HEALTH CLAIMS AND SCIENTIFIC SUBSTANTIATION OF FUNCTIONAL FOODS - JAPANESE SYSTEM AIMING THE GLOBAL STANDARD

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ABSTRACT: Health claims should always be substantiated scientifically and be in harmony with global international standards. The evaluation and approval system for health claims should be regulated by an independent organization. The Japanese Ministry of Health, Labor, and Welfare (MHLW) established a regulatory system of "Foods for Specified Health Use (FOSHU)" in 1991. Its goal is to evaluate the physiological functionality of foods and to provide, when appropriate, FOSHU approval for product-specific health claims. The Enhanced Functional Claims and the Disease Risk Reduction Claims were proposed by both the Codex and EU project in 1999. The Structure/Function Claims were expressed in the Dietary Supplement Health Education Act in the US in 1994. Both FOSHU and Structure/Function Claims are similar to the Enhanced Function Claims. The Nutrient Function Claim was included in the guidelines for use of nutrition claims, which was adopted by the Codex in 1997. The expressive claims primarily include nutrient function claims based on well-established, generally accepted knowledge and could be standardized without specific, individual substantiation. Innovative claims such as enhanced functional claims or structure/function claims, however, should be evaluated individually by independent experts in order to protect consumers from false or misleading descriptions. For this scientific substantiation, in addition to animal studies and in vitro studies, we also need human intervention studies.


INTRODUCTION

The proportion of senior citizens in relation to the general population is rapidly increasing in developed countries, especially in Japan. Today the percentage of people over 65 in Japan is approximately 17%, similar to European countries. However, this ratio is estimated to increase to 25% within 20 years in Japan and much higher in the other countries. With the rapid increase in the number of elderly people and the development of a senior society, chronic diseases such as diabetes, cardiovascular diseases, hypertension, osteoporosis, Alzheimer’s disease, and cancer are expected to increase. These diseases are referred to as lifestyle-related diseases by the Japanese government, as they are connected not only to age but also to lifestyle factors such as diet, nutrition, stress, and physical exercise. The need for medical treatment is expected to increase, especially among seniors, but in many cases it may not improve the quality of life. Therefore, the goal of functional foods is to improve or maintain quality of life and to prevent the lifestyle-related diseases before medical treatment is required.

In anticipation of this senior society, the Ministry of Education, Science, and Culture in Japan started in 1984 a project concerning food functionality. The project consisted of research in nutrition, pharmacology, psychology, and medical science. The project first defined the concept of functional food. That is, foods have three functions. The primary function is a nutritional function, which is essential to human survival. The secondary function is a sensory function involving both flavor and texture to satisfy sensory needs. The tertiary function is physiological functions such as regulation of bioretches, control of aging, the immune system, and body defense. The project defined a functional food as a food having some tertiary function. The project has identified many food items having tertiary function during the last decade, and scientific evidence is accumulating regarding study of the physiological function of food.

Bolstered by this scientific evidence regarding the health function of foods, a regulatory system for foods with health claims has been discussed in the United States and Japan. The Japanese Ministry of Health and Welfare (MHW) in 1988 established an expert committee to discuss setting up a regulatory system for functional foods. This resulted into creation in 1991 a regulatory system, Foods for Specified Health Use (FOSHU), to approve labeling statements regarding the effects of foods on the human body. With this system, prod-
ucts submitted to FOSHU are evaluated by the Ministry. In 2001, the Ministry enacted a regulatory system called “Foods with Nutrient Function Claims (FNFC)”, under which twelve vitamins and two minerals were standardized. The US established the Nutrition Labeling and Education Act (NLEA) in 1990. By this act, it became possible to claim that foods or those components approved by the Food and Drug Administration (FDA) may reduce the risk of specific diseases. The Dietary Supplement Health and Education Act (DSHEA) was passed in 1994 and allowed companies to claim for their products effects on the structure / function of the human body. In 1998, the European Commission Concerted Action on Functional Foods Science in Europe (FUFOSE) and the Codex Committee on Food Labeling (CCFL) proposed two kinds of health claims, Enhanced Function Claims and Disease Risk Reduction Claims. The labeling of functional foods is important for both consumers and companies as a tool for increasing public knowledge of health function. With more public information regarding the health benefits of foods than ever before, consumers’ interest in matters related to health and diet has become a leading factor in their purchasing decisions. Consumers have a right to information on food functionality that can assist them in purchasing the proper products. With labels claiming the health benefits of functional foods, food companies can differentiate their products from other ordinary foods and thereby increase sale. Therefore, the labeling should be clear and correct, and avoid any misunderstanding. In particular, the labeling regarding health claims on foods should be always substantiated scientifically. Other than in Japan, there are no practical regulatory systems in the world to evaluate the scientific substantiation of health claims. A product –specific evaluation system was set up in the Netherlands and Sweden in 1998 and 2001 respectively. But only two products were approved in the Netherlands. The author discusses herein the relationship between health claims and scientific substantiation, and proposes an evaluation system for these health claims.

**DEFINITION: FUNCTIONAL FOODS, DIETARY SUPPLEMENTS, AND HEALTH CLAIMS**

A Functional Food, as defined by Japanese ad hoc national project in 1984, should improve one or more of the following physiological functions - regulation of biorhythms, the neuro-system, the immune system, and body defense. Health claim means any presentation that states, suggests, or implies that a relationship exists between a food or a constituent of food and health. Health claims include Nutrient Function claims, Enhanced Function Claims, and Reduction of disease risk claims. This definition is the same as Proposed Draft Guidelines for Use of Health and Nutrition Claims of Codex in 1999 (Codex Committee on Food Labeling 28 Session). Structure/Function claim means the statements about the effects of dietary supplement on the structure or function of the body that is defined by Dietary Supplement, Health, and Educational Act in the US in 1994. Dietary supplement means a product intended to supplement the diet with one or more of the dietary ingredients, such as vitamins, minerals, herbs, amino acids, etc.

