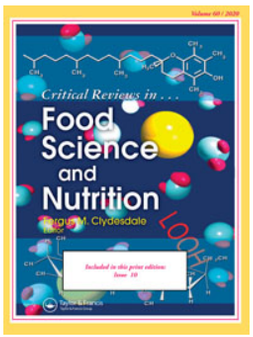

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REVIEW

The frontier between nutrition and pharma: The international regulatory framework of functional foods, food supplements and nutraceuticals

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ABSTRACT

The link between diet and human health status has been repeatedly proved by strong scientific evidence, and developed societies demand food products with an added value beyond the satisfaction of hunger and the provision of nutrients. Functional foods, food supplements and nutraceuticals are at the interface between nutrition and pharma and opens the doors for seeking new therapeutic alternatives for the prevention of nutrition-related diseases. The present review is aimed at clarifying the differences between functional foods, food supplements and nutraceuticals as well as describing its regulatory framework in Europe, United States and Japan. Specific harmonized regulation for these products is needed. Functional foods, food supplements and nutraceuticals exert health-promoting properties and could be considered as potential candidates in the management of chronic diseases in combination with prescribed medication. Further research is essential for establishing which nutrition-pharma combinations are most favorable and suitable for each chronic disease.

KEYWORDS

Food; pharma; functional products; nutrition-related diseases; regulation

1. Introduction

Modern societies are immersed in a change of the food concept and the population demand food products which present an added value providing something else beyond the necessary nutrients and the satisfaction of hunger. Strong evidence support the importance of diet in human health as unhealthy food habits constitute one of the multiple risk factors of chronic diseases (CD), a huge emerging problem in developed countries (Betoret et al. 2011; Landström, Hursti, and Magnusson 2009; World Health Organization (WHO) 2018). Functional products such as functional foods, food supplements and nutraceuticals meet these requirements as they are intended to enhance life quality by preventing nutrition-related diseases. Even though there are remarkable differences between these concepts, consumers generally confuse them and use them interchangeably. In most cases, no specific regulation exists and it depends on the nature of each product (Betoret et al. 2011; da Costa 2017; Küster-Boluda and Vidal-Capilla 2017; Saher et al. 2004; Santini et al. 2018).

The present review is aimed at clarifying the differences between functional foods, food supplements and nutraceuticals at the interface between nutrition-pharma as well as describing its regulatory framework in Europe, United States and Japan.

2. Food and medicine: poles apart

Food is essential for humans as it contains necessary components for the sustainability of crucial functions in human organism like production of energy, provision of nutrients, support of metabolic activities, growth and maintenance of the body. Food for human consumption is defined by Regulation (EC) No 178/2002 in Europe; Federal Food, Drug, and Cosmetic Act (1938) in United States (US); and Food Sanitation Act (1947) in Japan. As it can be seen in Table 1, there are some differences among definitions. American definition includes animal feed and any substance that migrates from the food article to the food, while Japanese definition is as not specific as the other ones.

In the opposite end, medicine is a product which has scientifically demonstrated at the recommended doses any pharmacological, immunological or metabolic action. European, American and Japanese regulation provide its own statutory definition for medicines (Table 2). In US, the Federal Food, Drug, and Cosmetic Act (1938) (latest amendment in 2018) approved two definitions which include the diagnosis, cure, mitigation, treatment, or prevention of disease in other animals apart from human beings. It results to be the main difference with European definitions. In Japan, the Pharmaceutical Affairs Act (1960) (latest amendment in 2013) discerns between 'pharmaceutical', whose definition is similar to the American, and 'quasi-drug', which includes items whose purposes (e.g. extermination of insects) are not covered by the European and American regulation.

Medicine can modify human physiological functions because they contain an 'active substance', defined as 'any substance or mixture of substances intended for the manufacture of a medicinal product and which, when used in its

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.

Table 1. Statutory definitions for food by international regulations.

