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Functional food products in Japan: A review

Shun Iwatani, Naoyuki Yamamoto*

School of Life Science and Technology, Tokyo Institute of Technology, Yokohama, Kanagawa, 226-8501, Japan

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ABSTRACT

Japan has a long history of using foods with health benefits and Japanese people are well-known for their longevity. In 1991, the Ministry of Health, Labor and Welfare introduced a functional food regulation called “foods for specified health uses” (FOSHU) in Japan. After the introduction of the functional food system, many clinically proven FOSHU products with health benefits have been developed and launched in the market. As a result, the net sales of FOSHU products reached 6.2 billion dollars in 2007. Most of the health claims relate to improving gastro-intestinal health using probiotics. Triglycerides, high blood pressure, high LDL-cholesterol, and high blood glucose are mainly associated with the related health claims. After 2007, the market for FOSHU products was almost saturated. However, a novel functional regulatory system called “Foods with Function Claims” was established in 2015 based on the Dietary Supplement Health and Education Act system established in the USA. Major health claims in the new regulation system are associated with fatigue, eyes, memory, stress, sleep, joints, blood flow, body temperature, muscles, and Body Mass Index. After the introduction of the new system, the total sales for functional foods including FOSHU products reached 8 billion dollars in 2018. The new functional regulatory system is more flexible in terms of health claims, the protocol for clinical studies, and the required results. Therefore, the market for new regulatory products is still growing. In the present paper, the potential of both regulatory systems and some related issues will be discussed.

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1. Introduction

Japanese people are well-known for their longevity, with the population aged 65 years and over increasing and being likely to reach 30% of the total population in 2025. Japanese people are likely conscious of health and realize the importance of a well-balanced life-style that includes healthy dietary habits. However, the mortality for cardiovascular disease is still high and almost the same as that for cancer in Japan because the current Westernized food style entails the risk of cardiovascular disease, obesity, diabetes, and high blood pressure. Therefore, the Japanese Ministry of Health, Welfare, and Labor established the “Food for Specified Health Uses” (FOSHU) as a regulatory system for “functional foods” in 1991.

After the introduction of the FOSHU regulation, the number of functional food products increased, especially from 1997 to 2007,

according to consumer demand, as shown in Fig. 1. The net sales of the FOSHU products were the highest in 2007 at 6.2 billion dollars (110 JPY/USD). Half of the health claims related to improving gastrointestinal tract (GI tract) health using probiotic lactobacilli, oligo-saccharide, and dietary fiber (Fig. 1). About 20% of the products made health claims linked to the serum triglyceride reduction. Another 20% made health claims relating to high blood pressure, high LDL-cholesterol, high blood glucose, tooth decay, and mineral uptake. After 2007, the market for FOSHU products was almost saturated, probably because FOSHU approval was not directly linked to product sales.

To overcome the shrinking market for functional foods, a novel functional regulatory system was established in 2015 based on the Dietary Supplement Health and Education Act (DSHEA) system already established in the USA. The DSHEA was introduced as a regulatory system for supplements with health benefits in the USA in 1994. The novel system called “Foods with function claims” (here called New Functional Foods) was established in 2015 based on the idea of the DSHEA. After the introduction of the new system, many New Functional Foods have been developed because of the more flexible health claims compared to FOSHU and the lack of a requirement for governmental approval. As a result, sales of New Functional Foods reached 1.8 billion dollars in 2018 and are still

* Corresponding author.

E-mail address: n-yamamoto@bio.titech.ac.jp (N. Yamamoto).

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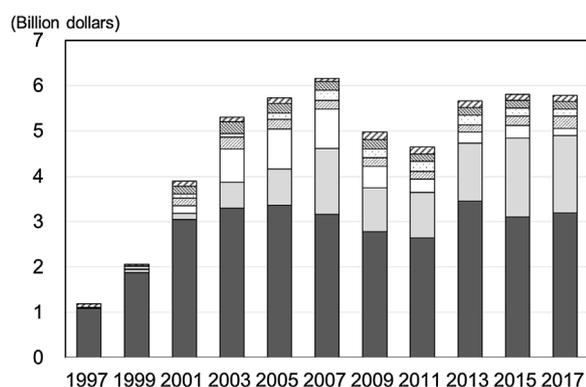


Fig. 1. Change in net sales for FOSHU products in Japan. ■: GI tract, ■: Triglyceride, □: Teeth, ▨: Cholesterol, ▩: Blood pressure, ▪: Blood sugar, ▫: Minerals.

