	Placebo	Score	68.38 ± 24.18	75.19 ± 15.61	75.91 ± 14.24	
			Δ		7.03 ± 17.87	7.48 ± 16.15	
		Active	Score	63.12 ± 26.54	70.82 ± 20.50	69.85 ± 19.47	
			Δ		7.73 ± 15.93	7.75 ± 15.79	
Cognitive Flexibility	Subject score	Placebo	Score	33.34 ± 13.97	37.75 ± 11.01	37.61 ± 9.73	
			Δ		4.45 ± 8.80	4.28 ± 10.61	
		Active	Score	32.12 ± 16.71	35.24 ± 14.78	35.39 ± 14.13	
			Δ		3.42 ± 8.25	4.06 ± 8.75	
	Standardized score	Placebo	Score	100.00 ± 13.03	103.78 ± 9.81	104.00 ± 8.06	
			Δ		3.84 ± 7.46	3.91 ± 8.49	
		Active	Score	100.30 ± 11.93	102.56 ± 10.44	103.06 ± 9.33	
			Δ		2.36 ± 6.37	3.19 ± 7.05	
	% score	Placebo	Score	53.00 ± 24.94	59.16 ± 22.43	59.91 ± 19.33	
			Δ		6.16 ± 14.23	6.66 ± 15.57	
		Active	Score	52.24 ± 25.33	57.41 ± 21.76	57.76 ± 21.25	
			Δ		5.48 ± 15.07	6.53 ± 14.22	
Processing Speed	Subject score	Placebo	Score	50.27 ± 8.61	51.75 ± 6.35	51.94 ± 6.68	
			Δ		0.84 ± 4.91	1.67 ± 6.57	
		Active	Score	51.91 ± 7.84	53.62 ± 8.68	53.09 ± 6.63	
			Δ		1.71 ± 5.42	1.52 ± 5.44	
	Standardized score	Placebo	Score	113.18 ± 10.87	115.28 ± 8.46	115.58 ± 9.37	
			Δ		1.47 ± 6.56	2.39 ± 8.48	
		Active	Score	115.88 ± 8.32	118.09 ± 10.00	117.61 ± 6.93	
			Δ		2.21 ± 7.03	2.03 ± 6.94	
	% score	Placebo	Score	75.82 ± 19.31	81.38 ± 15.09	81.24 ± 16.99	
			Δ		4.19 ± 10.52	5.42 ± 15.42	
		Active	Score	82.38 ± 14.27	84.26 ± 13.60	85.76 ± 9.67	
			Δ		1.88 ± 10.67	3.79 ± 10.66	
Executive Function	Subject score	Placebo	Score	33.97 ± 13.61	38.19 ± 11.01	37.97 ± 9.86	
			Δ		4.09 ± 8.58	4.00 ± 10.45	
		Active	Score	32.26 ± 16.65	36.09 ± 14.87	36.42 ± 13.94	
			Δ		3.82 ± 8.22	4.67 ± 9.29	
	Standardized score	Placebo	Score	99.52 ± 12.87	103.09 ± 9.85	103.15 ± 8.39	
			Δ		3.63 ± 7.35	3.64 ± 8.26	
		Active	Score	99.50 ± 11.88	102.29 ± 10.64	102.73 ± 9.33	
			Δ		2.79 ± 6.48	3.55 ± 7.70	
	% score	Placebo	Score	52.03 ± 24.21	57.66 ± 22.73	58.00 ± 19.95	
			Δ		5.66 ± 14.01	5.97 ± 15.41	
		Active	Score	50.53 ± 25.15	56.88 ± 21.99	57.00 ± 21.33	
			Δ		6.35 ± 15.26	7.21 ± 15.66	

Placebo group：excluded pre-intake results of ST_Stroop Commission Errors, Complex Attention, Cognitive Flexibility, NCI (n=1). excluded 24w results of Continuous Performance Test (CPT), Complex Attention, NCI (n=1).

Active group：excluded pre intake results of Stroop Test (ST), Reaction Time , Complex Attention, Cognitive Flexibility, NCI (n=1)

Mean ± standard deviation.

Δ：change compared to baseline.