Area/country	Item regulated	Definition	Regulation
Europe	'Food' or 'foodstuff'	'Any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. Drinks, chewing gum and any substance (including water) that is added to the food voluntarily during the manufacturing, preparation or treatment stages are considered foods. Feed, live animals (unless they are intended for human consumption), plants before harvesting, medicinal products, narcotic or psychotropic substances, cosmetics, tobacco and tobacco products, and residues and contaminants, are not included in this definition'.	Regulation (EC) No 178/2002 (latest amendment in 2018)
US	'Food'	'Articules used for food or drink for man or other animals, chewing gum and articles used for components of any such article'. This term includes human food, substances migrating to food from food-contact articles, pet food and animal feed'.	Federal Food, Drug, and Cosmetic Act (1938) (latest amendment in 2018)
Japan	'Food'	'Food and drink, excluding pharmaceutical products or quasi-pharmaceutical products specified by the Pharmaceutical Affairs Act (1960)'.	Food Sanitation Act (1947) (latest amendment in 2018)

Table 2. Statutory definitions for medicine by international regulations.

Area/country	Item regulated	Definition	Regulation
Europe	'Medicinal product'	'Any substance or combination of substances presented for treating or preventing disease in human beings'. 'Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings'.	Directive 2001/83/EC (latest amendment in 2011)
United States	'Drug'	'Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals'. 'Articles intended to affect the structure or any function of the body of man or other animals'.	Federal Food, Drug, and Cosmetic Act (1938) (latest amendment in 2018)
Japan	'Pharmaceutical'	'Any item (a) included in Japanese Pharmacopeia; (b) destined to be used in the diagnosis, treatment or prevention of human or animal diseases, excluding medical appliances and instruments; and (c) capable of affecting the structure and functions of human or animal body, with the exception medical appliances and instruments'.	Pharmaceutical Affairs Act (1960) (latest amendment in 2013)
	'Quasi-drug'	'Any item intended to (a) prevent nausea and other discomfort, heat rash, inflammation and the loss of the hair; (b) deodorize the smell of mouth and body; (c) grow or remove hair; and (d) exterminate and prevent mice, flies, mosquitoes, fleas or other similar creatures in order to protect both human and animal health'.	Pharmaceutical Affairs Act (1960) (latest amendment in 2013)

production, become an active component of this medicinal product intended to exert a pharmacological, immunological or metabolic action with the purpose of restoring, correcting or modifying physiological functions, or establishing a diagnosis' (Spanish Law 29/2006; last amendment in 2015). In Europe, US and Japan, 'foods for special medical purposes' (European Regulation (EU) No 609/2013; last amendment in 2017), 'medical foods' (American Orphan Drug Act, United States Congress 1983; last amendment in 2017) and 'medical foods for the ill' (Japanese Ministry of Health, Labor, and Welfare (MHLW) 2018a) are considered food products and not medicines as they do not contain an 'active substance'.

Apparently, it is clear the difference between medicine (with an immediate health effect) and food (with a more long-term health effect). As an example, in Europe there is an agreement that the recognized therapeutic active level of substances should be viewed as a 'cut off point' to make the proper difference. One product containing a substance with a lower recommended daily intake than this 'cut off point' would be under food products regulation. By contrary, if the recommended daily dosage is higher than this cut off point, the product would be regulated by medicines regulation (Eussen et al. 2011). However, the appearance of different functional products in the global market such as functional foods, food supplements and nutraceuticals has strongly increased the difficulty to distinguish between nutrition and pharma (Figure 1).

