Safety Evaluation of Theracurmin® in Healthy Japanese Adults

—A Randomized, Double-blind, Placebo-controlled Parallel-group Study—

■

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ABSTRACT

Objectives We aimed to evaluate the safety in humans of 4-week excessive and 12-week long-term intake of Theracurmin®（highly bioavailable curcumin）through a randomized, placebo-controlled, double-blind, parallel-group study.

Methods We conducted two trials from May to July 2018（trial Ⅰ, excessive intake trial）or May to October 2018（trial Ⅱ, long-term intake trial）. For both trials, participants who provided informed consent and met the inclusion criteria were allocated equally but randomly into either the Theracurmin® group（T group, $n=16$）or the placebo group（P group, $n=16$）, using a computerized random-number generator. In trial Ⅰ, participants took 10 capsules of either Theracurmin®（approximately 90 mg of curcumin/capsule）or placebo twice per day with water after breakfast and dinner（five capsules each meal）for 4 weeks. In trial Ⅱ, participants took two capsules per day of either Theracurmin® or placebo with water after breakfast and dinner（one capsule after each meal）for 12 weeks. The safety evaluation included physical examination, urinalysis, blood analysis, and subjective symptoms.

Results One participant did not have a satisfactory ingestion rate（＜90%）and thus was excluded from the analysis; the remaining 31 participants were analyzed as per protocol（T group $n=15$; P group $n=16$）in both trials Ⅰ and Ⅱ. No adverse effects were reported regarding the test food.

Conclusions These trials proved the safety of 4-week excessive and 12-week long-term intake of Theracurmin®.

Trial registration UMIN-CTR: UMIN000032640（trial Ⅰ, excessive intake）; UMIN000032641（trial Ⅱ, long-term intake）

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KEY WORDS Highly bioavailable curcumin, Excessive intake, Long-term intake, Safety evaluation

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INTRODUCTION

In recent years, the number of submissions to the Foods with Functional Claims system has increased in Japan, along with an increased demand for a guarantee of safety for these foods.

Curcumin is one of the polyphenolic compounds contained in turmeric, which has been demonstrated to have many functions *in vitro*, such as antioxidant and anti-inflammatory effects.[1] However, curcumin exhibits poor absorption with oral intake, and its bioavailability as shown in *in vivo* and clinical trials and the effects expected from *in vitro* studies have not been fully elucidated.[2] Therefore, a study on oral bioavailability has been performed to enhance the usefulness of curcumin in the body. Theracurmin®, the test compound evaluated in this study, is a highly absorptive oral curcumin agent. Previous *in vivo* studies and clinical trials have reported that bioavailability of Theracurmin® is significantly higher than the nonprocessed form of curcumin.[3–5] Curcumin has long been used in cuisine as a spice; however, the diffusion of Theracurmin® into the bloodstream is much higher than that of nonprocessed curcumin,[3] and adverse events from its excessive or long-term intake might be greater than that of nonprocessed curcumin due to the higher concentration of curcumin in the body. Furthermore, the high absorption efficacy of a curcumin leads to a smaller size of the final product; thus, excessive intake is easy to achieve. It is therefore important to evaluate the safety of excessive Theracurmin® intake.

This study was conducted to investigate the safety of 4-week excessive（trial Ⅰ）and 12-week long-term intake（trial Ⅱ）of Theracurmin® in healthy Japanese adults.

MATERIALS AND METHODS

1　Study design

The aim of this study was to determine the safety of Theracurmin® at an intake of five times higher than the daily recommended dose for 4 weeks（trial Ⅰ）and the safety of long-term administration of the recommended daily intake for 12 weeks（trial Ⅱ）. The recommended daily dose of Theracurmin® was set at 180 mg/day, calculated from the acceptable daily intake（the maximum amount of curcumin that can be ingested daily with no appreciable health risk）of curcumin（3 mg/kg/day）and the average body weight of Japanese adults（59.2 kg, men and women aged 20–59 years）. The acceptable daily intake was referenced by the Food and Agriculture Organization/World Health Organization Joint Expert Committee on Food Additives, and the average body weight of a Japanese adult was calculated according to the statistics collected by the Ministry of International Affairs and Communications in 2012. Both trials were designed as a randomized, double-blind, placebo-controlled, parallel-group study, with an allocation ratio of 1: 1. The ethics committee of the Takara Clinic, Medical Corporation Seishinkai（Tokyo, Japan）approved the study protocols on May 8, 2018（trial Ⅰ, excessive intake: 1805-1803-SR01-01-TC; trial Ⅱ, long-term intake: 1805-1803-SR01-02-TC）. The studies were conducted in accordance with the principles of the Declaration of Helsinki（2013）, the ethical guidelines for medical and health research involving human participants in Japan, and broader medical ethics. The protocols were registered at the University Hospital Medical Information Network Clinical Trials Registry（excessive intake: UMIN000032640; long-term intake: UMIN000032641）.

Table 1　The contents of test capsules（per 1 capsule）

Contents	Theracurmin® capsule	Placebo capsule
Theracurmin®	316 mg	0 mg
Food Yellow No. 4	0 mg	228 mg
Cornstarch	70.5 mg	108.5 mg
Calcium stearate	3.0 mg	3.0 mg
Silicon dioxide	0.5 mg	0.5 mg

2　Participants

In this study, the inclusion criterion was healthy Japanese adults. The exclusion criteria were as follows:（a）any medical history of a malignant tumor, heart failure, or myocardial infarction;（b）undergoing treatment for any of the following chronic diseases: cardiac arrhythmia, liver failure, kidney failure, cerebrovascular disorder, rheumatism, diabetes mellitus, dyslipidemia, hypertension, urinary bladder failure, or any other chronic diseases;（c）the presence of disease related to the biliary tract in the past or present;（d）daily intake of "Food for Specified Health Uses" and/or "Foods with Function Claims";（e）regular use of medications, including herbal medicines and/or supplements, particularly anticoagulants such as warfarin;（f）intake of natto（fermented soybeans）at least three times per day;（g）allergic reactions to medications and/or products associated with the study substances, particularly soybeans and fermented soybeans;（h）pregnant, lactating, or an expected/planned pregnancy during the study period;（i）participation in another

Table 2-1　Schedule of enrollment, intervention, and assessments（excessive intake study）

Time point	Enrollment	Before intake (Baseline)	Allocation	Intervention period		
				Start intake	2 weeks	4 weeks
Enrollment：						
Eligibility screen	●					
Informed consent	●					
Allocation			●			
Interventions：						
T group				⟷	⟷	⟷
P group				⟷	⟷	⟷
Assessments：						
Physical examination		●			●	●
Urinalysis		●			●	●
Blood analysis		●			●	●
Subjective symptoms		●			●	●
Daily record				⟷	⟷	⟷
Medical questionnaire		●			●	●

Closed circles（●）display the execution timing of each items

clinical study within the last 3 months prior to signing the study's informed consent document; and (j) anyone judged as ineligible to participate in this study by the principal investigator.

All participants registered on the website (https://www.go106.jp/) run by ORTHOMEDICO Inc. (Tokyo, Japan). The study protocols were comprehensively explained to all participants. Furthermore, all participants signed the informed consent document at the ORTHOMEDICO Inc. office prior to their participation in the study. No sponsors or funding companies' members participated in the studies. The examinations were conducted at Takara Clinic（Medical Corporation Seishinkai, Tokyo, Japan）.

3　Intervention

Table 1 shows the composition of the test compound (per capsule). All participants were asked to consume either Theracurmin® or placebo capsules. In the trial Ⅰ, the participants were asked to take 10 total capsules of either Theracurmin® or placebo twice per day with water after breakfast and dinner（5 capsules each meal）for 4 weeks. In the trial Ⅱ, the participants were asked to take 2 total capsules per day with water after breakfast and dinner（1 capsule after each meal）of either Theracurmin® or placebo for 12 weeks. Both capsules were declared identical in color, odor, and flavor by the ethics committee members.

