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

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

Title (PRISMA checklist # 1): A qualitative systematic literature review on quercetin, a functional substance contained in "XXX (product name)", maintaining and improving positive mood and motivation that tend to decrease with age

Product name: XXX (Product Name)

Name of functional substance: Quercetin

Proposed function claim: This product contains quercetin. Quercetin has been reported to have functions that help maintain a positive mood that tends to decrease with age in healthy elderly individuals.

Date of preparation: MM DD, 20YY

Reported by: XX

Abstract (PRISMA checklist #2)

Objective

A qualitative systematic literature review was conducted to verify whether the intake of quercetin-containing food helped maintain positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people.

Methodology

Three employees of the National Agriculture and Food Research Organization (NARO) performed a literature search using three databases (PubMed, Ichushi-Web, and JDreamIII) on the research question, "Is the intake of quercetin-containing food superior to placebo food in maintaining positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people?" Literatures identified by the search were screened to exclude those that did not meet the inclusion criteria, and those meeting a certain level of quality (QL3 or higher) were selected as included literatures by "article quality assessment". Positive mood and motivation were used as outcome measures to evaluate the overall evidence of the included literature.

For the overall evaluation of the systematic literature review, 6 academic experts of the Function Claim Assessment Committee for Agricultural, Forestry and Fish Products, the National Agriculture and Food Research Organization (NARO) were assigned and evaluated the [overall scientific evidence level], [level of "research type, quality, and quantity"], and [consistency level], with 5 grades (A to E); the systematic literature review would be appropriate as evidence for the proposed function claim if graded as A to C for all three criteria.

Results

One literature that met the inclusion criteria was included. The included literature demonstrated in healthy elderly subjects (including those with mild cognitive impairment [MCI]) that, compared with the placebo group, the food containing quercetin 50 mg/day was effective in maintaining a positive mood that tends to decrease with age (effective). This systematic literature review suggested that the intake of quercetin-containing food maintain a positive mood that tends to decrease with age in healthy older adults.

The function claim proposed by the systematic literature review was supported by the evaluation conducted by the NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products.

Conclusion

This systematic literature review suggested that the intake of quercetin 50 mg/day should help maintain a positive mood that tends to decrease with age in healthy older adults.

Introduction

(1) Rationale (PRISMA checklist #3)

The current Japanese society is aging rapidly. In 2019, 28.4% of the population was 65 years or older. Furthermore, it is predicted that, by 2065, approximately 1 of 2.6 will be 65 years or older (38.4%), and 1 of 3.9 will be 75 years or older (25.5%)[1] (Cabinet Office, Elderly Social White Paper 2020). The aging of society as such is expected to face important challenges concerning cognitive decline and associated changes in behavioral and psychological symptoms among the middle-aged/elderly population.

The incidences of depression, apathy, anxiety, irritability, sleep disorder, and other similar behavioral and psychological symptoms are reportedly increasing in patients with MCI, as well as the elderly population with normal cognitive function[2,3]. Symptoms like depression[4], apathy[5], and anxiety[6] are considered to be indicators of progression from MCI to Alzheimer's disease.

Quercetin is a type of flavonoid for which onion is the primary source of intake[7,8]. Benefits thereof reported in a meta-analysis of interventional studies of quercetin-based flavonol ingestion included a decrease in total cholesterol, LDL-cholesterol, blood glucose, and blood pressure and an increase in HDL-cholesterol[9]. However, studies of quercetin on behavioral and psychological symptoms are minimal, and there seems to be no related systematic literature review. Therefore, the decision was made to examine the effects of quercetin-containing food intake on aging-related decrease in positive mood and motivation among the healthy middle-aged and elderly population.

(2) Objective (PRISMA checklist #4)

A qualitative systematic literature review was conducted to verify whether the intake of quercetin-containing food in the healthy middle-aged and elderly population was superior to placebo food in maintaining positive mood and motivation that tend to decrease with age.

Methodology

(1) Protocol and Registration (PRISMA checklist #5)

According to the protocol for the systematic literature review specified by the Consumer Affairs Agency's "Model Project for the Evaluation of Food Products with Function Claims" held in FY2011, literature search, literature screening, article quality

assessment, data extraction, and systematic literature review preparation were performed by 3 NARO employees. The strength of evidence was evaluated by the NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products, which comprises 6 academic experts. The review protocol was not registered.

(2) Research question and inclusion criteria (PRISMA checklist #6)

[Research question]

Is the intake of quercetin-containing food superior to placebo food in maintaining positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people?

PICO were set out as follows based on the research question, and were used to select the research-specific inclusion criteria as shown below.

[PICO]

Participants (P)	:	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
Intervention (I)	:	Intake of quercetin-containing food
Comparison (C)	:	Intake of placebo food
Outcome (O)	:	Positive mood, motivation

[Inclusion criteria]

- Participants (P): Individuals aged ≥40 years with no disease.
- Intervention (I): Intake of food for which quercetin content is identifiable.
- Comparison (C): Placebo food (containing no quercetin).
- Literatures published in a peer-reviewed journal and published in English or Japanese.

(3) Source (PRISMA checklist #7)

The following three databases were used for the literature search: PubMed (date of final search: July 22, 2022), Ichushi-Web (date of final search: July 29, 2022), and JDreamIII (date of final search: July 22, 2022). No particular search period was set for any of the databases, and the search covered the entire databases up to the date of the final search. Unreported studies were searched for with the UMIN Clinical Trials Registry (UMIN-CTR); the last search date was July 22, 2022.

(4) Search (PRISMA checklist #8)

The search formula for each database was set as follows based on the research question. For UMIN-CTR, “quercetin, affective function”, and other relevant search words were entered in the “free text” column. Attachment (V)-9 shows the results.

