VISCERAL FAT-REDUCING EFFECT OF SUPPLEMENT CONTAINING APPLE POLYPHENOL AND OLEANOLIC ACID IN HEALTHY JAPANESE
— A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY —

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Abstract

Objectives: The objective of this research was to investigate the effectiveness of daily ingestion of a CUTTO tablet, which contains apple polyphenol and oleanolic acid on weight reduction and waist circumference reduction.
Methods: In this randomized, placebo-controlled, double-blind trial, 40 subjects were randomized. To evaluate this objective, visceral fat area and subcutaneous fat area were measured as the primary outcome. Weight, BMI, waist circumference and subjective reporting was also observed as the primary outcome.
Results: 3 subjects were withdrawn due to personal reasons and 8 subjects were excluded from efficacy analysis due to taking a meal before getting a CT scan and sending in adequate records. With 29 subjects, the visceral fat area of CUTTO decreased significantly compared with Placebo after 12 weeks of ingestion. Furthermore, significant difference was observed between the two groups in weight, BMI and waist circumference after 12 weeks. Moreover, 8 items out of 9 showed significant difference with results from a questionnaire, in the intergroup comparison of 12-week ingestion.
Conclusion: The present results suggest that daily ingestion of CUTTO tablets including apple polyphenol and oleanolic acid can reduce weight and waist circumference.

1. INTRODUCTION

In present-day Japan, as the society often allows excess intake of calories and irregular lifestyles, many people tends to be distressed about their obesity. Obesity is a state of excessive body fat accumulation than a prescribed level. Visceral fat obesity, the type of obesity that accumulates excessive fat around internal organs, especially causes high cholesterol and blood sugar level, and even leads to serious arteriosclerosis at the end[1]. Consequently, obesity becomes a major factor of many diseases including so-called "lifestyle diseases", therefore a prevention and solution of obesity are an expectation of many people in common.

An improvement of daily eating and exercise habits is obviously important for preventing and solving obesity. It should be also effective to take the supplement which utilizes functionality of food ingredients that can modestly control vital function, in addition to the improvement of the habits. There are several reports about the food ingredients that may work on sugar and fat metabolism of body and prevent obesity[2)3)].

As the proverb "An apple a day keeps the doctor away" says, the contribution of apple to our health has been focused for a long time. Apple contains ingredients such as fiber, minerals, and polyphenol which are regarded to have various physiological functionalities, and these ingredients are thought to contribute to our health[4]. Oleanolic acid, on the other hand, is the triterpene contained in olive and grape berry skin, and many reports explain its functions such as antioxidant effect[5].

Ingredients such as polyphenol and oleanolic acid reportedly have a function of preventing metabolic syndrome[6)7)], and are considered to be effective for preventing or solving obesity.

However, although many supplements containing the apple polyphenol are sold in Japan and several reports emphasizing its function exist[8], there are few published reports that discuss the effect and safety of the combined use of both polyphenol and oleanolic acid. In addition, their function for obesity is also unclear.

In this study, we examined the effect of apple polyphenol and oleanolic acid for weight reduction and waist circumference reduction and the safety of the combined use of them, by adopting a randomized, placebo-controlled, double-blind study using the

supplement containing both of these ingredients.

2. METHOD

2.1. Trial Design

A randomized, placebo-controlled, double-blind study was conducted with the aid of a fund from GRACEAS Corporation (Tokyo) at two centers (KUROSU HOSPITAL, Tokyo and JACTA, Tokyo).

The study period was 12 weeks, from July 28th to October 23th, 2015.

This study was conducted in accordance with the ethical principles of the declaration of Helsinki. The study protocol was approved by the Institutional Review Board of LLP. Pharmaceutical Law Wisdoms (Tokyo). Written informed consent was obtained from all Subjects.

The allocation of the test product to the subjects was carried out by the person in charge of allocation.

The allocation list was sealed and strictly controlled in a safe deposit box of JACTA until the end of the study.

2.2. Subject

Healthy subjects participated in the present study.

All of the subjects in this study were public volunteers who had enrolled in the monitor bank of Rabbits-coco (Tokyo), Stephens& Associates, Inc. (Tokyo) and Miyao Co., LTD. (Tokyo).