4　Examination items

Table 2-1 shows the trial Ⅰ schedule and **Table 2-2** shows the trial Ⅱ schedule. In the trial Ⅰ, safety was evaluated at screening and at 2 and 4 weeks after the test compound intake. In the trial Ⅱ, safety was evaluated at screening and at 4, 8, and 12 weeks after the test compound intake. All participants underwent physical examination, urinalysis, and blood tests, and completed a medical questionnaire.

The participants' height, weight, body mass index, body fat percentage, systolic and diastolic blood pressures, pulse rate, and body temperature were measured during physical examination. Height was only measured at baseline to calculate the body mass index.

Urine samples were collected to evaluate levels of protein, glucose, urobilinogen, bilirubin, ketone bodies, pH, and occult blood. These measurements were conducted by the LSI Medience Corporation（Tokyo, Japan）.

Hematological tests were conducted to assess the following: leukocyte count, erythrocyte count, hemoglobin, hematocrit value, platelet count, mean corpuscular volume（MCV）, mean corpuscular hemoglobin（MCH）, mean corpuscular hemoglobin concentration（MCHC）, and differentiation of white blood cells (percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Furthermore, biochemical tests evaluated the following: aspartate transaminase（AST）, alanine transaminase（ALT）, γ-glutamyl transpeptidase（γ-GT）, alkaline phosphatase（ALP）, lactate dehydrogenase（LAP）, total bilirubin, direct bilirubin（DBil）, indirect bilirubin（IBil）, cholinesterase, total protein, urea nitrogen, creatinine, uric acid, creatine kinase（CK）, calcium, serum amylase, total

Table 2-2　Schedule of enrollment, intervention, and assessments（long-term intake study）

Time point	Enrollment	Before intake (Baseline)	Allocation	Intervention period			
				Start intake	4 weeks	8 weeks	12 weeks
Enrollment：							
Eligibility screen	●						
Informed consent	●						
Allocation			●				
Interventions：							
T group				←—	——	——	—→
P group				←—	——	——	—→
Assessments：							
Physical examination		●			●	●	●
Urinalysis		●			●	●	●
Blood analysis		●			●	●	●
Subjective symptoms		●			●	●	●
Daily record				←—	——	——	—→
Medical questionnaire		●			●	●	●

Closed circles（●）display the execution timing of each items

cholesterol, high-density lipoprotein（HDL）cholesterol, low-density lipoprotein（LDL）cholesterol, triglycerides, glycoalbumin, serum iron, sodium, potassium, chloride, inorganic phosphorus, glucose, and hemoglobin A1c. The hematological and biochemical tests were performed by the LSI Medience Corporation.

Subjective symptoms were assessed using a questionnaire（Likert scale）, which comprised the following: I am tired for no reason; I feel feverish; my skin is itchy for no reason; my skin and lips become dry easily; I often have a stuffy nose; I feel pain and itchiness in the throat; I feel funny in the stomach without having diarrhea or constipation; I have diarrhea; I have constipation. These items were assessed on a 6-point grading scale as follows; 1, strongly disagree; 2, disagree; 3, slightly disagree; 4, slightly agree; 5, agree; 6, strongly agree.

Participants completed a medical questionnaire to determine their health status at each assessment point. Additionally, participants recorded medication dosages and any changes in their physical condition in a diary.

5　Sample size

The planned sample size for the excessive intake and long-term intake arms and the basis for it is as follows.

The number of participants required to detect with 90% accuracy at least one or more adverse events with an incident rate of 15% in each group was calculated from the following equation（1）.

$$n = \log(1-p)/\log(1-r) \qquad (1)$$

Here, n is the number of participants, p is the detection rate, and r is the adverse event rate,.

From equation（1）, the calculated sample size per group was determined to be 15 participants. One extra participant was included in each group（16 participants each group）in consideration of potential dropouts（10%）.

6　Selection, randomization, and blinding

In the trial Ⅰ, 32 eligible participants of a total of 48 who submitted informed consent were included. In the trial Ⅱ, 32 eligible participants of 53 who submitted informed consent were included. Participants who had been judged as eligible to participate in the trials by the physician were selected for each trials.

Test compounds were provided by the sponsor to the contract research organization. After declaring indistinguishability between the test compounds, a person in charge of shipping from the contract research organization gave the test compound code to an allocation controller who not directly involved in the trials. Participants were randomly allocated to either the Theracurmin® group（T group, $n=16$）or the placebo group（P group, $n=16$）based on a stratified randomized allocation of age and sex. The allocation was performed by the allocation controller using StatLight #11 Version 2.10（Yukms Co., Ltd., Kanagawa, Japan）, a computerized random-number generator, according to the provided codes. The allocation table with the coded test compounds was provided only to the person in charge of shipping, who

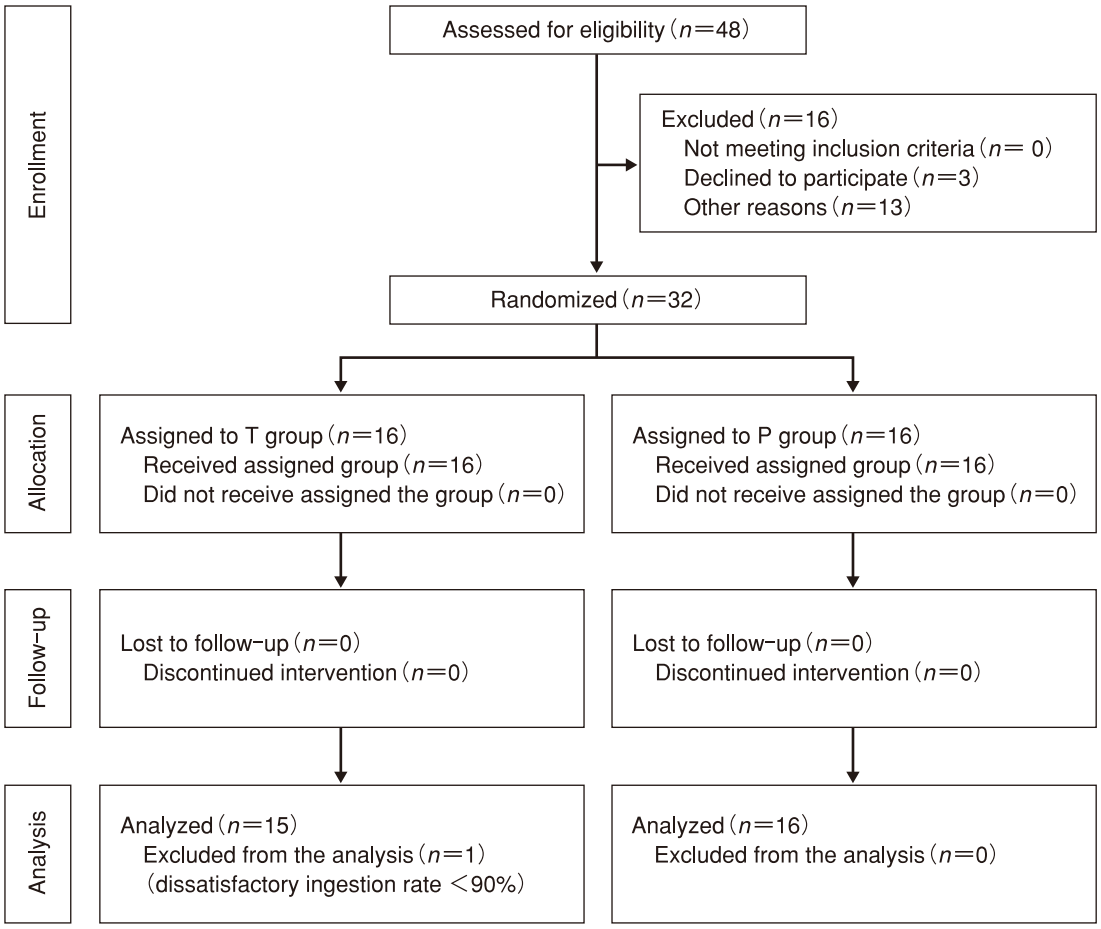

Fig. 1-1　The flowchart of participants in this study
（trial I, excessive intake trial）

sent the test compounds to each of the participants according to the allocation table. The allocation table was locked until key-opening day by the allocation controller. No individual related to the trials was in any way, aware of the group assignments or were involved in the allocation.