**1. Health Claims**

Health claims can be divided into three categories based on the Japanese regulatory system (Japan:Codex, 2000), the Scientific Concepts of Functional Foods in Europe(Diplock et al, 1999), and the draft guidelines for the use of Nutrition and Health Claims of Codex(Codex Committee on Food Labeling 28 Session) and DSHEA and NLEA in the US.

**a) Nutrient Function Claims**

According to the definition approved by FUFOSE (Diplock et al., 1999) in 1999, this claim is “a form of claims that refers to the physiological role of a nutrient in its relationship to growth, development, and normal body function”. The Scientific Concepts of CCFL (Codex Alimentarius, Guideline for Use of Nutritional Claims, 1997) defines similar claims with regard to Nutrient Function, such as claims that describe the physiological role of the nutrient in growth, development, and normal body function. The nutrients include three major nutrients, 10 vitamins, and 6 minerals. An example of such a statement is "calcium aids in the development of strong bones and teeth.”

The Japanese Ministry established Food with Nutrient Function Claims in 2001. The Nutrient Function Claims, with warning labeling of 12 vitamins (Vitamin A, B1, B2, B6, B12, C, E, D, Biotin, Pantothenic acid, Folic acid, and Niacin) and 2 minerals (calcium and iron) were standardized as follows:

- **Vitamin A (or β-carotene)** is a nutrient that helps to maintain vision in the dark.
- **Vitamin A (or β-carotene)** is a nutrient that helps to maintain skin and mucosa healthy.
- **Vitamin D** is a nutrient which promotes to absorb calcium in gut intestine and aids in the development of bone.
- **Vitamin E** is a nutrient which helps to protect fat in the body from being oxidized and to maintain the cell healthy.
- **Vitamin B1** is a nutrient which helps to produce the energy from carbohydrate and to maintain skin and mucosa healthy.
- **Vitamin B2** is a nutrient which helps to maintain skin and mucosa healthy.
- **Vitamin B6** is a nutrient which helps to produce the energy from protein and to maintain skin and mucosa healthy.
- **Niacin** is a nutrient which helps to maintain skin and mucosa healthy.
- **Biotin** is a nutrient which helps to maintain skin and mucosa healthy.
- **Pantothenic acid** is a nutrient which helps to maintain skin and mucosa healthy.
- **Folic acid** is a nutrient which aids in the red blood cell formation. Folic acid is a nutrient which contributes the normal growth of the fetus.
- **Vitamin B12** is a nutrient which aids in the red blood cell formation.
**Vitamin D** is a nutrient which promotes to absorb calcium in gut intestine and aids in the development of bone.  
**Vitamin C** is a nutrient which helps to maintain skin and mucosa healthy and has anti-oxidizing effect.  
**Calcium** is a nutrient which is necessary in the development of bone and teeth.  
Iron is a nutrient which is necessary in the red blood cell formation.

Attention and Warning Labeling are as follows,  
- **Every nutrient**: Excess intake of this product neither cures your disease nor promotes your health. Keep the optimum amount.  
- **Vitamin A**: Women who are pregnant or expect to be should be careful of excess intake.  
- **Folic acid**: Folic acid is a nutrient which contributes the normal growth of the fetus but does not improve the growth of fetus with the excess intake.

### b) Enhanced Functional Claims or Structure/Function Claims

FUFUSE (Diplock et al., 1999) has proposed, “Enhanced function claims concern specific beneficial effects of nutrients and non-nutrients on physiological, psychological functions or biological activities beyond their established role in growth, development and other normal functions of the body.”

The CCFL (Codex Committee on Food Labeling 28 Session) has proposed a similar definition, that is, “Enhanced Function Claims concern specific beneficial effects of the consumption of foods and their constituents in the context of the total diet on physical or psychological functions or biological activities but do not include Nutrient Function Claims. Such claims relate to positive contribution to health or to improvement of a function or to modifying or preserving health.”

The Structure/Function Claim, which was defined by the Dietary Supplement Health and Education Act (DSHEA) in the US, is a statement that describes the role of a nutrient or dietary ingredient intended to affect structure / function in humans or that characterizes the mechanism by which a nutrient or dietary ingredient acts to maintain such structure / function. Enhanced Functional Claims and Structure/Function Claims are practically similar statements regarding positive effects on growth, healthy physiological structure, and function of the body. The difference between them is that dietary supplements include nutrients, but the Enhanced Function Claim does not. The DSHEA in the US permits statements regarding vitamins, minerals, and herbs in relation to the structure / function of the human body. But nutrients, such as vitamins and minerals, are not included in the Enhanced Functional Claims proposed by Codex (Codex Committee on Food Labeling 28 Session).

**Health Claims of FOSHU**

FOSHU claims are similar to Enhanced Function Claims and Structure/Function Claims. FOSHU includes health functions that can have positive effects on human physiological functions, and the related foods are intended to be consumed for the maintenance or promotion of health or special health uses by people who wish to control their health conditions. The number of items approved by FOSHU has increased to total approximately 330 in January of 2003. FOSHU health claims must not include medical claims such as claims to “prevent”, “cure”, “treat”, and “diagnose” human diseases. The Japanese Ministry defines the allowed health claims as follows:

1. **Maintain or improve a marker determined by self-diagnosis or health check-up.**  
   - **Permitted claim**: e.g., this product helps to maintain normal blood pressure, blood sugar, or cholesterol.  
   - **Not permitted claim**: e.g., this product improves hypertension.