2.2.1. Inclusion Criteria

(1) Healthy female aged between 20 and 59 years;

2.2.2. Exclusion criteria

(1) Individuals with BMI ≥ 30 and diagnosed unhealthy;
(2) Individuals undergoing treatment of weight reduction;
(3) Individuals taking medication, including herbal medicines;
(4) Individuals judged to be unsuitable to participate in the trial by the doctor conducting present study.

2.2.3. Efficacy eligibility

With respect to the analysis of efficacy, we set the following criteria of exclusion:
(1)Participants who consumed a meal in the morning just before getting a CT scan
(2)Participants who consumed less than 80% of the expected dose;
(3)Participants who do not take adequate records;
(4)Participants who fell under the exclusion criteria after enrolment;
(5)Participants who had justifiable reason for exclusion.

2.3. Randomization

Recruited subjects were 71 persons. Subjects who fulfilled eligibility criteria were 40 persons. The inclusion was judged by the principle investigator.

All subjects were sequentially assigned based on a random number table to one of the masked products and randomized to group T (Test sample: 20) and group P (Placebo: 20). The allocation was pre-assigned on the basis of randomized numbers.

2.4. Description of test foods and blinding

The test food, "CUTTO" and placebo were prepared by GRACEAS Corporation. The amount of daily intake is 2 tablets (1 tablet contains 300mg, therefore 2 tablets contain 600mg). The compositions of CUTTO were apple polyphenol, oleanolic acid, etc., while Placebo was consisted of Comprecel, Pineapple fiber, etc. Both tablets were indistinguishable in shape, color or taste. Tablets were managed by the identification symbol. All involved were blinded.

2.5. Experimental procedures

2.5.1. Experimental protocol

Subjects consumed 2 tablets of the supplement with hot or cold water every day for 12 weeks. Subjects were instructed as follows: to take the assigned foods as indicated; to maintain their usual lifestyles and habits; to avoid excessive amounts of food, drink, or alcohol; to maintain a daily record of lifestyle factors such as all the food items or number of steps they took for the day during the test period; and to send the diary to the study coordinator every Friday (or Thursday night) by mobile email.

2.5.2. Outcome

The objective of this study is to verify the weight reduction and waist circumference reduction effect of ingesting food containing apple polyphenol with oreanolic acid. To evaluate this objective, visceral fat area and subcutaneous fat area were measured as the primary outcome.

This measurement was the result of CT images by Bright Speed (GE Healthcare, Tokyo). Several CT images around the umbilicus were obtained and single scan images at the precise point of the umbilicus were used for analysis. The visceral fat area and subcutaneous fat area were calculated from CT images using Power View Fat software (Vigoment Software Corp., Tokyo).

Weight, BMI, waist circumference and subjective reporting was also observed as the primary outcome. Height, body weight and BMI were scaled by AD-6228AP (A&D Company, Limited, Tokyo). Waist circumference, at the umbilical level, was measured using a non-elastic anthropometric tape measure.

The questionnaire covered: bowel movement, sensitivity to cold, clothing size variation, dryness of skin, fatigue, mood, rate of activity, sleeping quality and feeling lighter. The score of the answer is between 1 and 9. Score 5 is defined as the average status.

Blood biochemical and urine parameters were recorded to evaluate the safety of CUTTO as the secondary outcome. These assessments were conducted upon entry into the study (pre-intervention) and after 12 weeks (post-intervention).

To evaluate the safety of the test foods, adverse events were collected by means of a written questionnaire during the study.

According to the schedule shown **Table 1**, we measured parameters on efficacy and safety.

Table 1　Schedule for the study.

Item \ Term	Screening	Pre Trial Test	Test period (12 w)
Informed consent	●		
Selection and/or allocation	●		
Abdominal fat level		●	●
Anthropometric measurements		●	●
Subjective reporting		●	●
Biochemical analysis of the blood		●	●
Urine analysis		●	●
Ingestion of test foods			↔
Log			↔