3. The frontier between nutrition and pharma: functional foods, food supplements and nutraceuticals

As it was discussed previously, nutrition has always taken an important role in maintaining the proper balance of micro- and macronutrients and pharmaceuticals have traditionally been used for alleviating symptons and/or curing diseases. But this general focus is changing and the frontier between nutrition and pharma is narrower. In the Asian culture, the

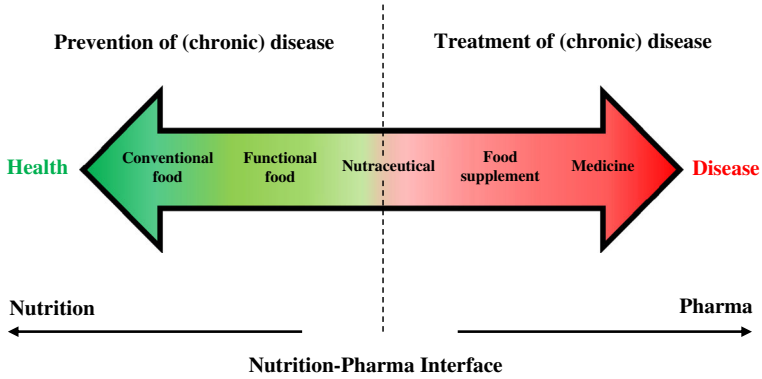

Figure 1. Nutrition-pharma interface.

idea that food can exert medicinal effects in the organism is reflected in its traditions of nutritional medicine. Food and medicine are basically considered the same as both have the same origin. It was in China where herbal medicines were developed and since then they have been used as crude medicines in China and Japan. Specific components present in plants and animals have been isolated, purified and made into ethical medicines, like morphine (obtained from opium) and steroids (from animal adrenal cortex) (Siegrist et al. 2015; Tanaka et al. 2004).

Medicines traditionally used to cure are now being intended to low risk factors of CD, that is prevention. Lipid- and pressure-lowering agents provide a good picture since they are able to reduce the risk of cardiovascular diseases. On the other hand, humans are looking for an optimal diet which can (1) promote health, (2) achieve a better well-being, life quality and an optimal function of organs and systems, and most importantly (3) reduce the risk of diseases (Carbajal Azcona 2013, Santini 2014). In Europe, US and Japan, functional products as functional foods, food supplements and nutraceuticals meet these requirements and are presented as a new potential strategy for reducing the risk and preventing CD (Stratton et al. 2015).

3.1. Functional foods concept and regulatory framework

The term 'functional food' was first introduced in Japan in 1984 as an end to improve human health. Then it was extensively used in Europe and US. Even though the concept of functional food derives from nutrition and not from pharmacology and functional foods are clearly foods and not drugs, the MHLW forbade the use of this term because it might imply drug-like effects and confuse consumers, who could expect the prevention or cure of diseases through these products. Thus, in 1991, functional food concept was integrated into the Foods for Specified Health Use (FOSHU) Japanese system and the term 'health food' was recognized and increasingly used by Japanese consumers, replacing the term 'functional food' (Ohama, Ikeda, and Moriyama 2014; Vukasovic 2017). However, this term is still broadly used in Europe and US. In Europe, functional foods are conventional and daily food that are consumed as a part of the normal diet but with one particular characteristic: they are composed of naturally occurring components which were absent or in low concentrations in the conventional ones. Functional foods do not only provide essential nutrients for survival but also improve well-being and life quality by reducing the risk of disease. They do not exert therapeutic function and positive effects on target functions beyond their nutritive value (da Costa 2017). The American Dietetic Association (ADA) pointed out that the appearance of functional foods in the market should not favor the wrong concept of 'good and bad food' since any food can be properly incorporated in a healthy diet.

Although there is no statutory definition for functional foods, it is surprising the great number of working definitions provided by Official Institutions (Table 3). After analyzing 26 definitions, the authors Doyon and Labrecque proposed in 2008 the following comprehensive definition for functional food: 'A functional food is, or appears similar to, conventional food. It is part of a standard diet and is consumed on a regular basis, in normal quantities. It has proven health benefits that reduce the risk of specific CD or beneficially affect target functions beyond its basic nutritional functions' (Doyon and Labrecque 2008).

