別紙様式（Ｖ）－１【添付ファイル用】

機能性の科学的根拠に関する点検表

１．製品概要

商品名	「カラダカルピス」500
機能性関与成分名	乳酸菌 CP1563 株由来の 10－ヒドロキシオクタデカン酸（10－HOA）
表示しようとする機能性	本品には独自の乳酸菌 CP1563 株由来の 10-ヒドロキシオクタデカン酸（10－HOA）が含まれ、体脂肪を減らす機能があるので、肥満気味の方に適しています。

２．科学的根拠

【臨床試験（ヒト試験）及び研究レビュー共通事項】

□（主観的な指標によってのみ評価可能な機能性を表示しようとする場合）当該指標は日本人において妥当性が得られ、かつ、当該分野において学術的に広くコンセンサスが得られたものである。

☑（最終製品を用いた臨床試験（ヒト試験）又は研究レビューにおいて、実際に販売しようとする製品の試作品を用いて評価を行った場合）両者の間に同一性が失われていないことについて、届出資料において考察されている。

☑最終製品を用いた臨床試験（ヒト試験）

（研究計画の事前登録）

☑UMIN 臨床試験登録システムに事前登録している[注1]。

□（海外で実施する臨床試験（ヒト試験）の場合であって UMIN 臨床試験登録システムに事前登録していないとき）WHO の国際臨床試験登録プラットフォームにリンクされているデータベースへの登録をしている。

（臨床試験（ヒト試験）の実施方法）

☑「特定保健用食品の表示許可等について」（平成 26 年 10 月 30 日消食表第 259 号）の別添２「特定保健用食品申請に係る申請書作成上の留意事項」に示された試験方法に準拠している。

□科学的合理性が担保された別の試験方法を用いている。

→□別紙様式（Ｖ）－２を添付

（臨床試験（ヒト試験）の結果）

□国際的にコンセンサスの得られた指針に準拠した論文を添付している[注1]。

☑査読付き論文として公表されている論文を添付している。

□（英語以外の外国語で書かれた論文の場合）論文全体を誤りのない日本語に適切に翻訳した資料を添付している。

☑研究計画について事前に倫理審査委員会の承認を受けたこと、並びに当該倫理審査委員会の名称について論文中に記載されている。

□（論文中に倫理審査委員会について記載されていない場合）別紙様式（Ｖ）

別紙様式（Ⅴ）－１【添付ファイル用】

－３で補足説明している。

☑掲載雑誌は、著者等との間に利益相反による問題が否定できる。

□最終製品に関する研究レビュー

□機能性関与成分に関する研究レビュー

□（サプリメント形状の加工食品の場合）摂取量を踏まえた臨床試験（ヒト試験）で肯定的な結果が得られている。

□（その他加工食品及び生鮮食品の場合）摂取量を踏まえた臨床試験（ヒト試験）又は観察研究で肯定的な結果が得られている。

□海外の文献データベースを用いた英語論文の検索のみではなく、国内の文献データベースを用いた日本語論文の検索も行っている。

□（機能性関与成分に関する研究レビューの場合）当該研究レビューに係る成分と最終製品に含有されている機能性関与成分の同等性について考察されている。

□（特定保健用食品の試験方法として記載された範囲内で軽症者等が含まれたデータを使用している場合）疾病に罹患していない者のデータのみを対象とした研究レビューも併せて実施し、その結果を、研究レビュー報告書に報告している。

□（特定保健用食品の試験方法として記載された範囲内で軽症者等が含まれたデータを使用している場合）疾病に罹患していない者のデータのみを対象とした研究レビューも併せて実施し、その結果を、別紙様式（Ⅰ）に報告している。

□表示しようとする機能性の科学的根拠として、査読付き論文として公表されている。

□当該論文を添付している。

□（英語以外の外国語で書かれた論文の場合）論文全体を誤りのない日本語に適切に翻訳した資料を添付している。

□PRISMA 声明（2009 年）に準拠した形式で記載されている。

□（PRISMA 声明（2009 年）に照らして十分に記載できていない事項がある場合）別紙様式（Ⅴ）－３で補足説明している。

□（検索に用いた全ての検索式が文献データベースごとに整理された形で当該論文に記載されていない場合）別紙様式（Ⅴ）－５その他の適切な様式を用いて、全ての検索式を記載している。

□（研究登録データベースを用いて検索した未報告の研究情報についてその記載が当該論文にない場合、任意の取組として）別紙様式（Ⅴ）－９その他の適切な様式を用いて記載している。

□食品表示基準の施行前に査読付き論文として公表されている研究レビュー論文を用いているため、上記の補足説明を省略している。

□各論文の質評価が記載されている[注2]。

□エビデンス総体の質評価が記載されている[注2]。

□研究レビューの結果と表示しようとする機能性の関連性に関する評価が記載されている[注2]。

□表示しようとする機能性の科学的根拠として、査読付き論文として公表されていない。

研究レビューの方法や結果等について、
□別紙様式（Ⅴ）－４を添付している。
□データベース検索結果が記載されている[注3]。
□文献検索フローチャートが記載されている[注3]。
□文献検索リストが記載されている[注3]。
□任意の取組として、未報告研究リストが記載されている[注3]。
□参考文献リストが記載されている[注3]。
□各論文の質評価が記載されている[注3]。
□エビデンス総体の質評価が記載されている[注3]。
□全体サマリーが記載されている[注3]。
□研究レビューの結果と表示しようとする機能性の関連性に関する評価が記載されている[注3]。

注１　食品表示基準の施行後１年を超えない日までに開始（参加者１例目の登録）された研究については、必須としない。
注２　各種別紙様式又はその他の適切な様式を用いて記載（添付の研究レビュー論文において、これらの様式と同等程度に詳しく整理されている場合は、記載を省略することができる。）
注３　各種別紙様式又はその他の適切な様式を用いて記載（別紙様式（Ⅴ）－４において、これらの様式と同等程度に詳しく整理されている場合は、記載を省略することができる。）

別紙様式（Ⅴ）-３【添付ファイル用】

表示しようとする機能性の科学的根拠に関する補足説明資料

１．製品概要

商品名	「カラダカルピス」500
機能性関与成分名	乳酸菌 CP1563 株由来の 10－ヒドロキシオクタデカン酸（10－HOA）
表示しようとする機能性	本品には独自の乳酸菌 CP1563 株由来の 10-ヒドロキシオクタデカン酸（10－HOA）が含まれ、体脂肪を減らす機能があるので、肥満気味の方に適しています。

