Chapter

Valuable Food Molecules with Potential Benefits for Human Health

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Abstract

The rapid development in the food supply chain has led to increased interest for quality in the food sector. In the last two decades, the human health and food safety have become essential. Health problems are highly related to diet and nutritional habits. The connection between nutrition and the development of various health problems is even more noticeable when close attention is given to every age group. Regarding the chemical composition of foods, a large number of bioactive compounds present in plants, fruits, vegetables, dairy products, meat, and fish are currently known. Bioactive compounds from food play an important role in prevention of illnesses. Covering essential aspects of health benefits of foods, the present chapter underlies without being exhaustive, the potential of valuable compounds such as soy isoflavones, phytochemicals, polysaccharides, probiotics, prebiotics, lipids, and marine proteins to be used as an effective prevention strategy for developing various human cancers, cardiovascular diseases, diabetes, and metabolic disorders.

Keywords: bioactive compounds, functional food, probiotics and prebiotics, phytochemicals, soy isoflavones, polysaccharides, seafood products

1. Introduction

The modifications occurred during globalization and the fast development of food production had led to new expectations from consumers regarding food and healthy diets [1]. Nowadays, as life expectancy has substantially extended, there is an acute demand for special foods that fulfill all the nutritional needs and help us maintain a balanced diet—a key role in sustaining human health [2]. Therefore, the food sector companies need to keep up with the consumers' interests and needs while designing novel products. Moreover, health authorities, food engineers, scientists, health insurers, and customers seem to highlight an increased interest in illnesses prevention.

Today, food market is richer than ever, but the demand and the challenges seem to increase even more. Due to the globalization of the food market, an increasing number of special diets such as vegetarian or vegan, various food allergies, and intolerances have gained attention. Thus, scientists, food engineers, and health authorities seem to look for foods that bring added value and may even prevent diseases. These desiderates have brought the concept of "functional food" [3]. Thus, the consumers can correlate this category of foods with recognized health benefits [4].

Functional foods are known as healthy foods, medicinal foods, regulatory foods, fortified foods, nutraceuticals, and pharmacological foods [5]. A main statement or a clear definition of functional foods does not exist since all foods (conventional foods) provide energy and nutritional functions. Beyond these, functional foods contain elements that have the potential to sustain human health or reduce the risk for certain diseases [6, 7].

According to the potential medical benefits and properties of their ingredients, functional foods can be classified in several groups: dietary fiber, sugar alcohols, amino acids, oligosaccharides, glycosides, peptides and proteins, vitamins, cholines, lactic acid bacteria, minerals, polyunsaturated fatty acids, and others (e.g., phytochemicals and antioxidants) [8].

Studies have shown that an individual health status is influenced by diet even from very early stages. Special attention should be given so consumers have a well-balanced diet in order to avoid undernutrition and functional decline. In this light, specific recommendations are comprised in a 2014 report of Joint Research Centre, the European Commission's in-house science service. The report summarizes the evidence on key micronutrient supplementations for preventing age-related diseases and draws attention on nutrition as a crucial element in healthy aging [9].

1.1 Consumer behavior: general overview

The quality of food is perceived by the consumers depending on intrinsic factors (freshness, organoleptic properties, health and hygiene safety) and external factors (origin, traceability, geographical indications and certification, labeling, health claims, production processes, etc.) [10].

In some countries, legislation policies have scrutinized the health claims labeling, as it represents a strategy that positively influences the purchase decision [11]. The European Union introduced important quality (origin) labels, in order to help consumers, namely Protected Designation of Origin (PDO) or Protected Geographical Identification (PGI) and Traditional Specialty Guaranteed (TSG). Moreover, the products' quality and safety are regulated by the ISO 9001 (International Organization for Standardization) standards, which define the requirements of a quality system in order to ensure control throughout the production process and to prevent or detect any non-conformities. As an operational tool, the Hazard Analysis Critical Control Points (HACCP) system has been implemented, whose purpose is to achieve self-checking objectives [12].

Broadly, functional food refers to any food or food ingredient that may provide a health benefit beyond the nutritional ones. The market of functional foods covers foods that contain bioactive molecules such as polyunsaturated fatty acids [13], plants' primary or secondary metabolites (polyphenols, anticipants, carotenoids, phytosterols [14–20], probiotics and/or prebiotics [21, 22] and others (**Figure 1**)).

The consumers' perception regarding functional food is highly influenced by various factors such as food attributes (e.g., taste and flavor), the consumption behavior, the consumer's knowledge, the potential benefits, purposes, diet preferences or restrictions, the consumer's health problems, advertising, the label

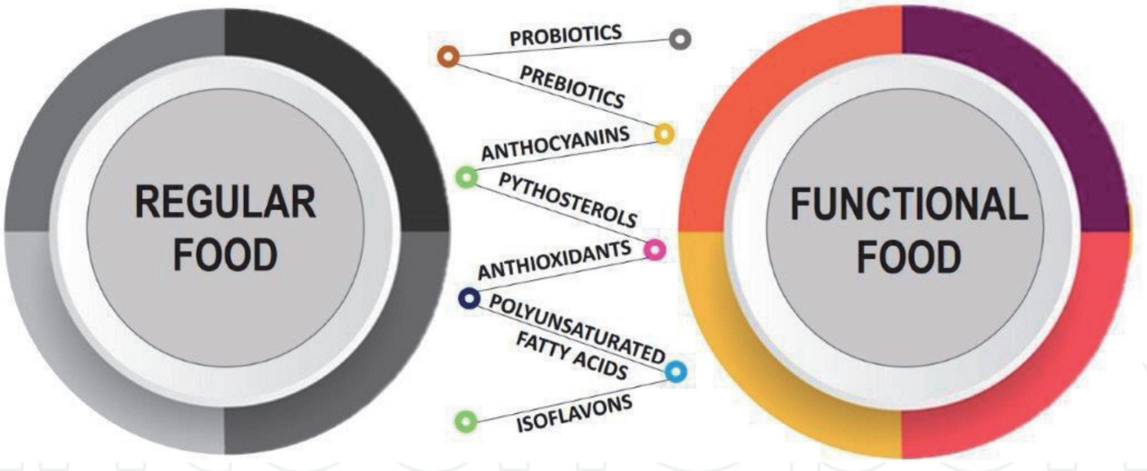


Figure 1.
The bioactive molecules which add a supplemental value to regular food and provide functional benefits to human health.

information, the packaging or the appearance, the brand and, not least, the product's price [23–26]. On the other hand, the food quality and safety play an important role in building the image of a product [27]. At the same time, attributes such as food palatability and healthiness are key elements in the consumer choices [28]. A recent research of Haasova and Florac has shown that manufactures need to focus on increasing the consumers' orientation toward health goals and on reducing the consumers' beliefs that healthy food equals tasteless food [29]. In another study, conducted in 2019 in the U.S., focused on consumers' perceptions on natural and healthy foods, it was shown that consumers buy food products according to the several factors such as taste, price, healthiness, safety, and naturalness. Also, young consumers valued the food naturalness more compared to older consumers [30].

In most cases, functional foods have attractive forms and are certainly not commercialized as tablets or capsules [31]. Food producers constantly analyze the consumers' behavior in relation to engineered foods, projected to maintain their health and prevent illnesses. The consumer's keen interest in consuming natural products has challenged food industry to create innovative food products, developed for functional applications, but to keep the product as natural as possible. Due to their special indications, these products are consumed for a limited period of time. Thus, the main objective is to obtain functional foods using natural compounds and with minimal processing. A 2013 report [32] has estimated that sales of these special products will double by 2020. Similar to any food products, the market life and attractiveness of functional foods are following a Gaussian curve. Scientists report [33, 34] that a large number of functional foods get recalled soon after they enter the market, in most cases due to the reliance on technology, coupled with the absence of a thorough market research [35]. In order to explain what triggers the market failure of functional foods, it is mandatory to understand the consumer's desire for products considered healthy.

In our opinion, the consumer's attitude toward the potential benefits of these products for disease prevention and health improvement is the rhyme factor which dictates the consumption behavior. Thus, the consumer's perception on the beneficial health effect of functional foods can essentially affect the purchasing process. These perceptions are, in turn, influenced by various factors such as involvement degree, lifestyle [36], food product characteristics (i.e., sensorial, nutritional, price, etc.) [37], package information, and package design [38]. In any case, the consumers' trust in the functional claims is decisive in the purchase decision [39]. Information about food products and healthy diets is known and available to customers, and they evaluate all this information. Therefore, understanding the customer's reasoning in evaluating the healthfulness of a functional product represents an important step in the process of designing functional foods. The big challenge is making the health benefits as credible as possible [40].

However, health claims are not the only factors that convince a customer to purchase functional foods. Other important factors are the product design, the cultural influences, the food matrix used as carrier for the active molecules, and the price. Among all the elements that influence the customer's decision to buy functional foods, the confidence of obtaining well-being effects weighs the most. The customer's certainty must represent the cornerstone for food products developers, stakeholders, and marketers.

1.2 Diet and health problems

Unhealthy diet is associated with regular consumption of foods and beverages rich in saturated fat, transfats, and polyunsaturated fats [41].

Worldwide, obesity is one of the major public health issues with multiple consequences: chronic diseases, including type 2 diabetes, coronary heart disease, and several cancers [42]. Besides the main factors that influence obesity, such as genetics, lack of physical activity, social and psychological factors, diet remains one of the major determinants that influences body weight. In the last 50 years, the prevalence of obesity has dramatically increased, reaching pandemic proportions, with more than 1 billion adults being overweight, of which at least 300 million are clinically obese. As a result, the consumption of functional foods has gradually expanded and gains more and more interest [43, 44].

