

Attachment (V)-4 [For files to be attached]

Explanatory material on the proposed function claims (systematic literature review)

Title: Systematic Literature Review on Reduction in Body Fat (Visceral Fat) by Apple-Derived Procyanidin Contained in “XXXX (Product Name)”

Product name: XXXX

Name of functional substance: Apple-derived procyanidin

Proposed function claim:

This product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat).

Date of preparation: MM DD, 20YY

Reported by: xxxxx

Abstract

Objective

The systematic literature review was conducted to verify whether continuous consumption of apple-derived procyanidins would reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who would be within the scope of subjects in studies of Foods for Specified Health Uses (FOSHU).

Methodology

Three employees of the Japan Health and Nutrition Food Association (hereinafter, "JHNFA") searched literatures using 3 databases (PubMed, JDreamIII, Ichushi-Web) based on the research question "Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?" Literatures identified by the search were screened based on the inclusion/exclusion criteria and then evaluated for their quality, and those which met a certain level of quality (QL3 or higher) were selected. Then, qualitative literature review was performed using clinical test items related to body fat (i.e., visceral fat area) in included literatures as outcome measures.

The evidence was comprehensively evaluated for 5 grades (A to E) on overall scientific evidence level, level of “research type, quality, and quantity,” and consistency level by the Function Claim Assessment Committee for Agricultural, Forestry and Fish Products, the National Agriculture and Food Research Organization (NARO), which consists of 6 academic experts.

Results

Two literatures were selected as the evidence consistent with the research question. These 2 literatures covered evaluation of body fat (visceral fat) in Japanese adult men and women with an obesity level near the upper limit of normal to grade 1 and without disease, who consumed 110 mg of apple-derived procyanidin per day for 12 weeks. Both literatures demonstrated a significant reduction of body fat (visceral fat) compared to placebo; therefore, 110 mg was selected as the recommended daily dose for the product.

Although further evidence is required, the consumption of the functional substance, apple-derived procyanidin, is suggested to reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU.

According to the assessments of the NARO Function Claim Assessment Committee, the overall scientific evidence level was B, the level of “research type, quality, and quantity” was C, and the consistency level was B.

Conclusion

Consumption of Y of XXXX (product name) per day (110 mg of apple-derived procyanidin) is considered to reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU.

Introduction

Rationale, Objective

Apple (*Malus pumila*) is a plant in Rosaceae family, and has its origin in the area from the vicinity of the Caucasus between the Caspian Sea and the Black Sea to the vicinity of the Tian Shan Mountains, Xinjiang, China. It is a fruit widely cultivated around the world, and is reported to contain approximately 50 types of polyphenols. Well-known polyphenols include chlorogenic acid, catechin, procyanidin, cyanidin glycosides, phloretin glycosides, and quercetin glycosides. Catechin and its polymer, procyanidins, are the most abundant polyphenols in apples, accounting for about 40% to 65%^{Reference 1)}.

Apple polyphenols including apple-derived procyanidin are reported to affect various human physiological functions, such as to inhibit increase of triglycerides^{Reference 2)}, lower cholesterol^{Reference 3,4)}, inhibit fatigue accumulation^{Reference 5)} and reduce visceral fat^{Reference 3,6)}.

However, there has been no systematic review or meta-analysis reported on the effect of apple-derived procyanidin on body fat (visceral fat).

Thus, for the people without disease and those who are within the scope of subjects in studies of FOSHU, this systematic literature review was conducted to verify how the consumption of apple-derived procyanidins affects the body fat (visceral fat) in such population based on the research question "Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?"

Methodology

Protocol and Registration

According to the protocol for systematic literature review by the Consumer Affairs Agency's "Model Project for the Evaluation of Food Products with Function Claims" held in FY2011, literature search, literature screening, quality assessments, data extraction, and systematic literature review preparation were performed by 3 JHNFA employees. The strength of evidence was evaluated by the Function Claim Assessment Committee of NARO, which consists of 6 academic experts. The review protocol was not registered.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria for the eligibility of studies were set as follows according to the PICOS described below.

- Participants (P) : People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
- Intervention (I) : Continuous consumption of foods containing apple-derived procyanidin
- Comparison (C) : No consumption of apple or consumption of a placebo (food not containing apple-derived procyanidin)
- Outcome (O) : Body fat (visceral fat area)
- Study design (S) : Randomized controlled trial (RCT)

[Inclusion criteria]

- ✓ A randomized controlled trial.
- ✓ A placebo group (no intake group) is established.
- ✓ The amount of apple-derived procyanidin is recorded.
- ✓ A study conducted in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
- ✓ Literature published in a peer-reviewed journal and published in English or Japanese.
- ✓ The amount of body fat (visceral fat area) is assessed by CT or impedance analysis (a device correlated with CT measurement), which are the methods of body fat evaluation specified in the "Cautions on Preparation of Application Forms for FOSHU".

[Exclusion criteria]

- ✓ Studies involving confounding factors that affect body fat (visceral fat area) other than apple-derived procyanidin.
- ✓ literatures on *in vitro* or *in vivo* studies.
- ✓ Literatures that is not an original article.
- ✓ Body fat (visceral fat area) is not evaluated.

Attachment (V)-4 [For files to be attached]

Source

Three databases were used as sources: PubMed (date of final search: August 25, 2017), JDreamIII (date of final search: August 28, 2017), and Ichushi-Web (date of final search: August 25, 2017). We searched for studies published between the inception of each database (the date it was established or installed) and the last date of search. Unreported studies were searched for by using UMIN-CTR Study Information (last date of search: September 1, 2017). No hand searches were performed.

Search

The search formulas used in each database were as follows.

The results were as described in Attachment (V)-5. For UMIN-CTR Study Information, "apple procyanidin" and "apple polyphenol" were entered as free text words; the search results are shown in Attachment (V)-9.

[Database search formula]

Database	PubMed
#	Search formula
1	apple
2	procyanidin OR polyphenols
3	#1 AND #2
4	"intra-abdominal fat" OR "visceral fat" OR "body fat"
5	#3 AND #4

Database	JDreamIII (JSTPlus+JST7580+JMEDPlus)
#	Search formula
1	"Apple"/AL OR "Malus pumila"/AL OR "Malus domestica"/AL OR "Malus pumila"/AL OR "Malus x domestica"/AL
2	"Polyvalent phenol"/AL OR "Polyphenol"/AL OR "Polyphenolic compounds"/AL OR "Polyphenols"/AL OR "Polyvalent phenolic compounds"/AL OR "Polyvalent phenols"/AL OR "Polyvalent phenolic compounds"/AL OR "Polyfunctional phenol"/AL OR "Polyfunctional phenol"/AL
3	"Procyanidin"/AL
4	#2 OR #3
5	#1 AND #4
6	Body fat OR Visceral fat
7	#5 AND #6
8	#7 AND (a1/DT)

Attachment (V)-4 [For files to be attached]

Database	Ichushi-Web
#	Search formula
1	Malus/TH or Apple/AL
2	Procyanidin/TH or Procyanidin/AL
3	Polyphenols/TH or Polyphenol/AL
4	#2 or #3
5	#1 and #4
6	Body fat/AL or (Intraperitoneal fat/TH or Visceral fat/AL)
7	#5 and #6

Selection of study

The literatures identified in each database were reviewed by the 3 JHNFA employees and sorted to those to be included and those to be excluded based on the inclusion and exclusion criteria.

