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Improvement in autonomic balance through 12-week supplementation of a novel curcumin formulation in healthy Japanese adults: A randomized, placebo-controlled study

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ABSTRACT

Background: Curcumin has several health benefits due to its potent antioxidant and anti-inflammatory properties, but its bioavailability is very low, limiting its potential. We have developed a novel curcumin formulation, TS-P1, which has an 85.2-fold higher bioavailability of curcumin than raw curcumin.

Objective: To investigate the efficacy of TS-P1 on fatigue, mood status, and autonomic function.

Methods: Ninety healthy Japanese adults were randomized to the placebo or TS-P1 group and took either the placebo or TS-P1 containing 150 mg of curcumin for 12 weeks. Visual Analogue Scale for Fatigue (VAS-F) scores, Profile of Mood States Questionnaire second edition (POMS2) scores, and autonomic functions were measured every 4 weeks.

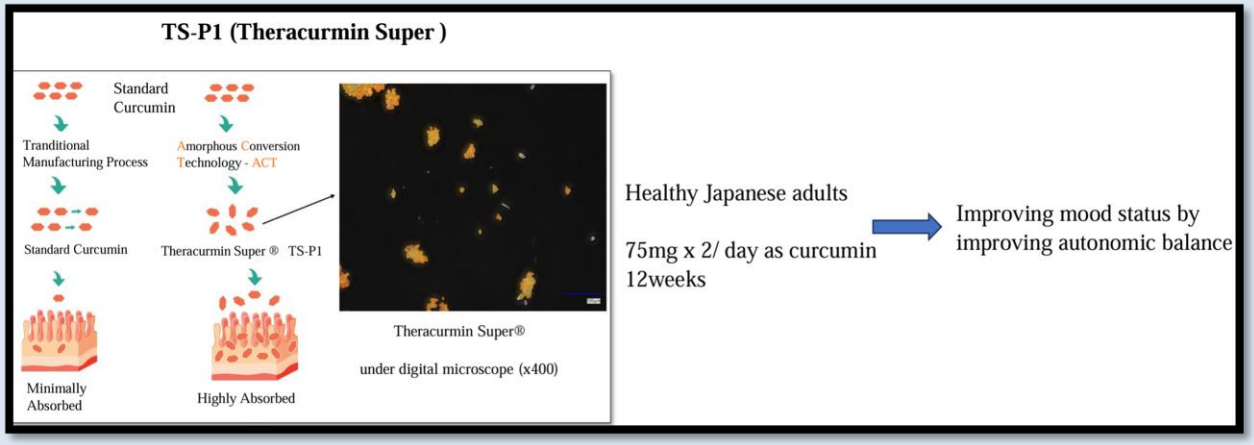
Results: Both groups showed an improvement in the VAS-F over the study period, but there was no significant difference between the placebo and TS-P1 groups. However, the mean change from baseline in the anger and depression scores of the POMS2, particularly in those aged 40 and over, in the TS-P1 group showed a greater range of decline at week 12. The mean change from baseline in LnLF and LF/HF also decreased in the TS-P1 group. Blood pressure also decreased in the TS-P1 group.

Conclusions: These data suggest that TS-P1 induced a parasympathetic dominant state, and that curcumin has an important role in the regulation of autonomic balance. 12 weeks of supplementation of TS-P1 is expected to improve both mood status and vascular function.

Trial registration: UMIN000050377

Foundation: Theravalues Corporation

Keywords: curcumin; TS-P1: Theracurmin Super; mood status; autonomic balance, parasympathetic dominance; vascular function



INTRODUCTION

Curcumin is a plant polyphenol derived from turmeric that is consumed worldwide for its potent antioxidant and anti-inflammatory properties. These properties are thought to have a variety of health benefits, including the prevention and improvement of lifestyle-related diseases and inflammatory disorders [1-2]. However, due to its low water solubility and low bioavailability, the benefits of curcumin cannot be fully obtained when taken orally. Therefore, many researchers have been working to improve its bioavailability [3-6].

Technological challenge of a novel curcumin formulation: In general, there are three typical formulation technologies to overcome insolubility: nanoparticle formulations (particle micritization), amorphous solid dispersions, and solubilized formulations (including self-emulsifying formulations). We have successfully developed curcumin with dramatically improved intestinal absorption (Theracurmin®) by combining curcumin micritization and dispersion processing technologies [7]. While the average particle size of raw curcumin is approximately 8 µm, Theracurmin® has an average particle size of 0.52 µm (Figure 1A) and is characterized by its high dispersibility in water (Figure 1B). A comparison of the bioavailability of Theracurmin® in humans with that of raw curcumin preparations showed that up to 12 hours after the ingestion of Theracurmin®, the Cmax and AUC were 20 and 42 times higher, respectively than those of the raw curcumin preparations [6]. We then confirmed the effects of Theracurmin® on liver function [8], knee pain [9], Crohn's disease symptoms [10], exercise-induced oxidative stress [11], and exercise-induced muscle pain [12]. In the brain, inflammation and oxidative stress are also important causes of disease, and there are some reports that curcumin improves cognitive and memory function in some populations, such as the elderly [13]. However, to have a more pronounced effect on the brain, more curcumin must

cross the blood-brain barrier. Therefore, it is desirable to further increase its concentration in the blood after oral intake to achieve widespread health benefits.

Development of TS-P1*:* We have developed a novel, highly absorbable curcumin formulation, TS-P1 (Thracurmin Super) [14]. It is known that the solubility of poorly soluble drugs can be improved via amorphization. We applied this technology (amorphous conversion technology: ACT) to curcumin and prepared amorphous curcumin mixed with excipient TS-P1. The presence of amorphous curcumin bound to excipients in the vicinity of the small intestine mucosa creates a supersaturated state, which is expected to increase the absorption of curcumin without reducing the membrane permeability (Figure 2).

Observation of TS-P1 via electron microscopy revealed an average particle size of approximately 100 µm, larger than that of raw curcumin (Figure 1A). However, this was clearly due to the binding of a significant number of amorphous curcumin particles to excipients when observed via digital microscopy (Figure 1C). TS-P1 is thought to have about 85.2 times greater bioavailability than raw curcumin [14].