In a recent study on health impact of dietary risks in 195 countries, authors have concluded that dietary habits are correlated with coronary heart sickness and other chronic non-communicable diseases, and urgent strategies to ameliorate the diet quality are required [45].

The diseases that prevail most in developed countries, the so-called "diseases of civilization," are affecting the life quality of 100 times more people than mortal accidents [46]. In preventing overweight, obesity, or any chronic diseases (cardiovascular illnesses, various cancers, depression, and type 2 diabetes), the customer's food choice can have a great impact on all related industries (i.e., food, pharmacy, etc.) [2, 47]. A first change in the consumers' behavior can start by limiting the excessive food quantities and adjustment to a controlled, moderate food amount.

The maternal nutrition both before and during pregnancy, as well as the child's nutrition after birth, will critically impact her or his later development and future health status [48]. The most common child health problems caused by an unbalanced diet are iron deficiency anemia, vitamin D deficiency, obesity, dental caries, and faltering growth [49]. In toddlers, the prevalence of iron deficiency anemia and severe obesity is each approximately 2%. Later in life, iron deficiency has been associated with potential neurodevelopmental impairments, while obesity in childhood may continue into adulthood, accompanied with adverse cardiometabolic outcomes [50].

Malnutrition, in all its forms, includes undernutrition (including wasting, stunting and micronutrient deficiency/insufficiency) and overweight and obesity. Acknowledging the need of accelerated actions against malnutrition and the need to promote a healthier maternal, infant and child nutrition, WHO has elaborated, in 2012, a group of six general nutrition targets that by 2025 aim to: (1) attain a 40% reduction in the number of children under 5 who are stunted; (2) achieve a 50% reduction of anemia in women of reproductive age; (3) achieve a 30% reduction in low birth weight; (4) ensure that there is no increase in childhood overweight; (5) increase in the rate of exclusive breastfeeding in the first 6 months up to at least

50%; and (6) reduce and maintain childhood wasting to less than 5% [51]. Some of these targets have been extended to 2030.

In adults, half of the total chronic disease deaths are attributable to cardiovascular diseases. Accelerating trends can be seen also for obesity and diabetes as more patients are diagnosed at an early age. The list of most common chronic diseases in adults and elderly is completed by hypertension, hypercholesterolemia, arthritis, depression, Alzheimer's disease, osteoporosis, and chronic obstructive pulmonary disease [52]. However, these chronic diseases are largely preventable and diet plays a key role in preventing or promoting chronic illnesses.

According to a standardized case-control study, eight of nine modifiable risk factors associated with acute myocardial infarction are influenced by diet. Most of these factors act by promoting atherogenesis, by modulating vasodilation, prothrombotic and pro-inflammatory processes that trigger the endothelial dysfunction, an early predictor of atherosclerosis [53, 54]. Apparently, vascular inflammation is associated with unhealthy dietary patterns, overweight and obesity, smoking habit, alcohol consumption and sedentarism [54].

In a population-based prospective cohort study, higher dietary intake of vitamin E, but not vitamin C, beta carotene, or flavonoids was modestly associated with lower long-term risk of dementia. Vitamin E antioxidant mechanisms are not fully understood, but it could improve cognitive performance by diminishing the effects of β-amyloid, as it was shown in experimental studies [55].

1.3 Health benefits of functional food

With the emergence of the term FOSHU (Foods for Specific Health Use), in the early 80s in Japan, the impact of food on health has gained much attention in the recent decades. However, the scientific community has not fully agreed on what is covered by the term "functional foods." The FUFOSE (Functional Food Science in Europe), for its part, has defined them as follows: "A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, thus either improving, the general physical condition or/and decreasing the risk of the generation of disease" [56]. However, the study of food, focused on therapeutics, is not something new and if we go back to the past, the classification of the use of food and plants with therapeutic properties goes back to the Mid Paleolithic age [57]. Also, during the history of humankind, the health benefits of food have been capitalized in traditional medicines such as Unani, Traditional Chinese Medicine, and Ayurveda. In this same sense, Persian Medicine (PM) in the Islamic era (980 AD) already considered the classification of certain foods as potential drugs with a significant role in health, not only as mere energy providers, but also as being able to affect the human body by changing even the temperament and personality of individuals. Faced with a disease, PM first considered a special diet for the patient using specific foods, and if the patient's health did not improve, drug therapy was the second option [58]. Already at that time, there was a classification for food and drugs very similar to the classification currently available for functional foods, nutraceuticals, and pharmaconutrients.

Foods are classified as functional after their effects have been demonstrated in well-designed and properly executed intervention studies in humans [8]. Functional food can play an essential role in disease treatment and prevention.

The beneficial health properties of various foods have been scientifically recognized thanks to the analytical development in identifying and characterizing their chemical composition and due to the clinical studies that have assessed their role in various pathologies. Studies based on *in vitro* and cell-culture systems, preclinical interventions using animals, and clinical trials have investigated the potential of functional foods to combat various human cancers, cardiovascular disease, diabetes, metabolic disorders, inflammation, high blood pressure, microbial, viral and parasitic infections, mental diseases, spasmodic disorders, ulcers, etc. [59].

The relationship between food and human health is extremely tight, and World Health Organization has stated that "A healthy diet helps to protect against malnutrition in all its forms, as well as noncommunicable diseases (NCDs), including such as diabetes, heart disease, stroke, and cancer. Unhealthy diet and lack of physical activity are leading global risks to health." Regarding the chemical composition of foods, a large number of bioactive compounds present in plants, fruits, and vegetables are currently known, such as polyphenols or carotenoids and nowadays it is known that the concentration of these bioactive compounds is variable depending on the parts of the plant, season, climate, and the particular growth phase [60].

The Global Burden of Disease study has reported that unhealthy diets represent a risk factor for disease, morbidity, and disability both in Canada and worldwide [61]. Certain diets, such as vegetarian diet (rich in antioxidants), the Mediterranean diet (high in olive oil with monounsaturated fatty acids), and the Okinawan diet (high in fruits, vegetables, and omega-3 fatty acids in fish) can impede the development of age-related diseases. More specifically, Everitt et al. reported in their study that epidemiological research consistently demonstrates that the intake of certain foods is correlated with cardiovascular disease risk [62].

Daily diet can be improved by including essential fatty acids, minerals, vitamins, and proteins from fish and meats and increasing the intake of calories and proteins from nutritionally appropriate sources (nuts and seeds, pulses, soy products, dairy products) [63].

2. How probiotics and prebiotics sustain human health: a correlation with functional food intake

A worldwide known fact is that the gut microbiota composition has a strong influence on the host health and metabolism [64, 65]. More than 500 species of bacteria coexist in the human gastrointestinal tract (GI), and among them, about 95% of the total number of cells in the colon [66]. Many of the indigenous GI habitants are probiotic bacteria cells that pertain to the genera *Lactobacillus*, *Bifidobacterium*, or *Enterococcus*. Notably utilized and commercialized probiotics are belonging to the first two genera. An extremely studied topic for the past two decades was the gut microflora, being in the spotlight of food and medicine scientists, food engineers, authorities, and customers as well. In the functional food market, the pathway has two lanes, namely how functional foods influence gut microbiota and how common foods can incorporate these valuable cells and become functional foods with important characteristics (**Figure 2**).

Even though the presence of probiotics in different functional food matrices has been widely studied, the amount of documented therapeutic applications and clinical trials is very modest. The influence of different functional foods on gut microbiota is now in the spotlight of many researchers. Most of the studies regarding the effect of functional foods on gut microbiota fail to prove the causative role. In most of the cases, the disease is treated with certain functional food and, afterward, the gut microbiota composition is tested and correlated, correct or not, with the cause of the disease alleviation. But, stating this may be as true as the affirmation "the consequences of diseases alleviation were the registered changes in the gut microbiota." Today, the concept of functional food (i.e., foods containing dietary fibers, polyunsaturated fatty acids, polyphenols, etc.) utilization in order to obtain

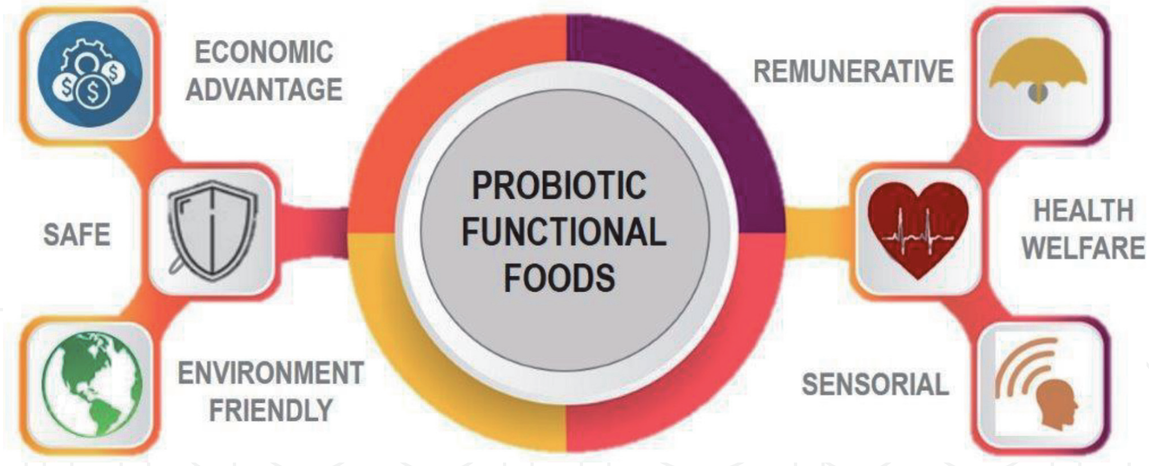


Figure 2.
Probiotic functional foods characteristics.

a certain response with respect to a disease is embraced by many customers, but the modulation of gut microbiota by changing eating patterns and/or diet composition is still a novel practice [67]. In the attempt to evaluate the changes in the gut microbiota composition in different diseases and after ingestion of functional foods, the literature reports two approaches for the *in vivo* tests on mice. The first one is the mice treatment with antibiotics to see whether disorder of the gut microflora could cut off the curative effects of functional foods on a certain illness. The limitations of this method arise from the fact that antibiotics could not entirely eradicate the effect of gut microbes on the evolution of the diseases, as they could not completely eliminate microbes from the gut. A different approach is the utilization of germ-free mice [68, 69]. Thus, it tests if a specific functional food product may be unsuccessful in the treatment of the targeted disease in germ-free mice. This fact reveals that the target of the ingested functional food may not be the gut microbiota. However, in these times when microbiota-targeted nutrition has become a frequently proposed technique, we predicted more studies that can establish a causal connection between functional foods ingredients, host health, and gut microbiota.

