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Current and Emerging Trends in the Formulation and Manufacture of Nutraceuticals and Functional Food Products

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1.1 Introduction

In the last few decades, emphases on the role of foods have shifted from substances consumed merely to quell hunger or to provide needed nutrients for normal cellular function to substances that can potentially promote health and wellness and, particularly, reduce risk of disease. These foods are frequently referred to as *nutraceuticals* and/or *functional foods* with various reported bioactive functions (e.g., immunomodulators, antihypertensives, osteoprotectives, hypocholesterolemics, antioxidatives, and antimicrobials). Nutraceuticals and/or functional foods are a fast-growing, multi-billion-dollar global industry that has been expanding annually. Strong market growths of these foods confirm their perceived nutritional benefits and, in some cases, provide a surrogate substantiation of their health claims. It also provides evidence of increasing product innovations, consumer acceptance of healthy-living lifestyles through nutrition, and a growing shift from pharmaceutically derived supplements. Consumers are interested in preventing

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and/or slowing the progression of illness and disability before they become irreversible and costly to quality of life. In response to this demand, food companies are developing technologies for processing health and wellness products that will improve the efficacy of these products, maximize the potential benefits to consumers, and be cost-effective for the industry's survival in a competitive marketplace.

1.2 Overview, Classification, and Benefits of Nutraceuticals and Functional Foods

There is no universal definition of nutraceuticals and/or functional foods as it varies across countries and markets. All foods are generally functional because they provide nutrients and energy to sustain growth and support vital cellular processes. Functional foods, however, are generally considered to go beyond the provision of basic nutrients to potentially offer additional benefits such as reducing the risk of disease and/or promoting optimal health to the consumer (Hasler 2002). A study presented at the annual meeting of the American Institute for Cancer Research, in Bethesda (Maryland, United States) on November 7, 2013, showed a correlation between poor diets (high in sugar and saturated fats) and the risk of early death caused by inflammation-related health conditions (gastrointestinal [GI] tract cancers – i.e., cancers of the esophagus, stomach, colon, and rectum). The study sample included 10,500 people who were followed from 1987 through 2003 (The Weekly 2013). Of the 259 participants that had died at the end of the study period, 30 had died from GI tract cancers. The study showed that the participants who lived on poor diets were four times as likely to die from GI tract cancers as a result of poor diets that cause inflammation than those participants who consumed plant-based diets purported to be anti-inflammatory to GI tracts.

According to Health Canada (1998), the governmental authority that oversees the approval of food health claims in Canada, a functional food "is similar in appearance to, or may be, a conventional food that is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions, i.e. they contain bioactive compounds." The Institute of Medicine's Food and Nutrition Board defines functional foods as "any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains." Other definitions of functional food are listed in Table 1.1. Health Canada (1998) further defines a nutraceutical as a "product isolated or purified from foods that is generally sold in medicinal forms not usually associated with foods. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease." Zeisel (1999) deduced the definition of nutraceuticals from the description of dietary supplements ("ingredients extracted from foods,

Table 1.1 Some definitions of functional foods

Organization	Definition
Academy of Nutrition and Dietetics	"Whole foods along with fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis at effective levels."
International Food Information Council	"Foods or dietary components that may provide a health benefit beyond basic nutrition and may play a role in reducing or minimizing the risk of certain diseases and other health conditions."
Institute of Food Technologists	"Foods and food components that provide a health benefit beyond basic nutrition (for the intended population)."
International Life Sciences Institute	"Foods that by virtue of the presence of physiologically active food components provide health benefits beyond basic nutrition."
European Commission	"A food that beneficially affects one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. It is part of a normal food pattern. It is not a pill, a capsule or any form of dietary supplement."
Japanese Ministry of Health, Labour, and Welfare	"FOSHU [Food for specified health uses] refers to foods containing ingredient with functions for health and officially approved to claim its physiological effects on the human body. FOSHU is intended to be consumed for the maintenance/promotion of health or special health uses by people who wish to control health conditions, including blood pressure or blood cholesterol."

Source: Academy of Nutrition and Dietetics 2013. Reproduced with permission of Elsevier.

herbs, and plants that are taken, without further modification outside of foods, for their presumed health-enhancing benefits intended to supplement the diet, that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical in the form of a capsule, powder, softgel, or gelcap, and not represented as a conventional food or as a sole item of a meal or the diet") as a "diet supplement that delivers a concentrated form of a biologically active component of food in a non-food matrix in order to enhance health."

As Table 1.1 indicates, the definition of a functional food depends on the demography and the designated regulatory authority involved. The vast array of different ingredients used in the formulation of functional foods helps to explain the endless options and combinations available in the marketplace. A casual observation in any supermarket will confirm the multitude of different categories of products available in this sub-sector including solid foods, beverages, and supplements, which continue to expand on a daily basis. Over 5,500 new types of these products have been introduced to the Japanese market since 1990, the birthplace of functional foods (Siró et al. 2008), and

537 products valued at US$6.3 billion have been granted FOSHU (Foods for Specific Health Use) status since 2005 (Hartmann and Meisel 2007).

The American Dietetic Association expands the definition by categorizing functional foods into four groups. These are conventional, modified, medical, and foods for special dietary use. Conventional foods include whole foods such as garlic, nuts, whole grains, oily fish, and tomatoes, which contain bioactive chemicals and polyunsaturated fatty acids (PUFAs). For instance, oatmeal is considered a functional food because it naturally contains soluble fiber that can help lower cholesterol levels. Modified foods are those that have been enriched, enhanced, or fortified to have or increase health benefits by adding bioactive substances such as phytochemicals or other antioxidants. Such foods include omega-3 (or ω-3) enriched eggs, yoghurts with live beneficial bacterial cultures, calcium-fortified orange juice, folate-enriched bread, and energy bars. Medical foods are those that serve specific medical purposes and those for dietary use, including products such as lactose-free milk and gluten-free breads. Some of these distinctions provide another basis for classifying functional foods, as shown in Table 1.2.

With increasing incidence of cardiovascular disease (CVD) – for example, coronary heart disease (CHD), which can result in heart attacks; and cerebrovascular disease, which can result in stroke and high blood pressure (hypertension) – it is estimated that 23.6 million people worldwide could die from heart disease and stroke by 2030 (WHO 2013). A growing body of literature on the role of diet on health shows that risk factors cumulating from unhealthy dietary lifestyle, obesity, high blood pressure, diabetes, and raised lipids can lead to high incidence of CVD. Similarly, oxidative stress and inflammation have been linked to the initiation and propagation of many diseases including hypertension and CVD. Despite the popularity of pharmacological interventions to disease and ill health, some drugs may have serious side effects, and some treatments may be unsuccessful. As a result, many consumers have turned to functional foods with bioactive components such as lycopene, conjugated linoleic acid (CLA), omega-3 fatty acids (FAs), and fiber, which are reported to play a role in the treatment and prevention of chronic and metabolic diseases such as obesity, diabetes, cancer, arthritis, and CVD (Paiva and Russell 1999; Gibson 2004; Krinsky and Johnson 2005; Spence 2006; Boots et al. 2008; Siró et al. 2008; Patisaul and Jefferson 2010; Plaza et al. 2010; Escobar et al. 2012; Karppi et al. 2012; Harms-Ringdahl et al. 2012; Xaplanteris et al. 2012; Houston 2013; Jacques et al. 2013). Indeed, the use of functional foods may in some instances offer safe and effective alternatives to prevent, mitigate, and/or treat some of these conditions. Tables 1.3 and 1.4 provide a list of some sources and components of foods and food ingredients reported to have potential health benefits.

Whereas there are no specific regulations regarding functional foods in most countries, standards have been set in other jurisdictions (e.g., the

Table 1.2 Categories of functional foods

Categories	Definition	Examples
Basic/whole/ unaltered products	Foods naturally containing increased content of nutrients or components	• Carrots (containing the natural level of the antioxidant β-carotene)
Fortified products	Foods with higher contents of existing nutrients through the addition of extra quantities of those nutrients	• Fruit juices with vitamin C
Enriched or supplemented products	Foods with added new nutrients or components not normally found in a particular food	• Margarine with plant sterol ester, probiotics, prebiotics • Yogurts with probiotics • Calcium-enriched fruit juice • Muffins with β-glucan • Drinks with herb blends
Altered products	Foods from which a deleterious component has been removed, reduced, or replaced with another substance with beneficial effects	• Fibers as fat releasers in meat or ice cream products
Enhanced products	Foods that have been enhanced to have more of a functional component (via traditional breeding, special livestock feeding or genetic engineering)	• Tomatoes with higher levels of lycopene • Oat bran with higher levels of beta glucan • Eggs with increased ω-3 achieved by altered chicken feed
Processed foods	Foods that have been processed to contain their natural levels of functional components	• Oat bran cereal (containing the natural level of β-glucan)

Source: Spence 2006. Reproduced with permission of Elsevier.

United States – Food and Drug Administration [FDA]; the European Union – European Food Safety Authority [EFSA]; and Canada – Health Canada) on how a product can be marketed (e.g., as a food additive, conventional food, or dietary supplement) and on the types of nutrient or health claims that can be made. The processes leading to accepting the evidence of health claims can be complex and rigorous due to the stringent rules and regulations set out by these bodies to protect consumers from false claims and especially to ascertain the safe use of these products. Marketers may use permitted labeling to highlight and communicate the beneficial

Table 1.3 Benefits of nutraceuticals and functional foods

Component	Source	Potential benefits
Carotenoids		
Alpha-carotene/ β-carotene	Carrots, fruits, vegetables	Neutralizes free radicals, which may cause damage to cells
Lutein	Green vegetables	Reduces the risk of macular degeneration
Lycopene	Tomato products (ketchup, sauces)	Reduces the risk of prostate cancer
Dietary Fiber		
Insoluble fiber	Wheat bran	Reduces risk of breast or colon cancer
Beta-glucan	Oats, barley	Reduces risk of cardiovascular disease; protects against heart disease and some cancers; lowers LDL and total cholesterol
Soluble fiber	Psyllium	Reduces risk of cardiovascular disease; protects against heart disease and some cancers; lowers LDL and total cholesterol
Fatty Acids		
Long-chain omega-3 FAs-DHA/EPA	Salmon and other fish oils	Reduces risk of cardiovascular disease; improves mental and visual functions
Conjugated linoleic acid (CLA)	Cheese, meat products	Improves body composition; decreases risk of certain cancers
Phenolics		
Anthocyanidins	Fruits	Neutralizes free radicals; reduces risk of cancer
Catechins	Tea	Neutralizes free radicals; reduces risk of cancer
Flavonones	Citrus	Neutralizes free radicals; reduces risk of cancer
Flavones	Fruits, vegetables	Neutralizes free radicals; reduces risk of cancer
Lignans	Flax, rye, vegetables	Prevention of cancer, renal failure
Tannins (proantho-cyanidins)	Cranberries, cranberry products, cocoa, chocolate	Improves urinary tract health; reduces risk of CVD
Plant Sterols		
Stanol esters	Corn, soy, wheat, wood oils	Lowers blood cholesterol levels by inhibiting cholesterol absorption
Prebiotics/Probiotics		
Fructo-oligosaccharides (FOS)	Jerusalem artichokes, shallots, onion powder	Improves quality of intestinal microflora and GI health
Lactobacillus	Yogurt, other dairy	Improves quality of intestinal microflora and GI health
Soy Phytoestrogens		
Isoflavones: Daidzein Genistein	Soybeans and soy-based foods	Helps alleviate menopausal symptoms such as hot flashes; protects against heart disease and some cancers; lowers LDL and total cholesterol

Source: AAFC 2012. What are functional foods and nutraceuticals? http://www.agr.gc.ca/eng/industry-markets-and-trade/statistics-and-market-information/by-product-sector/functional-foods-and-natural-health-products/functional-foods-and-nutraceuticals-canadian-industry/what-are-functional-foods-and-nutraceuticals-/?id=1171305207040.

Table 1.4 Sources of nutraceuticals and functional foods

Categories	Examples
Products extracted or purified from plants	• Beta-glucan (e.g., from oats) • Antioxidants (e.g., from blueberries) • Isoflavones (e.g., from soy) • Carotenoids (e.g., from carrots) • Lutein (e.g., from wheat) • Sterols (e.g., from wood pulp) • Essential FAs (e.g., from vegetable oil such as flax oil) • Soluble fiber (e.g., from fenugreek)
Products ground, dried, powdered, and pressed from plant materials	• Echinacea • Fenugreek • Valerian • Ginseng
Products produced, extracted, or purified from animals and microorganisms	• Omega-3 from fish oils • Essential FAs • Enzymes • Carotenoids (accumulated from the diet) • Probiotics
Products produced from marine sources	• Glucosamine • Chitosan • Fish oils

Source: AAFC 2012. What are functional foods and nutraceuticals? http://www.agr.gc.ca/eng/industry-markets-and-trade/statistics-and-market-information/by-product-sector/functional-foods-and-natural-health-products/functional-foods-and-nutraceuticals-canadian-industry/what-are-functional-foods-and-nutraceuticals-/?id=1171305207040.

health properties of their products by relying on consumer awareness and understanding of such claims.

Bioactive components in functional food and nutraceutical products are naturally found in plants, animals, bacteria, fungi, and microalgae, and their primary and secondary metabolites (Tables 1.3 and 1.4). When health benefits are proven, these natural food sources could serve as natural substitutes for synthetic pharmaceutical products for intervention purposes and to prevent potential adverse effects from the use of some pharmaceutical drugs.

Primary metabolites, which include amino acids, nucleic acids, and FAs, are required for normal healthy growth and development, while secondary metabolites, such as carotenoids, terpenoids, and alkaloids, are synthesized in specialized cell types under specific conditions. Apart from their role when ingested live in diary and non-dairy products to improve the quality of intestinal microflora and GI health (probiotic effect), some generally recognized as safe (GRAS) microorganisms may be indirect sources of high-yielding nutraceutical and functional ingredients (e.g., CLA, bioactive peptides, and vitamins liberated during fermentation). Probiotic microorganisms may further provide useful beneficial effects such as the prevention of food intolerance and/or sensitivity, and they may further decrease food allergies by degrading and decreasing allergenic epitopes required to elicit an inflammatory response (Gibson 2004; Champagne et al. 2005; Di Criscio et al. 2010; Vasudha and Mishra 2013).

