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Overview of the Regulation of Health Claims in Japan

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Abstract: According to the international guidelines of the Joint FAO/WHO Food Standards Program, Codex Alimentarius Commission, individual countries create health claims for foods. These health claims are regulated by government regulatory agencies such as the Food and Drug Administration (FDA) in the USA and the European Food Safety Authority (EFSA) in the European Union. In Japan, the Ministry of Health, Labor, and Welfare (MHLW) created "Food for Specified Health Uses (FoSHU)" in 1991 and "Food with Nutrient Function Claims (FNFC)" in 2001. Thereafter, rules similar to those in Japan have been created elsewhere in the world. Currently, the system is regulated and updated by the Food Safety Committee, the Consumer Affairs Agency, and the Consumer Committee. Special foods attached with health claims in Japan are categorized into the following two groups according to their functions for health, their users, and purposes: (1) Food for Special Dietary Uses (FOSDU) and (2) Food with Health Claims (FHC). FoSHU is categorized as both FOSDU and FHC. Scientific evidence of the claims and the safety are confirmed with the finished product by the government agency, and then the special label is used on these foods (Fig. 1). The FoSHU system was established 25 years ago and health problems have not occurred because of using it. This is because there are many scientific evidences about FoSHU's efficacy and safety. However, health foods used in Japan are mostly just so-called health foods, and the safety is not confirmed by the Japanese government. Furthermore, safety evaluations of these products are only general and specific toxicity studies, because these are just foods. The targets of health foods are not patients, but a previous study indicated that most patients used dietary supplements without consulting their physicians. If patients take medicines along with it, health problems such as food-drug interactions may occur. For medicines, not only general and specific toxicity studies but also pharmacokinetics studies are performed. Over 80% of drug-metabolizing reactions are oxidation reactions by cytochrome P450s (CYP), and drug interactions naturally occur via CYPs induction or inhibition. Generally, CYPs induction decreases drug efficacy, and CYPs inhibition increases drug efficacy. In health food-drug interactions as well, these reactions occur via CYPs. Finally, I discuss my recent studies on the safety of herbal extracts such as herb-drug interactions via inductions of hepatic drug-metabolizing enzymes.

Keywords: health food, health claim, regulation

1 INTRODUCTION

Due to the worldwide increase of the elderly population, aging- and lifestyle-related chronic diseases such as obesity, diabetes, hypertension, cardiovascular disease, and cancer have profoundly increased. These diseases are related to lifestyle factors such as dietary habits and physical exercise; however, people tend to use health foods rather than changing their lifestyles to improve or maintain their health condition. This has resulted in food science and technology developments.

In the USA, the Nutrition Labeling and Education Act (NLEA) established the regulation of nutrition and health claims in 1990, and subsequently, dietary supplements were set up between medicines and foods under the Dietary Supplement Health and Education Act (DSHEA) in 1994. In Japan, the Ministry of Health, Labor, and Welfare (MHLW) created "Food for Specified Health Uses (FoSHU)" as one of the nutrition and health claim regulations in 1991. At the international level, the Joint FAO/WHO Food Standards Program, the Codex Alimentarius Commission established the international guidelines for nutrition and health claims in 2004. These guidelines aim to protect consumers and promote fair trade for foods. According to the international guidelines, individual countries are required to set up nutrition and health claims for foods. These health claims are then regulated by the laws of each individual country through government regulatory agencies such as the Food and Drug Administration

(FDA) in the USA and the European Food Safety Authority (EFSA) in the European Union. In this paper, the Japanese regulatory system of health claims is discussed focusing on the differences in each category.