Another approach, in order to modulate the gut microflora, is to ingest functional foods, which have as active ingredient viable probiotic cells [70], prebiotics (the probiotic food) [71], and/or synbiotics (pro and prebiotics) [72]. Nowadays, probiotic cells are included in more and more products, extending the size of functional food market. Not long ago, probiotic cells were associated mostly with dairy and fermented foods, but things have been considerably changed. There are several studies that have demonstrated good viability cells in products such as chocolate [73, 74], bread [75], juices [76], jelly [77], meat [78, 79] and even edible films or coatings [80]. Results of these studies demonstrate, besides the good viability of the probiotics during processing, shelf life and even gastrointestinal passage, no negative changes regarding the food structure or sensorial properties [81]. However, reports regarding the concrete influence of functional foods probiotics on the consumer health are modest. Health benefits of probiotics intake are multiple and based on scientific evidence. Among the multiple well-being advantages related to probiotic consumption, we will discuss the most studied and known ones.

One of the health benefits of probiotic cell intake is its capacity to regulate the host's intestinal microflora and the general well-being. An individual's intestinal microflora composition is rather well balanced after early infancy, in healthy subjects, even though variations exist among subjects [82]. One of the most important actions of probiotics is to positively influence intestinal microbiota. Evidence shows that Lactobacilli intake ensures a reduction of pathogenic gram-negative anaerobes, such as *Clostridia* or *Enterobacteriaceae* [83]. Postsurgical period predisposes the individual to infections with gram-negative anaerobe bacteria or with sulfite-reducing *Clostridia*, leading to inflammatory response due to the secreted endotoxins. The mentioned pathogens are inhibited by *Lactobacillus* due to their capacity to produce antimicrobial metabolites (i.e., bacteriocins, hydrogen peroxide) and other valuable substances such as short-chain fatty acids. Beside *Lactobacillus*, *Bifidobacterium* intake may reduce the butyrate-producing anaerobes [84]. Another study [85] revealed the efficacy of *Lactobacillus* in *Rotavirus* infections. Probiotics proved to have a positive effect in reducing the duration of acute rotavirus diarrhea in children in comparison with control. Thus, we can conclude that the consumption of viable probiotic cells, trough functional foods or as supplements, can considerably improve the composition of intestinal microbiota, leading to health benefits that can confer a better life to the consumer.

Treatment or amelioration of diarrhea is a promising and extensively studied technique. Diarrhea causes may be multiple and need to be approached with different types of probiotic species, in single or multiple formulations. A review, published by Marteau et al., pointed out that these valuable cells have good results in treating diarrhea induced by antibiotic treatment, *Rotavirus* or/and *Gastroenteritis*, but they are less efficient for traveler's diarrhea [86]. Another appreciated health benefit induced by probiotic ingestion is the amelioration of irritable bowel syndrome (IBS) symptoms. Even if the cause of this disorder is still unknown, the symptoms are very clear, namely abdominal pain, constipation or diarrhea, and infrequent nausea, fluid retention, tiredness, and bloating. For most of the patients suffering from IBS, an imbalance in the intestinal microbiota can be found. In most of the cases, a decreased number of bifidobacteria can be observed, with an increase in the facultative anaerobes pathogens [87]. Many of the mentioned intestinal disorders may lead, in time, to carcinomas.

3. Phytochemicals: general overview, potential applications, and health benefits

Fruits are a source of active compounds, such as vitamins (C and A), minerals (electrolytes), and more recently phytochemicals, especially with antioxidant properties, which include phenolic compounds, flavonoids, lignins, tocopherol (vitamin E), carotenoids, betaine, colin, saponins, and phthalates [88]. Because of their importance, we are going to focus on polyphenols.

Polyphenols are natural compounds characterized by the presence of phenol, catechol, and resorcinol (benzene rings with several hydroxyl groups in *o*, *m,* and *p* positions). In phenolic acids, the presence of a carbonyl group, such as aromatic acid, ester, or lactone, enhanced its antioxidant activity as well as when its carbonyl group is separated from the aromatic ring [89, 90]. Phenolic acids are derivatives of hydroxycinnamic acid such as *p*-hydroxybenzoic, 3,4-dihydroxybenzoic, vanillic, syringic, *p*-coumaric, caffeic, ferulic, sinapic, chlorogenic acid, and rosmarinic acid. The derivatives of cinnamic acid are more active antioxidants than the derivatives of benzoic acid derivatives [90, 91]. There are three structure groups responsible for the determination of free-radical scavenging and antioxidant activities of flavonoids: a catechol moiety of the B-ring, the 2,3-double bond in conjugation with a 4-oxo function of a carbonyl group in the C-ring, and presence of hydroxyl groups at the 3 and 5 positions [90]. They are classified as flavonols, flavons, flavanons, flavanols, flavandiols, isoflavonoids, cathechins, chalcones, dihydrochalcones, anthocyanidins, leucoanthocyanidins, proanthocyanidins, or condensate tannins [92].

Some drinks such as coffee, tea, beer, and wine; fruits such as apple, orange, guava, papaya, and grape; vegetables such as, zucchini, beet, avocado, watercress, chili, and tomato; dry fruits as nuts; and cacao are important sources of polyphenols and other antioxidants [93–95]. Polyphenols possess several pharmacological activities and are characterized by their antioxidant activity, which depends on the substitution in either *ortho-* or *para*-position, while the substitution in *meta*-position has a rather limited effect. It is known that the polyphenols consumption could be related with the decrement of chronic and degenerative diseases such as diabetes, cancer, cardiovascular, neurodegenerative, and antitumoral diseases, promoter of the immune system, anti-inflammatory, skin protective effect from UV radiation, antibacterial and antifungal activities [96–100].

Free radicals are generated as a result of normal cell metabolism. These reactive oxygen species (ROS) cause lipids, proteins, and nucleic acids damage in cells and modulate several signaling pathways [101]. As a consequence, different pathologies such as chronic and degenerative diseases can develop. All aerobic organisms have antioxidant defenses, including antioxidant enzymes and antioxidant constituents to remove or repair the damaged molecules. Also, the natural antioxidants from certain foods can be beneficially used to remove oxygen and reactive oxygen species [90, 102].

Polyphenols are involved in cell cycle regulation and may inhibit the progression of cancer in many organs or even block latent tumors due to their anti-angiogenic and anti-inflammatory properties. As for the origins and causes of various cancer types, they are not yet well established. However, it is known that high levels of free radicals such as reactive oxygen species (ROS) produce lipid peroxidation that induces various cell injuries. These injuries can later lead to cancer development [103]. In this context, polyphenols studies have shown that they can regulate cell proliferation and specific protein modulators associated with cell cycle [104]. Likewise, polyphenols can control cancer cell progression in many organs [105]. They also have the capacity to block latent tumors by direct inhibition of tumor cells or by anti-angiogenic and anti-inflammatory properties and protect deoxyribonucleic acid (DNA) from lesions caused by reactive oxygen species. Using these mechanisms, cancer progression can be hindered and pro-apoptotic mechanisms are then triggered [105].

Flavonoids possess antioxidant activity due to their structures, which is capable of donating an electron or chelate metal ions. Some foods such as blueberry, red wine, green tea, and cocoa have been studied for their antioxidant properties in order to prevent diseases [106]. The group of antioxidants includes mainly vitamins (ascorbic acid, tocopherol) and flavonoids such as quercetin, pycnogenol, and flavan-3-ol monomers and oligomers [100, 107, 108]. Flavonoids and other phenolic compounds showed cardiovascular protection by improving the endothelial function, reducing the oxidative stress, lowering arterial pressure, improving the elasticity of the internal blood vessels' walls, or by inhibiting platelet agglutination. These properties could prevent blood clot formation in the arteries, and can positively influence blood lipid balance and insulin sensitivity [109, 110].

Specific components of fruits may also show protective effect in human organism. Quantitatively, the most important carotenoids in the human diet are β-carotene, lycopene, lutein, β-cryptoxanthin, zeaxanthin, and astaxanthin [111, 112]. Lycopene is a carotenoid found in brightly colored fruits and vegetables, and research suggests that foods containing carotenoids may protect against lung, mouth, and throat cancer [113, 114]. In addition, a study suggests that lycopene may help protect men against prostate cancer, especially in aggressive forms [115].

Finally, the consumption of fruits rich in polyphenols and carotenoids could reduce the incidence of developing chronic degenerative diseases, stroke, and cancer [106, 116–118]. Nowadays, the use of extracts and secondary metabolites of plants and foods in different pathologies is extremely well documented [105]. **Table 1** presents some pharmacological activities of several secondary metabolites.