In addition to the potential health benefits of nutraceuticals and functional foods, their production may also support economic development, as well as offer a way for some producers to diversify their agricultural and marine-based product offerings (Siró et al. 2008). The global nutraceuticals market is predicted to reach nearly US$207 billion by 2016, with a projected compound annual growth rate (CAGR) of 6.5% between 2011 and 2016 (BCC Research, 2011a). The functional beverages market sub-sector is experiencing the highest growth and is expected to reach approximately US$87 billion by 2016, followed by US$67 billion from food and around US$51 billion from the supplement sectors at CAGRs of 8.8%, 6.4%, and 4.8%, respectively, during the same 5-year period (i.e., 2011–2016).

1.2.1 Characteristics and Properties of Selected Bioactive Ingredients

Bioactive proteins and peptides, PUFAs, fibers, phenolics, probiotics, and prebiotics are some of the main active ingredients (Tables 1.3 and 1.4) contained in functional food and nutraceutical formulations. These compounds purportedly confer diverse health benefits and are believed to interfere with the pathogenesis of several diseases, including but not limited to GI inflammation, carcinogenesis, hypertension, CVD, developmental disorders, brain and cognitive disabilities, and aging (Gibson 2004; Phelan et al. 2009; Patisaul and Jefferson 2010; Jacques et al. 2013; Théolier et al. 2013). Most studies to date on these active ingredients are complex, confusing, controversial, and offer no clear consensus on the helpfulness or harmfulness (if any) of some of these ingredients, or if the potential benefits might be contraindicated for some groups of individuals based on age, sex, health status, and even the presence or absence of risk factors (Setchell et al. 2003; Bar-El and Reifen 2010; Patisaul and Jefferson 2010; Cederroth et al. 2012). In addition to the main active ingredient in a particular functional food or nutraceutical, synergistic interactions with other bioactive compounds present may contribute to their health effects (Spence 2006; Kris-Etherton et al. 2008; Kay et al. 2010; Ros 2010; Bao et al. 2013). As an example, a recent report from two prospective cohort studies involving nearly 120,000 people over 30 years (76,464 women in the Nurses' Health Study [1980–2010] and 42,498 men in the Health Professionals Follow-up Study [1986–2010]) confirmed the beneficial effects of consuming nuts. The report showed inverse associations between nut consumption and the risk of major chronic diseases, including CVD, type-2 diabetes, weight gain, and total and cause-specific mortality (Bao et al. 2013). The results were similar for all nuts, that is, nuts that grow underneath the earth, such as peanuts (groundnuts, a legume), and nuts that grow on trees, such as walnuts, hazelnuts, almonds, Brazil nuts, cashews, macadamias, pecans, pistachios, and pine nuts. In addition to high amounts of fats, mostly unsaturated FAs, nuts are also good sources of fiber (4–11 g/100 g), protein (7.9–38.1 g/100 g), PUFAs (1.5–47.2 g/100 g), phenolic compounds, and phytosterols (72–220 μg/100 g), and they contain traces of vitamins, minerals, as well as other bioactive substances (Table 1.5). In view of the wide-ranging nutrients, phytochemicals, and salutary health effects, most nuts hold an FDA-qualified health claim, such as follows: “eating 43 g (1.5 oz) per day of most nuts [such as name of specific nut] as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease” (FDA 2003).

Bioavailability, which refers to the body’s ability to fully or partially absorb ingested bioactives, is crucial to the ability to exert beneficial effects. The bioavailability and efficacy of active ingredients in nutraceuticals and functional foods are important considerations in their formulation (Charalampopoulos et al. 2002; Havrlentová et al. 2011). For instance, the bioavailability of active ingredients may be altered depending on the specific compound or isomer formed during formulation (Kurzer and Xu 1997; Rao et al. 1998; Benakmoum et al. 2008; Xaplanteri et al. 2012). Additionally, the fate, characteristics, and behavior of bioactive components subjected to varying conditions of processing and storage (e.g., high or low temperature) and their inherent properties (e.g., high heat stability or lability, pH tolerance, shear stress tolerance) and the possible alterations that could occur following ingestion, digestion, and absorption may variously affect their potential health benefits. Knowledge of these properties and susceptibilities is important to mitigate any adverse effects during processing and storage. Other factors that need to be considered include appropriate dosage (i.e., acute or large single exposures vs. continuous small exposures), mode of delivery (e.g., oral or topical), possible interactions, toxicology, fate of carrier materials, and short- and long-term side effects based on age, sex, and health status (Paiva and Russell 1999; Setchell et al. 2003; Patisaul and Jefferson 2010; Grooms et al. 2013).

Functional foods and nutraceuticals may also contain inert components or excipients as part of the formulation. While the active ingredients are the components that confer the actual benefit, the inert components are primarily the carriers that help deliver the active ingredients to the target organ (Brownlie 2007; Hébrard et al. 2010; Kuang et al. 2010; Wichchukit et al. 2013). These inert ingredients may enhance the utility of the product or provide benefits such as disguising a bad taste or flavor (e.g., tablets coated with

Table 1.5 Nutrient composition of some raw nuts (per 100 g)

Nuts	Energy (KJ)	Fats (g)	SFA (g)	MUFA (g)	PUFA (g)	LA (g)	ALA (g)	Protein (g)	Fiber (g)	Folate (μg)	PS (mg)	Ca (mg)	Mg (mg)	K (mg)	Na (mg)
Almonds	2418	50.6	3.9	32.2	12.2	12.2	0.00	21.3	8.8	29	120	248	275	728	1
Brazil nuts (dried)	2743	66.4	15.1	24.5	20.6	20.5	0.05	14.3	7.5	22	NR	160	376	659	3
Cashews	2314	46.4	9.2	27.3	7.8	7.7	0.15	18.2	5.9	25	158	37	292	660	12
Hazelnuts	2629	60.8	4.5	45.7	7.9	7.8	0.09	15.0	10.4	113	96	114	163	680	0
Macadamia nuts	3004	75.8	12.1	58.9	1.5	1.3	0.21	7.9	6.0	11	11	85	130	368	5
Peanuts	2220	49.2	6.8	24.4	15.6	15.6	0.00	25.8	8.5	145	220	92	168	705	18
Pecans	2889	72.0	6.2	40.8	21.6	20.6	1.00	9.2	8.4	22	102	70	121	410	0
Pine nuts (dried)	2816	68.4	4.9	18.8	34.1	33.2	0.16	13.7	3.7	34	141	16	251	597	2
Pistachios	2332	44.4	5.4	23.3	13.5	13.2	0.25	20.6	9.0	51	214	107	121	1025	1
Walnuts, English	2738	65.2	6.1	8.9	47.2	38.1	9.08	15.2	6.4	98	72	98	158	441	2

Source: Ros 2010.

sugar or wax) or making the tablet resistant to gastric acid such that it only disintegrates at the appropriate site as a result of enzyme action or alkaline pH (Gaudette and Pickering 2013; Jantzen et al. 2013; Nesterenko et al. 2013). Other examples of inert materials used in food formulation include surfactants, stabilizers (gums), emulsifiers, and colorants.

Brief reviews on specific bioactive components are provided in the following text. For more detailed information on the structure, distribution, metabolism, bioavailability, possible mechanism, and potential health benefits of various bioactive components, readers are referred to the following publications: bioactive proteins and peptides (Duranti 2006; Möller et al. 2008; Chatterton et al. 2013; Théolier et al. 2013), fiber (Gibson 2004; Havrlentová et al. 2011), PUFAs (Simopoulos 2002a, 2002b; Strobel et al. 2012; Ammann et al. 2013; AHA 2013; Brasky et al. 2013; Janczyk et al. 2013; van den Elsen et al. 2013), phytochemicals (De Pascual-Teresa et al. 2010; Patisaul and Jefferson 2010; Xaplanteris et al. 2012; Cederroth et al. 2012; Jacques et al. 2013; Vitale et al. 2013), and prebiotics and probiotics (FAO 2001; Gibson 2004; Champagne et al. 2005; Di Criscio et al. 2010; Hébrard et al. 2010; Śliżewska et al. 2012; Al-Sheraji et al. 2013).

1.2.2 Bioactive Proteins and Peptides

In addition to the dispensable and indispensable amino acids that proteins provide for structural and biological functions to sustain life, their potential health benefits beyond basic nutrition have been reported (Duranti 2006; Möller et al. 2008; Phelan et al. 2009; Mochida et al. 2010; Barbana and Boye 2010; Chou et al. 2012; Rui et al. 2012; Chatterton et al. 2013; Théolier et al. 2013). Plants (e.g., soybean, wheat, and other cereal grains and legumes) and animals (e.g., milk, eggs, other dairy products, meat, and fish) are important food sources of protein with encrypted biological activities (Lam and Lumen 2003; Hartmann and Meisel 2007; Phelan et al. 2009; Barbana and Boye 2010). Table 1.6 shows some plant protein sources and their estimated protein content, which can vary markedly.

Many food proteins have been used as precursors of bioactive peptides, which may be released upon hydrolysis during GI digestion by digestive or microbial enzymes, or by fermentation or ripening during food processing with isolated or microbial enzymes. These bioactive peptides may exert a wide variety of beneficial biological functions in the body (Table 1.7; Phelan et al. 2009), including, for example, regulating serum cholesterol and hypocholesterolemic effect through binding of bile acids (which are synthesized from cholesterol in the liver) (Kahlon and Woodruff 2002; Barbana et al. 2011). Eliminating bile acids may increase cholesterol metabolism and help reduce cholesterol levels in the blood. Bioactive hydrolysates and peptides may also produce inhibitory effects against angiotensin-I-converting enzyme

Table 1.6 Protein content of common edible legumes

Source	Protein (%)
Soybean	34.3
Peanut	27.6
Pea	24.5
Cowpea	22.0
Chickpea	19.5
Pigeon pea	19.5
Fava bean	24.8
Lupin	39.7
Winged bean	32.8

Source: Adapted from Lam and de Lumen 2003. Reproduced with permission of Elsevier.

Table 1.7 Immunomodulatory, antihypertensive, and osteoprotective proteins and peptides

Protein/Peptide	Effect	Model
Immunomodulatory		
Caseins (and digests)	T-lymphocyte proliferation ↑	Cell culture
	Immunoglobulin secretion ↑	Cell culture
Whey	Lymphocyte blastogenesis ↓	Cell culture
Proline-rich polypeptides (and derivates) from ovine colostrum	B-lymphocyte growth, differentiation ↑, antibody secretion ↑	Cell culture
		Animal culture
Fish protein	IgA-, IL-4-, IL-6-, IL-10-positive cells ↑	Animal culture
Antihypertensive		
α_{s1}- and β-casein	ACE ↓	In vitro
	Hypertension ↓	Animal
γ-Zein	ACE ↓	In vitro
Wheat germ	ACE ↓	In vitro
Hordein (barley)	ACE ↓	In vitro
Bonito	ACE ↓	In vitro
Osteoprotective		
Casein	Absorption of intestinal calcium ↑	Animal
Whey protein	Absorption of intestinal calcium ↑	Animal
Milk basic protein	Bone mineral density ↑	Human
Antilipemic		
Fish protein hydrolysate	mRNA of desaturases ↓, HDL-cholesterol/total cholesterol ↑	Animal
Lupin protein isolate	Total cholesterol ↓, LDL-cholesterol ↓	Animal
α′ subunits of soybean	Plasma cholesterol ↓, triglycerides ↓, VLDL receptor binding ↑	Animal

Source: Möller et al. 2008. Reproduced with permission of Springer.

(ACE) (by inhibiting the conversion of angiotensin I [decapeptide] to the more potent vasoconstrictor angiotensin II [octapeptide] by ACE) with possible blood-pressure-lowering effects (Vermeirssen et al. 2005; Barbana and Boye 2010; Rui et al. 2012). Bioactive hydrolysates and peptides may further possess antimicrobial activity and antioxidant properties that can enhance the body's defense mechanisms. Other bioactive proteins and peptides may produce immunomodulating, opioid, and anti-thrombotic activities, as well as provide positive influence on calcium absorption and dental health by inhibiting plaque-forming bacteria and tooth enamel demineralization (Table 1.6; Möller et al. 2008; Phelan et al. 2009; Chou et al. 2012; Nam et al. 2012; Théolier et al. 2013).

Peptide bioactivity can be affected by the source of protein, chemical composition, degree of hydrolysis, and the type of proteolytic enzyme used (Möller et al. 2008; Phelan et al. 2009; Nam et al. 2012; Théolier et al. 2013). Hydrolyzed proteins show higher digestibility and absorption compared to intact proteins and thus create new sources of functional foods. As sources of free amino acids, these bioactive hydrolysates have been used to potently increase the bioavailability of the building blocks of proteins for synthesis of contractile proteins, managing CVD and diabetes (Blomstrand et al. 2006; Schimomura et al. 2006; Greenfield et al. 2008; Mochida et al. 2010; Clemmensen et al. 2013; Higuchi et al. 2013; Nogiec and Kasif 2013). In sports nutrition, where performance and faster recovery following strenuous exercise are very important, hydrolyzed or predigested protein fractions are highly sought after. Amino acids acting alone or in conjunction with other amino acids have been demonstrated to be more effective in the synthesis of proteins that build muscle mass than intact proteins, as they promote better glucose uptake and synthesis of muscle glycogen, which promotes muscle restoration and recovery before, during, and after exercise (Nogiec and Kasif 2013). Branched-chain amino acids (BCAA) (i.e., leucine, valine, and isoleucine) are particularly useful in protein synthesis, especially after exercise (Blomstrand et al. 2006; Schimomura et al. 2006; Nogiec and Kasif 2013). It has recently been reported that BCAA may provide an immediate energy source needed for protein synthesis due to their preferential oxidization over glucose and FAs (Nogiec and Kasif 2013). Glutamine, however, has been shown not to be as effective in increasing protein synthesis and muscle mass as originally reported (Gleeson 2008; Greenfield et al. 2008); rather, it stimulates the release of glucagon-like peptide 1 (GLP-1), required to augment insulin secretion in obese- and type 2 diabetic individuals, and thereby improve glucose tolerance and clearance (Clemmensen et al. 2013). Amino acid L-arginine is a precursor of the endogenous vasodilator, nitric oxide, and may also play a role in promoting healthy blood pressure levels and vascular function, and in decreasing the risk of various diseases associated with vascular dysfunction (Clemmensen et al. 2013). Proteins are important sources of enzymes (e.g., protease inhibitors that inhibit protein degradation by selectively protecting proteins of interest or blocking the activity of endogenous proteolytic enzymes by reversibly or irreversibly binding to that protease). This may be important in the management of pathogens such as human immunodeficiency viruses, which break up large proteins into smaller peptides, which become precursors for assembling new viral particles (Liu et al. 2012; Koistinen et al. 2014). Although the virus can still replicate in the presence of protease inhibitors, the resulting virions are less able to infect new cells. Examples of proteases found in fruits include bromelain in pineapple (thiol proteinase, EC 3.4.22.4), papain in papaya (cysteine protease, EC 3.4.22.2), and actinidin in kiwi (sulfhydryl proteases, EC 3.4.22.14). These enzymes improve overall health by acting as digestive aids that may also reduce intestinal inflammation (Rutherfurd et al. 2011; Ha et al. 2012; Kaur and Boland 2013).