The included literatures are shown in Attachment (V)-7, and those excluded are shown in Attachment (V)-8.

The primary screening was performed on the title and the abstract of the studies to determine whether it would be applicable.

Literatures that could not be clearly identified to be excluded went through the secondary screening.

For the secondary screening, the whole text was obtained and carefully reviewed, and then decision was made to either include or exclude it. When excluded, the reason for exclusion was documented.

Data collection process

Data were collected from included literatures by the 3 JHNFA employees in accordance with Attachment (V)-7 and (V)-11a-2.

Data items

Attachment (V)-7 presents author, publication, title, study design, PICO, setting, subject characteristics, intervention, control, analysis method, primary outcome, secondary outcome, adverse events, the presence/absence of peer review, and COI information.

Attachment (V)-11a-2 shows the results of each study in included literatures.

Bias risk of individual studies

Each included literature was evaluated for its quality level based on the "Literature Quality" Scoring Sheet for Human Intervention Studies (prepared by JHNFA), and evaluated by 4 grades, QL1 (high quality) to QL4 (very low quality); those rated as QL4 were excluded. The definitions of QL1 to QL4 are as follows.

QL1: High quality (appropriate from all aspects of assessment)

QL2: Moderate quality (generally appropriate although not sufficient from some aspects of assessment)

QL3: Low quality (inappropriate from many aspects)

QL4: Very low quality (irrelevant for overall evaluation)

Attachment (V)-4 [For files to be attached]

In addition, Attachment (V)-11a-1 was used to evaluate the bias risk and indirectness of the outcome, body fat (visceral fat area).

Each parameter was evaluated on a 3-point scale, High (-2), Moderate/Suspected (-1), and Low (0) according to the evaluation method described in the "Guidelines for Notification of Foods with Function Claims". The summary was evaluated on a 3-point scale, High (-2), Moderate (-1), and Low (0).

[Evaluation of bias risk]

- ✓ Selection bias (randomization, concealment of allocation)
- ✓ Blinding bias (participants, outcome assessors)
- ✓ Attrition bias (ITT/FAS/PPS, incomplete outcome data)
- ✓ Selective outcome reporting
- ✓ Other biases
- ✓ Summary

[Evaluation of indirectness]

- ✓ Subjects
- ✓ Intervention
- ✓ Control
- ✓ Outcome
- ✓ Summary

Summary scales

Summary scales were not set because this systematic literature review was qualitative.

Consolidation of results

Results were not consolidated because this systematic literature review was qualitative.

Bias risk of all studies

Attachments (V)-13a and (V)-14 were used to evaluate the bias risk, indirectness, inaccuracy, inconsistency, and other (e.g., publication bias).

Additional analyses

Additional analyses were not performed because this systematic literature review was qualitative.

Overall evaluation of the systematic literature review

Included literature were sorted to “effective”, “indeterminable”, “no effect”, and “unfavorable effect”, and further sorted and listed by RCT/Non-RCT and QL1 to QL3, and the number of studies in each category was counted as shown in Attachment (V)-16 (Summary of overall evaluation). “Effective”, “indeterminable”, “no effect”, and “unfavorable effect” were defined as follows:

- Effective : Decreased body fat (outcome measure: visceral fat area) with a <5% significance probability for the difference between the intervention group and control group and/or between the baseline and after intervention.
- No effect : Decreased body fat (outcome measure: visceral fat area) with a $\geq 10\%$ significance probabilities for both the differences between the intervention group and control group and between the baseline and after intervention.
- Indeterminable : Not necessarily determined as “no effect,” or decreased body fat (outcome measure: visceral fat area) with a $\geq 5\%$ and $< 10\%$ significance probability for the difference between the intervention group and control group and/or between the baseline and after intervention.
- Unfavorable effect : Increased body fat (outcome measure: visceral fat area) with a <5% significance probability for the difference between the intervention group and control group and/or between the baseline and after intervention.

The overall assessments were performed by the NARO Function Claim Assessment Committee about [overall scientific evidence level], [level of “research type, quality, and quantity”], and [consistency level], with 5 grades (A to E). The definitions of grades A to E were as follows.

[Overall scientific evidence level]

- A: The function is clearly and sufficiently supported by evidence (High).
- B: The function is supported by favorable evidence (Moderate).
- C: The function is supported by suggestive evidence (Low).
- D: The function is not sufficiently supported by evidence.
- E: The function is ruled out by unfavorable evidence.

[Level of “research type, quality, and quantity”]

- A: 5 or more RCT literatures with high-quality supporting the effectiveness
- B: 3 or more RCT literatures with moderate or higher quality supporting the effectiveness (Other than RCTs, interventional studies that support the effectiveness will also be considered if available)
- C: 1 or more RCT literatures supporting the effectiveness (Other than RCTs, interventional studies that support the effectiveness will also be considered if available)
- D: Literature available on intervention studies supporting the effectiveness
- E: Literature available only on studies ruling out the effectiveness

[Consistency level]

- A: Almost all results consistently support the effectiveness.
- B: The results supporting the effectiveness far outnumber the results ruling out the effectiveness.
- C: The results supporting the effectiveness outnumber the results ruling out the effectiveness.
- D: Results are inconsistent.
- E: Almost all results consistently rule out the effectiveness.

Results

Selection of study

The literature search was performed in each database and selected 18 literatures in total for the primary screening (of which, 6 were overlapping) including 4 in PubMed, 8 in JDreamIII, and 6 in Ichushi-Web.