We then compared the effect of TS-P1 on common cold symptoms with that of Theracurmin® [15]. Both TS-P1 (150 mg/day as curcumin) and Theracurmin® (150 mg/day as curcumin) improved common cold symptoms, but TS-P1 also alleviated local symptoms such as sneezing, nasal discharge, nasal congestion, and cough. This local symptom improvement may be due to the greater activation of the immune system and the anti-inflammatory effects of TS-P1 using amorphous conversion technology. Therefore, TS-P1 is also expected to have a more significant effect on the brain.

Aim of this study: Therefore, in this study, we investigated the effect of TS-P1 on mood status indices such as fatigue, stress, and depression in healthy adults. Curcumin is also known to inhibit monoamine oxidase [16] and activate the dopaminergic nervous system [17]. However, the clinical effects of curcumin on fatigue and mental status have mainly been demonstrated in subjects with exercise overload and major depressive disorders [18-25], and there are few reports of studies in healthy normal subjects. In recent years, due to the changes in and diversification of social and living environments, an increasing number of people have been suffering from mental disorders that are not diseases, which not only affect their daily lives but also increase the number of people with pre-disease. TS-P1 is expected to reduce chronic inflammation and improve mood status by increasing blood curcumin levels. Therefore, in this study, we investigated the effect of long-term use of TS-P1 on mood indices such as fatigue, stress, and depression in healthy Japanese adults with residual daily fatigue.

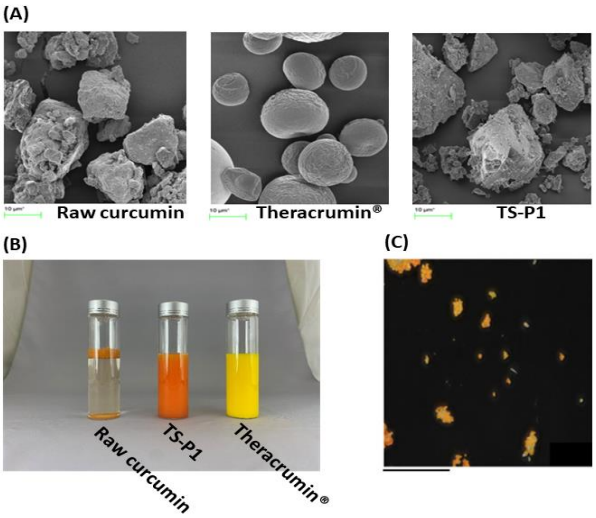


Figure 1. Photographs of physico-chemical features of TS-P1. (A) Particle size of each curcumin preparation. (B) Dispersibility of each curcumin preparation in water. (C) Digital microscope photograph of TS-P1. The light yellow-green color is the excipient, and the yellow color is molten curcumin.

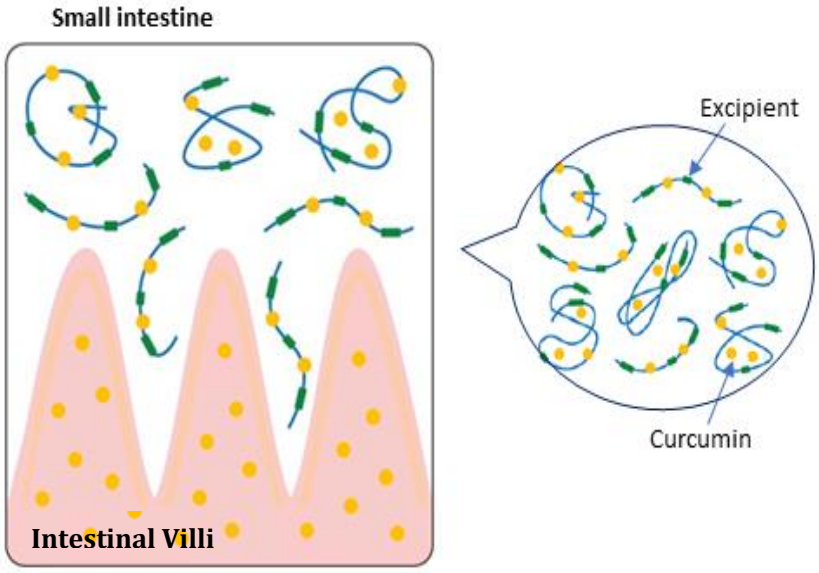


Figure 2. Schematic diagram of the intestinal absorption of curcumin after TS-P1 intake. The frequency of contact with the surface of the digestive tract is increased with excipient-bound TS-P1.

METHODS

Study design: We have taken ethical considerations very seriously in conducting our clinical trials. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects of the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare, and the Ministry of Economy, Trade, and Industry of Japan.

This study was approved by the Ethics Committee of Watanabe Hospital (Tokyo, Japan; approval date: 10 February 2023, approval ID: FA1-2209_ F05_ 001_ 000_ 20230210_1) and was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000050377).

This study was designed as a randomized, double-blind, placebo-controlled, parallel-group comparison study to investigate the effects of 12 weeks of supplementation with TS-P1 on fatigue and mental status in healthy Japanese adults. Fatigue and mental status were assessed every 4 weeks using the Visual Analogue Scale for Fatigue (VAS-F) and the Profile of Mood States Questionnaire second edition (POMS2) (Kaneko Shobo Co., Ltd., Tokyo, Japan). The outline of the study design is shown in Figure 3.

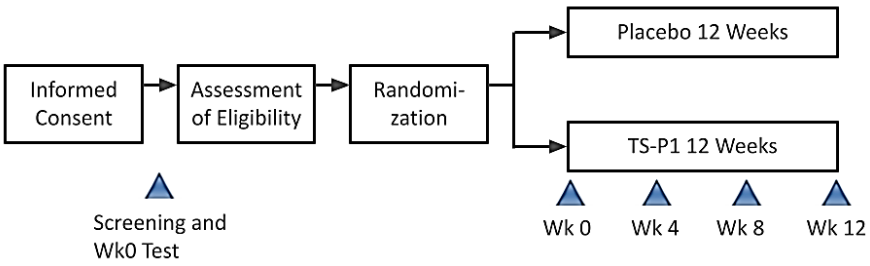


Figure 3. The outline of the study design.

Subjects: Inclusion and exclusion criteria were established to ensure the safety of the subjects and avoid confounding the efficacy evaluation.