２．補足説明

・試験食品と届出食品は同一である。
・試験食に配合されている乳酸菌 CP1563 株には 10－ヒドロキシオクタデカン酸（10－HOA）が 1.44mg 含まれている。これは論文記載の内容である。
・届出資料(Ⅶ)-1「作用機序に関する説明資料」にも記載しているが、乳酸菌 CP1563 株由来の 10-HOA には PPARα を活性化させることが確認されており、乳酸菌 CP1563 株由来の 10-HOA は本質的な機能性関与成分である。
・届出食品の製品規格において、機能性関与成分〔乳酸菌 CP1563 株由来の 10－ヒドロキシオクタデカン酸（10－HOA)〕量の規格値は、臨床試験における試験食品の関与成分含量(1.44mg)を賞味期限内で下まわらないよう設定されており、機能性は担保される。

Regulation of Adiposity by Para-metabobiotic *Lactobacillus amylovorus* CP1563 in Healthy Normal and Pre-obese Adult Individuals

—A Randomized Controlled Trial—

■

Shigeru Fujiwara[1)#]　Yu Ishida[1)#]　Yo Kameoka[2)]
Nobuhiko Shioya[2)]　Daisuke Sawada[1)*]　Sae Yanagihara[1)]
Tomonori Sugawara[1)]　Yumeko Aoki[1)]　Mamoru Oki[3)]

ABSTRACT

Objectives We aimed to evaluate the effect of daily ingestion of CP1563 on the reduction of abdominal visceral fat area（VFA）and subcutaneous fat area（SFA）and to confirm the benefits for ordinary people in their body mass indices（BMIs）from 23 or more but less than 30.

Method This study was investigated in a double-blind, randomized controlled trial of 200 healthy adults with wide variations in their BMIs from 23 or greater to less than 30 and including normal to pre-obese ranges according to the criteria of the World Health Organization（WHO）.

Result In the CP1563 group, the abdominal VFA and total fat area（TFA）were significantly decreased, and Apolipoprotein A-I（Apo A-I）plasma concentration was also significantly increased compared with those in the placebo group during the 24-week trial period. In stratified analyses, in Cluster I which included participants with a visceral fat area of less than 100 cm^2, body weight（BW）, BMI, VFA, SFA and TFA were significantly decreased. Moreover, plasma concentration of Apo A-I was simultaneously increased in the CP1563 group compared with those in the placebo group. In Cluster Ⅱ included participants without metabolic syndrome（MetS）and adiposity, the BW, BMI, VFA, TFA and apolipoprotein B（Apo B）/Apo A-I ratio were significantly decreased. In addition, Apo A-I plasma concentration was significantly increased in the CP1563 group compared with those in the placebo group.

Conclusions The fragmented para-probiotic CP1563 described in this report is effective in reducing VFA.（Trial registration：UMIN 000022842）

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KEY WORDS　Para-metabobiotics, Visceral fat, Body fat, Fatty acid oxidation, *L. amylovorus* CP1563

[1)]Core Technology Laboratories, Asahi Group Holdings, Ltd.　[2)]KSO Co., Ltd.　[3)]Seishukai Clinic
[#] These authors contributed equally to this work
[*]Corresponding author
5-11-10, Fuchinobe, Chuo-ku, Sagamihara-shi, Kanagawa, 252-0206, Japan.
E-mail: daisuke.sawada@asahigroup-holdings.com

INTRODUCTION

Obesity causes lifestyle-related metabolic disorders, including hypertension, dyslipidemia and diabetes, which lead to advanced atherosclerosis or cardiovascular diseases. Chronic low-grade adipose tissue inflammation and insulin resistance are closely associated with the development of metabolic dysfunction.[1-3] Lifestyle modifications are effective for the control of overweight and obesity; specifically, healthy dietary modifications and regular physical activity play key roles in preventing noncommunicable diseases.[4]

Despite the use of probiotics as an approach to improve overweight, obesity, obesity-related inflammation, obesity-related metabolic aberrations, and cardiovascular risk,[5-7] the effects are not necessarily certain. There may be differences in efficacy due to experimental conditions, between species employed, and even among strains of probiotics used. In addition to fluctuations in the reliability of the effect, the uncertainty about the mode of action is a point that also must be clarified. Another possible problem with probiotics is that they are often provided as fermented milk product（FM）. As FM is generally caloric, it is thought to be a technical hurdle to overcome.

CP1563 is a beneficial microbe that resides in the human intestine. Previously, we selected it as potentially the best para-probiotic because it shows high peroxisome proliferator-activated receptor（PPAR）alpha and gamma agonistic activities.[8] This characteristic makes it easy to understand the logic behind our selection because this action is assumed to easily exert beneficial regulation on abdominal adiposity. In other words, this is plainly a typical benefit of using para-probiotics such as CP1563. In a previous study, we screened bacterial strains that are used in making food due to their agonistic activities against PPAR alpha and gamma.[8] The results revealed that substances derived from CP1563 showed the highest dual agonistic activity for PPAR alpha and gamma *in vitro* among the strains screened. High-fat diet-induced obese mice administered fragmented CP1563 showed reduced visceral fat mass and serum and liver triglyceride（TG）levels and increased HDL-cholesterol（HDL-c）. PPAR alpha/gamma are transcription factors that are primarily expressed in the liver, skeletal muscle, and white and brown adipose tissues, and these proteins are master regulators of lipid catabolism and homeostasis, glucose homeostasis and lipid storage. PPAR alpha regulates TG-reducing steps and fatty acid oxidation. PPAR alpha pharmacological agonists（fibrates）reduce the concentration of TGs and increase the serum concentration of HDL-c. PPAR gamma is highly expressed in adipocytes and regulates adipocyte differentiation, lipid storage and glucose metabolism. Pharmacological PPAR gamma agonists（glitazones）improve insulin resistance and are widely used in the treatment of dyslipidaemia. Dual-PPAR（PPAR alpha/gamma）pharmacological agonists（glitazars）exert positive effects on both lipid and glucose metabolism and have recently been developed as promising agents for the treatment of type 2 diabetes mellitus with dyslipidaemia.[9,10] Anti-dyslipidaemic and body fat-reducing effects were observed in fragmented CP1563-fed mice compared with mice fed unprocessed bacterial cells.[8] PPAR alpha activation with fragmented CP1563 was also significantly higher than that observed with intact cells and was inversely correlated with the shred size, i. e., the length of the fragments. These observations suggested that the physical "fragmentation" of bacteria is a key step in inducing the high agonistic activity for PPAR alpha/gamma. This process might expose the agonistic constituents of CP1563 cells.