*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 2. Scores for each cognitive function domain in Cognitrax (PPS) (Part 3)

Item				pre-intake	12w		24w	
Simple Attention	Subject score	Placebo	Score	39.58 ± 0.87	39.50 ± 0.67		39.25 ± 1.63	
			Δ		-0.06 ± 0.91		-0.31 ± 1.15	
		Active	Score	39.15 ± 1.71	39.71 ± 0.58		39.36 ± 0.93	
			Δ		0.56 ± 1.56	#	0.24 ± 1.64	
	Standardized score	Placebo	Score	105.39 ± 8.46	104.69 ± 6.47		102.31 ± 15.36	
			Δ		-0.53 ± 8.67		-2.91 ± 10.75	
		Active	Score	101.35 ± 16.16	106.71 ± 5.37		103.45 ± 8.84	
			Δ		5.35 ± 14.94	#	2.30 ± 15.85	
	% score	Placebo	Score	64.06 ± 18.04	61.75 ± 15.35		60.06 ± 18.45	
			Δ		-1.91 ± 18.37		-3.59 ± 18.10	
		Active	Score	57.88 ± 22.53	66.59 ± 13.31		59.24 ± 19.60	
			Δ		8.71 ± 20.26	*	1.73 ± 24.29	
Motor Speed	Subject score	Placebo	Score	100.33 ± 12.18	102.56 ± 13.08		99.64 ± 11.65	
			Δ		2.41 ± 5.24		-0.70 ± 7.80	
		Active	Score	101.88 ± 13.06	102.21 ± 14.69		103.06 ± 13.25	
			Δ		0.32 ± 5.41		1.21 ± 5.31	
	Standardized score	Placebo	Score	98.36 ± 12.44	100.69 ± 13.28		98.15 ± 12.83	
			Δ		2.69 ± 5.33		-0.21 ± 7.18	
		Active	Score	100.15 ± 10.61	100.38 ± 12.05		101.42 ± 10.26	
			Δ		0.24 ± 5.32	#	1.15 ± 5.18	
	% score	Placebo	Score	46.21 ± 27.18	50.31 ± 25.90		45.36 ± 27.72	
			Δ		5.00 ± 10.96		-0.85 ± 16.46	
		Active	Score	50.26 ± 23.40	49.65 ± 25.05		52.70 ± 22.83	
			Δ		-0.62 ± 10.96	*	2.12 ± 11.64	

Placebo group：excluded pre-intake results of ST_Stroop Commission Errors, Complex Attention, Cognitive Flexibility, NCI (n=1).
excluded 24w results of Continuous Performance Test (CPT), Complex Attention, NCI (n=1).
Active group：excluded pre intake results of Stroop Test (ST), Reaction Time , Complex Attention, Cognitive Flexibility, NCI (n=1)
Mean ± standard deviation.
Δ：change compared to baseline.
*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 3. Muscle mass and related body composition analysis (PPS)

Item		pre-intake	12w	24w
Muscle mass (kg)				
Placebo	measured values	37.64 ± 6.44	38.00 ± 6.47	36.54 ± 6.30
	Δ		0.19 ± 0.75	-1.10 ± 0.69
Active	measured values	37.72 ± 6.93	38.05 ± 7.09	36.80 ± 6.66
	Δ		0.33 ± 0.77	-1.09 ± 0.93
Weight (kg)				
Placebo	measured values	53.72 ± 7.00	52.93 ± 6.84	53.28 ± 7.04
	Δ		-0.62 ± 1.11	-0.44 ± 1.39
Active	measured values	54.17 ± 10.22	53.71 ± 10.31	54.33 ± 10.22
	Δ		-0.46 ± 1.20	-0.15 ± 1.03
Body fat percentage (%)				
Placebo	measured values	25.79 ± 7.77	24.08 ± 7.35	27.34 ± 7.22
	Δ		-1.20 ± 1.57	1.55 ± 1.92
Active	measured values	25.69 ± 7.88	24.48 ± 7.56	27.58 ± 8.16
	Δ		-1.21 ± 1.39	1.79 ± 1.61
BMI (kg/m^2)				
Placebo	measured values	21.18 ± 2.12	20.81 ± 1.92	20.97 ± 1.95
	Δ		-0.24 ± 0.44	-0.20 ± 0.56
Active	measured values	21.55 ± 3.36	21.36 ± 3.31	21.61 ± 3.29
	Δ		-0.19 ± 0.45	-0.07 ± 0.39
Lean mass (kg)				
Placebo	measured values	39.85 ± 6.76	40.21 ± 6.77	38.72 ± 6.60
	Δ		0.19 ± 0.79	-1.12 ± 0.71
Active	measured values	39.95 ± 7.26	40.28 ± 7.43	39.01 ± 6.99
	Δ		0.34 ± 0.81	-1.12 ± 0.97
Skeletal muscle mass (kg)				
Placebo	measured values	21.53 ± 4.10	21.76 ± 4.13	20.78 ± 4.04
	Δ		0.11 ± 0.45	-0.75 ± 0.42
Active	measured values	21.64 ± 4.40	21.83 ± 4.51	20.98 ± 4.22
	Δ		0.19 ± 0.49	-0.78 ± 0.57
SMI (kg/m^2)				
Placebo	measured values	6.40 ± 0.78	6.43 ± 0.80	6.15 ± 0.81
	Δ		0.00 ± 0.17	-0.25 ± 0.18
Active	measured values	6.41 ± 0.94	6.44 ± 0.95	6.25 ± 0.89
	Δ		0.03 ± 0.17	-0.21 ± 0.21

