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Long-term safety study of the highly absorbable curcumin formulation TS-P1 in healthy Japanese adults: a randomized, placebo-controlled, double-blind, parallel-group comparative study

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ABSTRACT

Background: Curcumin, a yellow-colored molecule derived from the rhizome of *Curcuma longa*, has been identified as the bioactive compound responsible for numerous pharmacological activities of turmeric. However, its bioavailability is very low, limiting its potential. We have developed a novel curcumin formulation, TS-P1, which exhibits an 85.2-fold higher bioavailability than raw curcumin.

Objective: The aim of this study was to evaluate the safety of long-term intake of highly bioavailable curcumin, TS-P1, in healthy Japanese adults.

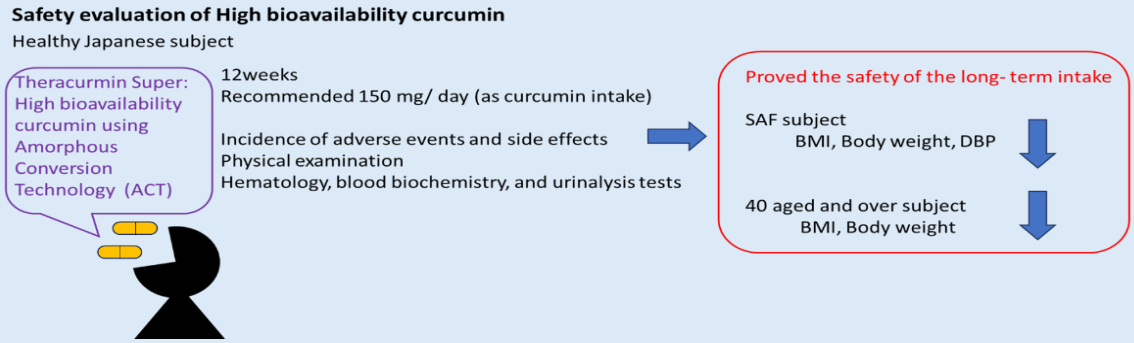
Methods: We conducted a randomized, placebo-controlled, double-blind, parallel-group comparison study. Ninety healthy Japanese adults were assigned to either the placebo or TS-P1 group and took 150 mg of curcumin or placebo daily for 12 weeks. Physical examinations, blood analysis, urinalysis, and medical examinations were performed every 4 weeks.

Results: There were no adverse events attributed to the test foods during the study period. The mean change in body weight and body mass index (BMI) at week 12 from baseline showed a significantly greater reduction in the TS-P1 group. As there was no change in food or calorie intake between the groups during the study period, the observed weight reduction in the TS-P1 group appeared to be due to the pharmacological effect of curcumin through improved bioavailability.

Conclusions: These results suggest that long-term intake of highly bioavailable curcumin, TS-P1 containing 150mg of curcumin, is safe.

Key word: Highly bioavailable curcumin; TS-P1: Theracurmin Super; Body index (BMI); Body weight

(UMIN ID: UMIN000050377)



Graphical Abstract:

INTRODUCTION

Curcumin is a plant polyphenol derived from turmeric, and its powerful antioxidant and anti-inflammatory effects are expected to have various health benefits, and it is consumed worldwide [1-2]. However, the clinical efficacy of raw curcumin is weak due to its poor water solubility and poor bioavailability, the effects of curcumin cannot be fully obtained by oral intake. Therefore, many processing methods have been proposed to improve its bioavailability [3-6].

We have developed Theracumin® (CR-033P) curcumin to improved intestinal absorption by combining two typical formulation technologies [6,7]. We also have successfully developed Theracumin Super (TS-P1) with Amorphous Conversion Technology (ACT) and TS-P1 leads to a total curcumin level of blood twice as high as that achieved with CR-033P [8].

Functional foods (FFs) have been developed to maintain health and reduce the risk of disease [9]. Functional foods (FFs) are sold not only in Japan but also in countries around the world. However, because definitions and distinctions vary from country to country, the Functional Food Center (FFC) has provided a process for the development of functional foods [10].

FFs are characterized by the presence of bioactive compounds (BC), and BC were reported to demonstrate beneficial biological activities. These compounds offer extra-nutritional benefits due to their antioxidant properties and preventative capabilities, and they also improve health through physiological mechanisms [11-13]. Curcumin, a yellow-colored molecule derived from the rhizome of Curcuma longa,

has been identified as the bioactive compound responsible for numerous pharmacological activities of turmeric. It has been used as a BC in FFs for a long time, and TS-P1 corresponds to Category C functional food product [10].

Recently, there has been a growing interest in the safety of healthy foods in Japan. [14]. As a result, there is a need for safety data on functional foods based not only on food experience but also on the implementation of safety evaluation tests.

In this study, we conducted a randomized, placebo-controlled, double-blind, parallel-group comparative study in healthy Japanese adult men and women aged 20 years or older to evaluate the long-term safety and effect on fatigue of TS-P1. In a previous paper, we evaluated and reported the effect on fatigue and improvement of autonomic nervous balance [15], but in this study, we report the results of various evaluations of safety.

METHOD

Study design: This study was conducted to investigate the safety and efficacy of 12 weeks of long-term intake of TS-P1 in healthy Japanese adults who have daily fatigue and was structured as a randomized, placebo-controlled, double-blind, parallel-group comparison study. The outline of the study design is shown in Figure 1.