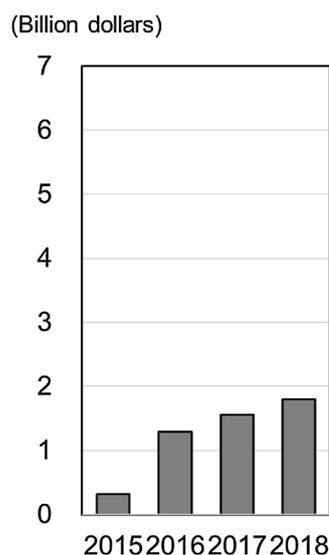


Fig. 2. Change in the net sales of New Functional Foods in Japan.

growing (Fig. 2). So, the total market for functional foods (FOSHU and New Functional Foods) in 2018 is estimated at 8 billion dollars.

2. The FOSHU and New Functional Foods systems

Both the FOSHU and New Functional Foods systems are regulatory systems for functional foods in Japan, but they have slight differences, as listed in Table 1. FOSHU products are approved by the Consumer Affairs Agency, but New Functional Products need no approval. So, companies are required to be responsible for the New Functional Products. After the notification, a New Functional Food can be launched 60 days after acceptance.

Regarding health claims, structural functional health claims are not approved in the FOSHU system but are available in the New Functional Foods system. So, a health claim about “calcium uptake” in FOSHU may be a more attractive health claim like “bone function” or “knee function” in a New Functional Product. Most of the health claims in the FOSHU system are linked to the GI tract or to the early stage of life-style-related disease metabolic syndrome, such as fatty acid uptake, control of serum triglyceride, blood sugar and cholesterol control, and the improvement of high blood pressure. In particular, the health claims with links to metabolic syndrome are considered to be strongly related to our health. In the New Functional Foods regulation, not only the health claims in FOSHOU but other health claims relating to skin, eyes, mental stress, joints,

Table 1
Differences between FOSHU and New Functional Foods.

Establishment	1991	2015
Approval	Government	-
Responsibility	Government	Company
Structural functional claim	No	Yes
Health claim	(e.g., Ca uptake) Limited for specific areas <ul style="list-style-type: none"> • Fatty acid • Triglyceride • Blood pressure • Blood sugar • Cholesterol GI tract • Teeth care • Calcium/mineral uptake 	(e.g., Bone function) More flexible <ul style="list-style-type: none"> • Fatty acid • Triglyceride • Blood pressure • Blood sugar • Cholesterol GI tract • Teeth care • Calcium/mineral uptake • Skin • Eye • Mental stress • Joint • Memory • Sleep • Bone • Fatigue • Blood circulation • Body temperature • Muscle • Liver • Walking • Backache etc
Clinical evidence	<ul style="list-style-type: none"> • Needs UMIN registration • Restricted protocol • Significant results at specific points • Required a dose dependency 	<ul style="list-style-type: none"> • Needs UMIN registration • Flexible protocol • Available scientific review
Others	Needs analytical method	Available for fresh foods

memory, sleep, bones, fatigue, circulation, body temperature, muscles, liver, walking, backache, and other functions are involved.

Both FOSHU and New Functional Foods need significant evidence from clinical studies, but the studies for FOSHU must be more controlled than those for New Functional Foods. There are protocols and guidelines covering matters such as target subjects for enrollment, significant points, and parameters for symptoms. In both types of study, healthy volunteers without medication are enrolled. So, control of basal food uptake and life-style, plus recruitment of appropriate subjects under a good protocol, is important to find clear evidence of the active component. The number of subjects must be large because detection of a significant effect with healthy volunteers is difficult.

The protocol for New Functional Foods is more flexible, so previous clinical results published by other groups are valid if they show clear evidence of the significant efficacy of the active component. To utilize a clinical study in this system, registration of the clinical study with the University Hospital Medical Information Network (UMIN) system is done to open the protocol first, and the outcome after the study is required for New Functional Foods. Currently, the FOSHU system also requires UMIN registration. Significant differences in various points and evidence that shows the reason for the minimum dosage from a dose-dependent study are required in the clinical trials for the FOSHU system. Moreover, clear evidence that explains the modes of action of the active components and the analytical method used for these components is required. In contrast, clinical studies for the New Functional Foods system must show a significant effect compared with a placebo group, but the design of the studies is more flexible than in the FOSHU system.