Mean ± standard deviation.
No significant difference between the groups.

Table 4. MMSE, SDS, Apathy Scale, and biochemical test (pentosidine and homocysteine) analysis

Item		pre-intake	12w	24w
MMSE (score)				
Placebo	measured values	28.2 ± 1.52		28.55 ± 1.06
	Δ			0.33 ± 1.34
Active	measured values	28.2 ± 1.44		28.48 ± 1.39
	Δ			0.30 ± 1.67
SDS (score)				
Placebo	measured values	39.8 ± 8.23	37.9 ± 7.58	36.97 ± 7.06
	Δ		-1.91 ± 7.30	-2.82 ± 8.48
Active	measured values	36.4 ± 8.45	36.5 ± 7.31	35.06 ± 7.73
	Δ		0.12 ± 6.17	-1.29 ± 5.69
Apathy Scale (score)				
Placebo	measured values	14.3 ± 6.23	14.2 ± 5.50	12.18 ± 5.52
	Δ		-0.15 ± 5.09	-2.12 ± 6.63
Active	measured values	12.2 ± 5.63	12.9 ± 5.42	11.65 ± 5.20
	Δ		0.74 ± 3.82	-0.56 ± 4.01
Pentosidine (ug/mL)				
Placebo	measured values	0.06 ± 0.01		0.06 ± 0.01
	Δ			-0.01 ± 0.02
Active	measured values	0.07 ± 0.02		0.06 ± 0.02
	Δ			-0.01 ± 0.02
Homocysteine (nmol/mL)				
Placebo	measured values	12.1 ± 7.45		13.10 ± 13.63
	Δ			0.98 ± 6.44
Active	measured values	11.8 ± 3.26		11.24 ± 2.86
	Δ			-0.57 ± 1.45

Mean ± standard deviation.
No significant difference between the groups.

Table 5. Baseline characteristics of participants in the subgroup

Item	Subgroup	
	Placebo (n=16)	Active (n=11)
Sex (Male/Female)	7/9	4/7
Age (years)	69.19 ± 3.39	68.45 ± 3.24
Height (cm)	159.51 ± 8.80	157.82 ± 6.77
Weight (kg)	54.71 ± 7.01	54.35 ± 10.26
Body fat percentage (%)	27.10 ± 9.42	26.29 ± 10.43
BMI (kg/m^2)	21.51 ± 2.26	21.93 ± 4.67
NCI_standardized score	102.94 ± 7.70	99.64 ± 7.51
Muscle mass (kg)	37.68 ± 7.09	37.13 ± 4.95

Mean ± standard deviation.
No significant difference between the groups.

6. Adverse events

No adverse events attributable to the active foods containing fermented rice bran or placebo foods were reported during the study period.

Discussion

In this study, we conducted a randomized, placebo-controlled, double-blind, parallel-group to assess the impact of fermented rice bran containing HMPA on cognitive function and muscle mass in older adults aged 65 or older and less than 80 years study. Participants were instructed to consume the test food and engage in light exercise over 24 weeks. The findings indicated that the combination of fermented rice bran containing HMPA and light exercise led to a significant improvement in reaction time (subject score) after 24 weeks compared to the placebo group. Thus, it is suggested that the combination of the active food and light exercise contributed to the enhancement of reaction time.

Furthermore, an additional analysis was conducted on a subgroup of participants with no exercise habits. The results revealed significant improvements in the active food group compared to the placebo group in the changes of NCI (standardized score, % score) after 24 weeks of intake, composite memory (subject score, standardized score, % score) after 24 weeks of intake, verbal memory (subject score) after 12 and 24 weeks of intake, and reaction time (% score) after 24 weeks of intake. These findings suggest that, among individuals with no exercise habits, the combination of consuming the active food and engaging in light exercise improved NCI, composite memory, verbal memory, and reaction time.