Current reports have indicated that some patients take health foods such as dietary supplements with their medications (Chiba, Sato, Nakanishi, Yokotani, Karino, et al., 2014a; Chiba, Sato, Nakanishi, Yokotani, Suzuki, et al., 2014b). Health foods contain not only vitamins or minerals but also natural products such as herbal ingredients, and the recent reports have shown an increase in the interactions between natural products and medicines. For example, St. John's wort induces cytochrome P450s (CYPs), which is a family of drug-metabolizing enzymes, and it especially affects CYP3A4 type, and leading to a decrease in blood concentrations of drugs and decline in the efficacy of drugs such as cyclosporine, indinavir, and digoxin (Barone, Gurley, Ketel, Lightfoot, & Abul-Ezz, 2000; Durr et al., 2000; Roby, Anderson, Kantor, Dryer, & Burstein, 2000). To avoid health food-drug interactions, accumulation of scientific evidence regarding safety, including pharmacokinetics and pharmacodynamics studies, are required. Therefore, I discuss my recent research on herb-drug interactions through the induction of hepatic drug-metabolizing enzymes.

2 REGULATION OF HEALTH CLAIMS IN JAPAN

There is a long history of Japanese health claims regulation. In 1952, special nutritional foods were established under the Japanese Nutrition Improvement Law (currently the Health Promotion Law). Thereafter, major changes in the regulation system have occurred, and the "FoSHU" and "Food with Nutrient Function Claims (FNFC)" were established by the Ministry of Health, Labor, and Welfare in 1991 and 2001, respectively. The current regulation system of Japanese health claims is divided into the following 2 basic categories: (1) Food for Special Dietary Uses (FOSDU) and (2) Food with Health Claims (FHC) (Fig.1) (Ministry of Health, Labour, and Welfare; Consumer Affairs Agency, 2011). FoSHU and FNFC are categorized as FHC. Furthermore, FoSHU is also categorized FOSDU. FoSHU was initially established under the FOSDU category in 1991, but now belongs to both the FOSDU and FHC categories. Apart from medicines, the oral intake of products is classified as foods, even in tablet and capsule form. Therefore, adding pharmaceutical ingredients to food with the labeling of disease treatment or prevention effects is prohibited.

2.1 The Food for Special Dietary Uses (FOSDU) system

FOSDU is appropriate for special dietary use, and consists of the following 5 categories :(1) formulas for pregnant or lactating women, (2) infant formulas, (3) foods for the elderly with difficulty in masticating or swallowing, (4) medical foods for the ill, and (5) FoSHU. Medical foods for the ill include "low-protein", "allergen-removed", and "lactose-free" foods, and these foods are individually approved by

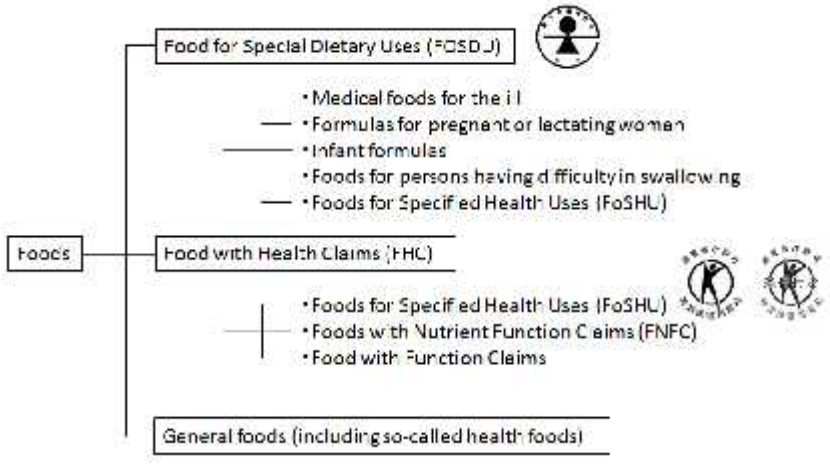

Figure 1. Current category of foods in Japan.

the Consumer Affairs Agency, with the approved products carrying the approval mark of FOSDU (Fig.1). Before using these foods, consumers should consult a medical professional, such as a physician, pharmacist, or registered dietitian, for usage advice.

2.2 The Food with Health Claims (FHC) system

FHC relates to foods that offer a health benefit to human body, and are classified into the following 3 groups according to their effects on health, their users, and their purposes: (1) FoSHU, (2) FNFC, and (3) Foods with Function Claims. These categories of foods were created to allow consumers make a decision about whether to use these foods by referring to the health claim labels.