The inclusion criteria were as follows: Japanese, (2) male or female, (3) aged ≥20 years, (4) healthy individuals, (5) subjects experiencing fatigue on a daily basis, and (6) subjects deemed eligible to participate in this study by the physician.

The exclusion criteria were as follows: (1) subjects undergoing medical treatment or with a history of

heart disease, pulmonary disease, digestive disease, malignant tumor, hypertension, or diabetes; (2) subjects allergic to the test foods; (3) subjects currently taking medications (including herbal medicines) and dietary supplements; (4) subjects who consumed 'foods for specified health uses', 'foods with functional claims', or other functional foods/beverages on a daily basis; (5) subjects who worked day and night shifts and those who planned to work night shifts during the study period; (6) subjects who were hospitalized for mental disorders or sleep disorders, or who had a history of mental illness; (7) subjects whose usual alcohol consumption exceeded 100 g alcohol equivalent per week; (8) subjects whose usual frequency of alcohol consumption exceeded 5 days per week; (9) subjects who usually smoked more than 20 cigarettes per day; (10) subjects who were participating in another clinical study or had participated in another clinical study within the last 3 months before agreeing to participate in this study, or those were planning to participate in another study during this trial; (11) subjects who were unable to maintain their daily lifestyle (diet, exercise, alcohol consumption, smoking, etc.); (12) subjects who had difficulty consuming the test food as directed; (13) subjects who were pregnant, breastfeeding, or planning to become pregnant; and (14) subjects who were deemed ineligible to participate in this study.

The study protocol was fully explained to all subjects, and all gave written informed consent before participating in the study. Watanabe Hospital (Tokyo, Japan) evaluated the data and managed the health of the subjects, and the examinations were performed at Watanabe Hospital.

Enrollment, randomization, and blinding: Randomization and blinding procedures were used to eliminate bias and ensure the tests' objectivity and reliability. Subjects whose eligibility was confirmed in the screening during the week 0 examination and who were finally selected to be included in the study were enrolled. The allocation manager randomized the group allocation according to the eligibility criteria, using VAS-F, sex, age, and smoking status as allocation factors in the screening during week 0 of examination so that there was no bias in each group.

The person responsible for allocation signed and sealed the bound allocation decision form together with the allocation list and kept the form together with the sealed trial food allocation record in a locked storage room until the time of allocation announcement.

Intervention: The subjects were randomized based on VAS-F, gender, age, and smoking status and were instructed to take either 4 placebo capsules or 4 capsules containing TS-P1 daily for 12 weeks. The subjects were instructed to take two capsules with water before breakfast and two before dinner. Each subject took a total of four capsules daily. This intervention was designed to deliver 150 mg of curcumin per day in the TS-P1 group. Consumption of the capsules began at the beginning of the study period, and the intervention period lasted 12 weeks. Fatigue and mental status were assessed 0, 4, 8, and 12 weeks after consumption of the test diet. The dose and duration were chosen to be at least capable of producing an anti-inflammatory effect based on previous work demonstrating efficacy in the symptoms of the common cold through anti-inflammatory effects.

Sample size: The sample size was based on the study by Nishimura et al. [26]. The between-group difference in the change from baseline in VAS-F after 12 weeks of treatment was 12.86 mm (intervention group: 11.22 ± 19.26 mm; placebo group: -1.64 ± 19.33 mm). The number of patients required for analysis was calculated on the assumption that the same level of efficacy would be achieved in the present study. Assuming a between-group difference of 12.9 mm with a standard deviation

of 19.3 mm, a two-sided significance level (α) of 5%, and a power (1-β) of 80%, the required number of cases for the t-test was calculated to be 37 for each group. Each group's target number of cases was 45, considering non-compliance and drop-outs during the study period.

Primary outcome: The primary outcome of this study was the VAS-F score, which was recorded and presented on a scale from 0 to 100 mm. The subjects were asked to complete the VAS-F self-administered questionnaires at baseline (week 0) and 4, 8, and 12 weeks after consumption of the test diet.

Secondary outcome*:* The secondary outcomes of this study were subjective mood, as assessed using the POMS2, and autonomic and vascular function, as assessed via APG. The POMS2 consists of 35 self-report questions divided into the following seven mood subscales: (1) Anger/Hostility (AH), (2) Confusion/Bafflement (CB), (3) Depression/Dejection (DD), (4) Fatigue/Inertia (FI), (5) Tension/Anxiety (TA), (6) Vigour/Activity (VA), (7) Friendliness (F), and Total Mood Disturbance (TMD).

To assess autonomic nervous function, heart rate variability (HRV) was measured via accelerated plethysmography (APG) using a TAS9VIEW (YKC Corporation, Tokyo, Japan). The autonomic nervous function was assessed using the following indicators: high frequency (HF), 0.15-0.40 Hz, which mainly reflects parasympathetic nervous activity [27]; low frequency (LF), 0.04-0.15 Hz, which mainly reflects sympathetic nervous activity [27-28]; and the LF/HF ratio, which indicates the balance of autonomic nervous activity.

The APG results were also used to assess vascular function. APG consists of a, b, c, and d waves, corresponding to the early systolic positive wave, early systolic negative wave, late systolic rising wave, and late systolic falling wave, respectively. Vascular age (EstAge and EstAge10) was calculated from a wave pattern obtained from this system using the software of this system [29-30].

Safety evaluation: The incidence of side effects and adverse events was recorded. In addition, the causal relationship between the test or control food and the adverse event was objectively established by the principal investigator in a blinded fashion.

Statistical analysis: The per protocol analysis set (PPS) was used for a comprehensive analysis. Summary statistics were calculated for each allocation group, and t-tests were used for between-group comparisons. The primary evaluation outcome was change at the 12-week visit (change from week 0), but changes at the 4- and 8-week visits were also included. The significance level for all tests was 5% two-sided. For the primary endpoint, sensitivity analysis was performed using the full analysis set (FAS); the results are not reported as the FAS and PPS (per protocol set) were the same. The subgroup analysis for age ≥40 years was performed.