The term "NCI" denotes an overall cognitive index derived from scores across cognitive domains, including composite memory, reaction time, cognitive processing speed, comprehensive powers of attention, and cognitive flexibility, serving as a composite measure of overall cognitive function (CNS Vital Signs LLC, 2019). "Composite memory" encompasses both verbal and visual memory abilities, calculated from combined scores of "verbal memory" and "visual memory" assessments. "Verbal memory" refers to the capacity to memorize and recall words such as names of others, kanji characters, and commitments (CNS Vital Signs LLC, 2019; Watanabe et al., 2020). Conversely, "visual memory" pertains to the capability to memorize and recall shapes and spatial information such as a person's faces, maps, and locations (CNS Vital Signs LLC, 2019; Watanabe et al., 2020). Furthermore, "reaction time" assesses the ability to promptly respond to simple and progressively more complex instructions (CNS Vital Signs LLC, 2019; Gualtieri et al., 2006), exemplified in daily activities by timely conversational responses and swift reactions to traffic signals (CNS Vital Signs LLC).

"Reaction time" and "memory" are known to be cognitive functions that typically decline with age (Kozaki, 2018). Aging is implicated as a significant common factor in various neurodegenerative diseases and dementia, associated with oxidative stress, amyloid-β accumulation, and neuroinflammation (Kandlur et al., 2020; Zecca et al., 2021; DiSabato et al., 2016). In research involving central nervous system glial cells (astrocytes), HMPA, a key component of fermented rice bran, was found to enhance the expression of aquaporin 4, crucial for brain waste product removal, and anti-inflammatory cytokines TGF-β and IL-10 (Nishitani, 2017). Moreover, exercise has been demonstrated to enhance cognitive function in elderly individuals (Soshi et al., 2021). Thus, the findings from this study suggest that the combined effects of HMPA present in the active food and light exercise may contribute to mitigating cognitive decline associated with aging.

This study has some limitations. We did not assess how HMPA improves cognitive function. In animal models,

Table 6. Scores for each cognitive function domain in Cognitrax (subgroup) (Part 1)

