ORIGINAL

Science-based Ratings of Safety and Effectiveness of Ingredients of Health Foods Distributed in Japan Differ among Health Food Categories

Hiroko Hashida[1], Mayumi Okuma[1], Fumio Shimura[1], Yuko Yamazaki[2*]

[1] *Department of Food and Nutritional Sciences, Graduate School of Human Life Sciences, Jumonji University, 2-1-28, Sugasawa, Niiza, Saitama 352-8510, Japan.*
[2] *Department of Food and Nutrition, Faculty of Human Life. Jumonji University, 2-1-28, Sugasawa, Niiza, Saitama 352-8510, Japan.*

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ABSTRACT ***Background and purpose.*** Health foods are increasingly popular in Asian countries including Japan. Professionals such as dietitians have a role to help consumers use health foods based on scientific evidence on safety and effectiveness in order to prevent health or economic problems. This requires knowledge and utilization of health food legal systems and reliable information sources. Health foods in Japan are divided into "Food with Health Claims" (FHC) as defined in the Health Promotion Act etc. and "So-called health foods" treated as general foods without legal regulations. FHC are further categorized into "Foods with Nutrient Function Claims" (FNFC), "Foods for Specified Health Uses" (FOSHU), and "Food with Function Claims" (FFC). There may be differences, as yet unknown, among categories in the safety and effectiveness evaluation of health food ingredients distributed in Japan. The verification of these differences was considered to be useful for nutrition practice activities in Asia and is the subject of the present study. ***Method.*** The safety and effective evaluation of health food ingredients in each category, FNFC, FOSHU, and "Popular Health Foods in Japan" (PHFJ), were compared and examined based on the ratings in the book version of the Natural Medicine Comprehensive Database (NMCD). In order to enable non-parametric statistical analysis, we converted the language ratings (nominal variables) by NMCD to rating scores (ordinal variables). ***Results.*** The ratio of ingredients unlisted in the NMCD was significantly higher for FOSHU. The average rank of FNFC ingredients was significantly higher in safety, effectiveness, and total rating scores than those of FOSHU and "PHFJ without FNFC+FOSHU" ingredients, but there was no significant difference between FOSHU and PHFJ. The average rank of ingredients of "FFC in PHFJ" was significantly higher in safety, effectiveness, and total rating scores than those of "non-FHC in PHFJ". Ingredients of Health foods distributed in Japan differed in their safety and effectiveness assessments by NMCD due to differences in legal regulations and systems. Also, the reliability of scientific evidence on safety and effectiveness seemed to be related to sales. ***Conclusion.*** The findings obtained in this study would serve as a reference for Asian professionals to know the Japanese health food regulatory systems and promote the use of health food based on scientific evidence on safety and effectiveness. In addition, the findings would be useful for Asian countries to develop health food systems.

Keywords: health food, scientific evidence, safety, effectiveness, legal systems, category

INTRODUCTION

In Asian countries, including Japan, there has been increasing attention to a variety of foods that are manufactured, sold, and used with suggestions or claims to be useful for health maintenance and promotion (1-4). These new kinds of foods are collectively called health foods in Japan (5, 6).

*To whom correspondence should be addressed: mitikawa@jumonji-u.ac.jp

Abbreviations: FHC, Foods with Health Claims; FNFC, Foods with nutrient function claims; FOSHU, Food for specified health uses; FFC, Foods with Function Claims; PHFJ, popular health foods in Japan; NMCD, Natural Medicines Comprehensive Database

Health foods, however, are sometimes associated with health or economic problems because of their diversity in terms of quality, safety and effectiveness (7, 8). The safe and secure use of health foods without problems requires consumer behaviour based on scientific information on safety and effectiveness. In turn, experts such as dieticians in charge of nutrition practice activities are required to have basic knowledge and related skills as information providers (4, 7). Legal systems of health foods and re liable sources of information are also key principle for providing fair and impartial information to consumers.

In Japan, health foods are classified into "foods with health claims" (FHC) stipulated by the Health

Promotion Act (7, 8) and so-called health foods that fall under general foods. Currently, FHC are further categorized into "Foods with Nutrient Function Claims" (FNFC), "Foods for Specified Health Uses" (FOSHU), and "Food with Function Claims" (FFC) (4, 5, 8, 9).

FNFC products are taken for the purpose of supplementing/ complementing nutritional ingredients when normal dietary intake is difficult due to aging, disorders in eating habits, etc. FNFC is under a legal system of standard regulation. Thus, to sell FNFC products, it is necessary to comply with government standards established from solid and extensive scientific evidence that has been historically accumulated on safety and effectiveness. Products that meet the standards can claim specified nutrient functions as FNFC (4, 10, 11).

FOSHU products contain some specific ingredients and can claim by labeling that those who take them for specified health purposes in their daily diets can expect the purposes. FOSHU is under a legal system of individual approval. In order to sell FOSHU products, the labeling of health claims must be approved by the Commissioner of Consumer Affairs Agency. The labeling is approved, as a general rule, through science-based strict screening by the government regarding the safety and effectiveness of each product (7, 12).

FFC products can be labeled with function claims based on scientific evidence under the responsibility of each food business operator. Because FFC is under a legal system of notification. Information on the evidence supporting the safety and effectiveness of the product must be submitted to the Commissioner of Consumer Affairs Agency before the product is placed on the market. FFC products are not individually pre-approved by the government unlike FOSHU and also do not comply with the strict standards established by the government unlike FNFC (4, 12). This status is similar to that of health foods other than FHC products in that their safety and effectiveness are under self-assessment, do not necessarily meet the standards established by the government, and have not been evaluated by the government.

In a general sense, health foods that comply with the governmental standards or approved by the government are presumed to be safer and more effective than those that do not. However, as far as we know, this speculation has not been verified and has to be resolved. Resolving this issue may be beneficial for nutrition practitioners in Asian countries to provide information on the safe and secure use of health foods.