RESULTS

Flowchart of this study and baseline characteristics: Figure 4 shows the flowchart of this study. A total of 90 eligible subjects were selected and randomized to either the placebo or TS-P1 group based on Visual Analogue Scale for Fatigue (VAS-F) scores, gender, age, and smoking status. There were no discontinuations or dropouts throughout the study. Table 1 summarizes the baseline characteristics of each group. There were no significant differences in baseline fatigue, gender, age, and smoking status between the placebo and TS-P1 groups. There was no significant difference in the participants' background in the SAF

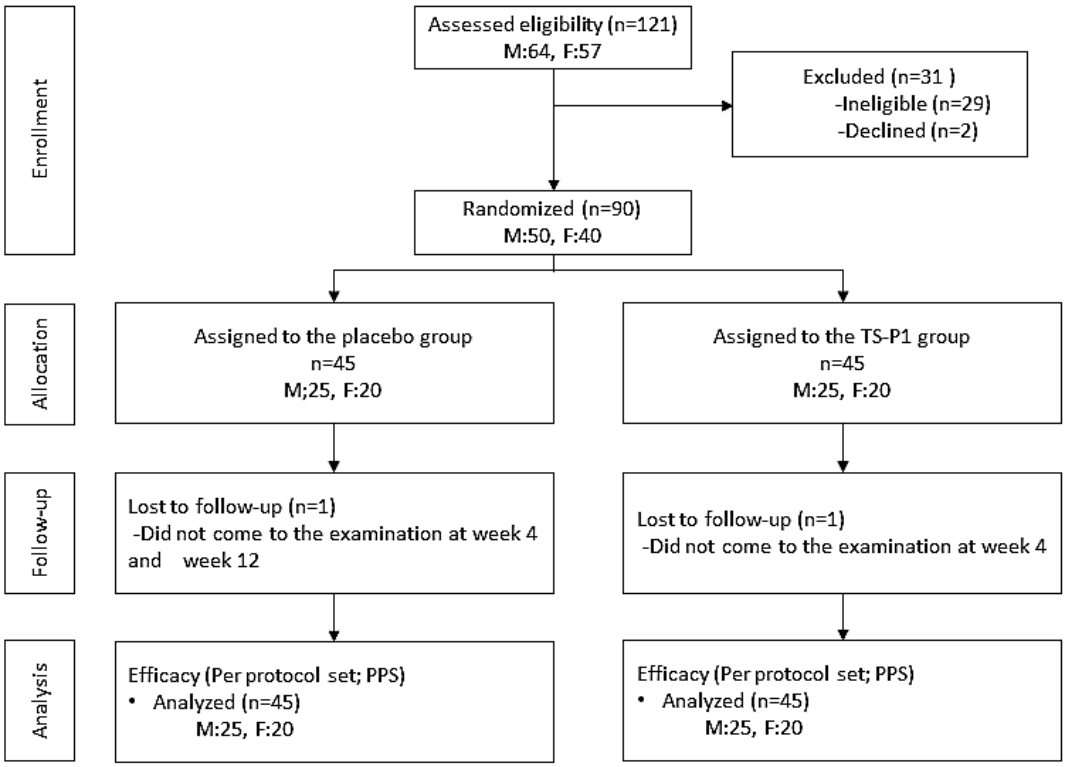


Figure 4. Flowchart of the subjects in this study.

Table 1. Baseline characteristics of the subjects. Mean ± SD

	Placebo Group	TS-P1 Group
VAS-F	68.3±8.4	67.9±8.4
Age (years)	45.7±10.6	45.8±10.3
Sex (M/F)	25/20	25/20
Smoking status	5 (11.1%)	4 (8.9%)

Primary outcome: VAS-F score: Fatigue was assessed using the VAS-F score. The mean VAS-F score and the mean change in the VAS-F score from baseline at each time point are shown in Table 2. Both placebo and TS-P1 groups showed an improvement in fatigue over the period of observation, but there were no significant differences between the placebo and TS-P1 groups.

Secondary outcomes: POMS2, autonomic balance, and vascular function: Mood status was assessed using POMS2. Autonomic and vascular function was assessed using accelerated plethysmography (APG). The mean POMS2 score and the mean change in the POMS2 score from baseline at each time point are summarized in Table 3. There was no significant difference in the POMS2 scores between the placebo and TS-P1 groups.

The results of the autonomic balance and vascular function assessment using the APG measurements are summarized in Table 4. HRV was calculated from the APG data. LnLF at weeks 4 and 12 in the TS-P1 group showed a range of decline, and the LF/HF ratio in the TS-P1 group tended to show a greater range of decline throughout the study period, but this was not statistically significant. In addition, for APG and blood pressure, TS-P1 tended to lower the systolic blood pressure and significantly lower the diastolic blood pressure compared to the placebo after 12 weeks of consumption. The estimated vascular age at week 12, calculated from the APG data, also showed a greater range of reduction in the TS-P1 group, suggesting that TS-P1 maintained vascular function as a result of improved autonomic balance. These data suggest that 12 weeks of supplementation of TS-P1 resulted in a parasympathetic dominant state. Therefore, to confirm this, we performed a sub-analysis of these points in subjects aged 40 years and older.

Table 2. The mean VAS-F score and mean change in the VAS-F score from baseline at each time point. VAS-F: Visual Analogue Scale for Fatigue

		Wk0			Wk4						Wk8						Wk12					
								Change from wk 0						Change from wk 0						Change from wk 0		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
VAS-F	**Placebo**	68.3	8.4	0.831	44.7	21.8	0.601	-23.8	20.9	0.484	43.2	20.3	0.344	-25.0	20.2	0.295	39.5	20.7	0.416	-28.6	21.1	0.381
	TS-P1	67.9	8.4		47.0	20.0		-20.8	20.1		47.4	20.7		-20.6	20.3		43.3	22.2		-24.6	21.4	

Table 3. Profile of mood status and the mean change in the mood status score from baseline at each time point. AH: Anger/Hostility, CB: Confusion/Bewilderment, DD: Depression/Dejection, FI: Fatigue/Inertia, TA: Tension/Anxiety, VA: Vigor/Activity, F: Friendliness, TMD: Total Mood Disturbance.