2. **Maintain [or improve] physiological function and organ function of the human body.**  
   - **Permitted claim**: e.g., this product enhances the absorption of calcium. / this product helps to improve the movement of the bowel.  
   - **Not permitted claim**: e.g., this product is an effective food for enhancing fat metabolism.

3. **Causes short-term changes in body condition, but not long-term changes.**  
   - **Permitted claim**: e.g., this product is good for or helps people who feel fatigue.  
   - **Not permitted claim**: e.g., this product has anti-aging effects.

The existing FOSHU health claims can be categorized into the following eight groups according to the health claims.

**Gastro-intestinal (GI) condition**: “This helps increase intestinal bifidobacteria and thus helps maintain a good GI condition.” The effective components are oligosaccharides, dietary fiber, and chitosan.

**Blood pressure**: “This is suitable for persons with slightly elevated blood pressure.” Components that could reduce blood pressure are lacto-tripeptide from fermented milk, dodecapeptide from casein, a group of peptides from sardines, and soy protein.

**Serum cholesterol**: “This helps people decrease serum cholesterol levels.” The effective components are soy protein, chitosan, low molecule sodium alginate, and phytosterol.

**Blood glucose**: “This is helpful for those who are concerned about their blood glucose levels.” The effective components are indigestive dextrin, wheat albumin, L-arabinose, and so on.

**Mineral absorption**: “This product has high bio-availability for humans and is suitable for supplementing calcium.” or
“This is suitable for people with mild anemia who need to supplement iron.” Fructo-oligosaccharides, Casein phosphopeptide, and so on, could improve calcium absorption in gut intestine, and heme iron has good iron bio-availability.

**Blood lipid:** “This helps reduce postprandial serum triglyceride levels. Additionally, a product containing diacylglycerol is permitted to claim that this product makes it difficult to increase the levels of body fat. Diacylglycerol and digesting globin could decrease serum triglyceride levels after meals.

**Tooth health:** “This product is a low- or non-cariogenic product.”, or “This makes teeth strong and healthy”. Some sugar alcohols such as xylitol, maltitol, erythritol, and palatinose are low cariogenic, and green tea polyphenol is non-cariogenic.

**Bone health:** “This could promote bone calcification.”, or “This could increase bone density and make bones healthy”. Vitamin K, and soy-isoflavones and milk proteins could promote bone calcification.

c) **Disease Risk Reduction Claims**

The Code in the UK (Code of Practice Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink products) expresses that “If the product is proven to provide a health benefit which can reduce the risk of disease, then it is acceptable to mention the part of the body which may benefit from the reduced risk of disease as long as the disease itself is not stated or implied.”

Codex has proposed that Disease Risk Reduction Claims relate to the consumption of a food or food constituent, in the content of the total diet, and to the reduced risk of developing a disease or health-related condition. Risk reduction means significantly altering a major risk factors for a disease or a health-related condition. Diseases have multiple factors, and altering one of these risk factors may or may not have a beneficial effect. The presentation of Risk Reduction Claims must ensure, for example, by use of appropriate language and reference to other risk factors, that consumers do not interpret them as prevention claims.”

The Nutrition and Labeling Education Act (NLEA) in the US began permitting these kinds of claims in 1990; for example, “Especially for teen and young adult women, adequate calcium in a healthful diet may reduce the risk of osteoporosis later in life.”

Most of the statements of the Japanese FOSHU are close to the category of Enhanced Functional Claims. Although FOSHU permits claims of improving effects on the preliminary stage of a disease or a borderline condition of an at-risk group due to an unbalanced nutrient state, a claim regarding improving symptoms related to a specific disease or to disease in general terms is not acceptable. Considering the international harmonization with Codex, the author believes that the Japanese government should discuss the addition of claims related to specific diseases in FOSHU.

In the expanded application of labeling contents, the reduction of the risk of diseases is a matter of considerable controversy throughout the world. Labeling statements regarding risk reduction for disease has been discussed from the perspective of differentiating it from the “prevention of diseases”, which is categorized as a medical claim. Consumers, especially elderly people, could benefit from valid health claims connected to disease, as it would provide them with information about these functional foods. They should not, however, be purposely misled into purchasing functional foods by health claims on foods expressing false or exaggerated claims of their efficacy, or be swayed into not taking proper medicines or consulting a medical doctor.

**SCIENTIFIC SUBSTANTIATION**

The draft guidelines for use of Nutrition and Health Claims in Codex (Codex Committee on Food Labeling 28 Session) propose that “health claims must be based on current relevant scientific substantiation and the level of proof must be sufficient to substantiate the type of claimed effect as recognized by generally accepted scientific review of the data and the scientific substantiation should be reviewed as new knowledge becomes available”. This statement seems to be in general agreement with global concepts. From the perspective of substantiation, health claims will be divided into two categories, as proposed by the Code of the UK, as follows:

1) **Generic Claims**

In the case of generic claims, specific substantiation is not required for individual products because those health claims have been widely accepted by scientific experts internationally.

Most nutrient function claims are generic claims. In 2001, the Japanese Ministry (MHLW) defined twelve vitamins and two minerals as Foods with Nutrient Function.