Regarding the regulatory framework, European regulation considers functional foods as a concept rather than specific food categories and they must meet general food laws. European Regulation (EC) 1925/2006 (amended by Regulation (EC) No 108/2008, Commission Regulation (EC) No 1170/2009, Commission Regulation (EU) No 1161/2011, Regulation (EU) No 1169/2011, Commission Regulation (EU) No 119/2014, Commission Regulation (EU) 2015/403 and by Commission Regulation (EU) 2017/1203) defines enriched/fortified food as 'food to which nutrients or ingredients have been added to add or emphasize particular nutritional characteristics'. Regulation (EC) 1925/2006 determinates by means of a positive list which vitamins, minerals and other substances as herbal extracts are accepted to be incorporated in food. Functional foods with novel ingredients or those which are made by novel processes fall under Regulation (EU) 2015/2283. This regulation demands a scientific assesment (prior to be launched on the market) of all novel foods and new food ingredients without a safe and significant consumption history before 15 May 1997. Regulation on dietetic food, genetically modified organisms (GMO) as well as on food supplements can also be applied to functional foods. Food enriched with mandatory

Table 3. Definitions of functional foods proposed by official institutions.

Official institution	Area/country	Definition
The FOSHU system. Nutrition Improvement Law Enforcement Regulations (1991).	Japan	'Foods that are expected to have certain health benefits, and have been licensed to bear a label claiming that a person using them for a specified health use may expect to obtain the health use through the consumption thereof'.
The Institute of Medicine's Food and Nutrition Board (IOM/FNB, 1994).	US	'Any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains'.
The International Food Information Services (IFIS 1998).	International	'Foods that provide benefits beyond basic nutrition'.
EU Project 'Functional Food Science in Europe' (FUFOSE), The International Life Sciences Institute (ILSI 1999).	Europe	'Foods that are satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. Functional foods must remain foods and they must demonstrate their effects in amounts that can normally be expected to be consumed in the diet: they are not pills or capsules, but part of a normal food pattern'.
US General Accounting Office (GAO 2000).	US	'Foods that claims to have health benefits beyond basic nutrition'.
The International Food Information Council (IFIC 2011).	International	'Foods that may provide health benefit beyond basic nutrition. Functional foods include a wide variety of foods and food components believed to improve overall health and well-being, reduce the risk of specific diseases, or minimize the effects of other health concerns. These foods include, for example, the naturally healthful components in fruits and vegetables, whole grains and fiber in certain breads and cereals, calcium in milk, and fortified foods and beverages such as vitamin D fortified milk. Functional foods, in its broadest definition, can also include dietary supplements'.

fortification of flour and margarine; food for particular nutritional uses or purposes (as defined by Regulation (EU) No 609/2013; last amendment in 2017) as well as food in which vitamins and minerals have been (1) used as food supplements (as defined by Directive 2002/46/EC; latest amendment in 2017) and (2) added for additive purposes (as defined by Regulation (EC) No 1333/2008; latest amendment in 2018) are not considered as enriched/fortified food. Regarding nutrition and health claims made on functional foods, Regulation (EC) No 1924/2006 ensures that any claim displayed on its labeling, presentation or advertising is clear, accurate and based on scientific evidence. The European Food Safety Authority (EFSA) is the body in charge of the evaluation of health claim applications. Food characterization must include information about the botanical source, chemical specifications and biological activity, batch-to-batch reproducibility and stability as well as the manufacturing process. Strong evidence concerning reduction of disease risk claims should be provided and demonstrate that the consumption of the food/constituent reduces (or beneficially affects) one or more risk factors of a disease, as it is the case of tomato products and CVD among others (Cámara et al., forthcoming). European national lists of approximately 44.000 health claims were provided to the European Commission. A consolidated list of 4600 health claims were finally sent to EFSA for evaluation. To date, 2337 health claims has been approved. That gives an idea of the difficulty of getting a health claim approval in Europe.

In US, functional foods are considered another food category, so they have to meet all requirements described for conventional food in Federal Food, Drug and Cosmetic Act (1938) (latest amendment in 2018).