		Wk0			**Wk4**						**Wk8**						**Wk12**					
								Change from wk 0						Change from wk 0						Change from wk 0		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
AH	**Placebo**	48.6	7.1	0.197	45.9	7.2	0.312	-2.7	6.9	0.849	45.2	6.4	0.098	-3.5	7.4	0.698	45.4	6.6	0.494	-3.2	7.1	0.482
	TS-P1	50.9	9.1		47.5	7.4		-3.0	6.5		48.0	9.4		-2.9	7.2		46.6	9.2		-4.3	7.4	
CB	**Placebo**	55.5	11.0	0.798	50.1	9.1	0.363	-5.7	8.9	0.290	48.1	7.5	0.980	-7.4	9.4	0.753	47.1	7.6	0.846	-8.3	9.9	0.867
	TS-P1	56.1	11.9		48.3	9.6		-7.6	7.7		48.2	9.4		-7.9	7.9		47.5	10.4		-8.6	8.3	
DD	**Placebo**	52.1	9.7	0.436	47.4	6.6	0.834	-4.8	7.7	0.606	45.9	5.1	0.208	-6.2	8.4	0.979	45.6	5.4	0.458	-6.5	9.4	0.754
	TS-P1	53.8	11.5		47.7	7.5		-5.6	7.5		47.7	8.0		-6.1	7.6		46.8	8.7		-7.1	8.3	
FI	**Placebo**	57.1	9.1	0.623	50.5	8.8	0.395	-6.5	7.8	0.169	47.8	7.9	0.274	-9.4	8.6	0.597	47.8	8.5	0.792	-9.1	8.7	0.391
	TS-P1	58.1	9.3		49.0	7.4		-8.9	8.3		49.6	8.0		-8.5	7.2		47.4	8.0		-10.7	8.5	
TA	**Placebo**	54.0	9.1	0.960	48.0	7.6	0.912	-6.0	7.6	0.979	46.3	6.0	0.726	-7.7	8.1	0.797	46.8	7.0	0.776	-7.2	8.8	0.720
	TS-P1	54.1	11.5		47.8	9.5		-6.0	8.2		46.9	8.8		-7.3	8.2		46.3	9.6		-7.8	7.4	
VA	**Placebo**	42.7	7.9	0.741	48.3	10.1	0.702	5.5	7.5	0.397	48.7	10.5	0.418	6.0	9.1	0.174	49.5	9.9	0.800	6.8	8.6	0.477
	TS-P1	43.3	9.2		47.5	9.3		4.2	6.8		47.0	9.4		3.7	6.7		48.9	9.4		5.6	7.5	
F	**Placebo**	46.2	10.0	0.569	48.9	10.5	0.966	2.9	7.2	0.297	48.2	10.4	0.511	2.0	8.1	0.123	49.4	11.2	0.755	3.3	9.2	0.766
	TS-P1	47.3	9.5		48.8	9.3		1.4	6.4		46.9	7.9		-0.5	6.8		50.1	9.3		2.7	6.9	
TMD	**Placebo**	54.6	9.0	0.625	48.4	8.2	0.990	-6.3	7.1	0.662	46.6	6.7	0.279	-8.0	7.9	0.612	46.4	7.2	0.765	-8.2	8.9	0.777
	TS-P1	55.7	11.1		48.4	8.5		-6.9	7.0		48.5	9.3		-7.2	7.4		47.0	9.8		-8.7	7.9	

Table 4. Autonomic nerve balance and vascular function at each time point. SDNN: Standard Deviation of the Normal and Normal Interval, PSI: Physical Stress Index, TP: Total Power, LF: Low Frequency, HF: High Frequency, EstAge: Estimated Vascular Age, EstAge 10: Estimated Vascular Age after 10 years, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HR: Heart Rate. *p<0.05 vs Placebo

		Wk0			Wk4						Wk8						Wk12					
								Change from wk 0						Change from wk 0						Change from wk 0		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
SDNN	**Placebo**	45.9	16.5	0.203	47.9	22.9	0.792	1.7	17.9	0.114	43.1	20.0	0.998	-2.8	17.4	0.187	48.1	24.0	0.929	2.4	21.7	0.375
	TS-P1	52.0	27.3		46.6	20.3		-4.9	20.8		43.1	18.9		-8.9	25.5		48.6	32.5		-3.4	37.5	
PSI	**Placebo**	256.5	236.0	0.515	234.1	193.3	0.559	-21.9	144.3	0.147	261.6	153.1	0.567	5.0	193.5	0.242	230.0	139.2	0.461	-29.5	223.5	0.152
	TS-P1	227.0	189.1		257.7	225.3		27.8	173.2		289.8	292.5		62.8	265.5		261.1	244.2		34.1	191.5	
LnTP	**Placebo**	6.7	0.8	0.285	6.7	0.9	0.857	0.1	0.7	0.139	6.6	0.9	0.974	-0.1	0.8	0.269	6.8	0.9	0.389	0.1	0.9	0.082
	TS-P1	6.9	0.9		6.7	1.0		-0.2	0.8		6.6	1.0		-0.3	0.9		6.6	1.1		-0.3	1.1	
LnLF	**Placebo**	5.4	1.0	0.072	5.5	1.3	0.853	0.1	0.9	0.025	5.2	1.1	0.873	-0.2	1.0	0.128	5.4	1.2	0.633	0.0	1.3	0.042
	TS-P1	5.8	1.2		5.4	1.4		-0.4*	1.1		5.3	1.4		-0.6	1.4		5.3	1.5		-0.6*	1.3	
LnHF	**Placebo**	5.0	1.0	0.718	4.9	1.2	0.360	0.0	0.8	0.579	4.7	1.1	0.679	-0.3	0.9	0.940	4.9	1.2	0.309	0.0	1.1	0.446
	TS-P1	4.9	1.3		4.7	1.2		-0.1	1.2		4.6	1.3		-0.3	1.2		4.6	1.5		-0.2	1.4	
LF/HF	**Placebo**	1.1	0.2	0.032	1.1	0.2	0.493	0.0	0.2	0.064	1.1	0.2	0.389	0.0	0.1	0.083	1.1	0.2	0.325	0.0	0.2	0.243
	TS-P1	1.3*	0.4		1.2	0.2		-0.1	0.4		1.2	0.3		-0.1	0.4		1.2	0.4		-0.1	0.5	
a peak	**Placebo**	761.5	96.5	0.208	804.0	86.9	0.350	41.7	103.9	0.714	820.4	68.1	0.684	58.8	102.2	0.134	802.6	76.9	0.155	42.3	91.6	0.020
	TS-P1	785.6	82.9		820.5	75.7		33.9	92.6		814.2	75.9		28.6	86.9		777.0	90.8		-8.6*	109.3	
b peak	**Placebo**	-572.2	123.5	0.556	-590.9	111.9	0.027	-17.5	104.2	0.056	-601.2	129.2	0.715	-29.1	120.0	0.795	-578.7	111.6	0.590	-6.3	111.3	0.949
	TS-P1	-586.8	110.2		-647.0*	118.5		-60.0	99.4		-610.0	95.4		-23.2	90.4		-591.6	113.1		-4.8	107.1	
C peak	**Placebo**	-100.6	105.9	0.810	-114.2	102.9	0.697	-14.3	81.3	0.537	-139.6	109.0	0.481	-39.0	92.9	0.588	-119.5	91.3	0.155	-20.7	76.8	0.210
	TS-P1	-95.4	100.8		-122.3	91.1		-25.4	85.0		-124.0	99.5		-28.6	87.1		-91.0	96.2		4.4	108.5	