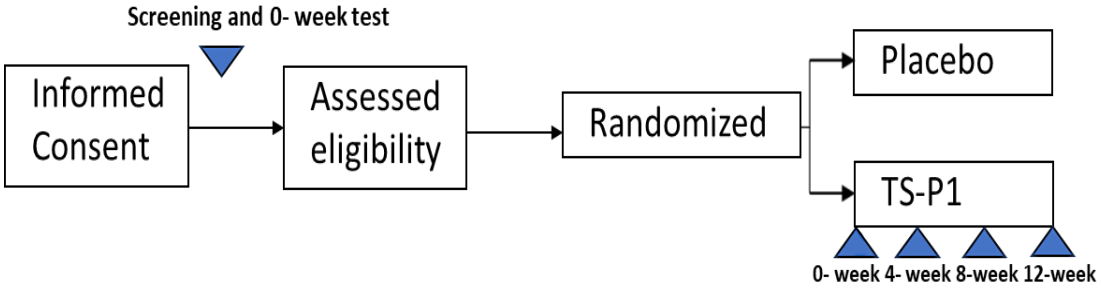


Figure 1: The outline of study design

Subject and method: This study was conducted in accordance with the Declaration of Helsinki (2013) and the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects (The Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labor and Welfare, Ministry of Economy, Trade and Industry of Japan, Notification on March 10, 2022, and enforcement April 1, 2022), with the protection of the rights of the participants considered.

This study was performed after receiving approval from the Ethics Committee of Watanabe Hospital Medical Corporation (approval date: February 10, 2023, approval ID: AF1-2209_F05_001_000_20230210_1) and registering for a clinical trial on the University Hospital Medical Information Network Clinical Trial Registry (UMIN000050377). In addition, this study was conducted by Apo Plus Station Co., Ltd. as a contracted study organization.

Subjects: In this study, the subjects were healthy adults who were applicable to the inclusion criteria below and not applicable to any exclusion criteria below.

Inclusion criteria were as follows: (1) Healthy Japanese individuals, (2) male or female, (3) aged 20 and above, (4) subjects who feel fatigued on a daily basis, and (5) subjects who are deemed eligible to participate as the principal physician.

Exclusion criteria included : (1) individuals currently receiving medical treatment or with a history of heart disease, respiratory disease, gastrointestinal disorders, malignant tumor, high blood pressure, or diabetes; (2) individuals with allergies to the study

foods or other foods; (3) individuals presently taking dietary supplements, herbal remedies, and medications; (4) individuals consuming foods marketed for specified health benefits, those with functional claims, or other functional foods and beverages daily; (5) individuals unable to discontinue their use of medications (excluding those for emergencies), quasi-drugs, foods marketed for specified health benefits, those with functional claims, or other functional foods and beverages; (6) individuals working day and night shifts or intending to work night shifts during the experimental period; (7) individuals with a history of mental health issues, such as past hospitalization for mental disorders or sleep disturbances; (8) individuals typically consuming more than 100 g of alcohol equivalent weekly (9) individuals habitually consuming alcohol on more than 5 days weekly; (10) individuals regularly smoking more than 20 cigarettes daily; (11) individuals currently enrolled in or who had participated in another clinical study within the past 3 months before consenting to participate in this trial or those intending to enroll in another study during the experimental period; (12) individuals who could not sustain their usual lifestyle, such as diet, exercise, alcohol intake, and smoking habits; (13) individuals who had difficulty consuming the study foods as instructed; (14) individuals who were pregnant, breastfeeding, or intending to conceive; and (15) individuals considered ineligible for participation in this study.

Selection criteria were as follows: (1) Subjects who deemed eligible to participate of the principal physician; (2) subjects who relatively lower fatigue VAS scores; (3) subjects who answered anything other than "I want to commit suicide" or "I intend to commit suicide if I have the chance" in question 9 of the Beck Depression Inventory-Second Edition;(4) subjects who have a full explanation of the purpose and content of the study and signed a consent form before the study began.

The study protocol was fully explained to all participants by the principal investigator, and all participants signed the informed consent document before participating in the study. Oversaw and evaluated data, subjects' health management, and conducted examinations performed by Watanabe Hospital in Tokyo, Japan.

Enrollment: The subjects who were confirmed to be eligible for the study through screening and the 0-week test were enrolled. The person in charge of allocation allocated the subjects (90 people) selected from the results of the preliminary test into two groups. The subjects were randomly allocated to each group based on the fatigue score (visual analog scale (VAS)) obtained during the screening and 0-week test, gender, age, and smoking status, to ensure that there was no bias in the groups. The person in charge of allocation signed and stamped the bound allocation decision form along with the allocation list that allocated the test subjects and stored it together with the sealed test food allocation record in a locked storage facility until the allocation was disclosed.

Restrictions and Prohibitions for Subjects: The subjects were required to follow the following rules during the study: (1) consume the test food as instructed by the study physician; (2) only allow the test food to be consumed by the study subject himself; (3) fill out a daily diary without omissions and submit it as specified; (4) refrain from taking or using any medicines, quasi-drugs, Food for Specified Health Uses (FOSHU), foods with functional claims, or other so-called FFs during the study. Additionally, subjects were

