August 2022

Japanese Functional Food Update Vol.1

Foods with Function Claims notifications as a final product: Reducing body fat

When planning a clinical trial for the purpose of submitting a notification of Foods with Function Claims (FFC) as a final product, many applicants are troubled by the design of the study. Major issues concern subjects, duration of interventions, and outcomes. In this Japanese Functional Food Update, we will introduce the results of a survey that focused on 29 FFC notifications that were accepted for labeling the health claim, “reducing body fat”, by using the results of clinical trials where the final product was studied (Table 1).

First, clinical trial designs that were used to obtain scientific evidence to sustain this health claim can be broadly divided into two types. Taking up 28 among 29 studies we reviewed, the first type falls under the category of evaluating the reduction of body fat after continuous consumption of the test food. On the other hand, only 1 study evaluated the effect of consumption of the test food on fat burning during exercise. Here, the former type of study will be focused in this article.

Various eligibility criteria were established for each study, and the intervention period was set between 8 and 24 weeks, where the majority was set at 12 weeks (Figure 1). Visceral fat

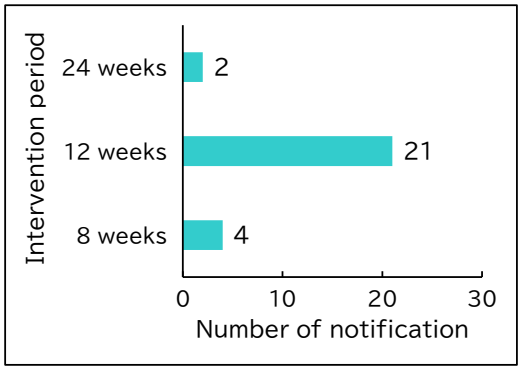

Figure 1. Different intervention periods of clinical trials aiming for notification submission

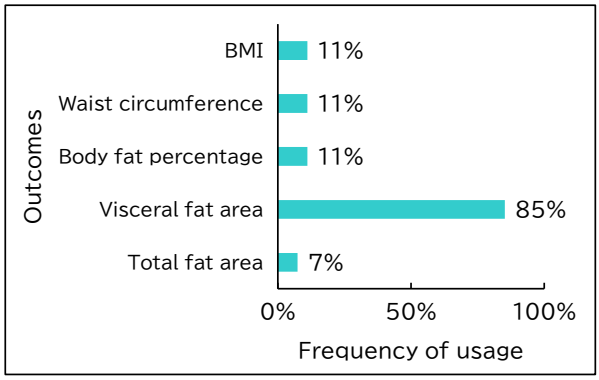

Figure 2. Frequency of outcomes used in functionality evaluation

area, total fat area, body mass index (BMI), body fat percentage and waist circumference were used individually or in combination to evaluate the said functionality, and in particularly visceral

ORTHO MEDICO
Contact Information
ORTHOMEDICO inc., Planning Department
2F Sumitomo Fudosan Korakuen Bldg.,
1-4-1, Koishikawa, Bunkyo-ku, Tokyo, 112-0002 Japan
Phone: +81-3-3818-0610
E-mail: planning-department@orthomedico.jp

fat area was the most commonly used (Figure 2).

As mentioned above, since visceral fat area is frequently used as an endpoint in many of these clinical trials, visceral fat area is a useful outcome measure that can be considered when designing such study in general. However, when we investigated the academic articles that were used as evidences of functionality in each notification, about half of the studies were found to have not specify their primary outcomes (Figure 3). In addition, there were cases

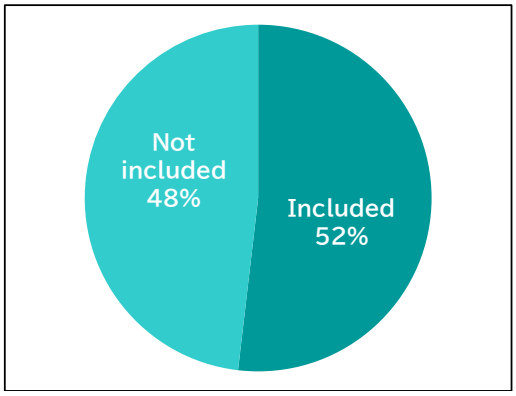

Figure 3. Percentages of clinical trials with or without a primary outcome

where although no significant difference was found for the primary outcome, the results of secondary outcome were used as evidences to support the health claim. With the release of the guidelines for post-notification regulation on FFC, it is expected that products with function claims that were based on such quality of evidence will likely be pointed out due to inadequacy of evidence. In some cases, even re-testing of the functionality by clinical trial may be required. In order to minimize such kind of risk, a thoroughly designed protocol should be written and high-quality clinical trials with evidence of little to no room of criticism should be sought after.

We, ORTHOMEDICO, strive to meet the wide range of needs of our clients to support them via trial proposal and conduction of high-quality clinical trials, systematic reviews and being an agent for notification of FFC to the Consumer Affairs Agency (CAA) of Japan, as well as related post-acceptance work and dealing with responses to the CAA and consumer organizations. Please feel free to contact us to know more.