Based on these backgrounds, we examined and compared how the safety and effectiveness of ingredients were evaluated for each category of health foods distributed in Japan. The categories of health food ingredients investigated were those of FNFC, FOSHU, and popular health food in Japan (PHFJ). The safety and effectiveness of health food ingredients in each category were compared and examined based on the evaluation by the book version of the Natural Medicines Comprehensive Database (NMCD). For comparison between categories by nonparametric statistical analysis, we converted language ratings (nominal variables) by NMCD to rating scores (ordinal variables). Through these procedures, we objectively demonstrated an intuitive prediction that health foods that comply with or are approved by government standards are safer and more effective than those that do not. The knowledge gained will be useful for the practice of Asian nutrition specialists and for the development of health food systems in Asian countries.

METHODS

1. Construction of ingredient lists by health food categories

To find the terms that correspond to ingredients in the original lists written in Japanese, we consulted the following information resources (13, 14). The English names of the ingredients in the lists shown below match the names used in NMCD monographs. In this paper, the notation of component, material, and ingredient, etc. are unified into “ingredient”.

1) Ingredients of Foods with Nutrient Function Claims (FNFC)

As of July 2019, the ingredients of FNFC approved for nutrient function claims are as follows: n-3 fatty acids, 6 minerals (zinc, potassium, calcium, iron, copper, magnesium), and 13 vitamins (niacin, pantothenic acid, biotin, vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, vitamin K, folic acid) (10). A list of these nutritional ingredients was constructed according to the criteria described below.

2) Ingredients of Foods for Specified Health Uses (FOSHU)

A list of approved FOSHU products (February 12, 2019 Final revision: Excel file) was downloaded from a webpage on administrative guidance of food labeling under the Consumer Affairs Agency of the Cabinet Office (15). In this FOSHU product list, 1,064 products are shown in ascending order of permission date with serial numbers, product names, applicants, types of food. Other items shown are as follows: ingredients involved in health functions (also simply described as ingredients in this report), display contents with permission, intake instructions, standard daily intake amount, classification, permission day, permission number. Based on this 1,064-product list, we have constructed a FOSHU ingredient list with 64 ingredients, using the Excel sorting function to sort ingredients of the 1,064 products and consolidate duplicate ingredients into one. This 64-ingredient list was further cleaned up and subjected to statistical analysis with the addition of information on safety and effectiveness as described below.

3) Ingredients of Popular Health Foods in Japan (PHFJ)

The popularity of a health food is probably reflected in its sales amount. Therefore, in this paper, we treated health food ingredients with high annual sales as popular health food ingredients in Japan. In particular, ingredients published in the annual magazine “Health Food Report®” (16) were used for list construction. Since the initial list thus constructed contained ingredients of FNFC and FOSHU, these ingredients were excluded to gain the PHFJ ingredient list composed of FFC and non-FHC ingredient

2. Collection and processing of information on the evaluation of safety and effectiveness of health food ingredients by NMCD monograph

We searched information on the safety and effectiveness of health food ingredients using the

book version of NMCD (17), a collection of monographs titled by ingredient names. NMCD is excellent in quality and quantity as a health food ingredient database, and is characterized by a safety and effectiveness rating (18). For the convenience of statistical analysis, ratings by language (nominal variables) in NMCD were converted into rating scores (ordinal variables) as previously reported (18). In brief: Likely Safe (2), Possibly Safe (1) Possibly Unsafe (-1), Likely Unsafe (-2), and Unsafe (-3). Similarly: Effective (3), Likely Effective (2), Possibly Effective (1), Possibly Ineffective (-1), Likely Ineffective (-2), Ineffective (-3). A rating score of "0" was given to the language rating of "INSUFFICIENT RELIABLE EVIDENCE to RATE". Ingredients unlisted in NMCD and those with rating of "insufficient reliable information available" were not assigned rating scores and were excluded from statistical analysis.

In adding rating scores to the lists for each categories of ingredients, a few more considerations were taken into account. An ingredient with a high effectiveness rating but a low safety rating cannot be used safely and securely. Therefore, the total score, the sum of safety and effectiveness scores, was regarded as an index of usefulness. For the safety rating, evaluation by intake of the health food, dietary supplement or drug was selected. When the rating in NMCD was on oral ingestion with the amount of ordinary food, the rating score was decreased by 1 point.

The effectiveness ratings added in the lists were those for health and medical uses such as effects on body structures and functions other than simple nutrient supplementation effects, and reduction of disease risks. The effectiveness of FNFC and FOSHU ingredients were selected only for NMCD ratings on functions approved or specified under the government regulation in Japan. When the effectiveness rating of PHFJ ingredients involve a wide range of functions, we selected the health purpose with the highest rating.

3. Statistical comparison between health food categories of the safety and effectiveness rating of ingredients

Results of mean rating score were expressed as mean ± standard deviation. In the comparison of the number of ingredients listed or unlisted in NMCD, when there was a significant difference in chi-square test, residual analysis was performed. In the comparison of the scores among 3 groups, when there was a significant difference in the Kruskal-Wallis test, the Steel-Dwass test was subsequently performed. In addition, the Mann-Whitney test was performed to compare 2 groups. BellCurve for Excel version 3.20 (Social Survey Research Information Co., Ltd.) software was used.

Table 1. Ingredients of Foods with Nutrient Function Claims (FNFC)

