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Functional Foods: Product Development, Technological Trends, Efficacy Testing, and Safety

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Abstract

Functional foods is a very popular term in the social and scientific media; consequently, food producers have invested resources in the development of processed foods that may provide added functional benefits to consumers' well-being. Because of intrinsic regulation and end-of-use purposes in different countries, worldwide meanings and definitions of this term are still unclear. Hence, here we standardize this definition and propose a guideline to attest that some ingredients or foods truly deserve this special designation. Furthermore, focus is directed at the most recent studies and practical guidelines that can be used to develop and test the efficacy of potentially functional foods and ingredients. The most widespread functional ingredients, such as polyunsaturated fatty acids (PUFAs), probiotics/prebiotics/synbiotics, and antioxidants, and their technological means of delivery in food products are described. The review discusses the steps that food companies should take to ensure that their developed food product is truly functional.

INTRODUCTION

It is widely known that foods are sources of vitamins and minerals that support bodily functions and health (e.g., breathing, energy production, immune response). Foods are mainly consumed as cell substrates for energy and cell differentiation and proliferation and as the basis for chemical barriers against cell oxidation. Within many types of foods, foods for specific dietary purposes (e.g., light, diet, low-fat) and those categorized as functional foods are the main categories studied in the past 20 years.

The term functional foods was first used in Japan in the 1980s, but their definition is often misunderstood because they are regulated but not legally recognized in most countries, resulting in no statutory definition (Ye et al. 2018). However, recently, Granato et al. (2017) defined functional foods as industrially processed or natural foods that when regularly consumed within a diverse diet at efficacious levels have potentially positive effects on health beyond basic nutrition. Additionally, before health claims are made for certain foods, randomized, double-blind, placebo-controlled clinical trials are necessary to establish functional efficacy (Assmann et al. 2014). This definition narrows the widespread use of the term functional such that without a proper clinical trial and substantial experimental evidence of safety (i.e., toxicology) and functionality, no fresh, unprocessed, or processed food can be regarded as functional.

In addition to their nutritional value as a conventional food, functional foods help in the promotion of optimal health conditions and may reduce the risks of one or more noncommunicable diseases, such as dyslipidemia, cancer, type-2 diabetes, stroke, and cardiovascular disease (CVD). However, to be functional, a food should be validated in intervention trials to comply with the regulations in each country, e.g., the Brazilian Health Regulatory Agency (ANVISA) in Brazil, the European Food Safety Authority (EFSA) in the European Union, and the Food and Drug Administration (FDA) in the United States (Brown et al. 2018, Cassidy et al. 2018, Mak et al. 2018). Together with the definition of functional foods, the main inclusion criteria for a certain functional claim for an ingredient or food on a food label are food safety, free access with no need for medical prescription (or medical advice), and evidence of health benefits when regularly consumed in a balanced diet (Eur. Parliam. 2006, Lenssen et al. 2018).

Although the definition and the basic criteria are understandable and comprehensive, many researchers still have misconceptions regarding terminology associated with functional foods. Some authors declare foods or ingredients functional when they are manufactured using potentially functional substances recovered from industrial by-products (Dalle Zotte & Szendrő 2011, Tahergorabi et al. 2015) or by adopting certain technological processes (Gutiérrez 2018), whereas others provide a functional food claim based on enrichment with essential minerals (Adadi et al. 2019). Furthermore, some authors still use the phrase "prevention of diseases" even though functional foods neither prevent nor cure any diseases, as other intrinsic and extrinsic factors (e.g., genetic factors, physical inactivity, caloric density and variety, hormones, age) play an important role in the etiology of noncommunicable diseases (Chibisov et al. 2019, Rao et al. 2019). Similarly, many authors declare foods or ingredients functional based on in vitro or animal-based protocols (Çalışkantürk Karataş et al. 2017, Gouw et al. 2017, Rana et al. 2015), whereas others confuse the difference between conventional and functional foods (Fedacko et al. 2019). Thus, it is important to note that functional foods are not medications, as they do not heal/cure/prevent diseases.

Consumers today demand foods that are sustainably produced and processed, deemed safe, fresh, and natural, and have nutritional value (Putnik et al. 2018b). As with all newly designed food products, functional food development is expensive, difficult, and laborious (Musina et al. 2017).

From January 1990 to June 2018, the most studied functional foods and ingredients, as bibliometrically evaluated by Yeung et al. (2018) analyzing the most cited and searched items in the literature, were prebiotics, probiotics, and antioxidants. As the functional food era is just beginning, the main aims of this review are to provide a definition and classification of functional foods, exemplify the most recent and relevant studies, and propose practical guidelines that can be used to develop and test the efficacy of potential functional foods/ingredients. The review is intended to provide an overview of the most interesting functional ingredients, such as polyunsaturated fatty acids (PUFAs), probiotics/prebiotics/synbiotics, and antioxidants, their technological means for delivery to food products, and their health-promoting properties. Finally, the review discusses the steps that food companies should follow to ensure that their developed food product is compliant with the definition of functional. **Table 1** was assembled to give an in-depth look into the main bioactive compounds (and food sources) and food ingredients that have recognized functional effects in humans.

FUNCTIONAL FOODS: DEVELOPMENT AND TRENDS

Trends in Novel Functional Food Products

The functional food market (United States, Japan, Asia Pacific, and European Union) is a lucrative niche of food production and is projected to grow globally. It is anticipated to reach $304.5 billion by 2020, with an average annual growth rate of 8.5% (Bogue et al. 2017). The most common functional food products on the market include yogurt (digestive health), cereals (cardiac health), margarines/butters (cholesterol metabolism), and energy/protein bars and drinks (hunger reduction) (Bogue et al. 2017). Below, we discuss certain innovative technologies used to develop potentially functional foods as well as technological tools that deliver bioactive ingredients/compounds.

Innovative processing technologies as a tool for development of novel functional foods. The development of functional foods is essential for food companies and includes the design, optimization, and development of different formulations as well as the processing techniques that are applied to food products before they are delivered to the market. For instance, the use of thermal processing has a decisive influence on the bioavailability of nutrients and bioactive compounds present in food (Koubaa et al. 2018). Over the past two decades, innovative processing technologies (e.g., high hydrostatic pressure, pulsed electric fields, ultrasounds, microwaves) have emerged as suitable food-processing alternatives (Bursać Kovačević et al. 2018). These sustainable technologies provide better preservation of native nutrients in fruits and vegetables, avoid microbial growth, and utilize less energy, and they can be applied to the exploitation of by-products while being eco-friendly (Putnik et al. 2017). Hence, they have positive impacts from the functional point of view as well as in the development of new functional products. There is a significant influx of various governmental funding for research, development, and implementation of such technologies in current and new food processing.