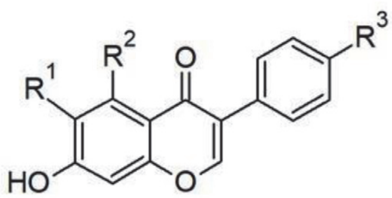
Cardioprotective activity	
Kaempferol, rutin, luteolin, quercetin, resveratrol	Activity against doxorubicin-induced cardiotoxicity [119]
Gallic, ellagic, syringic, ferulic, cinnamic acids, and quercetin	Attenuate oxidative stress in H9c2 cardiomyoblasts [120]
Aspalathin and phenylpyruvic acid-2-*O*-β-D-glucoside	Protect myocardial infarction caused by chronic hyperglycemia [121]
Puerarin	Protects myocardium from ischemia and reperfusion damage (Ca^{2+}-K^{+} channel and the protein kinase C activated) [122]
Naringenin-7-O-glucoside	Activity against doxorubicin-induced cardiotoxicity, protects against cardiomyocyte apoptosis [123]
Isorhamnetin	Effect against cardiotoxicity of doxorubicin [124]
Antibacterial activity	
Gliricidin 7-*O*-hexoside and quercetin-7-*O*-rutinoside	*Proteus mirabilis, P. vulgaris,* and *Pseudomonas aeruginosa* [125]
3,4,7-trihydroxyflavone	*Providencia stuartii* and *Escherichia coli* [126]
Pseudarflavone A and 6-prenylpinocembrin	*E. coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Enterococcus faecalis,* and *Staphylococcus aureus* [127]
2-(3,4 dihydroxy-phenyl) 3,5,7-trihydroxy-chromen-4-one	*Pseudomonas aeruginosa* [128]
Kaempferol	*P. acnes* [129]
Strictinin	*Propionibacterium acnes* and *Staphylococcus epidermidis* [130]
Anticancer activity	
Flavopiridol	Treatment of lymphomas and leukemia [131]
Quercetin	Induces apoptosis of each one of these cell lines: acute lymphoblastic leukemia MOLT-4 T-cells, human myeloma U266B1 cells, human lymphoid Raji cells Prostate adenocarcinoma LNCaP cells, human prostate PC3 cells Colon carcinoma CT-26 cells, Pheochromocytoma PC12 cells, Estrogen receptor-positive breast cancer MCF-7 cells, ovarian cancer CHO cells [132] Induces microRNAs involved in Notch signaling/cell-fate determination of the tested pancreatic cancer (primary pancreatic cancer cell line ASANPaCa, AsPC1, and PANC1) [133]
Gliricidin7-O-hexoside and Quercetin 7-O-rutinoside	Human hepatoma HepG2 and carcinoma HeLa cells [125]
Genistein	Inhibits the activation of Nuclear factor kappa B (NF-kB) involved in balance of cell survival and apoptosis on prostate cancer [134]
Curcumin	Acts as a pro-apoptotic agent in skin cancers [98] Inhibits melanoma cell proliferation related to epigenetic integrator UHRF1 [135] Inhibits the proliferation of human prostate cancer cell lines such as LNCaP and 22Rv1 cells [136]

Anti-inflammatory activity	
Apigenin, C-rhamnosyl flavones, and luteolin	Reduce nitric oxide levels in macrophages, inhibit the activity of phospholipase A2 [137]
Quercetin, apigenin, hesperidin, and luteolin	Anti-inflammatory effects [138]
Astilbin	Anti-inflammatory effects observed *in vitro* after lipopolysaccharide-induced inflammation suppresses nitric oxide production, tumor necrosis factor-α (TNF-α), mRNA expression of inducible nitric oxide synthase [139]
Acteoside	Inhibits inflammation in LPS-induced lung injury in mice, inhibits inflammation in lung epithelial cells A549, inhibits NF-kB activation in LPS-induced mice and lung epithelial cells A549 [140]
Skin protective effect from UV radiation	
Apigenin	Skin protective effect of damage caused by UV light [141]
Quercetin	Inhibits UVB-induced skin damage in hairless mice [142]
Silybin	Prevention of apoptosis in UVB-exposed human epidermal keratinocytes [143]
Genistein	Photoprotective activity in human skin against photocarcinogenesis by inhibiting UV-induced DNA damage [144]
Equol	Prevents damage from UV-induced erythema-associated edema, inhibits DNA photodamage [145]
Metabolic syndrome	
Genistein	Improves factors of risk for diabetes and cardiovascular disease in postmenopausal women with MetS [146]
Acteoside	Antihypertensive activity in lowering systolic blood pressure (SBP) and diastolic blood pressure (DBP) [147]

Table 1.
Pharmacological activities of secondary metabolites from food and plants.

4. Soy isoflavones: evidence-based health benefits and official recommendations

Isoflavones are polyphenolic plant metabolites produced almost exclusively by the members of the *Fabaceae* family. More specifically, isoflavones are part of the flavonoids group, which share the 2-phenylchromen-4-one backbone. Due to the structural similarity with 17-β-estradiol, the primary female sex hormone, isoflavones have been included in the wide family of phytoestrogens. The main sources of the natural isoflavones are soy beans, chickpeas, fava beans, pistachios, and peanuts. Of these, physiologically relevant amounts are found only in soybeans and soy-derived foods, and raw soybeans containing 1.2–4.2 mg/g dry weight isoflavones. Besides isoflavones, soy is also an excellent protein source and contains vitamins, minerals, and insoluble fibers. Genistein, daidzein, and glycitein (**Figure 3**) are the biologically active aglycones from soy-based foods and red clover. Other isoflavones present in various plants are biochanin A and formononetin, which can be converted through 4′-O-demethylation to genistein and daidzein, respectively. Generally, the soy aglycones are conjugated with a glucose moiety through the -OH group from position C7 (7-O-glucoside) and form the β-glycosides, genistin, daidzin, and glycitin [148, 149].



Isoflavone aglycone	R^1	R^2	R^3
Genistein	H	OH	OH
Daidzein	H	H	OH
Glycitein	OCH_3	H	OH
Biochanin A	H	OH	OCH_3
Formononetin	H	H	OCH_3

Figure 3.
The chemical structures of soy isoflavones.

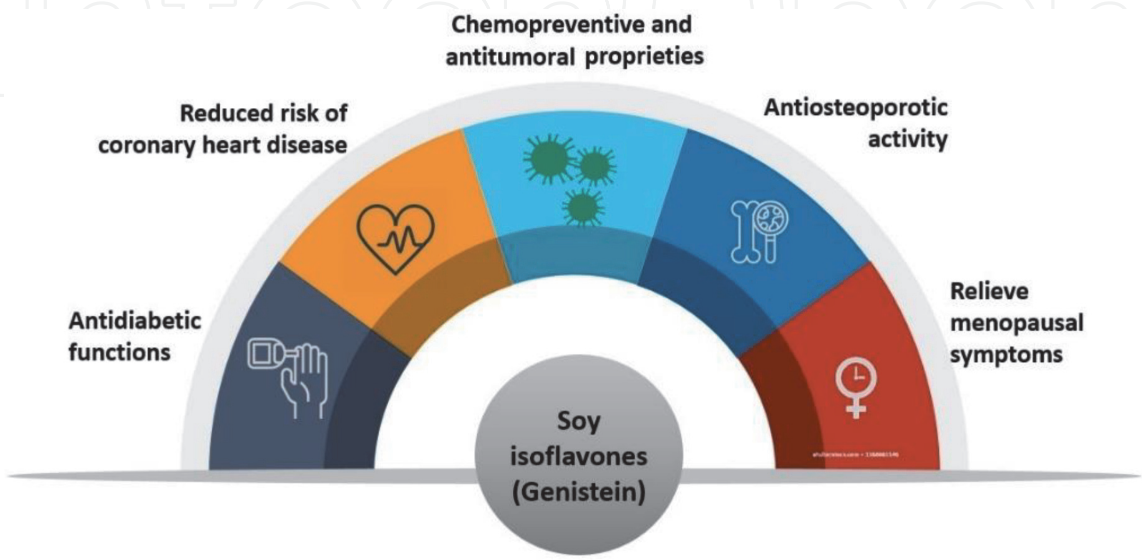


Figure 4.
The health benefits of soy isoflavones.

The aglycones are rapidly absorbed in the small intestine by spontaneous, passive diffusion. The free aglycone forms are only merely present, as soy beans and non-fermented soy foods mostly contain the glycosylated forms. These conjugates need to be prior converted to the bioactive aglycones. Their hydrolysis is completed by β-glucosidases from intestinal bacteria, or an enzyme in the intestinal mucosa. Daidzein and genistein aglycones can also derive from formononetin and biochanin A hydrolysis [150]. Soy isoflavones have drawn the attention of the scientific community due to their multiple medicinal and therapeutic proprieties. The health benefits provided by soy isoflavones are presented in **Figure 4** [151]. These potential benefits will be presented herein.

4.1 Soy isoflavones and cancer

Perhaps the most controversial aspect related to soy isoflavones is linked to their potential role in chemoprevention. Most studies have investigated the correlation between soy consumption and breast or prostate cancer, but several studies have also investigated the role of soy isoflavones in other malignancies, such as: colon cancer, liver adenocarcinoma, bladder cancer, or brain tumor [151].

The perception that soy isoflavones possess anticancer proprieties derives from epidemiological data, which showed that Asian women who regularly consume soy or soy-based foods have a significant lower breast cancer risk than Caucasian women who do not consume soy as part of their daily diet [152]. These epidemiological studies have indicated an inverse correlation between polyphenol-rich dietary intake and cancer development.