		Wk0			Wk4						Wk8						Wk12					
								Change from wk 0						Change from wk 0						Change from wk 0		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
d peak	**Placebo**	-206.4	104.4	0.595	-211.6	97.1	0.314	-8.3	75.5	0.414	-231.6	115.6	0.179	-25.2	83.0	0.307	-222.0	99.7	0.126	-16.6	86.7	0.267
	TS-P1	-195.2	95.0		-191.8	83.9		5.8	84.2		-202.3	88.1		-7.1	84.6		-191.8	84.4		3.4	82.6	
EstAge	**Placebo**	47.3	11.4	0.910	47.8	10.9	0.864	0.5	1.9	0.080	48.4	11.8	0.762	1.1	2.7	0.066	48.3	11.1	0.697	1.1	2.6	0.021
	TS-P1	47.5	10.9		47.4	10.6		-0.3	2.2		47.7	10.4		0.2	2.3		47.4	10.5		-0.1*	2.3	
EstAge 10	**Placebo**	57.3	11.4	0.910	57.8	10.9	0.864	0.5	1.9	0.080	58.4	11.8	0.762	1.1	2.7	0.066	58.3	11.1	0.697	1.1	2.6	0.021
	TS-P1	57.5	10.9		57.4	10.6		-0.3	2.2		57.7	10.4		0.2	2.3		57.4	10.5		-0.1*	2.3	
SBP	**Placebo**	116.8	15.9	0.244	115.2	16.9	0.065	-1.6	13.1	0.351	114.1	15.8	0.430	-2.7	13.0	0.692	116.3	16.9	0.061	-0.5	12.9	0.356
	TS-P1	113.0	14.8		109.0	15.1		-4.0	12.1		111.4	15.9		-1.6	14.6		110.3	12.9		-2.7	9.6	
DBP	**Placebo**	70.6	9.8	0.843	68.9	11.3	0.271	-1.7	8.9	0.231	68.7	10.4	0.372	-1.9	7.6	0.391	71.5	11.4	0.047	0.9	7.9	0.011
	TS-P1	70.2	11.4		66.2	11.7		-4.0	8.8		66.7	10.5		-3.4	9.2		66.9*	10.4		-3.3*	7.4	
HR	**Placebo**	70.3	8.9	0.419	74.6	9.2	0.134	4.2	8.4	0.430	74.4	8.8	0.166	4.1	8.9	0.518	72.2	8.0	0.224	1.9	9.2	0.731
	TS-P1	71.9	9.3		77.8	10.9		5.9	11.3		77.2	10.3		5.3	9.6		74.6	10.0		2.7	12.0	

Table 5. Mood status, autonomic nerve balance and vascular function at each time point in those aged 40 and over. *p<0.05 vs Placebo, **p<0.01 vs Placebo

		Wk0			Wk4						Wk8						Wk12					
								Change from wk 0						Change from wk 0						Change from wk 0		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
AH	**Placebo**	47.3	6.1	0.046	46.0	7.4	0.569	-1.3	5.7	0.143	45.2	6.8	0.156	-2.1	5.7	0.517	45.9	7.3	0.911	-1.3	5.4	0.021
	TS-P1	51.2*	8.8		47.0	6.2		-3.7	6.6		48.1	9.0		-3.1	6.7		46.2	8.4		-5.1*	6.9	
DD	**Placebo**	50.3	6.6	0.210	46.5	6.2	0.856	-3.8	5.7	0.107	45.6	5.3	0.479	-4.7	5.7	0.267	45.9	5.9	0.776	-4.4	5.8	0.0495
	TS-P1	53.3	11.5		46.2	6.0		-6.3	6.5		46.8	7.4		-6.5	7.3		45.4	7.9		-7.9*	7.9	
LnLF	**Placebo**	5.1	1.0	0.019	5.2	1.3	0.909	0.1	0.9	0.016	5.0	1.1	0.947	-0.1	1.1	0.034	5.1	1.3	0.858	0.1	1.4	0.089
	TS-P1	5.8*	1.3		5.2	1.4		-0.5*	1.2		4.9	1.4		-0.8*	1.5		5.2	1.6		-0.6	1.5	
LnHF	**Placebo**	4.8	1.1	0.997	4.8	1.2	0.638	0.0	0.9	0.717	4.6	1.2	0.658	-0.2	1.0	0.632	4.8	1.4	0.614	0.1	1.2	0.588
	TS-P1	4.8	1.3		4.6	1.2		-0.1	1.3		4.4	1.3		-0.4	1.4		4.6	1.5		-0.1	1.6	
LF/HF	**Placebo**	1.1	0.2	0.049	1.1	0.3	0.718	0.0	0.3	0.0501	1.1	0.2	0.575	0.0	0.1	0.051	1.1	0.3	0.491	0.0	0.2	0.145
	TS-P1	1.3*	0.5		1.1	0.3		-0.2	0.4		1.2	0.3		-0.1	0.4		1.1	0.3		-0.1	0.5	
b peak	**Placebo**	-547.1	133.0	0.569	-563.1	113.8	0.029	-12.6	105.0	0.068	-553.8	119.7	0.126	-6.7	115.9	0.393	-545.5	115..2	0.273	1.0	120.1	0.613
	TS-P1	-564.4	102.7		-628.1*	108.7		-64.2	107.6		-595.0	86.3		-30.6	102.4		-578.1	115.2		-13.8	106.8	
EstAge	**Placebo**	53.5	7.0	0.876	53.8	6.4	0.673	0.5	2.0	0.061	54.8	7.4	0.363	1.3	2.5	0.038	54.5	6.9	0.392	0.9	2.8	0.097
	TS-P1	53.2	7.6		53.0	7.3		-0.5	2.3		53.1	7.0		-0.1*	2.6		52.9	7.2		-0.3	2.6	
EstAge 10	**Placebo**	63.5	7.0	0.876	63.8	6.4	0.673	0.5	2.0	0.061	64.8	7.4	0.363	1.3	2.5	0.038	64.5	6.9	0.392	0.9	2.8	0.097
	TS-P1	63.2	7.6		63.0	7.3		-0.5	2.3		63.1	7.0		-0.1*	2.6		62.9	7.2		-0.3	2.6	
Aging Speed	**Placebo**	1.2	0.2	0.680	1.2	0.2	0.233	0.0	0.2	0.261	1.3*	0.2	0.041	0.1	0.2	0.148	1.2	0.2	0.188	0.0	0.2	0.353
	TS-P1	1.2	0.2		1.1	0.2		-0.1	0.2		1.2	0.2		0.0	0.3		1.1	0.3		-0.1	0.3	
SBP	**Placebo**	117.7	16.0	0.635	117.7	17.0	0.068	0.0	12.1	0.084	115.3	14.7	0.464	-2.4	12.9	0.817	118.9	16.2	0.0495	1.3	11.9	0.052
	TS-P1	115.8	15.4		110.3	14.3		-5.5	12.7		112.5	15.0		-3.2	16.5		111.5*	12.7		-4.3	9.9	
DBP	**Placebo**	71.6	9.8	0.603	70.5	11.7	0.109	-1.1	8.8	0.120	70.7	10.4	0.104	-1.0	7.6	0.213	74.1	11.3	0.009	2.4	8.3	0.005
	TS-P1	70.2	12.4		65.7	11.8		-4.5	8.1		66.3	10.6		-3.9	10.4		66.3**	11.3		-3.8**	8.5	