In a previous report, we examined the safety and efficacy of the oral administration of fragmented CP1563 on the depletion of body fat in a double-blind, parallel group randomized clinical trial（RCT）involving overweight and pre-obese subjects with BMIs ranging from 25 or more to less than 30.[11] Improvements in anthropometric measurements and markers were observed in obese class Ⅰ subjects in the test group. This result suggests that the consumption of foods containing CP1563 reduces body fat and prevents metabolic syndrome（MetS）.

In this report, another RCT was carried out to evaluate the plasticity of the effect of fragmented CP1563 on the reduction of abdominal VFA and SFA. The other purpose of the trial was to confirm the benefits for ordinary people by evaluating the anthropometric measurements and abdominal fat areas, including subjects who are in normal range（BMIs ranging from 23 or more but less than 25）.

METHODS

1 Subjects

A total of 200 healthy adults（100 men and 100 women, aged 21-64 years）with BMIs ranging from 23.1 to 29.8 were enrolled in the study. The subjects were recruited from a pool of volunteers from the K.

S. O. Corporation（Minato-ku, Tokyo, Japan）. The subjects were all healthy adult women and men who underwent a medical examination within a month before the trial at the Medical Corporation Seishukai Clinic. The selection criteria included healthy men and women classified as having normal weight and class Ⅰ obesity according to the guidelines of JASSO, having a BMI ranging from 23 or greater to less than 30, and not receiving treatment for any lifestyle-related diseases.[12)]

The exclusion criteria included the following: allergy to cow's milk and soy bean; use of medications and health foods affecting lipid metabolism; designation of unsuitable from the medical doctor in charge of the study; a history of severe disorders; a history of gastrointestinal tract surgery; pregnancy or breastfeeding; withdrawal of more than 400 mL of whole blood or blood components within the four months prior to the study and/or more than 200 mL of whole blood within the two months prior to this study; extremely irregular dietary habits; alternative work schedule or working a midnight shift; smoking; and high alcohol intake. Two hundred subjects who fulfilled the eligibility criteria agreed to participate in the study. All subjects were enrolled in the study prior to random allocation. Allocation to the test or placebo group was concealed from the investigator who enrolled the subjects, the nurses and the medical doctor in charge of the study.

This study was approved by the Institutional Review Board of the Medical Corporation Seishukai Clinic according to ethical principles and an experimental plan based on the Declaration of Helsinki（Approved date: June 18, 2016）. Prior to the trial, the medical doctor responsible（M. O.）provided the subjects with a full explanation of the purpose and methodology of the study. Written informed consent was obtained from all subjects. This study was registered at UMIN-CTR（Trial ID: UMIN 000022842）.

2 Study design

This study followed a randomized, double-blind, placebo-controlled design, and the experimental periods were divided into two weeks of observation before treatment, 18 weeks of treatment, and six weeks of observation after treatment. A study coordinator（N. S.）randomly and blindly assigned the 200 subjects into two groups of 100 that were matched according to gender, BMI and abdominal fat area. Volunteers in one group（n＝100）received the test beverages（a 500 mL bottle of active beverage per volunteer per day: CP1563 group）, and those in the other group（n＝100）received one placebo beverage per day（a 500 mL bottle of the beverage per volunteer per day: placebo group）. The subjects were instructed to ingest one bottle daily. The subjects were also instructed to assess their health and maintain healthy living practices, including diet and exercise.

The sample size was set to 100 individuals per group to detect changes in the abdominal fat areas between the CP1563 and placebo groups at weeks 6, 12, and 18 of treatment using a CT scanner at a p value of 0.05 with 80% power using ANCOVA with repeated measures according to the information from a preliminary dose-finding study（unpublished information）and the previous RCT.[13)]

3 Primary outcome

Differences in changes in the abdominal fat areas between the CP1563 and placebo groups were applied as the primary outcome.

4 Preparation of fragmented CP1563

CP1563 was cultured in an original food-grade medium and then heat-inactivated. After that, bacterial cells were collected and fragmented with a commercially available jet mill. The degree of fragmentation was evaluated to maintain PPAR alpha-agonist activity at a certain effective degree as previously reported.[8)]

5 Supplementary beverages

Test beverages were prepared by blending 200 mg of the fragmented CP1563 powder and other ingredients in water, pasteurizing and packaging into 500 mL bottles. The placebo beverage was prepared using the same formula and procedure as for the test beverage, but it did not contain CP1563 powder. The nutritional content of the CP1563 and placebo beverages nearly followed the standard that we used in the previous RCT.[13)] The only difference was that there was no carbon dioxide. The beverages were identical in energy, protein（1.5 g）, and carbohydrate（4.0 g）per bottle; they were indistinguishable in taste by standard organoleptic evaluation.

6 Study schedule and protocol

The study period consisted of a two-week lead-in period in which initial parameters were obtained for baseline measurements followed by an 18-week treatment period in which the initiation of consumption was designated week 0 and a six-week post-con-

sumption period.

We performed the following anthropometric measurements at the hospital: body weight, BMI, hip and waist circumferences, body fat percentage, systolic and diastolic blood pressures, pulse rate, body temperature, blood analysis, and urinalysis. Abdominal computed tomography（Alexion TSX-032A, Canon Medical Systems Corporation, Ohtawara, Tochigi, Japan）scans and dual bioelectrical impedance analysis（InBody770, InBody Japan Inc., Koto-ku, Tokyo, Japan）were conducted to measure the abdominal VFA and SFA at weeks 0, 6, 12, 18, and 24 and at the screening examination. Height was only measured at the screening examination, and BMI was calculated based on this measurement.

Each participant maintained a daily record of test or placebo beverage consumption and diet, exercise, and physical condition, including the presence of any subjective symptoms during the trial. The participants also maintained a detailed record of diet and pedometer measurements for three consecutive days before each visit: at the start of treatment（week 0）and at weeks 6, 12, 18, and 24. A managerial dietitian analysed the dietary records to determine the intake of total energy, protein, carbohydrate, fat, total fibre, magnesium, calcium, potassium and sodium using Excel Eiyokun ver. 8.0（Kenpakusha Co., Ltd., Tokyo, Japan）.