2) **Innovative Claims**

Innovative claims must be substantiated scientifically specifically for individual products. From the point of view of this procedure, this type of claims named as product-specific claims in the project of Sweden (Asp and Trossing, 2001).

The substantiation of innovative claims (or product-specific claims) should be based on experimental human studies in addition to in vivo animal and in vitro studies. In the FOSHU approval system, an applicant is required to substantiate the health claim by statistical analysis of clinical studies, animal studies, and in vitro metabolism and biochemical
studies. The protocol of clinical studies should be based on the results of animal studies. The applicant must demonstrate that the food provides a significant benefit to humans over a reasonable period of time, along with the dosage and frequency with which the food should be digested to achieve the benefit, the targeted consumers who can benefit from the food, the maximum amount of consumption without any adverse effect, the biological mechanism to achieve the effects, and the statistically significant differences from placebo. The available information on relevant associated research regarding the effective components and derivatives should be reviewed. Any new scientific evidence used to support the health-related claims must be published peer-reviewed scientific journals.

3) Substantiation for FOSHU

According to the above-mentioned eight groups of health claims, the human intervention studies scientifically substantiating health function in humans for FOSHU approval (Table 1) can be summarized using the following markers.

Gastro-intestinal (GI) condition: frequency and shape of stool, or short-chain fatty acid production.

Blood pressure: systolic blood pressure and diastolic blood pressure.

Serum cholesterol: LDL-cholesterol, HDL cholesterol, and total cholesterol.

Blood sugar: fasting blood glucose and postprandial blood glucose.

Absorption of mineral: stable isotope or pyridinoline and deoxypyridinoline for calcium absorption and hemoglobin and serum ferritin for iron absorption.

Blood lipids: serum triglyceride, chylomicron, cholesterol, and/or body fat rate.

Tooth Health: acidity with micro tip set in tooth.

Bone health: bone density or serum g-carboxylated osteocalcin.

Example of steps in Scientific Substantiation by FOSHU

In the eight groups, blood pressure is important not only as a marker of hypertension itself but also because of its close correlation with cardiovascular diseases. More than ten products claiming to maintain healthy blood pressure levels have been approved by FOSHU. The following article (Kajimoto et al., 2001) is an example of the substantiation of a health claim regarding blood pressure that was submitted in a FOSHU application.

a) Review of the Evidence

(1) Food materials, including sour milk (Nakamura et al., 1995a), which was obtained by fermenting skim milk using a starter containing Lactobacillus helveticus, were found to have anti-hypertensive effects (Maruyama and Suzuki, 1982; Fisher et al., 1984; Yoshikawa and Chiba, 1992) in spontaneously hypertensive rats. Two kinds of tripeptides (Val-Pro-Pro and Ile-Pro-Pro) were isolated and identified from the sour milk as angiotensin I-converting enzyme (ACE) inhibitors (Nakamura et al., 1995b). The ACE activity of the aorta in the circulating blood and various tissues of SHR have been reported to have decreased significantly (Masuda et al., 1996; Nakamura et al., 1996) and studies suggest that these tripeptides are absorbed and delivered to vascular tissue. A study in which sour milk was ingested for 8 weeks concomitant to the use of anti-hypertensive drugs in hypertensive patients confirmed a significant decrease in blood pressure (Hata et al., 1996). These findings indicate that there is coincidence between rats and humans when the dose required for demonstration of effects is calculated not based on body weight, but rather the per unit aortic surface area, and that these tripeptides reach the vascular tissue of the aorta.

b) Experimental Protocol

(i) Subjects (Target population)

Subjects were selected among those who maintained systolic blood pressure between 140 and 180 mmHg and diastolic blood pressure between 90 and 105 mmHg for 3 months before the start of the study, referring to hypertension treatment guidelines of the WHO/ISH (1999) (Guidelines Subcommittee, 1999), and excluded those with secondary hypertension, lactose intolerance, milk allergy, alcoholism, or severe other disease, or those who were taking some kind of oral drugs. The study was a placebo-controlled, double-blind study. The sour milk drink was given to one group (abbreviated as “sour milk group” hereinafter), while a placebo was given to the other (referred to as “placebo group” hereinafter). The 30 subjects included 12 men and 18 women aged 52.0 ± 6.1 years. The study was conducted with the approval of the institutional review board of Health Control Center, Osaka National University of Foreign Languages.

(ii) Supplementary drinks

The sour milk was packed in glass bottle (160 g) and contained 2.53 mg of valine-proline-proline (Val-Pro-Pro) and 1.52 mg of isoleucine-proline-proline (Ile-Pro-Pro). A placebo drink was prepared in the same way as the sour milk drink. Both drinks had a similar nutritional composition and acidity.

As a method of consumption, one bottle of the sample was taken every day in the morning for 8 weeks. The subjects were instructed not to change their daily life, including diet and exercise, except to drink the sample every day at a fixed time.
### Table 1. Examples of Health Claims and Scientific Substantiation of FOSHU

The text of health claims has no precedence over the pertinent approved terminology of FOSHU in the Japanese language. The information presented here is adapted from a Summary of Application File by Japan Health Food & Nutrition Food Association.