PubMed

#	Search formula
1	quercetin [Title/Abstract] OR quercetin glycoside [Title/Abstract]
2	mood [Title/Abstract] OR vigor [Title/Abstract] OR motivation [Title/Abstract] OR apathy [Title/Abstract] OR depression [Title/Abstract] OR anxiety [Title/Abstract]
3	clinical trial [All Fields] OR placebo-controlled trial [All Fields]
4	#1 AND #2 AND #3

Ichushi-Web

#	Search formula
1	(Quercetin/TH or quercetin/AL) or “quercetin glycoside”/AL or (Quercetin/TH or quercetin/AL) or quercetin glycoside/AL
2	(affection/TH or mood/AL) or vitality/AL or (motivation/TH or motivation/AL) or (vigor/TH or vigor/AL) or depression/AL or (affection/TH or mood/AL) or (strength/TH or vigor/AL) or (apathy/TH or apathy/AL) or (motivation/TH or motivation/AL) or ((depression/TH or depression/AL) or (depression/TH or depression/AL)) or (anxiety/TH or anxiety/AL) or (anxiety/TH or anxiety/AL)
3	#1 and #2

JDreamIII

#	Search formula
1	(quercetin) OR (quercetin glycoside) OR (quercetin) OR (quercetin glycoside)
2	(randomized controlled trial) OR (controlled clinical trial) OR (placebo-controlled trial) OR (randomized) OR (randomly) OR (placebo) OR (randomized controlled trial) OR (randomized) OR (placebo)
3	(human) OR (clinical trial) OR (human study) OR (clinical trial) OR (human)
4	(mood) OR (vitality) OR (motivation) OR (vigor) OR (depression) OR (anxiety) OR (mood) OR (vigor) OR (motivation) OR (apathy) OR (depression) OR (anxiety)
5	#2 AND #3
6	#1 AND #4 AND #5

(5) Selection of studies (PRISMA checklist #9)

The literatures identified in each database were reviewed by the 3 NARO employees and sorted into those to be included and those to be excluded based on the inclusion criteria. The primary screening was performed to exclude overlapping studies and verify the titles and the abstracts to determine whether they would be applicable. Literatures that could not be clearly identified to be excluded went through the secondary screening. The whole text was obtained and carefully reviewed for the secondary screening, and then the decision was made to include or exclude it. The included literatures are as shown in

Attachment (V)-7, and those excluded are as shown in Attachment (V)-8 with the reasons for exclusions. Unreported studies were checked against the trials information in UMIN-CTR and as appropriately specified in Attachment (V)-9.

(6) Data collection process (PRISMA checklist #10)

On the included literatures, 3 NARO employees independently reviewed and collected information on each study, including subjects, conditions for intervention, endpoints, that is, positive mood and motivation, adverse events, the presence/absence of conflict of interest (COI), and other relevant data as shown in Attachments (V)-7 and (V)-11a-2. After data collection, the results were collated, and if found to be inconsistent, the literature was rechecked and discussed to determine how it should be handled.

(7) Data items (PRISMA checklist #11)

Attachment (V)-7 presents the data from the included literatures, that is, 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 outcome measures of each literature.

(8) Bias risks of individual studies (PRISMA checklist #12)

The quality assessment of included literature was graded by four levels from QL1 to QL4 based on the "Scoring Sheet for Quality Assessment of Included Literature" (prepared by the Japan Health and Nutrition Food Association (JHNFA)). The definitions of QL1 to QL4 were as follows. Literatures above a certain research level (QL3 or higher) were included.

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)

Furthermore, bias risks and indirectness were evaluated based on Attachment (V)-11a-1. Each parameter was evaluated on a 3-point scale, High (−2), Moderate/Suspected (−1), and Low (0) per 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).

1) Evaluation of bias risks
- 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

2) Evaluation of indirectness
- Subjects
- Intervention
- Control
- Outcome
- Summary

(9) Summary scale (PRISMA checklist #13)

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

(10) Consolidation of results (PRISMA checklist #14)

The results were not consolidated because this systematic literature review was qualitative.

(11) Bias risks of all studies (PRISMA checklist #15)

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

(12) Additional analyses (PRISMA checklist #16)

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

Overall evaluation of the systematic literature review

The included literatures were sorted to "effective", "indeterminable", "no effect", and "unfavorable effect", and further sorted and listed by RCT/Non-RCT and QL1 to QL3. The number of studies in each category was counted as shown in Attachment (V)-16 (Assessment Sheet on the Relationship Between the Results of the Systematic Literature Review and the Proposed Functional Claim). "Effective", "indeterminable", "no effect", and "unfavorable effect" were defined as follows:

Effective:	The significance probability is <5% for the difference between the intervention group and the control group (if the result in the intervention group is positive for each endpoint) in terms of the outcome measures (positive mood, motivation).
Indeterminable:	The significance probability is unclear (including no assessment performed) for the difference between the intervention and control groups (if the result in the intervention group is positive for each endpoint) in terms of the outcome measures (positive mood, motivation).
No effect:	The significance probability is ≥5% for the difference between the intervention and control groups in terms of the outcome measures (positive mood, motivation).
Unfavorable effect:	The significance probability is <5% for the difference between the intervention and control groups (if the result in the intervention group is negative for each endpoint) in terms of the outcome measures (positive mood, motivation).

The overall evaluation of the systematic literature review was performed by the NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products, which comprises 6 academic experts. [Overall scientific evidence level], [level of "research type, quality, and quantity"], and [consistency level] were evaluated by 5 grades (A to E) based on the materials prepared. The definitions of grades A to E were as follows. The systematic literature review would be considered appropriate as evidence for the proposed function claim if graded as A to C for all three criteria.