Blood analysis and urinalysis were performed at LSI Medience Corporation（Chiyoda-ku, Tokyo, Japan）. The following biochemical and haematological parameters were measured: total protein, albumin, total bilirubin, aspartate aminotransferase（AST）, alanine aminotransferase（ALT）, lactate dehydrogenase（LD）, alkaline phosphatase（ALP）, γ-glutamyl transpeptidase（γ-GTP）, total cholesterol, HDL-c, LDL-cholesterol（LDL-c）, TG, uric acid, blood urea nitrogen, creatine, sodium, potassium, chloride, calcium, glucose, adiponectin, white blood cells, red blood cells, haemoglobin, haematocrit, and platelets.

In addition, apolipoproteins, including Apo A-I, Apo B, Apo C-Ⅲ, and Apo E, were also measured.

Protein, glucose, urobilinogen, bilirubin, ketone bodies, occult blood, pH, and density were determined through urinalysis. The participants were required to fast for at least 12 hours prior to the tests.

Medical examinations and inquiries were performed, and the medical doctor responsible（M. O.）assessed the subjective symptoms at each examination. All measurements were performed under the supervision of a doctor.

7　Abdominal fat areas

Five-slice abdominal computed tomography scans were taken at the level of lumbar vertebra 4-5 with 120-kVp tube voltage, 300-mAs tube current, 5-mm slice thickness and 430-mm field of view. Computed tomography scan images were analysed using Fat scan version 4 software（East Japan Institute of Technology Company Limited）to obtain abdominal VFA and SFA.

8　Statistical analysis

Statistical analyses were performed using JMP softwares（versions 11-2 and 13; SAS Institute Japan Ltd., Tokyo, Japan）and SPSS software（version 23; IBM SPSS Japan, Tokyo, Japan）. For comparisons between the groups, analysis of covariance（ANCOVA）for repeated measures was primarily used to assess the time course of treatment because of the wide ranges of the initial values of these parameters.

The per protocol analysis included all the data from participants except patient #82, who continued taking antibiotics during most of the treatment period because of tonsillitis. Compliance with the CP1563 or placebo beverage was assessed, and participants with ≥80% consumption of the beverages were considered eligible.

RESULTS

1　Screening and enrolment

In total, 200 subjects were enrolled, and 197 participants completed the present study. Three subjects who withdrew from the study are also included in the analysis. However, a subject who completed the study was eliminated from the analysis due to the influence of an excessive use of antibiotics on the intestinal environment throughout the treatment period. **Fig. 1** shows the flow diagram of the trial. Nutrient intake was also not significantly different between the groups throughout the study period.

2　Baseline characteristics of the subjects

Table 1 shows no significant differences in the baseline characteristics between the two groups. **Table 2** shows the nutrient intake throughout the treatment period. No significant differences in nutrient intake were observed between the groups throughout the trial period.

3　Body weight and other measures

No significant difference was observed in the changes in BW and BMI（**Table 3**）. However, the interaction

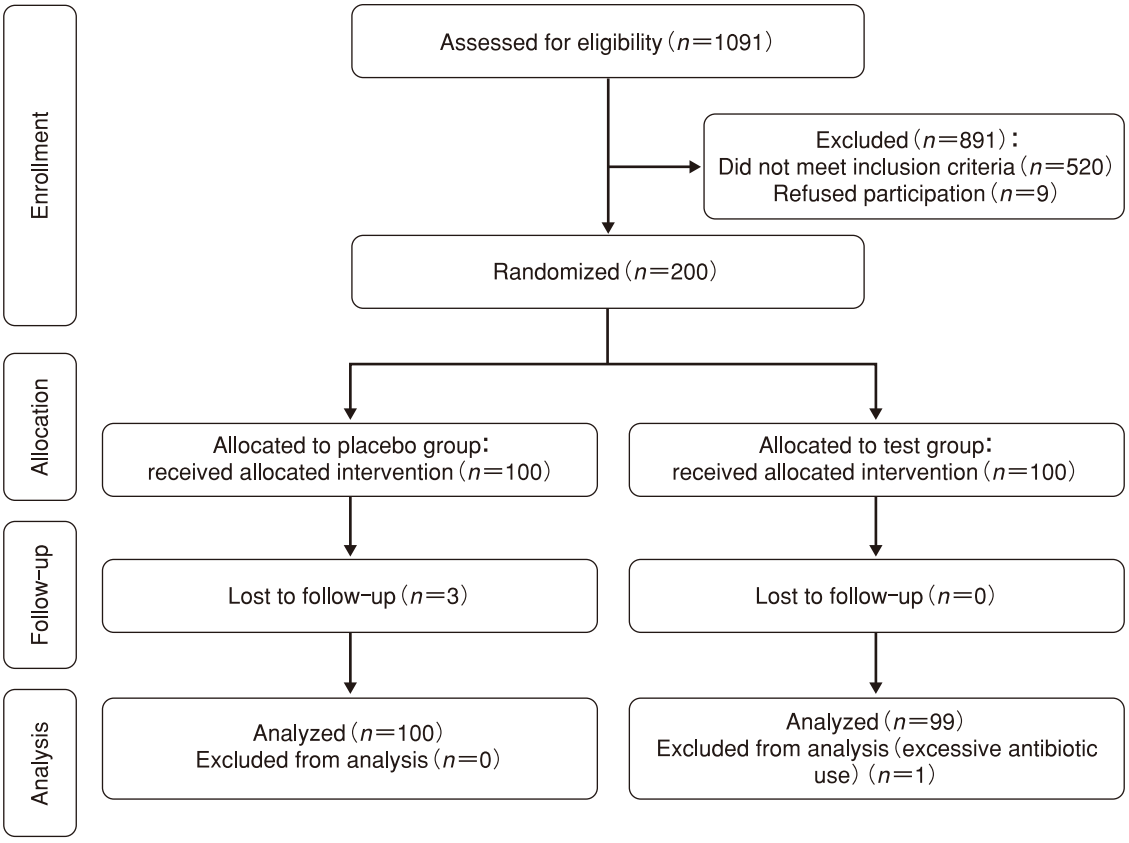

Fig. 1　Flow diagram for the trial

between the factors of group and baseline values for all items is highly significant（all $P<0.001$）; thus, there is a sub-cluster（s）of the measured items that is highly significant. Next, we attempted to identify the key discriminatory factor, and baseline VFA was found to be the one（data not shown）.

When we set a cut-off for VFA of 100 cm^2 and carried out a stratified analysis with ANCOVA for repeated measures in the cluster of subjects with VFA less than 100 cm^2（Cluster Ⅰ）, significant differences were observed in all measured items between both groups throughout the treatment period（$P<0.001$ for body weight and BMI）. This finding shows that the daily ingestion of CP1563 reduces body fat, and the reduction leads to loss of body weight.