Tools to deliver target compounds. The use of bioactive compounds for the development of functional foods is conditioned, in most cases, by low solubility and reduced stability and bioavailability. To overcome these problems, the use of oral administration systems based on nanoparticles or microparticles containing bioactive compounds or essential minerals can be an effective

Table 1 Possible beneficial effects of antioxidants, bioactive compounds, and ingredients on human health

Antioxidants, bioactive compounds, and ingredients	Food matrix	Health benefits	References
Carotenoids			
β-Carotene	Yellow, orange, and green leafy vegetables and fruits (e.g., carrot, mango, orange, etc.)	AOX, provitamin A, prevents eye diseases, radioprotective and antimutagenic, etc.	Kim 2016
Lutein	Green leafy vegetables (e.g., kale)	AOX, anti-inflammatory, antiatherogenic, antihypertensive, antidiabetic, antiulcer, ↓cancer risk, prevents eye diseases	Kim & Park 2016
Lycopene	Tomato, melon, peach, etc.	AOX, ↓CVD, ↓cancer risk	Costa-Rodrigues et al. 2018, Rodriguez-Concepcion et al. 2018
Zeaxanthin	Egg yolk, spinach, kale, etc.	AOX, provitamin A, anti-inflammatory, improves cognitive function, ↓cancer risk, ↓CVD	Buscemi et al. 2018
Curcumin	Curcuma	AOX, ↓DM risk, ↓NDs, ↓CVD, ↓IMs, and ↓CVD	Rivera-Mancía et al. 2018, Saeidinia et al. 2018, Salehi et al. 2019
Chlorophylls			
Chlorophyll A and B	Algae, seaweeds, etc.	AOX, ↓cancer risk	Chakdar & Pabbi 2017, Qin 2018
Fibers			
β-Glucan	Yeasts, oats, bacteria, etc.	↓CVD, controls diabetes, stimulates immune system	Bai et al. 2019, Bozbulut & Sanlier 2019, Jayachandran et al. 2018
Inulin	Asparagus, garlic, chicory, onion, etc.	Prebiotic effect, ↓atherosclerosis, ↑satiety	Roshan et al. 2019, Shoaib et al. 2016
Organosulfur compounds			
Glucosinolates	Brassica family: Brussels sprouts, cabbage, cauliflower, etc.	↓Risk of cancer and metastasis, protect cells from redox imbalance, ↓chronic inflammatory diseases	Traka 2016
Isothiocyanates	Brassica family: Brussels sprouts, cabbage, broccoli	↓NDs and ↓cancer risk	Giacoppo et al. 2015, Mitsiogianni et al. 2018
Phytosterols			
Sterol and stanol	Wheat germ, rapeseed oil, peanuts	↓TC, ↓LDL-C, anti-inflammatory, and ↓NDs	Gylling et al. 2014, Plat et al. 2019, Vanmierlo et al. 2015

(*Continued*)

Table 1 (*Continued*)

Antioxidants, bioactive compounds, and ingredients	Food matrix	Health benefits	References
Polyphenols			
Anthocyanins, proanthocyanidins	Litchi, grape, blueberries, grapeberries, cocoa	AOX, prevent and treat hyperuricemia and/or gout, ↓CVD	Li et al. 2012, 2017; Moriwaki et al. 2011
Isoflavones	Soy, miso, tofu, soy-based foods, flaxseeds	↓CVD, ↓LDL-C, ↓osteoporosis, ↓DM risk, and ↓liver disease	de Piano et al. 2019, Duru et al. 2018
Lignans	Sesame seeds, broccoli, strawberries, Brussels sprouts, olives, etc.	↓CVD and ↓hormonal cancer risk	Kiyama 2016, López-Biedma et al. 2016, Yoder et al. 2015
Resveratrol	Red grape, blueberries, blackberries, cocoa	↓CVD, ↓LDL-C	Gambini et al. 2015, Kuršvietienė et al. 2016, Pannu & Bhatnagar 2019
Prebiotics			
Inulin, fructooligosaccharides, xylooligosaccharides	Chicory, onions and garlic, Jerusalem artichoke, dandelion greens, leeks, asparagus	↓Depression symptoms, bifidogenic effect, ↓atherosclerosis, ↑satiety	Kazemi et al. 2019, Roshan et al. 2019, Shoaib et al. 2016
Probiotics			
Lactobacillus casei, *Lactobacillus acidophilus*, *Bifidobacterium lactis*	Fermented milks, desserts, nondairy foods supplemented with probiotic microorganisms	Gut microbiota management, ↓weight gain, ↓waist circumference, ↓serum glucose, ↓insulin, and HOMA-IR, ↓LDL-C, ↑GSH serum levels in blood, ↓oxidized products in blood, ↓inflammation markers, ↓hypertension, ↓hyperglycemia, ↑HDL-C	Ejtahed et al. 2019, Rezazadeh et al. 2019, Roshan et al. 2019, Salami et al. 2019, Kassaian et al. 2018
Synbiotics			
L. casei, *L. acidophilus*, *B. lactis* plus inulin, fructooligosaccharides, xylooligosaccharides	Foods supplemented with probiotics and prebiotic ingredients: ice creams, desserts, granolas, chocolates	↓Inflammation markers, ↑serum/plasma total antioxidant capacity, ↑GSH levels in blood, ↑NO, ↓infection risk, ↓hypertension, ↓hyperglycemia	Kassaian et al. 2018, Wu et al. 2018, Zheng et al. 2019

Abbreviations: AOX, antioxidant; CVD, cardiovascular disease; DM, diabetes mellitus; GSH, glutathione; HDL-C, high-density lipoprotein–cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; IM, inflammatory mediator; LDL-C, low density lipoprotein-cholesterol; ND, neurological disorder; NO, nitric oxide; TC, total cholesterol.