● : Implementation
↔ : Daily practice during the test period

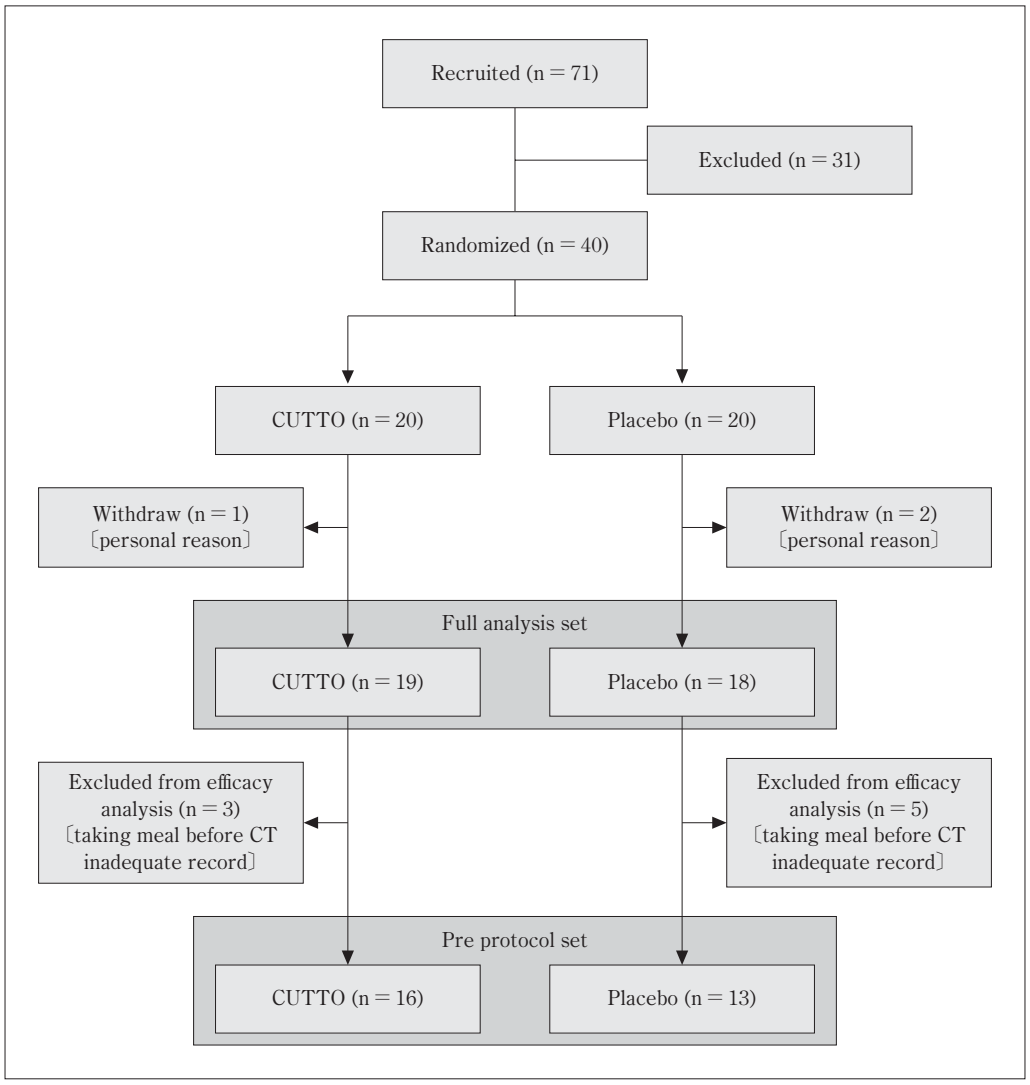

Fig. 1　Flow diagram of subject disposition

2.6. Data Analysis

All analyses were performed on the on-treatment population in the study. The Par protocol set principal was adopted in the present study and no sample size design was used. Data were expressed as mean ± SD. For the Abdominal fat level, anthropometric measurements and biochemical analyses of blood and urine, changes from the baseline in the same group were assessed using the paired t-test. Student's t-test was used for intergroup comparisons of changes from the baseline.