In addition, in the non-adiposity and MetS sub-cluster（Cluster Ⅱ）, which is discriminated based on the definition from the JASSO, CP1563 significantly improves all the measured items（$P<0.001$ for body weight, and $P=0.037$ for BMI）.

Table 1　Baseline characteristics of the participants

Parameters	Placebo（$n=100$）	CP1563（$n=100$）
Male	50	50
Female	50	50
Age（y）	47.7±9.7	47.7±8.2
Body weight（kg）	75.2±8.6	74.3±9.7
Height（cm）	165.6±8.8	165.1±9.3
Body mass index（kg/m^2）	27.3±1.5	27.2±1.6
Waist circumference（cm）	94.0±4.8	94.0±5.6
Hip circumference（cm）	99.9±4.0	99.6±4.4
Visceral fat area（cm^2）	100.0±18.5	96.6±19.1
Nutrient intake		
Energy intake（kJ/day）	7619.9±1807.6	7450.8±1912.9
Protein（g/day）	66.4±18.3	64.0±16.8
Fat（g/day）	60.1±19.2	57.7±18.8
Carbohydrate（g/day）	237.2±57.4	232.5±62.7
Cholesterol（mg/day）	332.6±140.0	331.1±137.8
Dietary fibre（g/day）	10.4±3.5	10.1±3.3
Calcium（mg/day）	397.2±194.0	357.6±154.2
Sodium chloride（g/day）	9.4±2.6	9.0±2.6

Values are means±SDs.
No significant difference was observed between groups.

4　Abdominal fat areas

Table 4 shows that the time-dependent changes in VFA and TFA in both groups were significantly differ-

Table 2　Changes in nutrient intake

Parameters	Groups	*n*	Treatment Period					Factor
			Baseline	Week 6	Week 12	Week 18	Week 24	Group Group-by-initial
Energy intake (kJ/day)	Placebo	100	7620.0±255.6	7858.5±152.2	7847.3±164.5	8169.0±155.7	8044.8±160.3	$P=0.40$
	CP1563	99	7451.0±270.6	7705.8±152.9	7874.0±162.8	7714.1±154.1	7730.6±158.7	$P<0.001$
Protein (g/day)	Placebo	100	66.4±2.6	70.4±1.6	69.5±1.7	71.9±1.6	71.7±1.7	$P=0.71$
	CP1563	99	64.0±2.4	69.4±1.6	70.1±1.7	68.6±1.6	67.9±1.7	$P<0.001$
Fat (g/day)	Placebo	100	60.1±2.7	63.0±1.8	62.4±1.9	67.9±2.0	66.3±2.1	$P=0.47$
	CP1563	99	57.7±2.7	63.6±1.8	64.1±1.9	61.3±2.0	62.0±2.1	$P<0.001$
Carbohydrates (g/day)	Placebo	100	237.2±8.1	245.1±4.8	245.9±5.2	251.1±4.6	246.7±4.8	$P=0.89$
	CP1563	99	232.5±8.9	234.1±4.8	243.1±5.1	241.6±4.5	241.7±4.7	$P<0.001$
Cholesterol (mg/day)	Placebo	100	332.6±19.8	375.0±15.2	341.0±14.6	376.0±15.1	377.3±14.3	$P=0.63$
	CP1563	99	331.1±19.5	385.1±15.2	372.4±14.4	359.6±15.0	328.1±14.2	$P<0.001$
Dietary fibre (g/day)	Placebo	100	10.4±0.5	10.6±0.3	11.3±0.3	11.6±0.3	11.2±0.3	$P=0.87$
	CP1563	99	10.1±0.5	10.3±0.3	10.6±0.3	10.5±0.3	10.7±0.3	$P<0.001$
Calcium (mg/day)	Placebo	100	397.2±27.4	386.0±14.2	391.5±15.8	432.4±15.0	394.8±15.3	$P=0.67$
	CP1563	99	353.6±22.0	381.2±14.3	387.4±15.8	372.8±14.9	394.9±15.2	$P<0.001$

Values are means±SEMs.
No significant difference was observed between groups.

Table 3　Changes in body weight and BMI

Stratified	Parameters	Groups	Treatment Period					Factor
			Baseline	Week 6	Week 12	Week 18	Week 24	Group Group-by-baseline
All volunteers with BMIs between 23.1 and 29.8 ($n=199$)	Body weight (kg)	Placebo	74.4±0.8	74.0±0.1	74.0±0.2	74.0±0.3	74.2±0.3	$P=0.19$
		CP1563	73.7±0.9	73.5±0.1	73.5±0.2	73.4±0.2	73.6±0.3	$P<0.001$
	BMI (kg/m^2)	Placebo	27.1±0.1	27.0±0.1	26.9±0.1	26.9±0.1	27.0±0.1	$P=0.87$
		CP1563	26.9±0.2	26.9±0.1	26.8±0.1	26.8±0.1	26.9±0.1	$P<0.001$
Cluster Ⅰ: Volunteers with VFAs less than 100 cm^2 ($n=56$)	Body weight (kg)	Placebo	72.8±0.9	72.2±0.2	72.3±0.4	72.6±0.5	72.9±0.5	$P<0.001^{***}$
		CP1563	70.7±0.9	70.2±0.2	69.9±0.4	69.6±0.5	69.8±0.5	$P<0.001$
	BMI (kg/m^2)	Placebo	26.9±0.1	26.9±0.1	26.9±0.1	27.0±0.2	27.1±0.2	$P<0.001^{***}$
		CP1563	26.7±0.2	26.5±0.1	26.4±0.1	26.3±0.2	26.4±0.2	$P<0.001$
Cluster Ⅱ: Volunteers without metabolic syndrome criteria and adiposity ($n=32$)	Body weight (kg)	Placebo	72.1±2.0	72.0±0.4	72.1±0.6	72.2±0.6	72.2±0.7	$P<0.001^{***}$
		CP1563	68.7±1.6	68.2±0.3	67.7±0.5	67.3±0.5	67.2±0.5	$P<0.001$
	BMI (kg/m^2)	Placebo	26.3±0.5	26.2±0.2	26.2±0.3	26.2±0.3	26.2±0.3	$P=0.037^{*}$
		CP1563	25.9±0.5	25.8±0.1	25.6±0.2	25.5±0.2	25.4±0.2	$P<0.001$

Values are means±SEMs
VFA＝visceral fat area
Cluster Ⅰ includes volunteers who have VFAs less than 100 cm^2.
Volunteers in Cluster Ⅱ are stratified according to the definition from the guidelines for the management of obesity 2016 (edited by the Japan Society for the Study of Obesity).
$^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$

ent ($P=0.048$ and $P=0.014$, respectively). On the other hand, no significant difference was observed in SFA ($P=0.86$). Thus, it is thought that most of the body fat mass decrease with CP1563 supplementation is due to the decrease in visceral fat mass.