7　Statistical analysis

The examination items were assessed before intake and at 2 and 4 weeks after intake（3 assessment points）in the trial Ⅰ, and in the trial Ⅱ assessments occurred before intake and at 4, 8, and 12 weeks after intake（4 assessment points）. The baseline was set before intake.

The participants' backgrounds and demographic data were aggregated based on sex, age, and physical characteristics and were compared with the P group using Student's *t*-test. The physical examination and blood analysis data were expressed as the mean and standard deviation, and baseline values were analyzed using Student's *t*-test. The physical examinations and blood analyses at 2, 4, 8, and 12 weeks after intake were analyzed using the analysis of covariance（ANCOVA）. When the ANCOVA was used for data analyses, the baseline value was used as a covariate. Furthermore, urinalysis data were set to a code in which "1" was identified as within the normal range and"0"was identified as outside the normal range. The data were expressed as number of participants（*n*）and were analyzed using the chi-squared test. Subjective symptoms were analyzed between groups using the Mann-Whitney *U*-test at baseline and at 2, 4, 8, and 12 weeks after intake.

All statistical analyses were 2-sided, and we set the significance level at 5% with no adjustment for multiple comparisons. The data analysis was performed using Windows SPSS Version 23.0（IBM Japan, Ltd., Tokyo, Japan）and Microsoft Excel 2016（Microsoft Japan Co., Ltd., Tokyo, Japan）.

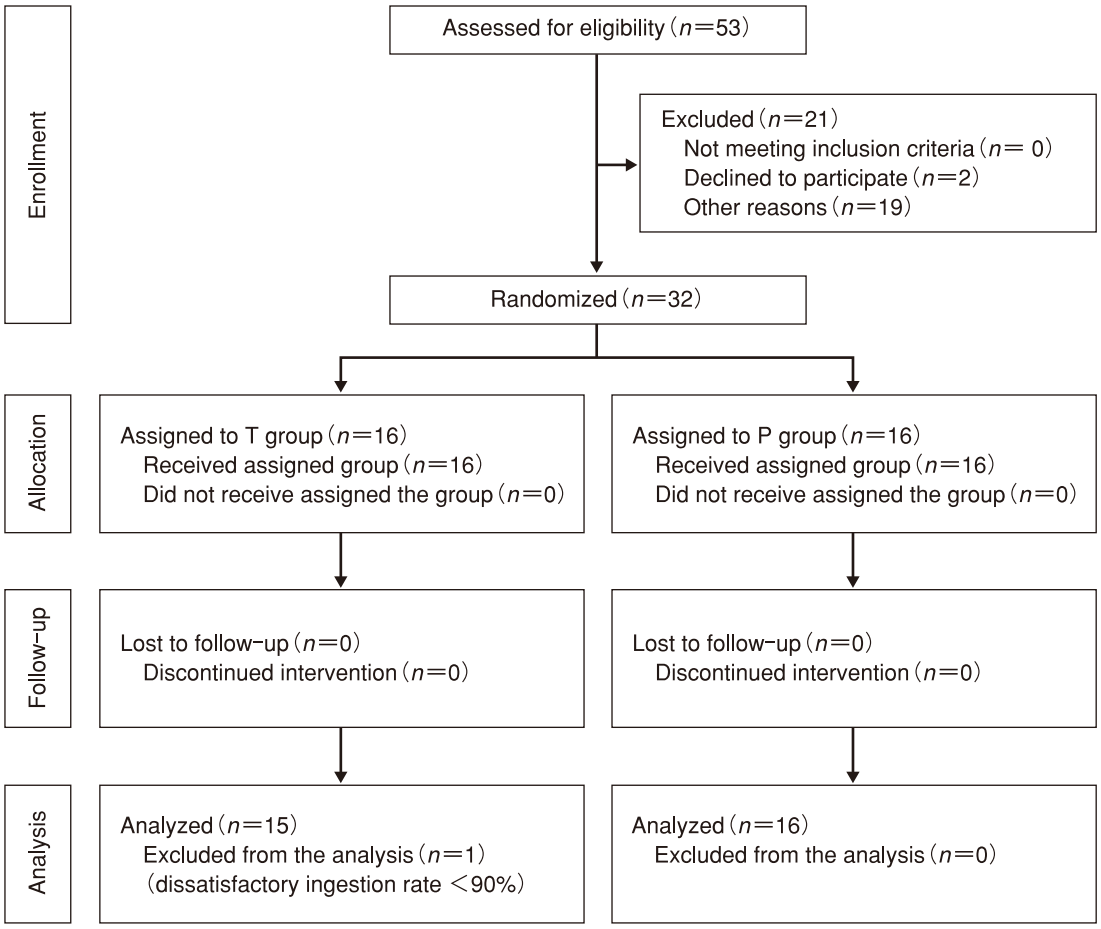

Fig. 1-2　The flowchart of participants in this study
（trial II, long-term intake trial）

Table 3-1　Subjective's backgroud information (excessive intake study)

Item（Unit）	T group (*n*＝15)		P group (*n*＝16)		*P*-value
	Mean	SD	Mean	SD	
Age（years）	49.6	13.4	49.8	13.1	0.98
IgE（RIST）（IU/mL）	104.8	124.1	649.6	1848.1	0.26

The data are presented as the means±standard deviation.

Table 3-2　Subjective's backgroud information（long-term intake study）

Item（Unit）	T group (*n*＝15)		P group (*n*＝16)		*P*-value
	Mean	SD	Mean	SD	
Age（years）	44.1	12.4	45.0	13.5	0.84
IgE（RIST）（IU/mL）	296.9	551.3	220.9	318.0	0.64

The data are presented as the means±standard deviation.

RESULTS

1　Trial Ⅰ（excessive intake）

1）Analysis set

Fig. 1-1 shows the flowchart of trial Ⅰ. Participants were recruited from May to June, 2018, and the trial Ⅰ was conducted from June to July, 2018. Confirmation of the diary and an interview with participants revealed that one participant had an ingestion rate＜90% of the test compound. Thus, we excluded this participant from the analysis. The analysis was per-protocol, and included 15 participants（eight males and seven females）in the T group and 16 participants（eight males and eight females）in the P group. There were no significant differences between groups（**Table 3-1**）.

2）Physical examination

The results of the physical examination are shown in **Table 4-1**.

At 2 weeks after intake, body temperature was

Table 4-1 The results of physical examination (excessive intake study)

Item (Unit)	Baseline					2 weeks					4 weeks				
	T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Height (cm)	163.2	6.7	164.1	10.2	0.76	—	—	—	—	—	—	—	—	—	—
Body weight (kg)	56.8	8.4	60.0	10.9	0.38	57.0	8.3	60.1	11.1	0.99	56.9	8.3	60.1	11.4	0.87
BMI (kg/m^2)	21.3	2.2	22.1	2.2	0.30	21.3	2.2	22.1	2.3	0.84	21.3	2.2	22.1	2.3	0.96
Body fat percentage (%)	20.8	6.2	22.4	6.0	0.46	20.7	6.3	22.8	5.9	0.31	20.2	6.4	22.6	6.1	0.19
Systolic blood pressure (mmHg)	116.2	9.3	116.2	14.4	0.99	115.2	10.4	119.4	14.8	0.14	116.9	9.5	114.3	17.6	0.49
Diastolic blood pressure (mmHg)	72.8	9.3	73.8	11.6	0.79	73.9	10.3	74.9	12.1	0.98	74.5	8.9	71.7	12.6	0.22
Pulse rate (bpm)	74.8	11.1	77.8	11.6	0.47	75.7	11.2	76.6	10.0	0.71	74.3	11.1	73.3	12.3	0.38
Temprature (℃)	36.2	0.5	36.2	0.5	0.83	36.1	0.4	36.4	0.4	0.020*	36.3	0.3	36.2	0.4	0.82

The data are presented as the means±standard deviation.
BMI=body mass index
*P<0.05