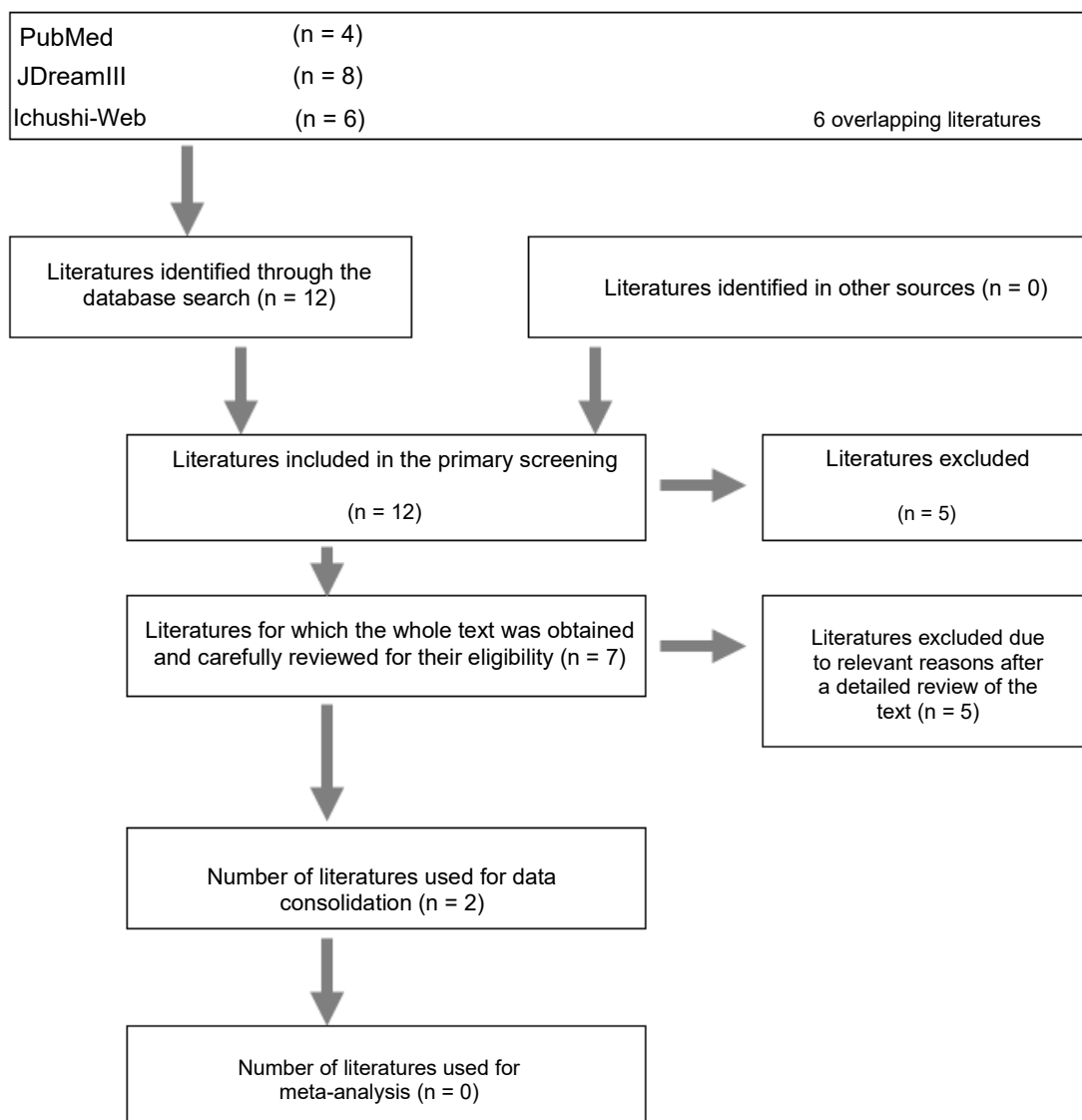
After the primary screening, 5 were excluded, and the remaining 7 were subjected to the secondary screening. As a result, 5 literatures were excluded, and 2 were included in the end.

The flow chart for the literature search is as shown below and in Attachment (V)-6.

The included literatures are shown in Attachment (V)-7, and those excluded are shown in Attachment (V)-8.

Unreported studies were searched for by using UMIN-CTR Study Information; through which, 1 study was found but had a different outcome definition. Therefore, it was judged that there was no effect on this systematic literature review. The outline is presented in Attachment (V)-9.

[Literature Search Flow Chart]



Attachment (V)-4 [For files to be attached]

Characteristics of study

Attachment (V)-7 shows the characteristics of the 2 included literatures.

The 2 included literatures covered studies in adult Japanese men and women with an obesity level near the upper limit of normal to grade 1 without disease. Furthermore, the both studies were RCTs to evaluate body fat (visceral fat area) as an endpoint. The quality of these articles were as follows: Literature No. 1 was QL2, and Literature No. 2 was QL1. The numbers of studies are summarized as follows.

		Effective		Indeterminable		No effect		Unfavorable effect	
Human interventional study	Total	2 literatures		0 literature		0 literature		0 literature	
		RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT
Total: 2 literatures		QL1: 1 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature
		QL2: 1 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature
		QL3: 0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature

Bias risk within each study

Attachment (V)-11a-1 presents the results of the bias risk and indirectness assessments. The details are as follows.

[Evaluation of bias risk]

The selection bias (randomization) was Low (0) for both studies; neither had an issue.

The selection bias (concealment of allocation) was Moderate/Suspected (-1) for both studies because neither study mentioned it.

The blinding bias (participants, outcome assessors) was Low (0) for both studies; neither had an issue.

The attrition bias (ITT, FAS, PPS) was High (-2) for both studies because the analysis sets were PPS.

The blinding bias (incomplete outcome data) was Low (0) for both studies; neither had an issue.

Selective outcome reporting was rated as Low (0) because it was not confirmed in either study.

Other biases were assessed as Moderate/Suspected (-1) because the authors had conflicts of interest in both studies.

Based on the above results, the overall bias risk was rated as Moderate (-1) for both studies.

[Evaluation of indirectness]

It was rated as Low (0) for both literatures because none of the criteria had an issue in either studies.

Based on the above results, the overall indirectness was rated as Low (0) for both included literatures.

Results of individual studies

In both of the included literature, CT was used as a method to evaluate body fat (visceral fat area) and demonstrated that body fat decreased by the consumption of apple-derived procyanidin, the functional substance. Neither study showed the absence of such effect.

The both included literatures covered studies using apple polyphenol containing apple-derived procyanidin as an investigational food. In an *in vitro* study using porcine pancreatic lipase, the IC₅₀ of apple polyphenols for lipase inhibition was 5.6 µg/mL. Moreover, apple polyphenols were separated to apple-derived procyanidin and other polyphenols, and the lipase inhibitory activity was measured; the IC₅₀ was 1.4 µg/mL for apple-derived procyanidin and 115.9 µg/mL for other types of apple polyphenols. Thus, apple-derived procyanidins that showed a stronger lipase-inhibiting activity ^{Reference 2)} was judged to be the primary factor. Based on this, we concluded that the lipase inhibitory effect of apple-derived procyanidin causes fat to be excreted as feces without being degraded, resulting in the inhibition of fat accumulation and the reduction of body fat (visceral fat area). The outcome measures used in the literature and their results are shown in Attachment (V)-11a-2.

[Included Literature No. 1] Literature quality assessments: QL2; RCT study (effective)

A randomized, parallel-group, double-blind, placebo-controlled study in 94 men and women aged 20 to 65 years with grade 1 obesity (BMI ≥ 25 and < 30) (analysis population: 87 subjects). Subjects were randomized to a placebo group (n = 47) or an apple-derived procyanidin 110 mg/day group (n = 47), and consumed the investigational food (in the form of beverage) for 12 weeks.

The analysis population was 43 subjects in the placebo group and 44 in the apple-derived procyanidin 110 mg/day group; among whom, the apple-derived procyanidin 110 mg/day group was the only group in which the body fat (visceral fat area) at Week 8 and Week 12 of consumption significantly decreased from the baseline (before consumption), and they were also significantly lower than those in the placebo group.