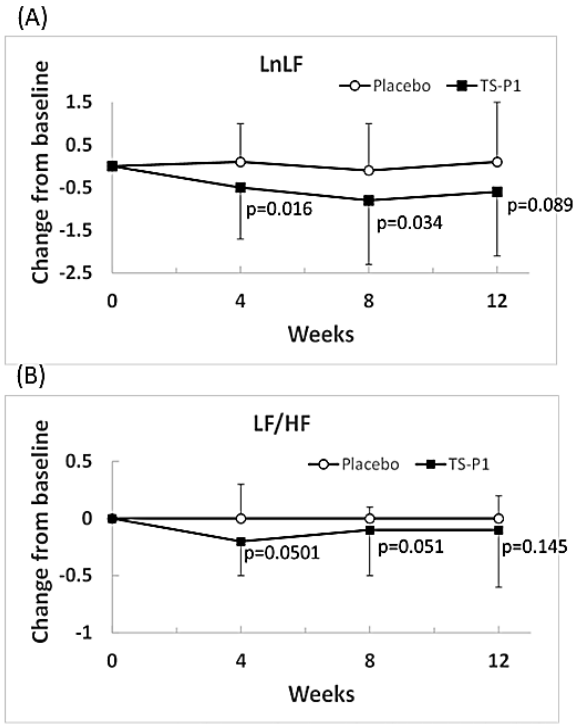


Figure 5. The mean change in (A) LnLF and (B) the LF/HF ratio from baseline throughout the study period in subjects aged 40 and over. Mean ± SD. LF: low frequency; HF: high frequency.

Sub-analysis of subjects aged 40 years and older: Table 5 shows the results of the sub-analysis of POMS2, HRV, APG, and blood pressure. In the subgroup aged 40 and over (N=31 at wk0, 30 at wk4, 31 at wk8, 31 at wk12 for TS-P1 group; N=31 for wk0, 31 at wk4, 31 at wk8, 30 at wk12 for placebo group), the mean change in Anger/Hostility and Depression/Dejection of the POMS2 in the TS-P1 group showed a greater range of decline at week 12. The mean change in LnLF in the TS-P1 group showed a greater range of decline than in the placebo group after 4 weeks of consumption. As LnHF did not reveal a significant difference between the placebo and TS-P1 groups, the mean change in the LF/HF ratio tended to show a greater range of decline throughout the study period (Figure 5).

In addition, the systolic and diastolic blood pressures also decreased in the TS-P1 group at week 12, and the mean change in the estimated vascular age showed a greater range of decline in the TS-P1 group. Furthermore, the b-peak obtained from APG decreased at week 4 in the TS-P1 group. These data suggest that long-term use of TS-P1 resulted in a parasympathetic dominant state, particularly in those aged 40 years and over, and consequently contributed to notable improvements in mood and vascular function.

General safety and tolerability: The test food was well tolerated, with no clinically relevant adverse events reported. Additionally, the safety parameters remained within the normal clinical range, affirming the safety of continuous consumption of the test food, as confirmed by the physician.

DISCUSSION

Curcumin has been reported to prevent and ameliorate various diseases, including lifestyle-related and inflammatory diseases, due to its potent antioxidant and anti-inflammatory effects [1-2]. In recent years, chronic inflammation has been identified as one of the critical factors in the onset and development of various diseases, and curcumin is attracting attention as one of the substances that can maintain health and prevent