Table 4-2 The results of physical examination (long-term intake study)

Item (Unit)	Baseline					4 weeks					8 weeks					12 weeks				
	T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Height (cm)	164.7	7.3	162.3	9.5	0.44	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Body weight (kg)	57.9	7.8	55.6	10.2	0.49	57.6	8.3	54.8	10.1	0.39	57.5	8.7	55.0	10.2	0.87	57.6	8.5	54.8	10.1	0.48
BMI (kg/m^2)	21.3	1.8	21.0	2.3	0.70	21.1	2.0	20.7	2.2	0.38	21.1	2.2	20.8	2.3	0.87	21.1	2.2	20.7	2.3	0.50
Body fat percentage (%)	20.8	4.9	20.5	4.9	0.86	20.4	5.0	19.4	5.2	0.26	20.2	5.4	19.5	5.1	0.52	19.8	5.7	19.4	5.0	0.90
Systolic blood pressure (mmHg)	113.5	13.2	118.4	17.9	0.39	114.8	13.0	115.2	14.4	0.38	116.8	11.1	115.0	14.7	0.044*	117.8	14.4	115.6	15.8	0.060
Diastolic blood pressure (mmHg)	71.2	11.8	72.0	11.5	0.86	73.1	7.0	71.2	10.7	0.29	74.2	7.8	72.2	10.5	0.23	75.5	8.3	74.4	12.0	0.54
Pulse rate (bpm)	73.9	10.1	78.2	15.0	0.37	72.1	9.8	78.1	16.7	0.45	72.2	10.5	75.9	12.0	0.75	71.6	7.5	74.9	11.9	0.78
Temprature (℃)	36.3	0.3	36.4	0.4	0.40	36.2	0.3	36.4	0.5	0.39	36.3	0.4	36.4	0.4	0.76	36.3	0.5	36.3	0.4	0.69

The data are presented as the means±standard deviation.
BMI=body mass index
*P<0.05

Table 5-1　The results of urinalysis（excessive intake study）

Item	Assessment point	T group（n=15）		P group（n=16）		P-value
		Within the reference range	Outside the reference range	Within the reference range	Outside the reference range	
Protein	Baseline	14	1	15	1	1.00
	2 weeks	11	4	14	2	0.39
	4 weeks	14	1	16	0	0.48
Glucose	Baseline	15	0	16	0	NA
	2 weeks	15	0	16	0	NA
	4 weeks	15	0	16	0	NA
Urobilinogen	Baseline	15	0	16	0	NA
	2 weeks	15	0	16	0	NA
	4 weeks	15	0	15	1	1.00
Bilirubin	Baseline	15	0	16	0	NA
	2 weeks	15	0	16	0	NA
	4 weeks	15	0	16	0	NA
pH	Baseline	15	0	16	0	NA
	2 weeks	15	0	15	1	1.00
	4 weeks	15	0	16	0	NA
Occult blood	Baseline	12	3	15	1	0.33
	2 weeks	12	3	16	0	0.10
	4 weeks	11	4	15	1	0.17
Ketone bodies	Baseline	14	1	16	0	0.48
	2 weeks	15	0	16	0	NA
	4 weeks	15	0	16	0	NA

The data are presented as number of participants and was analysed.
NA＝Not available

significantly lower in the T group（36.1±0.4℃）compared with those in the P group（36.4±0.4℃; P=0.02）.

3）Urinalysis

There were no significant differences between groups（**Table 5-1**）.

4）Blood analysis

The results of the blood analysis are shown in **Table 6-1**.

DBil was significantly higher at 2 and 4 weeks in the T group（0.19±0.13 mg/dL and 0.21±0.14 mg/dL, respectively）compared with that of the P group（0.08±0.05 mg/dL and 0.08±0.04 mg/dL; P<0.001 and P<0.001, respectively）.

The DBil/IBil ratio was significantly higher at 2 and 4 weeks in the T group（0.26±0.15 and 0.28±0.17, respectively）compared with that of the P group（0.09±0.07 and 0.09±0.05; P<0.001 and P<0.001, respectively）.

Urea nitrogen was significantly higher at baseline in the T group（15.1±4.5 mg/dL）compared with that of the P group（12.5±2.0 mg/dL; P=0.042）.

LDL cholesterol was significantly lower at 4 weeks in the T group（117.0±39.5 mg/dL）compared with that of the P group（119.4±23.5 mg/dL; P=0.01）.

Triglycerides were significantly lower at 4 weeks in the T group（85.7±48.5 mg/dL）compared with those of the P group（125.1±118.3 mg/dL; P<0.01）.

5）Subjective symptoms

No significant differences were observed（**Table 7-1**）.

2　Trial Ⅱ（long-term intake）

1）Analysis set

Fig. 1-2 shows the flowchart of trial Ⅱ. Participants were recruited from May to June, 2018, and trial Ⅱ was conducted from July to October, 2018. Confirmation of the diary and an interview with participants revealed that one participant had an ingestion rate< 90% of the test food. Thus, we excluded the participant from analysis. The analysis was per-protocol analysis, and included 15 participants（eight males and seven females）in T group and 16 participants（eight males and eight females）in P group. There were no significant differences between groups（**Table 3-2**）.

2）Physical examination

The results of the physical examination are shown in **Table 4-2**.

Table 5-2　The results of urinalysis（long-term intake study）

Item	Assessment point	T group（n=15）		P group（n=16）		P-value
		Within the reference range	Outside the reference range	Within the reference range	Outside the reference range	
Protein	Baseline	13	2	14	2	1.00
	4 weeks	13	2	15	1	0.60
	8 weeks	12	3	13	3	1.00
	12 weeks	13	2	15	1	0.60
Glucose	Baseline	15	0	16	0	NA
	4 weeks	15	0	16	0	NA
	8 weeks	15	0	16	0	NA
	12 weeks	15	0	16	0	NA
Urobilinogen	Baseline	15	0	15	1	1.00
	4 weeks	15	0	16	0	NA
	8 weeks	15	0	15	1	1.00
	12 weeks	15	0	16	0	NA
Bilirubin	Baseline	15	0	16	0	NA
	4 weeks	15	0	16	0	NA
	8 weeks	15	0	16	0	NA
	12 weeks	15	0	16	0	NA
pH	Baseline	15	0	14	2	0.48
	4 weeks	14	1	16	0	0.48
	8 weeks	14	1	14	2	1.00
	12 weeks	15	0	15	1	1.00
Occult blood	Baseline	14	1	13	3	0.60
	4 weeks	13	2	15	1	0.60
	8 weeks	14	1	11	5	0.17
	12 weeks	14	1	14	2	1.00
Ketone bodies	Baseline	15	0	16	0	NA
	4 weeks	15	0	15	1	1.00
	8 weeks	15	0	15	1	1.00
	12 weeks	15	0	16	0	NA

The data are presented as number of participants and was calculated.
NA＝Not available

Systolic blood pressure was significantly higher at 8 weeks in the T group（116.8±11.1 mmHg）compared with that of the P group（115.0±14.7 mmHg; P=0.04）.

3）Urinalysis

There were no significant differences between groups（**Table 5-2**）.

4）Blood analysis

The results of the blood analysis are shown in **Table 6-2**.

The platelet count was significantly lower at 8 weeks in the T group（25.5±5.5×10^4/μL）compared with that of the P group（30.2±5.0×10^4/μL; P=0.04）.

Urea nitrogen was significantly lower at baseline in the T group（12.2±2.1 mg/dL）compared with that of the P group（15.5±4.2 mg/dL; P=0.02）.

CK was significantly lower at 8 and 12 weeks in the T group（83.3±49.2 U/L and 84.9±64.5 U/L, respectively）compared with that of the P group（120.5±56.7 U/L and 134.0±82.5 U/L; P=0.01 and P=0.03, respectively）.

Inorganic phosphorus was significantly lower at baseline in the T group（3.7±0.4 mg/dL）compared with that of the P group（4.3±0.9 mg/dL; P=0.04）.

5）Subjective symptoms

The results of the subjective symptoms are shown in（**Table 7-2**）.