In Cluster Ⅰ, in addition to the significant decreases in VFA and TFA in the CP1563 group compared with those in the placebo group ($P<0.001$ and $P=0.001$, respectively), a significant reduction in SFA in the CP1563 group was also observed ($P<0.001$).

In Cluster Ⅱ, changes in SFA were not significant, unlike those in Cluster Ⅰ. However, the changes in SFA in the CP1563 group were extremely close to significance ($P=0.051$). During the course of the study, meaningful and significant changes were detected in VFA and TFA between both groups ($P=0.012$ for VFA and $P=0.031$ for TFA).

Table 4　Changes in body weight, BMI, and body fat percentage

Stratified	Parameters	Groups	Treatment Period					Area under curve (Weeks 0 to 18) (average (cm^2×week))	Factor Group Group-by-baseline
			Baseline	Week 6	Week 12	Week 18	Week 24		
All volunteers with BMIs between 23.1 and 29.8 (n=199)	Total fat measured (cm^2)	Placebo	353.6±5.7	362.7±5.5	358.8±5.8	351.9±6.2	348.7±6.5	65.0	P=0.014*
		CP1563	352.9±5.4	359.6±6.3	353.7±6.4	354.5±6.8	350.0±7.1	53.3	P<0.001
	Visceral fat (cm^2)	Placebo	130.5±4.0	133.8±4.2	133.0±4.4	127.9±4.4	125.2±4.1	16.6	P=0.048*
		CP1563	130.0±3.6	130.8±3.9	128.9±6.4	129.9±4.3	126.9±4.4	−1.3	P<0.001
	Subcutaneous fat (cm^2)	Placebo	223.2±5.0	229.0±4.8	224.0±5.3	224.5±5.1	223.6±5.6	48.4	P=0.86
		CP1563	222.8±4.7	228.8±5.1	224.8±5.0	224.5±5.1	223.0±5.2	54.6	P<0.001
Cluster Ⅰ: Volunteers with VFAs less than 100 cm^2 (n=56)	Total fat (cm^2)	Placebo	318.7±5.7	332.2±5.7	328.6±5.6	326.0±6.4	327.7±7.5	135.2	P=0.001**
		CP1563	322.0±5.4	332.3±6.0	316.8±5.9	319.2±6.8	306.3±7.9	−23.9	P<0.001
	Visceral fat (cm^2)	Placebo	85.3±4.0	92.7±2.5	90.4±2.6	88.9±3.0	87.0±3.3	80.0	P<0.001***
		CP1563	87.1±3.6	94.3±2.6	86.8±2.7	88.0±3.2	82.8±3.5	5.4	P<0.001
	Subcutaneous fat (cm^2)	Placebo	233.3±5.0	239.5±4.2	238.2±4.8	237.1±5.0	240.7±5.5	55.2	P<0.001***
		CP1563	234.8±4.7	238.0±4.4	229.9±5.0	231.2±5.3	223.6±5.8	−29.3	P<0.001
Cluster Ⅱ: Volunteers without metabolic syndrome criteria and adiposity (n=32)	Total fat (cm^2)	Placebo	319.8±10.4	333.2±10.6	329.0±10.7	324.2±11.6	317.4±12.4	149.2	P=0.031*
		CP1563	333.5±11.8	337.1±8.6	319.8±8.7	318.3±9.4	305.6±10.1	−105.7	P<0.001
	Visceral fat (cm^2)	Placebo	109.2±10.7	119.4±7.2	115.8±6.3	111.1±6.6	105.6±7.8	106.2	P=0.012*
		CP1563	107.4±7.5	111.0±6.0	101.2±5.2	102.1±5.5	97.1±6.5	−31.7	P<0.001
	Subcutaneous fat (cm^2)	Placebo	210.6±14.5	213.8±6.2	213.2±7.9	213.1±7.8	211.8±8.3	43.0	P=0.051†
		CP1563	226.1±13.5	226.1±5.1	218.6±6.5	216.2±6.4	208.5±6.8	−74.0	P<0.001

Values are means±SEMs　VFA＝visceral fat area

Cluster Ⅰ includes volunteers who have VFAs less than 100 cm^2.

Volunteers in Cluster Ⅱ are stratified according to the definition from the guidelines for the management of obesity 2016（edited by the Japan Society for the Study of Obesity）.

*P<0.05,　**P<0.01,　***P<0.001

Table 5　Changes in plasma cholesterol and related apolipoproteins

Stratified	Parameters	Groups	Treatment Period					Factor Group Group-by-baseline
			Baseline	Week 6	Week 12	Week 18	Week 24	
All volunteers with BMIs between 23.1 and 29.8 (n=199)	Apo A-I (mg/100 mL)	Placebo	142.2±1.8	142.7±1.8	143.9±1.8	146.2±1.8	141.0±1.9	P=0.005**
		CP1563	142.1±2.2	143.5±1.8	142.5±1.8	147.3±1.9	142.2±2.2	P<0.001
	Apo B (mg/100 mL)	Placebo	95.7±1.9	94.8±1.9	96.4±2.0	94.3±2.0	96.9±2.0	P=0.39
		CP1563	94.5±1.8	94.3±1.8	95.4±1.6	93.7±1.7	95.4±1.9	P<0.001
	Apo B/Apo A-I ratio	Placebo	0.69±0.02	0.67±0.02	0.68±0.02	0.66±0.02	0.70±0.02	P=0.34
		CP1563	0.68±0.02	0.67±0.02	0.68±0.02	0.65±0.02	0.69±0.02	P<0.001
Cluster Ⅰ: Volunteers with VFAs less than 100 cm^2 (n=56)	Apo A-I (mg/100 mL)	Placebo	146.7±4.3	148.1±4.1	148.4±4.1	149.3±3.5	143.1±3.9	P<0.001***
		CP1563	147.4±4.2	147.4±4.2	147.3±4.1	153.6±4.3	149.3±4.2	P<0.001
	Apo B (mg/100 mL)	Placebo	92.2±3.3	92.3±3.1	92.2±3.6	89.6±3.0	91.4±3.5	P=0.18
		CP1563	83.5±3.9	83.5±3.9	86.1±3.6	82.9±3.5	84.0±3.8	P<0.001
	Apo B/Apo A-I ratio	Placebo	0.65±0.03	0.64±0.03	0.64±0.04	0.61±0.03	0.66±0.04	P=0.27
		CP1563	0.58±0.03	0.58±0.03	0.60±0.04	0.56±0.03	0.58±0.04	P<0.001
Cluster Ⅱ: Volunteers without metabolic syndrome criteria and adiposity (n=32)	Apo A-I (mg/100 mL)	Placebo	144.8±4.3	147.5±4.2	147.9±4.3	147.5±3.9	140.8±4.8	P=0.002**
		CP1563	152.9±7.8	150.5±5.0	152.6±4.1	159.3±4.9	154.1±4.7	P<0.001
	Apo B (mg/100 mL)	Placebo	81.5±4.4	84.7±4.0	87.2±3.1	81.2±4.6	81.8±4.6	P=0.16
		CP1563	86.6±3.3	87.7±3.6	86.8±3.9	84.4±3.1	85.7±3.2	P<0.001
	Apo B/Apo A-I ratio	Placebo	0.57±0.03	0.58±0.03	0.60±0.03	0.55±0.03	0.59±0.03	P=0.009**
		CP1563	0.59±0.04	0.59±0.03	0.58±0.03	0.54±0.03	0.57±0.03	P<0.001