The differences between the daily isoflavone intake in the US, Europe, and Asia are significant: non-Asian populations consume less than 3 mg isoflavones per day, whereas Japanese and Shanghai Chinese populations consume approximately 40 mg or more [153]. Moreover, the prostate cancer incidence in Asian immigrants moved to Western countries was found to be higher compared to the one from their countries of birth [154]. Also, when Asian women migrate to the West, their daughters born in the West have a higher risk for developing breast cancer compared to their mothers [152]. This growth can be attributed to dietary patterns and underlines, once more, the importance of nutritional factors in cancer development.

Concerns related to the potential proliferative effects of soy isoflavone on breast cancer cells have emerged with *in vitro* data, when the effects of isoflavones were tested on estrogen receptor positive breast cancer cell lines. According to several cell-based studies, isoflavones, and, especially genistein, exhibited a dose-dependent effect. When estrogen-dependent cells were exposed to relatively low concentrations of genistein (0.01–10 μM), the cell growth and proliferation were promoted, while higher concentrations of genistein (>20 μM) have displayed inhibitory effects. In contrast, in estrogen-independent breast cancer cells, this twofold effect was not observed. In these cells, isoflavones have induced only antiproliferative effects, particularly after high dose exposure [155–158]. These observations have concluded that genistein can induce estrogenic and antiestrogenic effects (depending on the dose), but other cytotoxic mechanisms might be involved as well.

The dual effect of genistein observed in *in vitro* studies was confirmed using a postmenopausal animal model. In low-estrogen conditions, dietary genistein acted in a cumulative manner to stimulate cell growth, suggesting that consumption of genistein-rich products might not be completely safe for postmenopausal women diagnosed with estrogen-dependent breast cancer [159]. However, rodents have higher circulating concentrations of biologically active genistein compared to humans due to a different phase II metabolism of isoflavones. Thus, gaining insight into the effects of isoflavones, especially genistein, using a mouse model might cast doubt and conclusions might not be extrapolated to humans [160].

Behind the antiestrogenic effect, isoflavones can act through a plethora of cellular and molecular mechanisms to inhibit breast cancer cell growth. Genistein was shown to interfere in cell proliferation and survival by blocking important signaling pathways such as NF-κB pathway activation or PI3K/Akt/mTOR pathway. Moreover, genistein can trigger cell apoptosis, promote antioxidant defense and DNA repair, and inhibit the progress of tumor angiogenesis and metastasis. The aglycone can also interfere in other important ER-independent signal transduction pathways [157].

The non-cytotoxic effects of genistein and other isoflavones have been validated by the extensive clinical and epidemiologic data. Clinical trials consistently showed that isoflavone consumption does not adversely affect the markers of breast cancer risk. Furthermore, soy intake after breast cancer diagnosis significantly reduced the cancer recurrence and improved the overall survival [161].

A recent notification made by the American Cancer Society (ACS) reassures breast cancer survivors that soy foods are healthy and safe. Moreover, the health benefits of soy consumption appear to outweigh any potential risk and eating traditional soy foods such as tofu, tempeh, miso, and soymilk may even lower the risk of breast cancer, especially among Asian women. Beyond its isoflavone content, soy also represents an excellent protein source. However, patients are advised against taking soy supplements, which contain much higher isoflavone concentrations than food, until more research is done [162].

A similar position was adopted also by the American Institute for Cancer Research, which states that consumption of moderate amounts of soy foods does not increase a breast cancer survivor's risk of recurrence or death. The institute also explains that a moderate amount of soy consumption is represented by 1–2 standard servings (one serving averages about 7 g of protein and 25 mg isoflavones) daily of whole soy foods (tofu, soy milk, edamame, and soy nuts). According to studies, up to 3 servings/day—up to 100 mg/day of isoflavones—consumed in Asian populations long-term does not link to increased breast cancer risk [163].

4.2 Soy isoflavones and cardiovascular diseases

Clinical trials have shown that soy isoflavones can attenuate blood pressure, but this effect is more probable to occur in hypertensive or equol-producing individuals [164]. Also, a daily average consumption of 30 g soy protein was associated with a significant improvement in lipoprotein risk factors for coronary heart disease [165]. Similar to soy proteins, soy isoflavones were also shown to improve cardiovascular disease risk markers. Apparently, supplementation of soy protein with isoflavones (15 g soy protein with 66 mg isoflavone) for 6 months significantly improved the cardiovascular markers in women during the early menopause compared to soy protein alone (15 g soy protein) [166].

The molecular mechanism explaining the cardiovascular effects of soy isoflavones are multiple. First, isoflavones can mimic estrogen action and interact with estrogen receptors inducing receptor conformations similar to the action of selective estrogen receptor modulators (SERMs). Moreover, isoflavones can promote the activation of endothelial nitric oxide synthase in blood vessels through signaling pathways such as ERK1/2, PI3-Kinase/Akt, and cAMP. Apart from vasculature, isoflavones can also have a renal mechanism, increasing renal blood flow and sodium excretion. Finally, soy isoflavones can have humoral mechanisms, interacting with the renin-angiotensin-aldosterone axis [167].

The cardioprotective effects of soy have been demonstrated in multiple clinical trials, which have finally led to the FDA approval of soy consumption in order to lower the cardiovascular risk. According to 101.82 FDA health claim "Soy protein and risk of coronary heart disease (CHD)," the daily dietary intake level of soy protein that has been associated with reduced risk of coronary heart disease is 25 grams or more per day of soy protein. Moreover, when soy protein is included in a low saturated fat and cholesterol diet, it helps lower blood total and LDL cholesterol levels [168].

In 2017, the FDA proposed to revoke the healthy claim released in 1999 for soy protein, citing mixed results in more recent studies of the heart benefits of soy. However, a recent cumulative meta-analysis of the data selected by the FDA indicates continued significance of total cholesterol and low-density lipoprotein cholesterol reduction after soy consumption [169].

4.3 Soy isoflavones in diabetes mellitus

There are multiple animal and cell-culture studies demonstrating that soy isoflavones, and particularly genistein, exert anti-diabetic effects at physiologically relevant concentrations ($<10\ \mu M$) [170]. However, a clear conclusion over the anti-diabetic properties of soy isoflavones has not been drawn.

In humans, data on soy isoflavone intake are relatively limited. Still, most studies have linked soy consumption to positive outcomes on glycemic control and insulin resistance. A meta-analysis of observational studies suggested an inverse association between soy food consumption and risk of type 2 diabetes, especially in women and

Asians [171]. This is in accordance with another study, which suggested that post-menopausal women who consumed a high soy diet had a lower fasting insulin, compared with those with no daily genistein consumption. Besides, women with high genistein intake had a significantly lower body mass index and waist circumference [172]. Recently, another study has drawn a similar conclusion, that dietary soy intake is inversely associated with risk of type 2 diabetes in Japanese women, but not in men [173].

As a molecular mechanism, most studies showed that genistein treatment increased β-cell proliferation in cell culture models and reduced apoptosis, protecting against β-cell mass destruction. The exact mechanisms appear to involve cAMP/PKA, NF-κB, and ERK-1/2 pathways signaling pathway and several studies suggested an effect on epigenetic regulation of gene expression. Furthermore, genistein has been shown to protect against oxidative stress and inflammation, and to enhance glucose homeostasis through stabilization of pancreatic β-cell function [170, 174].

Although many studies have investigated the benefit of soy isoflavone consumption of blood glucose, well-designed studies are needed to fully understand the underlying mechanisms and evaluate the exact effects of soy isoflavones on diabetes.

In April 2018, the American Diabetes Association (ADA) released a nutrition report with eating recommendations to help manage and prevent diabetes, and also to prevent complications such as heart disease. In this report, there are no amendments related to soy consumption for diabetic patients. The only specific remark is for patients with diabetic kidney disease and macroalbuminuria, who can change to a more soy-based source of protein in order to improve the cardiovascular disease risk factors but proteinuria is not altered [175].

4.4 Soy isoflavones and osteoporosis

The connection between soy consumption and bone health has emerged with epidemiologic studies, which found that Asian women have a lower hip fracture incidence in the elderly compared to Caucasian women. Later, it was confirmed that consumption of soybean and soy-based products, much higher among Asians, could potentially lower the bone loss rate and decrease the risk of fracture [176].

To date, the exact effects of dietary soy isoflavones on osteoporotic bone loss remain inconclusive, and results vary from study to study. Most studies, performed *in vitro* or using animal models, have found an inverse relation between the consumption of soy isoflavones and the percentage of bone loss. As an example, genistein was shown to reduce biochemical markers of bone metabolism, to prevent trabecular bone loss, and affect thyroid follicular cells in a male rat model of osteoporosis [177].

In humans, a post-hoc analysis of a multicenter randomized controlled trial suggested that genistein may be useful not only in postmenopausal osteopenia, but also in osteoporosis. Also, genistein has possible implications for the reduction of fracture risk in postmenopausal women with osteoporosis. These effects seem to be time-dependent and a long-term intake of genistein will produce ongoing effects on bone health [178].

The exact regulating model of soy isoflavones is still unclear, but mechanisms usually imply stimulation of bone formation and/or inhibition of bone resorption. Specifically, genistein was found to retard bone resorption by decreasing the viability of 1,25-dihyroxyvitamin D-induced osteoclasts. Other mechanisms implied enhanced bone formation by increasing serum osteocalcin concentration, femoral insulin-like growth factor 1 mRNA transcription, and serum alkaline phosphatase activity [176].

However, clinical trials outcomes are still conflicting and more well-designed studies are warranted to delineate the underlying mechanisms, the efficacy, and safety of soy isoflavones in osteoporosis. Perhaps due to these current uncertainties, the National Center for Complementary and Integrative Health (NCCIH) declared that soy isoflavone combinations do not lower the rate of bone loss in Western women during or after menopause [179].