Item				pre-intake	12w	24w
NCI	Standardized score	Placebo	Score	102.94 ± 7.70	106.00 ± 7.85	103.88 ± 7.39
			Δ		2.80 ± 3.10	0.94 ± 3.23
		Active	Score	99.64 ± 7.51	103.82 ± 6.72	105.18 ± 6.13
			Δ		4.18 ± 4.02	5.55 ± 4.57 *
	% score	Placebo	Score	57.25 ± 19.02	64.07 ± 18.53	59.38 ± 18.29
			Δ		6.13 ± 7.39	2.13 ± 7.46
		Active	Score	49.45 ± 18.76	59.45 ± 16.46	63.09 ± 15.18
			Δ		10.00 ± 10.01	13.64 ± 11.39 *
Composite Memory	Subject score	Placebo	Score	95.50 ± 4.99	97.47 ± 5.30	94.19 ± 7.33
			Δ		1.20 ± 4.72	-1.31 ± 5.94
		Active	Score	93.09 ± 7.99	96.64 ± 6.19	98.36 ± 5.71
			Δ		3.55 ± 9.47	5.27 ± 6.71 *
	Standardized score	Placebo	Score	104.25 ± 9.16	107.53 ± 11.21	101.88 ± 13.64
			Δ		2.13 ± 8.30	-2.38 ± 10.44
		Active	Score	99.45 ± 13.82	105.64 ± 8.90	108.73 ± 9.00
			Δ		6.18 ± 16.91	9.27 ± 11.90 *
	% score	Placebo	Score	60.00 ± 21.72	64.80 ± 22.44	56.13 ± 28.24
			Δ		2.07 ± 15.46	-3.88 ± 21.80
		Active	Score	49.91 ± 30.64	63.09 ± 20.85	69.64 ± 20.09
			Δ		13.18 ± 38.85	19.73 ± 27.06 *
Verbal Memory	Subject score	Placebo	Score	52.44 ± 4.90	53.40 ± 4.45	51.38 ± 6.24
			Δ		0.20 ± 3.30	-1.06 ± 4.78
		Active	Score	51.18 ± 5.76	55.18 ± 4.26	54.45 ± 3.27
			Δ		4.00 ± 5.00 *	3.27 ± 6.13 *
	Standardized score	Placebo	Score	108.81 ± 14.09	111.20 ± 13.77	105.63 ± 18.59
			Δ		0.40 ± 9.88	-3.19 ± 14.46
		Active	Score	105.09 ± 16.13	116.91 ± 11.09	114.55 ± 9.26
			Δ		11.82 ± 14.61 *	9.45 ± 17.66 #
	% score	Placebo	Score	67.50 ± 29.17	72.33 ± 27.40	65.00 ± 32.20
			Δ		0.87 ± 19.45	-2.50 ± 22.97
		Active	Score	58.45 ± 32.07	82.18 ± 20.42	79.91 ± 16.65
			Δ		23.73 ± 31.65 #	21.45 ± 35.62 #
Visual Memory	Subject score	Placebo	Score	43.06 ± 3.36	44.07 ± 3.43	42.81 ± 3.04
			Δ		1.00 ± 5.76	-0.25 ± 5.20
		Active	Score	41.91 ± 6.71	41.45 ± 3.96	43.91 ± 3.73
			Δ		-0.45 ± 6.98	2.00 ± 4.96
	Standardized score	Placebo	Score	98.63 ± 10.13	101.73 ± 12.09	98.13 ± 10.76
			Δ		3.33 ± 17.30	-0.50 ± 15.77
		Active	Score	94.91 ± 20.91	93.09 ± 11.48	100.73 ± 10.28
			Δ		-1.82 ± 21.37	5.82 ± 15.05
	% score	Placebo	Score	47.94 ± 21.63	53.13 ± 26.38	45.56 ± 24.69
			Δ		5.67 ± 38.88	-2.38 ± 35.71
		Active	Score	40.55 ± 35.44	36.64 ± 22.61	51.91 ± 24.19
			Δ		-3.91 ± 35.31	11.36 ± 20.79
Psychomotor Speed	Subject score	Placebo	Score	152.19 ± 16.45	158.07 ± 16.68	153.81 ± 18.40
			Δ		4.93 ± 4.88	1.63 ± 10.52
		Active	Score	153.64 ± 16.36	154.18 ± 12.77	157.36 ± 14.82
			Δ		0.55 ± 6.31 #	3.73 ± 4.88
	Standardized score	Placebo	Score	106.06 ± 12.21	109.40 ± 12.32	107.13 ± 14.08
			Δ		3.13 ± 3.27	1.06 ± 7.02
		Active	Score	105.55 ± 8.58	106.09 ± 8.54	107.91 ± 6.36
			Δ		0.55 ± 4.55	2.36 ± 3.32
	% score	Placebo	Score	62.38 ± 25.74	68.87 ± 23.97	64.13 ± 29.34
			Δ		6.20 ± 7.83	1.75 ± 16.08
		Active	Score	62.73 ± 19.91	63.82 ± 18.94	68.64 ± 13.83
			Δ		1.09 ± 11.26	5.91 ± 7.85

Mean ± standard deviation.

Δ : change compared to baseline.

*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 6. Scores for each cognitive function domain in Cognitrax (subgroup) (Part 2)