Values are means±SEMs　VFA＝visceral fat area

Cluster Ⅰ includes volunteers who have VFAs less than 100 cm^2.

Volunteers in Cluster Ⅱ are stratified according to the definition from the guidelines for the management of obesity 2016（edited by the Japan Society for the Study of Obesity）.

*P<0.05,　**P<0.01,　***P<0.001

5　Plasma apolipoproteins

Table 5 shows time-dependent changes in plasma concentrations of apolipoproteins in both groups. These changes were not largely different between groups except those observed in Apo A-I（$P=0.005$）.

In Cluster Ⅰ, a significant increase in the plasma concentration of Apo A-I in the CP1563 group was observed（$P<0.001$）.

In Cluster Ⅱ, the plasma concentration of Apo A-I was significantly increased（$P=0.002$）, and the ratio of Apo B/Apo A-I was accordingly decreased in the CP1563 group（$P=0.009$）.

6　Daily life and adverse events

No irregularities in daily life or adverse events related to the daily intake of the beverage containing 200 mg of fragmented CP1563 were observed throughout the study according to the diary record and repeated interviews with doctors. The results of blood tests（TG, total cholesterol, LDL-c, HDL-c, remnant lipoprotein-cholesterol, phospholipids, leptin, high-molecular-weight adiponectin, blood glucose, HbA1c, insulin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltranspeptidase, alkaline phosphatase, L-LD, total bilirubin, creatine kinase, total protein, albumin, globulin, total ketone body, acetoacetic acid, 3-hydroxybutyric acid, uric acid, blood urea N, creatinine, Na, Cl, K, Ca, P, Mg, Fe, ferritin, total ion-binding capacity, unsaturated ion-binding capacity, leucocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, erythrocytes, haemoglobin, haematocrit and platelets）also showed that most measurements were normal and without extreme outliers, and no physiologically significant changes were observed throughout the study（data not shown）.

DISCUSSION

The present study demonstrated a significant reduction in VFA in the CP1563 group compared with that of the placebo group during the study period. This finding is related to the significant reduction in TFA because the contribution of VFA reduction by CP1563 ingestion was larger than that of SFA. Interestingly, fragmented cells from para-probiotic CP1563 showed potency in that the VFA reduction was higher in a cluster of subjects who had a relatively small initial visceral fat area（i. e., less than 100 cm^2）, a result that was determined from a stratified analysis. Moreover, a clearer reduction in VFA, SFA, and TFA was observed in healthy subjects in Cluster Ⅱ. Although fluctuations in CT measurements between time points were thought to be due to a possible bias of the instrument settings or operator, the analytical procedure used here was able to eliminate the anticipated analysis problem.

It was suggested by a stratified ANCOVA analysis for repeated measures with initial VFA value as the covariant that initial VFA is a key covariant, and the analysis suggested that there is a significant contribution from a cluster（s）of participants. The cluster included participants with an initial VFA of less than 100 cm^2. In other words, this might suggest a preventive effect of para-probiotic CP1563 against adiposity. Para-probiotic CP1563 may contribute to the health maintenance of ordinary people who care for their metabolic disorders. Observations near the end of the consumption period（week 18）and thereafter（week 24）showed decreases in magnitude over time（**Table 4**）. This also suggested that continuous consumption of para-probiotic CP1563 is essential to maintain its influence.

The study conditions of the present study were nearly the same as those of a previous study,[13] except for the BMI range of participants, as mentioned previously. The participants were healthy volunteers who had wide variations in their initial VFA. Energy and nutrient intake estimated from dietary records were considered normal, and no difference between groups was observed throughout the trial, as shown in **Table 2**. There have been several reports about the risk of underestimating actual calorie intake using this method.[14,15] Under-reporting has been noted in several studies. It cannot be denied that there is a risk in this study that possible unreported additional energy intake caused fluctuations in the changes in abdominal fat areas and other anthropometric indicators over the course of the study. For this reason, the primary assessment of the energy intake data in **Table 2** should be that there were no significant differences between the groups during the study period. Nevertheless, undeniable factors other than energy intake are related to aspects of a modern lifestyle, such as keeping late hours and exposure to stressful conditions;[16,17] a possible ethnic propensity to gain abdominal fat[18] might be involved in the tendency towards obesity, although the exact reasons are still uncertain.

A particularly important finding of the study is the significant reduction in VFA in the para-probiotic CP1563 group throughout the trial period. In addition, the tendency is clear in the subgroup of participants with a lower initial VFA of less than 100 cm^2（Cluster Ⅰ）and is clearer in the participants in Cluster Ⅱ,

which contained participants without MetS and adiposity criteria according to the definition in the JASSO guidelines, as previously mentioned（**Table 4**）. The results indicate that continuous ingestion of para-probiotic CP1563 may prevent MetS and abdominal adiposity in the general population. The reduction in VFA is the main cause of the decrease in TFA, and it is thought that it is the root of the usefulness of para-probiotic CP1563.