4.5 Soy isoflavones and menopausal symptoms

The use of soy-based foods or soy supplements in alleviating menopausal symptoms such as hot flashes, night sweats, and vaginal dryness has long been a controversial subject. A systematic review and meta-analysis published in 2016 has shown that individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes and vaginal dryness score, but no significant reduction in night sweats. However, the study concludes that further rigorous studies are needed to determine the exact association of plant-based and natural therapies with menopausal health [180]. Also, a recent analysis concluded that frequent consumption of soy products (e.g., soy beans, tofu and tempeh), but not soy milk, may be associated with a reduced risk of subsequent vasomotor menopausal symptoms [181]. In contrast, a Cochrane systematic review determined that there is no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in perimenopausal or postmenopausal women. Still, the study admits that genistein concentrates might pose beneficial effects, which should be further investigated [182].

The 2011 North American Menopause Society report on the role of soy isoflavones in menopausal health has concluded that initial treatment with soy-based isoflavones is reasonable for stressful vasomotor symptoms in postmenopausal women. The starting isoflavone dose should be 50 mg/day or higher, for at least 12 weeks. Supplements providing higher proportions of genistein or S(Y)-equol may provide more benefits. If a woman responds to isoflavone supplementation, treatment can continue with monitoring for side effects, but if a woman does not respond after 12 weeks, other treatment options should be discussed. The report also emphasizes on the urge of larger clinical studies aimed to investigate the exact role and mechanisms of isoflavones in postmenopausal women [183].

5. Polysaccharides' contribution to health

Polysaccharides are natural polymers, found in various plants, algae, animals, and microorganisms. These polymers have exceptional properties and essential roles to sustain life. They are an important class of polymeric molecules composed of long chains of monosaccharide units bound together by glycosidic linkages [184]. General classification of polysaccharides is highly diverse; they are classified in different ways, based on their composition, function, and origin [185].

Therefore, an overview of the main polysaccharides, including their potential food and medical applications, is presented in **Table 2**. Depending on the single sugar moieties (glucose, galactose, fructose, mannose), polysaccharides are classified in two groups: (1) *homo-polysaccharides*, which contain only one kind of polymerized sugar unit like starch, xylan, galactan, and froctan, and (2) *hetero-polysaccharides,* containing two or more kinds of sugar units such as pectin [186].

Polysaccharides	Major sources	Applications in health care	Ref.
Starch (amylose/ amypectin)	Cereals, tubers, legumes	Starch esters—matrix former in capsules for medical application Maintaining human colonic function and preventing colonic disease	[189] [188] [186] [185] [187] [198] [190]
Cellulose	Fungi, algae, fruit and vegetables	Oxidized cellulose and regenerated cellulose are widely used as excellent hemostatic materials in various surgical operations and postsurgical adhesion prevention layers Antitumor, immunostimulant, wound healing, and adhesion—prevention properties Drug delivery systems	
Inulin	Chicory root, wheat, onion, garlic	Hypolipidemic effects, prebiotic properties which influence gut microbiota Reduces the plasma total cholesterol, LDL-cholesterol, triglycerides, and increases HDL-cholesterol concentrations Decreases adipose tissue pro-inflammatory cytokines	
Pectins	Citrus peel and apple pomace Spruce bark, mango waste	Gelling and thickening agents In the pharmaceutical industry, as an excipient due to its non-toxicity Specific drug delivery Immunomodulating activities In tissue engineering applications for bone cells culture	
Xylans	Beechwood Perennial plants, fruit, legumes, and nuts	Adsorption, separation, and drug release applications Wound dressing and antimicrobial agents Anticoagulant properties, anti-inflammatory and anticancer effects Immunomodulating activity	
Alginate	Brown seaweed	Cartilage regeneration agent Microencapsulation agent Drug delivery system, bionanoreactors, nanofiltration, and biosensors	
Chitin/chitosan	Shells of crabs and shrimp, cuticles of insects	Target drug delivery In oral administration for lowering serum cholesterol concentration and hypertension Orthopedic/periodontal materials, wound-dressing materials, tissue engineering Drug delivery systems Hemostatic action, anti-inflammatory effect, antitumoral antibacterial, and fungicidal properties Antibacterial coating	
(Galacto) glucomannans	Guar, locust, and carob beans (seeds), fungi and alga, spruce and *Aloe vera*	Thickeners and stabilizers agents Drug delivery system Anticoagulant and antithrombotic drugs Immunomodulating and radical-scavenging activities	
Xyloglucan	Tamarind seed and most land plant	Hypocholesterolemic and hypotriglyceridemic effects Antitumor activity Drug delivery system Gelling and thickening agents	

Table 2.
Main groups of polysaccharides, their origin and applications.

Polysaccharides, in many forms, play a central role in all living organisms for supply and storage of energy and/or structural integrity and protection of cells. Polysaccharide-based substances are increasingly used in health and cosmetic products manufacturing, food and feed production, and for obtaining cellulose-derived materials [187].

Recently, there has been an increased interest for polysaccharides use in various novel applications due to their biocompatibility, biodegradability, non-toxicity, and several specific therapeutic activities [188]. The relationships between polysaccharides, the effects of processing on their structures and interactions, and their behavior in the gastrointestinal tract are crucial for elucidating the relationships between diet and health [189]. Many foods contain a great number of polysaccharides that cannot be completely digested by the digestive system. These indigestible polysaccharides can be called dietary fibers [186]. The class of polysaccharides such as pectin, inulin, and gums are able to slow the food movement in the digestive tract and to slow the sugar absorption from food into blood. The specific action of polysaccharide at digestive tract is given by the fermentable process. Prebiotics are selectively fermented ingredients that result in specific changes of the gastrointestinal microbiota. They improve the mucosal barrier function of the intestine by reducing the expressions of pro-inflammatory cytokines [190].

Therefore, regular consumption of polysaccharides is suggested to beneficially enhance the gut physiology and the metabolic balance by influencing metabolic functions [185]. Intestinal microbiota degrades the polysaccharides to produce metabolites and many intestinal bacteria can use these polysaccharides as unique carbon sources during the fermentation process. An *in vitro* study, which simulated the human colonic fermentation and used two types of indigestible polysaccharides (apple pectin and inulin) as energy sources to three different human bowel microorganisms, showed that the low degree of polymerized inulin positively modulated the intestinal microbiota and improved the flora diversity [186]. However, pectin may also treat or prevent several diseases/disorders such as intestinal infections, atherosclerosis, cancer, and obesity. The oral administration of β-glucan reduced the intestinal inflammation levels and exerted a protective effect on other intestinal diseases and symptoms, especially celiac disease and constipation [191].

Incidence of inflammatory bowel disease has increased considerably in recent years. Therefore, the development of a new adjuvant therapy strategy that may involve natural sources such as dietary modifications is a challenging task [190]. Non-starch polysaccharides such as pectin, cellulose, hemicellulose, β-glucan, pentosane, and xylan are selected targets to reduce the incidence of inflammatory bowel disease, due to the resistance to hydrolyzation by endogenous digestive enzymes of human [192]. The inflammatory symptoms were decreased after the oral administrations of a guar gum or partially hydrolyzed guar gum mixture, a pectin-type polysaccharide; also, the bowel movement, stool consistency, the abdominal pain and diarrhea were improved [186, 193].

Current research shows that the immune-stimulating and immune-modulating functions [194, 195] of polysaccharides; these polysaccharides are called bioactive polysaccharides, they can also stimulate the immune system against cancer cells by increasing immunoglobulin. [186]. The apple-derived pectin is one of the polysaccharides that have been reported to ameliorate metabolic syndrome, and it reduces body weight and the excessive accumulation of fat. Also, the exopolysaccharides isolated from Kefir grains present the same effects as pectin. [186]. Studies have shown that moderate intakes of dietary fiber like polysaccharides can effectively lower risks for developing diabetes. [188]. Diabetes mellitus is a chronic metabolic disease characterized by dysfunctions of carbohydrate, lipid, and [A1] lipoprotein metabolism, which affects approximately 4% of population worldwide and is expected to increase in next decades [186, 196]. Oral administration of β-D-glucans and other soluble non-starch polysaccharides, such as arabinoxylans, had anti-diabetic activities. The major effect of soluble non-starch polysaccharides in slowing glucose absorption is therefore of considerable benefit in terms of diabetes risk and management but also has implications for overall starch digestion [197]. In recent decades, new exploitation of polysaccharides and their derivatives focused on tissue engineering applications, such as biological signaling, cell adhesion, cell proliferation, cell differentiation, and cell responsive degradation. The obtained results showed that a variety of polysaccharides, such as alginate, chitin/chitosan, cellulose and starch and their derivatives, have been developed as biomaterials for tissue engineering applications. For example, chitin/chitosan possesses the requisite properties to act as a scaffold for tissue engineering, regarding their degradability, immunogenicity, and mechanical strength [188].

5.1 Effects of processing on polysaccharides structure and composition

In the initial processing stage, there are several factors that may trigger important modifications of polysaccharide properties. A careful attention paid to these factors is essential in establishing the polysaccharides use in food and biomedical applications. Mechanical fractionation has action on crystalline structure of starch. Dehulling and milling of cereal grains and peeling and chopping of potatoes cause physical damage to a proportion of starch granules. However, this type of starch damaged possesses a water absorption capacity 10 times greater than native starch and it is more prone to gelatinization with implications for end-use properties and digestion [189, 199].