Table 2 Subject demographics

Item	Unit	CUTTO	Placebo
Subjects*	−	16	13
Age	years	48.5±6.8	44.9±8.0
BMI	kg/m^2	26.5±2.0	25.7±2.3

* Number of subjects
mean ± SD

Table 3 Changes in abdominal fat areas, weight, BMI and waist circumference

Item	Unit	Time points	Values		Between-group difference (P-value)
			CUTTO group (n=16)	Placebo group (n=13)	
Visceral fat area	cm^2	Baseline	93.9±51.1	88.5±42.2	
		Week 12	87.9±40.8	95.7±42.7 †	
		Change	−6.0±17.6	7.2±12.9	0.033 #
Subcutaneous fat area	cm^2	Baseline	216.3±67.5	237.6±55.0	
		Week 12	208.3±63.3*	230.2±57.6	
		Change	−8.0±14.3	−7.4±17.0	0.919
Weight	kg	Baseline	64.3±6.6	62.7±6.1	
		Week 12	61.6±6.6 **	63.4±6.1 *	
		Change	−2.7±0.8	0.7±0.9	< 0.001 ##
BMI	Kg/m^2	Baseline	26.5±2.0	25.7±2.3	
		Week 12	25.3±2.0 **	25.8±2.1	
		Change	−1.1±0.3	0.1±0.4	< 0.001 ##
Waist circumference	cm	Baseline	89.3±7.6	89.2±8.9	
		Week 12	86.7±7.3 **	89.1±8.6	
		Change	−2.6±0.6	−0.1±0.8	< 0.001 ##

Values are expressed as the mean ± SD.
† $p < 0.1$, * $p < 0.05$, ** $p < 0.01$ against baseline.
# $p < 0.05$, ## $p < 0.01$ between-group difference in change from baseline.

For subjective reporting, changes from baseline in the same group were assessed using Wilcoxon signed-rank test. The Mann-Whitney U test was used for intergroup comparisons of changes from the baseline. Student's t-test was used to compare subject backgrounds between groups. Statistical analyses were performed using Statcel 3 (Yanai, 2011). The results were considered significant at the <5% level in the two-sided test.

3. RESULT

3.1. Participant Demographics

From all of 71 applicants, 31 were eliminated according to exdusion criteria. The 40 subjects were randomly assigned to an intervention group and made a start with ingestion. 3 were withdrawn due to personal reasons and the remaining 37 subjects completed the study. Out of 37 subjects, 8 revealed to fall under the exclusion criteria for evaluation of efficacy as described in "Efficacy eligibility" (2.2.3). 5 subjects consumed a meal in the morning just before getting a CT scan (2.2.3. (1)). 3 subjects did not send adequate records (2.2.3. (2).)

Thus, data obtained with 29 subjects were used for the analysis of efficacy **(Fig. 1)**. There were no significant differences in the mean age or BMI between groups **(Table 2)**.

3.2. Abdominal fat level

Table 3 shows changes in abdominal fat areas. For the change, visceral fat area of the CUTTO group decreased significantly compared with the Placebo group after 12 weeks of ingestion.

3.3. Weight, BMI and waist circumference

Table 3 shows the results of test analyses. After 12 weeks of ingestion, the CUTTO group showed a significant difference in weight, BMI and waist circumference, whereas the Placebo group showed no significant difference. Furthermore, significant difference was observed between the two groups of the change in all three criteria after 12 weeks of ingestion.

3.4. Questionnaire analyses

The results of questionnaire analyses are shown in **Table**

Table 4　Results of questionnaire analyses

Item	Time points	Scores		Between-group difference (P-value)
		CUTTO group (n=16)	Placebo group (n=13)	
Bowel movement	Baseline	5.0±0.0	5.0±0.0	0.003 ##
	Week 12	6.3±1.3 **	4.8±0.9	
	Change	1.3±1.3	− 0.2±0.9	
Sensitivity to cold	Baseline	5.0±0.0	5.0±0.0	0.003 ##
	Week 12	6.1±1.3 **	5.0±0.7	
	Change	1.1±1.3	0.0±0.7	
Clothing size variation	Baseline	5.0±0.0	5.0±0.0	0.203
	Week 12	5.6±0.9 *	5.2±0.6	
	Change	0.6±0.9	0.2±0.6	
Dryness of skin	Baseline	5.0±0.0	5.0±0.0	< 0.001 ##
	Week 12	6.5±1.3 **	5.0±0.6	
	Change	1.5±1.3	0.0±0.6	
Fatigue	Baseline	5.0±0.0	5.0±0.0	0.027 #
	Week 12	5.9±0.9 **	5.2±0.6	
	Change	0.9±0.9	0.2±0.7	
Mood	Baseline	5.2±0.8	5.1±0.3	0.034 #
	Week 12	6.3±1.0 **	5.4±0.7 †	
	Change	1.1±1.1	0.3±0.5	
Rate of activity	Baseline	5.0±0.0	5.1±0.3	0.037 #
	Week 12	6.4±1.2 **	5.5±1.2	
	Change	1.4±1.2	0.5±1.1	
Sleeping quality	Baseline	5.0±0.0	5.2±0.6	0.002 ##
	Week 12	6.6±1.5 **	5.0±1.3	
	Change	1.6±1.5	− 0.2±1.1	
Feeling lighter	Baseline	5.0±0.0	5.3±0.6	0.001 ##
	Week 12	5.9±0.9 **	5.1±1.1	
	Change	0.9±0.9	− 0.2±0.7	