to refrain from taking any foods that advertise anti-fatigue properties as possible. If it is unavoidable to use medicines, quasi-drugs, or herbal medicines, or if subjects have been used, they must contact the study consultation desk and report the product names, amounts used, and reasons for use, and record this in a daily diary; (5) Lifestyle habits during the study period must not be significantly changed from before the study began, and must be maintained as similar as possible (binge drinking/eating, dieting, changes to diet due to overseas travel, etc., abruptly stopping previous exercise, or starting a new exercise program, etc. must not be allowed); (6) Refrain from excessive food and alcohol intake during the study period; (7) Refrain from excessive exercise during the study period; (8) During the study period, the subject will not be allowed to participate in studies that involve the consumption of other foods or medicines, or studies that involve the application of cosmetics or medicines; (9) Alcohol intake is prohibited from the day before all tests until the end of the tests on the day of the test; (10) Fast for at least 6 hours from the day before all tests until the start of the tests on the day of the test; (11) Exercise is prohibited from the day before all tests until the start of the tests on the day of the test (including going up and down stairs, etc.); (12) On the day of the test, subjects must fast before coming to the hospital, and must drink the minimum amount of water necessary (about 200 mL); (13) On the days of the 4-week and 8-week tests, the patient will come to the hospital without consuming the test food, and will consume it after the test is completed (however, if the patient comes in the afternoon, they will consume the test food as usual); (14) On the day of the test, the patient will be required to abstain from smoking until the end of the test; (15) The patient will not reveal any information about the test or the test food to others. This includes postings on SNS (social networking services) such as X (formerly Twitter), Facebook, blogs, and bulletin boards.

Intervention: The subjects were allocated adjustment of (1) sex, (2) age, (3) smoking status, and (4) score of VAS- F (the visual analog scale (VAS)) and were randomized. The subjects were instructed to take either 4 placebo capsules or 4 capsules containing TS-P1 twice per day with water after breakfast and dinner for 12 weeks. This intervention was designed to be ingested at 150 mg/day as curcumin per day in the TS-P1 group. Safety and mental status were assessed 0, 4, 8, and 12 weeks after intake of the test food. The study was conducted from February 10, 2023 to September 2023.

Safety evaluation items: At 0, 4, 8, and 12 weeks after the intake of the test food, physical examination (height, weight, temperature, BMI, systolic blood pressure, diastolic blood pressure, and pulse rate), hematological examination (white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit value (Ht), platelet count (Plt), white blood cell picture (neutrophil count (Neut), neutrophil ratio (Neut-R), neutrophil/lymphocyte ratio (Neut/Lymph), basophil ratio (Baso), eosinophil ratio (Eosino), lymphocyte ratio (Lymph), monocyte percentage (Mono), blood biochemistry test (AST, ALT, γ-GTP, alkaline phosphatase (ALP), LD (LDH), LAP, total protein (TP), total bilirubin (T-Bil), direct bilirubin (D-Bil), indirect bilirubin (I-BIL), ZTT, creatine kinase (CK), serum amylase (Amy), urea nitrogen (BUN), uric acid (UA), total cholesterol (T-cho), triglyceride (TG), glucose (Glu), cholinesterase The subjects were

examined for serum iron (Fe), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), HbA1c, and glycoalbumin (GA), and urine tests (protein, glucose, urobilinogen, ketone body, pH, specific gravity, and occult blood test). The subjects were also interviewed by the principal investigator to determine the occurrence of symptoms. During the study, the subjects themselves recorded their lifestyle habits, such as intake of the test foods, physical condition, medication, alcohol intake, fatigue, and lethargy. The subjects also recorded their dietary records for the three days prior to the screening and the 0-week test, the 4-week test, the 8-week test, and the 12-week test.

Statistical analysis: After the study was completed, the principal investigator determined the cases to be analyzed and the handling of the data based on clinical judgment, and the contracted data management officer fixed the data. After the data was fixed, the randomization officer opened the test food allocation records and prepared an allocation disclosure report. The analysis population was determined at the time of data fixation, in accordance with the handling of the subjects. Regarding safety, the group excluding cases who had not taken the test food even once after the start of the study was defined as the safety analysis population (SAF). Background information on the subjects was compiled in a table, and frequency data by category or summary statistics were compiled by group. Group comparisons were performed using t-tests for quantitative data (continuous data) and Fisher's exact test for count data (categorical data). SAS release 9.4 for Windows and Microsoft Office 365 Apps for enterprise were used for this analysis.

For safety data, summary statistics were calculated for each group at each evaluation time point (screening and 0, 4, 8, and 12 weeks after test foods). In addition, the measurements at the 0-week test were used as the baseline for each group, and summary statistics were calculated for the changes at the 4-week, 8-week, and 12-week visits. For hematological and blood biochemistry tests, a two-sample t-test was used to compare the measurements and changes at each evaluation time point between groups, and for urine tests, a Wilcoxon rank sum test was used. Fisher's exact test was used to compare the incidence of adverse events. For body weight and BMI, subgroup analysis was performed for cases aged 40 years or older using the same method as above. Values are shown as mean ± standard deviation, and the significance level was set at 5% on both sides.

RESULTS

The flowchart of trial and subject background: Subjects who wished to participate in the study applied during the recruitment period (April 14, 2023 to May 15, 2023) and were evaluated for eligibility, and 90 people who met the inclusion criteria and did not violate the exclusion criteria were selected. Figure 2 shows the flowchart of this study. A total of 90 eligible subjects were selected and randomly assigned to the placebo group and the TS-P1 group based on fatigue score (visual analog scale (VAS)), gender, age, and smoking status. Table 1 summarizes the background of each group. There were no significant differences in baseline fatigue level, gender, age, smoking status, height, weight, or BMI between the placebo group and the TS-P1 group. There were no discontinuations or dropouts during the study period, and the safety analysis population (SAF), full analysis set (FAS), and efficacy analysis set (Per protocol analysis set (PPS)) were all 90 cases (TS-P1 group: 45 cases, placebo group: 45 cases).