The score of“my skin and lips become dry easily”was significantly lower at 8 weeks in the T group（median: 1.0, Q1: 1.0, Q3: 2.0）compared with that of the P group（median: 2.5, Q1: 1.8, Q3: 4.0; P=0.02）.

DISCUSSION

This study was conducted two trials and investigated

Table 6-1　The results of blood analysis（excessive intake study）

Item（Unit）	Reference range	Baseline				*P*-value	2 weeks				*P*-value
		T group（*n*＝15）		P group（*n*＝16）			T group（*n*＝15）		P group（*n*＝16）		
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Leukocyte count（/μL）	3300-9000	5466.7	1242.5	5856.3	1596.7	0.46	5000.0	1150.8	5487.5	1137.8	0.36
Erythrocyte count（×10^4/μL）	Men：430-570 Women：380-500	449.5	39.3	466.7	36.5	0.22	445.3	43.2	463.4	37.5	0.81
Hemoglobin（g/dL）	Men：13.5-17.5 Women：11.5-15.0	13.8	1.3	14.3	1.2	0.32	13.7	1.3	14.2	1.2	0.71
Hematocrit value（%）	Men：39.7-52.4 Women：34.8-45.0	43.3	3.4	44.4	2.9	0.34	43.4	3.7	44.5	3.2	0.81
Platelet count（×10^4/μL）	14.0-34.0	24.8	4.9	26.6	4.9	0.33	25.0	5.5	25.4	4.5	0.18
MCV（fL）	85-102	96.4	3.7	95.3	5.1	0.50	97.7	4.0	96.3	5.5	0.71
MCH（pg）	28.0-34.0	30.7	1.4	30.6	1.7	0.80	30.9	1.5	30.7	1.7	0.64
MCHC（%）	30.2-35.1	31.9	0.8	32.1	1.2	0.54	31.7	0.9	31.9	1.0	0.80
Neutrophils（%）	40.0-75.0	57.5	9.1	57.5	7.5	1.00	55.3	9.9	57.1	9.6	0.36
Lymphocytes（%）	18.0-49.0	33.3	8.5	33.7	7.1	0.88	35.1	8.8	34.0	9.6	0.41
Monocytes（%）	2.0-10.0	5.6	2.4	5.2	1.4	0.53	5.4	2.3	5.1	1.5	0.98
Eosinophils（%）	0.0-8.0	2.9	2.0	2.8	1.3	0.91	3.5	2.2	3.0	1.8	0.40
Basophils（%）	0.0-2.0	0.63	0.44	0.72	0.47	0.58	0.75	0.54	0.84	0.53	0.97
AST（U/L）	10-40	17.8	2.7	19.6	3.2	0.11	17.1	3.3	19.9	4.0	0.19
ALT（U/L）	5-45	14.8	7.1	15.5	5.6	0.76	13.9	9.7	17.0	10.6	0.21
γ-GT（U/L）	Men：≤80 Women：≤30	22.0	8.6	20.6	6.7	0.61	22.0	13.7	21.5	7.8	0.52
ALP（U/L）	100-325	176.4	46.9	185.3	44.3	0.59	168.1	43.7	183.0	49.1	0.35
LD（U/L）	120-240	178.4	26.9	187.8	36.4	0.42	176.7	24.0	186.3	32.1	0.65
LAP（U/L）	Men：45-81 Women：37-61	48.4	7.1	49.4	4.0	0.64	48.8	8.4	50.4	4.5	0.61
Total bilirubin（mg/dL）	0.2-1.2	1.03	0.48	1.01	0.32	0.89	0.96	0.38	1.02	0.36	0.48
DBil（mg/dL）	0.0-0.2	0.09	0.09	0.08	0.04	0.83	0.19	0.13	0.08	0.05	＜0.001**
IBil（mg/dL）	0.2-1.0	0.95	0.41	0.93	0.30	0.91	0.77	0.30	0.94	0.33	0.067
Direct bilirubin/Indirect bilirubin	—	0.09	0.08	0.09	0.06	0.81	0.26	0.15	0.09	0.07	＜0.001**
Cholinesterase（U/L）	Men：234-493 Women：200-452	313.5	95.3	346.3	52.2	0.24	311.0	106.0	343.1	51.9	0.71
Total protein（g/dL）	6.7-8.3	6.9	0.4	7.2	0.3	0.063	6.9	0.4	7.1	0.2	0.32
Urea nitrogen（mg/dL）	8.0-20.0	15.1	4.5	12.5	2.0	0.042*	14.4	3.7	14.1	3.9	0.13
Creatinine（mg/dL）	Men：0.61-1.04 Women：0.47-0.79	0.75	0.12	0.70	0.13	0.28	0.74	0.14	0.70	0.13	0.85
Uric acid（mg/dL）	Men：3.8-7.0 Women：2.5-7.0	4.8	1.0	5.1	1.1	0.52	4.8	1.1	5.2	1.2	0.44
CK（U/L）	Men：60-270 Women：40-150	110.2	50.1	114.8	48.8	0.80	105.7	55.1	101.4	40.2	0.54
Sodium（mEq/L）	137-147	141.3	1.7	141.4	1.7	0.95	141.5	2.0	140.9	1.5	0.35
Potassium（mEq/L）	3.5-5.0	3.8	0.2	3.8	0.2	0.26	3.8	0.3	3.8	0.3	0.93
Chloride（mEq/L）	98-108	102.7	2.3	102.6	1.5	0.88	103.1	1.9	102.4	1.7	0.34
Calcium（mg/dL）	8.4-10.4	8.9	0.2	9.1	0.3	0.19	8.9	0.3	9.1	0.2	0.35
Inorganic phosphorus（mg/dL）	2.5-4.5	3.7	0.4	3.6	0.6	0.69	3.8	0.5	3.9	0.6	0.56
Serum iron（μg/dL）	Men：50-200 Women：40-180	133.3	50.1	111.3	28.8	0.14	124.6	61.0	114.5	40.2	0.89
Serum amylase（U/L）	40-122	75.2	16.3	77.6	29.2	0.78	72.1	14.6	79.4	27.2	0.12
Total cholesterol（mg/dL）	120-219	201.5	44.5	212.6	31.3	0.42	199.5	41.2	212.7	31.5	0.53
HDL cholesterol（mg/dL）	Men：40-85 Women：40-95	73.2	20.3	68.5	16.2	0.48	68.3	21.4	66.5	15.5	0.30
LDL cholesterol（mg/dL）	65-139	112.6	36.3	130.4	24.1	0.12	113.1	34.2	126.1	22.6	0.51
Triglyceride（mg/dL）	30-149	111.9	62.4	93.1	56.0	0.39	106.7	63.3	126.1	105.4	0.055
Glucose（mg/dL）	70-109	81.5	5.9	82.9	6.5	0.53	82.9	8.3	83.6	6.8	0.98
Hemoglobin A1c（%）	4.6-6.2	5.3	0.3	5.4	0.2	0.49	5.4	0.2	5.4	0.2	0.16
Glycoalbumin（%）	12.3-16.5	13.8	1.1	13.7	1.3	0.80	14.0	1.1	13.8	1.4	0.49