3. Health claims in FOSHU

The number of approved FOSHU products as of Jan. 29, 2019, was 1063. As shown in Fig. 1, total sales of FOSHU products increased to 6.2 billion dollars in 2007, but then dropped slightly. Half of the health claims related to improving GI tract health using probiotic lactobacilli, oligo-saccharide, and dietary fiber (Fig. 1). About 20% of the products made health claims linked to the serum triglyceride reduction. Another 20% made health claims about high blood pressure, high LDL-cholesterol, high blood glucose, tooth decay, and mineral uptake. Major active components often used in these functional foods will now be reviewed.

3.1. GI tract disorder control

Fifty-five percent of the health claims in FOSHU related to improving GI tract health using probiotic lactobacilli and Bifidobacterium, oligo-saccharide, and dietary fiber (Fig. 1). Most of the probiotic bacteria are used in yogurt and yogurt-like fermented milk. Probiotic fermented milk is considered useful for improving constipation and diarrhea [1,2]. About half of yogurt products have the potential to help with GI tract disorder and have FOSHU approval. Dietary fiber and oligo-sugar are also used for GI tract disorder but such products only have a market share of under 10%.

3.2. Triglyceride reduction

The second category of FOSHU is triglyceride control; as of 2017, sales of these products constituted about 29% of the market. In this field, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are major active components; the mechanism utilizes the reduction of VLDL production and the increase of its use in the liver (Table 2) [3]. Indigestible dextrin (dietary fiber) and tea polyphenol are often used in this field to reduce the absorption of fatty acid. About 20% of these products are linked to serum triglyceride reduction.

3.3. Cholesterol reduction

Chitosan, a polyglucosamine derived from chitin, is one of the most attractive compounds for reducing blood cholesterol. Chitosan extracted from crabs, lobsters, and shrimps cannot be digested by the digestive enzymes of humans, so it can increase the amount of fat eliminated in the stool [4,5]. Thus, chitosan has been used as a dietary supplement for serum cholesterol reduction [6]. A mixture of chitin and chitosan proved to be able to prevent an increase in the body weight of diet-induced obese mice via enhancing fat excretion and inhibiting lipid absorption [7]. Soy protein hydrolysate can decrease serum total cholesterol and LDL cholesterol [8].

3.4. Blood pressure control

High blood pressure is considered to be directly linked to cardiovascular disease. To improve high blood pressure, various kinds of antihypertensive peptide originating from food proteins have been used. Most of the used antihypertensive peptides have inhibitory activities against angiotensin I-converting enzyme (ACE) that catalyzes the release of the potent vasoconstrictor angiotensin II from angiotensin I. Val-Pro-Pro and Ile-Pro-Pro isolated from *Lactobacillus helveticus* in fermented milk showed significant antihypertensive effects in many clinical studies [9–11]. These peptides were also developed by casein hydrolysis [11]. These ACE inhibitory peptides have been mostly isolated from the proteolysis of food protein sources and fermented products. Antihypertensive peptides originating from fermented milk and milk casein hydrolysates

Table 2
Bioactive components used in major New Functional Products.

Active components	Triglyceride	Blood sugar	Body fat	GI tract	Blood pressure	Cholesterol	Bone	Skin	Fatigue	Eyes	Memory	Stress	Sleep	Joint	Blood flow	Body temperature	Muscle	BMI
Dietary fiber	152	152	61															
GABA																		
EPA, DHA	115				89				24		39	59	9					
Ginko flavonoid											70				14			
Hyaluronic acid								62										
Kudzu isoflavon			52						48			22	48					41
L-teannin																		
Lutain																		
Probiotics			10	53														
Soebean isoflavon							39											
Hesperidin	5				1										24	25		
Acetic acid			29		1													
Antocyanine					14				26	29		17						
γ									1									
Collagen																		
Salacta salacinol		26																
Coenzyme																		
Anthocyanidin																		
Glucosamine																		
Barley β-glucan				7														
3-hydroxy-3-methylbutyrate		3																
Peptides					12													13

Bioactive components specific to Functional products with health claim (<https://www.fld.caa.go.jp/caaks/cssc01/>) were shown by shadow.

have been developed [12–15]. Some other antihypertensive peptides are also used in FOSHU products [16,17]. γ -aminobutylic acid has the potential to act on the central nervous system and showed antihypertensive effects in both animal and human studies [17–20].