Item				pre-intake	12w	24w	
Reaction Time	Subject score	Placebo	Score	786.56 ± 108.61	766.73 ± 107.09	786.06 ± 96.26	
			Δ		-18.47 ± 34.26	-0.50 ± 55.52	
		Active	Score	779.27 ± 107.21	739.09 ± 85.24	722.64 ± 44.15	
			Δ		-40.18 ± 72.16	-56.64 ± 88.26	#
	Standardized score	Placebo	Score	93.75 ± 14.01	95.73 ± 13.60	94.06 ± 11.74	
			Δ		2.13 ± 3.94	0.31 ± 6.13	
		Active	Score	94.36 ± 12.26	98.82 ± 8.78	100.55 ± 4.93	
			Δ		4.45 ± 7.99	6.18 ± 10.03	#
	% score	Placebo	Score	39.88 ± 25.70	43.60 ± 26.19	39.00 ± 22.89	
			Δ		3.73 ± 9.67	-0.88 ± 13.47	
		Active	Score	40.18 ± 19.83	47.91 ± 21.34	51.36 ± 12.67	
			Δ		7.73 ± 12.37	11.18 ± 14.39	*
Complex Attention	Subject score	Placebo	Score	6.38 ± 4.56	4.13 ± 2.75	5.31 ± 3.88	
			Δ		-2.13 ± 4.19	-1.06 ± 3.09	
		Active	Score	11.00 ± 9.37	7.36 ± 6.36	7.64 ± 7.16	
			Δ		-3.64 ± 4.97	-3.36 ± 5.87	
	Standardized score	Placebo	Score	109.06 ± 8.98	112.93 ± 5.02	111.00 ± 7.62	
			Δ		3.80 ± 7.89	1.94 ± 5.76	
		Active	Score	101.36 ± 15.49	107.64 ± 10.81	107.36 ± 10.92	
			Δ		6.27 ± 8.17	6.00 ± 10.14	
	% score	Placebo	Score	70.63 ± 20.71	79.60 ± 8.92	75.38 ± 17.00	
			Δ		8.93 ± 18.71	4.75 ± 12.07	
		Active	Score	54.09 ± 32.79	67.91 ± 24.77	67.55 ± 23.27	
			Δ		13.82 ± 19.61	13.45 ± 21.09	
Cognitive Flexibility	Subject score	Placebo	Score	35.38 ± 9.99	40.47 ± 8.28	39.25 ± 7.65	
			Δ		4.73 ± 8.00	3.88 ± 6.26	
		Active	Score	29.00 ± 19.37	34.18 ± 14.37	35.64 ± 15.67	
			Δ		5.18 ± 8.11	6.64 ± 9.99	
	Standardized score	Placebo	Score	101.75 ± 9.96	105.40 ± 7.96	104.94 ± 7.60	
			Δ		3.67 ± 6.82	3.19 ± 5.39	
		Active	Score	96.64 ± 14.79	100.55 ± 11.58	102.09 ± 10.85	
			Δ		3.91 ± 6.41	5.45 ± 8.79	
	% score	Placebo	Score	55.13 ± 22.66	62.53 ± 18.73	61.88 ± 18.57	
			Δ		7.40 ± 14.46	6.75 ± 11.29	
		Active	Score	45.55 ± 29.51	53.64 ± 23.48	55.73 ± 24.23	
			Δ		8.09 ± 15.57	10.18 ± 14.70	
Processing Speed	Subject score	Placebo	Score	51.44 ± 9.50	53.80 ± 6.26	53.00 ± 7.13	
			Δ		0.93 ± 4.59	1.56 ± 7.48	
		Active	Score	52.45 ± 7.24	54.18 ± 7.40	53.64 ± 5.80	
			Δ		1.73 ± 4.69	1.18 ± 4.79	
	Standardized score	Placebo	Score	114.50 ± 12.33	117.20 ± 9.20	116.44 ± 10.24	
			Δ		1.27 ± 6.01	1.94 ± 9.66	
		Active	Score	115.27 ± 8.97	117.45 ± 10.63	116.91 ± 6.47	
			Δ		2.18 ± 6.05	1.64 ± 6.09	
	% score	Placebo	Score	77.13 ± 22.86	83.73 ± 16.25	82.06 ± 18.59	
			Δ		3.60 ± 9.50	4.94 ± 18.20	
		Active	Score	81.00 ± 15.39	83.18 ± 15.84	85.18 ± 10.27	
			Δ		2.18 ± 6.35	4.18 ± 7.95	
Executive Function	Subject score	Placebo	Score	36.00 ± 9.89	40.80 ± 8.27	39.63 ± 7.72	
			Δ		4.40 ± 7.84	3.63 ± 6.16	
		Active	Score	29.36 ± 19.30	35.00 ± 14.45	36.64 ± 15.34	
			Δ		5.64 ± 8.45	7.27 ± 10.56	
	Standardized score	Placebo	Score	101.06 ± 9.80	104.73 ± 7.95	104.06 ± 7.84	
			Δ		3.67 ± 6.52	3.00 ± 5.16	
		Active	Score	95.73 ± 14.91	99.91 ± 11.90	101.64 ± 10.88	
			Δ		4.18 ± 6.57	5.91 ± 9.48	
	% score	Placebo	Score	53.63 ± 22.19	61.13 ± 19.09	59.81 ± 19.26	
			Δ		7.47 ± 13.99	6.19 ± 11.31	
		Active	Score	44.00 ± 29.19	52.55 ± 23.55	54.82 ± 24.32	
			Δ		8.55 ± 15.66	10.82 ± 15.40	

Mean ± standard deviation.

Δ : change compared to baseline.