No.	Nutrient	Rating score			Nutrient Function Claims of FNFC *
		Safety	Effectiveness	Total	
1	n-3 Fatty acid	2	-	-	Maintain skin
2	Zinc	2	1	3	Maintain normal taste and helps to maintain healthy skin and mucous membranes.
3	Potassium	2	1	3	Maintain proper blood pressure.
4	Calcium	2	2	4	Development of bone and teeth.
5	Iron	2	3	5	Necessary in the red blood cell formation.
6	Copper	2	2	4	Form red blood cells and helps the proper function of many body enzymes and bone formation.
7	Magnesium	2	3	5	Development of bone and teeth. Maintain proper blood circulation, and helps proper function of many body enzymes and energy generation.
8	Niacin	2	2	4	Maintain skin and mucosa health.
9	Pantothenic acid	2	3	5	Maintain skin and mucosa health.
10	Biotin	2	2	4	Maintain skin and mucosa health.
11	Vitamin A	2	3	5	Maintain vision in the dark. Maintain skin and mucosa healthy.
12	Vitamin B1	2	3	5	Produce the energy from carbohydrate and to maintain skin and mucosa health.
13	Vitamin B2	2	3	5	Maintain skin and mucosa health.
14	Vitamin B6	2	3	5	Produce energy from protein and to maintain skin and mucosa health.
15	Vitamin B12	2	3	5	Aids in red blood cell formation.
16	Vitamin C	2	3	5	Maintain skin and mucosa health and has anti-oxidizing effect.
17	Vitamin D	2	3	5	Promotes absorption of calcium in gut intestine and aids in the growth of bone.
18	Vitamin E	2	3	5	Protect fat in the body from being oxidized and to maintain the cell health.
19	Vitamin K	2	3	5	Maintain proper blood coagulability.
20	Folic acid	2	3	5	Aids in the red blood cell formation, and contributes the normal growth of the fetus.
	mean ± SD	2.00 ± 0.00	2.58 ± 0.69	4.58 ± 0.69	

Note: This table should not use for the purpose of providing information to consumers because the information is very limited. Refer to the NMCD for details of ingredient.

*: "Nutrient Function Claims of FNCN" are shown in simplified forms (reference 10, 11).

RESULTS

1. Lists of Health Food Ingredients with Information on Safety and Effectiveness

1) Ingredients of Foods with Nutrient Function Claims (FNFC)

Nutrient function claims of FNFC are regulated by the Food Labeling Law, and 20 nutrients are currently approved to be used as functional ingredients in FNFC products. NMCD contains monographs on all these ingredients except n-3 fatty acids. For n-3 fatty acids, monographs of the equivalent ingredients DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid), fish oil, and α-linolenic acid were available instead.

Table 2. Ingredients of Foods for Specified Health Uses (FOSHU)

No.	Functional ingredient【NMCD monograph name】	Rating score			Health claims approved as FOSHU *1
		Safety	Effectiveness	Total	
1	Agar【AGAR】	1	-	-	Gastrointestinal conditions
2	Reduced molecular weight sodium alginate【ALGIN】	1	-	-	Gastrointestinal conditions, Blood cholesterol level
3	Barley young leaf, barley【BARELY】	2	-	-	Gastrointestinal conditions, Blood sugar levels
4	Plant sterol【BETA-SITOSTEROL】	2	2	4	Blood cholesterol level
5	Bifidobacteria【BIFIDOBACTERIA】	2	1	3	Gastrointestinal conditions
6	Psyllium seed coat-derived dietary fiber【BLOND PSYLLIUM】	2	3	5	Gastrointestinal conditions
7	Calcium【CALCIUM】	2	2	4	Osteogenesis (Reduction of disease-risk)
8	Calcium hydrogen phosphate / CPP-ACP (Casein phosphopeptide – amorphous calcium phosphate as calcium) / POs-Ca (Phosphorylated oligosaccharide calcium)【CALCIUM】	2	1	3	Dental health
9	Lactotripeptide【CASEIN PEPTIDE】	-	0	-	Blood pressure
10	Chitosan【CHITOSAN】	1	0	1	Blood cholesterol level
11	DHA･EPA【DHA･EPA】*2	2	0	2	Blood triacylglycerol level
12	Green tea-derived fluorine【FLUORIDE】	2	3	5	Dental health
13	Fructo-oligosaccharides【FRUCTO-OLIGOSACCHARIDES】	1	0	1	Gastrointestinal conditions
14	Gamma-aminobutyric acid (GABA)【GABA】	-	-	-	Blood pressure
15	Tea catechins, Tea polyphenol【Green tea】	1	1	2	Blood cholesterol level
16	Guava leaf polyphenol【GUAVA】	1	-	-	Blood sugar levels
17	Monoglucosyl hesperidin【HESPERIDIN】	1	-	-	Blood triacylglycerol level, Blood pressure
18	Kudzu flower extract (Tectorigenin)【KUDZU】	1	-	-	Body fat
19	Lactobacillus【LACTOBACILLUS】	2	2	4	Gastrointestinal conditions
20	Medium chain triglycerides【MEDIUM CHAIN TRIGLYCERIDE】	2	-	-	Body fat
21	*Bacillus subtilis* K-2 (spore)【NATTOKINASE】	1	-	-	Gastrointestinal conditions
22	Quercetin glycoside (as isoquercitrin)【QUERCETIN】	1	-	-	Body fat
23	Soy oligosaccharide, Soy isoflavone, Soy protein, Beta conglycinin【SOY】	2	1	3	Gastrointestinal conditions, Osteogenesis, Blood triacylglycerol level, Blood cholesterol level
24	High molecular weight black tea polyphenol (as theaflavin)【TEAFLAVIN】	-	-	-	Blood triacylglycerol level
25	Vitamin K2 (menaquinone-4, menaquinone-7)【VITAMIN K】	2	0	2	Osteogenesis
26	Wheat bran / Whole wheat and wheat hulls-derived dietary fiber【WHEAT BRAN】	2	1	3	Gastrointestinal conditions
27	MBP® (Milk Basic Protein) (as cystatin 20μg)【WHEY PROTEIN】	2	-	-	Osteogenesis
28	Xylitol【XYLITOL】*2	1	2	3	Dental health
	mean ± SD	1.56 ± 0.51	1.19± 1.05	3.00± 1.25	

Note: This table should not use for the purpose of providing information to consumers because the information is very limited. Refer to the NMCD for details of ingredient.

*1: "Health claims approved as FOSHU" are shown in simplified forms (reference 11, 15).

*2: Approved for products at contain mixture functional ingredients (DHA and EPA), (Xylitol, maltitol, calcium hydrogen phosphate, and fukuronori extract).