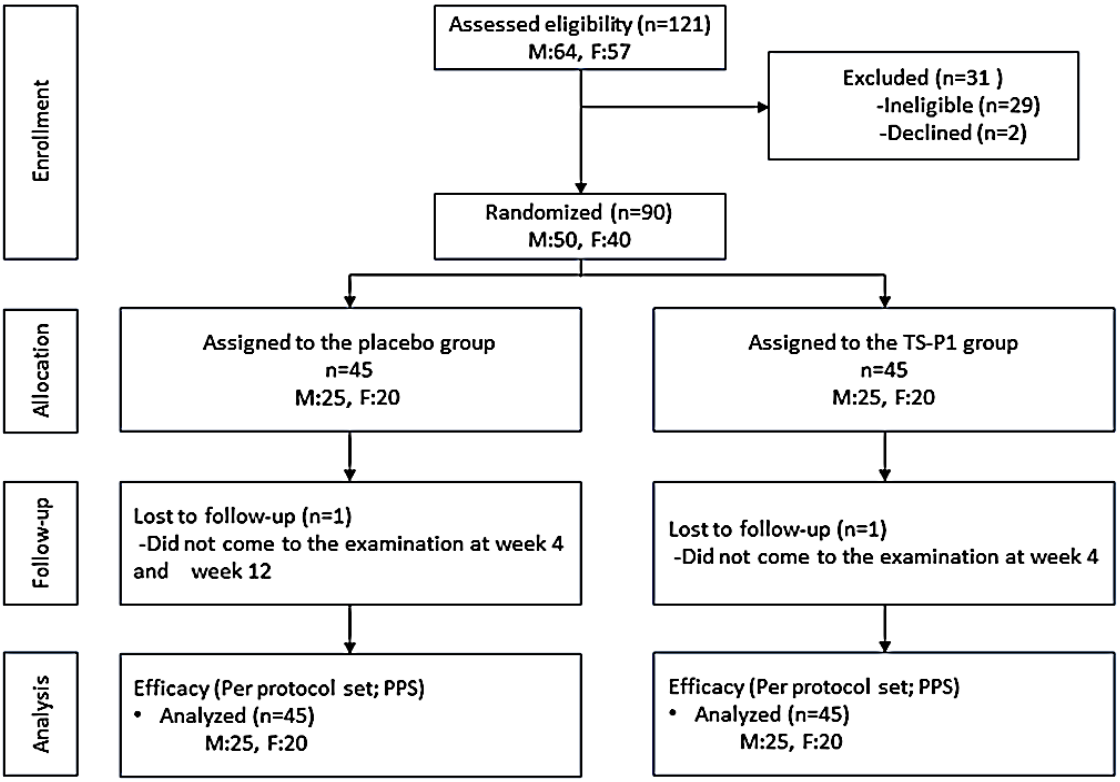


Figure 2: The flowchart of participation

Table 1: Subjects' background information

	Placebo Group	TS-P1 Group
Age (years)	45.7±10.6	45.8±10.3
Sex (M/F)	25/20	25/20
Fatigue score	68.3±8.4	67.9±8.4
Hight (cm)	164.38±7.57	164.59±8.47
Body Weight (kg)	61.36±11.29	61.13±12.19
BMI (kg/m2)	22.59±3.11	22.41±3.25
Smoking status	5 (11.1%)	4 (8.9%)

Mean±SD

Table 2: Adverse events and side effects expression

Analysis group : SAF

		Placebo group	TS-P1 group	Comparison between group
Number of subject to assessment		45	45	-
Adverse events	Number of cases of expression	11 (24.4 %)	11 (24.4 %)	1.000
	Number of incidents	24	36	-
Side effects	Number of cases of expression	0 (0.0 %)	0 (0.0 %)	-
	Number of incidents	0	0	-

Fisher's exact test

Safety Evaluation

Adverse events, side effects: Table 2 illustrates the occurrence of adverse events and side effects during the study period, and Table 3 shows a list of adverse events. Adverse events are any unwanted or unintended injuries, signs of such injuries, or illnesses observed in subjects during the trial period. These events may or may not be causally related to the test diet. A side effect is an adverse event for which a causal relationship with the test diet cannot be excluded. Adverse events occurred in 11 cases (24.4%) and 24 events in the placebo group, and 11 cases (24.4%) and 36 events in the TS-P1 group, with no significant difference in incidence between the groups. Furthermore, the principal investigator determined that all adverse events were mild in severity and had no causal relationship to the test food. Additionally, there were no side effects in either the placebo group or the TS-P1 group.

Table 3: List of adverse events

	Placebo group（Case）	TS-P1 group（Case）
ALT high value	0	1
AST high value	1	0
CK high value	1	0
Cold symptom	1	2
A slight fever	0	1
Feel feverish	1	0
COVID-19	1	0
Sinusitis	0	1
Stomachache	0	1
Acute gastroenteritis	0	1
Nausea	0	2
Indigestion	0	1
Abdominal pain	2	1
Diarrhea	0	2
Fatigue	1	1
Malaise	3	2
General malaise	1	0
Heatstroke	1	0
Sole pain	0	1
Cervical syndrome	0	2
Muscle fatigue	0	1
Lower back pain	0	2
Muscle cramps	1	0
Period pain	5	5
Premenstrual syndrome (PMS)	1	1
Headache	3	6
Vagal reflex	0	1
Arrhythmia	1	0
Hangover	0	1

The patient with Covid19 had symptoms of fever, sore throat, and cough, but no gastrointestinal symptoms. The sensation felt after physical or mental exertion was described as 'Malaise', while the 'sluggishness' felt during periods of inactivity was described as 'General Malaise'. Sole pain refers to pain in the sole of the foot,

which is known to be caused by several factors, including plantar fasciitis and flat feet. Alcohol consumption was slightly higher in the hangover subject, but not excessive.