[Included Literature No. 2] Literature quality assessments: QL1; RCT study (effective)

A randomized, parallel-group, double-blind, placebo-controlled study in 148 men and women aged ≥ 20 with obesity level near-upper limit of normal to grade 1 (BMI ≥ 23 and < 30) (analysis population: 134 subjects). Subjects were randomized to a placebo group, an apple-derived procyanidin 55 mg/day group, or an apple-derived procyanidin 110 mg/day group, and consumed the investigational food (in the form of beverage) for 12 weeks. The analysis population was 44 subjects in the placebo group, 45 in the apple-derived procyanidin 55 mg/day group, and 45 in the apple-derived procyanidin 110 mg/day group; among whom, the apple-derived procyanidin 110 mg/day group was the only group in which the body fat (visceral fat area) at Week 12 of consumption significantly decreased from the baseline (before consumption), and was also significantly lower than those in the placebo group.

Consolidation of results

Results were not consolidated because this systematic literature review was qualitative.

Bias risk of all studies

Attachments (V)-13a and (V)-14 present the results of assessments on bias risk, indirectness, inaccuracy, inconsistency, and other (e.g., publication bias).

On bias risk, the “summary” assessment result was Moderate (-1) for both of the selected studies, and therefore, the bias risk was rated as Moderate/Suspected (-1) for overall evidence.

With regards to indirectness, the Summary assessment result was Low (0) for both of the included literatures; therefore, the indirectness was rated as Low (0) for overall evidence.

Inaccuracy was rated as Low (0) because no particular issues were found.

Inconsistency was rated as Low (0) because both showed consistent results as effective.

Other (publication bias) was rated as Moderate/Suspected (-1) because there were only 2 studies selected and a possibility of publication bias could not be ruled out.

Additional analyses

Additional analyses were not performed because this systematic literature review was qualitative.

Overall evaluation of the systematic literature review

Assessments by the NARO Function Claim Assessment Committee were as follows.

Overall scientific evidence level (strength of evidence)	: B
Level of “research type, quality, and quantity”	: C
Consistency level	: B

Discussion

Summary of evidence

This systematic literature review was performed to evaluate the effectiveness of apple-derived polyphenols in reducing body fat (visceral fat); the endpoint was body fat (visceral fat) measured on CT or impedance analysis (a device correlated with CT measurement), which are the methods of body fat evaluation specified in the "Cautions on Preparation of Application Forms for FOSHU".

Two studies that were consistent with the research question were selected. The 2 included literatures covered studies in adult Japanese men and women with an obesity level near the upper limit of normal to grade 1 without disease. In both included literatures, the endpoint was body fat measured on CT, and the investigational food was demonstrated to be effective.

However, both literatures covered studies using apple polyphenol that contained apple-derived procyanidin as the investigational food. In an *in vitro* study using porcine pancreatic lipase, the lipase-inhibiting activity was compared between apple polyphenols and apple-derived procyanidin; the IC₅₀ of apple polyphenols was 5.6 µg/mL. Apple polyphenols were separated into apple-derived procyanidin and other polyphenols, and their inhibitory activities were measured; according to the results, the IC₅₀ was 1.4 µg/mL for apple-derived procyanidin and 115.9 µg/mL for other types of apple polyphenols. Thus, apple-derived procyanidins that showed a stronger inhibitory activity^{Reference 2)} was judged to be the primary factor.

Based on this, we concluded that the lipase inhibitory effect of apple-derived procyanidin causes fat to be excreted as feces without being degraded, resulting in the inhibition of fat accumulation and the reduction of body fat (visceral fat area).

The results of the systematic literature review suggested that consumption of apple-derived procyanidins was effective in reducing body fat.

Limitation

[Bias risks]

For overall evidence, the indirectness, inaccuracy, and inconsistency seemed to be low, but the risk of bias and other (publication bias) could not be ruled out.

However, the results of both studies were favorable and consistent and do not deny the proposed function claim, although the evidence needs to be further reinforced.

[Description of food]

The food forms in the included literatures were beverages containing powder made from apples, which was different from the form of the proposed product (apple fruit).

However, according to another study (which was excluded from this review because it contained data in patients with diseases), powder-capsules made from apples and cloudy juice squeezed from apples were also similarly effective in relation to body fat^{References 3,7)}, suggesting the food form does not have a major affect on digestion and absorption of the functional substance. Therefore, there should be no issues in extrapolating this evidence to the proposed product. The 2 included literatures presented the content of apple polyphenol in the investigational food; 600 mg of apple polyphenol is said to be equivalent to 110 mg of apple-derived procyanidin.

[Subjects]

Subjects in the 2 literatures were both adult Japanese men and women with obesity levels near the upper limit of normal to grade 1 with no disease; thus, there should no problems extrapolating the data to the Japanese population.

Based on the above, the proposed function claim should be applicable to the consumers of the proposed product.

[Daily standard intake]

Both included literatures demonstrated 12-week consumption of apple-derived procyanidin 110 mg per day as an effective diet in reducing body fat; accordingly, the recommended intake of apple-derived procyanidin should be ≥ 110 mg/day for ≥ 12 weeks.

Because the proposed product contains 110 mg of apple-derived procyanidin as the recommended daily intake, it should be effective in reducing body fat (visceral fat).

[Relationship between the outcome index in the systematic literature review and the proposed function claim]

The outcome measure "body fat (visceral fat area)" used in the systematic literature review is a body fat-related endpoint specified in the "Cautions on Preparation of Application Forms for FOSHU", and has been widely validated in the Japanese population and widely accepted as academic consensus.

The consumption of apple-derived procyanidin has been shown to reduce body fat (visceral fat area), the outcome measure, which should thus be highly related to the proposed function claim: This Product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat).

Conclusion

The result of systematic literature review showed that consumption of apple-derived procyanidin, the proposed functional substance, contributes to the reduction of body fat (visceral fat).

There is a favorable scientific evidence (evidence level B) for reduction of body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who would be within the scope of subjects in studies of FOSHU. Therefore, it should be appropriate to set the proposed function claim as “This Product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat).”

Sponsor/co-sponsor and conflict of interest subject to declaration

Funding source

This systematic literature review was conducted by JHNFA on behalf of NARO.

Role of each reviewers

Role: Literature search, literature screening, quality assessments, data extraction, and systematic literature review preparation

Performed by: 3 JHNFA employees (A, B, C)

Role: Overall evaluation of the systematic literature review

Performed by: NARO Function Claim Assessment Committee (6 academic experts)

Compliance with PRISMA Statement Checklist (2009)

Mostly compliant.