Scores are expressed as the mean ± SD.

† $p < 0.1$, * $p < 0.05$, ** $p < 0.01$ against baseline.

# $p < 0.05$, ## $p < 0.01$ between-group difference in change from baseline.

4 The data of the CUTTO group showed a significant difference in all nine items of “bowel movement”, “sensitivity to cold”, “clothing size variation”, “dryness of skin”, “fatigue”, “mood”, “rate of activity”, “sleeping quality” and “feeling lighter”, whereas in the Placebo group no item showed difference. Moreover, significant difference was detected between the two groups of the change in 9 items excluding “clothing size variation” after 12 weeks of ingestion.

3.5. Blood and Urine Test

Table 5 and 6 show the blood biochemical and urine parameters.

With respect to the blood test, a significant difference was observed in the changes of Total Protein and Potassium of the CUTTO group after 12 weeks of ingestion. However, since the difference was within range of the baseline and just a shade of difference, the investigator judged it as the range of physiological variation (or clinically safe).

Meanwhile no significant change was depicted in the urine test.

3.6. Adverse Event

No adverse effects were observed after the ingestion of food.

4. DISCUSSION

We conducted a randomized, placebo-controlled, double-blind study for examining the efficacy of a supplement containing apple polyphenol and oreanolic acid. The objective of this study is to verify the weight reduction

Table 5 Changes in biochemical blood test

Item	Unit	Std. Value	Time points	Values	
				CUTTO group (n=19)	Placebo group (n=18)
Total Protein	mg/dL	6.7-8.3	Baseline	7.0±0.4	7.3±0.3
			Week 12	7.2±0.4 *	7.1±0.3 *
			Change	0.1±0.2	−0.1±0.2 ##
Albumin	g/dl	3.8-5.2	Baseline	4.2±0.3	4.3±0.2
			Week 12	4.3±0.2	4.2±0.3
			Change	0.0±0.2	0.0±0.2
A/G	ratio	1.1-2.0	Baseline	1.51±0.24	1.46±0.17
			Week 12	1.49±0.22	1.48±0.19
			Change	−0.01±0.14	0.03±0.12
AST (GOT)	U/L	10-40	Baseline	20.1±8.3	16.8±3.7
			Week 12	20.7±9.4	17.1±4.0
			Change	0.6±2.6	0.3±2.7
ALT (GPT)	U/L	5-45	Baseline	17.2±11.0	13.5±5.0
			Week 12	18.5±12.4	13.6±5.2
			Change	1.4±5.3	0.1±4.5
LD (LDH)	U/L	120-240	Baseline	196.6±33.1	191.1±24.9
			Week 12	205.3±30.4 †	191.1±29.8
			Change	8.6±18.0	0.0±13.5
Total Bilirubin	U/L	0.2-1.2	Baseline	0.68±0.18	0.64±0.16
			Week 12	0.69±0.18	0.65±0.16
			Change	0.01±0.14	0.01±0.18
ALP	U/L	100-325	Baseline	195.1±72.7	178.4±52.3
			Week 12	197.6±67.1	174.4±49.0
			Change	2.5±19.6	−4.0±15.0
γ-GT (γ GTP)	U/L	30 and under	Baseline	24.7±17.9	18.8±6.2
			Week 12	31.1±37.1	20.3±9.4
			Change	6.4±25.1	1.5±6.1
CK (CPK)	mg/dL	40-150	Baseline	112.6±76.3	86.8±34.0
			Week 12	106.3±62.6	74.2±25.5 †
			Change	−6.3±55.4	−12.7±29.3
Urea Nitrogen	mg/dL	8-20	Baseline	12.6±3.0	12.0±2.9
			Week 12	12.6±3.6	11.1±3.0
			Change	0.0±3.5	−0.9±2.6
Creatinine	mEq/L	0.47-0.79	Baseline	0.66±0.12	0.68±0.08
			Week 12	0.64±0.10 †	0.68±0.07
			Change	−0.02±0.06	−0.01±0.05
Sodium	mEq/L	137-147	Baseline	141.2±1.7	142.6±2.2
			Week 12	141.3±1.8	141.7±2.1 *
			Change	0.1±2.2	−0.9±1.6
Chloride	mEq/L	98-108	Baseline	102.2±1.9	103.3±2.2
			Week 12	102.3±1.6	102.0±2.7 *
			Change	0.1±1.7	−1.3±2.6 ‡
Potassium	mg/dL	3.5-5.0	Baseline	3.9±0.2	4.0±0.3
			Week 12	4.0±0.2 **	4.0±0.3
			Change	0.2±0.2	−0.0±0.3 #
Calcium	mg/dL	8.4-10.4	Baseline	9.4±0.6	9.3±0.2
			Week 12	9.4±0.6	9.3±0.3
			Change	0.0±0.3	0.0±0.3
Inorganic Phosphorus	mg/dL	2.5-4.5	Baseline	3.7±0.4	3.8±0.7
			Week 12	3.6±0.5	3.8±0.6
			Change	−0.1±0.4	0.0±0.4
Total Cholesterol	mg/dL	120-219	Baseline	214.9±42.2	210.7±42.2
			Week 12	223.8±48.0 †	210.6±44.0
			Change	8.9±20.9	−0.1±29.5
Neutral Fat (TG)	mg/dL	30-149	Baseline	95.0±55.5	95.9±26.6
			Week 12	92.4±53.0	94.5±43.7
			Change	−2.6±28.6	−1.4±29.0
Glucose	mg/dL	70-109	Baseline	88.7±8.0	85.7±6.8
			Week 12	87.6±9.3	83.2±11.3
			Change	−1.2±6.6	−2.5±8.1