Hematology, blood biochemistry, and urinalysis tests: Table 4 shows the results of hematological and blood biochemistry tests. There were occasional points where significant differences between groups were observed in lymphocyte count percentage, direct bilirubin, and inorganic phosphorus, but all of these were within the reference range and the principal investigator determined that they would not affect safety. Table 5 shows the results of urine tests. No significant differences were observed between the groups in any of the items.

Table 4: Blood tests and blood chemistry tests

		Wk0			Wk4			Wk8			Wk12		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
WBC (/μL)	Placebo	5695.6	1586.3	0.802	5986.7	1640.3	0.652	5951.1	1592.5	0.739	5566.7	1496.5	0.251
	TS-P1	5611.1	1599.0		5831.1	1618.5		5844.4	1436.3		5953.3	1672.3	
RBC (10^4/μL)	Placebo	461.1	45.7	0.650	459.8	47.8	0.678	457.4	44.4	0.672	458.7	42.2	0.869
	TS-P1	465.4	42.7		463.8	43.7		461.5	46.3		460.3	48.1	
Hb (g/dL)	Placebo	13.80	1.23	0.411	13.74	1.28	0.845	13.70	1.19	0.630	13.73	1.12	0.850
	TS-P1	14.01	1.14		13.79	1.19		13.82	1.29		13.78	1.43	
Ht (%)	Placebo	43.05	3.88	0.358	43.28	3.70	0.433	42.86	3.54	0.555	43.10	3.26	0.531
	TS-P1	43.75	3.21		43.85	3.25		43.32	3.82		43.58	3.97	
Plt (10^4/μL)	Placebo	26.91	6.63	0.706	26.61	5.29	0.998	27.12	5.94	0.876	27.61	6.61	0.794
	TS-P1	26.45	4.71		26.61	5.30		26.92	5.63		27.26	5.94	
Neut (/μL)	Placebo	3420.6	1230.1	0.984	3555.3	1414.6	0.845	3489.7	1207.5	0.821	3270.3	1142.8	0.113
	TS-P1	3425.9	1220.3		3500.3	1235.7		3545.3	1111.8		3697.5	1375.5	
Neut-R (%)	Placebo	59.40	8.78	0.685	58.30	8.00	0.593	58.14	7.57	0.260	58.08	7.98	0.067
	TS-P1	60.09	7.11		59.20	7.88		59.96	7.67		61.20	7.98	
Neut/Lymph	Placebo	2.09	0.90	0.976	2.00	0.94	0.759	1.90	0.66	0.139	1.96	0.76	0.070
	TS-P1	2.08	0.65		2.05	0.73		2.11	0.68		2.29	0.97	
Baso (%)	Placebo	0.75	0.31	0.212	0.76	0.35	0.712	0.79	0.29	0.975	0.83	0.37	0.716
	TS-P1	0.84	0.40		0.79	0.39		0.79	0.39		0.86	0.44	
Eosino (%)	Placebo	2.66	1.42	0.074	2.84	1.41	0.108	2.65	1.37	0.098	2.91	1.62	0.161
	TS-P1	3.39	2.27		3.54	2.51		3.43	2.82		3.58	2.75	
Lymph (%)	Placebo	31.72	8.35	0.419	32.53	7.89	0.323	33.00	7.43	0.049	32.34	7.37	0.024
	TS-P1	30.50	5.64		31.00	6.69		30.18*	5.85		29.03*	6.23	
Mono (%)	Placebo	5.46	1.33	0.319	5.57	1.28	0.738	5.41	1.42	0.496	5.84	1.64	0.088
	TS-P1	5.18	1.39		5.48	1.36		5.63	1.62		5.33	1.14	
AST (U/L)	Placebo	19.6	4.6	0.844	20.9	9.1	0.294	20.5	6.0	0.656	20.9	5.6	0.823
	TS-P1	19.8	6.0		19.2	6.2		21.7	17.0		20.6	6.6	
ALT (U/L)	Placebo	18.4	7.9	0.557	18.2	7.7	0.144	18.3	7.0	0.868	19.1	7.8	0.657
	TS-P1	17.4	8.6		15.9	7.0		18.8	20.3		18.3	10.4	
γGTP (U/L)	Placebo	26.5	21.5	0.882	27.8	23.3	0.682	28.0	23.2	0.910	30.0	24.0	0.926
	TS-P1	27.4	34.9		25.5	29.7		28.7	33.4		30.7	37.6	
ALP (U/L)	Placebo	65.7	19.2	0.834	67.8	22.0	0.431	67.6	19.9	0.695	69.3	18.8	0.715
	TS-P1	64.9	19.0		64.5	18.1		65.9	19.9		67.8	19.2	
LDH (U/L)	Placebo	168.9	24.2	0.987	175.6	27.7	0.841	178.7	26.4	0.768	175.6	27.8	0.582
	TS-P1	168.8	28.9		174.5	25.7		177.1	26.4		172.3	28.6	
LAP (U/L)	Placebo	48.0	7.7	1.000	49.4	8.6	0.507	49.5	8.6	0.923	49.4	9.2	0.919
	TS-P1	48.0	12.7		48.2	7.8		49.3	10.9		49.2	13.2	
T-Bil	Placebo	0.83	0.31	0.756	0.78	0.24	0.497	0.77	0.23	0.103	0.76	0.28	0.553