Basic information including product name (each yellow cell is linked with relevant fields in forms (1) to (11) and will be automatically entered)



Product name: XXXX (TBD)	XXX	← Cell A4
Title	Systematic Literature Review on Apple Procyanidin-Containing “XXXX” in Reducing Body Fat (Visceral Fat)	← Cell B6
Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?	← Cell B7
P (Subjects)	People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU	← Cell B9
I(E) (Intervention)	Continuous consumption of foods containing apple-derived procyanidin	← Cell B10
C (Control)	No consumption of apples or consumption of a placebo (food not containing apple-derived procyanidin)	← Cell B11
O (Outcome)	Body fat (visceral fat area)	← Cell B13

Attachment (V)-5 (a modified version of the template provided by the Consumer Affairs Agency)

Database search results

Product name: XXXX (TBD)

Title	Systematic Literature Review on Apple Procyanidin-Containing “XXXX” in Reducing Body Fat (Visceral Fat)
Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?
Date	Aug. 25, 2017 (PubMed), Aug. 28, 2017 (JDreamIII), Aug. 25, 2017 (Ichushi-Web)
Searched by:	Japan Health and Nutrition Food Association

Database: PubMed

#	Search formula	Number of literatures
1	apple	12,757
2	procyanidin OR polyphenols	16,425
3	#1 AND #2	509
4	"intra-abdominal fat" OR "visceral fat" OR "body fat"	34,585
5	#3 AND #4	4

Partially modified from “Minds Guide for Preparation of Treatment Guideline 2014” Edited by Tsuguya Fukui and Naoto Yamaguchi. Igaku-Shoin. 2014.

[Cautions for review]

This sheet is for viewing only. Note that improper use can result in violation of laws and regulations such as the Copyright Act.

Attachment (V)-5 (a modified version of the template provided by the Consumer Affairs Agency)

Database search results

Product name: XXXX (TBD)

Title	Systematic Literature Review on Apple Procyanidin-Containing "XXXX" in Reducing Body Fat (Visceral Fat)
Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?
Date	Aug. 28, 2017 (JDreamIII), Aug. 25, 2017 (Ichushi-Web)
Searched by:	Japan Health and Nutrition Food Association

Database: JDreamIII (JSTPlus + JST7580 + JMEDPlus)

#	Search formula	Number of literatures
1	"Apple"/AL OR "Malus pumila"/AL OR "Malus domestica"/AL OR "Malus pumila"/AL OR "Malus x domestica"/AL	46,184
2	"Polyvalent phenol"/AL OR "Polyphenol"/AL OR "Polyphenolic compounds"/AL OR "Polyphenols"/AL OR "Polyvalent phenolic compounds"/AL OR "Polyvalent phenols"/AL OR "Polyvalent phenolic compounds"/AL OR "Polyfunctional phenol"/AL OR "Polyfunctional phenol"/AL	312,135
3	"Procyanidin"/AL	2,334
4	#2 OR #3	312,532
5	#1 AND #4	2,504
6	Body fat OR Visceral fat	27,644
7	#5 AND #6	23
8	#7 AND (a1/DT)	8

Partially modified from "Minds Guide for Preparation of Treatment Guideline 2014" Edited by Tsuguya Fukui and Naoto Yamaguchi. Igaku-Shoin. 2014.

[Cautions for review]

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Attachment (V)-5 (a modified version of the template provided by the Consumer Affairs Agency)

Database search results

Product name: XXXX (TBD)

Title	Systematic Literature Review on Apple Procyanidin-Containing “XXXX” in Reducing Body Fat (Visceral Fat)
Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?
Date	Aug. 25, 2017 (Ichushi Web)
Searched by:	Japan Health and Nutrition Food Association

Database: Ichushi Web

#	Search formula	Number of literatures
1	Malus/TH or Apple/AL	608
2	Procyanidin/TH or Procyanidin/AL	170
3	Polyphenols/TH or Polyphenol/AL	9,715
4	#2 or #3	9,744
5	#1 and #4	117
6	Body fat/AL or (Intraperitoneal fat/TH or Visceral fat/AL)	15,876
7	#5 and #6	6

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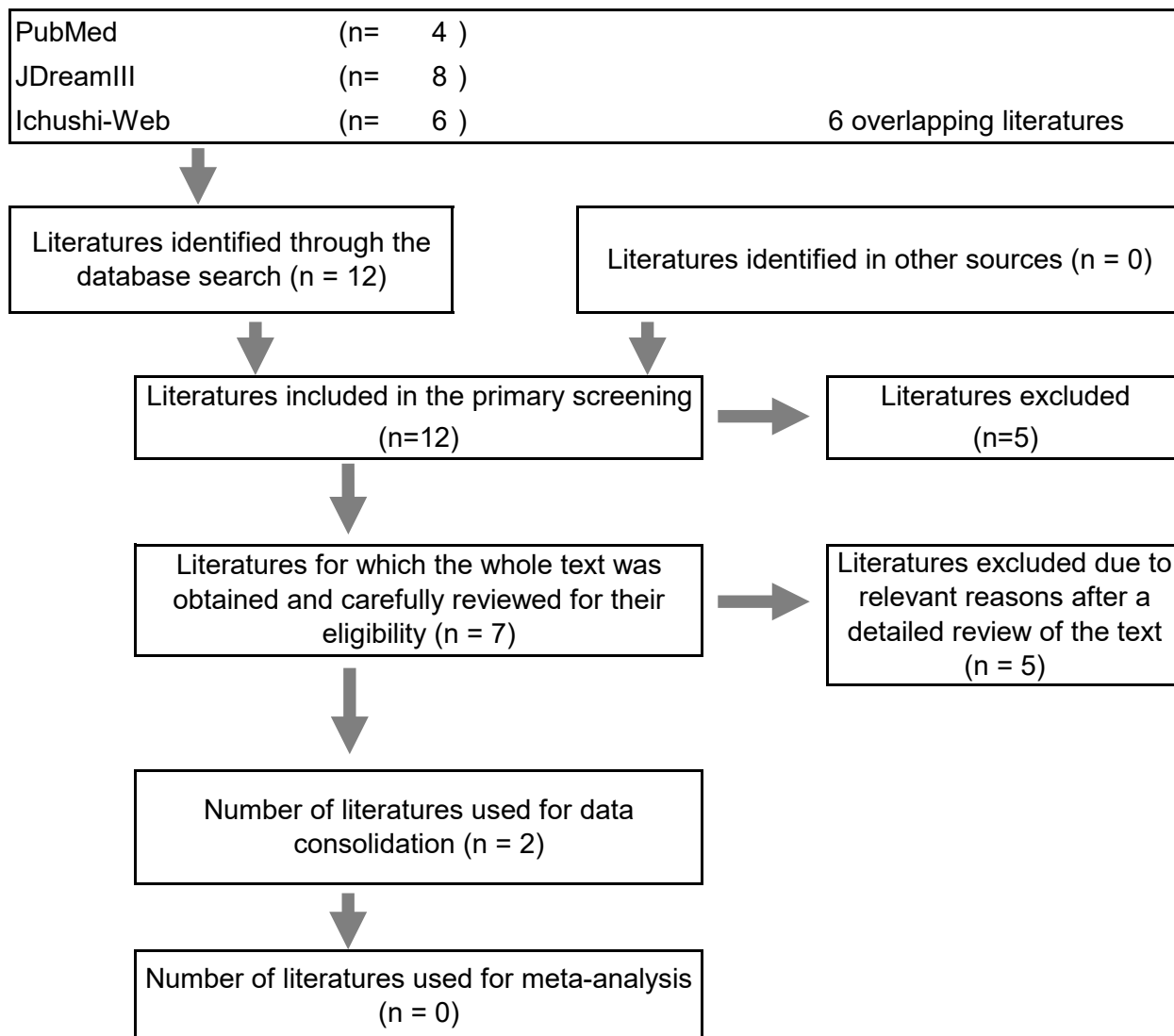
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Attachment (V)-6 (a modified version of the template provided by the Consumer Affairs Agency)