[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

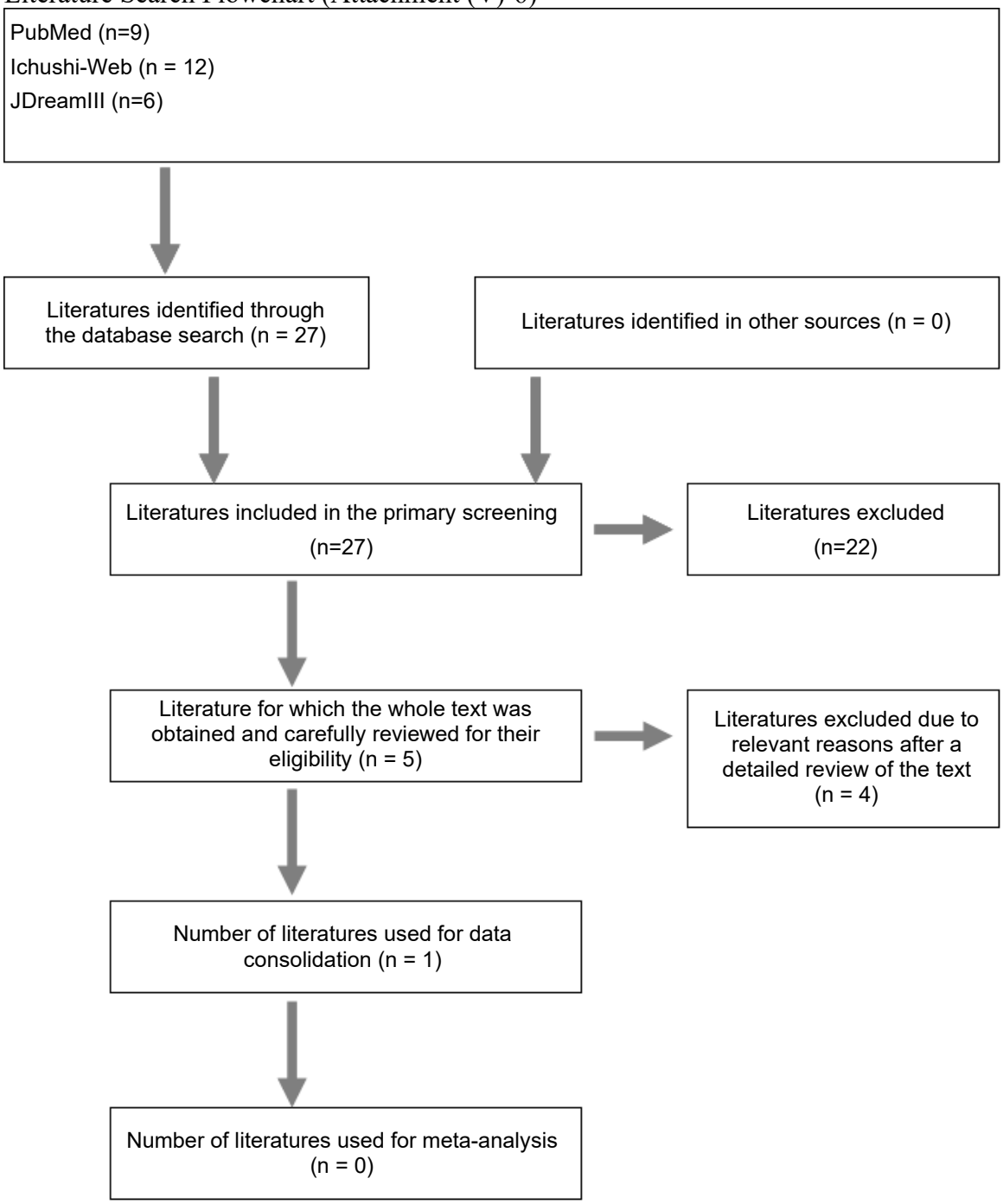
(1) Selection of studies (PRISMA checklist #17)

As a result of searching the three databases (PubMed, JDreamIII, and Ichushi-Web), 9 literatures from PubMed, 12 from Ichushi-Web, and 6 from JDreamIII were selected; thus, a total of 27 were included in the primary screening. Of these, 22 were excluded for overlapping or not meeting the inclusion criteria in terms of the title and abstract. For the remaining 5 literatures, the whole texts were obtained and reviewed in details to verify whether they met the inclusion criteria.

Finally, 4 literatures were excluded, and only 1 was included. No meta-analysis was performed; the qualitative research review was based on 1 literature. The flowchart of the literature search was as presented below and in Attachment (V)-6. Attachments (V)-7 and (V)-8 show the literature included and literature excluded, respectively. Unreported studies were checked by using UMIN-CTR Study Information, and no study was found as shown in Attachment (V)-9.

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

Literature Search Flowchart (Attachment (V)-6)



(2) Study characteristics (PRISMA checklist #18)

A literature that was the one included was written in English.

The study was a randomized, parallel-group, double-blind, placebo-controlled study.

It was conducted in healthy Japanese men and women aged ≥60 to <80 years (including MCI), and a stratified analysis was also performed for those who were not on any regular medication. Quercetin intake in the intervention group was 50 mg/day in powder form.

CADi2 (Cognitive Assessment for Dementia iPad Version) was used to evaluate the outcome. CADi2 is used in Japan for brain screening in dementia patients and healthy

individuals to evaluate cognitive function and affective function (Self-rating Depression Scale [SDS] and the Apathy Scale)[10-12]. Both the SDS and Apathy Scale are used widely in Japan. The affective function was rated by the depression scale (SDS, mood assessment) and motivation (Apathy scale). Improved depression scales and motivation leads to the improvement in depressed mood and vigor, which contribute to the maintenance of a positive mood and increased motivation.

Attachment (V)-7 shows the details of the literature.

(3) Bias risks within the study (PRISMA checklist #19)

Attachment (V)-11a-1 details the quality assessment (QL1 to QL4), bias risk, and indirectness of the included articles. The article quality was evaluated, and the included literature was QL1.

"Selection bias (randomization)" was "Low (0)" because of an RCT article.