<table>
<thead>
<tr>
<th>Health Claims</th>
<th>Key Component Form</th>
<th>Marker</th>
<th>Subjects</th>
<th>Test Period</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>This product contains dietary fiber (indigestible dextrin), makes up for the loss of fiber in dietary habit, and maintains a good GI condition.</td>
<td>Indigestible dextrin (refreshing beverage)</td>
<td>Defecation frequency and fecal quantity</td>
<td>45 healthy adults</td>
<td>Single-blind cross-over, 20 and 10 days for both intake and non-intake periods</td>
<td>Ingesting the test food was effective in significantly increasing defecation frequency and fecal quantity compared to those in non-ingesting period or ingesting of placebo.</td>
</tr>
<tr>
<td>Since this yogurt contains live Bifidobacterium longum, the product helps increase bifidobacteria in the intestine, maintain intestinal environment and keep good GI condition.</td>
<td>Bifidobacterium longum BB536 fermented milk</td>
<td>Defecation frequency and fecal condition, fecal level of ammonia and organic acids</td>
<td>39 healthy women</td>
<td>3 weeks</td>
<td>Taking the test food was effective as follows; bacterial flora in the intestine was improved, fecal level of ammonia decreased, in contrast those of organic acids increased, defecation frequency significantly increased, softening and yellowing of feces were appeared, and also defecation feeling improved.</td>
</tr>
<tr>
<td>This product is a processed food of dried bonito oligopeptides and is suitable for people with rather high blood pressure.</td>
<td>Dried bonito oligopeptides</td>
<td>Blood pressure</td>
<td>37 individuals with borderline hypertension or mild hypertension</td>
<td>5 weeks, cross-over</td>
<td>In each period, it was appeared that blood pressure lowered mildly after taking the test food, and significant efficacy of lowering blood pressure after the period in all groups.</td>
</tr>
<tr>
<td>Since the main component of this product is CSPHP which moderates the absorption of cholesterol, the product helps people who tend to take cholesterol-rich diet or people with rather high serum cholesterol level.</td>
<td>CSPHP powdered refreshing beverage</td>
<td>Serum cholesterol</td>
<td>21 male with hypercholesterolemia from 55 to 65 divided into 3 groups; CSPHP 0.3,6g/day intake</td>
<td>3 months</td>
<td>The serum total cholesterol and LDL-cholesterol levels significantly decreased, in contrast HDL-cholesterol level significantly increased after taking CSPHP3g/day. The efficacy was dose dependent.</td>
</tr>
<tr>
<td>The main component of this oil is diacylglycerol. Compared with other types of cooking oil, the product can moderate the postprandial serum triglyceride levels and accumulation of excess fat on the body. And also, since the product contains phytosterol which moderates the absorption of cholesterol, it can lower the levels of serum cholesterol, especially LDL-cholesterol. It is recommended not only to maintain good health, but also for people with rather high cholesterol and/or triglyceride levels and who are rather overweight.</td>
<td>Diacylglycerol, phytosterol, sitosterol, cooking oil</td>
<td>Total serum cholesterol, LDL-cholesterol</td>
<td>38 healthy adults</td>
<td>4 weeks control-period.</td>
<td>*The body weight and BMI score significantly decreased in the test group on 8 weeks and 12 weeks compared to those in the control group. *The body fat significantly decreased in the test group on 4 weeks and 12 weeks compared to it in the control group. *The visceral fat significantly decreased in the test group on 4 weeks compared to it in the control group. *The hepatic fat significantly decreased in the test group on 8 weeks and 12 weeks compared to it in the control group.</td>
</tr>
</tbody>
</table>
## Health Claims and Scientific Substantiation

<table>
<thead>
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<tr>
<td>Since the ingredient of this product is indigestible dextrin (dietary fiber), which moderates glucose absorption, the product is suitable for people who are worried about their blood glucose levels.</td>
<td>Indigestible dextrin refreshing beverage</td>
<td>Postprandial blood glucose at 30 min.</td>
<td>32 healthy adults (21 males, 11 females)</td>
<td>Single administration</td>
<td>The blood glucose levels at 30 minutes after the meal ingestion with the test food significantly decreased in the subjects who tend to heighten the peak blood glucose level (&gt;155mg/dl at 30 min.), in contrast those in other subjects had no significant change.</td>
</tr>
<tr>
<td>This beverage is suitable for people who are worried about their bone health, since the product contains isoflavone, which is related to calcium dissolution in bones.</td>
<td>Soy bean isoflavone refreshing beverage</td>
<td>Urinary bone absorption markers (pyridinoline, deoxypyridinoline)</td>
<td>26 healthy women 20 postmenopausal</td>
<td>2 weeks, cross-over</td>
<td>The levels of pyridinoline were appeared to lower and the levels of deoxypyridinoline significantly decreased after taking the test food compared to those before taking the food.</td>
</tr>
<tr>
<td>This product is suitable for people who need iron supplementation due to slight anemia.</td>
<td>Heme iron refreshing beverage</td>
<td>Hemoglobin, serum ferritin</td>
<td>Total 154 women; pregnant with iron-deficiency anemia, women with hysteromyoma, adenomyosis, endometriosis, or functional bleeding</td>
<td>3 months</td>
<td>Pregnant; the hemoglobin levels improved with taking the test food generally. Increasing of the serum ferritin was also detected in the pregnant whose ferritin levels were lower than the lower limit in normal pregnant. Non-pregnant; the test food was effective in improving the levels of hemoglobin or serum ferritin.</td>
</tr>
<tr>
<td>This natto is designed to activate the potency of bone protein (osteocalcin), which promotes bone calcification by containing vitamin K2 high-productive Bacillus subtilis OUV23481.</td>
<td>vitamin K2 high-productive B. subtilis (NattoÅj)</td>
<td>Serum -carboxylated osteocalcin</td>
<td>39 healthy adults from 20s to 40s</td>
<td>14 days</td>
<td>The test natto was effective significantly, in increasing serum -carboxylated osteocalcin level throughout the test period, in contrast the control (ordinary natto) was not detected the efficacy on day7, 10 and 14.</td>
</tr>
</tbody>
</table>
(iii) Measurements