In Japan, functional foods are considered as specific food categories. Japan is the sole country in the world which has implemented a specific approval process for functional foods, the Food with Health Claims (FHC) system. FHC can be classified in two groups depending on the purpose and function: FOSHU and Foods with Nutrient Function Claims (FNFC). Article 21 of the Ordinance for Enforcement of the Food Sanitation Act (The FOSHU system 1947) (latest amendment in 2018) defined FOSHU as 'foods for which it is declared that consumption can be expected to contribute to the maintenance and promotion of health of the people who consume such foods for a specific health maintenance purpose', and FNFC as 'foods for which it is declared that consumption can be expected to provide a specified nutritional component, in compliance with the standards designated by the Minister, for people who consume such foods for the purpose of acquiring said specified nutritional component'. FOSHU are approved by the Minister of Consumer Affairs Agency of the Government of Japan under certain requirements: proven effectiveness and safety on the human organisms, proper nutritional profile (e.g. avoidance of excessive salt), existence of quality control methods (specifications of products and ingredients, processes and methods of analysis) and guarantee of compatibility with product specifications by the time of consumption. FOSHU which comply with these standards are categorized as 'Standardized FOCHO'. FNFC which meet designated specifications and standards are allowed to be marketed without filling an application or registration (MHLW 2018b).

Depending on process applied, functional foods can be generally classified in four groups: fortified products, enriched products, altered products and enhanced commodities. The most common examples are margarine enriched with phytosterols or/and phytostanols, yoghurt with specific bacterias added, juices fortified with vitamins and minerals as well as products rich in fiber (Cámara et al. 2014; Franco,

Table 4. Groups of functional foods: characteristics and examples.

Group of functional foods	Characteristic	Example
Fortified products	Increased content of existing nutrients (in the conventional product)	E.g. Fruit juices with additional vitamin C
Enriched products	Incorporation of new nutrients (not normally found in the conventional product)	E.g. Fruit juices with calcium
Altered products	Replacement of existing nutrients (in the conventional product) by others with beneficial functions	E.g. Milk with oleic acid (replacement of satured fat)
Enhanced commodities	Alteration of nutrient composition by changes in the raw commodities	E.g. Fruis with enhanced content of vitamins

Table 5. Statutory definitions for food supplements in Europe and US.

Area/country	Item regulated	Definition	Regulation
Europe	'Food supplement'	'Foodstuff the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities'.	Directive 2002/46/EC (latest amendment in 2017)
US	'Dietary supplement'	'A product (other than tobacco) intended to supplement the diet by its ingestion in the form of powder, softgel, gelcap. It is not represented for use as a conventional or as a sole item of a meal or the diet. A food supplement can not have had approved as a drug, or have been under investigations as a drug with clinical studies having been instituted, or can not be intentionally used a a drug'.	Dietary Supplement Health and Education Act (DSHEA 1994)

Iseppi, and Taverna 2018; Iwu 2017; Longoria-García et al. 2018; Spence 2006). Table 4 summarizes these functional foods groups.

3.2. Food supplements concept and regulatory framework

Food supplements are consumed in order to complement the normal diet and ensure the proper intake of specific components (vitamins, minerals …) for a specific period of time. They may also be capable of reducing the risk of disease. As medicines, food supplements take the pharmaceutical forms (pills, tablets, capsules, sirups …), which results to be the most remarkable difference with functional foods (da Costa 2017). Unlike functional foods, food supplements have a statutory definition in Europe and US (Table 5).

Related to the regulatory framework in Europe, Directive 2002/46/EC (amended by the Commission Directive 2006/37/EC, the Commission Regulation (EC) 1170/2009, the Commission Regulation (EU) No 1161/2011, the Commission Regulation (EU) No 119/2014, the Commission Regulation (EU) 2015/414 and the Commission Regulation (EU) 2017/1203) provides two lists with the vitamins and minerals (Annex I) and vitamin and mineral substances (Annex II) permitted in the manufacture of food supplements. The incorporation of other nutrients and substances with a nutritional or physiological effect in food supplements are regulated by national rules. In Spain, the Royal Decree 130/2018 allows manufacturers to include other ingredients different from vitamins and minerals (omega-3 fatty acids, L-carnitine, lycopene, fructooligosaccharides …) in the composition of food supplements within the maximum limits.