"Selection bias (concealment of allocation)" was "Low (0)".

"Blinding bias (participants)" was "Low (0)".

"Blinding bias (outcome assessors)" was "Low (0)" because of the double-blind study.

"Attrition bias" was "High (-2)" because the PPS analysis was performed.

"Selective outcome reporting" was "Low (0)".

"Other biases" was rated as "Moderate/Suspected (−1)" because the research used the matching fund of the NARO, Bio-oriented Technology Research Advancement Institution (BRAIN) and included NARO staff as authors.

Based on the above results, it was rated as "Moderate/Suspected (−1)".

"Indirectness" was rated as "Low (0)" because it matched all the PICO.

(4) Results of individual study (PRISMA checklist #20)

The study results described in the included literature were as follows.

[Literature 1] Article quality assessment: QL1 (a randomized, parallel-group, double-blind, placebo-controlled study, effective)

Thirty-eight healthy Japanese men and women (aged ≥60 to <80 years) who were not on any regular medication were included. Subjects in the intervention group received a powder containing quercetin 50 mg/day (test meal) daily for 24 weeks, and subjects in the control group received a powder containing no quercetin (placebo meal) daily for 24 weeks. CADi2 was measured before the start of intake, at 12 weeks, and 24 weeks of intake.

The intervention group showed a significant decrease (improvement) in SDS (depression scale) compared with the control group ($P < 0.01$) at 24 weeks after intake. A change in the Apathy Scale (motivation) at 24 weeks after intake also tended to be lower (improved) in the intervention group than in the control group ($P = 0.099$). These results suggest that a positive mood was maintained in the intervention group.

(5) Consolidation of results (PRISMA checklist #21)

The results were not consolidated because this systematic literature review was qualitative.

(6) Bias risks of all studies (PRISMA checklist #22)

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

Bias risk was rated as “Moderate/Suspected (-1)” for reasons such as decreased subjects.

Indirectness was rated as “Low (0)”.

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

Inconsistency was rated as “Moderate/Suspected (−1)” as it was indeterminable, as only 1 literature was included.

Publication bias was rated as “Moderate/Suspected (−1)” because the possibility of bias could not be ruled out, as the number of included literatures was limited.

Based on the above results, the study was judged to have involved no significant risk that would affect the entirety of the evidence.

(7) Additional analyses (PRISMA checklist #23)

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

Overall evaluation of the systematic literature review

Of the outcomes of the systematic literature review assessed by the NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products, the assessment results on “positive mood” were considered appropriate as evidence for the proposed function claim.

Discussion

(1) Summary of evidence (PRISMA checklist #24)

[Results of this systematic literature review]

One literature that was consistent with the research question was included. The included literature demonstrated the effectiveness of quercetin-containing food compared with the control group in maintaining positive mood that tend to decrease with age (effective). While further evidence is necessary, the results of this systematic literature review generated positive result, suggesting that the intake of quercetin-containing food should help maintain a positive mood that tends to decrease with age in healthy older adults. No adverse event was reported in the included literature; besides, safety was confirmed.

[Subjects]

The included literature covered healthy elderly Japanese men and women, which should be appropriate for extrapolation to the anticipated users of the product to be registered, that is, the healthy elderly Japanese population.

[Description of food]

The test meal in the included literature was in powder form.

(Once the registered product that is the subject of this systematic literature review is decided, a discussion is needed to verify its equivalence with the product.)

[Daily standard intake]

Quercetin intake in the included literature was 50 mg/day. Accordingly, the intake of quercetin 50 mg/day should help maintain a positive mood that tends to decrease with age in older adults.

(Once the registered product that is the subject of this systematic literature review is decided, a dose corresponding to the product should be selected.)

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

This systematic literature review included a literature evaluating an outcome index related to affective function in older adults. In a included literature, the results were "effective," showing a significant improvement in affective function measured by SDS (depression scale, mood assessment) compared with the control group; moreover, the Apathy Scale (motivation) tended to improve as well. Improved depression scale leads to maintaining a positive mood in daily life.

Therefore, the outcome index used in this systematic literature review should be highly related to a part of the proposed function claim (maintaining a positive mood that tends to decrease with age in the elderly population).

(2) Limitation (PRISMA checklist #25)

One limitation of this systematic literature review is that only a single literature was included. Another limitation is that the duration of quercetin intake was only 24 weeks; the effects of longer-term intake remain unknown.

While further evidence is necessary, this systematic literature review generated results suggesting the effectiveness of quercetin intake in maintaining a positive mood that tends to decrease with age.

(3) Conclusion (PRISMA checklist #26)

The intake of quercetin 50 mg/day was demonstrated to be effective in maintaining a positive mood that tends to decrease with age. The subjects covered in the included literature were healthy Japanese older men and women, consistent with the anticipated consumers of this product.

The effectiveness of quercetin intake in maintaining a positive mood in elderly people demonstrated by this systematic literature review is backed up positively by a scientific rationale, supporting the appropriateness of the proposed function claim, "This product contains quercetin. Quercetin has been reported to have functions that help maintain a positive mood that tends to decrease with age in healthy elderly individuals."

Sponsor/cosponsor and conflict of interest subject to declaration (PRISMA checklist #27)

No declaration needs to be made on sponsor/cosponsor or conflict of interest associated with this systematic literature review.

Role of each reviewer (PRISMA checklist #27)

Role: Perform the systematic literature review (literature search, literature screening, article quality assessment, data extraction, and preparation of systematic literature review report)
Staff: 3 reviewers (Reviewer A, Reviewer B, and Reviewer C) from the National Agriculture and Food Research Organization

Role: Perform the systematic literature review (overall evaluation of the research review)

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

Staff: NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products (6 academic experts in agriculture, pharmaceutical science, nutrition, statistics, and other areas)

Compliance with PRISMA Statement Checklist (2009)
☑ Mostly compliant.