Values are expressed as the mean ± SD.
† $p < 0.1$, * $p < 0.05$, ** $p < 0.01$ against baseline.
‡ $p < 0.1$, # $p < 0.05$, ## $p < 0.01$ between-group differences in change from baseline.

Table 6　Transition of Urinalysis

Item	Unit	Std. Value	Time points	Values	
				CUTTO group (n = 19)	Placebo group (n = 18)
Specific Gravity	mg/dL	1.006-1.030	Baseline	1.021±0.008	1.023±0.008
			Week 12	1.019±0.008	1.021±0.007
			Change	−0.002±0.010	−0.002±0.009
pH	g/dL	5.0-7.5	Baseline	6.3±0.9	5.9±0.4
			Week 12	6.3±0.9	6.0±0.7
			Change	0.0±1.1	0.0±0.7

Values are expressed as the mean ± SD.

and waist circumference reduction effect of the supplement. As the primary outcome, the study showed the significant differences in visceral fat area, weight, BMI and waist circumference. In addition, several categories on the questionnaire conducted to search the subjective evaluation of the test product showed the significant differences, and this result indicates the improvement of QOL. As the secondary outcome, the observation of clinical findings such as medical interview, blood test and urine test revealed no abnormal changes had been triggered by the ingestion of the test product.

Main Findings

In this study we examined the changes of abdominal fat level, weight, BMI and waist circumference of the test group after 12-week ingestion of the test product, compared to the Placebo group. As for the abdominal fat level, the level of the visceral fat area of the test group in particular showed a significant reduction compared to the Placebo group, and the weight, BMI and waist circumference of the test group also showed some significant reduction compared to the Placebo. The level of subcutaneous fat area, on the other hand, both groups showed the similar tendency of reduction, therefore no significant difference was observed between them.

In addition, we conducted the questionnaire to search the subjective evaluation of the test product. The result of the test group showed the significant difference in all 9 categories, and among them in 8 categories (except the category "clothing size variation") the significant difference was detected between the two groups. In the Placebo group, on the other hand, no category showed the significant difference after 12-week ingestion period.

Among the categories of the questionnaire there is a negative-type question such as "fatigue", but overall the improvement of QOL by the ingestion of the test product was indicated.