The high cost of traditional protein sources is leading to more innovation in identifying new protein ingredients. Plant-sourced proteins from legumes, as an example, are attractive alternatives to animal-derived proteins, due to their relatively lower cost, inherent and unique nutritional profile, anti-allergenic properties, and increasingly greater consumer acceptance (Barbana and Boye 2010; Rui et al. 2012). Soybean is an example of a protein source with official FDA acknowledgement of beneficial health effects (Duranti 2006; FDA 2013a). Foods that contain soy protein can carry the approved health claim stating that "25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease."

1.2.3 PUFAs

The role of specific FAs in human health is still highly debated (Gebauer et al. 2011; Tan et al. 2012; AHA 2013; Ammann et al. 2013; Brasky et al. 2013; Janczyk et al. 2013; Roncaglioni et al. 2013; Zheng et al. 2013). The basic functions of fats in structural, membrane, metabolism, and gene expression are widely known. The American Heart Association (AHA 2013) recommends that 25–35% of daily total calories be obtained as fats from oils and fats in foods. PUFAs are FAs with more than a single carbon–carbon double bond. These are an interesting group of FAs, well-studied and extensively investigated for their health benefits (Simopoulos 2002a, 2002b; Strobel et al. 2012; Ammann et al. 2013; Brasky et al. 2013; Janczyk et al. 2013). Examples of their reported beneficial effects include anti-inflammatory, immunomodulatory, cardioprotective, and antiatherosclerotic effects. The low incidence of CVD among Greenland Eskimos has long been known and attributed to a high-fish diet.

Well-known examples of PUFAs are the long-chain ω-3 FAs, which are considered to be essential because they cannot be effectively synthesized by the body due to the low activity of the rate-limiting enzyme

Δ6-desaturase. Mammals also have limited ability and efficiency to convert the shorter-chained ω-3 FAs, such as α-linolenic acid (ALA, 18:3), to the more important long-chain ω-3 PUFAs (LC ω-3 PUFA), eicosapentaenoic acid (EPA; 20:5), and docosahexaenoic acid (DHA, 22:6), and this is also further impaired with aging. Functional foods may compensate for these insufficient endogenous essential FAs needed to cover metabolic requirements. Omega-3 FAs (i.e., ALA, EPA, and DHA), stearidonic acid (STA; 18:4), and ω-6 FAs (i.e., gamma-linolenic acid [GLA] and arachidonic acid [ARA]), as well as conjugated linoleic acid (CLA, 18:2), an isomer of ω-6, have all been identified as functional lipids (Simopoulos 2002a; Strobel et al. 2012). While long-chain ω-3 PUFAs may help reduce inflammation, ω-6 FAs such as GLA and ARA tend to promote inflammation (Simopoulos 2002a, 2002b; Strobel et al. 2012). A lower ratio of ω-3/ω-6 FAs is more desirable, since it reduces the risk and pathogenesis of many diseases, whereas the reverse exerts suppressive effects. Formulated foods containing a mixture of ω-3 and ω-6 FAs are also preferred over a dominance of either one.

Different types of fish – including anchovies, salmon, mackerel, herring, sardines, tuna, and trout, and marine mammals are uniquely rich sources of PUFAs (Table 1.8). The long-chain ω-3 PUFA and total fat content of fish and fish products vary greatly depending on fish species, feeding conditions (wild or farmed), and processing and preparation methods (e.g., fillet, breaded, pre-fried fishes, etc.) (Gebauer et al. 2006; Strobel et al. 2012; Raatz et al. 2013), which is why it is advisable to consume a variety of different fish species and fish products. Regular ingestion of fried fish has been associated with a 32% increased risk for prostate cancer; environmental chemicals such as polychlorinated biphenyls (PCBs), heavy metals, and other toxic chemicals may affect the quality of fish or fish oil and also contribute to prostate cancer (Mullins and Loeb 2012).

Other natural sources of PUFAs include human milk and cultivated marine algae. Omega-6 FAs such as GLA are found in plant-based oils such as evening primrose oil, blackcurrant seed oil, and borage seed oil. Other known sources of PUFAs are avocados, peanut butter, many nuts and seeds (e.g., flaxseeds, chia seeds, walnuts, pumpkin seeds), and the oils of canola (rapeseed), corn, olive, flaxseed, sesame, soybean, and sunflower. Table 1.9 shows the ALA content of selected oils, seeds, and nuts, and the amounts needed to obtain the adequate daily intake levels for men and women.

Several physiological processes affected by PUFAs may account for their perceived benefits (Simopoulos 2002a; Furuhjelm et al. 2009; Janczyk et al. 2013; Roncaglioni et al. 2013). For instance, some beneficial effects on cellular physiology have been attributed to the presence of long-chain ω-3 PUFAs in cardiac and brain membrane phospholipids (especially DHA). PUFAs also serve as precursors for prostaglandins, leukotrienes, and eicosanoids such as resolvins and protectins, which are known for their anti-inflammatory and neuroprotective activities. Other beneficial effects of long-chain PUFAs

Table 1.8 Omega-3 content of fish and seafood (g/100 g)

Fish	Total ω-3	EPA	DPA	DHA
Farmed				
Salmon, Atlantic	2.359	0.862	0.393	1.104
Trout, rainbow	0.824	0.217	0.091	0.516
Catfish, channel	0.089	0.017	0.015	0.057
Wild				
Herring, Pacific	1.830	0.969	0.172	0.689
Salmon, Atlantic	1.723	0.321	0.287	1.115
Herring, Atlantic	1.626	0.709	0.055	0.862
Sardine, Pacific, canned in tomato sauce	1.457	0.532	0.061	0.864
Whitefish, mixed species	1.421	0.317	0.163	0.941
Mackerel, canned	1.334	0.434	0.104	0.796
Salmon, pink, canned	1.166	0.334	0.089	0.743
Sardine, Atlantic, canned in oil	0.982	0.473	0.000	0.509
Tuna, white (Albacore), canned in water	0.880	0.233	0.018	0.629
Bass, striped	0.754	0.169	0.000	0.585
Mollusks, oyster, Pacific	0.708	0.438	0.020	0.250
Trout, rainbow	0.693	0.167	0.106	0.420
Sea bass, mixed species	0.671	0.161	0.076	0.434
Salmon, Chinook, smoked (lox), regular	0.523	0.183	0.073	0.267
Catfish, channel	0.464	0.130	0.100	0.234
Mollusks, mussel, blue	0.463	0.188	0.022	0.253
Cisco	0.405	0.095	0.053	0.257
Pike, walleye	0.349	0.086	0.038	0.225
Crustaceans, crab, blue	0.320	0.170	0.000	0.150
Croaker, Atlantic	0.306	0.123	0.086	0.097
Flatfish (Flounder/Sole)	0.273	0.137	0.028	0.108
Crustaceans, crab, Dungeness	0.237	0.219	0.010	0.008
Tuna, light, canned in water	0.228	0.028	0.004	0.196
Halibut, Atlantic and Pacific	0.210	0.066	0.016	0.128
Cod, Atlantic	0.194	0.064	0.010	0.120
Crustaceans, lobster, northern	0.176	0.102	0.006	0.068
Pollock, Alaska	0.169	0.049	0.004	0.116
Tilapia	0.134	0.005	0.043	0.086
Haddock	0.136	0.042	0.005	0.089
Cod, Pacific	0.134	0.034	0.004	0.096
Mollusks, clams, mixed species	0.114	0.043	0.007	0.064
Mollusks, scallop, mixed species	0.106	0.042	0.003	0.061
Crustaceans, shrimp, mixed species	0.064	0.030	0.003	0.031

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Table 1.9 α-Linolenic acid (ALA) content of selected oils, seeds, and nuts and the amounts needed to obtain recommended adequate daily intake (RDI)

Source of ALA	ALA (g/tbsp)	Amount needed by men to meet RDI of 1.6 g ALA/d (tbsp)	Amount needed by women to meet RDI of 1.1 g ALA/d (tbsp)
Pumpkin seeds	0.051	31.4	21.6
Olive oil	0.103	15.5	10.7
Walnuts, black	0.156	10.3	7.05
Soybean oil	1.231	1.3	0.89
Rapeseed oil	1.302	1.2	0.84
Walnut oil	1.414	1.1	0.78
Flaxseeds	2.350	0.68	0.47
Walnuts, English	2.574	0.62	0.43
Flaxseed oil	7.249	0.22	0.15

Source: Gebauer et al. 2006. Reproduced with permission of American Society for Nutrition.

include lowering plasma triglyceride concentration, improving plasma lipoprotein profile, supporting fetal brain and eye development, cognitive health and maintenance, better performance or preservation of cognitive function in aging persons, improved cardiovascular health, and reduced risk of metabolic-syndrome-related conditions such as obesity and insulin resistance syndrome. Dietary supplementation with long-chain ω-3 PUFAs during pregnancy and in early stages of life may play a critical role in reducing allergic sensitization in children (Furuhjelm et al. 2009; Kremmyda et al. 2011; Noakes et al. 2012; van den Elsen et al. 2013). The role of PUFAs in promotion of the synthesis of inflammatory cytokines and autoimmune diseases such as rheumatoid arthritis and certain cancers has been described (Simopoulos 2002b).

Dietary intake of fish is the most desirable way to increase marine ω-3 PUFA intake, owing to the higher amount of long-chain ω-3 PUFAs in circulation and tissue stores after fish intake compared to fish oil supplements. This suggests a larger uptake from fish than from fish oil supplements, which may be due to differences in physiochemical structure of the lipids and better digestion and absorption of the former. Based on these perceived benefits, various professional groups and health organizations worldwide have made dietary recommendations for EPA and DHA and fish intake to primarily lower triglyceride, and to reduce risk of and treat existing CVD (Gebauer et al. 2006; Lucas et al. 2009). Recommendations also have been made for DHA intake for pregnant women and infants (Table 1.10). Table 1.11 shows the PUFA content of some commonly eaten fish and shellfish in the United States.

Table 1.10 Recommendations for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intake

Organization	Year	Recommendations
UK Committee on Medical Aspects of Food Policy	1994	100–200 mg/d EPA and DHA
Eurodiet	2000	200 mg/d
Apports Nutritionnels Conseillés (France)	2001	450 mg/d (DHA, 110–120)
Health Council of the Netherlands	2001	200 mg/d
American Heart Association/American Heart Association Nutrition Committee (United States)	2002, 2006	Two servings of fatty fish per week for general health (~430–570 mg/d) 1,000 mg/d of ω-3 EPA and DHA for patients with CHD 2,000–4,000 mg/d of ω-3 EPA/DHA for patients with high triglycerides
Food and Nutrition Board of the Institute of Medicine of the National Academies of Science	2002	130–270 mg/d (EPA and DHA can contribute up to 10% of total ω-3 intake and, therefore, up to this percentage can contribute toward the adequate intake of α-LA (1.3–2.7 g/d)
European Society of Cardiology	2003	1,000 mg/d of ω-3 EPA/DHA for patients with CHD
WHO/FAO	2003	400–1,000 (1–2 fish meals/week)
International Society for the Study of Fatty Acids and Lipids Workshop	2004	≥500 mg/d
UK Scientific Advisory Committee on Nutrition	2004	Minimum two fish meals/week (one fatty fish) ~450 mg
National Health and Medical Research Council (Australia)	2005	430 mg/d EPA, DHA, DPA for women 610 mg/d EPA, DHA, DPA for men
Dietitians of Canada	2007	Two fish meals/week (fatty fish), 8 oz cooked fish ~500 mg
European Food Safety Authority	2010	250 mg/d EPA and DHA for adults 250 EPA and DHA mg/d plus 100–200 mg DHA for pregnant/lactating women

Source: Gebauer et al. 2006. Reproduced with permission of American Society for Nutrition.

Table 1.11 Total eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) (and amount needed to get 500 mg), and mercury content cost of commonly eaten fish and shellfish in the United States

Fish	EPA + DHA (mg/serving)	Amount needed to get 500 mg EPA + DHA/d (serving)	Amount needed to get 500 mg EPA + DHA/d (serving/week)	Mean Mercury Concentration (ppm)
Cod	134	307	25.9	0.11
Catfish	151	3.3	23.1	0.05
Haddock	203	2.5	17.5	0.03
Clams	241	2.1	14.7	ND
Shrimp	267	1.9	13.3	ND
Flounder	426	1.2	804	0.05
Pollock	460	1.1	7.7	0.06
Flatfish	498	1	7	0.05
Tuna, canned	733	0.68	4.8	0.12 (light); 0.35 (Albacore)
Salmon	1825	0.27	1.9	0.01

Source: Gebauer et al. 2006. Reproduced with permission of American Society for Nutrition.

EPA and DHA were recently approved for three heart health claims by the EU/ESFA (EFSA 2012; Eur-Lex 2013). The permitted health claims state that "DHA contributes to the maintenance of normal blood triglyceride levels," "DHA and EPA contribute to the maintenance of normal blood pressure," and "DHA and EPA contribute to the maintenance of normal blood triglyceride levels." The main difference between the second and the third claims is a daily intake of 3 g of DHA–EPA in the former and 2 g in the latter. The claim may be used only for food that provides a daily intake of 2 g of DHA in combination with EPA, and also should inform consumers not to exceed a supplemental daily intake of 5 g of EPA and DHA combined per day. All three claims must contain these conditions.