Product name and other basic information

Product name: XXXX (TBD)

Title	A qualitative systematic literature review on quercetin, a functional substance contained in “XXX (product name)”, maintaining and improving positive mood and motivation that tend to decrease with age
Research question	Is the intake of quercetin-containing food superior to placebo food in maintaining positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people?

Functional substance	Quercetin
Proposed function claim	This product contains quercetin. Quercetin has been reported to have functions that help maintain a positive mood that tends to decrease with age in healthy elderly individuals.
P (Subjects)	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
I (E) (Intervention)	Intake of quercetin-containing food
C (Control)	Intake of placebo food

O2 (Outcome)	Positive mood, motivation

Attachment (V)-5 [Template, for files to be attached]

Database search results

Product name: XXXX (TBD)

Title:	A qualitative systematic literature review on quercetin, a functional substance contained in “XXX (product name)”, maintaining and improving positive mood and motivation that tend to decrease with age
Research question:	Is the intake of quercetin-containing food superior to placebo food in maintaining positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people?
Date:	July 22, 2022 (PubMed, JDreamIII), July 29, 2022 (Ichushi-Web)
Searched by:	(National Research and Development Agency) National Agriculture and Food Research Organization

Database: PubMed

#	Search formula	Number of literatures
1	(quercetin [Title/Abstract]) OR (quercetin glycoside [Title/Abstract])	21,752
2	(mood [Title/Abstract]) OR (vigor [Title/Abstract]) OR (motivation [Title/Abstract]) OR (apathy [Title/Abstract]) OR (depression [Title/Abstract]) OR (anxiety [Title/Abstract])	647,537
3	(clinical trial [ALL Fields]) OR (placebo-controlled trial [ALL Fields])	1,334,388
4	#1 AND #2 AND #3	9

Database: Ichushi Web

#	Search formula	Number of literatures
1	(Quercetin/TH or quercetin/AL) or “quercetin glycoside”/AL or (Quercetin/TH or quercetin/AL) or quercetin glycoside/AL	1,461
2	(affection/TH or mood/AL) or vitality/AL or (motivation/TH or motivation/AL) or (vigor/TH or vigor/AL) or depression/AL or (affection/TH or mood/AL) or (strength/TH or vigor/AL) or (apathy/TH or apathy/AL) or (motivation/TH or motivation/AL) or ((depression/TH or depression/AL) or (depression/TH or depression/AL)) or (anxiety/TH or anxiety/AL) or (anxiety/TH or anxiety/AL)	259,400
3	#1 and #2	12

Database: JDreamIII (JSTPlus + JST7580 + JMEDPlus)

#	Search formula	Number of literatures
1	(quercetin) OR (quercetin glycoside) OR (quercetin) OR (quercetin glycoside)	14,512
2	(randomized controlled trial) OR (controlled clinical trial) OR (placebo-controlled trial) OR (randomized) OR (randomly) OR (placebo) OR (randomized controlled trial) OR (randomized) OR (placebo)	268,259
3	(human) OR (clinical trial) OR (human study) OR (clinical trial) OR (human)	3,535,293
4	(mood) OR (vitality) OR (motivation) OR (vigor) OR (depression) OR (anxiety) OR (mood) OR (vigor) OR (motivation) OR (apathy) OR (depression) OR (anxiety)	847,550
5	#2 AND #3	150,166
6	#1 AND #4 AND #5	6

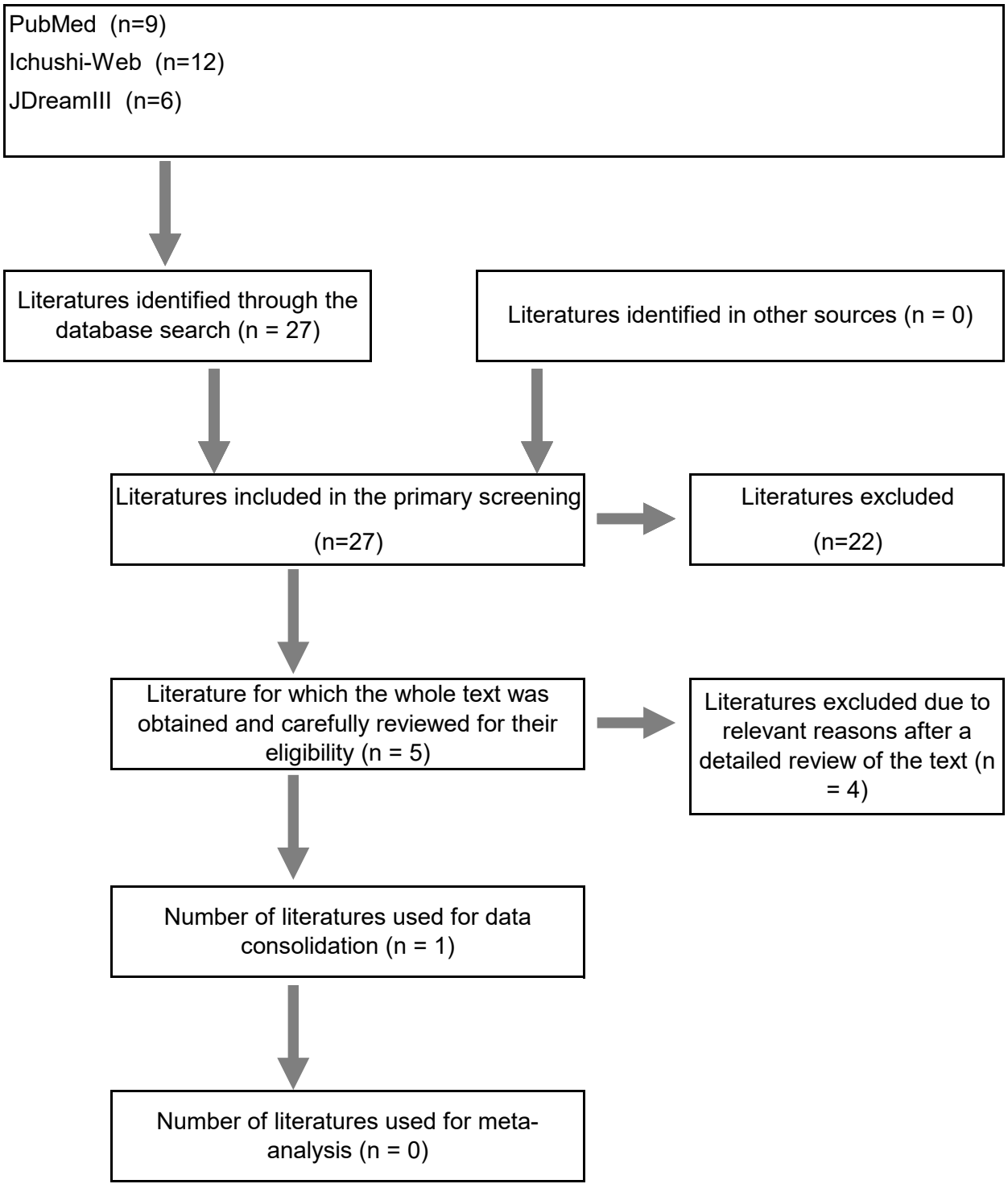
Partially modified from “Minds Guide for Preparation of Treatment Guideline 2014” Edited by Tsuguya Fukui and Naoto Yamaguchi. Igaku-Shoin. 2014.