Table 3. Ingredients of FOSHU products unlisted in NMCD monographs

No.	Functional ingredient	No.	Functional ingredient
1	Acetic acid	19	Lactulose
2	Apple-derived procyanidins	20	L-arabinose
3	Broccoli, cabbage-derived S-methylcysteine sulfoxide (natural amino acid)	21	Maltitol
4	Chinese gutta percha (as geniposidic acid)	22	Neokotalanol
5	Chlorogenic acids (as 5-caffeoylquinic acid)	23	Nori (*Porphyra yezoensis*) oligopeptide (as Ala-Lys-Tyr-Ser-Tyr)
6	Coffee bean mannooligosaccharide (as mannobiose)	24	Oolong tea polymerized polyphenols (as oolonghomobisflavan B) *
7	Erythritol	25	Palatinose
8	Eucalyptus extract (as macrocarpal C)	26	Polydextrose
9	Fukuronori (*Gloiopeltis furcata*) extract (as funoran)	27	Polyglutamic acid
10	Galacto-oligosaccharides	28	Products of propionic acid bacteria (as 1, 4-dihydroxy-2-naphthoic acid)
11	Globin protein degradation product (as Val-Val-Tyr-Pro)	29	Royal jelly-derived peptides (Val-Tyr, Ile-Tyr, Ile-Val-Tyr)
12	Glucosyl ceramide	30	Sardine peptide (as Val-Tyr)
13	Highly cross-linked phosphate cross-linked starch (as dietary fiber)	31	Sesame peptide (as Leu-Val-Tyr)
14	Indigestible dextrin	32	*Streptococcus thermophilus*
15	Indigestible recrystallized amylose (as α-1, 4 glucan aggregate)	33	Water-soluble corn bran fiber
16	Isoleucyltyrosine	34	Wheat-derived albumin
17	Isomaltooligosaccharides	35	Xylooligosaccharide
18	Lacto-sucrose	36	Yang long flavonoids (as hyperoside and isoquercitrin)

*: Although there is the NMCD monograph of oolong tea, it was excluded from Table 2 because there was no description as oolonghomobisflavan.

Table 1 shows the NMCD evaluation of the safety and effectiveness of each ingredient as rating scores (ordinal variables) converted from ratings (nominal variables) by the procedure above. In addition, the nutrient functions that were evaluated for effectiveness are shown in simplified forms.

NMCD has rated all the 20 nutrient function ingredients including n-3 fatty acid-equivalent fatty acids as “likely safe”, thus the mean rating score of the safety of FNFC ingredients was 2.00 ± 0.00.

Table 1 excludes the effectiveness rating of n-3 fatty acid-equivalent fatty acids. This is because the monographs provide no information on the effectiveness of the allowed nutrient function labeling to help maintain the skin. The effectiveness ratings of 19 ingredients other than n-3 fatty acid-equivalent fatty acids are tallied as follows: “Effective (rating score of 3; 13)”, “Likely Effective (rating score of 2; 4)”, and “Possibly Effective (rating score of 1; 2)”. Thus, the mean rating score ± standard deviation was 2.58 ± 0.69. The total mean rating score and standard deviation of the 19 ingredients were very high at 4.58 ± 0.69, of which 13 ingredients had the highest score of 5.

2) Ingredients of Foods for Specified Health Uses (FOSHU)

FOSHU products contain some ingredients for specified health use and can be sold with labelling of health claims approved by the Commissioner of Consumer Affairs Agency (7, 12). The official list (last revised on February 12, 2019) of FOSHU products, downloaded from the website of the Consumer Affairs Agency of the Cabinet Office, contained 1,064 products (15). Functional ingredients of these 1,064 products were organized and integrated into 64 ingredients by putting together the same and similar ingredients. Searching of the 64 ingredients by the English term, converted from Japanese name using several sources (13, 14), we found NMCD monographs corresponding to 28 ingredients but not to the remaining 36 ingredients. The 28 ingredients for which monographs were found are listed in Table 2, together with the rating scores derived from NMCD ratings in nominal variables of the safety and effectiveness. The effectiveness rating scores in this table are limited to those for specified health uses approved to the FOSHU products. Calcium is also approved as a “reduction of disease-risk FOSHU” other than “ordinary FOSHU” (11). Therefore, two health claims, osteogenesis and dental health, are included in Table 2.

Table 2 shows the 28 FOSHU ingredients whose monographs are contained in NMCD, and a considerable number of them have been used as functional ingredients in many FOSHU products as follows: Chitosan (49 products), Tea catechin (45 products), Lactobacillus (37 products), and others. Twenty-five of the 28 ingredients were evaluated for safety by NMCD as follows: "Likely safe (rating score of 2; 14)", "Possibly safe (rating score of 1; 11)". The mean safety score for the 25 ingredients was 1.56 ± 0.51.

For 16 ingredients in Table 2, NMCD monographs have rated the effectiveness of health function claims approved for FOSHU products as follows: "Effective (rating score of 3; 2)", "Likely Effective (rating score of 2; 4)", and "Possibly Effective (rating score of 1; 5)". Five ingredients of the 28 ingredients were rated as "INSUFFICIENT RELIABLE EVIDENCE to RATE (rating score of 0)" for the effectiveness in health functions approved to for FOSHU products. Ratings for effectiveness of 12 ingredients were not described in NMCD monographs. The mean effectiveness rating score of the 16 ingredients was 1.19 ± 1.05. In addition, the mean total score, the sum of safety rating score and effectiveness rating score, was 3.00 ± 1.25. Of the 36 ingredients unlisted in NMCD monographs (Table 3), indigestible dextrin (to improve gastrointestinal condition, blood sugar levels, blood triacylglycerol level) had an outstanding occupancy rate of about 36.2% (385 products) as a functional ingredient used in FOSHU products. Although FOSHU products are individually approved through a fair and strict governmental review, most of their functional ingredients have not been monographed by NMCD (56%: 36/64).

3) Ingredients of Popular Health Foods in Japan (PHFJ)

The popularity of a health food is probably reflected in its sales amount. Therefore, in this paper, we handled health food ingredients with high annual sales as popular health food ingredients in Japan. In particular, ingredients enumerated in the annual magazine "Health Food Report®", a valuable and concise information resource on the health food market status in Japan, were selected for list construction.