Blood pressure and pulse rate: In the pre-consumption observation period (2 weeks), the consumption period (8 weeks), and the post-consumption observation period (4 weeks), medical examination by a doctor and measurement of blood pressure and pulse rate were conducted every 2 weeks. The subjects were instructed to arrive at the registered hospital by 8:30 under fasting and, after 30-minute rest, the measurements were made three times at 2-minute intervals in the left upper arm in a sitting position with clothes but without shoes between 9:00 and 9:30. If there was a difference of 10 mmHg or more between the maximum and minimum values of the systolic blood pressure or a difference of 6 mmHg in the diastolic blood pressure in any of the three measurements, the subject was instructed to rest again and, when the differences became within the above ranges, the medians were adopted.

Body weight and height: Body weight and height were measured at the time of the medical examination. Serum biochemical examination and urinalysis: Serum biochemical and hematological examination and urinalysis test paper method were performed immediately before and after taking the sample. The subjects were instructed to arrive at the prescribed hospital at 08:30 under fasting, and urinalysis was performed first, followed by blood sampling after 30-minute rest. Blood samples were taken between 8:30 and 9:30 by a nurse.

Medical inquiry: Medical inquiry was conducted at the same time as the measurement of blood pressure, pulse rate, and body weight. The occurrence of subjective symptoms and side effects such as dry cough, headache, vertigo, digestive symptoms, and an itching feeling were examined.

(iv) Statistical Analysis

All measured values are indicated as the means ± standard deviation. Two-way analysis of variance was used for group comparisons of changes in blood pressure during the ingestion period, and was used to analyze both test substances of the sour milk group and the placebo group as well as major effects and interactions between ingestion periods. In addition, Dunnett’s multiple comparison test was used to assess comparisons with baseline (start of intake) blood pressure values. Moreover, the paired t-test was used for serum biochemical values. SPSS Ver. 10 (SPSS Japan Inc.) was used for the statistical software, and p < 0.05 was considered statistically significant.

(c) Results

(i) Blood pressure and pulse rate

Interactions between the objective substance and the intervention period were observed with respect to systolic blood pressure as a result of two-way analysis of variance, and the variations in systolic blood pressure during the ingestion period exhibited different patterns between the groups (p<0.05).

In the sour milk ingestion group (sour milk group), in which the blood pressure immediately before ingestion was 157.8±13.0 mmHg, systolic blood pressure decreased significantly to 147.5±11.9 mmHg at 2 weeks after ingestion (p<0.001). Persistent and stable lowering-effects were also observed thereafter, with systolic blood pressure decreasing to 144.1±8.7 mmHg after 8 weeks at the completion of the ingestion period (p<0.001). In addition, significant anti-hypertensive effects were observed as compared with immediately before ingestion, even after 2 weeks had passed following completion of ingestion, indicating a gradual reversion of systolic blood pressure. In contrast, in the placebo ingestion group (placebo group), there were no significant changes in blood pressure observed throughout the ingestion period. The systolic blood pressure of the sour milk group was significantly lower than that of the placebo group at 4 weeks, 6 weeks, and 8 weeks after ingestion (t-test: p<0.05).

Diastolic blood pressure at 6 and 8 weeks after ingestion was significantly lower in the sour milk group than in the placebo group (p<0.05). In addition, there were no significant changes observed in pulse rate between the groups.

These results suggest that the lowering of blood pressure gradually occurs with the continuous ingestion of sour milk for at least 2 weeks, and that mild lowering of blood pressure starts from 4 weeks of ingestion. With respect to the progress of the subjects following completion of the ingestion period, a gradual reversion was observed, with systolic blood pressure continuing to be significantly decreased as compared with prior to ingestion, even at 2 weeks following completion of the ingestion period.

(ii) Body weight, height, and BMI

There were no significant changes in BMI due to ingestion observed in either group.

(iii) Serum biochemical and uric analyses

The differences in the serum biochemical examination conducted before and after ingestion (0 and 8 weeks) were only slight and within the respective normal ranges.

(iv) Safety as food (Medical examinations and questioning)

Although side effects consisting of symptoms of diarrhea in 1 subject of the sour milk group and 1 subject of the placebo group were observed within 1 week after the start of ingestion, both were temporary and required no treatment. There were no other occurrences of coughing, headache, and dizziness, or other symptoms indicative of side effects observed in either group, and no abnormal variations observed in blood biochemical and urinalysis findings before or after ingestion. The occurrence of coughing associated with ACE inhibitors is thought to involve the accumulation of substances such as bradykinin and substance P stimulating the C fiber receptors of the bronchial tubes, resulting in coughing (Nakamura et al., 1996). The lack of coughing seems to have been due to the low levels of VPP and IPP peptides in the sour milk ingested.
in this study and the possibility of a tissue-specific action in arterial tissue ACE, as suggested by animal studies (Yoshikawa and Chiba, 1992) The sour milk is estimated to be a safe food product at an effective dosage.