We will continue to provide you with information about the Japanese functional food regulation and market. Looking forward to working with you in the future.

Contact Information
ORTHOMEDICO inc., Planning Department
2F Sumitomo Fudosan Korakuen Bldg.,
1-4-1, Koishikawa, Bunkyo-ku, Tokyo, 112-0002 Japan
Phone: +81-3-3818-0610
E-mail: planning-department@orthomedico.jp

Table 1. List of published clinical trials that studied final product and showed scientific evidence for “fat reduction” function

Notification No. of FFC	Publication	Functional ingredient	Intervention period	Primary outcome	Outcomes used in functionality evaluation
A1	Ono T, et al (2010)[1]	Lactoferrin	8 weeks	Unknown	Visceral fat area
A9 A111 A242 C300 C337 C338 C362	Kamiya T, et al (2012)[2]	Isoflavones from pueraria flower extract	12 weeks	Unknown	Visceral fat area
A16	Nagatomo A, et al (2015)[3]	Tiliroside from rosehip extract	12 weeks	Abdominal fat area, body fat percentage	Total fat area
A46	Takano Y, et al (2013)[4]	*Lactobacillus gasseri* SBT2055	12 weeks	Unknown	Visceral fat area
A226	Akazome Y, et al (2005)[5]	Polyphenols derived from apples	12 weeks	Body weight, body fat, BMI, CT scan (Abdominal fat area)	Visceral fat area
B20 B413	Nakamura F, et al (2016)[6]	*Lactobacillus amylovorus* CP1563	12 weeks	Unknown	Body fat percentage, visceral fat area
B330	Isii Y, et al (2016)[7]	*Bifidobacterium longum* BB536, *Bifidobacterium breve* B-3 and N-acetyl glucosamine	24 weeks	Visceral fat area, BMI	BMI
B587 E463	Najima M, et al (2016)[8]	Procyanidin B2 derived from apples, oleanolic acid	12 weeks	Visceral fat area, subcutaneous fat area	BMI, waist circumference
C297	Takano A, et al (2017)[9]	Isoflavones from pueraria flower extract	12 weeks	Visceral fat area, liver function	Abdominal visceral fat area
C356 D421	Morimoto-Kobayashi Y, et al (2016)[10]	Matured hop bitter acids	12 weeks	Abdominal fat area	Visceral fat area
D23	Ono T, et al (2018)[11]	Lactoferrin	8 weeks	Unknown	Visceral fat area
D272	Seki S, et al (2017)[12]	salacinol, dietary fiber, epigallocatechin gallate and mono-glucosylrutin	8 weeks	Visceral fat area	Visceral fat area
D278	Fujiwara S, et al (2018)[13]	10-HOA derived from *Lactobacillus amylovorus* CP1563	24 weeks	Abdominal fat area	Visceral fat area
D379	Yosihno S, et al (2018)[14]	Polymethoxyflavone from *Kaempferia parviflora* extract	12 weeks	Visceral fat area	Abdominal fat area, blood triglyceride
D401	Tanaka K, et al (2018)[15]	Polymerized polyphenols and catechin gallate derived from fermented tea leaves mixture containing loquat leaves (As EGCg)	8 weeks	Unknown	Visceral fat area
D414	Minami J, et al (2018)[16]	*Bifidobacterium breve* B-3	12 weeks	Visceral fat area	Visceral fat area
D419	Ueda K, et al (2018)[17]	Mixture of alanine, arginine and phenylalanine	12 weeks	Abdominal fat area	Total fat area
D458	Hama R, et al (2018)[18]	Gallic acid from *Terminalia bellirica*	12 weeks	Abdominal visceral fat area	Visceral fat area
E547	Yamaguchi Y, et al (2019)[19]	Psicose	Single intake	Area under the curve (AUC) for fat oxidation	Fat oxidation

Reference

1. Ono T, et al. Potent anti-obesity effect of enteric-coated lactoferrin: decrease in visceral fat accumulation in Japanese men and women with abdominal obesity after 8-week administration of enteric-coated lactoferrin tablets. Br. J. Nutr.2010; 104: 1688-95.