solution (Tapia-Hernández et al. 2019, R. Wang et al. 2019). In fact, these systems can be developed in liquid forms, such as gels and pastes, and solid forms. For instance, Bonat Celli & Abbaspourrad (2018), McClements (2020), and Nikmaram et al. (2017) explained the trendiest delivery systems tailored for bioactive ingredients in food systems, including microemulsions, nanoemulsions, emulsions, solid-lipid nanoparticles, liposomes, and microgel biopolymers. The use of electrospinning for the encapsulation of bioactive compounds, both hydrophilic and hydrophobic, has been shown to be a suitable approach, as it does not involve any severe conditions of temperature, pressure, or harsh chemicals (Zhang et al. 2019). Even though a great variety of studies was carried out to develop stable systems that increase the solubility, stability, and bioavailability of bioactive compounds, one of the biggest challenges that remains is the difficulty of scaling the laboratory results up to commercial levels. Issues often occur as the ingredients or processing operations are not commercially practical. Likewise, there is the downside that after the addition of functional compounds, the matrices that incorporate bioactive compounds may lose flavor, texture, appearance, and stability. Furthermore, the development of an adequate administration system is expensive because there must be rigorous testing on humans and animals to evaluate accurately their bioavailability and potential toxicity. For example, it is necessary to evaluate whether the administration of a bioactive-rich system allows the bioactive compound(s) to be stable and biologically active during transit through the gastrointestinal tract and its subsequent absorption.

BIOACTIVE INGREDIENTS FOR FUNCTIONAL FOOD DEVELOPMENT

Probiotics, Prebiotics, and Synbiotics

By definition, probiotics are ingested living microorganisms that in adequate amounts induce health benefits in the host (Hill et al. 2014). To be considered probiotic, the microorganism (e.g., *Lactobacillus* and *Bifidobacterium* genera) must survive an acidic environment and exposure to bile salts found in the human body while having a good capacity for absorption in the intestine and a clear link to some health marker in clinical trials (Champagne et al. 2018). Similarly, prebiotics are consumed so that microorganisms can selectively utilize them and provide health benefits to the host (Gibson et al. 2017). Prebiotics have the ability to improve the survival, growth, metabolism, and beneficial health activities of probiotics in the digestive system. The most known examples from the diet are nonactive food constituents that move to the colon and are selectively fermented, such as lactulose, galactooligosaccharides, fructooligosaccharides, xylooligosaccharides, and inulin as well as their hydrolysates. Finally, synbiotics are a combination of probiotics and prebiotics that provides beneficial effects to the host by efficiently improving the survival of live microbes in the digestive tract compared to either probiotics or prebiotics alone (Mohanty et al. 2018). Interestingly, the best-case scenario for synbiotics is that each constituent (pro- and prebiotic) has a beneficial additive effect. The synbiotic terminology is divided into complementary (i.e., the prebiotic component is not necessarily fermented by the probiotic strain and could theoretically support other members of the gastrointestinal microbiota without registering any ecological advantage to the probiotic strain) and synergistic (i.e., prebiotic ingredient is added to a food formulation with the specific purpose of supporting the growth of the probiotic strain) (Krumbeck et al. 2018).

Regarding the technological applications of probiotics, prebiotics, and synbiotics, much attention is dedicated to delivery strategies that are able to increase their chemical stability and viability during shelf life (Sanders & Marco 2010). Hence, the development of solutions to improve a product's stability throughout storage conditions is required. Some of these alternatives are the manufacture of nondairy foods (Ranadheera et al. 2018), microencapsulation of probiotic microorganisms and their introduction to unfermented foods (Panghal et al. 2018), assessment of novel sources of prebiotic ingredients (Dávila et al. 2019, de Borba Gurpilhares et al. 2019, Zeng et al. 2018), assessment of different functional effects (Chen et al. 2018), and engineering of edible coatings for probiotic bacteria entrapment and delivery (P. Singh et al. 2019). Regardless of technology, it is important to perform clinical trials to evaluate efficacy, correct dosage, and consequence of long-term exposure to probiotics, prebiotics, and/or synbiotics in humans.

Recently, paraprobiotics, which are inactivated probiotic microorganisms that are able to provide health benefits, have drawn attention (de Almada et al. 2016). However, the mechanisms of such actions are not completely elucidated, so this requires additional in vitro studies and clinical trials to understand the interactions between the physiological effects of paraprobiotics in humans (Nishida et al. 2017, Sawada et al. 2016).

More recently, postbiotics were defined as soluble compounds or metabolic by-products that are released by bacteria during their lives or after their lysis in the gastrointestinal tract (Aguilar-Toalá et al. 2018). Short-chain fatty acids, enzymes, peptides, endo- and exopolysaccharides, and cell-surface proteins are included in this group. Some health benefits of postbiotics include the lowering of low-density lipoprotein cholesterol (LDL-C) and antioxidant, immunomodulatory, and antimicrobial effects, as described by Aguilar-Toalá et al. (2018) and Foo et al. (2019). However, the mechanisms of action are not fully elucidated. Therefore, it is important to provide optimal processing parameters that guarantee the maximum production, isolation, and purification as well as correct dosage of postbiotics.

Antioxidants

Beginning in the 1930s, antioxidants (i.e., ascorbic acid and tocopherols) were solely used as additives to prevent oxidation of oils/fats in foods with high concentrations of lipids (Carocho et al. 2018). In the 1970s, clinical trials revealed those dietary antioxidants inhibited the oxidation processes and prevented oxidative stress in related diseases. From this moment onward, the use of antioxidants soared worldwide, not only as food additives but also as dietary supplements, because of their beneficial effects in humans (Cömert & Gökmen 2018).

Halliwell & Gutteridge (2015, p. 77) stated that "an antioxidant is a substance that, when present at a low concentration compared with that of an oxidizable substrate in the medium, inhibits oxidation of the substrate." Under this classification, phenolic compounds (e.g., flavonoids, phenolic acids, stilbenoids, coumarins, lignoids), carotenoids (e.g., carotenes and xanthophylls), terpenoids (e.g., monoterpenes, triterpenes, and sesquiterpenes), and some lipids (e.g., tocopherols and tocotrienols) are considered antioxidant agents. From the physiological perspective, there are three different mechanisms for protecting cells/organs: (*a*) single-electron transfer, (*b*) hydrogen-atom transfer, and (*c*) transition metal chelation. According to the place of origin, antioxidants may be endogenous (e.g., catalase, glutathione reductase, superoxide dismutase) or exogenous (tocopherols, carotenoids, phenolic compounds, and terpenoids). More details on these topics can be found elsewhere (Granato et al. 2018b, Pellegrini et al. 2019).