Whereas the overwhelming conclusion is that of a plausible association of long-chain PUFA intake and several health benefits, there are some inconsistencies in reported literature. Previous and recent studies using various analytical assessments, including prospective or retrospective cohort studies, nested case-control, case-cohort assessment, and randomized controlled trials of the perceived effects of PUFAs, have been mixed (Tan et al. 2012; Ammann et al. 2013; Brasky et al. 2013; Galet et al. 2013; Janczyk et al. 2013; Roncaglioni et al. 2013; Zheng et al. 2013). A recent study involving 834 men found increased prostate cancer risk among men with high blood concentrations of long-chain ω-3 PUFAs (Brasky et al. 2013). However, previous studies reported the opposite. For instance, in a study involving 6,272 Swedish men who were followed for 30 years, an association between fish consumption and decreased risk of prostate cancer was reported (Terry et al. 2001). Men who ate no fish had a twofold to threefold increase in the risk of developing prostate cancer compared with those who consumed moderate to large amounts of fish in their diet. Similar studies with American men also suggested the association of ω-3 FAs from fish intakes with lower risk of prostate cancer. In another study carried out by the Harvard School of Public Health for over 12 years involving 47,882 men, eating fish more than three times a week reduced the risk of prostate cancer. The study also showed the greater impact of the consumption of these fats on the risk of metastatic prostate cancer. For instance, for each additional 500 mg of marine fat consumed, the risk of metastatic disease decreased by 24% (Augustsson et al. 2003). A recent report on a follow-up study supported the previous findings that daily fish oil supplementation in conjunction with a low-fat diet slows the growth of cancer cells in men with prostate cancer (i.e., lower amounts of pro-inflammatory substances in their blood and a lower cell cycle progression score, a measure that correlates prostate cancer aggression and likelihood of recurrence) (Galet et al. 2013). In another study involving 1,575 older people (average age 67 years) who were free of dementia, Tan et al. (2012) reported an association between lower red blood cells, DHA levels, and smaller brain volumes, and a vascular pattern of cognitive impairment even in persons free of clinical dementia. However, recent studies involving women aged 65 years and older did not find any difference in memory and thinking test scores based on levels of ω-3 FAs in the blood (Ammann et al. 2013).

Other studies have investigated the role of dietary ω-3 PUFAs in health. In a large general-practice cohort of 12,513 patients with multiple cardiovascular risk factors but no history of myocardial infarction, daily treatment with ω-3 FAs did not reduce cardiovascular mortality and morbidity (Roncaglioni et al. 2013). In a study involving 76 patients, aged 5–19 years, long-chain ω-3 PUFAs were found to improve the lipid profile by lowering triglycerides and decreasing insulin resistance and cytokine synthesis, thereby tackling the mechanisms involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) (Janczyk et al. 2013). In a meta-analysis involving 883,585 women, the intake of marine ω-3 PUFAs were inversely associated with risk of breast cancer. Women with the highest intake of marine-sourced ω-3 PUFAs were found to have a 14% reduction in their risk of developing breast cancer compared with women with the lowest intake (Zheng et al. 2013).

CLAs have also been a focus of several studies due to their potential health benefits (Hasler 2002; Schmid et al. 2006; Kelley et al. 2007; Larsson et al. 2009; Gebauer et al. 2011). CLA is a collective term for a group of octadecadienoic acids that are geometric-, positional-, and stereo-isomers of LA with a conjugated double bond. Dietary sources of CLA are predominant in ruminant-derived foods such as meat and milk and their products due

Table 1.12 Amounts of total FAs and conjugated linoleic acid in commonly consumed ruminant products

Food	Total fat (g/100 g)	TFA (g/100 g)	TFA (% total fat)	TFA (g/serving)	CLA (mg/g fat)
Dairy products					
Cheese, cheddar (28 g, 1 oz)	36.4	0.87	2.39	0.24	3.6 (93)
Milk, whole (244 g, 1 cup)	3.10	0.09	2.90	0.21	5.5 (92)
Yogurt, plain, low-fat (255 g, 1 cup)	1.16	0.03	2.59	0.06	4.4 (86)
Meat					
Meat, beef, ground, 20.8% fat, raw (115 g, 4 oz)	21	0.79	3.76	0.91	4.3 (85)
Meat, beef, ground, 22.1% fat, raw (115 g, 4 oz)	22.1	0.93	4.21	1.07	4.3 (85)

Source: Gebauer et al. 2011. Reproduced with permission of American Society for Nutrition.

Table 1.13 Conjugated linoleic acid (CLA) concentration of raw meat

Source	CLA (mg/g fat)
Lamb	4.32–19.0
Beef	1.2–10.0
Veal	2.7
Pork	0.6–0.7
Chicken	0.7–1.5
Turkey	2.0–2.5

Source: Schmid et al. 2006. Reproduced with permission of Elsevier.

to the action of rumen microorganisms in PUFA bio-hydrogenation and/or isomerization. Cheese, beef, yogurt, and milk, respectively, contain ~3.6, 4.3, 4.4, and 5.5 mg of CLA per gram of fat (Table 1.12). The concentration of CLA also varies substantially among raw meat of commonly consumed animals (Table 1.13). CLA contents in these sources were not negatively altered with cooking and storing (Schmid et al. 2006).

In CLA-rich sources such as beef and dairy products, the most abundant (>90%) isomer is *cis*-9, *trans*-11 (c9, t11–18:2). Other positional and geometric isomers such as c9, t10, c12, t9, and t11 have been identified. Physiological properties of CLA include anticarcinogenic, antiatherosclerotic, and antiatherogenic effects, as well as beneficial influence on body composition.

The mechanisms by which mixtures of CLA isomers may inhibit tumor growth may include inhibiting the initiation, promotion, progression, and metastasis of malignant tumors (Kelley et al. 2007). These were attributed to the role of CLA in altering lipid peroxidation, tissue FA composition, eicosanoid metabolism, gene expression, cell cycle regulation, and proliferation and apoptosis. As previously discussed for long-chain PUFAs, reports of the beneficial effects of CLA intake on health have been inconsistent, with some recording an inverse relationship, no association, or simply inconclusive results (Gebauer et al. 2011). For instance, in a cohort study of 61,433 cancer-free Swedish women over a period of 3 years (1987–1990), no evidence of the protective effect of dietary intake of CLA on the risk of breast cancer was observed (Larsson et al. 2009).

Partial hydrogenation has been used industrially to produce *trans* FAs (TFAs), an analog of CLA, primarily to increase shelf life of foods and as an alternative to animal fats (lard, tallow, and butter) from vegetable oil. The c9, t11-CLA is essentially a TFA derived from ruminants. Several studies have linked vegetable-oil-derived TFA to CHD, certain risk factors of CVD, and various cancers (Gebauer et al. 2011), recently prompting the FDA (2013b) to issue a preliminary determination that *trans fats* are not GRAS. This could eventually lead to the classification of *trans fats* as a food additive and subject them to premarket regulatory approval. Health Canada (2007) has adapted the Trans Fat Task Force recommendation of limiting *trans* fats to 2% of total fat content in vegetable oils and margarine, and 5% in all other foods.

1.2.4 Phytochemicals and Phytoestrogens

Phytochemicals are a group of plant secondary metabolites valued for their health benefits (e.g., as radical scavengers and quenchers of singlet oxygen) (Di Majo et al. 2005; Fanga and Bhandaria 2010; De Pascual-Teresa et al. 2010). Reactive oxygen species (ROS) are continuously produced in cells and can damage cell membranes, tamper with DNA, and even cause cell death. These reactive species are considered to be the cause of oxidative stress and inflammation involved in several diseases. Inflammation normally occurs in response to tissue damage caused by either physical or ischemic injuries, infections, and toxins. The body's response may cause cellular changes and immune responses at the site of injury. In certain cancers, inflammation may promote the spreading and mutation of cancer cells, angiogenesis, and an alteration of signaling pathways (De Pascual-Teresa et al. 2010; Patisaul and Jefferson 2010). Chronic inflammation can increase the risk of disease by creating a conducive environment for its development, bolster treatment resistance, and exacerbate the problem. The biological effects of phytochemicals may thus extend well beyond their antioxidant properties. Whereas there are many aspects to consider when treating inflammation, such as slowing the progression of a disease, it seems logical to use nutraceuticals as non-pharmacological interventions to prevent and manage inflammation, especially considering their role in quenching singlet oxygen (De Pascual-Teresa et al. 2010; Patisaul and Jefferson 2010; Cederroth et al. 2012).

Phytochemicals possess a broad spectrum of health benefits, and have been shown to safely suppress pro-inflammatory pathways, reduce low-density lipoprotein (LDL) cholesterol, protect against damage caused by LDL cholesterol, and reduce the risk of atherosclerosis or plaque build-up in arteries that can lead to heart attack or stroke and contribute to CHD (Adolphe et al. 2010). Their antimicrobial properties may prevent the reversible and epigenetic changes in the body's cells often linked to diseases. Phytochemicals include flavonoids (flavanols, flavones, flavanones, isoflavones, catechins, anthocyanidins, and proanthocyanidins), carotenoids, as well as other polyphenols (Scalbert et al. 2005; Boots et al. 2008; De Pascual-Teresa et al. 2010; Vitale et al. 2013), and are found in a variety of foods (Tables 1.14 and 1.15).

Flavonoid is the collective name given to a group of compounds characterized by two aromatic rings linked by a three-carbon bridge. Flavanols, flavones, and flavanones are the main flavonoids that occur in citrus. Several studies have suggested that the high concentrations of flavanols found in cocoa-rich products and dark chocolates increase the formation of endothelial nitric oxide, which promotes vasodilation and therefore may reduce blood pressure and risk of CVD (Taubert et al. 2007; Ried et al. 2010; 2012; Shrime et al. 2011; Hooper et al. 2012). Their anti-cancer mechanisms include immunomodulating properties by interfering in the initiation, enhancement, and progression of cancer as a result of regulating different enzymes and receptors in signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, metastasis, and reversal of multi-drug resistance (Adolphe et al. 2010; De Pascual-Teresa et al. 2010). The role of polyphenols in general in the prevention of degenerative diseases such as CVD and cancers is based on their antioxidant properties and modulation of oxidative stress (De Pascual-Teresa et al. 2010). The properties of the various flavonoids are dependent on the chemical structure, structural class, degree of hydroxylation, substitutions and conjugations, and degree of polymerization (Di Majo et al. 2005; Park et al. 2006; Christensen 2009). The spatial arrangements of the groups may have greater influences on the antioxidant property than the flavan backbone by determining the stability of the radicals (Di Majo et al. 2005).

Phytoestrogens are plant-derived phenolic compounds that are structurally and/or functionally similar to mammalian estrogens (Kurzer and Xu 1997; Patisaul and Jefferson 2010). They include isoflavones, coumestans, and lignans, which are most notably found in soybeans, clover and alfalfa sprouts, and oilseeds (such as flaxseed), respectively. Soybean is

Table 1.14 Sources and properties of polyphenols

Polyphenol	Forms	Sources	Properties
Anthocyanidins	Cyanidin, pelargonidin, peonidin, petunidin, delphinidin, malvidin, and their glycosides	Red, blue, and purple berries, flowers	Natural pigments; highly sensitive to temperature, oxidation, pH, and lights; water soluble
Catechins	Catechin, epicatechin, epigallocatechin, gallocatechin, and epigallocatechin gallate	Tea	Sensitive to oxidation, lights, and pH; astringent and bitter; slightly soluble in water
Flavanones	Hesperetin, homoeriodictyol, hesperidin, naringenin, naringin	Citrus	Sensitive to oxidation, lights and pH; aglycones are insoluble in water but glycosides are soluble in aqueous solutions
Flavones	Apigenin, luteolin, tangeritin	Thyme, oregano, parsley, rosemary, and some fruits and vegetables	Natural pigments; sensitive to oxidation and pH; aglycones slightly soluble but glycosides soluble in water
Flavonols	Kaempferol, myricetin, quercetin, and their glycosides	Onions and citrus fruits and vegetables	Sensitive to oxidation, lights, and pH; aglycones slightly soluble but glycosides soluble in water
Isoflavones	Daidzein, genistein, glycitein	Soybeans, peanuts	Sensitive to alkaline pH; astringent and bitter; soy smell; water soluble
Hydroxybenzoic acids	Gallic acid, ρ-hydroxybenzoic, vanillic acid	Berries, tea, wheat	Sensitive to temperature, oxidation, pH, and light; most soluble in water
Hydroxycinnamic acids	Caffeic acid, ferulic acid, ρ-coumaric acid, sinapic acid	Fruit, oats, rice	Sensitive to oxidation and pH; most slightly soluble in water
Lignans	Pinoresinol, podophyllotoxin, steganacin	Flax, sesame, vegetables	Relatively stable under normal conditions; unpleasant flavor; water soluble.
Tannins (proanthocyanidins)	Castalin, pentagalloyl glucose, procyanidins	Tea, wines, cocoa, berries, grape	Sensitive to high temperature and oxidation; astringent and bitter; water soluble

Source: Boots et al. 2008. Reproduced with permission of Elsevier.

Table 1.15 Total polyphenolic content of some plant foods and beverages

Food	Total Polyphenols	Food/Beverages	Total Polyphenols
Cereals (mg/100 g dm)		**Vegetables (mg/100 g fm)**	
Barley	1,200–1,500	Black currant	140–1,200
Corn	30.9	Blueberry	135–280
Millet	591–1,060	Cherry	60–90
Oats	8.7	Apple	27–298
Rice	8.6	Cranberry	77–247
Sorghum	170–10,260	Gooseberry	22–75
Wheat	22–40	Grape	50–490
Legumes (mg/100 g dm)		Grape fruit	50
Black gram	540–1,200	Orange	50–100
Chickpeas	78–230	Pear	2–25
Cowpea	175–590	Plum	4–225
Common beans	34–280	Raspberry	37–429
Green gram	440–800	Red currant	17–20
Pigeon peas	380–1,710	Strawberry	38–218
		Tomato	85–130
Nuts (% dm)		**Fruit Juices (mg/L)**	
Betel nuts	26–33	Apple juice	2–16
Cashew nuts	33.7	Orange juice	370–7,100
Peanuts	0.04		
Pecan nuts	8–14		
Vegetables (mg/100 g fm)		**Beverages**	
Brussels sprouts	6–15	Tea (mg/200 mL)	150–210
Cabbage	25	Coffee (mg/150 mL)	200–550
Leek	20–40	White wine (mg/L)	200–300
Onion	100–2,025	Red wine (mg/L)	1,000–4,000
Parsley	55–180	Beer (mg/L)	60–100
Celery	94		

Source: Sivam, 2002. Reproduced with permission of Taylor & Francis Group (dm, dry matter; fm, fresh matter).

uniquely rich in the isoflavones genistein (4′,5,7-trihydroxyisoflavone) and daidzein (4′,7-trihydroxyisoflavone), and, to a small extent, glycitein. Isoflavones may exist in various isomeric forms: unconjugated (aglycones: daidzein and genistein), glucoside (daidzin, genistin, and glycitin), acetyl-glucoside (6′′-O-acetyldaidzin, 6′′-O-acetylgenistin, 6′′-O-acetylglycitin), and malonylglucoside (6′′-O-malonyldaidzin, 6′′-O-malonylgenistin, 6′′-O-malonylglycitin). The 4′-methyl ethers isomers (daidzein: formononetin, and genistein: biochanin) are found in clover. Flaxseeds contain the lignan secoisolariciresinol diglucoside, matairesinol, pinoresinol, and lariciresinol (Adolphe et al. 2010).