*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 6. Scores for each cognitive function domain in Cognitrax (subgroup) (Part 3)

Item				pre-intake	12w		24w	
Simple Attention	Subject score	Placebo	Score	39.44 ± 1.15	39.60 ± 0.51		38.94 ± 2.21	
			Δ		0.20 ± 0.94		-0.50 ± 1.51	
		Active	Score	38.18 ± 2.60	39.55 ± 0.69		38.91 ± 1.30	
			Δ		1.36 ± 2.46		0.73 ± 2.49	
	Standardized score	Placebo	Score	104.06 ± 11.17	105.47 ± 5.08		99.31 ± 20.70	
			Δ		1.87 ± 8.84		-4.75 ± 14.00	
		Active	Score	91.82 ± 24.50	104.82 ± 6.11		98.73 ± 12.28	
			Δ		13.00 ± 23.58		6.91 ± 24.13	
	% score	Placebo	Score	61.56 ± 23.07	63.47 ± 12.68		56.94 ± 20.98	
			Δ		2.93 ± 16.94		-4.63 ± 21.39	
		Active	Score	43.09 ± 26.52	61.91 ± 15.25		48.82 ± 25.94	
			Δ		18.82 ± 26.27	#	5.73 ± 28.71	
Motor Speed	Subject score	Placebo	Score	100.25 ± 11.84	103.87 ± 13.37		100.25 ± 13.15	
			Δ		4.00 ± 4.42		0.00 ± 8.31	
		Active	Score	100.36 ± 11.48	99.18 ± 10.11		102.82 ± 11.55	
			Δ		-1.18 ± 3.28	*	2.45 ± 4.59	
	Standardized score	Placebo	Score	98.06 ± 12.10	101.07 ± 12.65		98.06 ± 13.27	
			Δ		3.80 ± 4.26		0.00 ± 8.01	
		Active	Score	97.18 ± 8.60	96.09 ± 7.84		99.45 ± 8.14	
			Δ		-1.09 ± 3.24	*	2.27 ± 4.50	
	% score	Placebo	Score	45.25 ± 27.01	51.00 ± 25.26		46.31 ± 28.67	
			Δ		7.73 ± 9.15		1.06 ± 18.02	
		Active	Score	43.36 ± 19.90	40.36 ± 19.03		48.27 ± 19.82	
			Δ		-3.00 ± 7.66	*	4.91 ± 10.71	

Mean ± standard deviation.

Δ : change compared to baseline.

*P <0.05 vs. Placebo, #P <0.1 vs. Placebo in Δ.

Table 7. Muscle mass and related body composition analysis (subgroup)

Item		pre-intake	12w	24w
Muscle mass (kg)				
Placebo	measured values	37.68 ± 7.09	38.25 ± 7.03	36.63 ± 6.91
	Δ		0.21 ± 0.69	-1.04 ± 0.80
Active	measured values	37.13 ± 4.95	37.29 ± 5.06	36.34 ± 5.28
	Δ		0.16 ± 0.65	-0.79 ± 0.94
Weight (kg)				
Placebo	measured values	54.71 ± 7.01	53.98 ± 6.99	54.16 ± 7.23
	Δ		-0.42 ± 0.93	-0.56 ± 1.59
Active	measured values	54.35 ± 10.26	53.50 ± 10.09	54.14 ± 10.26
	Δ		-0.85 ± 1.38	-0.21 ± 1.13
Body fat percentage (%)				
Placebo	measured values	27.10 ± 9.42	25.13 ± 8.49	28.39 ± 8.27
	Δ		-0.97 ± 1.48	1.29 ± 1.91
Active	measured values	26.29 ± 10.43	24.98 ± 9.65	27.61 ± 10.13
	Δ		-1.31 ± 2.06	1.32 ± 1.84
BMI (kg/m^2)				
Placebo	measured values	21.51 ± 2.26	21.09 ± 2.06	21.24 ± 2.00
	Δ		-0.17 ± 0.36	-0.28 ± 0.64
Active	measured values	21.93 ± 4.67	21.56 ± 4.45	21.82 ± 4.54
	Δ		-0.36 ± 0.54	-0.11 ± 0.41
Lean mass (kg)				
Placebo	measured values	39.90 ± 7.42	40.48 ± 7.35	38.83 ± 7.23
	Δ		0.21 ± 0.74	-1.07 ± 0.83
Active	measured values	39.33 ± 5.14	39.49 ± 5.31	38.53 ± 5.52
	Δ		0.16 ± 0.69	-0.80 ± 0.99
Skeletal muscle mass (kg)				
Placebo	measured values	21.53 ± 4.48	21.91 ± 4.48	20.81 ± 4.41
	Δ		0.14 ± 0.36	-0.72 ± 0.45
Active	measured values	21.24 ± 3.17	21.36 ± 3.29	20.67 ± 3.36
	Δ		0.13 ± 0.47	-0.56 ± 0.61
SMI (kg/m^2)				
Placebo	measured values	6.38 ± 0.89	6.45 ± 0.89	6.13 ± 0.91
	Δ		0.02 ± 0.15	-0.25 ± 0.21
Active	measured values	6.32 ± 0.73	6.36 ± 0.77	6.19 ± 0.83
	Δ		0.05 ± 0.14	-0.13 ± 0.24