Table 4 shows the top 49 PHFJ ingredients enumerated in the "Health Food Report®" in order of sales amounts, with English keywords for searching NMCD monographs, along with NMCD rating scores on their safety and effectiveness. This table also shows the overlap between the top 49 PHFJ ingredients and FHC ingredients. We could find NMCD monographs corresponding to 40 ingredients out of the 49 PHFJ ingredients (Table 4). However, monographs matching "Multi-vitamin", "Amino acids", and "Vitamin B complex" were undetectable, because these keywords did not specify a single ingredient. Thirty seven of the 49 PHFJ ingredients were also used for health foods in any of the FHC category. (FNFC, FOSHU, and FFC). According to NMCD monographs, the safety of the 37 PHFJ ingredients are rated as follows in tally: "Likely safe (rating score of 2; 17)", "Possibly Safe (rating score of 1; 20)". The safety of gamma-aminobutyric acid and ornithine was not described in the monographs. The mean safety score of the 37 ingredients was 1.46 ± 0.51.

For 36 ingredients in Table 4, NMCD monographs have rated the effectiveness on health function as follows: "Effective (rating score of 3; 4)", "Likely Effective (rating score of 2; 5)", "Possibly Effective (rating score of 1; 16)", "INSUFFICIENT RELIABLE EVIDENCE to RATE (rating score of 0; 10)", and "Possibly Ineffective (rating score of -1; 1)". Ratings for effectiveness of 4 ingredients were not described in NMCD monographs. The mean effectiveness rating score of the 36 ingredients was 1.03 ± 1.00. In addition, the mean total score, the sum of safety rating score and effectiveness rating score, was 2.57 ± 1.36.

"PHFJ without FNFC + FOSHU" in Table 4 shows the PHFJ ingredients excluding those that overlap with FNFC and FOSHU. Of the 49 ingredients of PHFJ, 28 ingredients did not overlap with FNFC or FOSH, 3 of which were unlisted on the NMCD. For the remaining 25 ingredients, the mean safety score was 1.32 ± 0.48, the mean efficacy score was 0.81 ± 0.81, and the mean total score was 2.25 ± 1.12.

2. Statistical comparison between health food categories of the safety and effectiveness rating of ingredients

Whether the ratio of the ingredients listed in NMCD differed among health food categories was performed by chi-square test and subsequent residual analysis. As shown in Table 5, the ratio of ingredients unlisted in NMCD was found to be significantly higher in FOSHU ingredients.

In Table 6, NMCD rating scores of ingredients were statistically compared among health food categories. PHFJ ingredients were analyzed excluding those that overlapped with FNFC and FOSHU ingredients ("PHFJ without FNFC+ FOSHU"). The means of the safety, effectiveness, and total scores of the ingredients in each category increased in the order of "PHFJ without FNFC+FOSHU" < FOSHU < FNFC. The rating score, however, is an ordinal variable and not suitable for testing the difference between the mean values. Therefore, we used the Kruskal-Wallis test, an independent multi-group nonparametric test method, and found that there were significant differences in rating scores of ingredients among the three categories FNFC, FOSHU, and "PHFJ without FNFC+FOSHU" (Table 6). Multiple comparisons of post-hoc by the Steel-Dwass method showed that the average rank of FNFC ingredients was significantly higher in safety, effectiveness, and total rating scores than those of FOSHU and "PHFJ without FNFC+FOSHU" ingredients (Table 6). PHFJ consists of FHC (FNFC, FOSHU, and FFC) and legally undefined health foods other than FHC (Table 4). FFC is a legally defined category of health foods but is neither approved by the government nor strictly regulated by government standards. Thus, the comparison may be meaningful between the FFC included in PHFJ ("FFC in PHFJ") and PHFJ excluding FHC ("non-FHC in PHFJ"). As shown in Table 7, the average rank of ingredient of "FFC in PHFJ" was significantly higher in safety, effectiveness, and total rating scores than those of "non-FHC in PHFJ".

Table 4. Ingredients of Popular Health Foods in Japan (PHFJ)