The test product contains apple polyphenol and oreanolic acid. Apple polyphenol is a polyphenol whose principal ingredients are procyanidins[9], and other than procyanidins it also contains catechins and chlorogenic acid[10]. These polyphenols have a strong antioxidant effect, and there are a lot of reports that show the improvement of lipid metabolism[6)8)11)]. Also, the procyanidins, the principal ingredients of apple polyphenol, are reported to have high-functioning inhibition of a pancreatic lipase activity[12]. As the pancreatic lipase activity is inhibited, the fatty acid absorption from the intestine is suppressed. This contributes to the reduction of the amount of the fatty acid absorption, and eventually it possibly enables the inhibition of fat accumulation. In addition, it is reported that apple polyphenol decreases the transcription of genes involved in fatty acid synthesis and upregulate the β(beta)-oxidation of fat[13]. These facts suggest that apple polyphenol increases lipolysis and may be effective for the reduction of fat itself.

On the other hand, oreanolic acid is reported to have functionalities of downregulating the genes controlling fat synthesis and suppressing the production of fatty acid[7].

Therefore, it can be said that by ingesting this test product (CUTTO), both apple polyphenol and oreanolic acid contained in CUTTO functioned as the inhabitation and/or reduction of fat accumulation, and accomplished the weight reduction and waist circumference reduction of the subjects.

Secondary Findings

And in this study, it was observed that based upon clinical findings such as blood test and urine test, no abnormal change was triggered by ingestion of the test product. In the blood test, significant difference was observed in the changes of Total protein and Potassium of the CUTTO group after 12-week ingestion. On the other hand, no difference was observed with the urine test. In either case, since the difference was within a range of baseline and a shade of difference, the investigator judged it as the range of physiological variation (or clinically safe). Therefore, based upon the medical interview, blood test and urine test, we observed no harmful influence against biochemical and/or physiological matters of the subjects which seem to have causal relationship with CUTTO.

During the study, three subjects were withdrawn due to personal reasons and eight were revealed to fall under the exclusion criteria. Among eight, five subjects consumed meal in the morning just before getting CT

scan, whereas three subjects did not send adequate records. In either case, they were not related to the adverse event caused by the test product.

Therefore, these results indicated the safety of the ingestion of the test product (CUTTO) for the 12-week test period.

General Information

Obesity not only leads to the diseases such as "lifestyle diseases", but also causes deterioration of the external appearance and especially for women, it can trigger off the serious degradation of QOL. In addition, the fact that Japan is facing the aging society accelerates their pursuit of "anti-aging", which is basically aimed at "younger-looking" or "more-beautiful looking". Apple polyphenol contained in the test product is regarded as a highly-safe ingredient and is registered as GRAS (generally recognized as safe), one of the safety standards of food in the US. Oreanolic acid, on the other hand, is the ingredient can be seen widely throughout nature, such as in rape or olive leaves. As illustrated so far, these ingredients have an antioxidant effect in addition to an improvement of lipid metabolism, therefore they are useful in preventing allergies or reducing oxidant stress[14)15)]. For these reasons, it is considered that the combination of the improvement of daily eating and exercise habits and the ingestion of this test product can prevent obesity, improve the external appearance and keep our body in good health.

Limitations

For this study we used the test product (supplement) containing apple polyphenol and oreanolic acid, and each ingredient reportedly own the functionality of improving lipid metabolism[7)11)~13)]. Therefore the outcome of this study should be strongly related to these findings. However, the functional mechanism of these reports is mainly based upon the in-vitro settings or the research using rats, and the behavior in the human body is a matter of speculation. In addition, we have not yet discovered the mutual influences between apple polyphenol and oreanolic acid. Furthermore, in this study we did not find any significant differences in subcutaneous fat area, but could not find whether these ingredients were truly not functional for that area, or the test period was too short to have certain result and the longer test period was required to reveal some significant differences. Therefore, these points should be further scrutinized in the future.

Conclusion

In conclusion, we found out that the ingestion of the supplement (CUTTO) containing apple polyphenol and oreanolic acid for 12 weeks contributed to the weight reduction and waist circumference reduction. In addition, no safety-related matter occurred during 12-week test period.

CONFLICT OF INTEREST

Hirofumi Wada and Emiko Wada are directors of GRACEAS Corporation. All remaining authors have declared no conflicts of interest.

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