Phytoestrogens may play an important role in obesity and diabetes by improving glucose control and insulin resistance via pancreatic insulin secretion mechanisms. Phytoestrogens are also of particular importance in women's health, and their role includes reducing the risk of osteoporosis, heart disease, breast cancer, and menopausal symptoms, among others (Kurzer and Xu 1997; Setchell et al. 2001; 2003; Christensen 2009; Adolphe et al. 2010; Patisaul and Jefferson 2010; Cederroth et al. 2012). It is well established that estrogens promote breast tumorigenesis. Under certain conditions, isoflavones (genistein and daidzein) bind to both estrogen receptors (ER-alpha and ER-beta) but preferentially bind to and activate ER-beta and exert estrogen-like effects by stimulating the growth of estrogen-sensitive tumors (Kurzer and Xu 1997; Christensen 2009; Vitale et al. 2013). It is therefore recommended that women with serious risk factors for breast cancer or a family history of breast cancer be cautious about incorporating soy in their diets (Patisaul and Jefferson 2010). Phytoestrogens have also been identified as endocrine disruptors with adverse effects on numerous molecular and cellular targets that can impact reproductive development and endocrine systems (Bar-El and Reifen 2010; Cederroth et al. 2012). Consequently, there has been some concern about the safety of soy isoflavone phytoestrogens genistein and daidzein in infant formula and the threat that these compounds may pose to infant development (Bhatia and Greer 2008; Patisaul and Jefferson 2010). Advisories on the use of soy in formulas have so far been confusing (Patisaul and Jefferson 2010). The removal of the outer fiber layer of some grains, legumes, and vegetables during processing tends to reduce lignan content (Bhathena and Velasquez 2002), and judicious selection of processing conditions may also help to reduce the level of isoflavone in soy products.

Carotenoids are natural pigments synthesized by plants and are responsible for the bright colors of various fruits and vegetables (Paiva and Russell 1999; Krinsky and Johnson 2005). They are made up of two main classes: xanthophylls (which contain oxygen) and carotenes (which are purely hydrocarbons, and contain no oxygen). Examples of carotenes are α- and β-carotene and lycopene, whereas xanthophylls include lutein and zeaxanthin. In addition to the red anthocyanin and yellow xanthophyll pigments, carotenes are responsible for the bright red to pink lycopene and orange pigments in fruits and vegetables. According to a report from BCC research (2011b), the market value of commercially used carotenoids is expected to reach US$1.4 billion in 2018 with a CAGR of 2.3%; β-carotene is predicted to reach almost US$334 million by 2018 at a CAGR of 3.1% a year; and lutein is expected to reach US$309 million (CAGR of 3.6%) by 2018. Carotenoids are valued for their antioxidant properties and their ability to reduce the risk of certain cancers and eye disease. Dietary levels of carotenoids (including β-carotene) were found to promote health in certain sub-populations (Paiva and Russell 1999). Epidemiologic studies have also shown an inverse relationship between dietary carotenoids or blood carotenoid levels and various cancers. However, intervention trials with high dose of β-carotene did not show protective effects against cancer or CVD, while the high-risk population commonly comprising of smokers and asbestos workers in the trials showed an increase in cancer and angina cases (Paiva and Russell 1999). Alpha- and β-carotene are involved in cellular metabolism. Beta-carotene can be converted to vitamin A, unlike lycopene (because of the absence of a terminal β-ionone ring). Lutein and zeaxanthin help to filter and absorb the damaging blue light that enters the eye. Tomato and tomato products are the most significant dietary sources of lycopene, whereas egg yolk and dark-green leafy vegetables (spinach and kale) are highly bioavailable sources of lutein and zeaxanthin (Ma and Lin 2010). Other sources of lycopene are pink grapefruit, watermelon, papaya, guava, and other fruits.

Increased lycopene intake has been reported to reduce the incidence of CVD and coronary heart disease by 17% and 26%, respectively, and improve the functioning of blood vessels compared to effects observed at lower intake levels (Xaplanteris et al. 2012; Jacques et al. 2013). Tomato juice was recently shown to reduce biomarkers of oxidative stress and damage, after exhaustive exercise or in patients with diabetes, cardiovascular diseases, and inflammation (Harms-Ringdahl et al. 2012). The authors suggested that the antioxidant effect of tomato juice was primarily due to lycopene (the most abundant and stable carotenoid in industrial-processed tomato juice) and not the other components of tomatoes (e.g., vitamin C, tocopherols, and polyphenols), which tend to be easily destroyed during processing. Increased intake of tomatoes and tomato-based products, and therefore high serum concentrations of lycopene, was also found to decrease the risk of stroke including ischemic stroke in men (Karppi et al. 2012). Medium-term (14 d) daily consumption of 70 g of tomato paste (containing 33.3 mg of lycopene) improved the function of blood vessels in healthy adults by improving flow-mediated dilation; a measure of a blood vessel's ability to relax, due to enhanced carotenoid bioavailability with tomato processing and cooking in olive oil (Xaplanteri et al. 2012).

Phenolic compounds further play a major role in the sensory attributes of many food products, such as enhancing organoleptic properties in smoked food, cheese, and other dairy products (guaiacol, eugenol, syringol, cresol, and phenol); extending shelf-life of processed foods (catechins); controlling Maillard reaction (caffeic acid); and enhancing color development in wine and dairy products (anthocyanins). They can also cause food deterioration (e.g., beer haze [protein–phenolic compound interactions] and the development of off-flavor in fruit juices [conversion of ferulic acid to guaiacol]) (O'Connell and Fox 2001).

1.2.5 Fiber

Fiber, also known as "non-starch polysaccharide," is derived from the cell wall of plants such as cellulose, hemicellulose, and pectin. As with other carbohydrates, its primary function is to provide energy. It is a complex carbohydrate that is metabolized differently from other forms of carbohydrates, generally resistant to digestion and absorption. It is also classified as an unavailable carbohydrate with a different nutritional classification to available carbohydrates (starch and soluble sugars). Fiber is further classified as soluble (food gums/hydrocolloids and pectin) and insoluble (cellulose and hemicellulose). The soluble components of the dietary fiber is degraded by microflora, resulting in a substantial stimulation of microbial growth and an increased fecal bulk. Soluble fiber also affects glucose and lipid absorption into the bloodstream by lowering serum cholesterol. Insoluble fiber is resistant to breakdown by the microflora and has been identified for their role in laxation and bowel habit by retaining water within the cellular structure, intestinal transit time, production of short-chain FAs, and prebiotic effect (Havrlentová et al. 2011). Their indigestible and fermentable nature mainly defines their nutraceutical and functional properties. Apart from the physiological properties of this fibrous material, fibers are suitable fermentable substrates adjuncts for probiotics and encapsulation shells (Charalampopoulos et al. 2002; Havrlentová et al. 2011). Several studies have reported the hypocholesterolemic effect of fiber and its role in lowering blood pressure and inflammation, reducing the risk of CVD, and inhibiting and decreasing the growth of certain cancer cells and tumors (Havrlentová et al. 2011; Grooms et al. 2013). Table 1.16 provides the total dietary fiber content of some common cereal grains. Recently, a health claim for plums of "prune"

Table 1.16 Fiber content of cereal grains

Categories	Total dietary fiber (%, dwb)
Legumes	13.6–28.9
Rye	15.5
Corn	15
Triticale	14.5
Oat	14
Wheat	12
Sorghum	10.7
Barley	10
Rice	3.9

Source: Charalampopoulos et al. 2002. Reproduced with permission of Elsevier.

cultivars (*Prunus domestica* L.) in maintaining normal bowel function was approved by the EFSA. In order to obtain the claimed effect, about 100 g of dried plums (prunes) must be consumed daily (EFSA 2012). Prunes contain both dietary soluble and insoluble fiber. The cholesterol-lowering effect of fiber may be related to β-glucan mediation in increasing bile acid secretion. Beta-glucan is recognized as the main functional component of some cereal fibers. A recent study by Grooms et al. (2013) involving 23,168 subjects over the period 1999–2010 strengthened the association between low dietary fiber intake and reduction of cardio-metabolic risks such as metabolic syndrome, cardiovascular inflammation, and obesity. The limited digestion and low glycemic index of fiber helps in glycemic (blood sugar) control by slowing the release of energy, delaying gastric (stomach) emptying, retarding the entry of glucose into the bloodstream, and lessening the postprandial (post-meal) rise in blood sugar, thereby stabilizing blood sugar in diabetic individuals or those predisposed to diabetes (Childs 1999; Grooms et al. 2013). Keeping blood sugar low and stable may also impact the production of advanced glycation end products (AGEs), known for their role in vascular (atherosclerosis) and renal complications and for their association with diabetes and aging (Raj et al. 2000; Daroux et al. 2010; Yamagishi 2013). In weight control and obesity, fiber may help to control hunger, regulate food intake, increase satiety, reduce overconsumption, and displace other nutrients such as lipids. Despite this knowledge, several investigators have found that dietary fiber intake consistently falls below the recommended amount (Grooms et al. 2013). The Institute of Medicine recommends dietary fiber intake levels according to age and sex: 38 g per day for men aged 19–50 years, 30 g per day for men 50 and over, 25 g for women aged 19–50 years, and 21 g per day for women over 50 years. The data from the recent study reveals that the mean dietary fiber intake was only 16.2 g per day across all demographics during that study time period (Grooms et al. 2013). Health Canada suggests the consumption of 26–35 g of fiber daily by healthy adults and 25–50 g per day by people with diabetes. Present fiber intake in Canada only averages 4.5–11 g a day, according to Health Canada. Fiber is ubiquitous in grains, legumes, and vegetables. Wheat bran and whole grains, as well as the skins of many fruits and vegetables, and seeds, are rich sources of insoluble fiber. Soluble fiber is found in oats, legumes (peas, kidney beans, and lentils), some seeds, brown rice, barley, oats, fruits (e.g., apples), some green vegetables (e.g., broccoli), and potatoes.

FDA has permitted product labels to carry health claims stating that oatmeal and oat cereals may reduce the risk of heart disease – as part of a diet low in fat and cholesterol. Products made of whole-grain oats or oat fiber with a minimum of 0.75 g β-glucan per serving size qualify for the FDA health claim. Table 1.17 provides the β-glucan content of some common cereal-based foods. Oats and barley have the highest β-glucan content among cereals.

Table 1.17 Soluble β-glucans content in some cereal-based food

Cereal	Food	Soluble β-glucans (g/100 g dry weight)
Wheat	Whole meal	0.39
	Bran	1.38
	Groat	0.42
Barley	Whole meal	3.35–3.95
	Bran	4.14
	Groat	5.28
Oat	Whole meal	2.66–4.51
	Groat	3.5–5.0
	Bran concentrate	7.48–17.0
	Flakes	2.64–4.6

Source: Reproduced from Cereal β-glucans and their significance for the preparation of functional foods – a review by Havrlentová et al. with permission from Czech Journal of Food Sciences.

Health Canada suggests increasing the amount of fiber by eating more grains and unpeeled but well-washed fruit and vegetables. Fiber is utilized in the formulation of breakfast cereals and bread, and commercial preparations such as Agarol® (agar) and Metamucil® (psyllium). The strong gelling and water-absorbing capacities of psyllium may prevent the incorporation of the required amount in one serving of a food product to permit the use of the cholesterol-lowering claim on the food label (Childs 1999; Anderson et al. 2000).

1.2.6 Prebiotics and Probiotics

Prebiotics and probiotics have received tremendous interest and have found wide application in the food industry, as is evident in consumer acceptance and the volume of production worldwide. According to BCC reports, probiotics was a US$21.6 billion industry in 2011 (BCC Research 2011c), and it is expected to reach US$31.1 billion by 2015, with a CAGR of 7.6% for the next 5-year period. Unlike other nutraceuticals and functional products, probiotic foods account for 90.1% of this value, followed distantly by 6.4% for supplements. The FAO/WHO define *probiotics* as live microorganisms that when administered in adequate amounts confer a health benefit on the host (FAO 2001), while a *prebiotic* has been defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon and thus improves host health (Gibson 2004). The importance of probiotics and prebiotics as nutraceutical and functional foods stems from their ability to improve intestinal microflora, and to reduce and inhibit the growth of pathogenic strains such as *E. coli* and *Salmonella* (known for their roles in causing infectious diseases in the GI tract), allergic disorders, diarrhea, and inflammatory bowel disease (Gibson 2004; Champagne et al. 2005; Di Criscio et al. 2010). For dietary products, bacterial count of at least 106 CFU ml^{-1} is commonly accepted. The effect of probiotics is strain specific. Bacterial strains from the genera *Lactobacillus*, *Bifidobacterium*, and *Bacillus* are three known sources of probiotics. Three new bacterial strains with potential probiotic effects – *Lactobacillus paracasei* CNCM I-4034, *Bifidobacterium breve* CNCM I-4035, and *Lactobacillus rhamnosus* CNCM I-4036 – isolated from the feces of breastfed infants have recently been identified (Muñoz-Quezada et al. 2013). *Saccharomyces boulardii*; a yeast strain is commercially available as a probiotic for human use (Martins et al. 2005). Currently, several strains of *Saccharomyces cerevisiae* (905 and L11), *Kluyveromyces marxianus* L10, and *Kluyveromyces lactis* L13 from different environments (insect association, tropical fruit, and cheese) are being considered for use as potential probiotics (Martins et al. 2005; Binetti et al. 2013). Known examples of prebiotics include non-digestible oligosaccharides such as inulin (fruits and vegetables), fructo-oligosaccharides, galacto-oligosaccharides, lactulose, and resistant starch (Table 1.18) (Charalampopoulos et al. 2002; Śliżewska et al. 2012; Al-Sheraji et al. 2013). The limited digestibility in the small intestine and fermentation by intestinal bacteria of these non-digestible oligosaccharides in the colon may slow energy release in individuals predisposed to diabetes, increase satiety, and reduce hunger. They may also play an important role in colonic health and other GI illnesses by stimulating the beneficial activity and proliferation of specific members of the intestinal microflora, prevent colonization by potential pathogens, produce beneficial short-chain FAs (such as acetic acid, propionic acid, and butyric acid, which are used by the host organism as an energy source), and stimulate calcium absorption from food (Bosscher et al. 2006; Al-Sheraji et al. 2013). Prebiotics and probiotics in foods and beverages and as supplements may enhance health independently, or in combination (also referred to as *synbiotics*) (Champagne et al. 2005; Di Criscio et al. 2010).