The data are presented as the means±standard deviation. *$P<0.05$, **$P<0.01$

4 weeks				
T group (n=15)		P group (n=16)		P-value
Mean	SD	Mean	SD	
5120.0	1155.9	5256.3	1150.6	0.70
444.5	45.1	462.3	34.3	0.79
13.6	1.3	14.1	1.1	0.68
43.3	4.0	44.6	3.5	0.76
23.9	5.1	24.5	3.8	0.40
97.4	3.2	96.4	4.9	0.90
30.6	1.4	30.5	1.5	0.81
31.4	0.7	31.6	0.7	0.69
57.7	8.9	56.8	8.2	0.72
32.3	9.2	33.8	7.3	0.62
6.1	2.0	5.4	1.3	0.33
3.3	2.1	3.2	2.0	1.00
0.53	0.39	0.75	0.50	0.18
18.8	7.4	19.3	3.5	0.49
15.1	8.6	14.2	5.4	0.25
21.3	14.4	20.1	6.6	0.84
168.1	49.9	179.6	46.7	0.71
184.2	29.1	186.2	34.6	0.23
48.7	7.9	49.1	4.5	0.65
1.04	0.47	0.96	0.31	0.47
0.21	0.14	0.08	0.04	$<$0.001**
0.83	0.39	0.88	0.28	0.45
0.28	0.17	0.09	0.05	$<$0.001**
309.1	110.4	335.9	53.2	0.28
6.8	0.4	7.0	0.3	0.98
13.6	3.2	13.2	3.6	0.12
0.75	0.12	0.72	0.13	0.54
4.8	0.8	5.3	1.4	0.30
136.5	113.3	129.1	109.4	0.79
141.3	1.2	140.8	1.6	0.22
3.8	0.2	3.8	0.3	0.25
102.0	1.7	102.0	1.9	0.93
8.9	0.3	9.0	0.2	0.94
3.7	0.7	3.7	0.4	0.90
103.1	42.3	105.8	34.0	0.65
71.8	16.7	74.3	21.0	0.78
201.9	48.1	203.6	29.7	0.20
68.7	19.0	63.3	16.5	0.58
117.0	39.5	119.4	23.5	0.012*
85.7	48.5	125.1	118.3	0.010**
81.5	7.8	81.3	5.8	0.56
5.3	0.3	5.4	0.2	0.92
13.5	1.3	13.6	1.3	0.39

the safety of 4-week excessive and 12-week long-term intake of Theracurmin® on healthy Japanese adults.

1　Trial Ⅰ（excessive intake）

Regarding the physical examination, the body temperature of the T group was significantly higher than that of the P group at 2 weeks after intake; however, the fluctuation in body temperature was minor, with no medically problematic changes in physical conditions during the intervention period.

The blood analysis results revealed that DBil（2 w, 4 w）, the DBil/IBil ratio（2 w, 4 w）, urea nitrogen（baseline）, LDL cholesterol（4 w）, and triglycerides（4 w）were significantly different between the groups. The mean values of urea nitrogen, LDL cholesterol, and triglycerides were within the reference range[6,7] in both the T and P groups, and the mean values of DBil remained within the reference range or slightly higher than the maximum of the reference range.[6–9] On the other hand, the mean DBil value in the T group was slightly higher than the maximum of the reference range at 4 weeks after intake, and the number of participants whose DBil level was outside the reference range had an increased constant throughout the intervention period（data not shown）. Regarding the individual participant data, participants who once exceeded the DBil reference range maintained DBil levels outside the reference range until the end of the trial Ⅰ（data not shown）.

Hemolysis is suspected when total bilirubin and IBil concentrations are high.[10] However, total bilirubin and IBil did not significantly increase throughout the intervention period. In addition, no blood sample with hemolysis was found during the assessment at the medical institution or at the clinical examination facility. Therefore, the possibility of hemolysis caused by intake of the test compounds was dismissed.

Drug-induced liver injury（DILI）can be caused not only by drugs, but also health foods and supplements. DILI is divided into three classes: “hepatitis type”with high AST and ALT levels,“cholestatic type” with high ALP and γ-GT levels, and “mixed type”.[11] When the liver injury is caused by an allergic reaction, neutrophils sometimes increase more than 6%.[11,12] Diagnostic criteria for DILI fall under the following three types according to the Japan Society of Hepatology: ALT level greater than two times higher than the maximum of the reference range; ALP higher than the maximum of the reference range; or both.[13] In this trial Ⅰ, although AST and neutrophil levels related to

Table 6-2　The results of blood analysis（long-term intake study）

Item（Unit）	Reference range	Baseline					4 weeks				
		T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Leukocyte count（/μL）	3300-9000	5913.3	1405.0	5200.0	1141.9	0.13	5353.3	1425.2	5400.0	1779.9	0.17
Erythrocyte count（$\times 10^4$/μL）	Men：430-570 Women：380-500	467.2	39.4	450.6	36.9	0.23	470.3	39.5	453.5	36.1	0.73
Hemoglobin（g/dL）	Men：13.5-17.5 Women：11.5-15.0	14.2	1.4	13.4	1.7	0.17	14.2	1.2	13.6	1.6	0.89
Hematocrit value（%）	Men：39.7-52.4 Women：34.8-45.0	44.3	3.8	42.6	4.7	0.27	45.0	3.1	43.3	4.2	0.57
Platelet count（$\times 10^4$/μL）	14.0-34.0	26.0	6.7	29.7	5.3	0.11	25.8	6.4	28.9	4.6	0.85
MCV（fL）	85-102	94.9	5.4	94.7	7.6	0.92	96.0	4.9	95.5	6.7	0.68
MCH（pg）	28.0-34.0	30.5	1.7	29.8	3.0	0.47	30.2	1.5	29.9	2.7	0.071
MCHC（%）	30.2-35.1	32.0	0.8	31.5	1.1	0.11	31.5	0.6	31.3	1.1	0.63
Neutrophils（%）	40.0-75.0	58.2	7.0	59.7	4.9	0.50	57.7	6.9	60.4	9.0	0.48
Lymphocytes（%）	18.0-49.0	32.3	6.2	31.3	4.5	0.61	32.8	6.9	31.0	8.2	0.68
Monocytes（%）	2.0-10.0	5.7	1.4	5.6	1.1	0.78	5.8	1.1	5.4	1.3	0.46
Eosinophils（%）	0.0-8.0	3.2	2.0	2.8	2.7	0.63	3.0	1.8	2.4	1.9	0.37
Basophils（%）	0.0-2.0	0.65	0.40	0.74	0.45	0.59	0.73	0.45	0.72	0.44	0.46
AST（U/L）	10-40	18.5	5.2	20.3	6.2	0.40	18.1	5.1	19.3	4.9	0.94
ALT（U/L）	5-45	17.3	11.8	16.4	7.5	0.82	16.1	6.7	14.4	5.8	0.36
γ-GT（U/L）	Men：≤80 Women：≤30	27.1	20.7	24.7	16.5	0.72	25.5	19.3	25.0	16.6	0.31
ALP（U/L）	100-325	200.5	56.1	183.2	53.3	0.38	193.4	59.0	184.1	54.2	0.28
LD（U/L）	120-240	163.3	18.9	172.9	23.9	0.23	167.0	20.6	173.4	25.0	0.49
LAP（U/L）	Men：45-81 Women：37-61	51.3	7.3	51.4	8.0	0.97	51.3	6.9	53.4	8.5	0.071
Total bilirubin（mg/dL）	0.2-1.2	0.90	0.25	0.85	0.32	0.63	0.97	0.28	0.94	0.29	0.92
DBil（mg/dL）	0.0-0.2	0.08	0.06	0.09	0.05	0.70	0.09	0.03	0.10	0.04	0.65
IBil（mg/dL）	0.2-1.0	0.82	0.22	0.76	0.29	0.54	0.88	0.28	0.84	0.27	0.85
Direct bilirubin/Indirect bilirubin	—	0.09	0.06	0.12	0.09	0.29	0.11	0.05	0.12	0.05	0.64
Cholinesterase（U/L）	Men：234-493 Women：200-452	299.2	68.3	313.4	81.5	0.60	299.7	72.0	312.9	74.8	1.00
Total protein（g/dL）	6.7-8.3	7.0	0.3	7.2	0.4	0.35	7.1	0.4	7.3	0.4	0.37
Urea nitrogen（mg/dL）	8.0-20.0	12.6	3.0	13.9	3.4	0.26	12.2	2.1	15.5	4.2	0.022*
Creatinine（mg/dL）	Men：0.61-1.04 Women：0.47-0.79	0.71	0.12	0.67	0.14	0.41	0.71	0.11	0.70	0.13	0.19
Uric acid（mg/dL）	Men：3.8-7.0 Women：2.5-7.0	4.9	1.2	4.8	1.4	0.81	4.9	1.3	5.0	1.5	0.30
CK（U/L）	Men：60-270 Women：40-150	109.9	127.3	106.6	30.5	0.92	92.1	73.0	102.1	37.6	0.16
Sodium（mEq/L）	137-147	141.1	1.8	140.9	1.7	0.76	140.7	1.8	139.9	2.6	0.36
Potassium（mEq/L）	3.5-5.0	3.9	0.2	3.9	0.3	0.76	3.9	0.3	4.0	0.4	0.19
Chloride（mEq/L）	98-108	101.5	1.8	101.6	1.6	0.96	101.1	1.4	101.2	2.6	0.96
Calcium（mg/dL）	8.4-10.4	9.0	0.3	9.0	0.3	0.74	9.0	0.4	9.1	0.4	0.64
Inorganic phosphorus（mg/dL）	2.5-4.5	3.7	0.4	4.3	0.9	0.038*	3.9	0.6	3.9	0.8	0.30
Serum iron（μg/dL）	Men：50-200 Women：40-180	106.4	41.3	106.1	62.1	0.99	117.3	42.9	137.3	66.8	0.18
Serum amylase（U/L）	40-122	86.1	31.8	80.0	25.8	0.56	85.8	39.3	77.3	20.5	0.56
Total cholesterol（mg/dL）	120-219	216.9	38.2	207.9	34.0	0.49	212.8	33.3	209.6	30.2	0.68
HDL cholesterol（mg/dL）	Men：40-85 Women：40-95	66.2	14.8	72.6	18.7	0.30	64.4	13.2	71.1	18.6	0.66
LDL cholesterol（mg/dL）	65-139	132.1	39.2	121.5	35.9	0.44	132.7	28.9	123.1	26.7	0.59
Triglyceride（mg/dL）	30-149	101.9	102.9	85.3	36.1	0.55	85.2	45.9	85.7	41.8	0.36
Glucose（mg/dL）	70-109	80.5	6.6	82.3	7.1	0.46	83.8	5.4	82.6	11.6	0.44
Hemoglobin A1c（%）	4.6-6.2	5.4	0.1	5.4	0.3	0.54	5.2	0.2	5.3	0.3	0.57
Glycoalbumin（%）	12.3-16.5	13.9	0.7	14.0	1.2	0.66	13.8	0.8	13.8	1.3	0.63