Ranking	Ingredient【NMCD monograph name】*1	Rating score			Symptoms described in the effectiveness of NMCD	Overlapping with FHC *2
		Safety	Effectiveness	Total		
1	Multi-vitamin【UNLISTED】					A
2	Vitamin C【VITAMIN C (ASCORBIC ACID)】	2	3	5	Vitamin C deficiency	A
3	Vitamin E【VITAMIN E】	2	3	5	Vitamin E deficiency	A
4	*Aojiru* (green juice)【CABBAGE (Kale)】*3	1	0	1	Cancer, etc.	
5	Protein 【WHEY PROTEIN】	2	1	3	Athletic performance	B
6	Calcium【CALCIUM】	2	3	5	Hypocalcemia	A, B
7	Enzyme (fermented plant extract)【UNLISTED】					
8	Collagen【GERATIN】	1	0	1	Osteoarthritis	C
9	Dietary fiber【BLOND PSYLLIUM (Dietary fiber)】	2	3	5	Constipation	B, C
10	Amino acid【UNLISTED】					C
11	Lactic acid bacteria【LACTOBACILLUS】	2	2	4	Rotaviral diarrhea	B, C
12	Blueberry【BLUEBERRY】	1	-	-		
13	Royal jelly【ROYAL JELLY】	1	0	1	Hyperlipidemia	B
14	Aloe【ALOE】	1	1	2	Constipation	C
15	Ginkgo biloba【GINKGO】	2	1	3	Age-related memory impairment, etc.	C
16	Turmeric【TURMERIC】	1	1	2	Dyspepsia	C
17	Glucosamine【GLUCOSAMINE SULFATE】	2	2	4	Osteoarthritis	C
18	Yeast【BREWER'S YEAST】	1	1	2	Premenstrual syndrome	
19	Sesame【UNLISTED】					B
20	DHA【DHA (DOCOSAHEXAENOIC ACID)】	2	1	3	Coronary artery disease	A, B, C
21	Vitamin B complex【UNLISTED】					A
22	Reishi【REISHI MUSHROOM】	1	0	1	Postherpetic neuralgia	
23	Astaxanthin【ASTAXANTHIN】	1	-	-		C
24	EPA【EPA (EICOSAPENTAENOIC ACID)】	2	1	3	Coronary artery disease	A, B, C
25	Gamma-aminobutyric acid【GABA (GAMMA-AMINOBUTYRIC ACID)】	-	-	-		B, C
26	Chlorella【CHLORELLA】	1	0	1	Fibromyalgia, Glioma	
27	Korean ginseng【GINSENG, PANAX】	1	1	2	Diabetes	
28	*Shijimi* (fresh water clam)【UNLISTED】					
29	Ginger【GINGER】	2	1	3	Morning sickness	C
30	Soy isoflavone【SOY】	2	1	3	Breast cancer (prevention)	B, C
31	Dextrin (indigestible dextrin)【UNLISTED】					B, C
32	Nattokinase【NATTOKINASE】	1	0	1	Deep vein thrombosis	B
33	Hyaluronic acid【HYALURONIC ACID】	-	-	-		C
34	Polyphenol 【COCOA】	2	1	3	Hypertension (as cacao polyphenol)	B, C
35	Lutein【LUTEIN】	2	2	4	Lutein deficiency	C
36	Agaricus【AGARICUS MUSHROOM】	1	0	1	Chemotherapy	
37	Olive 【OLIVE】	2	2	4	Constipation (as olive oil)	C
38	Ornithine【ORNITHINE】	-	-1	-	Athletic performance	C
39	Catechin【GREEN TEA (Epigallo Catechin Gallate)】	1	1	2	Hyperlipidemia	B, C
40	Kudzu flower-derived isoflavone 【KUDZU】	1	0	1	Alcoholism, Angina	B, C
41	Vinegar【APPLE CIDER VINEGAR】	1	0	1	Diabetes, Gastroparesis	B, C
42	Coenzyme Q10【COENZYME Q-10】	2	2	4	Coenzyme Q-10 deficiency	C
43	Ceramide (N-acylsphingosine)【UNLISTED】					B, C
44	Garlic【GARLIC】	2	1	3	Hypertension	C
45	Placenta【UNLISTED】					
46	Propolis【PROPOLIS】	1	0	1	Common cold	
47	Maca【MACA】	1	1	2	Sexual desire	
48	French marine pine bark extract【PYCNOGENOL】	1	1	2	Allergic rhinitis	C
49	Lactoferrin【LACTOFERRIN】	1	1	2	Hepatitis C	C
	PHFJ: mean ± SD	1.46 ± 0.51	1.03 ± 1.00	2.57 ± 1.36		
	PHFJ without FNFC+FOSHU *4: mean ± SD	1.32± 0.48	0.81 ± 0.81	2.25± 1.12		

Note: This table should not use for the purpose of providing information to consumers because the information is very limited. Refer to the NMCD for details of ingredient.

*1: This is the order of top-selling rankings from the "Health Food Report®" (Reference 16), up to 49th. The NMCD monograph name is shown in【】. The mixture ingredients showed【unlisted】because it cannot be specified as one ingredient.

*2: Overlapping ingredients with FHC, A: FNFC, B: FOSHU, C: FFC.

*3: *Aojiru* with index number 16056 was described as "kale juice" in "Standard food composition table in Japan-2015- (7th revised edition)".

*4: PHFJ ingredients excluding those that overlapped with FNFC and FOSHU ingredients.

Table 5. Comparison of the number of listed and unlisted health food ingredients in the three categories of the NMCD monograph

	Listed	(%)	Unlisted	(%)	residual analysis *2	
FNFC	20	(100)	0	(0)	*P <0.001*	Listed > Unlisted
FOSHU	28	(44)	36	(56)	*P <0.001*	Listed < Unlisted
PHFJ without FNFC+FOSHU	24	(86)	4	(14)	*P <0.01*	Listed > Unlisted
Chi-square test *1	*p<0.001*					

*1,2: After the chi-square test, residual analysis was performed.

Table 6. Analysis of rating score of FNFC, FOSHU, and PHFJ without FNFC+FOSHU ingredients

	Safety*1			Effectiveness*1			Total*1		
	mean ±SD	n*2	average rank (n = 67)	mean ±SD	n*2	average rank (n = 56)	mean ±SD	n*2	average rank (n = 54)
FNFC	2.00 ± 0.00	20	20.00 ^{x,a}	2.58 ± 0.69	19	12.79 ^{b,c}	4.58 ± 0.69	19	12.21 ^{d,e}
FOSHU	1.56 ± 0.51	25	34.74 ^{x}	1.19 ± 1.05	16	32.25 ^{b}	3.00 ± 1.25	15	29.80 ^{d}
PHFJ without FNFC+FOSHU	1.32 ± 0.48	22	42.84 ^{a}	0.81 ± 0.81	21	37.19 ^{c}	2.25 ± 1.12	20	37.60 ^{e}
Kruskal-Wallis test *3	*p < 0.001*			*p < 0.001*			*p < 0.001*		

*1: Data are the mean ± standard deviation and average rank.

*2: The score of ingredients unlisted in NMCD was regarded as a missing value and excluded from statistical analysis.

*3: The Kruskal-Wallis test was performed on the differences between categories for each rating score, and the Steel-Dwass test was used for multiple comparisons between three groups with significant differences. Same superscript letters are significantly different.; a, b, c, d, e: ($p < 0.001$); x: ($p < 0.01$).

Table 7. Analysis of rating score of FFC and non-FHC in PHFJ

	Safety *1			Effectiveness *1			Total *1		
	mean ±SD	n *2	average rank (n = 22)	mean ±SD	n *2	average rank (n = 21)	mean ±SD	n *2	average rank (n = 20)
FFC in PHFJ	1.54 ± 0.52	13	9.00	1.08 ± 0.86	13	8.00	2.83 ± 1.03	12	8.00
non-FHC in PHFJ *3	1.00 ± 0.00	9	13.00	0.38 ± 0.52	8	13.00	1.38 ± 0.52	8	12.00
Mann–Whitney *U* test *4	*p < 0.01*			*p < 0.05*			*p < 0.01*		

*1: Data are the mean ± standard deviation and average rank.