Multiple publications have associated higher consumption of fruits and vegetables (rich with antioxidants) with a lower risk of all-cause mortality, particularly cardiovascular mortality (Parohan et al. 2019). Additional studies reported that a significant inverse association is commonly observed for cardiovascular mortality with higher consumption of fruits and vegetables, whereas this was not associated with risk of cancer mortality (Nguyen et al. 2016). In a recent study conducted by Du et al. (2017), authors concluded that regular consumers of fruits (≥4 days/week) versus nonregular consumers had 27% lower all-cause mortality, 34% lower CVD mortality, 17% lower digestive tract cancer mortality, and 42% lower mortality from chronic obstructive pulmonary disease. More importantly, there was a log-linear dose–response relationship between the amounts of consumed fruits and the lower mortality index.

In a prospective and observational study with septic Spanish patients ($n = 319$), serum antioxidant capacity (SAC) was correlated with mortality rate. Authors found that lower SAC levels during the first week of sepsis are associated with higher lipid peroxidation, sepsis severity, and sepsis mortality, and they could be used as a prognostic biomarker (Lorente et al. 2018). Similarly, two prospective cohort studies of middle-aged and elderly Chinese adults ($n = 134{,}358$) in urban Shanghai were carried out to assess the effects of intake of ascorbic acid and β-carotene as dietary supplements (consumed continuously at least three times per week for longer than two months). Authors observed significant inverse associations among consumption of total dietary β-carotene and ascorbic acid with the risk of CVD mortality (Zhao et al. 2017).

Initially, because data for antioxidants showed that they delayed the onset of oxidative reactions both in vitro and in vivo, sales of dietary antioxidants as antiaging agents in the 2000s gained more momentum and more marketing. A large database containing the oxygen radical absorbance capacity (ORAC) of more than 1,000 foods was released by the US Department of Agriculture (USDA) in 2012, only to be removed from their website after stating that in vitro measurement of antioxidant capacity (i.e., ORAC) has no physiological relevance in humans. In addition, the USDA discouraged the use of ORAC on supplements and foods for marketing purposes. Halliwell (2012) also stated that the consumption of large doses of antioxidants (e.g., pills and tablets) generally failed to prevent human diseases, in part because they do not decrease oxidative damage in vivo. Additionally, an overdose of dietary antioxidants could present pro-oxidant effects, thus causing deleterious effects in humans, which is not desired (Sarangarajan et al. 2017). For instance, with cancer patients, Khurana et al. (2018) concluded that several randomized clinical trials showed that the consumption of antioxidants during chemotherapy decreased the effectiveness of the medical treatment. Gostner et al. (2015) reviewed the pros and cons of dietary antioxidant intake and concluded that the overall uptake of antioxidants exceeds the recommended requirements. Some of these compounds include food additives such as vitamins, colorants, flavoring agents, and preservatives that are often strong antioxidants. In addition, dietary antioxidants lower leptin, thus interfering with satiety regulation and, consequently, trigger food intake (Gostner et al. 2015).

Another main issue in food science is finding antioxidants and chemically measuring their antioxidant effectiveness by multiple in vitro and ex vivo methods (Fidelis et al. 2018, Jiao et al. 2018). We also need to optimize their extraction conditions to obtain more target compounds from different food and herbal sources (Escher et al. 2018, Ochiai et al. 2019, Santos et al. 2018). As assessments, in vitro chemical assays have several disadvantages and pitfalls (Schaich et al. 2015); cell-based methods (i.e., cytotoxic and antiproliferative effects) may be the new, reliable assays for the antioxidant activity of food-based extracts (Kellett et al. 2018). Recently, Xiao (2018) evoked the need to strengthen the legitimacy of studies with the chemical stability of polyphenols when these substances are tested for anticarcinogenic and antiproliferative activities in cell-based methods. The author stated that some polyphenols are not stable and potentially may produce unsafe end products without any bioactivity.

Currently, continuous demand from modern consumers is pushing the food industry to decrease or even eliminate the use of synthetic additives in manufacturing; thus, numerous research and technological applications have switched to focus on natural counterparts. Hence, bioactive compounds are extracted from herbs, foods, and industrial by-products so they can be applied as antioxidants in food production (Chen & Xu 2019). These extracts are obtained using either water or ethanol (or their binary combination) and are then assessed to identify physicochemical and functional properties (Ochiai et al. 2019, Shi et al. 2019). Consequently, they can be applied in the production of different foods, such as dairy products (Granato et al. 2018a, Karnopp et al. 2017), meat-based foods (Bajpai et al. 2019), oil-in-water emulsions (Elder et al. 2019), edible oil (Utama-ang et al. 2017), protein concentrates from marine microalgae (Kazir et al. 2019), bread (Mikulec et al. 2019), crackers and bars (Gamel et al. 2019), and snacks (Ramírez-Jiménez et al. 2018) as well as packaging materials (Rambabu et al. 2019).

Although in vitro chemical and cell-based methods may provide a quantitative result (e.g., high in antioxidants), clinical and epidemiological data are inconclusive at this point. Thus, more research is needed to confirm or refute the hypothesis that foods rich in antioxidants can be considered functional foods. The final message should be clear: High chemical antioxidant activity measured by different in vitro methods may not be translated to in vivo antioxidant activity, and, therefore, foods with high chemical antioxidant activity cannot be automatically considered functional.

Polyunsaturated Fatty Acids

PUFAs with multiple double bonds in the main carbon skeleton are widely present in foods, where they play an important role in human metabolism. Among the several PUFAs, n-3 and n-6 are the most studied families because of their nutritional importance and their biological functions. The scientific literature is largely composed of studies regarding essential PUFA, particularly linolenic (LA; 18:2, n-6), alpha-linolenic (ALA; 18:3, n-3), the long-chain PUFA (LCPUFA) eicosapentaenoic acid (EPA; 20:5, n-3), and docosahexaenoic acid (DHA; 22:6, n-3). To exploit the potential health benefits associated with the consumption of such compounds, focus is given to their dietary sources, which include oilseeds, cereals, fish, and fish oil (Kaur et al. 2012).