(v) Dosage
Considering another human intervention study, it is believed that the effects can be expected at this study’s tripeptides dose in the sour milk, that is 2.66 mg/day (approx. 0.045 mg/kg/day) for Val-Pro-Pro and 1.6 mg/day (approx. 0.027 mg/kg/day) for Ile-Pro-Pro.

d) Approved health claim
In 1997, the Ministry approved the health Claim “This product is suitable for persons with slightly elevated blood pressure” with the warning labeling “This is not a medicine for remedy or prevention of hypertension,” based on the results of this human study as well as other human studies, animal studies and in-vitro studies

4) International Comparison
The Code of Practice for Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink Products (Code of Practice Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink products) in the Netherlands was published in 1998. It states that scientific evidence regarding health benefits is assessed by an independent panel at the request of the party using or intending to use the health claim for the marketing of a product. The evidence must be based on relevant scientific data on human subjects. The data must concern normal use by the target population, and the product must carry a health benefit relevant to the target group.

The Code of Practice on Health Claims in the UK (Code of Practice on Health Claims on Foods in UK Joint Health Claim Initiative in UK, 1998) proposed that substantiation or scientific evaluation of innovative claims is essential and that the food will cause or contribute to a significant and positive physiological benefit when consumed by the target population as a part of their normal diet.

The Swedish Code of Practice (Asp and Trossing, 2001) “Health Claims in the Labeling and marketing of Food Products” was extended to the following Product-specific physiological claims (PFP) in 2001. For PFP labeling, independent experts evaluate the scientific document supporting the effect of the food product, which is put on the market with a product-specific physiological claim. Product-Specific Physiological Claims must be based on studies that are scientifically sound and unobjectionable, showing the effects that are claimed. The studies must be performed on human beings, and the study group must be representative of the group of people that the marketing is aimed to reach. Furthermore, studies must be performed with a supply relating to normal use of the food product during the study period, and must be long enough to show a lasting effect.

The following three general concepts of substantiation of health claims of FOSHU are similar to that of innovative claims of the Code in the UK (Code of Practice on Health Claims on Foods in UK Joint Health Claim Initiative in UK, 1998), the health benefits of the Code in the Netherlands (Code of Practice Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink products), or product-specific claims of the Swedish Code.
1. Scientific substantiation must be evaluated by an independent expert party.
2. The scientific evidence must be based on the human studies.
3. The human studies must be performed with the product’s target population.

The methodology, procedure, and evaluation for FOSHU were improved for the more than 330 products approved during one decade in Japan. These experiences and discussions were helpful in establishing a global standard for the scientific substantiation of functional foods.

IV) REGULATORY SYSTEM
Definition and classification of health claims have been discussed many times in Codex and other international committees, but there has been little discussion of the regulatory system for these health claims. From a practical perspective, the establishment of regulatory system is as important as the definition and classification.

A regulatory system for health claims on foods could be classified as follows.

1) Standard regulation system
The Code in the UK and Sweden defines a generic claim as a health claim based on well-established, generally accepted knowledge from scientific data. In the case of generic health claims, no specific substantiation is required individually. These claims could be standardized by an expert authority. The Swedish Code standardizes generic claims related to eight well-established diet and health relationships. These eight connections are: (1) obesity - energy content; (2) cholesterol levels in the blood – fat quality or some soluble dietary fiber; (3) blood pressure – salt (sodium chloride); (4) arteriosclerosis (blood cholesterol level / blood pressure) – n-3 fatty acids in fish products; (5) constipation – dietary fiber; (6) osteoporosis – calcium; (7) caries – absence of sugars and other easily fermented carbohydrates; (8) iron-deficiency anemia – iron.

Foods with Nutrition Function Claims in Japan standardized twelve vitamins and two minerals, as explained previously. The examples of the claims are as follows: “calcium is a nutrient that is necessary to form bones and teeth,” and “Vitamin D is a nutrient that promotes calcium absorption to gut intestine and aids in bone formation.” The upper and lower levels in the daily portion of these nutrients and warning labeling are also set up. Most Nutrient Function Claims could be standardized as generic claims in many countries such as Japan.
2) Individual approval system;
In the Code of Practice in the Netherlands (Code of Practice Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink products), with its panel of experts established in 1998, the scientific evidence regarding health benefits was assessed by an independent panel at the request of the party using or intending to use the health claim for the marketing of a product. The Swedish Code of Practice (Asp and Trossing, 2001) “Health Claims in the Labeling and marketing of Food Products” was extended to the following product-specific physiological claims (PFP) in 2001. For PFP labeling, independent experts evaluate the scientific document substantiating the effects of the food product with a product-specific physiological claim. Product-specific physiological claims must be based on studies that are scientifically sound and unobjectionable, showing the effects that are claimed.


3) Approval Procedure of FOSHU
The claims of FOSHU are innovative health claims other than the generic health claims. Therefore, the claims must be based on individual scientific substantiation. The Japanese Ministry validates the scientific evidence in support of the health claim filed by the applicant files.
(a) Requirement for Application
In order to apply FOSHU approval, there are three essential requirements for FOSHU approval. The first is effectiveness based on scientific evidence, including clinical studies. The second is food/product safety and additional safety studies in human. The last is analytical determination of the effective component. All available literature regarding the related function, safety, and analysis of the related functional components and related food should be reviewed.

Documentation regarding positive effects on body functions should be prepared on the basis of substantiation not only by human clinical studies but also by in vitro metabolism and biochemical studies and animal studies. These data should demonstrate statistically significant differences. Basically, a human study should be conducted by using the food in question over a reasonably long-term period (e.g. more than 2 or 3 months).

Concerning the documentation of safety, both in vivo and in vitro studies should be carried out to obtain preliminary data confirming safe intake by humans. The safety data for humans should be required for at least three times the minimum effective dosage.

Documentation of the methods for analysis of related functional components should submit the suitable and reliable methods of quantitative/qualitative analytical determination.