		Wk0			Wk4			Wk8			Wk12		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
(mg/dL)	TS-P1	0.81	0.29		0.81	0.28		0.86	0.29		0.79	0.25	
D-Bil	Placebo	0.09	0.05	0.016	0.12	0.04	0.013	0.11	0.04	0.009	0.10	0.04	0.106
(mg/dL)	TS-P1	0.12*	0.05		0.15*	0.06		0.14**	0.06		0.12	0.05	
I-Bil	Placebo	0.74	0.29	0.455	0.66	0.22	0.860	0.66	0.21	0.222	0.66	0.26	0.731
(mg/dL)	TS-P1	0.70	0.27		0.67	0.25		0.73	0.27		0.67	0.23	
ChE	Placebo	323.0	62.3	0.523	320.1	57.9	0.393	321.0	54.4	0.237	327.9	61.6	0.191
(U/L)	TS-P1	313.2	81.7		307.7	78.1		304.2	77.9		307.6	82.8	
ZTT	Placebo	8.74	4.57	0.328	9.16	6.26	0.235	9.47	6.30	0.325	9.07	5.96	0.297
(U)	TS-P1	7.96	2.65		7.93	2.82		8.44	2.94		8.05	2.73	
TP	Placebo	7.05	0.38	0.907	7.19	0.42	0.690	7.15	0.41	0.619	7.17	0.38	0.735
(g/dL)	TS-P1	7.04	0.34		7.15	0.37		7.11	0.39		7.14	0.42	
BUN	Placebo	12.70	2.93	0.661	12.88	3.56	0.856	13.06	3.06	0.414	13.30	3.50	0.054
(mg/dL)	TS-P1	12.44	2.72		12.75	3.51		12.49	3.50		11.86	3.49	
Cre	Placebo	0.795	0.159	0.862	0.776	0.162	0.632	0.786	0.156	0.830	0.782	0.142	0.989
(mg/dL)	TS-P1	0.789	0.156		0.792	0.163		0.793	0.157		0.783	0.155	
UA	Placebo	5.28	1.44	0.394	5.35	1.51	0.544	5.41	1.43	0.633	5.28	1.37	0.715
(mg/dL)	TS-P1	5.54	1.36		5.56	1.71		5.56	1.56		5.40	1.50	
CK	Placebo	111.2	63.0	0.638	187.2	409.1	0.293	146.7	137.3	0.069	118.2	62.7	0.889
(U/L)	TS-P1	118.3	80.1		121.2	80.0		105.5	58.4		120.4	80.9	
Amy	Placebo	79.1	18.7	0.368	77.8	19.9	0.480	79.1	21.2	0.723	81.6	21.4	0.174
(U/L)	TS-P1	75.1	22.8		74.5	23.4		77.2	30.7		74.9	24.4	
Glu	Placebo	86.8	7.4	0.613	89.4	9.4	0.152	89.6	14.5	0.388	86.9	8.1	0.984
(mg/dL)	TS-P1	86.0	8.0		86.8	7.4		87.2	12.7		86.8	12.9	
HbA1c	Placebo	5.37	0.23	0.525	5.37	0.27	0.390	5.50	0.27	0.342	5.46	0.28	0.242
(%)	TS-P1	5.34	0.32		5.32	0.31		5.44	0.30		5.39	0.29	
GA	Placebo	13.72	1.10	0.780	13.94	1.04	0.585	13.91	1.03	0.615	13.94	1.11	0.725
(%)	TS-P1	13.79	1.23		14.08	1.32		14.03	1.18		14.03	1.22	
T-cho	Placebo	209.1	34.8	0.446	203.0	37.2	0.618	203.1	34.2	0.498	204.6	35.8	0.383
(mg/dL)	TS-P1	203.3	36.6		199.2	35.2		198.0	36.8		197.8	37.8	
HDL-C	Placebo	67.4	18.3	0.451	67.4	17.5	0.539	67.7	18.1	0.828	67.1	16.8	0.954
(mg/dL)	TS-P1	70.2	15.9		69.7	17.4		68.5	16.7		66.9	16.0	
LDL-C	Placebo	121.4	30.9	0.333	115.3	33.7	0.446	118.4	30.7	0.372	120.0	34.3	0.333
(mg/dL)	TS-P1	115.1	30.2		110.3	27.4		112.5	31.7		113.2	31.9	
TG	Placebo	98.1	51.7	0.168	101.4	45.1	0.410	93.7	54.8	0.971	96.8	65.6	0.922
(mg/dL)	TS-P1	82.8	52.8		91.9	62.4		93.2	81.7		98.4	87.8	
Fe	Placebo	102.0	36.3	0.551	102.5	37.0	0.118	94.7	34.1	0.836	92.2	35.5	0.678
(μg/dL)	TS-P1	97.2	38.6		90.7	34.0		96.4	40.5		88.6	46.3	
Na	Placebo	140.8	1.6	0.406	140.1	1.7	0.205	140.3	1.8	0.630	140.7	1.7	0.312
(mEq/L)	TS-P1	140.5	1.7		140.6	1.4		140.1	2.1		140.4	1.9	
K	Placebo	4.36	0.43	0.697	4.16	0.25	0.239	4.19	0.33	0.473	4.34	0.33	0.760
(mEq/L)	TS-P1	4.33	0.25		4.22	0.23		4.23	0.25		4.32	0.29	
Cl	Placebo	103.2	2.2	0.833	103.2	1.8	0.207	103.0	1.8	0.662	103.3	1.7	0.530
(mEq/L)	TS-P1	103.3	1.8		103.7	1.8		103.2	2.1		103.0	2.3	
Ca	Placebo	9.40	0.38	0.163	9.32	0.36	0.686	9.34	0.43	0.246	9.36	0.37	0.213
(mg/dL)	TS-P1	9.30	0.29		9.30	0.31		9.25	0.27		9.27	0.29	
IP	Placebo	3.65	0.53	0.034	3.67	0.56	0.271	3.49	0.48	0.325	3.66	0.50	0.055
(mg/dL)	TS-P1	3.42*	0.46		3.55	0.47		3.40	0.44		3.46	0.46	