3.5. Blood sugar level

For the control of blood sugar, indigestible dextrin is used in FOSHU products. Indigestible dextrin competitively inhibits maltase and sucrase and can reduce absorption of glucose by the intestine. So, reduction of blood glucose is expected if the dextrin is taken with meals. Indigestible dextrin is often used to promote triglyceride reduction and also for the reduction of blood sugar level. Guava polyphenol can also reduce blood glucose through the inhibition of α -amylase [21].

3.6. Tooth care

Palatinose, maltitol, erythritol, and xylitol are not hydrolyzed by oral micro-bacteria in mice. So, the oral pH does not decrease and promote the growth of pathogenic bacteria [22]. On the other hand, tea polyphenol can reduce the risk of tooth decay because of the preventive effect of *Streptococcus mutans*, a major pathogen for it [23].

3.7. Mineral uptake

A casein phosphopeptide (CPP) prepared from the beta-casein in cow's milk enhances calcium absorption by the small intestinal lumen by increasing the concentration of soluble calcium [24]. The effect of Ca-bound CPP on the bones of aged ovariectomized rats was studied as a model for post-menopausal bone loss and Ca-CPP improved the decreased bone mineral density after 17 weeks' feeding [25]. Absorption of calcium was tested by using a mixed calcium citrate-malate salt in both rats and humans. In both studies, the calcium-malate salt exhibited excellent absorption [26]. However, the clinical outputs presented contradictory findings [27,28].

4. Health claims in New Functional Products

As shown in Fig. 2, the net sales for the New Functional Foods with health benefits increased from their introduction in 2015 to reach almost 2 billion dollars in 2018. The number of New Functional Products as of Jan. 31, 2019, was 1753 [29]. Generally, most of the active components used in FOSHU products are also used in New Functional Foods. In Table 2, major health claims in the new regulatory system are listed. Some health claims—relating to fatigue, eyes, memory, stress, sleep, joints, blood flow, body temperature, muscles, and Body Mass Index—not approved for FOSHU products were added to New Functional Products. Some active components have multiple functions and are used in different types of functional product with different health claims. Some active ingredients are developed by the maker company and the ingredients and all data about the active components are available. In Table 2, health benefits represented by shadowed columns were also included under the FOSHU regulations. Now, I will explain the new health claims added to the systems.

4.1. GI tract, triglyceride, blood sugar, blood pressure, blood cholesterol levels

Health claims available in the FOSHU system are usually applied to New Functional Products as well; this is probably because of the easy application process and low risk of rejection, as listed in Fig. 3 (see shadowed column). For instance, if a recipe for an FOSHU product is changed, a new clinical result for the new recipe is required in

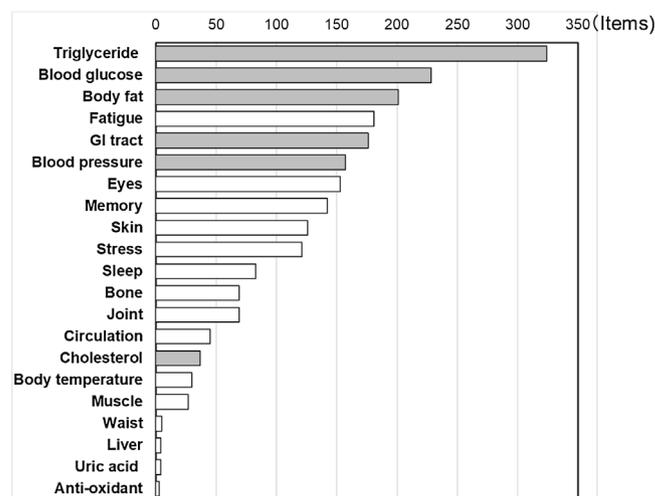


Fig. 3. The number of New Functional Foods.

the FOSHU system. However, no additional clinical study is necessary for New Functional Products if the clinical evidence has already been collected in a previous study. So, many companies try to apply for the new regulatory system using these health claims instead of the FOSHU system.