1.3 Production of Nutraceuticals and Functional Foods

Nutraceuticals and functional foods may be produced with the same ingredients in various formats to meet specific physiological requirements and needs of target groups. As an example, functional foods may be formulated as liquid shakes for infants and senior citizens and as solids for adults. Liquid foods permit easy ingestion in infants and children, whereas the solid form may be more convenient for adults. Nutraceuticals and functional food ingredients

Table 1.18 Sources and production of prebiotics

Prebiotic	Source	Production
Inulin	Chicory, *Agave tequilana*	Extraction from raw material
Fructooligosaccharides	Asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato, and rye	• Transglycosylation of the polysaccharides • Transfructosylation of sucrose using β-fructofuranosidase • Hydrolysis of chicory inulin
Xylooligosaccharides	Bamboo shoots, fruits, vegetables, milk, honey, and wheat bran	• Enzyme hydrolysis of xylan-containing lignocellulosic material • Chemical fractionation of xylan from lignocellulosic material followed by enzymatic hydrolysis of xylan • Hydrolytic degradation of xylan by steam, water, or dilute solutions of mineral acids
Galactooligosaccharides	Human's milk and cow's milk	Enzymatic hydrolysis (transglycosylation) of lactose by β-galactosidase
Cyclodextrins	Water-soluble glucans	Transglycosylation and hydrolysis of starch using cyclodextrin glucosyltransferases
Raffinose oligosaccharides	Seeds of legumes, lentils, peas, beans, chickpeas, mallow composite, and mustard	Water or aqueous methanol or ethanol extraction
Soybean oligosaccharide	Soybean	Extraction from the by-product of soybean protein isolate/concentrate production (whey)
Lactulose	Lactose (milk)	Alkali isomerization of lactose glucose moiety to fructose residue
Lactosucrose	Lactose	Transglycosylation of lactose and sucrose
Isomaltulose (Palatinose)	Sucrose, honey, sugarcane juice	Enzymatic rearrangement of the glycosidic linkage in sucrose from α (1, 2)-fructoside to α (1, 6)-fructoside followed by crystallization

Table 1.18 (*continued*)

Prebiotic	Source	Production
Maltooligosaccharides	Starch	Debranching of starch by pullulanase and isoamylase, combined with hydrolysis by various α-amylases
Isomaltooligosaccharides	Starch	• Transglucosidation (transgalactosylation) of starch maltose using α-glucosidase • Enzymatic synthesis from sucrose
Arabinoxylooligosaccharides	Wheat bran	Enzymatic depolymerization of raw material (lignocellulosic materials)
Enzyme-resistant dextrin	Potato starch	Chemical modification of starch

Source: Śliżewska et al. 2012. Reproduced under a Creative Commons License; http://creativecommons.org/licenses/by/3.0/ and Al-Sheraji et al. 2013. Reproduced with permission of Elsevier.

and products may be formulated dry as wettable or dispersible powders, or wet as soluble, suspension, emulsifiable concentrate, dispersion, or encapsulated agents, using processes such as emulsification, agglomeration, retorting, spray-drying, extrusion, precipitation, fermentation, and ultrafiltration to preserve, modify, or deliberately incorporate the active ingredients. Detailed information of these methods have been reported in the literature (Ozdemir and Cevik 2007; Barbana and Boye 2010; Mochida et al. 2010; and references therein), and further relevant details are provided elsewhere in this book. Functional foods may be incorporated and consumed in a muffin, other bread products, baked goods, or breakfast products. Second-generation products (e.g., soy foods such as soymilk, miso, tofu, and tempeh) are also very popular.

Both polar and non-polar solvents such as ethanol, chloroform, petroleum ether, hexane, and acetonitrile are commonly used in different ratios with or without water to extract ingredients with functional and nutraceutical properties such as phenolics and anthocyanins (Dunford et al. 2010; Plaza et al. 2010). The pre-treated/non-treated raw material is exposed to the solvent, which preferentially extracts compounds of interest and also other agents such as flavors and colorings. The extracted sample may be separated by centrifugation or filtration to remove solid residue, and the solvent is evaporated and the extract recovered and concentrated. The main drawbacks to solvent extraction in some instances include the toxicity and danger of these solvents to humans and environment, and the labor-intensive and extensive downstream processes required to rid the product of the solvents used.

Acids, bases, and enzymes have been used to partially or extensively hydrolyze proteins to produce hydrolysates and release bioactive peptides (Clemente 2000; Humiski and Aluko 2007; Potier and Tomé 2008; Rui et al. 2012). Enzymes have received increased attention due to the mildness of their reactions and the production of fewer undesirable side reactions. GI enzymes, such as trypsin, pepsin, chymotrypsin, peptidases, and pancreatin, as well as commercial endo- and exopeptidases such as Alcalase™, Flavourzyme™, and Thermolysin™, have been used sequentially or in combination to hydrolyze the peptide bonds in proteins. Enzymatic hydrolysis is a useful tool in producing bioactive peptides with preferred characteristics such as molecular weight (MW), size, functional properties, and potential health benefits (Clemente 2000; Potier and Tomé 2008). Fermentation of milk with proteolytic starter cultures may also be used to generate bioactive peptides. Alpha and β-amylases, isoamylase, pullulanase, and amylopullulanase are some examples of enzymes used to hydrolyze starch and other polysaccharides (Tomasik and Horton 2012; Al-Sheraji et al. 2013; Śliżewska et al. 2012).

Soy concentrate (65–90% protein) is produced by water or alcohol extraction to remove soluble carbohydrates and also to improve functionality. This process may, however, denature some proteins and reduce the concentration of isoflavones (Table 1.9; Bhathena and Velasquez 2002). The use of techniques such as milling, air classification, salt extraction (micellization), isoelectric precipitation, chromatography (ion exchange), electrodialysis, ultrafiltration, and other membrane technologies have resulted in various purities (concentrate or isolate) and overall quality of the protein fraction (Boye et al. 2010; Barbana and Boye 2013).

Most nutraceuticals and functional ingredients found in fruits, vegetables, legumes, and animal-derived sources may have low bioavailabilities, partially as a result of their slow release from the food matrix (Kurzer and Xu 1997; Rao et al. 1998; Benakmoum et al. 2008; Xaplanteri et al. 2012). Processing technologies used in the development of nutraceutical and functional food ingredients often strive to improve product bioavailability or create novel foods enriched with isolated and/or concentrated fractions of the bioactive ingredients. As an example, enzymatic deglycosylation has been used to increase the bioavailability and antioxidant activity of flavonoids (Park et al. 2006; Christensen 2009). Additionally, it should be mentioned that observed *in vitro* effects may not be directly correlated with *in vivo* effects due to degradation, fragmentation, or modification in the GI tract or other parts of the body (Anguelova and Warthesen 2000; Reboul et al. 2005; Binetti et al. 2013). Probiotics must also survive in the GI environment and maintain at least one beneficial function (e.g., colonization resistance against pathogenic microorganisms, immunomodulation or nutritional contribution) (Martins et al. 2005) to be considered useful.

Various formulation options have been explored in the quest to produce simpler, safer, and more efficacious food products with uniform appearance and acceptable taste. The influence of particle size, pH, solubility, hydrophobicity/hydrophilicity, and stability of both the bioactive and excipient (inert) components on bioavailability is a critical factor to consider during formulation. Formulations are usually developed to be close to the preparation that will ultimately be on the market. In addition to a series of downstream processes, several tests may be carried out to determine the effects of temperature, humidity, oxidation, or photolysis (ultraviolet light or visible light) on the stability of a product, as well as the loading efficiency, dissolution, and release rates in encapsulated formulation (Brownlie 2007; Hébrard et al. 2010; Wichchukit et al. 2013). For nutraceuticals, dose and site-specific and release profiles are very crucial. Acid-labile ingredients must be protected from gastric pH, and thus digestive aids may be used in the formulations to preferentially help them dissolve faster and be rapidly released as small-sized nanocapsules with shorter gastric resident times, allowing them to traverse the stomach quickly to reach the site of interest (Hébrard et al. 2010). Alternatively, bioactive ingredients may be formulated for extended or delayed release (Brownlie 2007). Sufficient numbers of live probiotic microorganisms, as an example, may reach the large intestine (colon) when protected from gastric pH, bile, and other nutrients/compounds in the gut (Hébrard et al. 2010; Wichchukit et al. 2013).

Processing affects the quality and properties of bioactive ingredients to different extents with varying nutritional implications (Rao et al. 1998; Anguelova and Warthesen 2000; Bhathena and Velasquez 2002; Reboul et al. 2005). Fish oil refining processes such as neutralization, degumming, and winterization help to improve sensory attributes, such as off-flavors and off-taste, and/or safety, but they may also lead to chemical reactions such as autoxidation, hydrolysis, isomerization, polymerization, and pyrolysis, which can influence the quality of the oil. Fermented, sprouted, and germinated immature/green beans of the same legume can contain varied amounts of bioactive compounds, as shown in Table 1.19. Unprocessed soybeans contain 1.2–4.2 mg/100 g of isoflavones, whereas some high-protein soy products such as soy flour and textured soy protein contain 1.1–1.4 mg/g dry weight of isoflavones. Second-generation soy foods such as tofu, yogurt, and tempeh burger contain varied amounts of isoflavones, since most of the components of the matrices in these foods are non-soybean constituents. The presence (glucoside) or absence (aglycone) of the sugar moiety will further affect the absorption and bioavailability of many flavonoids in humans. Glucose-conjugated isoflavones are highly polar and water-soluble compounds that are hardly absorbed by the gut. This consequently reduces

Table 1.19 Isoflavone content of some selected foods (mg/100 g)

Food Product	Daidzein	Genistein	Glycitein	Total Isoflavones
Dairy				
Ensure plus, liquid nutrition	0.20	0.35	0.00	0.60
Ensure, liquid nutrition	1.40	2.58	0.28	4.33
Non-dairy creamer, with added soy flour or soy protein	0.06	0.14	–	0.21
Baby Food				
Infant formula, Abbott nutrition, SIMILAC, ISOMIL, with iron, powder, not reconstituted	6.03	12.23	2.73	25.82
Infant formula, Abbott nutrition, SIMILAC, ISOMIL, with iron, ready-to-feed	0.73	1.37	0.21	2.21
Infant formula, ENFAMIL Next Step, powder, soy formula, not reconstituted	7.23	14.75	3.00	25.00
Infant formula, PBM products, ULTRA bright beginnings, soy, liquid concentrate	0.98	2.69	0.35	3.81
Infant formula, PBM PRODUCTS, Ultra bright beginnings, soy, powder	5.70	13.55	2.05	28.01
Infant formula, PBM products, Ultra bright beginnings, soy, ready-to-feed	0.75	1.60	0.28	2.63
Fats and Oils				
Mayonnaise, made with tofu	5.50	11.30	–	16.80
Soups, Sauces, and Gravies				
Black bean, sauce	5.96	4.04	0.53	10.26
Miso soup	0.78	0.73	0.03	1.52
Miso soup mix, dry	29.84	40.0	–	69.84
Sausages and Luncheon Meats				
Frankfurter, beef	1.00	0.80	0.10	1.90
Frankfurter, beef, fat free	0.60	1.00	0.10	1.70
Breakfast Cereals				
Cereals ready-to-eat, Kashi Golean by Kellogg's	8.40	7.70	1.40	17.40
Cereals ready-to-eat, KELLOGG'S, Smart start soy protein	41.90	41.90	10.20	93.90
Cereals ready-to-eat, KELLOGG'S, KELLOGG'S start (purchased in the United Kingdom)	0.01	0.01	–	0.02
Cereals ready-to-eat, NESTLÉ'S Shreddies (purchased in the United Kingdom)	0.02	0.04	–	0.06
Vegetables and Vegetable Products				
Clover sprouts, raw	0.04	0.21	–	0.25
Clover, red	11.0	10.0	–	21.0
Soybeans, green, cooked, boiled, drained, without salt (includes edamame)	7.41	7.06	4.60	17.92
Soybeans, green, raw (includes edamame)	20.34	22.57	7.57	48.95
Soybeans, mature seeds, sprouted, cooked, steamed	5.0	6.7	0.8	12.50
Soybeans, mature seeds, sprouted, raw	12.86	18.77	2.88	34.39

Table 1.19 (*continued*)

Food Product	Daidzein	Genistein	Glycitein	Total Isoflavones
Nuts and Seeds				
Nuts, pistachio nuts, raw	1.88	1.75	0.00	3.63
Seeds, flaxseed	0.02	0.04	0.06	0.12
Legumes and Legume Products				
Bacon bits, meatless	64.37	45.77	8.33	118.50
Bacon, meatless	2.20	5.66	1.50	9.36
Beans, common, raw (*Phaseolus vulgaris*)	0.29	0.30	0.00	0.59
Beans, kidney, red, mature seeds, raw	0.01	0.01	–	0.02
Beans, navy, mature seeds, raw	0.01	0.20	–	0.21
Beans, scarlet runner, mature seeds, cooked	0.04	0.05	–	0.09
Beans, scarlet runner, mature seeds, raw	0.05	0.07	0.00	0.12
Broadbeans (fava beans), mature seeds, fried	0.00	1.29	–	1.29
Broadbeans (fava beans), mature seeds, raw	0.33	0.15	0.28	0.63
Chicken nuggets, meatless, canned, prepared (Worthington FriChik)	4.35	9.35	0.90	14.60
Chicken nuggets, meatless, canned, unprepared (Worthington FriChik)	3.45	7.90	0.85	12.20
Chicken patties, meatless (Morningstar farms Chik Patties Original)	1.80	2.20	0.40	4.40
Frankfurter, meatless (purchased in Germany)	5.78	6.43	0.06	12.27
Instant beverage, soy, powder, not reconstituted	40.07	62.18	10.90	109.51
Miso	16.43	23.24	3.00	41.45
Natto	33.22	37.66	10.55	82.29
Sausage patties, meatless (Morningstar Farms Veggie, sausages, patties)	2.00	2.30	0.30	4.60
Sausage, meatless	4.46	9.23	2.30	14.34
Soy cheese, American	5.75	8.70	3.50	17.95
Soy cheese, Monterey Jack, fat-free	7.80	8.80	2.10	18.70
Soy cheese, mozzarella	1.14	2.60	2.28	6.02
Soy drink	2.75	5.10	–	7.85
Soy fiber	18.80	21.66	7.90	44.43
Soy flour (textured)	67.69	89.42	20.02	172.55
Soy flour, defatted	64.55	87.31	15.08	150.94
Soy flour, full-fat, raw	72.92	98.77	16.12	178.10
Soy flour, full-fat, roasted	89.46	85.12	16.40	165.04
Soy meal, defatted, raw	80.77	114.71	16.12	209.58
Soy paste	19.71	17.79	6.05	38.24
Soy protein concentrate, aqueous washed	38.25	52.81	4.94	94.65
Soy protein concentrate, produced by alcohol extraction	5.78	5.26	1.57	11.49
Soy protein drink	27.98	42.91	10.76	81.65
Soy protein isolate	30.81	57.28	8.54	91.05
Soy sauce made from soy and wheat (shoyu)	0.78	0.39	0.14	1.18
Soy yogurt	13.77	16.59	2.80	33.17