Mean ± standard deviation.

No significant difference between the groups.

HMPA revealed its potential absorption at millimolar levels in the bloodstream after oral administration (Kitano et al., 2023). Additionally, in vitro tests using central nervous system glial cells (astrocytes) showed that HMPA promotes the expression of aquaporin 4, which aids in brain waste removal, and TGF-β and IL-10, which are anti-inflammatory cytokines (Nishitani Y. JP Patent 6236185). These reports suggest that HMPA may have an effect on glial cells and improve cognitive function. However, the ability of HMPA to cross the blood brain barrier has not been adequately studied. Future research should explore the mechanisms by which HMPA combined with light exercise improves cognitive function in aging animal models. No significant differences in muscle mass or body composition were observed between the active food group and the placebo group in either the PPS analysis or the additional analysis. It is well-documented that muscle mass and body composition vary between genders, and studies have shown differences in how these metrics change with age as well (Iwamura et al., 2015). Future research should explore the specific effects of gender and age in greater detail. While this study did not show significant differences in pentosidine and homocysteine levels, the markers were lower in the active food group after 24 weeks of intake compared to before intake. Pentosidine and homocysteine are recognized as advanced glycation end products (AGEs)

that typically increase with age and are used as markers for bone quality assessment (Saito, 2013). The precise mechanism by which HMPA affects these bone quality markers remains unclear. Since this study did not include other evaluations related to bone health, further research is warranted to elucidate this mechanism.

Regarding safety, consistent with previous studies (Yoshino et al., 2021; Yoshino et al., 2022a; Yoshino et al., 2022b; Yoshino et al., 2023), no adverse events related to the test foods were observed in this study. It was confirmed that there are no safety concerns associated with healthy adult men and women aged 65 or older and less than 80 years consuming foods containing fermented rice bran with HMPA over 24 weeks.

Conclusion

A randomized, placebo-controlled, double-blind, parallel-group study was conducted among healthy men and women aged 65 or older and less than 80 years to assess the effects of 24 weeks of continuous consumption of fermented rice bran containing HMPA (ACTIBODY® RB), combined with light exercise, on cognitive function and muscle mass.

The study revealed improvements in reaction time with the combined intake of fermented rice bran containing HMPA and light exercise.

Additionally, an analysis of participants who do not engage in regular exercise showed enhancements in NCI, composite memory, verbal memory, and reaction time with this combined regimen of fermented rice bran containing HMPA and light exercise.

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Author contributions

Rikiya Shiwaku, Susumu Yoshino, Takashi Tagawa, and Hiroshige Kuwahara conceptualized and designed the study, interpreted the findings, and contributed to the manuscript's writing, and Aiko Tanaka managed the study contract. Hiroyo Kagami-Katsuyama conducted the data analysis, while Naoyuki Honma oversaw the study's execution. Jun Nishihira served as the principal investigator, responsible for conducting the study and performing safety evaluations. All authors have critically reviewed and approved the final version of the manuscript.

Conflicts of interest

This study received funding from Maruzen Pharmaceuticals Co., Ltd. and was conducted by Hokkaido Information University under commission for the study. The test foods were provided by Maruzen Pharmaceuticals Co., Ltd. Authors Rikiya Shiwaku, Susumu Yoshino, Takashi Tagawa, and Hiroshige Kuwahara are employees of Maruzen Pharmaceuticals Co., Ltd. Similarly, Aiko Tanaka, Hiroyo Kagami-Katsuyama, Naoyuki Honma, and Jun Nishihira are affiliated with Hokkaido Information University. There are no other conflicts of interest to report.

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