[Cautions for review]

Attachment (V)-6 [Template, for files to be attached]

Literature Search Flow Chart

Product name: XXXX (TBD)



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)-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, and 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	Jun Nishihira, Mie Nishimura, Masanori Kurimoto, Hiroyo Kagami-Katsuyama, Hiroki Hattori, Toshiyuki Nakagawa, Takato Muro and Masuko Kobori	J. Clin. Biochem. Nutr., 21 May 2021, 1-13 (doi:10.3164/jcbn.21-17)	The effect of 24-week continuous intake of quercetin-rich onion on age-related cognitive decline in healthy elderly people: a randomized, double-blind, placebo-controlled, parallel-group comparative clinical trial	A randomized, parallel-group, double-blind, placebo-controlled study	P: Healthy elderly I: Quercetin-containing onion powder C: Placebo food O: SDS (Self-rating Depression Scale), Apathy scale (motivation)	Electronics Development Computer College, Hokkaido Information University, Health Information Science Center	[Study participants] 38 healthy Japanese men and women (with normal cognitive function or mild cognitive impairment and not on any regular medication) Age: 60–79 years; MMSE >23 [Intervention group (analysis set)] 19 subjects, MMSE 27.1 ± 1.6 [Control group (analysis set)] 19 subjects, MMSE 27.9 ± 1.1	- Take onion powder containing quercetin 50 mg daily for 24 weeks	- Onion powder containing no quercetin	PPS	Affective function - CADi2: Self-rating Depression Scale (SDS) - CADi2: Apathy Scale (motivation)		No	Present	The research used the matching fund of the NARO, Bio-oriented Technology Research Advancement Institution (BRAIN) and included NARO staff as authors.

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

[Cautions for review]

Attachment (V)-8 [Template, for files to be attached]

List of excluded literatures

Product name: XXXX (TBD)

No.	Authors	Publication	Title	Reason for exclusion
1	Olson CA, Thornton JA, Adam GE, Lieberman HR	J Clin Psychopharmacol 2010 Oct;30(5):573-578	Effects of 2 adenosine antagonists, quercetin and caffeine, on vigilance and mood	Outcome not matching
2	Bigelman KA, Chapman DP, Freese EC, Trilk JL, Cureton KJ	Mil Med. 2011 May;176(5):565-572	Effects of 6 weeks of quercetin supplementation on energy, fatigue, and sleep in ROTC cadets	Outcome not matching
3	Cheuvront SN, Fly BR, Kenefick RW, Michniak-Kohn BB, Rood JC, Sawka MN	Am. J. Physiol.Regul. Integr. Comp. Physiol. 2009 Feb;296(2):R394-401	No effect of nutritional adenosine receptor antagonists on exercise performance in the heat	Outcome not matching
4	Chekalina NI, Shut SV, Trybrat TA, Burmak YH, Petrov YY, Manusha YI, Kazakov YM	Wiad Lek. 2017;70(4):707-711	Effect of quercetin on parameters of central hemodynamics and myocardial ischemia in patients with stable coronary heart disease	Outcome not matching

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

[Cautions for review]

Attachment (V)-9 [Template, for files to be attached]

List of unreported studies

Product name: XXXX (TBD)

The search was conducted on July 22, 2022 using UMIN-CTR. One study was identified via the search using the free word, “quercetin affective function”. No studies were detected via search words “quercetin apathy”, “quercetin motivation”, “quercetin mood”, or “quercetin depression”. The identified study had been published, and corresponded to the Literature 1 included for this systemic literature review.