PUFAs are also associated with many health benefits; for example, there is a well-known association between a high proportion of PUFAs (particularly long-chain n-3 PUFAs) and reduced risk for CVDs. The protective effect of these fatty acids is even more evident when measuring the amounts from the diet (Sekikawa et al. 2015). Sekikawa et al. (2015) compared clinical trials from Japan and the United States and found that although a cardiovascular protective effect was reported in Japan, most studies from the United States did not report the same beneficial effects (high consumption in Japan versus low consumption in the United States). Another PUFA health benefit is their positive effects against inflammation. The consumption of small amounts of n-3 PUFAs (1.8 g of EPA + 1.3 g of DHA/day) for 21 days has been associated with reduced levels of airway inflammatory markers among adults with asthma and hyperpnoea-induced bronchoconstriction (Williams et al. 2017). Furthermore, a recent review and meta-analysis supported the central role of PUFAs in the reduction of inflammation biomarkers, especially for C-reactive protein production among type-2 diabetes mellitus carriers (Lin et al. 2016).

The current strategy to develop PUFA functional foods is mainly focused on the addition of one or a combination of PUFAs from natural sources to foods to increase their individual and total content. It is important to explore alternative strategies to produce functional foods containing PUFAs from less common sources as well as to introduce these substances into unexplored food products. This includes considering new physiological processes along with those that are already known. Exploring other PUFA involvement in LCPUFA synthesis is an interesting strategy because it would favor nutritional benefits while promoting health. Stearidonic acid (SDA; 18:4, n-3) is an interesting option for further studies among PUFAs because of the potential increase in EPA synthesis (at nutritional level) and the potential for reducing risks of cancer and CVDs and improving inflammatory status in vivo (Cardoso et al. 2018, Whelan 2009). In addition, SDA also improved glucose disposal in insulin-resistant monkeys, indicating that human studies are necessary to confirm this functional effect (Kavanagh et al. 2013).

It is also important to develop the current PUFA sources and explore new ones. Less common sources of PUFA for the functional food industry are algae, microorganisms, krill (Delarue & Guriec 2014), insects (Belluco et al. 2013), and even the liver of domesticated species (Gheysen et al. 2018). The addition of PUFAs, particularly n-3 PUFAs, requires an appropriate benchmark to fulfill nutritional requirements and consequently provide scientific support for the development of novel PUFA functional foods. Regarding the risk of CVD, the n-3 index is defined as the percent sum of EPA and DHA, which indicates undesirable (0–4%), intermediate (4–8%), and desirable (>8%) fatty acid profiles (Harris et al. 2007).

The current challenges in the manufacture of PUFA functional foods are the susceptibility to oxidative reactions and changes in sensory properties and texture (Jiménez-Martín et al. 2015, Lorenzo et al. 2016). Some of the most relevant factors to consider in oxidative stabilization of PUFAs are the presence and composition of physical barriers and droplet size, the presence of antioxidant compounds, and exposure to high temperatures, UV radiation, and atmospheric oxygen (Kaushik et al. 2015).

To overcome the issues imposed by processing and storage, multiple strategies have been explored, such as the use of antioxidants (Espinosa et al. 2015, Qiu et al. 2017), encapsulation approaches (e.g., freeze-drying, spray-drying, and spray granulation) (Anwar & Kunz 2011), coacervation (Eratte et al. 2014), electrospray (Gómez-Mascaraque & López-Rubio 2016), and microgels (Chen et al. 2017). Furthermore, the evaluation of such strategies in food systems has shown promising results regarding product quality (Munekata et al. 2017, Penko et al. 2015).

Finally, the most recent products supplemented with PUFAs and subjected to clinical trials were yogurt and juice (Ottestad et al. 2016), margarine (Burak et al. 2017), spreads and vegetable oils (Vafeiadou et al. 2015), cooked rice (Sun et al. 2016), and a multicomponent meal composed of a muffin and a strawberry-flavored milkshake (Chang et al. 2016, Teng et al. 2015). The variety of PUFA functional products that show a successful association with health benefits are important facts that support PUFAs' role as one of the main functional ingredients.

Phytosterols

Phytosterols and stanols are lipophilic compounds that are naturally found in plants in the free unbound form or covalently bound via an ester or glycosidic bond. These compounds are associated with fluidity and the permeability of vegetable cell membranes (Moreau et al. 2018). From a chemical standpoint, phytosterols and stanols have structures and roles similar to those of cholesterol in animal cells. The main phytosterols from vegetable oils, nuts, seeds, cereals, fruits, and vegetables are stanol, campesterol, sitosterol, stigmasterol, sitostanol, and campestanol (Alkhalf et al. 2018, Putnik et al. 2019, Vu et al. 2019, M. Wang et al. 2019). Because of chemical similarity to cholesterol, phytosterols and stanols have been clinically shown to reduce cholesterol absorption (which reduces serum cholesterol) both in vitro and in vivo (Danesi et al. 2016, Yi et al. 2016). The mechanism associated with the reduction of serum cholesterol by phytosterols is the inhibition of cholesterol absorption in the intestinal tract. In addition, it is suggested that phytosterols decrease the activity of lipases and cholesterol esterases on cholesterol, induce the formation of insoluble mixed crystals by cocrystallization with cholesterol, and compete for dietary mixed micelles at the physiological level (Trautwein et al. 2003).

Because of the inhibitory effects of phytosterols on cholesterol at physiological and molecular levels, several studies were dedicated to evaluating the impact on cardiovascular biomarkers, such as the hypocholesterolemic effect. As circulating cholesterol, especially LDL-C, is one of the major risk factors for CVD, impeding cholesterol absorption potentially leads to a reduced risk of heart diseases (Ferguson et al. 2018). Phytosterols and stanols are toxicologically safe at standard concentrations found in natural and processed foods (up to 20 g/day).

Many studies have shown that phytosterols and stanols confer other health-promoting effects, e.g., improving immune response to cancer recognition; affecting hormone-dependent endocrine tumor growth (Shahzad et al. 2017); acting as chemical antioxidants, free-radical scavengers, and anti-inflammatory constituents in vitro (Alkhalf et al. 2018); and functioning as cytotoxicants against NIH/3T3, HeLa, and MCF-7 tumor cells (Ayaz et al. 2019), by participating in different physiological pathways. A meta-analysis was conducted by Rocha et al. (2016) in which the authors concluded that the consumption of <10 g/day of phytosterols (average of 2.24 g/day) for more than two weeks did not change the C-reactive protein (inflammation marker), high-density lipoprotein (HDL), and triacylglycerol levels in humans (Rocha et al. 2016). Conversely, Devaraj et al. (2011) performed a clinical trial with 72 healthy volunteers that received either plain orange juice or plant sterol–rich orange juice (2 g/480 mL per day) and analyzed the inflammation markers [interleukin (IL)-1b and IL-6 tumor necrosis factor alpha (TNF-α), IL-8, and IL-10)] after 8 weeks of treatment. There were significant reductions in IL-1b and IL-6 levels with sterol-fortified orange juice versus the baseline group. The authors concluded that the sterol-fortified orange juice was able to effectively lower biomarkers of inflammation in healthy human volunteers.