(*continued overleaf*)

Table 1.19 (*continued*)

Food Product	Daidzein	Genistein	Glycitein	Total Isoflavones
Soy-based liquid formula for adults, Abbott nutrition, Enrich	0.14	0.40	–	0.54
Soybean butter, full fat, Worthington Foods, Inc.	0.22	0.30	0.05	0.57
Soybean chips	26.71	27.45	–	54.16
Soybean, curd, fermented	12.18	21.12	2.30	34.68
Soybeans, flakes, defatted	37.47	91.22	14.23	131.53
Soybeans, flakes, full-fat	21.75	39.57	1.12	62.31
Soybeans, green, mature seeds, raw	61.70	60.07	7.07	128.83
Soybeans, mature seeds, canned	26.15	25.15	6.10	52.82
Soybeans, mature seeds, dry roasted (includes soy nuts)	62.14	75.78	13.33	148.50
Soybeans, mature seeds, raw (Australia)	39.88	65.64	17.12	120.84
Soybeans, mature seeds, raw (Brazil)	29.09	67.57	13.10	99.82
Soybeans, mature seeds, raw (China)	53.38	57.98	11.71	118.28
Soybeans, mature seeds, raw (Japan)	45.95	74.33	9.01	130.65
Soybeans, mature seeds, raw (Taiwan)	27.77	45.88	13.24	85.68
Soybeans, mature seeds, raw (United States)	61.33	86.33	13.33	159.98
Soymilk (all flavors), low-fat, with added calcium, vitamins A and D	1.01	1.51	0.04	2.56
Soymilk (all flavors), non-fat, with added calcium, vitamins A and D	0.30	0.41	0.00	0.70
Soymilk skin or film (Foo jook or yuba), cooked	17.81	25.15	2.69	44.67
Soymilk skin or film (Foo jook or yuba), raw	80.03	101.40	15.43	196.05
Soymilk, made from soy isolate (purchased in Australia)	2.80	3.10	–	5.90
Soymilk, original and vanilla, fortified or unfortified	4.84	6.07	0.93	10.73
Sufu	7.50	5.46	0.78	13.75
Tempeh	22.66	36.15	3.82	60.61
Tempeh burger	6.40	19.60	3.00	29.00
Tempeh, cooked	13.12	21.14	1.39	35.64
Tempeh, fried	32.90	39.90	–	72.80
Tofu yogurt	5.70	9.40	1.20	16.30
Tofu, dried–frozen (koyadofu)	29.59	51.04	3.44	83.20
Tofu, firm, cooked	10.26	10.83	1.35	22.05
Tofu, fried	13.80	18.43	2.93	34.78
Tofu, okara	3.62	4.47	1.30	9.39
Tofu, salted and fermented (fuyu)	20.72	23.83	4.95	48.51
Tofu, silken	9.15	8.42	0.92	18.04

Table 1.19 (*continued*)

Food Product	Daidzein	Genistein	Glycitein	Total Isoflavones
Tofu, smoked	7.50	5.60	–	13.10
Tofu, soft, Vitasoy-silken	8.59	20.65	–	29.24
Veggie burgers or soy burgers, unprepared	2.36	5.01	0.55	6.39
Baked Products				
Bread, soy and linseed (purchased in Australia)	4.87	9.13	0.67	14.67
Bread, white, commercially prepared, with added soy flour or soy protein	0.74	0.68	0.10	1.48
Bread, whole grain, commercially prepared, with added soy flour or soy protein	0.29	0.28	0.00	0.57
Bread, whole meal, commercially prepared, with added soy flour or soy protein	0.16	0.14	–	0.30
Doughnuts, cake-type, plain (includes unsugared, old-fashioned)	2.58	2.44	0.29	5.31
Doughnuts, with added soy flour or soy protein	1.30	3.22	–	4.52
Sweets				
Desserts, frozen, Glace Soymilk	7.00	6.20	0.90	14.00
Desserts, frozen, Tofutti non-dairy original premium	1.10	1.70	0.10	2.90
Pudding, made with soymilk	3.50	5.63	0.00	9.13
Cereal Grains and Pasta				
Noodles, egg, dry, enriched	0.01	0.01	–	0.02
Rice, brown, long-grain, raw	0.03	0.04	–	0.07
Semolina, enriched	0.01	0.02	–	0.03
Fast Foods				
Jack in the Box, Beef monster taco	2.60	13.10	0.20	15.90
Pizza, with added soy flour or soy protein	0.23	0.24	0.47	3.00
Subway, meatball sandwich	3.00	2.70	0.30	6.00
Snacks				
Bar, Tiger's Milk protein rich	4.90	5.90	0.70	11.50
Formulated bar, Balance yogurt honey peanut flavor	11.80	13.60	1.20	26.60
Formulated bar, Cliff Luna nuts over chocolate flavor	8.10	8.40	1.20	17.70

Source: USDA (2008). Courtesy of USDA-Agricultural Research Service.

their biological activity compared to the unconjugated aglycone. In some instances, glycosylated isoflavones may be deconjugated to aglycones by colon microbial families. Non-fermented soy food (tofu) has high amounts of glucosides, while fermentation has been shown to increase the levels of the bioactive unconjugated isoflavone aglycones in soybean (tempeh). Processing of soybean can result in various amounts of isoflavone genistein and daidzein in the finished product (Table 1.18) (Bhathena and Velasquez 2002). Minimal processing results in soy flour with malonyl isoflavones isomers (6′′-O-malonyldaidzin and 6′′-O-malonylgenistin), whereas texturing by heat treatment during extrusion converts malonyl isoflavones to their acetyl forms (6′′-O-acetyldaidzin and 6′′-O-acetylgenistin). Textured soy protein (50–70% protein) may be used as a meat substitute in hotdogs, hamburgers, and sausages, and to fortify numerous products, as shown in Table 1.19. Soy protein isolate (≥90% protein) has been used to enrich energy bars, sports drinks, infant formula, cereals, granola bars, imitation dairy products, mayonnaise, ice cream, cheese, and even doughnuts.

Lycopene in tomatoes can be concentrated by processing into a juice, sauce or paste as ketchup, spaghetti, and pizza sauce. The content and bioavailability of lycopene is also markedly modified by processing and the chemical environment (Table 1.20; Rao et al. 1998; Anguelova and Warthesen 2000; Reboul et al. 2005; Xaplanteri et al. 2012). The presence of environmental factors such as air, light, and temperature may result in autoxidation and reversible isomerization of the predominant *trans* lycopene isomers in fresh tomatoes to the more oxidizable *cis* isomers, which may cause a decrease in total lycopene content and proportion of *trans* isomers, color loss, and development of grassy off-flavors (Anguelova and Warthesen 2000). The increase in bioavailability with processing may involve the breakdown of cell walls, which weakens the bonding forces between lycopene and tissue matrix, making lycopene more accessible. Dehydrated and powdered tomatoes have poor lycopene stability due to the conversion of the *trans* isomers to the more oxidizable bioavailable *cis* isomers (Rao et al. 1998). The enrichment of tomato paste with tomato peel increased the content of lycopene and β-carotene by >50% and ∼100%, respectively, without any sensory changes (Reboul et al. 2005).

Cereal grains such as oats are milled into powder/flour or used for porridge (rolled oats: de-husked oat groats, steamed and rolled into flat flakes), muesli cereals (mixture of uncooked rolled oats, nuts, and fresh or dried fruits), baked goods (bread, muffin, and cakes), toppings (on pastries and desserts), pasta and noodles, soups, as meat extenders in meat products (sausage, burgers, nuggets, meatballs), as fat replacers (Nutrim®; concentrated β-glucan) in cheese, snack bars (bar-shaped pressed–baked muesli or granola), or incorporated into granola (mixture of uncooked rolled oats, nuts, and honey) for increased convenience. These processes may influence the quantity and bioavailability of the active compounds in cereals.

Table 1.20 Lycopene content of tomatoes and tomato products

Group	Product	Lycopene (ppm) mean ± SEM, n=5
Products for food preparation	Tomato paste	365.0 ± 3.6
	Tomato puree	365.0 ± 3.6
	Crushed tomatoes	223.8 ± 0.9
Sauces	Tomato sauce	130.6 ± 1.2
	Spaghetti sauce	191.2 ± 1.3
	Pizza sauce	121.7 ± 0.8
	Seafood sauce	185.6 ± 2.5
	Chilli sauce	168.3 ± 1.6
Condiments	Tomato ketchup	123.9 ± 2.1
	Light ketchup	141.1 ± 2.1
	Barbecue sauce	42.9 ± 0.6
Readily consumed	Tomato juice	101.6 ± 0.6
	Condensed soup	72.7 ± 0.2
	Ready to serve soup	44.1 ± 0.6
	Clam cocktail	43.3 ± 0.2
	Bloody Mary mix	42.3 ± 0.3

Source: Rao et al. 1998. Reproduced with permission of Elsevier.

There is growing interest to develop formulations that are protected and effectively delivered at specific targets and at controlled rates (Champagne and Fustier 2007; Ozdemir and Cevik 2007; Kuang et al. 2010; Jung et al. 2013). Several encapsulation procedures have been established, and predominant among them are emulsion, extrusion, and spray drying (Jantzen et al. 2013). Spray drying is routinely used to convert liquids into dry powders and for its dual functionality to both form a capsule and dry in a single step. Several shell materials such as polysaccharides, proteins, waxes, FAs, gums, and their derivatives that do not elicit immune responses and have low toxicities in humans have been approved for food use (Kuang et al. 2010; Nesterenko et al. 2013). The shell may have a hydrophobic cavity and hydrophilic exterior where lipid-based compounds interact with the interior of the shell to form an inclusion complex that dissociates on target. Encapsulation may improve the stability of the active ingredient under conditions encountered in food processing and storage conditions (temperature, oxygen, light), or in the GI tract (pH, enzymes, presence of other nutrients). Encapsulation has been used to maximize the proportion of the active ingredient that remains available following intake and improve gastric residence time, product permeability, solubilization at the site of action, bioavailability, and potential health benefits (Lee et al. 2007; Shen et al. 2010). Emulsions and self-microemulsifying formulations have been introduced using surfactants to increase bioavailability and absorption of poorly water-soluble ingredients such as isoflavones (Lee et al. 2007; Kuang et al. 2010; Shen et al. 2010).

Table 1.21 Beneficial effects of probiotic encapsulation

Benefits	Product
Facilitates the production of oxygen-sensitive cultures	Dried probiotic culture
Facilitates the recovery of centrifugation-sensitive cultures	
Facilitates the recovery of high EPS-producing cultures	
Less contamination problems	
Cultures can be air-dried	
Improved survival on exposure to gastric and bile solutions	Nutraceutical
Improved stability during storage in dried form	
Improved acidification rate	Dried sausages
Improved survival on heating	Biscuits, powder
Improved survival on freezing	Ice cream, milk-based medium, cranberry juice
Improved retention in the finished product	Cheese
Protection against bacteriophages and yeast contaminants	Fermented milks
Improved survival during storage	Yoghurt, mayonnaise, milk

Source: Champagne and Fustier 2007. Reproduced with permission of Elsevier.

The technique creates fine droplets of emulsion when reconstituted with water or with body fluids. Encapsulation can enhance the delivery of viable cells into dairy and bakery products during processing and storage, and equally improve their survival and facilitate controlled delivery in the GI tract following consumption (Champagne and Fustier 2007) as well as other benefits (Table 1.21).

Jung et al. (2013) detailed the preservation and increased bioactivity and bioavailability of microencapsulated green tea catechin. Green tea catechin reportedly has a protective effect on the cardiovascular system by mitigating the adverse features of myocardial fibrosis and high serum uric acid levels and increasing hepatic catalase activity. Carotenoids may also be encapsulated due to their highly unsaturated structure to improve thermal or oxidative stability during processing and storage, as well as to reduce the production of undesirable flavors and loss of potential health value (Champagne and Fustier 2007; Ozdemir and Cevik 2007). Some unprocessed functional foods may contain bitter endogenous compounds while processing, or deliberate addition may introduce bitterness-eliciting compounds (Table 1.22). Unlike pharmaceuticals drugs, the health claim appeal of functional foods and a positive perception of their benefits and sensory attributes are important to encourage their acceptance, purchase, and commercial success; various de-bitterness techniques and bitterness-modifying additives have therefore been used to enhance taste (Champagne and Fustier 2007; Gaudette and Pickering 2013;

Table 1.22 Some commercial functional food products containing endogenous or added bitter-eliciting functional ingredients

Product	Active functional ingredient	Company
Broccoli sprout juice	Glucosinolates (sulforaphane)	Garden Gate Farms, Ontario, Canada
Green tea energy drink Enviga™	Green tea phenolics (can include epigallocatechin gallate and (+)-catechin)	The Coca-Cola Company, Georgia, United States
Catechin-enriched green tea powder	Green tea phenolics	Shizuoka Tea, Japan
Matcha green tea yogurt	Green tea phenolics	Trader Joe's®, California, United States
Yogurt with green tea extract Silhouette 0+®	Green tea phenolics	Danone, Incorporated, Quebec, Canada
Chocolate bar CocoaVia®	Cocoa flavonoids (can include epicatechin and procyanidin B2)	Mars, Incorporated, Virginia, United States
Chocolate dietary supplement drink CirkuHealth™	Cocoa flavonoids (can include epicatechin and procyanidin B2)	Mars, Incorporated, Virginia, United States
Water Vitaminwater™-"sync" berry-cherry	Berry phenolics	Glaceau Vitaminwater®, New York, United States
Grape skin powder Cabernet Grape Powder – used to fortify breads	Grape phenolics (can include trans-resveratrol, quercetin, (+)-catechin, and (-)-epicatechin)	Vinifera For Life Canada™, Ontario, Canada
Sports drink Xilarate™ Sports Power Fluid	Grape-seed extract	Xilarate, Ontario, Canada
Polyphenolic-enhanced wine	Resveratrol	The Wine Doctor Resveratrol Enhanced Wines, NSW, Australia
Nutrition bar soy protein bar	Soy isoflavones	GeniSoy®, Oklahoma, United States

Source: Gaudette and Pickering 2013, Table 1. Reproduced with permission of Taylor & Francis Group; www.tandfonline.com

Nesterenko et al. 2013) and to remove molecules that cause off-flavors or undesirable tastes of certain functional ingredients.