No.	Study owner	Name/ID of the clinical study registration database	Title	Status (e.g., Ongoing)
1	Hokkaido Information University	UMIN-CTR/ UMIN000036276	Beneficial Effects of Quercetin-Rich Onion on Cognitive function	Completed (Literature 1 is the report on the results of this study)

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

[Cautions for review]

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Attachment (V)-10 [Template, for files to be attached]

List of references

Product name: XXXX (TBD)

No.	Author, title, journal
1	Cabinet Office, Elderly Social White Paper 2020, Chapter 1, Section 1, https://www8.cao.go.jp/kourei/whitepaper/w-2020/zenbun/02pdf_index.html
2	Y.E. Geda et al., The Prevalence of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Normal Cognitive Aging: A Population-Based Study, Arch. Gen. Psychiatry, 65(10), 1193-1198, 2008
3	E. Martin & L. Velayudhan, Neuropsychiatrc Symptoms in Mild Cognitive Impairment: A Literature Review, Dement. Geriatr. Cogn. Disord., 49, 146-155, 2020
4	Y. Arai et al., Dietary Intake of Flavonols, Flavones and Isoflavones by Japanese Women and the Inverse Correlation between Quercetin Intake and Plasma LDL Cholesterol Concentration, J. Nutr., 130, 2243-2250, 2000
5	N. Otaki et al., Distribution and Major Sources of Flavonoid Intake in Middle-Aged Japanese Women, J. Clin. Biochem. Nutr., 44, 231-238, 2009
6	R. Menezes et al., Impact of Flavonols on Cardiometabolic Biomarkers: A Meta-Analysis of Randomized Controlled Human Trials to Explore the Role of Inter-Individual Variability, Nutrients, 9(2), 117, 2017
7	K. Onoda et al., Validation of a new mass screening tool for cognitive impairment: Cognitive Assesment for Dementia, iPad version, Clin. Interv. Aging, 8, 353-360, 2013
8	Keiichi Onoda, Shuhei Yamaguchi, An iPad application on mass–screening for dementia： The development and validation of CADi, Higher brain function research, 34(3), 331-334, 2014
9	K. Onoda & S. Yamaguchi, Revision of the Cognitive Assessment for Dementia, iPad version (CADi2), PLOS ONE, 9(10), e109931, 2014

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

[Cautions for review]

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

Quality assessment sheet for each article (clinical study [human study])

Product name: XXXX (TBD)

Subjects	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
Intervention	Intake of quercetin-containing food
Control	Intake of placebo food

Outcome	Positive mood, motivation

*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/Suspected (-1)”, and “Low (0)”.

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	Research quality (QL)		Randomi-zation	Conceal-ment of allocation	Participants	Outcome assessor	ITT, FAS, PPS,	Incomplete outcome data				Subjects	Inter-vention	Control	Outcome	Summary
Literature 1	J. Clin. Biochem. Nutr., 21 May 2021, 1-13 (doi:10.3164/jcbn.21-17)	A randomized, parallel-group, double-blind, placebo-controlled study	QL1	Evaluation Results	0	0	0	0	-2	0	0	-1	-1	0	0	0	0	0
				Comments					PPS			The research was funded by the NARO, Bio-oriented Technology Research Advancement Institution (BRAIN) and included NARO staff as authors.						

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

Attachment (V)-11a-2(1) (if continuous variables are used as indices) (partially modified from the template provided by the Consumer Affairs Agency)

Quality assessment sheet for each article (clinical study [human study])

Product name: XXXX (TBD)

Subjects	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
Intervention	Intake of quercetin-containing food
Control	Intake of placebo food

Outcome	Positive mood

*NS: Not significance

Individual study				Pre-/post-intervention values in each group															
Study code	Publication	Study design	Research quality (QL)	Subjects	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. Clin. Biochem. Nutr., 21 May 2021, 1-13 (doi:10.3164/jcbn.21-17)	A randomized, parallel-group, double-blind, placebo-controlled study	QL1	60 to 79 year-old Japanese men and women with normal cognitive function (MMSE >23, including mild cognitive impairment) who were not regularly on any medication (19 subjects in the control group and 19 in the intervention group)	CADi2: Positive mood	Self-rating Depression Scale (mood)	32.9±6.4	After 12 weeks	-	-0.7±6.2	-	32.5±8.1	After 12 weeks	-	-1.2±3.4	-	-0.5	N.S.	
								After 24 weeks	-	0.9±3.4	-		After 24 weeks	-	-3.0±5.6	-	-3.9	p=0.004	

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[Cautions for review]

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

Quality assessment sheet for each article (clinical study [human study])

Product name: XXXX (TBD)

Subjects	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
Intervention	Intake of quercetin-containing food
Control	Intake of placebo food

Outcome	Motivation

*NS: Not significance

Individual study				Pre-/post-intervention values in each group														
Study code	Publication	Study design	Research quality (QL)	Subjects	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. Clin. Biochem. Nutr., 21 May 2021, 1-13 (doi:10.3164/jcbn.21-17)	A randomized, parallel-group, double-blind, placebo-controlled study	QL1	60 to 79 year-old Japanese men and women with normal cognitive function (MMSE >23, including mild cognitive impairment) who were not regularly on any medication (19 subjects in the control group and 19 in the intervention group)	CADi2: Motivation	Apathy Scale (Motivation)	4.3±4.0	After 12 weeks	-	-0.5±3.0	-	6.3±5.0	After 12 weeks	-	-0.3±3.6	-	0.2	N.S.	
								After 24 weeks	-	-0.2±2.9	-		After 24 weeks	-	-2.3	-	-2.3	p=0.099	

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

[Cautions for review]

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	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
Intervention	Intake of quercetin-containing food
Control	Intake of placebo food

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
Positive mood, motivation	RCT / 1 report	Evaluation Results	-1	0	0	-1	-1		(C)	
		Comments	Attrition bias and other bias risks were involved.			Consistency was unclear, as only 1 literature was included.	The possibility cannot be ruled out, as the number of included literatures was too small.		The overall scientific evidence level rated by NARO Function Claim Assessment Committee	

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

*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).

[Cautions for review]

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	Is the intake of quercetin-containing food superior to placebo food in maintaining positive mood and motivation that tend to decrease with age in healthy middle-aged and elderly people?