*2: The score of ingredients not listed in NMCD was regarded as a missing value and excluded from statistical analysis.

*3: PHFJ excluding FHC (FHC: Food with Health Claims, categorized into FFC, FOSHU and FFC).

*4: Mann–Whitney *U* test was performed on the differences between categories.

We further investigated the relationship between the rating of health food ingredients and their sales amounts. For PHFJ ingredients overlapping with FNFC and FOSHU ("FNFC+FOSHU in PHFJ"), strong positive correlations were found between effectiveness, and total rating scores and sales amounts ($r = 0.76$, $r = 0.74$, respectively) (Fig. 1). However, such correlations were not observed for PHFJ ingredients other than "PHFJ without FNFC+FOSHU".

DISCUSSION

Health foods are increasingly popular in Asian countries including Japan (1-4). Professionals such as dietitians have a role to help consumers use health foods based on scientific evidence on safety and effectiveness in order to prevent health or economic problems. This requires knowledge and utilization of health food legal systems and reliable information sources. As described in the Introduction, in Japan, due to differences in legal regulations, health foods are classified as FHC and so-called health foods, and FHC is further categorized as FNFC, FOSHU, and FFC (4, 5, 8, 9). FNFC, FOSHU, and FFC are under legal systems of standard regulation, individual approval, and notification, respectively. The status of FFC is similar to that of health foods other than FHC. Because both products neither necessarily comply the standards established by the government nor receive evaluation by the government for their safety and effectiveness. Therefore, the safety and effectiveness of health food products may differ

among health food categories. In turn, the safety and effectiveness of health food products are probably most strongly influenced by the safety and effectiveness of ingredients. However, so far, it is unclear whether the evaluation of safety and effectiveness of health food ingredients distributed in Japan differs among categories. Based on these considerations, we examined and compared how the safety and effectiveness of ingredients were evaluated for FNFC, FOSHU, and popular health foods including FFC but excluding FNFC and FOSHU. For this purpose, the evaluations by NMCD monographs of each ingredients were extensively and deeply examined. NMCD is a well-established information source of health food ingredients with an abundant number (more than 1,100) of listed ingredients and with excellent quality characterized by its ratings of the safety and effectiveness of ingredients (17).

In this study, we used a unique approach of assigning a rating score to the rating of safety and effectiveness in NMCD monographs of each ingredient. This enabled statistical comparison and examination between categories of health food ingredients, so that some objective findings described in the result2 were obtained. Here, we will discuss these objective findings and will not mention other interesting but detailed findings in the list of health food ingredients by category.

As shown in Table 5, the ratio of ingredients listed in NMCD monographs was significantly lower in FOSHU ingredients than FNFC and "PHFJ without FNFC+FOSHU" ingredients. This situation is probably due to both characteristics of FOSHU products and NMCD editorial policy. FOSHU products are individually reviewed strictly by the government for safety and effectiveness and allowed to be labeled for specified health uses (7, 12). Each FOSHU product thus guarantees to some extent the safety and effectiveness of the product per se and its ingredients. Planning and development of almost all FOSHU products have been achieved by Japanese companies, from basic research on their functional ingredients to product design. Distribution and use of FOSHU products are also almost limited to Japan.

On the other hand, NMCD is a database compiled by a United States civilian agency. In the US, health claims by foods, such as structure/function claims, general well-being claims, and nutrient deficiency disease claims, are exclusively permitted to dietary supplements defined by the Dietary Supplement Health and Education Act of 1994 (19). Unlike