Because of strong evidence that phytosterols and stanols have beneficial effects in humans, various lawmakers permitted the use of these compounds in foods and made them eligible to bear the disease risk–reduction claims on the food labels (Kalliny & Zawistowski 2019). Regarding phytosterols as functional foods, several clinical trials supported the use of this class of compounds in different lipid-rich products. Some of these foods include margarine (Law 2000), milk and processed dairy products (Clifton et al. 2004, Ribas et al. 2017), fruit juices (Abd-Razak et al. 2019), sterol-based oleogels (Martins et al. 2019), soy drinks (Weidner et al. 2008), and phytosterol-rich chocolate (Botelho et al. 2014).

The current research trends associated with the addition of phytosterols/stanols during food manufacturing are related to two main topics: oxidative instability and physiological delivery to assure bioavailability in humans. Therefore, current technological demands center research on the technological means for their delivery. As a result, modern approaches emerged, such as encapsulation by spray-drying with different carrying agents (Di Battista et al. 2017), supercritical carbon dioxide impregnation of phytosterols into nanoporous starch aerogels (Ubeyitogullari & Ciftci 2017), and complex coacervation (Comunian et al. 2017). These methods were shown to enhance their chemical stability toward oxidation in foods, which influences food shelf life and sensory properties. Phytosterols/stanols must be finely dispersed prior to exposure to bile salts, preferably in particles smaller than 25 μm, to reduce the sandy mouthfeel while still favoring their incorporation into the micellar phase in the intestine. Owing to their hydrophobic and water-insoluble nature, phytosterols/stanols have difficulties forming stable dispersions, which limits their use in intermediate or final aqueous-based food products (Di Battista et al. 2018).

However, more studies are necessary to overcome some drawbacks in the production of functional foods with plant sterols. The first limitation is the possible reduction in physiological absorption of fat-soluble antioxidants and bioactive dietary compounds. For instance, the absorption of carotenoids, tocopherols, and lipophilic vitamins has been shown to be limited by phytosterols (Rocha et al. 2011). Another relevant aspect is oxidation of plant sterols during preparation of the foods and during storage with formation of hydroxy, epoxy, keto, and triol derivatives, collectively known as phytosterol oxidation products (POPs) (O'Callaghan et al. 2014). Chemical and enzymatic pro-oxidants in food and the human body can induce the formation of 7-keto-sitosterol, 7-keto-campesterol, and 7β-OH- and 7α-OH-oxyphytosterols. Such compounds induced important physiological modifications in animal models, such as liver hyperplasia (Liang et al. 2011). In addition, POPs have no beneficial effects on lowering total cholesterol in vivo. Thus, limiting the oxidation of plant sterols in final products is an essential technological focus for functional food manufacturing.

TOOLS TO EVALUATE THE BIOLOGICAL EFFECTS AND SAFETY OF FUNCTIONAL FOODS: TESTING EFFICACY AND SAFETY

As mentioned above, a new functional food must be clinically evaluated to prove it is beneficial to humans and to corroborate safety. The assessment of functionality and the health-claim formulations of potentially functional foods and ingredients should be based on in vivo testing. These steps are necessary to select proper biomarkers to evaluate the existence and magnitude of potential health benefits (or deleterious effects related to safety). In vitro and animal models cannot establish cause-and-effect in humans, but they do provide supportive evidence for functionality and are related to the functional substance. A double-blind randomized controlled clinical trial (RCT) with placebo controls, with either a parallel (one treatment is evaluated) or cross-over method (≥2 products are assessed with a washout period) is the gold standard for clinical research (Weaver & Miller 2017) to assess the health claims and safety of potential functional foods (Nieburg 2013). RCTs eliminate problems with bias and confounding in the research while allowing the causal inference that provides lawmakers with facts to permit health claims on medicinal and food labels. More details on clinical study design can be found in the epidemiologic literature (Ahrens & Pigeot 2014). Therefore, the full details regarding the experimental methodology and precise and in-depth discussion of the obtained data are necessary to reflect on the quality of the foods with functional claims. This ensures evidence-based, unbiased judgment of the validity and reliability of the results. Furthermore, the data should be published in a peer-reviewed scientific journal to allow for a critical assessment by the scientific community (Kamioka et al. 2019). Valid and reliable results generated by the RCT should be passed to the public and government and focus on the protection of public health.

However, if a food product is already known and widely studied, a systematic review of this food or its functional substance(s), preferably by meta-analysis, may be acceptable. After a careful and rigorous analysis, experts from the FDA or EFSA must reach an evidence-based agreement (consensus) to determine whether or not the food/ingredient claim is supported (Frestedt 2017, Lenssen et al. 2018). For instance, the claim that apple juice is a functional food because it contains (+)-catechins and some anthocyanins, which are well-known protectants of the cardiovascular system, is unsupported. Rather, human RCTs are needed to validate that this matrix reliably modulates a certain physiological function (versus placebo juice) to legally claim functional properties on the food label (Tanemura et al. 2018).

RCTs need significant human and financial resources and must integrate work essential for obtaining precise and reliable results from multidisciplinary areas (e.g., the nutrition, food engineering, pharmacology, and medical sectors) (Granato et al. 2017). Apart from such basic requirements, Brown et al. (2018) mentioned additional technical difficulties that confront the research team. These challenges are found in each of the three distinct phases of a trial: the initial organization of the trial, running the trial, and, finally, the dissemination of the data following successful completion of the trial. Thus, performing clinical trials is not a quick and easy business. Those working in the technological, nutritional, and medical areas need to work closely to deliver results that can be used by scientists and lawmakers as well as the food sector in research and development (Tanemura et al. 2018).

Efficacy and safety tests of new ingredients and potential functional foods must incorporate many epidemiologic principles that are commonly used in the medical and pharmaceutical sectors. Ideally, the test should be carefully planned RCTs and take into consideration the important technical and practical parameters to ensure that obtained information is relevant and leads to reliable and valid conclusions (Brown et al. 2018).