*p<0.05 vs Placebo、**p<0.01 vs Placebo

Table 5-1: Urinalysis

		Wk0			Wk4			Wk8			Wk12		
		mean	SD	p-value	mean	SD	p-value	mean	SD	p-value	mean	SD	p-value
pH	Placebo	6.14	0.64	0.728	6.16	0.60	0.738	6.16	0.62	0.736	6.27	0.63	0.087
	TS-P1	6.10	0.57		6.20	0.65		6.20	0.63		6.06	0.52	
Specific gravity	Placebo	1.0169	0.0065	0.595	1.0172	0.0078	0.284	1.0181	0.0078	0.716	1.0168	0.0074	0.731
	TS-P1	1.0162	0.0065		1.0190	0.0077		1.0187	0.0084		1.0174	0.0073	

Table 5-2: Urinalysis

			Wk0		Wk4		Wk8		Wk12	
			n	p- value	n	p- value	n	p- value	n	p- value
Urinary sugar	Placebo	−	44	0.328	44	0.328	44	0.328	45	1.000
		±	1		0		1		0	
		+	0		1		0		0	
	TS-P1	−	45		45		45		45	
Albuminuria	Placebo	−	45	0.160	44	0.167	42	0.060	43	0.139
		±	0		1		3		2	
	TS-P1	−	43		41		36		39	
		±	2		2		7		5	
		+	0		2		2		1	
Qualitative test of urobilinogen	Placebo	−	0	0.082	0	1.000	0	1.000	0	0.328
		±	42		45		44		44	
		+	3		0		0		1	
		2+	0		0		1		0	
	TS-P1	−	0		0		0		0	
		±	45		45		44		45	
		+	0		0		1		0	
Ketone body	Placebo	−	45	0.328	45	1.000	44	0.586	45	0.160
		±	0		0		0		0	
		+	0		0		0		0	
		2+	0		0		1		0	
	TS-P1	−	44		45		43		43	
		±	0		0		0		0	
		+	1		0		2		1	
		2+	0		0		0		1	
Reaction of occult blood	Placebo	−	43	0.224	40	0.355	41	0.733	43	0.076
		±	2		2		2		1	
		+	0		1		0		1	
		2+	0		1		1		0	
		3+	0		1		1		0	
	TS-P1	−	40		37		40		38	
		±	2		2		2		3	
		+	0		1		1		0	
		2+	2		4		1		2	
		3+	1		1		1		2	

Compared between group (Wilcoxon signed-rank test)

Table 6: Physical Examination

		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
Body weight	**Placebo**	61.36	11.29	0.927	61.06	11.16	0.814	-0.30	0.99	0.187	61.28	11.21	0.733	-0.08	1.26	0.055	61.34	11.26	0.713	-0.01	1.28	0.049
	TS-P1	61.13	12.19		60.48	12.04		-0.65	1.46		60.43	12.32		-0.70	1.74		60.43	12.24		-0.70*	1.93	
BMI	**Placebo**	22.59	3.11	0.779	22.49	3.08	0.636	-0.11	0.36	0.187	22.57	3.14	0.529	-0.02	0.45	0.039	22.59	3.13	0.511	0.00	0.47	0.042
	TS-P1	22.41	3.25		22.17	3.22		-0.23	0.53		22.14	3.30		-0.26*	0.62		22.15	3.27		-0.26*	0.69	
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	

*p<0.05 vs Placebo、**p<0.01 vs Placeb

Table 7: Body weight and BMI in those aged 40 and over.

		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
Body weight	Placebo	59.97	10.26	0.431	59.85	10.18	0.569	-0.12	0.93	0.039	60.26	10.21	0.723	0.29	1.18	0.002	60.17	10.16	0.702	0.20	1.41	0.006
	TS-P1	62.31	12.85		61.51	12.48		-0.80*	1.55		61.31	12.83		-1.00**	1.82		61.29	12.71		-1.02**	1.94	
BMI	Placebo	22.54	3.06	0.896	22.50	3.06	0.870	-0.04	0.34	0.049	22.65	3.09	0.651	0.12	0.43	0.001	22.62	3.08	0.680	0.08	0.52	0.006
	TS-P1	22.65	3.34		22.37	3.27		-0.28*	0.56		22.28	3.34		-0.36**	0.64		22.28	3.32		-0.36**	0.70	

*p<0.05 vs Placebo、**p<0.01 vs Placebo

Physical Examination: Table 6 shows the changes in weight, BMI, blood pressure, and heart rate. In the placebo group, weight and BMI remained almost unchanged over the 12 weeks, whereas in the TS-P1 group, the reduction from week 0 to week 12 was significantly greater than in the placebo group (both $p<0.05$). Additionally, in terms of diastolic blood pressure, the measured values and changes after 12 weeks were significantly lower in the TS-P1 group than in the placebo group (both $p<0.05$). There were no major changes in lifestyle during the study period in either group, and no significant differences were observed between groups in terms of food intake or calorie intake throughout the study period. (data not shown）

Physical examination and Subgroup analysis: To investigate the weight loss effect of TS-P1 in more detail, the weight and BMI trends were analyzed for the subgroup of subjects aged 40 years or older. The weight loss from 0-week was significantly greater in the TS-P1 group at all time points from 4- week onwards (Table 7). There were no significant changes in lifestyle in the subgroup of subjects aged 40 years or older, and no significant differences were observed between the groups in terms of food intake and calorie intake throughout the study period. (data not shown）

DISCUSSION

In this study, the safety and efficacy of TS-P1 containing 150 mg of curcumin was examined in healthy Japanese adult men and women aged 20 years or older for 12 weeks in a placebo-controlled, randomized, double-blind, parallel-group comparative study.