Thermal degradation has an important action with respect to dynamic distribution of polysaccharides' molecular weight. High temperature accelerated the degradation of high-molecular weight polysaccharides to low-molecular weight oligosaccharides and monosaccharide. Thermal processes induce two different major reaction pathways, such as the Maillard reaction, which takes place in the presence of amino acids, and caramelization, that occurs when simple sugars are heated at high temperatures [200, 201]. The predominant products of thermal decomposition of pure starch in toasted bread are the dehydrated oligomers of glucose and individual molecules of dehydrated glucose, which are involved in the Maillard reaction [189]. However, in the case of starch, the thermal decomposition showed no significant relationship between microstructure (crystallinity, granule size) and the thermal degradation process [189, 202]. Heating to higher temperatures of β-glucan solutions induces depolymerization. Similarly, β-glucan in food products that are heat treated at higher temperatures (100) has been shown to become depolymerized as a result of the processing, which was also interpreted to influence their beneficial health effects [189, 203]. It should be noted that many dietary products containing polysaccharides are processed by thermal treatment, and the chemical structure of the carbohydrates is dramatically altered by heat treatment [203, 204]. The main effect of physical modification is to truncate the original polysaccharide backbone to get fragments with lower molecular weights and only cause some conformational changes.

Microwave exposure could degrade polysaccharide structure, and thus increase solubility and biological activity. Microwave heating is described as more homogeneous, selective, and efficient as compared to conventional heating, resulting in faster reactions with fewer or no side products. The polysaccharide degradation in a microwave oven is generated by the interaction between electromagnetic field and chemical constituents of polysaccharide, due to molecular vibration and intense friction [205].

New applications of microwave heating were used in the grafting modifications of polysaccharides, with the precise control of the graft polymer. Microwave irradiation can be a method for the development of valuable products with tailor made properties [206]. It has been shown that the properties of microwave-synthesized graft polysaccharides are normally superior to the derivatives synthesized conventionally, but it still requires very careful control of reaction parameters to obtain polysaccharides with suitable properties and grafting efficiency.

Microwave application has advantages of economical usage of time and power energy, and also, it is easy to operate [205–207]. Another type of physical treatment is application of ultra-high pressure widely used in food and medicine. Depolymerization is the main effect caused by the application of high pressure treatment on polysaccharides; it was shown that the effect of high pressure was found to be dependent on the structure and conformation of the polysaccharides and strongly on their structure: globular branched structures similar to gum arabic are nearly unaffected, while linear stiff polymers undergo depolymerization [208, 209].

Gum arabic was found not to be affected by the high pressure treatment, probably because of its branched and globular structures [208]; the same effect was also identified on cellulose [210]. Radiation processing of natural polymers has received much less attention over the years because most of the natural polymers undergo chain scission reaction when exposed to high-energy radiation and because of the difficulty in processing natural polymers in various forms and sizes [211]. There have been many reports about the effects of gamma irradiation on the degradation of polysaccharides, including the treatments of chitosan [211], cellulose [212], β-glucan [213], and so on. Gamma irradiation improved the solubility and decreased the viscosity of β-glucan by the radiolysis of the glycosidic bonds, and this effect was dependent upon the absorbed dose. Therefore, gamma irradiation could be used in commercial processes as an effective method to resolve the physical problems involved in the use of β-glucan with high viscosity and low solubility [213]. Regarding the effect of gamma irradiation on starch, the result showed increased water solubility and water absorption and, also, an increase of antioxidant activity [205].

Besides new technologies based on polysaccharides, irradiation can be used for the decontamination of food and food additives as well as for the sterilization of materials containing polysaccharides. The irradiation of polysaccharide-containing systems has already found or has potential to find use in plastics technology, in nanotechnology, in medicinal and pharmaceutical areas, in the food industry, and in the chemical and other technical industries [214].

6. Marine bioactive compounds: functional properties

Seafood products are considered inherently functional due to their many valuable compounds and bioactive molecules possessing health benefits [215, 216]. Bioactive components can be isolated from seafoods and seafood co-products and further added to various foods to enhance their functionality in terms of human health [217]. According to recent studies, biologically active protein and lipid compounds can be extracted from fish and other marine organisms like sponges, tunicates, sea hares and slugs, soft corals, bryozoans, as well as marine animals and seafood side streams.

The bioactives with strong health-promoting effects include vitamins, fish muscle proteins, marine peptides and depsipeptides, collagen and gelatin, fish oil, PUFAs, etc. [218–220]. Some of these bioactive components are of particular pharmaceutical and nutraceutical interest due to claimed health benefits [221]. A big part of marine bioactive compounds has been isolated, characterized, and further modified for the development of analogs with improved activities [222–224].

Bioactive peptides extracted from marine organisms and seafood by-products have been reported to possess various activities, including antimicrobial, immunomodulatory, antithrombotic, antioxidant, mineral binding, hypocholesterolemic, and antihypertensive actions [225]. These bioactive compounds can also be used in diverse therapeutic applications for the prevention and/or treatment of chronic diseases, as well as modulation and improvement of physiological functions [224]. The following extraction methods have been mainly used to obtain lipid and protein bioactive ingredients from seafood sources: solvent extraction, heating/cooking, enzymatic hydrolysis, and microbial fermentation of marine proteins. However, heating and enzymatic hydrolysis are the most preferred methods in the food and pharmaceutical industries due to lack of residual organic solvents and/or toxic chemicals in the end products [224, 226].

Fish is a rich source of valuable protein and lipid components worldwide [227]. Moreover, fish muscle proteins possess the potential of providing bioactive peptides to the food, pharmaceutical, and nutraceutical industries [228]. Other marine sources for bioactive peptides include sponges, ascidians, tunicates, and mollusks. A number of these marine species have been studied in depth for presence of bioactive peptides and depsipeptides, including clinical assays, and an extensive group of bioactive peptides has been found [224].

The reported group of bioactive peptides includes compounds with antitumor activities such as Aurilide from tunicate *Dolabella auricularia* [229], Didemnin from tunicate *Trididemnum sp*. [230], Homophymines from sponge *Homophymia* sp. [231], Trunkamide A from ascidian *Lissoclinum* sp. [232], and Keenamide A from mollusk *Pleurobranchus forskalii* [233]. Antiproliferative bioactivities were found in Mollamide from ascidian *Didemnum molle* [234] and other bioactive peptides such as Geodiamolide H, Phakellistatins, and Jaspamide isolated from sponges of the genus *Geodia* sp. [235], *Phakellia carteri* [236], and *Jaspis* sp. [237], respectively. The most preferred method to extract bioactive peptides is enzymatic hydrolysis. Enzymatic hydrolysis results in several peptides with different bioactivities, which offers a huge potential to use them in pharmaceuticals and nutraceuticals.

The biological activity of small peptides present in protein hydrolysates depends on their molecular weight and amino acid sequences [238]. A fractionation step is generally applied to crude hydrolysates to separate individual peptides by using different techniques, such as gel permeation chromatography or reverse-phase high-performance liquid chromatography (RP-HPLC) [219, 239]. Bioactive peptides recovered by enzymatic hydrolysis are usually consisted of 2–20 amino acid residues, and their activities are influenced by their amino acid composition and sequence. A high number of hydrolyzed proteins extracted from seafood by-products have been assayed for various bioactivities, such as antioxidant, antiproliferative, antitubulin, and cytotoxic activities [225]. These biological activities can possess anticancer potential, providing the opportunity to use the recovered peptides in cancer therapy [224]. As mentioned above, seafood side streams and co-products resulting after fish processing are rich sources of valuable protein ingredients for further exploitation in the production of new products such as feed, functional foods, cosmetics, and nutraceuticals [240].

Various seafood rest raw materials such as heads, skin, cut-offs, frame, bone, and viscera can be utilized to isolate a number of bioactive protein ingredients [241]. Fish rest raw material resulting after filleting contains high amounts of high-value proteins containing all essential amino acids. Enzymatic hydrolysis can be used to obtain fish protein hydrolysates (FPH) for further isolation of bioactive peptides. FPH have been shown to contain peptides with, for example, immunostimulating and blood pressure-lowering (ACE-inhibiting) properties, in addition to antiproliferative (antimicrobial), anticoagulant, and immunomodulatory effects. These peptides may be used in novel formulations of nutraceuticals and cosmeceuticals [242]. Bioactive peptides generally include 3–20 amino acid residues and their biological activities are based on their molecular weights and amino acid sequences.

Fish bones and skin are a good source of gelatin and collagen. Collagen finds wide applications in pharma/nutra/cosmeceutical, biomedical, tissue engineering, and film/coating industries either as collagen polypeptide/peptide or gelatin (denatured form of collagen consisting of low-molecular weight peptides and proteins) [243–245]. Gelatin is formed from collagen polypeptide chains by partial thermal hydrolysis. Thus, gelatin is a denatured form of native collagen. Gelatin has been reported to possess unique rheological properties including gel strength, thermal stability, and viscoelastic properties [246]. It is widely applied in the food industry as gelling agent to improve the texture, water-holding capacity, and stability for certain food products. Gelatin can be also used as carrier of active substances such as antimicrobials, antioxidants, flavors, and colors, for production of coatings, as well as microencapsulation of bioactive compounds in pharma-/nutraceuticals [247].

Nevertheless, collagen is characterized by greater mechanical strength, higher enthalpy and resistance to protease hydrolysis, as well as more dense structure with more rigid and firm fibril networks compared to gelatin [248]. Collagen can be successfully used both as a drug carrier and in the treatment of hypertension and pain associated with osteoarthritis, in tissue engineering and inhibition of angiogenic diseases, as well as in production of wound dressings and skin substitutes [249]. Marine collagen and gelatin have attracted a great interest for their unique properties and potential applications in pharma/nutraceuticals, cosmeceuticals, and food manufacturing. The extraction and characterization of collagen and gelatin has been reported from different fish species, including hake [250], ocellate puffer fish [251], Pacific [252], Baltic cod [253], logbarbel catfish [248], Jumbo squid [254], golden goatfish [254], red tilapia and barramundi [255], rainbow trout [256], albacore tuna [257], African catfish [258], Atlantic salmon [259], channel catfish [260], bluefin tuna [261], and others.