FUTURE PERSPECTIVES: FUNCTIONAL FOOD ERA

Development of Functional Foods for Cardiovascular Function

According to the World Health Organization (WHO 2017), CVDs are disorders of the heart and blood vessels and mainly include coronary heart disease, cerebrovascular disease (stroke), rheumatic heart disease, peripheral vascular disease, heart failure, cardiomyopathies, and hypertension. Every year, 17 million people die globally of CVD, particularly from heart attacks and strokes, representing approximately 80% of CVD deaths and approximately 32% of all global deaths. Although heart attacks and strokes are major killers in all parts of the world, 80% of premature deaths from these causes could be prevented by controlling the main risk factors: tobacco consumption, unhealthy/unbalanced dieting (including the excessive consumption of ethanol), and lack of physical activity (WHO 2017).

A balanced and healthy diet, regular physical activity, moderate consumption of alcohol, and smoking abstinence are the classic approaches to preventing CVDs and remaining at low risk for inflammatory-type diseases. In practice, approximately 23% of the world population suffers from metabolic syndrome, a serious health condition composed of at least three of the following five health risk factors: obesity, dyslipidemia, hypertension, hyperglycemia, or diabetes (Am. Heart Assoc. 2016). Metabolic syndrome places the world population at higher risk for diseases and morbidities that are related to fatty buildups in artery walls (atherosclerosis). The main causes of metabolic syndrome are overweight and obesity, physical inactivity, genetic factors, and older age. However, it is not uncommon that in young adults (and even some youngsters), inappropriate eating habits and lifestyle can induce the onset of metabolic syndrome (Mohamed 2014).

Opportunities to formulate food products that can deliver specific health benefits regarding CVDs and fulfill basic nutritional requirements (conventional food) have been pursued over the past two decades (Ejike et al. 2017, Kurtz et al. 2018). Evidence is mounting that greater consumption of potentially functional foods can significantly reduce morbidity/mortality associated with CVDs by modulating specific biomarkers (Bitok & Sabaté 2018, Fedacko et al. 2019). In this interdisciplinary view, considerable medical and scientific interest was dedicated to the identification of foods with demonstrated in vivo (humans) functional effects that can help decrease abnormalities and onset of CVDs.

The development of processed foods with low sodium content is a good strategy to control salt-induced hypertension in humans (Davis 2019). These foods are classified as foods for special needs and cannot be categorized as functional. New ingredients have emerged as potentially functional for CVDs, such as bioactive peptides obtained from various origins.

Peptides are small compounds, comprising 2–20 amino acids, that have been produced for possible food development (Gallego et al. 2018). For instance, bioactive peptides from microalgae were tested and showed antioxidant and antihypertensive properties (Ejike et al. 2017). Similarly, peptides from hydrolyzed brewer's yeast possess antioxidants and angiotensin-I converting enzyme (ACE-I) as shown in vitro and in vivo (Amorim et al. 2019). Peptides produced during milk fermentation with probiotic microorganisms displayed antihypertensive effects (normalization of blood pressure) in spontaneously hypertensive rats (Ahtesh et al. 2018). Peptides from cowpea displayed antioxidant activity and inhibited cholesterol synthesis and cholesterol solubilization into micelles in vitro (Marques et al. 2015).

According to Arnoldi et al. (2019), the main critical steps for the identification of new functional peptides are the hydrolysis, purification, and separation of peptides that are tested with the target food matrix. To ensure safety, initial in vitro and in vivo screening tests (chemical and cell-based) are needed. Recommendations for some specific functionalities of purified fractions and/or isolated peptides (e.g., inhibition of ACE-I; antioxidant activity) include the correct identification of chemical structure together with clinical trials for the validation of the biological activities (preferably multicentric RCT).

A good example is Montoro-García et al.'s (2017) RCT, which followed 40 healthy Spanish individuals (with untreated high–normal blood pressure) to assess the functional effects of a dry-cured ham rich in bioactive peptides. Individuals received either dry-cured ham (80 g/day for one month) or cooked, uncured ham (negative control). The intake of dry-cured ham decreased the total cholesterol, fasting glucose, LDL-C, and triacylglycerol levels. No statistical difference

($p > 0.05$) was observed for HDL cholesterol (HDL-C), triacylglycerol/HDL, and LDL/HDL index. This study showed that a functional product can be developed to replace the consumption of peptides via pills with functional foods as part of a balanced diet.

Because most people do not consume enough fruits and vegetables in their diet, the use of isolated chemical compounds, commonly called nutraceuticals, added in capsules and tablets has emerged. Classical studies still focus on the evidence that such chemical compounds isolated from food sources present some functional properties, so they may reduce the risks of CVDs by modulating cardiac, endothelial, and/or vascular functions (Mak et al. 2018). Among these compounds, carotenoids are the most known and used nutraceuticals (Yeung et al. 2018).

Lycopene consumed up to 30 mg/day for up to 60 days was shown to reduce total cholesterol, triacylglycerols, Apo-B, and LDL-C levels and elevate HDL-C and Apo A1 levels and the activity of LDL receptors (Costa-Rodrigues et al. 2018, Kulczyński et al. 2017). Astaxanthin doses of up to 20 mg/day for up to 4 months decreased the total cholesterol, LDL, and Apo B levels in overweight patients (Choi et al. 2011). Nutraceutical astaxanthin administration in dosages of 0, 6, and 12 mg/day for 8 weeks versus placebo presented lipid-modulating activity, antioxidant, and anti-inflammatory effects in type-2 diabetes while decreasing total cholesterol, triacylglycerol, IL-6, TNF-α, and LDL levels (Chan et al. 2019).

β-Carotene inhibited LDL-C oxidation in a concentration-dependent manner (2.5, 12.5, and 25 mg/L) during an in vitro cell–based protocol (Carpenter et al. 1997). However, an RCT with type-2 diabetics showed that a mixture of palm carotenoids (21 mg/day) administered for eight weeks had no effects on vascular function or CVD risk factors (Stonehouse et al. 2016). Bacchetti et al. (2019) analyzed the dietary intake of carotenoids and total antioxidant capacity (TAC) of healthy subjects ($n = 83$; 40 ± 10 years) for 15 days using a food frequency questionnaire and measured the plasma levels of β-carotene, TAC, lipid hydroperoxides, and oxidized LDL (ox-LDL)-C. Here, it is important to note that the uptake of ox-LDL-C by macrophages inside the arterial wall is a crucial step for the development of atherosclerotic disease (Zuliani et al. 2013). Therefore, any food or isolated compound that tends to decrease the ox-LDL in humans may be important in decreasing the incidence of CVDs. The results showed significant correlations between the individual ox-LDL and β-carotene ($r = -0.41$, $p \leq 0.01$), β-carotene and TAC in plasma ($r = 0.34$, $p \leq 0.05$), and plasma hydroperoxides and TAC ($r = -0.42$, $p \leq 0.05$) or plasma hydroperoxides with β-carotene ($r = -0.37$, $p \leq 0.05$).