Contact Information
ORTHOMEDICO inc., Planning Department
2F Sumitomo Fudosan Korakuen Bldg.,
1-4-1, Koishikawa, Bunkyo-ku, Tokyo, 112-0002 Japan
Phone: +81-3-3818-0610
E-mail: planning-department@orthomedico.jp

2. Kamiya T, et al. Consumption of pueraria flower extract reduces body mass index via a decrease in the visceral fat area in obese human. Biosci. Biotechnol. Biochem. 2012; 76(8): 1511-17.
3. Nagatomo A, et al. Daily intake of rosehip extract decreases abdominal visceral fat in preobese subjects: a randomized, double-blind, placebo-controlled clinical trial. Diabetes Metab. Syndr. Obes.: Targets Ther. 2015; 8, 147-56.
4. Takano Y, et al. Visceral Fat-reducing Effect of Fermented Milk Containing the Probiotic Lactobacillus gasseri SBT2055. Jpn. Pharmacol. Ther. 2013; 41(9): 895-903.
5. Akazome Y, et al. Evaluation of Safety of Excessive Intake and Efficacy of Long Term Intake of Beverage Containing Polyphenols Derived from Apples. Jpn. Pharmacol. Ther. 2005; 33(9): 893-911.
6. Nakamura F, et al. Effect of fragmented Lactobacillus amylovorus CP1563 on lipid metabolism in overweight and mildly obese individuals: a randomized controlled trial. Microb. Ecol. Health. Dis. 2016; 27: 30312.
7. Isii Y, et al. Clinical trial to investigate the effect of Bifidobacterium breve B-3, Bifidobacterium longum BB536 and N-acetyl glucosamine on adiposity in adults with obese tendencies. A randomized, double-blind, placebo-controlled, parallel-group clinical trial. JASSO. 2016; 22(2): 133-44.
8. Najima M, et al. Visceral Fat-Reducing Effect of Supplement Containing Apple Polyphenol and Oleanolic Acid in Healthy Japanese -A Randomized, Double-Blind, Placebo-Controlled Study-. Medical Consultation & New Remedies. 2016; 53(3): 237-44.
9. Takano A, et al. A Subgroup Analysis Study on the Effect of Food Containing Pueraria Flower Extract on Visceral Fat in Non-Obese Subjects -A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study-. Pharmacometrics. 2017; 93(1/2): 1-6.
10. Morimoto-Kobayashi Y, et al. Matured hop extract reduces body fat in healthy overweight humans: a randomized, double-blind, placebo-controlled parallel group study. Nutrition Journal. 2016; 15: 25.
11. Ono T, et al. Anti-Obesity Effect of Lactoferrin; Subgroup Analysis Excluding Subjects with Obese and/or Hyper-LDL Cholesterolemia. Immun., endoc. & metab. agents in med. chem. 2018; 18(1): 105-9.
12. Seki S, et al. Effects of Composite Supplements on Obesity -A Randomized, Double-blind, Placebo-controlled, Parallel-group Study-. Jpn. Pharmacol. Ther. 2017; 45(6):

Contact Information
ORTHOMEDICO inc., Planning Department
2F Sumitomo Fudosan Korakuen Bldg.,
1-4-1, Koishikawa, Bunkyo-ku, Tokyo, 112-0002 Japan
Phone: +81-3-3818-0610
E-mail: planning-department@orthomedico.jp

957-66.
13. Fujiwara S, et al. Regulation of Adiposity by Para-metabobiotic Lactobacillus amylovorus CP1563 in Healthy Normal and Pre-obese Adult Individuals -A Rondomized Controlled Trial-. Jpn. Pharmacol. Ther. 2018; 46(9): 1601-12.
14. Yosihno S, et al. Daily intake of Kaempferia parviflora extract decreases abdominal fat in overweight and preobese subjects: a randomized, double-blind, placebo-controlled clinical study. Diabetes Metab. Syndr. Obes.: Targets Ther. 2018; 11: 447-58.
15. Tanaka K, et al. Effects of Fermented Tea Leaves Made by Tea-Rolling Processing of Loquat Leaves and Third Crop Green Tea Leaves on Visceral Fat -A Randomized, Double-blind, Placebo-controlled, Parallel-group Comparative Study-. Jpn. Pharmacol. Ther. 2018; 46(4): 539-47.
16. Minami J, et al. Effects of Bifidobacterium breve B-3 on body fat reductions in pre-obese adults: a randomized, double-blind, placebo-controlled trial. Biosci. Microbiota. Food. Health. 2018; 37(3): 67-75.
17. Ueda K, et al. Randomized trial of amino acid mixture combined with physical activity promotion for abdominal fat reduction in overweight adults. Diabetes Metab. Syndr. Obes.: Targets Ther. 2018; 11: 23-33.
18. Hama R, et al. Effect of Food Containing TerminαZia bellirica Extract on Visceral Fat -A Randomized, Double-blinded, Placebo controlled, Parallel group Study-. Jpn. Pharmacol. Ther. 2018; 46(12): 2091-8.
19. Yamaguchi Y, et al. Effects of a Single Intake of Psicose (Allulose) on fat Oxidation during exercise-a randomized, double-blind, placebo-controlled, cross-over-trial-. Jpn. Pharmacol. Ther. 2019; 47(3): 517-25

Contact Information
ORTHOMEDICO inc., Planning Department
2F Sumitomo Fudosan Korakuen Bldg.,
1-4-1, Koishikawa, Bunkyo-ku, Tokyo, 112-0002 Japan
Phone: +81-3-3818-0610
E-mail: planning-department@orthomedico.jp