In US, food supplements can contain (a) vitamins; (b) minerals; (c) herbs and other botanicals; (d) amino acids; (e) dietary substances for use by humans to supplement the diet by increasing the total dietary intake; or (f) concentrates, metabolites, constituents, extracts or combinations of ingredient mentioned in (a), (b), (c), (d) or (e) categories (Dietary Supplement Health and Education Act (DSHEA) 1994). All food supplements' ingredients marketed before the implementation of the DSHEA are considered safe and they can be used. However, those which were launched on the market after this date are considered novel ingredients and they have to be assessed by the Food and Drug Administration (FDA). Likewise, any manufacturer who is going to market a food supplement with a new dietary ingredient must notify it to FDA 75 days before the marketing.

In Japan, there are only two defined categories: 'food' and 'medicine', and food supplements fall under the category of 'food'. There is no legal definition for food supplement itself. Food supplements are included in the term 'health food', which is used by Japanese population instead of the term 'food supplement'. Food supplements must meet food regulation. All components which can be added to these products are regulated by the Food Sanitation Act (1947) (latest amendment in 2018), whilst all substances designated as medicine are under the Pharmaceutical Affairs Act (1960) (latest amendment in 2013) and they can not be considered as 'health food'.

3.3. Nutraceuticals concept and regulatory framework

Nutraceuticals, as a concept, are considered to be in the border between nutrition and pharma. In fact, the term

Table 6. Differences between the concepts 'food', 'functional foods', 'food supplements', 'nutraceuticals' and 'medicines' in European Union countries.

Concepts	Presentation(s)	Regularity of consumption	Function(s)
'Food'/'Foodstuffs'	Food	Daily	Maintenance of the proper nutrition balance
'Functional foods'	Food	As part of the normal and daily diet	Enhancement of human well-being and health Reduction of the risk of disease
'Nutraceuticals'	Pharmaceutical form (pills, tablets, capsules, sirups)	During a specific period of time	Promotion of human well-being Prevention of diseases Treatment of diseases
'Food supplements'	Pharmaceutical form (pills, tablets, capsules, sirups)	During a specific period of time	Complementing normal and daily diet by ensuring the intake of concrete component(s) (vitamins, minerals, etc.) Possible reduction of the risk of disease
'Medicines'	Pharmaceutical form (pills, tablets, capsules, sirups, injectables, etc.)	During a specific period of time (according to medical prescriptions)	Treatment and cure of a specific disease

'nutraceutical' is a portmanteau of the words 'nutrient' and 'pharmaceutical' which was coined in 1989 by Stephen L. DeFelice (founder and chairman of the Foundation of Innovation Medicine) who defined it as 'a food or parts of food that provide medical or health benefits, including the prevention and/or treatment of disease'. In order to understand the complexity of this concept, people used to associate it with the alleged Hippocratic principle 'let food be thy medicine and medicine be thy food', which was responsible of the widespread misunderstanding that food was synonymous of medicine. Nutraceuticals are totally different to medicines, whose purposes are mere pharmacological and are administrated with controlled doses according to medical prescriptions for the treatment of a concrete disease. In 2016, the European Nutraceutical Association (ENA) gave a new definition for nutraceuticals: 'nutritional products that provide health and medical benefits, including the prevention and treatment of disease'. Recently, a redefinition of this concept has been proposed, and nutraceuticals has been defined as 'the phytocomplex if they derive from a food of vegetal origin, and as the pool of the secondary metabolites if they derive from a food of animal origin, concentrated and administered in the more suitable pharmaceutical form, which are capable of providing beneficial health effects, including the prevention and/or the treatment of a disease' (Bragazzi et al. 2016; da Costa 2017; Daliu, Santini, and Novellino, 2019; Reis et al. 2017, Santini and Novellino 2018; Santini et al. 2018).