Another cross-sectional study was performed among non-overweight Japanese ($n = 951$; 30–79 years) and looked at associated dietary patterns and risk factors for CVDs (Higuchi et al. 2015). The authors observed that serum β-carotene levels were inversely correlated with smoking status, insulin resistance, and low insulin sensitivity. Indeed, β-carotene is a carotenoid with recognized in vivo antioxidant and anti-inflammatory activities; thus, it can decrease oxygen/nitrogen reactive species that cause insulin resistance and pancreatic β-cell dysfunction (Facchini et al. 2000). The consumption of green/yellow vegetables, dairy foods, and fruits were the main food groups linked to the higher serum β-carotene levels. These results showed that carotenoids not only increased the TAC of plasma but also modulated lipid metabolism and thus are useful for decreasing the risks of CVDs.

TECHNOLOGICAL ASPECTS: EXTRACTION OF RAW MATERIALS FOR FUNCTIONAL FOOD PRODUCTION

As mentioned above, one of the main raw materials for functional food production is the biologically active compounds, which are chemically diverse and extracted from various sources. Accordingly, it is not surprising that numerous extraction technologies employed for recovering bioactive compounds generally fall into one of two main categories: conventional extractions and, less frequently used in industry, innovative alternatives. Some of these alternative technologies are called novel or emerging, which might be a misleading label because many of them have been known for quite some time and are commonly used in various fields other than food production (e.g., plasma technology in medicine).

Appropriate extraction technology for each type of target compound should be employed. Other than conventional technologies, the most commonly applied extraction technologies include microwave-assisted extraction, ultrasound-assisted extraction, high-pressure-assisted extraction, high-voltage electric discharge–assisted extraction, pulsed electric field–assisted extraction, and supercritical fluid extraction (Poojary et al. 2017). No matter the technology used, policy makers, consumers, and industry strongly favor functional food production using green concepts, which are sensitive to environmental concerns and engineer safe and high-quality, environmentally friendly food products (Chemat et al. 2015). Details about the appropriateness of each technology for particular target compounds can be found elsewhere (Putnik et al. 2018b).

Even though conventional extraction is a widely applied technology, it is not usually sustainable, as it comes with the problem of toxic waste disposal. Also, their thermal treatments tend to denature certain portions of unstable, but valuable, compounds. In contrast, the abovementioned alternatives to conventional extraction are faster and sustainable, selective, and thermally sensitive; however, on the downside, they are less tested for industrial scale-up and have higher initial implementation costs, making them less favored by industry. To tackle this problem, governmental grant donors provide funds for the development and testing of innovative solutions for the industry. One good example is the 3D-SustJuice project (hurdle technology and 3D printing for sustainable fruit juice processing and preservation) funded by the Croatian Science Foundation. The 3D-SustJuice project employs innovative and sustainable technology to develop, implement, and promote the use of safer and more environmentally friendly food manufacturing.

Aside from having miscellaneous sources of raw materials, one of the main challenges is to define the most appropriate extraction technology. One issue to be overcome is the objective comparison of different technologies that employ different sources of energy and other engineering aspects. For instance, conventional extraction technologies (e.g., solid–liquid extraction) are affordable but time-consuming (i.e., batch-based process), whereas novel electrotechnologies are faster (e.g., continuous processes) but with lower yield. Statistical optimization studies should be conducted in detail to change this reality.

The current research offers few unbiased comparisons of diverse multiple extraction technologies in which the influence of each parameter can be clearly singled out. Ideally, an objective comparison should be based on the same raw material that accounts for climate, chemotype, and harvesting effects. Second, regardless of the extraction type, there should be some objective way to evaluate the usefulness of dissimilar extraction technologies. Recently, the use of extraction rate to compare different extraction technologies was proposed (Putnik et al. 2018a). Putnik et al. (2018a) compared the milligrams of a target compound in a gram of a dry matter that is extracted in one minute of high hydrostatic pressure extraction. Essentially, this represents the extraction rate, obtained via liquid chromatography, of a given compound. In other words, extraction rate, quantified as velocity of extraction, can be applied to most of the available extraction technologies or those that contain the two most common parameters, extraction time and amount of extracted compound. Similar approaches can provide other relevant rates as objective sources of variation, similar to heating or pressurizing rates, to valorize their usefulness in the extraction of relevant compounds.

Mathematically speaking, associating extraction rate data with those for energy balance can be a useful foundation for estimating resource cost–benefit for extraction of bioactive compounds.

This and other similar concepts should fill the gap in the literature and provide industry with useful tools for optimizing their production. After comparing the extractions, the best alternative should be complemented with statistical optimization of the extraction parameters (e.g., solvent type, particle size, vegetal-to-solvent ratio, time and temperature of extraction, pressure) for the most cost-effective production with the best-quality extracts. For this particular step, authors are referred to Croarkin (2013).

COMMENTS AND FUTURE PROSPECTS

Functional foods, beverages, and ingredients will play a decisive role in human nutrition as long as the concept of functional foods is widespread in the general population. Because of financial burdens, governments worldwide should incentivize the establishment of companies that are devoted to the research and development of foods that can actively have potentially positive effects on human health beyond basic nutrition. Food scientists and technologists should bear in mind that functional foods require in vitro, in vivo (animals), and clinical trials to support any health claims. Without these prerequisites, the developed food is only nutritious rather than functional. Food scientists should associate with professionals in other fields to gain a multidisciplinary view of foods and study their impacts on human metabolism. A strong alliance between science, technology, and health is the best way to understand and create functional foods.

Extracting technologies should be used and experimental conditions should be optimized to increase the yield and chemical stability of these chemical compounds. New research focusing on the application of natural extracts in different food matrices and the impact on sensory, physicochemical, rheological, and functional properties should be studied in detail. Overall, we still have a long way to go to understand the relationships between functional chemical compounds, and their dosage, safety, stability, delivery systems, and price. In fact, considering the current scientific advancements in human nutrition and food science, the functional food market must still be explored from the technologic and marketing standpoints.

DISCLOSURE STATEMENT

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