4.2. Fatigue, stress, and sleep functions

Theanine is generally used in New Functional Products to relieve stress. An animal study reported stress reduction by L-theanine (γ -glutamylethylamide) extracted from green tea. In a clinical trial, an L-theanine-based nutrient significantly reduced the salivary cortisol response to a stressor [30,31]. Stress relief is closely linked to deep sleep and fatigue improvement. Recent studies suggest that theanine affects inhibitory neurotransmission. In an animal study, theanine enhanced the synthesis of nerve growth factor and neurotransmitters and promoted central nervous system maturation [32].

4.3. Eye function

Lutein with anti-inflammatory carotenoid has several beneficial effects, especially on eye health.

Lutein has a strong antioxidant effect [33,34], especially when it comes to protecting the retina from phototoxic light damage [35]. The effect has also been associated with a reduced risk of age-related diseases [36]. To evaluate the protective effect of blueberry anthocyanins on retinal pigment epithelium cells (which are susceptible to excessive light and UV radiation), blueberry anthocyanin extracts were tested for their ability to protect cells from light-induced damage [37].

4.4. Memory function

Demand for the improvement of memory activity is increasing in Japan. To improve memory activity, Ginkgo biloba, which has many associated studies (especially in Europe), and DHA are used in New Functional Foods. Ginkgo biloba reduces attenuates hippocampal neuronal damage and cognitive dysfunction [38,39]. The health benefit of Ginkgo biloba on cognitive scores has been investigated in many clinical trials. However, there is a discrepancy in the outcomes of clinical studies between active and placebo groups. Some studies showed an improvement in the behavioral and psychological symptoms of dementia [40,41]. DHA and EPA are considered to help delay aged-related cognitive decline. Both

components can regulate gene expressions with links to brain functions by binding to nuclear receptors such as the retinoid X receptors and the retinoic acid receptors, thus delaying brain aging [42].

4.5. Joint function

Locomotive syndrome is a condition that leads to reduced mobility due to impairment of the locomotive organs. Japanese people's prolonged life expectancy has elevated their interest in locomotion dysfunction. Collagen hydrolysate and glucosamine are generally used for the improvement of joint function. In a clinical study, collagen hydrolysate improved the visual analogical scale for joint pain compared to a placebo [43]. Glucosamine sulfate decreased the risk of developing radiographic knee osteoarthritis [44,45].

4.6. Blood flow and body temperature

In several countries, Ginkgo biloba extract has been used in an attempt to minimize decreases in cognitive activity in elderly people. In a clinical study, after treatment with Ginkgo biloba extract, a reduction in blood viscosity, improved cerebral perfusion in specific areas, and improved global cognitive functioning were observed [46]. Hesperetin exerts an antiatherogenic effect, leading to a subsequent increase of endothelial NO production, which promotes vasodilation activity [47].

5. Perspective

After the registration of the functional food regulation as FOSHU in 1991, the market for FOSHU products increased, peaking in 2007 and then shrinking. The reasons for this downward trend in FOSHU could be 1) difficulty detecting a significant effect in healthy volunteers in clinical studies, 2) the long period from approval to registration and slow responses to additional requests, and 3) the difficulty of balancing research costs and profits. So, companies are hesitant to apply for FOSHU approval and are trying to shift to the New Functional Products.

The New Functional Products regulation was started in 2015 and is still growing (a dossier including clinical results is available at the web site [29]). After the introduction of the new regulatory system, the total market reached 8 billion dollars in 2018. The reasons for this increase are most likely 1) the health claims and categories are more flexible, 2) the acceptance of "scientific reviews" instead of clinical studies, and 3) the lower risk involved in launching products.

Regarding "scientific reviews," they are a good way to prevent additional clinical studies if there is enough previous evidence about the active components. However, sometimes, there are contradictory results, probably because of different protocols and subjects. Moreover, it is not easy to extrapolate previous results to the expected target.

Since the introduction of New Functional Products, the total market for functional foods has grown in Japan. However, after the launch of functional foods, inspections of the final products regarding the quantity of the active components became necessary. This was already announced by the Consumer Affairs Agency, but not as part of the general process. Moreover, the quality of the results, including unpublished results, are different depending on the studies. So, to realize certain health benefits by consuming functional food products, the selection of functional foods from among many products is important.

Most Japanese people hope to maintain their health through a well-balanced life-style, including balanced food intake and continuous exercise, but not through medication use. So, functional

foods have the potential to keep them healthy in combination with general food-based nutrients in the future in Japan.

Conflicts of interest

The authors have no conflicts of interest and they all agree to publish this paper.

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