FoSHU are foods that can have positive physiological effects on the human body. There is scientific evidence to support the health claims of these foods and the safety of the finished product. This evidence is individually confirmed by the appropriate government agency such as the Food Safety Committee, the Consumer Affairs Agency, and the Consumer Committee. Requirements for FoSHU approval are shown in Table 1. FoSHU products can display the special approved mark (Fig.1). These foods are designed to improve the user's dietary habits, and to maintain or to promote the user's health condition.Current approved FoSHU health claims are classified into 8 groups (Table 2), and there were approximately 1,270 products approved in August 2016. Currently, the health claims of FoSHU comprise the following 4 groups: (1) regular FoSHU, (2) standardized FoSHU, (3) qualified FoSHU, and (4) FoSHU with a disease risk reduction. Standardized FoSHU is applied to foods with sufficient FoSHU approvals and accumulation of scientific evidence. This type does not require a detailed review process for food products that already meet the established standards and specifications, so it is a short-cut process. Qualified FoSHU is applied to foods that are not substantiated by scientific evidence that meets the level of regular FoSHU, and as a result, "evidence of efficacy has not necessarily been established" must be stated on the label. The only permitted FoSHU with a disease risk reduction claim are calcium and folic acid for the prevention of osteoporosis and neural tube defects, respectively. Furthermore, daily intake is defined as 300-700 mg/day of calcium and 400-1000 μg/day of folic acid.

Table 1. Requirements for FoSHU approval.

1. Improvement of dietary habits and contribution to health maintenance and enhancement can be expected by consuming the product.
2. Scientific evidence for the claimed health benefit is available.
3. Clinical and nutritional intake level of the product and/or its functional component is established.
4. The product and/or its functional component is safe for human consumption.
5. Following items regarding functional component are defined:
   a) Physical, chemical, and biological characterization and its methods
   b) Methods of qualitative and quantitative analytical determination
6. Nutrient constituent of same type of foods is not significantly changed.
7. The food is intended to be consumed on a daily basis and not on rare occasions.
8. The product or its functional component is not included in the medical drug list.

FNFC is used for nutrition supplementation, such as vitamins and minerals, which tend to be deficient in a daily diet. Currently, it can be used on the labels of nutritional ingredients, including 12 vitamins (vitamins A, E, D, B_1, B_2, B_6, B_{12}, C, folic acid, niacin, pantothenic acid, and biotin), 6 minerals (calcium, magnesium, potassium, zinc, iron, and copper), and n-3 fatty acid. Furthermore, it can be used to label not only foods in tablet or capsule form but also conventional or fresh foods. These foods can use the claims without approval from the Japanese government under obligation of the established standards and specifications. Concretely, the amount of the nutritional ingredients in the recommended daily intake of the product must be within a specified range, and warning indications must be displayed alongside the nutrient function claims (Table 3). The lower daily level is based on the standard values for the nutrition labeling as per the Japanese Dietary Reference Intakes, and the upper daily level is set as the upper amount of nutrient items in quasidrugs.

The new system of "Foods with Function Claims" was established in April 2015 in order to make more of the products available clearly labeled with certain nutritional or health functions, and to enable consumers to make more informed choices. This system was made with reference to the regulatory system for dietary supplements in the USA. This system belongs to the FHC category. The FHC category includes FoSHU and FNFC.

Characteristics of this new system are as follows: (1) Foods with

Table 2. Approved health claims and ingredients on FoSHU.

Health uses	Food category	Ingredients (example)	Health claims (example)
GI function	Table sugar Yogurt	Oligosaccharides Lactic acid bacteria (LAB)	Helps maintain good GI condition Helps improve bowel movement
Cholesterol level	Soft drink Cooking oil	Chitosan, phytosterol	Helps lower cholesterol level
Triacylglycerol, body fat	Cooking oil Oolong tea	Medium-chain fatty acid Polyphenol	Helps resist body fat gain For those concerned about body fat
Blood pressure	Instant soup, candy	Peptides, chlorogenic acid	For those with high blood pressure
Bone	Soft drink	Soy isoflavone, vitamin K2	Promotes calcium absorption, supports bone health
Teeth	Chewing gum	Sugar alcohol	Helps maintain strong and health teeh
Blood glucose level	Soft drink , Instant miso soup	Indigestible dextrin , polyphenol	For those concerned about blood glucose level

Table 3. Example of standards and specifications for FNFC.