As mentioned before, using specific physical and chemical pre-treatments (heat, enzymes, etc.) followed by tailored extraction procedures, seafood rest raw materials might provide bioactive protein components (protein hydrolysates, bioactive peptides, collagen/gelatin, etc.). Some peptide fractions can be individually isolated from hydrolysates using tailored biotechnological processes for potential applications in various industries. Recovery and separation of low- and high-weight peptides from different protein fractions resulting from seafood co-products could provide valuable streams for exploitation in different sectors. The complete exploitation of seafood side streams is often compromised by their high susceptibility to microbiological spoilage and oxidation, as well as proliferation of pathogenic agents. In addition, despite a potential to recover bioactive proteins from seafood side streams, there is still a challenge to meet the growing consumer demands for sensory characteristics of the recovered protein ingredients and foods prepared thereof.

Moreover, a crucial step in the transformation of seafood co-products into new protein ingredients is the use of technological processes that permit the production of microbiologically and biochemically stable ingredients, while minimizing loss of bioactive, nutritional, and functional properties. Marine lipids play role of valuable components of cell membranes, while being carriers of fat-soluble vitamins and energy providers. They also serve as an excellent source of polyunsaturated fatty acids (PUFAs) such eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are part of the omega-3 group. These fatty acids cannot be found in plant sources. Plant oils contain another type of omega-3 fatty acids called α-linolenic acid, which is a metabolic precursor of the omega-3 fatty acids found in fish and fish oils [262].

Although human body is able to convert dietary α-linolenic acid into eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids found in marine lipids, this conversion cannot be considered efficient for modern consumers proffering typical Western diet rich in saturated fat and omega-6 fatty acids [263]. Thus, consuming foods rich in α-linolenic acid, our tissues are exposed to very little action of EPA and DHA. Regardless the fact that some biological activity has been associated with the action of plant-derived omega-3 fatty acids, the main health benefits are attributed to the conversion of α-linolenic acid to EPA and DHA [262]. Omega-3 fatty acids are mainly found in the body of fatty fish (salmon, mackerel, herring, tuna, etc.), the liver of white lean fish (cod), and the blubber of marine mammals feeding on phytoplankton or other aquatic species containing these fatty acids [220]. Microalgae play role of the main generators and suppliers of omega-3 fatty acids to the whole marine ecosystem [264]. In addition, omega-rich algal oils can be obtained via fermentation processes or from kelp and seaweed [265] and are currently in huge demand due to a number of positive effects and industrial applications [266] in the food and feed industries, fisheries, aquaculture, agriculture, pharmacy, and cosmetics. The omega-3 fatty acids that are highly sought after by the nutraceutical and pharmaceutical industries are cis-5,8,11,14,17-eicosapentaenoic acid (EPA) and cis-4,7,10,13,16,19-docosahexaenoic acid (DHA).

They are essential components of a healthy diet and are indispensable for the proper development and function of the nervous system, brain, and eyes, as well as serve as a preventative for cardiovascular diseases and inflammation [267, 268]. Their health benefits also include lowering of triacylglycerols and reducing the incidence of non-communicable diseases such as metabolic syndrome, type-2 diabetes, cancer, arrhythmias, as well as inflammatory diseases and immunomodulatory effects [220]. Other beneficial effects ascribed to PUFAs include antithrombotic, hypolipidemic, antiarrhythmic, and antihypertensive properties [269, 270]. The first studies regarding the health benefits of PUFAs have investigated the diet of the Eskimo population of Greenland, characterized by high intake of seafood rich in omega-3 fatty acids. The research performed by Bjerregaard et al. in these individuals has revealed a correlation between the high consumption of PUFA-rich foods and the low incidence of cardiovascular diseases [271]. These pioneer investigations became a starting point for further epidemiological and interventional studies on the cardioprotective role of omega-3 fatty acids [272]. PUFAs contribute to the formation of special biologically active compounds called eicosanoids, which include prostaglandins, leukotrienes, and thromboxanes [273]. Lipoxins, resolvins, and neuroprotectins with strong anti-inflammatory effects are also derived from EPA and DHA [274].

In addition, the products of PUFA metabolism participate in the maintenance of cell membrane architecture [275] and support homeostasis and vasoconstriction [276]. The cell membrane is exposed to various positive modifications under the influence of the long hydrocarbon chains and double bonds in EPA and DHA. These PUFAs enhance fluidity of the cell membrane [277] and change the distribution and size of lipid rafts in aortic endothelial cells [278]. A number of research investigations have also revealed that PUFAs can successfully prevent weight gain [279, 280]. Omega-3-rich marine lipids were shown to reduce the activity of some nuclear receptors, among which is peroxisome proliferator-activated receptor γ

(PPAR γ) regulating the transcription of several genes responsible for lipid metabolism. Thus, low PPAR γ activity leads to low fat deposits in the adipose tissue and the brain, decreasing the stimulus to consume fat-rich products [281, 282]. The main challenge associated with EPA and DHA is that these omega-3 fatty acids are highly polyunsaturated and readily undergo oxidation [283, 284]. Out of the biological context, DHA and EPL are highly sensitive to oxidation by molecular oxygen present in air due to their polyunsaturated nature. In the enzymatic path of PUFA oxidation, fatty acid oxygenases control the formation of fatty acid-peroxyl radicals. Thus, peroxyl radicals generated during the reaction of PUFAs with molecular oxygen upon biosynthesis of fatty acid peroxides as intermediates in autacoid formation are instantly reduced within the enzyme active site to form the corresponding peroxide. However, in the non-enzymatic path of PUFA oxidation, a temporarily generated peroxyl radical targets at abstracting a hydrogen atom from any of the nearby hydrogen-donating molecules. This molecule can be an antioxidant or a nearby-situated PUFA molecule if the concentration of reduced antioxidants is low enough to effectively scavenge peroxyl radicals formed [285]. At later stages of non-enzymatic peroxidation reactions, secondary lipid oxidation products are formed in the chain reactions involving fatty acid peroxides.

Generation of secondary lipid oxidation products depends on the initial formation and further consumption of fatty acid peroxides. Alkoxy radicals generated from the previously formed peroxides can be involved in reactions with conjugated dienes derived upon earlier hydrogen abstraction-promoted double bond rearrangements, thus fostering the formation of chain-shortened α, β-unsaturated aldehydes through cleavage of the fatty acid chain [285]. The entire description of the free radical-mediated oxidation reactions involving PUFAs is extremely complex and depends on many factors [286]. Thus, marine lipids exposed to oxygen are subjected to fast quality deterioration due to the free radical-mediated propagation of PUFA peroxidation. PUFA-rich marine oils are highly prone to oxidation under ambient conditions. Nevertheless, the oxidation rate can be significantly slowed down by adding and maintaining sufficiently high concentrations of antioxidants and limiting exposure to external factors such as air, heat, and light [287]. According to quality requirements established by GOED (Global Organization for EPA and DHA Omega-3 s), omega-3 PUFA-rich oils should comply with the following limits: 1) on primary oxidation: peroxide value (PV) less than 5 meq O_2/kg and 2) secondary oxidation: para-anisidine value (p-AV) less than 20, as well as a combined measurement of total oxidation comprising both the level of primary and secondary oxidation (TOTOX < 26) [288].

7. Conclusions

Today, food market is richer than ever and consumers have begun to pay more and more attention to what they consume. In this light, functional foods, also known as medicinal or pharmacological foods, have experienced a tremendous growth, as various health-related claims are dispatched on their label. One of the most appealing groups of functional foods is represented by probiotics. Although there are numerous studies that highlight good viability profiles with excellent sensorial properties of a wide range of probiotic functional foods, an obvious conclusion has not yet been drawn. Therefore, more *in vivo* studies are needed to establish a concrete relation between probiotic functional foods intake and prevention, amelioration, or treatment of specific disorders (e.g., colon cancer). In case of secondary metabolites, their pharmacological activities have been widely demonstrated in numerous researches. Apparently, these functional molecules can reduce the incidence of developing chronic degenerative diseases, stroke, and cancer. A distinctive class of secondary metabolites, soy isoflavones provide a series of health benefits such as chemoprotective and chemotherapeutic effects, help reduce the menopause-related symptoms, prevent postmenopausal osteoporosis, or reduce the risk of coronary heart diseases.

Another important group of functional biomolecules is represented by polysaccharides. Several studies have found a positive interaction between polysaccharide-rich diet and metabolic health in the sense of reducing obesity, diabetes, and cardiovascular diseases, and also an inverse relationship between dietary fiber intake and body weight.

A similar positive impact on human health was observed after increasing the consumption of seafood and enrichment of food products with bioactive components extracted from fish, shellfish, seaweed, and seafood co-products. Therefore, for a healthy diet, it is extremely important to promote the consumption of seafood products, while reducing the consumption of high-sugar and high-fat foods.

All data presented herein aim to provide current, precise, and relevant information for nutritionists, education specialists, public health organizations, different organizations (prevention education programs), policy makers, and food industries. They represent key players that can influence consumers to make healthier food selections through labeling and nutrition information on food and beverages. Only in this way, customers will benefit from balanced and healthy diets that are essential to prevent diseases and illnesses.

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Conflict of interest

The authors declare no conflict of interest.

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