Literature Search Flow Chart

Product name: XXXX (TBD)



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Attachment (V)-7 [Template, for files to be attached]

List of included literatures

Product name: XXXX (TBD)

No.	Name of author (For people belonging to overseas institutions, also specify the name of the country)	Publication	Title	Study design	PICO or PECO	Setting (place where the study was conducted; for studies conducted overseas, also specify the name of the country)	Subject characteristics	Intervention (types of food and functional substances, amount of intake, period of intervention [intake])	Control (placebo, no intake)	Analysis method (ITT, FAS, PPS)	Primary outcome	Secondary outcomes	Harm	Presence/absence of peer review	COI information in literatures (Mainly COI related to the funder, providers of investigational foods, and statistical analysts)
Literature 1	Akazome Y, Kametani N, Kanda T, Shimasaki H, Kobayashi S.	J Oleo Sci. 2010;59(6):321-38	Evaluation of safety of excessive intake and efficacy of long-term intake of beverages containing apple polyphenols.	Randomized Double-blind Parallel group Controlled study	[P] Adult men and women of obesity grade 1 without disease [I] Continuous consumption of beverage containing apple-derived procyanidin [C] Consumption of placebo beverage [O] Body fat	University of Human Arts and Sciences (Japan)	[Study participants] 94 subjects (56 men, 38 women) Mean age: 45.3 years Mean BMI: 27.1 kg/m ² [Analysis population] Efficacy: 87 subjects Safety: 91 subjects [Inclusion criteria] Age: 20 to 65 years BMI ≥25 to <30 (obesity grade 1)	[Form of investigational food] Beverage containing apple-derived procyanidin 340 g per bottle containing 110 mg of apple-derived procyanidin *Using ApplePhenon (Asahi Food & Healthcare) [Amount of intake] 1 bottle/day, taken at dinner [Duration] 12 weeks	Placebo beverage	PPS	Visceral fat area	Total fat area, Subcutaneous fat area, Body composition (body weight, BMI, body fat percentage, waist size, hip size, and waist/hip ratio), Serum lipids	A total of 44 adverse events occurred in 31 of 91 subjects, but no events were related to the consumption of the beverage containing apple-derived procyanidin.	Present	No mentioning of COI. [Author information] Authors include employees of the investigational food supplier.
Literature 2	Ryuji Takeda, Satoshi Miyata, Kotaro Hashimoto, Katsuhiko Sato, Tomomasa Kanda	Japanese Pharmacology & Therapeutics. 2017;45(4):635-651	Reducing Effect of Apple Polyphenols Beverage Consumption on Human Body Fat	Randomized Double-blind Parallel group Controlled study	[P] Adult men and women with obesity levels near the upper limit of normal to grade 1 [I] Continuous consumption of beverage containing apple-derived procyanidin [C] Consumption of placebo beverage [O] Body fat	Soiken Inc. (Japan)	[Number of subjects enrolled] 153 [Number of subjects randomized] 148 [Analysis population] 138 subjects (67 men, 71 women) [Inclusion criteria] Age: Men and women aged ≥20 years BMI >23 to ≤30 [Re-analysis population] 134 subjects (except subjects with BMI ≥30 kg/m ²) [Mean BMI] 110-mg group: 25.7 kg/m ² 55-mg group: 25.9 kg/m ² Placebo group: 25.9 kg/m ²	[Form of investigational food] Beverage containing apple-derived procyanidin Each 340 g bottle contains 110 mg or 55 mg of apple-derived procyanidin. *Using ApplePhenon (Asahi Food & Healthcare) [Amount of intake] 1 bottle/day, taken at dinner [Duration] 12 weeks	Placebo beverage	PPS	Visceral fat area	Total fat area, Subcutaneous fat area, Physical examination (body weight, BMI, and body fat percentage)	[110-mg group] Common cold: 5 subjects Diarrhoea: 1 subject Headache: 1 subject [55-mg group] Common cold: 2 subjects Diarrhoea: 1 subject Headache: 1 subject [Placebo group] Common cold: 3 subjects Diarrhoea: 1 subject Headache: 2 subjects *None was related to the investigational beverage as judged by the physician.	Present	[Funding] The costs for article preparation were paid by Asahi Group Holdings. [Author information] Authors include employees of the investigational food supplier.

Alternative forms, if used, should be at least as detailed as this form.

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Attachment (V)-8 (partially modified from the template provided by Consumer Affairs Agency)

List of excluded literatures

Product name: XXXX (TBD)

No.	Authors	Publication	Title	Reason for exclusion
1	Barth SW, Koch TC, Watzl B, Dietrich H, Will F, Bub A.	Eur J Nutr. 2012;51(7):841-50	Moderate effects of apple juice consumption on obesity-related markers in obese men: impact of diet-gene interaction on body fat content.	Data includes subjects with BMI ≥ 30 kg/m ² and LDL-C ≥ 140 mg/dL which are not covered by this program.
2	Nagasako-Akazome Y, Kanda T, Ohtake Y, Shimasaki H, Kobayashi T.	J Oleo Sci. 2007;56(8):417-28	Apple polyphenols influence cholesterol metabolism in healthy subjects with relatively high body mass index.	Data includes subjects with LDL-C ≥ 140 mg/dL, which is not covered by this program.
3	Junichi Nakamura	The Journal of Japan Polyphenol Society. 2016;5(1):31-3	Effect of polyphenol in reducing body fat	The literature is not an original article (review article)
4	Masahito Nishitani, Yoko Akazome, Tomomasa Kanda	Japanese Journal of Complementary and Alternative Medicine. 2009;6(2):69-74	Effectiveness of the apple polyphenol "Applephenon" on the lifestyle-related disease	The literature is not an original article (review article)
5	Yoko Akazome, Tomomasa Kanda, Yasuyuki Ohtake, Hidenori Hashimoto, Norihiro Kametani, Katsuhiko Sato, Tadashi Nakamura, Yoshitaka Kajimoto	Japanese Pharmacology & Therapeutics. 2005;33(9):893-911	Evaluation of safety of excessive intake and efficacy of long term intake of beverage containing polyphenols derived from apples	Data includes subjects with BMI ≥ 30 kg/m ² , which is not covered by this program.

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Attachment (V)-9 (partially modified from the template provided by Consumer Affairs Agency)

List of unreported studies

Product name: XXXX (TBD)

On UMIN-CTR, "apple procyanidin" and "apple polyphenol" were used as free text words to search for studies; as a result, the following study was extracted.