Nutrient	Range of nutrient	Nutrition function claims	Warning indication
Vitamin A	135 - 600 µg	Helps to maintain vision in the dark, and helps to maintain skin and mucosa healthy.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake. Women within the third months of pregnancy or women considering to be pregnant should be careful of over consumption.
VitaminB1	0.30 - 25 mg	Helps to produce the energy form carbohydrate and to maintain skin and mucosa healthy.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake.
Zinc	2.1 - 25 mg	Necessary nutrient to maintain normal taste and helps to maintain healthy skin and mucosa membranes. It is involved in the metabolism of protein and nucleic acids and is helpful in maintaining health.	Increased intake of this product will not result in curing diseases nor promoting health. Too much intake of zinc might inhibit absorption of copper. Please comply with the advisable daily intake. Infants and young children should avoid use of this product.

Function Claims are for people not suffering from any disease (also excluding minors, pregnant woman including those planning a pregnancy, or who are lactating women). (2) All food products including fresh products are subject to this system. (3) Prior to market entry, food business operators are required to submit information, such as data on food safety and effectiveness. There is a system in place to collect information on adverse health effects, and report them to the Secretary-General of Consumer Affairs Agency. (4) Unlike FoSHU, the government does not evaluate the safety and effectiveness of the submitted product. (5) The submitted information is disclosed on the website of the Consumer Affairs Agency. The biggest difference between this new system and the FoSHU or FNFC systems is that it ensures the scientific evidences for the safety and efficacy of the products is collected by the food business operators themselves. The scientific evidence for any function claims must be obtained from clinical trials or systematic literature reviews.

2.3 Current problem in usage of foods with health claim and so-called health foods

According to recent studies, some FoSHU or dietary supplement users expect these foods to have the same positive effects as medicines, and some users on medication have used FoSHU or dietary supplements with similar health claims to medicines. Furthermore, the users took these foods without first consulting their physician (Chiba, et al., 2014a; Chiba, et al., 2014b). This is because users think that FoSHU or dietary supplements are as safe as general foods. Intrinsically, FoSHU aims to improve user's lifestyles, such as dietary and exercise habits, and hence, does not have therapeutic efficacies. Consumers tend not to understand the appropriate usage of FoSHU. Fortunately, there are no reports of serious adverse events with FoSHU because of the scientific evidence regarding efficacy and safety. However, most health foods used in Japan are only so-called health foods like dietary supplements, which are not regulated in Japan. In other words, the safety and the efficacy of these so-called health foods are not confirmed by the Japanese government. So-called health foods include not only vitamins or minerals but also herbal/botanical extracts or ingredients. Previous studies have indicated that herbal/botanical extracts or ingredients can cause serious adverse events such as hepatotoxicity and drug-interactions (Bunchorntavakul & Reddy, 2013; Choi et al., 2016; Fasinu, Bouic, & Rosenkranz, 2012; Haslan, Suhaimi, & Das, 2015). This is because safety evaluations of these products only include general and specific toxicity studies. In contrast, medicines require not only general and specific toxicity studies but also pharmacokinetics and pharmacodynamics studies to be performed. Over 80% of drug-metabolizing reactions are oxidative reactions by CYPs, and drug interactions naturally occur via CYPs induction or inhibition. Generally, CYPs induction decreases drug efficacy, and CYPs inhibition increases drug efficacy. In health food-drug interactions, similar reactions can also occur via CYPs. To avoid these interactions, further studies of safety evaluations and accumulation of scientific evidence are needed. Furthermore, consumers should be educated about the appropriate use of health foods. Importantly, patients on medication should not use health foods or should first ask their physician whether they can use health food.