The data are presented as the means±standard deviation. *$P<0.05$, **$P<0.01$

8 weeks					12 weeks				
T group (n=15)		P group (n=16)		P-value	T group (n=15)		P group (n=16)		P-value
Mean	SD	Mean	SD		Mean	SD	Mean	SD	
5226.7	1175.0	5481.3	2565.5	0.15	5606.7	1504.0	4906.3	1237.5	0.58
468.1	46.3	448.9	42.2	0.74	465.6	39.1	453.2	43.2	0.74
14.2	1.2	13.4	1.6	0.80	14.2	1.3	13.6	1.8	0.62
44.5	3.6	42.2	4.5	0.31	44.0	3.3	42.6	4.7	0.94
25.5	5.5	30.2	5.0	0.043*	26.4	5.6	31.1	5.8	0.14
95.3	4.9	94.2	6.9	0.28	94.9	5.4	94.1	6.9	0.49
30.3	1.6	29.9	2.7	0.25	30.5	1.7	30.0	2.7	0.79
31.8	0.5	31.8	1.2	0.21	32.2	0.7	31.9	1.1	0.80
58.0	4.7	59.3	10.0	0.82	60.4	7.6	59.2	8.2	0.41
32.6	4.6	32.1	8.9	0.94	30.8	6.1	31.9	7.0	0.39
5.7	1.4	5.8	2.2	0.85	5.1	1.2	5.5	1.3	0.30
3.1	1.9	2.2	2.1	0.13	3.1	2.0	2.6	2.0	0.71
0.61	0.35	0.70	0.38	0.64	0.61	0.32	0.74	0.50	0.52
18.5	6.0	19.3	3.9	0.82	18.9	6.2	20.1	4.8	0.99
16.2	9.3	15.5	6.8	0.91	16.9	9.1	16.2	7.3	0.93
26.6	15.2	23.9	14.6	0.69	24.5	14.0	25.1	17.4	0.30
193.4	55.5	181.9	63.2	0.62	198.4	58.2	204.9	105.2	0.44
167.0	17.8	176.9	27.8	0.83	163.9	20.3	175.2	29.1	0.71
52.1	5.3	52.6	8.2	0.77	50.6	5.1	51.8	8.3	0.42
0.91	0.30	0.83	0.19	0.51	0.85	0.23	0.93	0.27	0.24
0.10	0.04	0.09	0.05	0.32	0.10	0.04	0.09	0.04	0.28
0.81	0.28	0.74	0.16	0.60	0.75	0.21	0.84	0.24	0.20
0.13	0.05	0.12	0.06	0.40	0.14	0.06	0.11	0.05	0.23
302.1	75.9	306.0	71.9	0.35	300.7	73.0	308.7	71.7	0.68
7.0	0.4	7.1	0.3	0.61	7.0	0.3	7.1	0.3	0.45
11.4	2.5	13.7	4.9	0.24	12.3	2.8	14.0	2.6	0.22
0.72	0.14	0.68	0.13	0.75	0.71	0.12	0.69	0.13	0.62
5.1	1.4	4.9	1.5	0.61	4.9	1.5	5.0	1.4	0.33
83.3	49.2	120.5	56.7	0.014*	84.9	64.5	134.0	82.5	0.025*
140.9	2.1	140.6	2.4	0.72	140.5	2.0	140.1	1.8	0.54
3.9	0.2	3.9	0.3	0.61	4.0	0.3	4.0	0.2	0.87
101.3	2.2	100.8	3.4	0.57	101.1	2.1	100.9	2.8	0.80
9.0	0.3	9.0	0.4	0.87	9.0	0.4	9.1	0.4	0.50
3.9	0.6	4.0	0.8	0.50	3.7	0.6	3.8	0.7	0.11
112.9	39.8	101.2	39.4	0.40	97.4	31.9	125.0	53.7	0.052
86.5	34.8	83.0	35.9	0.42	96.5	53.9	83.0	26.1	0.42
213.5	34.4	199.4	34.9	0.37	213.5	43.6	209.4	29.6	0.67
63.5	14.0	70.4	21.2	0.77	64.7	15.3	71.2	18.3	0.79
134.1	31.9	116.9	32.7	0.18	130.2	39.3	122.4	25.8	0.99
95.5	46.9	82.8	49.0	0.67	97.2	58.2	80.6	46.0	0.53
82.1	6.4	82.9	8.6	0.95	82.0	5.3	83.4	8.8	0.79
5.3	0.2	5.4	0.3	0.49	5.3	0.2	5.5	0.3	0.053
14.0	0.6	14.2	1.5	0.85	14.0	0.7	14.2	1.5	0.90

Table 7-1　The results of subjective symptoms（excessive intake study）

Question	Baseline						*P*-value	2 weeks						*P*-value
	T group（*n*＝15）			P group（*n*＝16）				T group（*n*＝15）			P group（*n*＝16）			
	Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3	Median	Q1	Q3	
I am tired for no reason.	2.0	1.0	3.0	2.0	2.0	4.0	0.35	2.0	1.0	3.0	2.5	2.0	4.0	0.29
I feel feverish.	1.0	1.0	1.0	1.0	1.0	1.0	0.87	1.0	1.0	2.0	1.0	1.0	1.0	0.33
My skin is itchy for no reason.	1.0	1.0	2.0	1.0	1.0	1.3	0.52	2.0	1.0	2.5	1.0	1.0	2.0	0.47
My skin and lips become dry easily.	1.0	1.0	2.0	2.0	1.0	3.3	0.29	2.0	1.0	3.0	1.0	1.0	2.3	0.43
I often have a stuffy nose.	1.0	1.0	2.0	1.0	1.0	2.3	0.65	1.0	1.0	2.0	1.5	1.0	2.3	0.90
I feel pain and itchiness in the throat.	1.0	1.0	2.0	1.0	1.0	1.3	0.88	1.0	1.0	2.0	1.0	1.0	1.0	0.56
I feel funny in the stomach without having diarrhea or constipation.	1.0	1.0	2.0	1.0	1.0	2.0	0.62	1.0	1.0	2.0	1.0	1.0	2.3	0.42
I have diarrhea.	1.0	1.0	1.0	1.0	1.0	1.0	0.60	1.0	1.0	1.0	1.0	1.0	1.0	0.76
I have constipation.	1.0	1.0	1.5	1.0	1.0	1.3	0.81	1.0	1.0	1.0	1.0	1.0	2.0	0.46