(Date of search: September 1, 2017)

No.	Study owner	Name/ID of the clinical study registration database	Title	Status (e.g., Ongoing)
1	National Agriculture and Food Research Organization, National Institute of Fruit Tree Science	UMIN Clinical Trial Registration System (UMIN-CTR) UMIN000011751	Effects of Apple Polyphenols on Carbohydrate and Lipid Metabolism in Human Study: A Randomized, Double-Blinded, Placebo-Controlled Trial	Completed

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Attachment (V)-10 (partially modified from the template provided by Consumer Affairs Agency)

List of references

Product name: XXXX (TBD)

No.	Authors	Publication	Title
1	Toshihiko Shoji	Food & Packaging. 2013;54(3):143-9	Fruit/Fruit Juice Beverages and Functional Ingredients (4) Apple and Functional Ingredients - Science of Apple Polyphenol
2	Sugiyama H, Akazome Y, Shoji T, Yamaguchi A, Yasue M, Kanda T, Ohtake Y.	J Agric Food Chem. 2007;55(11):4604-9	Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption.
3	Nagasako-Akazome Y, Kanda T, Ohtake Y, Shimasaki H, Kobayashi T.	J Oleo Sci. 2007;56(8):417-28	Apple polyphenols influence cholesterol metabolism in healthy subjects with relatively high body mass index.
4	Nagasako-Akazome Y, Kanda T, Ikeda M, Shimasaki H.	J Oleo Sci. 2005;54(3):143-51	Serum cholesterol-lowering effect of apple polyphenols in healthy subjects.
5	Ataka S, Tanaka M, Nozaki S, Mizuma H, Mizuno K, Tahara T, Sugino T, Shirai T, Kajimoto Y, Kuratsune H, Kajimoto O, Watanabe Y.	Nutrition. 2007;23(5):419-23	Effects of Applephenon and ascorbic acid on physical fatigue.
6	Yoko Akazome, Tomomasa Kanda, Yasuyuki Ohtake, Hidenori Hashimoto, Norihiro Kametani, Katsuhiko Sato, Tadashi Nakamura, Yoshitaka Kajimoto	Japanese Pharmacology & Therapeutics. 2005;33(9):893-911	Evaluation of safety of excessive intake and efficacy of long term intake of beverage containing polyphenols derived from apples
7	Barth SW, Koch TC, Watzl B, Dietrich H, Will F, Bub A.	Eur J Nutr. 2012;51(7):841-50	Moderate effects of apple juice consumption on obesity-related markers in obese men: impact of diet-gene interaction on body fat content.

Alternative forms, if used, should be at least as detailed as this form.

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Attachment (V)-11a-1 (if continuous variables are used as indices) (partially modified from the template provided by the Consumer Affairs Agency)

Literature quality assessment sheet (clinical study [human study])

Product name: XXXX (TBD)

Subjects	People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
Intervention	Continuous consumption of foods containing apple-derived procyanidin
Control	No consumption of apples or consumption of a placebo (food not containing apple-derived procyanidin)

*Each item was evaluated according to a 3-rank scale of high (-2), moderate/suspected (-1), and low (0).
The summary was reflected to the overall evidence using 3 grades: high (-2), moderate (-1), and low (0).

Outcome	Body fat (visceral fat area)
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A separate sheet was prepared for each outcome.

Individual study				Bias risks*										Indirectness*				
				[1] Selection bias		[2] Blinding bias	[3] Blinding bias	[4] Attrition bias		[5] Selective outcome reporting	[6] Other biases	Summary						
Study code	Publication	Study design	Study quality (QL)	Randomization	Concealment of allocation	Participants	Outcome Assessors	ITT, FAS, PPS,	Incomplete Outcome Data				Subjects	Intervention	Control	Outcome	Summary	
Literature 1	J Oleo Sci. 2010;59(6):321-38	Randomized, parallel-group, double-blind, controlled study	QL2	Evaluation result	0	-1	0	0	-2	0	0	-1	-1	0	0	0	0	0
				Comments		No provided			PPS			Authors involved conflict of interest.						
Literature 2	Japanese Pharmacology & Therapeutics. 2017;45(4):635-651	Randomized, parallel-group, double-blind, controlled study	QL2	Evaluation result	0	-1	0	0	-2	0	0	-1	-1	0	0	0	0	0
				Comments		No provided			PPS			Authors involved conflict of interest.						

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Attachment (V)-11a-2 (if continuous variables are used as indices) (partially modified from the template provided by the Consumer Affairs Agency)

Literature quality assessment sheet (clinical study [human study])

Product name: XXXX (TBD)

Subjects	People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
Intervention	Continuous consumption of foods containing apple-derived procyanidin
Control	No consumption of apples or consumption of a placebo (food not containing apple-derived procyanidin)
Outcome	Body fat (visceral fat area)

Individual study				Pre-/post-intervention values in each group											
Study code	Publication	Study design	Study quality (QL)	Outcome measure	Control group (Pre-intervention value)	Control group (Post-intervention value)	Mean difference in the control group	p-value	Intervention group (Pre-intervention value)	Intervention group (Post-intervention value)	Mean difference in the intervention group	p-value	Intervention group vs Control group Mean difference	p-value	Comments
Literature 1	J Oleo Sci. 2010;59(6):321-38	Randomized, parallel-group, double-blind, controlled study	QL2	Visceral fat area (cm ²)	99.2±31.5	(8w)104.1±35.6	4.9±11.4	N.S.	106.1±34.3	(8w)101.1±30.6	-5.0±11.6	P<0.05	-9.9	P<0.01	Values are expressed as mean ± standard deviation.
						(12w)101.3±35.2	2.1±12.0	N.S.		(12w)98.2±28.2	-7.9±16.2	P<0.01			
Literature 2	Japanese Pharmacology & Therapeutics. 2017;45(4):635-651	Randomized, parallel-group, double-blind, controlled study	QL1	Visceral fat area (cm ²)	92.3±38.5	90.8±38.0	-1.45±13.64	N.S.	(55-mg group) 100.4±44.7	96.7±42.6	-3.65±13.56	N.S.	-1.80	N.S.	Values are expressed as mean ± standard deviation.
									(110-mg group) 96.1±45.0	87.2±40.9	-8.91±15.48	P<0.01			

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Attachment (V)-13a (if continuous variables are used as indices) (partially modified from the template provided by Consumer Affairs Agency)

Overall evidence quality assessment sheet

Product name: XXXX (TBD)

Subjects	People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
Intervention	Continuous consumption of foods containing apple-derived procyanidin
Control	No consumption of apples or consumption of a placebo (food not containing apple-derived procyanidin)

Overall evidence

Outcome	Study design / Number of studies		Bias risks*	Indirectness*	Inaccuracy*	Inconsistency*	Other (e.g., publication bias*)	Increasing factor (Observational study*)	Evidence level (A to E**)	Comments
Body fat (visceral fat area)	RCT/2	Evaluation Results	-1	0	0	0	-1		B	
		Comments	Of the 2 reports, 2 were categorized as moderate (-1) in the summary of bias risk.				The number of included literatures was small (2).		Overall scientific evidence level rated by NARO Function Claim Assessment Committee	

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*Each item was rated by a 3-rank scale of high (-2), moderate/suspected (-1), or low (0).