Adverse events occurred in both the placebo and TS-P1 groups but there was no causal relationship to the test food.

Adverse events occurred in both the placebo and TS-P1 groups, but there was no significant difference in the number of events, and it was determined that there was no causal relationship between the test diet and the event. Hematological and blood biochemistry tests showed significant differences between the two groups in some items, but all were within the reference range and were determined not to affect the safety of TS-P1. Urine tests showed no significant changes.

Physical examinations showed significant decreases in weight, BMI, and blood pressure from 0-week in the TS-P1 group, but no changes were observed in the subjects' lifestyle habits or the amount or quality of their meals.

Taking into account other test items and the results of the doctor's examination, it was considered highly likely that these were not safety issues but were the result of the pharmacological effects of curcumin. From the above, the safety of 12 weeks of continuous intake of TS-P1 containing 150 mg of curcumin was confirmed.

Curcumin is expected to have various health benefits, but its low bioavailability has been an issue. We have previously developed Theracurmin®, which has 20 times higher maximum plasma concentration (Cmax) and 42 times higher area under the curve (AUC) of curcumin after oral intake compared to raw curcumin [6]. We have now developed TS-P1, which has twice the bioavailability of curcumin compared to Theracurmin® [8]. A previous study suggested TS-P1 for each of the common cold symptoms than CR-033P, significantly decreased ‘sneezing’, ‘nasal discharge’, ‘nasal obstruction’, and ‘coughing’ in a cumulative number of days [16].

Previous studies proved the safety of the long-term intake and excessive intake of TS-P1[17] and the same results were obtained in this study.

As the safety of long-term intake of TS-P1 has been confirmed by this study, it is expected that many health benefits can be achieved by taking TS-P1.

The weight loss observed in the TS-P1 group is believed to be due to the pharmacological action of curcumin, since there were no significant changes in

lifestyle, food intake, or dietary content, and calorie intake was not different from that of the placebo group. The weight loss and anti-obesity effects of curcumin have been reported in many animal and human studies [18-21]. The mechanisms of curcumin's weight loss effect include activation of β3-adrenergic receptor signaling [22], activation of AMPK [23], induction of brown adipocyte differentiation [23, 24], promotion of GLP-1 secretion [25], and improvement of intestinal flora [26, 27]. In a mouse study, we have confirmed that Theracurmin® induces brown adipocyte differentiation from white adipocytes via anti-inflammatory macrophages, and that this effect is not observed with raw curcumin at the same dose [28]. Since TS-P1 has a higher bioavailability than Theracurmin®, the weight loss effect observed in this study may be, at least in part, mediated by these mechanisms. Most obesity treatment drugs developed to date have been based on the mechanisms of action of lipase inhibition [29], inhibition of gastrointestinal motility by GLP-1 receptor agonists [30, 31], or appetite suppression by acting on the central nervous system [30-32], and these are known to have various side effects including gastrointestinal symptoms. The results of this study suggest that TS-P1 may be able to control weight without side effects and without affecting appetite. In addition to its anti-obesity effect, it has been reported that curcumin may have various effects such as improving liver function [33], improving knee pain [34], improving Crohn's disease symptoms [35], improving muscle pain caused by exercise [36,37], antidepressant effects [38], and improving cognitive function [39]. Therefore, it is believed that TS-P1 can safely provide the various health benefits expected of curcumin.

CONCLUSION

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted on healthy Japanese adult men and women aged 20 years or older to investigate the safety of taking TS-P1 containing 150 mg of curcumin for 12 weeks. As a result, no clinically significant changes were observed in blood tests, urine tests, or physical examinations. Weight loss was observed due to the intake of TS-P1, but there was no effect on food intake, etc., which was thought to be due to the pharmacological effect of curcumin. No other side effects indicating a relationship with TS-P1 were observed, confirming the safety of taking TS-P1 containing 150 mg of curcumin for 12 weeks.

List of Abbreviations: FFs, Functional foods; FOSHU, Food for Specified Health Uses; SAF, safety analysis set; BMI, body Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; FHC, food with Health Claims; FFC, Function Food Center; ACT, amorphous conversion technology; BC,bioactive compounds; VAS, visual analogue scale; WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Ht, hematocrit value; Plt, platelet count; Neut , neutrophil count; Neut-R, neutrophil ratio; Neut/Lymph, neutrophil/lymphocyte ratio; Baso, basophil ratio; Eosino, eosinophil ratio; Lymph, lymphocyte ratio; Mono, monocyte percentage; AST, ALT, γ-GTP, alkaline phosphatase (ALP), LD (LDH), LAP;TP, total protein; T-Bil, total bilirubin; D-Bil, direct bilirubin; I-BIL, indirect bilirubin; CK, creatine kinase; Amy, serum amylase; BUN, urea nitrogen ; UA, uric acid; T-cho, total cholesterol ; TG, triglyceride; Glu, glucose; Fe,serum iron; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; HbA1c, and GA, glycol albumin; FAS, full analysis set; PPS, Per protocol analysis set; Cmax, maximum plasma concentration; AUC, Area under the curve.

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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