As additional documentation, the stability of related functional components should be confirmed. If a product is in the form of tablets or capsules, experiments should be conducted regarding disintegration or dissolution.
(b) Evaluation by the Ministry
The application including the above documentation will be evaluated by expert committees, whose member consists of medical doctors, nutritionists, and pharmacologist. After evaluation by the expert committee in charge, the National Institute of Health and Nutrition validates the method and determines the content of the effective component.

The applicant should validate the quality, effectiveness, and safety of the product approved by FOSHU, taking the new scientific studies and the post-marketing research into consideration. Competent authorities in the Ministry can inspect manufacturing plants and evaluate the effectiveness and safety of FOSHU products, when necessary, by requiring related documentation.

4) Notification system
Under the DSHEA in the US, dietary supplement manufacturers can sell their product with any structure/function claims by notification regarding the claim they are making (Disclosed information of the Ministry of Health, Welfare and Labour). Substantiation of any structure/function claims are not required to be checked for accuracy by any independent experts or to be open to the public.

A notification system for innovative structure/function claims would be appropriate only in a country where manufacturing companies are absolutely honest and able to scientifically substantiate both the effectiveness and safety of their products, considering the totality of the evidence, that is, from in vitro and animal studies as well as human studies that are published in journals with evaluation by expert referees. But it is difficult for a manufacturer who can scientifically substantiate the effects and safety of their product independently because the methodology of scientific substantiation to support-related claims has not been confirmed and is now under discussion internationally. Consumers usually expect that health-related claims are substantiated and have been checked for accuracy by independent experts prior to use.

5) International Comparison
The author has classified health claims (Table 2) in comparison with international discussion. Most Nutrient Function Claims proposed by Codex could be generic claims. Generic claims such as Nutrient Function Claims based on well-established, generally accepted knowledge from evidence could be standardized by an authorized organization without specific, individual substantiation.

Both enhanced Function Claims and Disease Risk Reduction Claims could be innovative claims for the first step of development. These innovative claims should be evaluated and approved by an expert authority such as the FOSHU system.
CONCLUSIONS

Japanese citizens enjoy the greatest longevity in the world. One of the main reasons is their eating habits, which prevent life style-related diseases such as diabetes, hypertension, arteriosclerosis and obesity. Characteristics of the Japanese diet are its low fat content, high levels of dietary fiber, high levels of plant protein, and high levels of polyunsaturated fatty acids from fish. Research and development over the last two decades have proved that these components positively influence the function of the human body to maintain good health and prevent life style-related diseases.

However, westernized eating habits have surged in Japan, and the fat content is increasing while that of dietary fiber and polyunsaturated fatty acids is decreasing in the diet of Japanese people, and especially younger people. Moreover, the ratio of elderly people is rapidly increasing. Aging is closely related to life style-related diseases, which are referred to as elderly persons’ diseases. As such, the Japanese Ministry has researched the physiological function of foods and established a regulatory system for health claims, as represented by FOSHU and FNFC.

The following matters should be basic concepts to establish the regulatory system of health claims on foods and evaluate its scientific substantiation.

Totality of Evidence

FOSHU documentation must be reviewed systematically, not only the experimental data but also all available scientific evidence, including published scientific literature. This concept is similar to that regarding the totality of evidence in the Code in the UK (Code of Practice on Health Claims on Foods in UK Joint Health Claim Initiative in UK, 1998), which states, “Any innovative health claim must be supported by documentation of the scientific evidence demonstrating the specific physiological effect which is claimed. The documentation must provide key evidence to substantiate the innovative health claim and reflect the totality of the evidence available including relevant associated research. There must be systematic evaluation of all the data, and the conclusion on which the innovative health claim is based should reflect the extent and quality of the data.”

Human Intervention Study

As to the method of confirming benefits and safety, the existence of a human intervention study and identification of undesirable or adverse effects in a human study are essential.

International harmonization

The labeling of health-related foods should be based on scientific evidence, but always being in harmony with global international standards. Nutrient Function Claims are included in the guidelines for use of nutrition claims, which was adopted by the Codex in 1997. Newly establishing claims of FNFC in Japan are equivalent to the Nutrient Function Claims. Most statements of the Japanese FOSHU are close to the category of the Structure/Function Claims in the US or the Enhanced Functional Claims proposed by the Codex and EU project.

Following establishment of the NLEA and DSHEA in the US and Consensus Documents of the EU project, federal regulation has clarified structure/function claims in the US and some European countries are establishing their own code. Japan began research and development 20 years ago and established a new regulatory system for food function claims. It is now desirable for national governments as well as international organizations of both consumers and industries cooperating with Codex to together make an effort to establish international standards for not only health-related claims on foods but also the regulatory system.

REFERENCES


Code of Practice Assessing the Scientific Evidence for Health Benefits stated in Health Claims on Food and Drink products: The Text of Vdingscentrum 5-13


Codex Committee on Food Labeling 28 Session: Proposed Draft Recommendations for the Use of Health Claims Revised Text for the discussion


Disclosed information of the Ministry of Health, Welfare and Labour


Health Claims in Labeling and Marketing of Food Products, www.snf.iden.se

Japan Codex (2000). Proposed draft recommendations for the use of health claims, Comments from Japan, CX/FL00/9-CRD.33, Codex, 2000


Masuda, O., Nakamura, Y., Takano, T. (1996) Antihypertensive peptides are present in aorta after oral administration of sour milk containing these peptides to spontaneously hypertensive rats. Journal of Nutrition 126, 3063-3067