**The evidence was categorized to the following 5 levels: Clearly and sufficiently supported by evidence (A), Supported by favorable evidence (B), Supported by suggestive evidence (C), Not sufficiently supported by evidence (D), and Ruled out by unfavorable evidence (E).

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Attachment (V)-14 (partially modified from the template provided by Consumer Affairs Agency)

Summary sheet (qualitative systematic literature review)

Product name: XXXX (TBD)

Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?
P	People without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU
I(E)	Continuous consumption of foods containing apple-derived procyanidin
C	No consumption of apples or consumption of a placebo (food not containing apple-derived procyanidin)
O	Body fat (visceral fat area)
Summary of bias risk	<p>The selection bias (randomization) was Low (0) for both studies; neither had an issue.</p> <p>The selection bias (concealment of allocation) was Moderate/Suspected (-1) for both studies because neither study mentioned it.</p> <p>The blinding bias (participants, outcome assessors) was "Low (0)" for both reports; neither had an issue.</p> <p>The attrition bias (ITT, FAS, PPS) was High (-2) for both studies because the analysis sets were PPS.</p> <p>The attrition bias (incomplete outcome data) was Low (0) for both studies; neither had an issue.</p> <p>Selective outcome reporting was rated as Low (0) because it was not confirmed in either study.</p> <p>Other biases were assessed as Moderate/Suspected (-1) because the authors had conflicts of interest in both studies.</p> <p>Based on the above results, the summary was evaluated as Moderate (-1) for both studies, and the bias risk was Moderate/Suspected (-1).</p>
Summary of indirectness	<p>It was rated as Low (0) for both literatures because none of the criteria had an issue in either studies.</p> <p>Based on the above results, the summary was evaluated as Low (0) for both literatures, and the indirectness was Low (0).</p>
Summary of inconsistency and other	<p>The inconsistency was evaluated as Low (0) because the results were effective in and consistent between the studies.</p> <p>Other (publication bias) was rated as Moderate/Suspected (-1) because there were only 2 included literatures and the possibility of publication bias could not be ruled out.</p>
Comments	<p>The results were supported by a favorable scientific evidence (evidence level B) for reduction of body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who would be within the scope of subjects in studies of FOSHU. Therefore, it should be appropriate to set the proposed functional claim as "This product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat)."</p> <p>Assessments by the NARO Function Claim Assessment Committee</p> <p>Overall scientific evidence level (strength of evidence): B</p> <p>Level of "research type, quality, and quantity": C</p> <p>Consistency level: B</p>

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Attachment (V)-16 (partially modified from the template provided by Consumer Affairs Agency)

Summary of the overall evaluation

Product name: XXXX (TBD)

Name of functional substance	Apple-derived procyanidin
Proposed function claim	This product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat).

Research question	Can continuous consumption of apple-derived procyanidins reduce body fat (visceral fat) in people without disease (except minors, pregnant women, and lactating women) and people who are within the scope of subjects in studies of FOSHU, compared to the control group?
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		Effective		Indeterminable		No effect		Unfavorable effect	
Human studies	Total	2 literature(s)		0 literature(s)		0 literature(s)		0 literature(s)	
		RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT
Grand total: 2 literature(s)	QL1:	1 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature
	QL2:	1 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature
	QL3:	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature

Discussion of the relationship between the results of the systematic literature review and the proposed functional claim
<p>[Results of this systematic literature review] Two studies that were consistent with the research question were selected. The included literatures covered the Japanese population without disease. In both literatures, the endpoint was body fat (visceral fat area), and the investigational food was demonstrated to be effective. The results of the systematic literature review suggested that consumption of apple-derived procyanidins was effective in reducing body fat (visceral fat area).</p> <p>[Description of food] The food forms in the 2 included literatures were beverages containing powder made from apples, which was different from the form of the proposed product (apple fruit). However, according to another study (which was excluded from this review because it contained data in patients with diseases), powder-capsules made from apples and cloudy juice squeezed from apples were also similarly effective in relation to body fat^(References 3,7), suggesting the food form does not have a major affect on digestion and absorption of the functional substance. Therefore, there should be no issues in extrapolating this evidence to the proposed product. The 2 included literatures presented the content of apple polyphenol in the investigational food; 600 mg of "apple polyphenol" is said to be equivalent to 110 mg of apple-derived procyanidin.</p> <p>[Subjects] Subjects in the 2 literatures were both adult Japanese men and women with obesity levels near the upper limit of normal to grade 1 with no disease; thus, there should no problems extrapolating the data to the Japanese population. Based on the above, the proposed function claim should be applicable to the consumers of the proposed product.</p> <p>[Daily standard intake] Both included literatures demonstrated a 12-week consumption of apple-derived procyanidin 110 mg as an effective diet in reducing body fat; accordingly, the recommended consumption of apple-derived procyanidin was set to ≥110 mg/day for ≥ 12 weeks. Because the proposed product contains 110 mg of apple-derived procyanidin as the recommended daily intake, it should be effective in reducing body fat (visceral fat).</p> <p>[Relationship between the outcome index in the systematic literature review and the proposed function claim] The outcome measure "body fat (visceral fat area)" used in the systematic literature review is a body fat-related endpoint specified in the "Cautions on Preparation of Application Forms for FOSHU", and has been widely validated in the Japanese population and widely accepted as academic consensus. The consumption of apple-derived procyanidin has been shown to reduce body fat (visceral fat area), the outcome measure, which should thus be highly related to the proposed function claim, "This Product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat)."</p>

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Explanatory material on mechanism of action

1. Product overview

Product name	XXXX
Name of functional substance	Apple-derived procyanidin
Proposed function claim	This product contains apple-derived procyanidins. Apple-derived procyanidins are reported to reduce body fat (visceral fat).

2. Mechanism of action

Consumed fat is first emulsified by bile in the duodenum and then degraded to fatty acids and glycerol by the digestive enzyme lipase. Free fatty acids are transported to the liver and oxidized by beta-oxidation. Glycerol is converted to glycerol 3-phosphate and then resynthesized into fat or decomposed by glycolytic enzymes.

In an *in vitro* study using porcine pancreatic lipase, the IC₅₀ of apple polyphenols for lipase inhibition was 5.6 µg/mL. Moreover, apple polyphenols were separated to apple-derived procyanidin and other polyphenols, and the lipase inhibitory activity was measured; the IC₅₀ was 1.4 µg/mL for apple-derived procyanidin and 115.9 µg/mL for other types of apple polyphenols. Thus, apple-derived procyanidins that showed a stronger lipase-inhibiting activity was judged to be the primary factor.

Thus, the mechanism of body fat reduction by apple-derived procyanidin, the proposed functional substance, involves inhibition of the lipase activity that degrades fat into fatty acids and monoglycerides in the duodenum which prevents fat from being absorbed in the small intestine and is excreted into the feces without being metabolized. Therefore, fat accumulation is suppressed and body fat (visceral fat area) is reduced.

(Reference material)

1) Sugiyama H., et al., Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption, Journal of Agricultural and Food Chemistry 2007;55(11):4604-9