P	Individuals aged ≥40 years with no disease (excluding pregnant/lactating women)
I (E)	Intake of quercetin-containing food
C	Intake of placebo food

O2	Positive mood, motivation
Summary of bias risk	A included literature used for evaluating the overall evidence was a randomized, parallel-group, double-blind, placebo-controlled study. PPS was used for the analysis method; thus, attribution bias risk was suspected. Based on the above results, the bias risk was rated as moderate/suspected (−1).
Summary of indirectness	A included literature used for evaluating the overall evidence was on healthy Japanese adults meeting the inclusion criteria. The intervention and control met the inclusion criteria. The outcome was positive mood (SDS) and motivation (Apathy scale). Based on the above results, indirectness was rated as Low (0).
Summary of inconsistency and other	A included literature used for evaluating the overall evidence demonstrated the results of “effective” with a significant difference from the control group. Although UMIN-CTR was utilized, the possibility of publication bias could not be ruled out, as the number of included literatures was limited, that is, only 1 report. Based on the above results, the inconsistency was rated as moderate/suspected (−1).
Comments	The results of the evaluation by the NARO Function Claim Assessment Committee for Agricultural, Forestry and Fish Products were as follows. Overall scientific evidence level: C Level of “research type, quality, and quantity”: C Consistency level: C

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

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

Assessment sheet on the relationship between the results of the systematic literature review and the proposed function claim

Product name: XXXX (TBD)

Outcome: Positive mood		Effective		Indeterminable		No effect		Unfavorable effect	
Human studies	Total	1 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: 1 literature(s)	QL1:	1 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature	0 literature
	QL2:	0 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

Outcome: Motivation		Effective		Indeterminable		No effect		Unfavorable effect	
Human studies	Total	0 literature(s)		0 literature(s)		1 literature(s)		0 literature(s)	
		RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT	Non-RCT
Grand total: 1 literature(s)	QL1:	0 literature	0 literature	0 literature	0 literature	1 literature	0 literature	0 literature	0 literature
	QL2:	0 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 function claim

[Results of this systematic literature review]
One literature that was consistent with the research question was included. The included literature confirmed that the intake of quercetin-containing food in the elderly (including mild cognitive impairment) was significantly superior to the control group in maintaining a positive mood that tends to decrease with age. Furthermore, motivation tended to improve. While further evidence is necessary, the results of this systematic literature review generated positive results, suggesting that the intake of quercetin-containing food should help maintain a positive mood that tends to decrease with age in healthy older adults.

[Description of food]
The test meal in the included literature was in powder form.

(Once the registered product that is the subject of this systematic literature review is decided, a discussion is needed to verify its equivalence with the product.)

[Subjects]
The included literature covered elderly Japanese men and women with normal cognitive function or mild cognitive impairment, which should be appropriate for extrapolation to the anticipated users of the product to be registered, that is, the healthy elderly Japanese population.

[Daily standard intake]
Quercetin intake in the included literature was 50 mg/day. Accordingly, the intake of quercetin 50 mg/day should be beneficial in maintaining a positive mood that tends to decrease with age in the elderly population.

(Once the registered product that is the subject of this systematic literature review is decided, a dose corresponding to the product should be selected.)

[Relationship between the outcome index in the systematic literature review and the proposed function claim]
This systematic literature review included a literature evaluating an outcome index related to affective function in older adults. In a included literature, the results were “effective,” showing a significant improvement in SDS (depression scale, mood) compared with the control group, Besides, the Apathy Scale (motivation) tended to improve, although no significant difference was confirmed. The improved depression scale (mood) leads to maintaining a positive mood in daily life. Therefore, the outcome index used in this systematic literature review should be highly related to the proposed function claim (maintaining a positive mood that tends to decrease with age in the elderly population).

Explanatory material on mechanism of action

1. Product overview

Product name	XXX (Product name)
Name of functional substance	Quercetin
Proposed function claim	This product contains quercetin. Quercetin has been reported to have functions that help maintain a positive mood that tends to decrease with age in healthy elderly individuals.

2. Mechanism of action

As humans age, functional alterations of brain occur, resulting in the loss and decrease of neurons, as well as senile changes including neurofibrillary degeneration and senile plaques. Neurodegenerative diseases, such as dementia, are a pathological manifestation of such changes[(1)]. Symptoms of dementia include not only cognitive decline but also psychiatric symptoms and behavioral abnormalities[(2)], which are also prevalent among the elderly with mild cognitive impairment[(3,4)] and normal cognitive function[(4)]. Of these, the incidences of depression, apathy (lack of motivation/interest), anxiety, irritability, and sleep disorder are increasing today. Oxidative stress caused by active oxygen is one of the mechanisms of neurodegeneration. Active oxygen damages neuron proteins, lipids, and DNA, resulting in neuronal death[(5)]. In addition, aging reduces brain antioxidant status, thereby increasing neuron damage[(6)].

Meanwhile, depression is also suggested to relation to neuronal death[(7)] and suppressed hippocampal neurogenesis[(8)], and brain inflammation could be involved in depression/depression-like symptoms[(9–11)]. Furthermore, quercetin has been shown to reduce depression-like behavior in several animal models of depression-like behavior[(12,13)].

Quercetin reduces oxidative stress-induced damage to neurons, either directly or indirectly, by eliminating active oxygen and free radicals and through metal chelating activity. In the molecular structure of quercetin, 3- and 5-hydroxyl, in particular, are assumed to contribute to its potent antioxidant effects[(14)]. Moreover, quercetin provides anti-inflammatory effects[(15, 16)] through the inhibition of NF-kappa B (nuclear factor-kappa B) activity and effects on hippocampal neurogenesis[(17)] through BDNF (brain-derived neurotrophic factor) and is considered to protect neurons. In animal models of depression-like behavior, quercetin has been shown to improve depression-like symptoms and, at the same time, improve antioxidant functions and decrease the damage caused by inflammation[(12,18,19)].

Thus, it is suggested that quercetin’s oxidative stress-reducing effects and anti-inflammatory effects interact mutually to help maintain a positive mood that tends to decrease with age.

3. References

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