The National Institute of Health and Nutrition has created an online database of evidence-based information on the safety of drug-interactions and the efficacy of health foods for consumers and medical professionals, such as physicians, pharmacists, and dietitians (National Institute of Health and Nutrition, 2004). This database can be used as a consumer education tool, and as a connection between the consumers and medical professionals.

3 HERB-DRUG INTERACYION VIA HEPATIC CYTOCHROME P450 INDUCTION MECHANISM

The use of herbal supplements has increased worldwide (Gershwin et al., 2010), due to the belief that herbal extracts or ingredients are safe because they are natural and have been used for centuries in oriental cultures. However, this is not true. In fact, the incidence of adverse events associated with herbal supplement intake has been increasing, with herb-drug interactions becoming a particular source of serious concern. This is because herbal supplement users often simultaneously take medicines. In addition, a decrease in efficacy or an increase in the adverse effects of prescribed drugs might interfere with appropriate medical care and have a fatal outcome. Herbal extracts have various qualities and their safety is not fully evaluated. To ensure the safety of herbal extracts, it would be necessary to clarify not only general toxicities but also interactions with drugs, at least at the ingredient level.

Weight-loss supplements are popular; however, they can cause health problems (Pittler, Schmidt, & Ernst, 2005). *Coleus forskohlii* is a member of the mint family, native to India, and is a popular herbal ingredient used in weight loss health foods (Bhat, Bajwa, Dornauer H., & de Souza, 1977). The root contains the diterpene forskolin, which increases cAMP concentrations via the activation of adenylate cyclase, thereby stimulating lipolysis (Allen, Ahmed, & Naseer, 1986; Okuda, Morimoto, & Tsujita, 1992). Accordingly, *Coleus forskohlii* extract (CFE) standardized with 10% (w/w) forskolin is added to weight loss products. However, even at the ingredient level, little is known about the safety of CFE with regard to drug interactions. Therefore, this research focuses on whether CFE influences hepatic drug-metabolizing enzymes, especially CYPs, and influences the therapeutic efficacy of medicines metabolized by CFE-induced CYPs.

Feeding mice on standardized 10% (w/w) forskolin containing CFE diets significantly increased the ratio of liver weight to body weight. Hepatic CYP activities and expression of mRNA also increased in a dose-dependent manner; especially, CYP2B, CYP2C, and CYP3A types were markedly induced (Virgona et al., 2012). This phenomenon was observed at a dietary dose of 0.05% CFE (corresponding to about 60 mg of CFE/kg body weight). When this dose is translated to a human equivalent dose (Reagan-Shaw, Nihal, & Ahmad, 2008), it is approximately 5 mg/kg body weight, which is the recommended dose for humans found in CFE containing weight loss products. The induction of CYPs by CFE was observed after 1 week of feeding, which rapidly recovered when CFE was discontinued.

The induction of hepatic CYPs by CFE indicates an interaction of CFE with medicines that are metabolized by CFE-induced CYPs. Warfarin, an anticoagulant, interacts with various foods and drugs, resulting in adverse events (Holbrook et al., 2005). Warfarin is metabolized by the CYP2C subfamily, which is induced by CFE (Kumar et al., 2006). Warfarin-induced anticoagulation was attenuated by CFE in parallel with CYP2C induction (Yokotani et al., 2012). In addition, CFE directly inhibited CYP2C activity in mouse and human liver microsomes *in vitro*. These findings indicate that CFE interacts with warfarin *in vivo* through the induction of hepatic CYP2C, and it increases the risk of thrombus formation with concomitant use of CFE and warfarin. CFE also markedly induced the CYP3A subfamily, which catalyzes the metabolism of more than 50% of medicines (Tompkins & Wallace, 2007). Thus, interactions between CFE and other medicines may also occur. To ensure the safety of CFE in health food products, it is important to refer the present findings, and to identify the compounds that induce drug-metabolizing enzymes, and reduce or remove them from CFE ingredients.

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