Shaikh and Sreeja[19] mentioned the characteristics of probiotics: "Probiotics are said to confer a number of health benefits on the host through their varied mechanisms of action in the human gastrointestinal tract. However, a number of limitations exist with use of live probiotics. We are yet to be sure about the optimal dosage of probiotics, their specific mode of action, duration of the beneficial effects and the nature of the final results." This seems to be true of probiotics.

Intestinal microbiomes and the beneficial microbes isolated from them are also becoming popular among researchers who are interested in the prevention of MetS. Accumulating studies have indicated curative properties of probiotics, including glycaemic control, serum lipid modulation, and abdominal adiposity.[20–23] The application of probiotics as prospective biotherapies in the management of metabolic disorders, including obesity and diabetes, has been explored. When we first found that *Lactobacillus gasseri* SBT2055（LG2055）reduced the visceral fat of senescence-accelerated mice during life-long feeding of its live form as a probiotic candidate for metabesity（Japan patent: P2003-252772A）, it seemed difficult to explain the exact mechanism（s）of probiotics. There was a decrease in visceral fat mass first and need to take the process to investigate the working mechanism without a clue. Thereafter,[24] confirmed the effect of LG2055 in Zucker rats, and since then, the research has reached the level of clinical trials.[6,25] Researchers spent the next few years developing an account of inflammation inhibition in visceral white adipose tissue;[26–30] however, a clear explanation of the relationship has not been shown between the event（s）occurring in the gastrointestinal tract during daily ingestion of the probiotics and inflammatory inhibition in the visceral adipose tissue. This bacterial strain has the ability to colonize the human intestine even in adults.[31] Colonization by the strain may help to maintain the integrity and function of intestinal epithelial cells, resulting in control of intestinal inflammation. Thus, ingestion of this bacterial strain may contribute to the reduction in abdominal adiposity.

In any event, the efficiency and mechanisms of probiotic effects are essentially determined by the relationship between probiotics and either the microbiota of the host or the immunocompetent cells of the intestinal mucosa.[32] To date, several assumptions have been presented about the mechanism of action of probiotics that ameliorate MetS, including modifications of gut microbial composition, involvement in energy homeostasis, stimulation of insulin signalling, modulation of inflammatory signalling pathways, interference with the immune system, and down-regulation of cholesterol levels. Among the molecular mechanisms, short-chain fatty acids, conjugated linoleic acid, bile-salt hydrolase, metabolic endotoxaemia and the endocannabinoid system, which are associated with the normalization of adipogenesis and the regulation of insulin secretion, fat accumulation, energy homeostasis, and plasma cholesterol levels, are thought to be involved in the beneficial action of probiotics; these mechanisms result in anti-obesity and anti-inflammatory effects, glycaemic control improvements and serum lipids modulation. However, the effect of FM consumption on MetS is unconcluded.[33] Furthermore, at present, no information has been obtained on what happens in the gut following the consumption of probiotics and how these events relate to metabolic function. Intriguingly, Higashikawa, et al.[34] reported a comparative clinical trial on abdominal adiposity between probiotics and para-probiotics of the same strain. Only the heat-treated, para-probiotic form of *Pediococcus pentosaceus* LP28 showed an anti-obesity effect with significant reductions in BMI, body fat and waist circumference. This distinction suggests that the presence of the cell body is not always important to maintain metabolic activity, but the contents discharged from the bacterial cell body may be critical, as in the case of CP1563. In **Table 5**, we show an increase in the plasma concentration of Apo A-I in the para-probiotic CP1563 group compared with that of the placebo group throughout the study. This phenomenon may relate to PPAR alpha activation by the fragmented para-probiotic CP1563 *in vivo*, as it is well known that fibrates, typical PPAR agonists, induce PPAR alpha activation in humans; thus, the activation results in increased plasma Apo A-I concentrations.[35] It is possible that the PPAR alpha induction activity of para-probiotic CP1563 is related to the reduction in VFA through the stimulation of fatty acid catabolism.[36]

Compositional alterations in the intestinal micro-

biota were not examined in this study. It has been suggested but is unknown whether the composition of colonic microbiota estimated from that of faecal samples has a direct influence on abdominal adiposity; the causal relationship between obesity and alterations in the intestinal microbiota is not certain.[37,38] An accurate connection between compositional changes in intestinal microbiota and supplementation with para-probiotic CP1563 will be needed. Participants in the present study maintained their lifestyles, including diet, exercise, and sleep habits, and there was no strict dietary control. To determine the role of intestinal microbiota composition changes on adiposity, a clinical trial including strict dietary control and a random sequence-based analysis of the intestinal microbiota is needed.

Since screening, the purpose of CP1563 development has been clarified, and the reason for using this examination strategy to determine the mechanism of action of the CP1563 anti-obesity effect is simple. Thus, in the case of CP1563, it is much easier to explain the mechanism that relates to the activation of fatty acid beta oxidation from excess storage fat in adipose tissues and stimulation of the re-proliferation of adipocytes through the activation of PPAR alpha/gamma. These facts may vividly show the typical advantage of para-probiotics that it can narrow down a screening target plainly. The technical terms "para-probiotics",[39] "biogenics"[40] and "metabiotics"[19] have been suggested to cover the territory that the term "probiotics" cannot cover by itself. These terms roughly mean non-living probiotics, metabolic substances and bacterial structural component(s), respectively. The latter two working substance-based concepts can be easily understood and used for their lactic acid bacteria involvement with abdominal fat-reducing effect. Recently, we obtained some fractions which possessed PPARα-agonist activity via column chromatography from the ethanolic extract of CP1563. The major component was purified and then identified as 10-hydroxyoctadecanoic acid (10-HOA).[41] Also we confirmed 1.44 mg of 10-HOA was contained in the supplementary drink used in this study. As for 10-HOA, two studies recently reported attract attention. One was reported by Goto, et al.,[42] they found that fatty acids including 10-HOA were produced by gut lactic acid bacteria from linoleic acid and 10-HOA had PPAR alpha agonistic activity. Another one was reported by Igami et al.,[43] their study revealed that 10-HOA was identified as PPAR alpha/gamma agonist in ginseng fermented by Lactobacillus paracasei A221. Consequently, this may be candidate to explain the mode of action of the CP1563, in addition, a useful tool for the quality control in functional food. However, further investigation is necessary on the working component(s) and the mechanisms of action underlying the advantageous benefit of the para-probiotic CP1563. We are now preparing manuscript regarding these points and report in soon.

In conclusion, the fragmented para-probiotic CP1563 described in this report is effective in reducing VFA and, to the best of our knowledge, the first-reported "para-metabobiotic", which is a combined term for both "para-probiotics" and "metabolic syndrome".

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