The data are presented as median and interquartile range（Q1, Q3）.
1, strongly disagree；2, disagree；3, slightly disagree；4, slightly agree；5, agree；6, strongly agree

Table 7-2　The results of subjective symptoms（long-term intake study）

Question	Baseline						*P*-value	4 weeks						*P*-value
	T group（*n*＝15）			P group（*n*＝16）				T group（*n*＝15）			P group（*n*＝16）			
	Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3	Median	Q1	Q3	
I am tired for no reason.	2.0	1.5	2.5	3.0	2.0	3.3	0.097	2.0	1.0	3.0	3.0	2.0	3.0	0.37
I feel feverish.	1.0	1.0	1.0	1.0	1.0	1.0	0.48	1.0	1.0	1.0	1.0	1.0	2.0	0.12
My skin is itchy for no reason.	1.0	1.0	1.5	2.0	1.0	2.0	0.24	1.0	1.0	2.0	2.0	1.0	4.0	0.16
My skin and lips become dry easily.	2.0	1.0	2.5	2.0	1.0	4.0	0.42	2.0	1.0	2.5	3.0	1.0	4.0	0.17
I often have a stuffy nose.	1.0	1.0	2.0	1.0	1.0	2.0	0.80	1.0	1.0	1.0	1.5	1.0	2.3	0.11
I feel pain and itchiness in the throat.	1.0	1.0	2.0	1.0	1.0	2.0	0.86	1.0	1.0	1.0	1.0	1.0	3.0	0.16
I feel funny in the stomach without having diarrhea or constipation.	1.0	1.0	2.0	1.5	1.0	2.5	0.32	1.0	1.0	2.0	2.0	1.0	2.0	0.28
I have diarrhea.	1.0	1.0	1.0	1.0	1.0	1.0	0.48	1.0	1.0	1.0	1.0	1.0	1.0	0.53
I have constipation.	1.0	1.0	1.5	1.5	1.0	4.0	0.073	1.0	1.0	1.5	1.0	1.0	2.5	0.27

The data are presented as median and interquartile range（Q1, Q3）.
1, strongly disagree；2, disagree；3, slightly disagree；4, slightly agree；5, agree；6, strongly agree
$^{*}P<0.05$

DILI were higher than the reference range in some participants, these participants did not meet the diagnostic criteria for DILI. Thus, we considered they did not have DILI.

A high level of DBil is suspected to indicate an abnormal state of the biliary system.[14] Although the DBil/IBil ratio was significantly higher in the T group than in the P group throughout the intervention period, no one met the diagnostic criteria for DILI or became jaundiced. In this regard, an increase in the DBil/IBil ratio in the T group could be affected by the color of Theracurmin®. The enzymatic method, used in this study for DBil measurement, has been known to exhibit false high values due to reacting with substances not originally targeted, such as the pigments contained in foods.[15] Curcumin, contained in Theracurmin®, presents a yellow color tone the same as bilirubin. In trial Ⅰ, all the participants who exceeded the reference range for DBil belonged to the T group; therefore, DBil levels in some participants might be false high values caused by curcumin color. Based on medical observations and results of the other examination items, participants with results outside the DILI-related reference range items were not medically problematical. For these reasons, the possibility of liver injury caused by intake of the test foods was dismissed.

Urinalysis and subjective symptoms revealed no significant differences between the groups, and there was no problem with allocation or continued participation in trial Ⅰ.

2　Trial Ⅱ（long-term intake）

Physical examination results revealed that the systolic

4 weeks						
T group（n＝15）			P group（n＝16）			P–value
Median	Q1	Q3	Median	Q1	Q3	
2.0	1.0	3.0	2.5	1.8	3.0	0.40
1.0	1.0	1.0	1.0	1.0	2.0	0.57
1.0	1.0	2.0	1.0	1.0	2.3	0.99
2.0	1.0	2.5	1.0	1.0	2.3	0.83
1.0	1.0	3.0	1.0	1.0	2.0	0.36
1.0	1.0	1.5	1.0	1.0	1.3	0.84
1.0	1.0	2.5	1.0	1.0	2.0	0.56
1.0	1.0	2.0	1.0	1.0	1.0	0.18
1.0	1.0	2.0	1.0	1.0	2.0	0.82

8 weeks							12 weeks						
T group（n＝15）			P group（n＝16）			P–value	T group（n＝15）			P group（n＝16）			P–value
Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3	Median	Q1	Q3	
2.0	1.5	2.5	2.0	1.8	3.3	0.64	2.0	1.0	3.0	2.5	2.0	3.0	0.27
1.0	1.0	1.0	1.0	1.0	2.3	0.22	1.0	1.0	1.0	1.0	1.0	1.3	0.30
1.0	1.0	2.0	1.0	1.0	3.3	0.87	1.0	1.0	2.0	1.5	1.0	3.3	0.31
1.0	1.0	2.0	2.5	1.8	4.0	0.018*	1.0	1.0	2.5	2.5	1.8	4.0	0.093
1.0	1.0	2.0	1.0	1.0	2.0	0.66	1.0	1.0	2.0	1.0	1.0	2.0	0.71
1.0	1.0	1.5	1.0	1.0	2.0	0.67	1.0	1.0	2.0	1.0	1.0	1.3	0.54
2.0	1.0	2.5	2.0	1.0	2.3	0.74	1.0	1.0	2.0	2.0	1.0	2.0	0.16
1.0	1.0	1.0	1.0	1.0	2.0	0.44	1.0	1.0	1.0	1.0	1.0	1.3	0.42
1.0	1.0	2.0	2.0	1.0	3.3	0.15	1.0	1.0	2.0	1.5	1.0	2.3	0.68

blood pressure of the T group was significantly higher than that of the P group at 8 weeks after intake. The fluctuation in systolic blood pressure was within the normal range prescribed in the Japanese Society of Hypertension Guidelines for the Management of Hypertension,[16] and it was not a medically problematic change.

Urinalysis revealed no significant differences between the groups.

Regarding the blood analysis, inorganic phosphorus was significantly different between the groups at baseline. After intake of the test foods, a significant difference between the groups was observed in platelet counts, urea nitrogen, and CK. However, all the mean values of the four items were within the reference range in both groups[17–21]; based on medical observations and the results of other examination items, participants with results outside the reference range were not medically problematic.

The results of the subjective symptoms score in trial Ⅱ revealed that the T group score of“my skin and lips become dry easily”was significantly lower than that of the P group at 8 weeks after intake. Comparing the data of both groups throughout the intervention period, the number of participants who selected higher than 4（slightly agree）for“my skin and lips become dry easily”were two participants in the T group and five participants in the P group, which means the subjective symptoms of the P group were poorer than those of the T group. The P group score tended to decline through the intervention period, whereas the T group score at 8 weeks after intake was improved. Thus, this improvement trend of“my skin and lips become dry easily”could have induced a statistically

significant difference between the groups at 8 weeks. However, the subjective symptoms score in the T group at 12 weeks after intake was similar to the score at baseline and at 4 weeks after intake. Thus, we could not declare that a significant difference at 8 weeks after intake was caused by continuous intake of the test food. However, Theracurmin® and placebo capsules were determined to be safe because participants did not exhibit medically problematic changes.

Based on the safety evaluation results, although significant differences between the T and P groups were observed, mean values remained within the reference ranges or fluctuation was minimal, indicating no medically problematic change in the participants' conditions. Furthermore, no adverse events were reported by the participants.

CONCLUSIONS

We investigated the safety of 4-week excessive and 12-week long-term intake of Theracurmin® (approximately 90 mg of curcumin/capsule) or placebo in healthy Japanese adults. The intake of excessive and long-term Theracurmin® capsules was found to be safe under the study conditions.

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