and improve disease through diet. However, curcumin has low solubility and oral absorption; thus, it is necessary to increase its bioavailability to achieve its effects through oral intake. Although we have developed Theracurmin® with improved bioavailability [7], we have also developed a novel, highly absorbable curcumin formulation, TS-P1. TS-P1 has been confirmed to provide superior elevated bioavailability [14] and has been reported to improve cold symptoms in Japanese adults [15]. In addition to its anti-inflammatory and antioxidant effects, curcumin is also known to have effects on the central nervous system through monoamine oxidase inhibition, dopamine receptor activation, and brain-derived neurotrophic factor (BDNF) production [16-17,31]. Therefore, increased brain exposure to curcumin through TS-P1 is expected to have an effect on mood status, even in healthy people. The effects of curcumin on mood status have been reported in patients with psychiatric disorders such as major depressive disorders [19-25]. However, in recent years, amidst drastic environmental changes such as climate change and the spread of COVID-19 infection, improving fatigue and maintaining mood status are extremely significant global health issues, even for healthy people. There are several reports regarding the effect of curcumin on mood status in non-depressed subjects with some health issues, such as overweight [32-33], premenstrual syndrome [34], type 2 diabetes [35], digestive complaints [36], and hypertension [37], as well as elderly individuals [38]. Addressing these issues through food and nutrients is attracting much attention, especially in healthy people. Therefore, in this study, we investigated the effects of TS-P1 on fatigue and mood status in people without any health problems. The VAS questionnaire and POMS2 were used as they are widely used mood indices. In the present study, although TS-P1 was not found to be effective against fatigue, as assessed using the VAS-F, TS-P1 was found to be effective in reducing anger and improving depressive symptoms, as changes in AH and DD of the POMS2 at age 40 and over were lower in the TS-P1 group after 12 weeks of treatment. The effect of TS-P1 on these mood measures suggests that it can be expected to be effective against fatigue, at least mental fatigue, which is thought to be related to inflammation in the brain. As the VAS-F score is a subjective assessment that includes both mental and physical fatigue, a quantitative objective assessment is needed. In addition, in the current study, the effect of TS-P1 was seen in subjects aged 40 years and over. As the bioavailability of drugs is known to increase in the elderly due to changes in drug metabolism [39-40], the same may have occurred with curcumin without any safety issues. Another possibility is that sensitivity to stress and anger was higher in those aged over 40, which may have made it easier to detect changes in mood status.

Autonomic balance is also known as a factor that can influence mood status. In this study, the heart rate variable was measured to assess the balance between the sympathetic and parasympathetic nervous systems, and a trend towards a decrease or significant decrease in LnLF and LF/HF from baseline was observed with TS-P1 intake. These effects were also more pronounced in people over the age of 40, suggesting that taking TS-P1 suppressed sympathetic nervous system activity and produced a parasympathetic nervous system dominant state. Blood pressure was also significantly lowered by TS-P1, and vascular age estimated from the results of APG [29-30] was also reduced from baseline to a greater extent in the TS-P1 group, suggesting that parasympathetic dominance also contributed to the maintenance of cardiovascular function. In addition, we have previously reported that Theracurmin® can reduce left ventricular afterload in postmenopausal women [41]. In this study, a significant reduction in the pulse wave b-peak was observed,

which also suggests a reduction in afterload in healthy subjects, suggesting that improved autonomic balance may have contributed.

The effect of curcumin on autonomic balance has been reported in animal studies via a reduction in plasma free fatty acids in a high-fat diet challenge animal model [42]. However, there are no reports that have analyzed the effect on autonomic balance in humans in relation to mood status. The results obtained here suggest such an association for the first time. The mechanism by which curcumin improves autonomic balance is a subject for future investigation, but we have previously reported that curcumin acts in the brain to improve cognitive function [43] and to increase BDNF production [31]. Therefore, it is possible that the present effects on autonomic balance may also be due to curcumin being transported into the brain. Curcumin is also known to inhibit monoamine oxidase [16], activate dopaminergic neurons [17], and inhibit neuronal death [44]; therefore, the increased concentration of curcumin may exert its effects by increasing serotonin and dopamine and inhibiting neuronal cell death. Although curcumin has been known to have multifactorial physiological effects on the body, this study highlights, for the first time, an important role of curcumin in the regulation of autonomic balance.

Curcumin has been ingested for a long time, attracting attention as supplements for supporting health maintenance. Furthermore, curcumin is an ingredient used as a food with Health Claims (FHC) and has been proven to be safe in previous studies [8, 45]. The Function Food Center (FFC) had provided a new system for categorizing functional foods. According to this system, TS-P1 is a category C functional food product that is certified as functional only [46]. As the study was conducted with the minimum number of cases required to detect the effect of TS-P1 on mood status, validation on a larger scale is needed to make the results of this study more robust.

CONCLUSIONS

The present study demonstrated a novel action of curcumin using TS-P1 with significantly improved bioavailability in improving mood status by improving autonomic balance in healthy subjects. This study suggests, for the first time, an important role of curcumin in the regulation of autonomic balance. This also suggests that TS-P1 may be effective in maintaining and improving mood status and play a very important role in maintaining cardiovascular function. Curcumin is consumed worldwide and has attracted much attention as a health ingredient, and long-term human validation on a global scale will undoubtedly be a challenge in the future.

List of Abbreviations: ITT, intention to treat; SAF, safety analysis set; AH, Anger/Hostility; CB, Confusion/Bewilderment; DD, Depression/Dejection; FI, Fatigue/Inertia; TA, Tension/Anxiety; VA, Vigor/Activity; F, Friendliness; TMD, Total Mood Disturbance.SDNN, Standard Deviation of the Normal and Normal Interval; PSI, Physical Stress Index; TP, Total Power; LF, Low Frequency; HF, High Frequency; EstAge, Estimated Vascular Age; EstAge 10, Estimated Vascular Age after 10 years; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; FHC, food with Health Claims; FFC, Function Food Center; ACT, amorphous conversion technology.

Competing interests: The sponsor of this study, Theravalues Corporation, entrusted Apoplus Station Co., LTD. with conducting the study. Yoshitaka Kuwabara, Hyunjin Lee, and Akiko Hirose are members of Theravalues Corporation, and Yuji Makino is the professor at the Institute for Pharmaceutical Research at Musashino University. He has been conducting research on high bioavailable curcumin. Kyohei Hashimoto and Misaki Sakata are employees of Apoplus Station Co., LTD. Tadashi Watanabe, the

principal investigator of this study, is a director of Watanabe Hospital, and he monitored all conditions of the participants.

Author's contributions: Yoshitaka Kuwabara: Conceptualization, Methodology, Funding acquisition, Project administration, Visualization writing original draft preparation and Writing -review; Hyunjin Lee: Conceptualization, Methodology, Funding acquisition, Visualization, writing original draft preparation and Writing -review; Akiko Hirose: Conceptualization and Funding acquisition; Yuji Makino: Conceptualization; Tadashi Watanabe: Conceptualization and Investigation; Misaki Sakata: Methodology, Data curation, writing original draft preparation and Writing -review; Kyohei Hashimoto: Methodology, Data curation and Formal analysis.

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