No specific regulation in Europe, US and Japan provides a statutory definition for nutraceuticals. Thus, the term 'nutraceutical' is incorrectly used to refer to a great number of products, ranging from isolated ingredients, nutrients and food components, to food, processed food, functional foods, herbal products and above all, food supplements. Nutraceuticals are commercialized as 'food-pharma products' with a non-clear-cut publicity about its capacity to treat or prevent disorders, which creates an atmosphere of ambiguity confusing consumers. A clear and comprehensive definition as well as an international specific regulation are highly needed so that nutraceuticals could be used 'beyond the diet but before the drugs' in the management of specific diseases (Santini, Tenore, and Novellino 2017; Santini et al. 2018).

As is evident from this review, it is beyond question that the categorization of a product as a conventional food, functional food, food supplement, nutraceutical or medicine is sometimes not as clear as it could seem and strongly confuses consumers. Although the way of presentation of a product and its metabolic, immunological or pharmacological action make this categorization easier, in Europe one product with identical composition and doses can be sold both as food supplement and medicine within a country (e.g. Ginkgo biloba and Valerian in the Netherlands). Making a decision on if one product has to meet or not the medicinals legal requirements is competence of the Member States (Eussen et al. 2011). In Japan, FOSHU products can surprisingly appear in the market in pharmaceutical forms (capsules, tablets) since 2001. According to Chiba, Sato, Suzuki, and Umegaki (2015), the 20–90% of the Japanese cancer patients take functional products in order to complement the medical treatment or even as an alternative to medicines. Because FOSHU products and food supplements are presented in a pharmaceutical form, Japaneses believe that they have the same effectiveness as medicines (Siró et al. 2008).

For a better understanding, and as an example, Table 6 summarizes the differences between all the above-explained concepts in European Union countries.

4. Future opportunities for functional products

Functional foods, food supplements and nutraceuticals could play an important role in human health by reducing risk factors of CD and contributing to improve health status. Individuals with moderate risk factors of CD could consume functional products as a part of a healthy diet or as an end to improve an unhealthy one. Beyond this and under doctors supervision, functional products could be used as a complement in individuals with an established medicine therapy, most importantly in cases where prescribed medicines are not enough to aim goals. Examples of nutrition-pharma combinations are the following: calcium-fortified products/calcium supplements + hormone replacement therapy (for the management of osteoporosis); products enriched with plant stanols/red yeast rice + statins therapy, products enriched with long-chain ω-3 polyunsaturated fatty acids/ω-3 supplements + antihypertensive agents as well as products containing lycopene from tomato (for cardiovascular disease); berberine extracted from Coptis root (dried root and rhizome of *Coptis trifolia*) and *Phellodendron amurense* (a tree belonging to the Rutaceae family) + oral hypotensor (for treating hypertension). Nutrition-pharma combinations

could reduce the required doses of prescribed medicines without interfering in the pharmaceutical effect as well as the side effects, as they normally appear with higher doses. However, there are remarkable issues that must be dealt with: efficacy, food-medicine interactions, indirect stimulation of self-medication and long-term effects of nutrition-pharma combinations (Cámara and Fernández-Ruiz 2009; Eussen et al. 2011; Santini, Tenore, and Novellino 2017; Santini and Novellino 2018).

5. Conclusions

Functional foods, food supplements and nutraceuticals are at the interface between nutrition and pharma. As it can be deduced from the European, American and Japanese regulation, there is a lack of specific legislation regarding these products. The ambiguity around them confuses consumers, who have no previous experience of these products. Harmonized regulation concerning these functional products is needed.

Functional products could be able to reduce the risk of CD as well as promote and maintain human health status, well-being and life quality. They could represent another viable option in the management of CD in combination with prescribed medication. Proper communication about nutrition-pharma combinations is highly necessary to prevent food-medicine interactions and the replacement of medicinal therapies by the consumption of these functional products. Further research in the near and long term is essential to establish which of these combinations provide the most favorable benefit-risk and cost-effectiveness ratio for each chronic disease.

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Disclosure statement

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