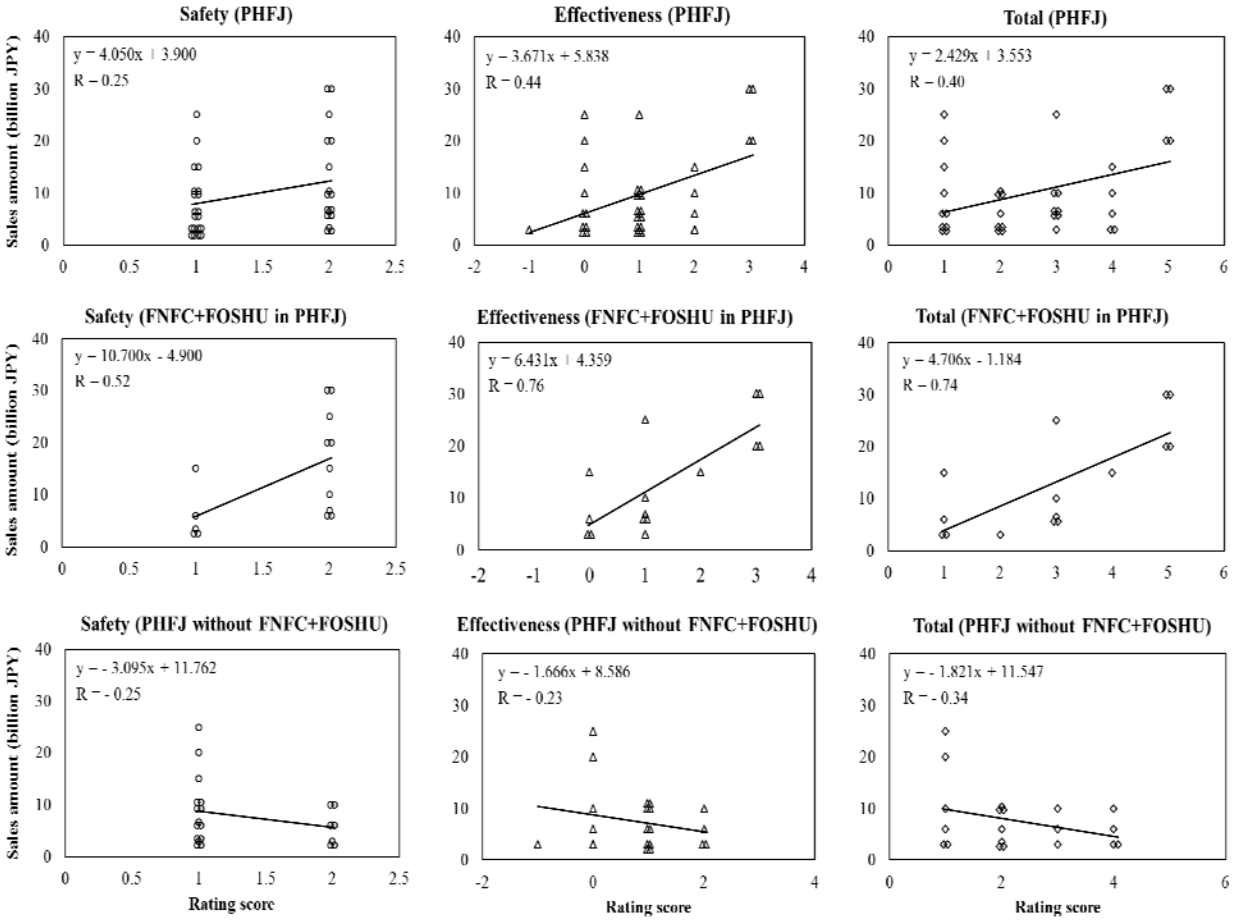

Fig 1. Correlation between rating score and market size about PHFJ
"Sales amount" was referred to Reference 16. "Rating score" was based on the data in Table 4.

FNFC and FOSHU in Japan, dietary supplements are self-assessed for safety and effectiveness, so that they do not necessarily meet government-established standards and also are not evaluated by the government. NMCD evaluates the safety and effectiveness of dietary supplements with these characteristics from a third-party perspective. NMCD is an extremely valuable information source for consumers to use dietary supplements safely and securely based on scientific evidence. Therefore, it is natural that the target of evaluation by NMCD is mainly the ingredients of dietary supplements that are widely distributed in the United States, not the ingredients of FOSHU that are locally distributed in Japan.

FNFC products can be marketed in compliance with governmental standards, which are established based on historically and internationally recognized strong and extensive evidence on safety and effectiveness. Therefore, it can be easily assumed that the safety and effectiveness of the FNFC ingredients are higher than those of the other categories. In this study, we could objectively confirm the validity of this assumption. Post-hoc multiple comparisons by the Steel-Dwass procedure subsequent to the Kruskal-Wallis test showed that the average rank of FNFC ingredients was significantly higher in safety, effectiveness, and total rating scores than those of FOSHU and "PHFJ without FNFC+FOSHU" ingredients (Table 6).

Since FOSHU products are approved through the individual and strict review by the government (7, 12), each FOSHU ingredient is guaranteed to some extent for safety and effectiveness. However, there was no statistically significant difference between the safety, effectiveness and total scores of the FOSHU ingredients and those of the "PHFJ without FNFC+FOSHU" ingredients (Table 6). Again, one of the reasons for this is probably that FOSHU is unique to Japan and NMCD is a database constructed by a civilian institution in the US. Most FOSHU ingredients are unlisted in NMCD monographs as shown in Table 5, even though FOSHU ingredients have scientific bases for their safety and effectiveness to endure various criticism upon strict approval reviews. The fact that many academic papers on FOSHU ingredients are written in Japanese may also make FOSHU ingredients difficult to be properly evaluated.

The Mann–Whitney *U* test showed that the average ranks of ingredients of "FFC in PHFJ" were significantly higher in safety, effectiveness, and total rating scores than those of "non-FHC in PHFJ" (Table 7). In other words, within the top 49 health foods by sales, FFC ingredients were superior in terms of these evaluation indicators to the ingredients of health foods legal undefined. The results in Table 7 suggest that food business operators are steadily committed to the research, development, and product design of FFC based on scientific bases of safety and effectiveness rather than the experience and the oral tradition with poor evidence in order to fulfill their responsibilities.

Sales amounts of health foods possibly reflect consumer preference and consumption behavior. Interestingly, upon analysis from this point of view, we found positive correlations between sales amounts and effectiveness rating scores of PHFJ ingredients (Fig. 1). Further sub-analysis revealed positive correlations between the sales amounts and the safety, effectiveness, and total rating scores of ingredients of PHFJ overlapping with FNFC and FOSHU (Fig. 1). Such correlations were not observed for PHFJ ingredients other than FNFC and FOSHU ingredients. According to these results, many consumers are presumably taking consumption behavior based on the scientific basis of safety and effectiveness of health foods. Although details are unknown, information on the category of health foods, health claims in labeling, consultation with advisory staff such as dietetics, and other factors may facilitate consumer's informed-choices.

In this study, we have obtained new objective findings about Japanese health foods by assigning rating scores for the safety and effectiveness ratings of each ingredient in NMCD monographs. The NMCD is a comprehensive database constructed from extensive surveys of research papers on the effects of health food ingredients on human subjects and provides rating based on predetermined criteria for study design and scale. The information provided by NMCD, including interactions with drugs, is comprehensive and suitable for providing various information to consumers. In addition to providing information to consumers about each product, NMCD can be used to statistically understand the state of health food ingredients as in this study. The Internet version of NMCD (20), where information is constantly updated, is convenient for providing information to consumers, but in this study, the book version was used from the viewpoint of the invariance of information.

The overall evidence in this study suggests that health foods distributed in Japan differed in their safety and effectiveness ratings by NMCD due to differences in their legal regulations and systems. Also, the safety and effectiveness ratings also seemed to relate to sales amounts. Information on the category of health foods, health claims in labeling, consultation with advisory staffs, and others may facilitate consumer's informed-choices.

In Asian countries where health foods are gaining popularity, specialists such as dietitians have a role to help consumers use health foods based on scientific evidence on safety and effectiveness to prevent health and economic problems. The findings obtained in this study would serve as a reference for Asian professionals to understand the Japanese health food regulatory systems and promote the use of health food based on scientific evidence on safety and effectiveness. In addition, the findings would be useful for Asian countries to develop health food systems of their own.

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Conflict of interests:

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