Although it is reasonable and useful to consume more oil-rich fish and fish products, as another example, dietary preference and sensory attributes (smell and taste) may present a barrier to consumers' choices. Encapsulation has been used to circumvent these unacceptable effects (Champagne and

Fustier 2007), and encapsulated PUFAs have been used to enrich or fortify various food products. Fish oils and vegetarian algae-based PUFAs are incorporated into a wide range of products such as beverages and juices, baby food and pediatric juices, breads and bakery products, dairy products, processed meats, and cooking oils. Complexation with cyclodextrin provides an alternative method similar to encapsulation to improve the physicochemical characteristics of some bioactive substances in order to enhance their absorption and distribution to target tissues (dos Santos et al. 2011; Beig et al. 2013).

1.4 Current Formulation Trends and the Modern Marketplace

Robust science continues to demonstrate the beneficial health effects of bioactive proteins and peptides, PUFAs, fibers, phytochemicals, probiotics, and prebiotics in improving general health and reducing markers and risks of certain illnesses. Combined with a thriving and still largely untapped market for some of these nutraceuticals and functional foods, food manufacturers seeking higher profit margins from the sale of these food products are using various formulations and production technologies to expand growth opportunities. Important drivers and challenges include increasing production costs, sustainability concerns, growing health issues, and changes in consumer preferences including an increased desire for product differentiation and efficacy (Siró et al. 2008). Additionally, manufacturers are looking for alternative improved methods to the current labor-intensive and time-consuming purification procedures that must meet strict quality standards. Manufacturers are using superior handling techniques to improve stability during processing, and to enhance recovery of the final product. These approaches may prove to be cost-effective in the long term, while creating a competitive advantage in the marketplace to ensure sustained growth and consumer satisfaction. It is estimated that the total cost of developing and marketing functional foods may far exceed the US$1–2 million required to develop conventional new food products (Siró et al. 2008), owing to the more arduous requirements such as proof of product efficacy and hurdles to obtain health claim approvals for use on packaging in the marketing of the former.

In the future, new formulation and product development will likely focus on products for healthy aging, healthy breakfast and snacking, cognitive function, muscle building, and personalized nutrition, among others. Currently, examples of popular products developed to address market needs include fortified orange juice with calcium to serve lactose-intolerant consumers; soy-based products as sources of protein for vegetarians; ω-3-enriched eggs or pasta or preformed DHA products; and products fortified with EPA and/or DHA for those who do not like seafood, vegans, individuals who are allergic or cannot eat fish, those concerned about mercury levels in foods, and those who elect not to include fish in their diets.

Current formulation trends seek to offer products in which natural health choices and convenience have converged. Ready-to-drink (RTD) tea is one of the fastest-growing beverage categories globally, due to consumer preferences and convenience. Nestea® and its different varieties are produced by The Coca-Cola Company and Nestlé. These beverages are a combination of the strong antioxidant powers of tea and the benefits of drinking water. Several brands and forms of tea (e.g., black, green, herbal, fruit/spice-flavored and decaf, HONEST, and Celestial Seasonings' "Brew Over Ice") are available.

Healthy-ingredient snacks are shaping up as a new consumer trend and an emerging functional food market to contrast the well-known sweet and salty attributes of snacks. Functional foods as snacks and mini-meals including nuts and seeds have been formulated and packaged as bars, vegetable/fruit chips, dried fruit, and nut and seed blends to provide greater convenience. Probiotics are commonly consumed as part of fermented foods, such as kefir, kurut, and yogurt, or as dietary supplements. Other products such cheese, fermented milk, yog-ice cream, cheese-based dips, probiotic fermented lactic beverages, probiotic fiber-enriched fermented milks, starch-based dairy desserts, and non-fermented frozen vegetarian desserts are also commercially available (Di Criscio et al. 2010; Escobar et al. 2012; Minervini et al. 2012; Castro et al. 2013). Food manufacturers are finding new ways to incorporate alternative sources of functional ingredients into mainstream products, such as energy bars, breakfast cereals, meat alternatives, and beverages. Several probiotic foods and beverages have been formulated to contain other bioactive compounds such as fruits, vegetables, and herbs known for their minerals, vitamins, dietary fibers, and phytochemicals content with multi-functional health benefits provided in a single food (Table 1.23).

Foods such as yoghurt have low content of phenolics (Karaaslan et al. 2011). A recent study described the supplementation of yoghurt with grape extracts or grape callus cultures for their inherent phenolic compounds and potential free radical scavenging activity (Karaaslan et al. 2011; Chouchouli et al. 2013). Blending of milk and legume proteins into cheese may be used to reduce fat and cholesterol content without adversely affecting texture. Breakfast meals are being formulated to contain a combination of one or more of products such as whole grains, fiber, protein, omega-3 FAs, and antioxidants.

Table 1.24 provides a sample of products formulated with bioactive peptides as well as ingredients for various applications. Alternative protein ingredients are growing in importance, and they include plant protein sources such as grains and legumes, consumed as is and formulated into processed foods. Legume flours from pulses have been introduced into the food processing chain, where they contribute protein, starch, and fiber (Boye et al. 2010). Pulse proteins especially represent a small but growing segment of the overall protein market, a market dominated for many years by soybean and animal

Table 1.23 Examples of commercial probiotic products

Brand/trade name	Description	Producer
Actimel	Probiotic drinking yogurt with *Lactobacillus casei Imunitass®* cultures	Danone, France
Activia	Creamy yogurt containing *Bifidus ActiRegularis®*	Danone, France
Gefilus	A wide range of *Lactobacillus rhamnosus* GG (LGG) products	Valio, Finland
Hellus	Dairy products containing *Lactobacillus fermentum ME-3*	Tallinna Piimatööstuse AS, Estonia
Jovita Probiotisch	Blend of cereals, fruits, and probiotic yogurt	H&J Bruggen, Germany
Pohadka	Yogurt milk with probiotic cultures	Valašské Meziříčí Dairy, Czech Republic
ProViva	Refreshing natural fruit drink and yogurt in many different flavors, containing *Lactobacillus plantarum*	Skåne mejerier, Sweden
Rela	Yogurts, cultured milks, and juices with *Lactobacillus reuteri*	Ingman Foods, Finland
Revital Active	Yogurt and drink yogurt with probiotics	Olma, Czech Republic
Snack Fibra	Snacks and bars with natural fibers and extra minerals and vitamins	Celigüeta, Spain
SOYosa	Range of products based on soy and oats, including a refreshing drink and a probiotic yogurt-like soy–oats product	Bioferme, Finland
Soytreat	Kefir-type product with six probiotics	Lifeway, United States
Yakult	Milk drink containing *Lactobacillus casei* Shirota	Yakult, Japan
Yosa	Yogurt-like oats product flavored with natural fruits and berries containing probiotic bacteria (*Lactobacillus acidophilus*, *Bifidobacterium lactis*)	Bioferme, Finland
Vitality	Yogurt with pre- and probiotics and omega-3	Müller, Germany
Vifit	Yogurt drink with *Lactobacillus rhamnosus* GG (LGG), vitamins, and minerals	Campina, The Netherlands

Source: Siró et al. 2008. Reproduced with permission of Elsevier.

Table 1.24 Commercially available functional foods or ingredients containing food-derived bioactive peptides

Product name	Type of food	Health claim	Manufacturer
BioZate	β-LG hydrolysate (whey-derived peptides)	Hypotensive	Davisco, United States
Calpico (Europe) or Calpis AMEAL S (Japan)	Fermented milk (β- and $_{\kappa}$-casein)	Hypotensive	Calpis Co., Japan
Casein DP Peptio Drink	Soft drink (casein-derived dodecapeptide)	Hypotensive	Kanebo, Japan
C12 Peptide	Ingredient (casein-derived dodecapeptide)	Hypotensive	DMV, Netherlands
Evolus	Fermented milk, calcium enriched (β- and $_{\kappa}$-casein)	Hypotensive	Valio, Finland
Peptide Soup	Soup (Bonito-derived peptides	Hypotensive	NIPPON, Japan
BioPURE-GMP	Whey protein hydrolysate (glycomacropeptide)	Anticarcinogenic, antimicrobial, antithrombotic	Davisco, United States
Capolac	Ingredient (CPP)	Aids mineral absorption	Arla Foods, Denmark
CE90CPP	Ingredient (20% CPP)	Aids mineral absorption	DMV, Netherlands
Kotsu Kotsu calcium	Soft drink (CPP)	Aids mineral absorption	Asahi, Japan
Tekkotsu Inryou	Soft drink (CPP)	Aids mineral absorption	Suntory, Japan
PeptoPro	Ingredient (beverages, gels)	Improves athletic performance	DSM Food Specialists, Netherlands
ProDiet F200	Milk drink, confectionary (α_{S1}-casein (fragment 91–100))	Reduces stress	Ingredia, France
Glutamin peptide WGE80GPA WGE80GPN WGE80GPU	Dry milk protein hydrolysate (glutamine-rich peptides)	Immunomodulatory	DMV, Netherlands

Source: Hartmann and Meisel 2007. Reproduced with permission of Elsevier.

protein. It has become increasingly important as a replacement for soy in many foods over time due to the similarity in their properties and the allergenicity of soy and dairy protein (Table 1.19).

While milk and milk products continue to be the main vehicle for administering probiotics and prebiotics, non-dairy matrices such as fruits and vegetables, cereal grains, and meat have been considered for the delivery of probiotics (Siró et al. 2008; Rivera-Espinoza and Gallardo-Navarro et al. 2010). Innovations in the development of non-dairy-based probiotic foods are receiving attention due to dietary habits and preferences, and also because of lactose intolerance and allergenicity to dairy products that might prevent dairy usage by certain segments of the population (Vasudha and Mishra 2013). These matrices may be sources of other bioactive ingredients such as prebiotics, proteins, and fibers. Traditional fermented foods are a source of mixed cultures of yeast, fungi, and bacteria (lactic acid bacteria); some of them have been shown to exhibit probiotic characteristics (Table 1.25). Soybean, wheat, rye, millet, sorghum, and maize cereals have been used to replace dairy products to make beverages such as Boza, Bushera, Mahewu, Pozol, and Togwa (Vasudha and Mishra 2013). Several non-dairy, fruit- or vegetable-based beverages such as Hardaliye that contain probiotics are commercially available. Grainfields Wholegrain Liquid is a non-dairy beverage formulated with fermented grains, beans, and seeds of malted organic oats, maize, rice, alfalfa seeds, pearl barley, linseed, mung beans, rye grain, wheat, millet using lactobacillus (*Lb*.), and yeast cultures such as *Lb. acidophilus*, *Lb. delbreukii*, *Saccharomyces (Sc.) boulardii*, and *Sc. Cerevisiae*. Biola juice is a 95% fruit drink made with *Lb. rhamnosus* GG with no added sugar, by Tine BA, in Norway. It is available in orange–mango and apple–pear flavors. Rela fruit juice (*Lb. reuteri* MM53), BioGaia ProDentis lozenges (*Lb. reuteri* Protectis), BioGaia ProTectis straw (*Lb. reuteri* Protectis), and BioGaia ProTectis drops (*Lb. reuteri* DSM 17938 (*Lb. reuteri* Protectis)) are a few of the beverages and supplements from Biogaia, Sweden (Biogaia Global). Vita Biosa is a beverage made in Denmark from a mixture of fermented aromatic herbs and other plants, using a combination of lactic acid and yeast cultures.

"Ancient grains" such as kamut, teff, quinoa and amaranth, buckwheat, spelt, chia, and freekeh are called "super grains" due to their perceived health benefits. They are available as whole kernel, cut, flakes, crushed, and in flour forms, and have been employed in formulating various products such as soups, side dishes, hot cereals, ready-to-eat cereals or snack mixes, meat-free dishes (veggie-burgers, meatballs, or tacos), breads, and cookies.

Formulating synbiotic fermented milks, using strains of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium sp*. as probiotics, and fructo-oligosaccharides, galacto-oligosacharides, lactulose, and inulin-derived products as prebiotics, is another trend (Champagne et al. 2005; Di Criscio et al. 2010). In addition to their individual advantages, the combination of probiotics and prebiotics in a synergetic mix may improve the survival of the

Table 1.25 Potential probiotic traditional fermented foods

Product	Probiotic microorganisms	Substrates
Adai	Lactic acid bacteria (LAB)	Cereal, legume
Agbelima	*Lactobacillus (Lb.) plantarum*, *Lb. brevis*, *Lb. fermentum*, *Leuc. mesenteroides*	Cassava
Atole	LAB	Maize
Ben-saalga	LAB	Pearl millet
Boza	*Lb. plantarum*, *Lb. brevis*, *Lb. rhamnosus*, *Lb. fermentum*, *Leuc. mesenteroides subsp. dextranium*	Cereals
Dosa	*Leuc. mesenteroides*, *Lb. fermentum*, *Sacch. cerevisiae*	Rice and Bengal gram
Idli	*Leuc. mesenteroides*, LAB, yeast	Cereal, legume
Ilambazi lokubilisa	LAB	Maize
Kecap	LAB	Wheat, soybean
Kenkey	*Lb. casei*, *Lb. lactis*, *Lb. plantarum*, *Lb. brevis*, *Lb. acidophilus*, *Lb. fermentum*, *Lb. casei*, yeast	Maize
Kimchi	*Lb. plantarum*, *Lb. curvatus*, *Lb. brevis*, *Lb. sake*, *Leuc. mesenteroides*	Vegetables
Kishk	LAB	Cereal and milk
Kisra	*Lactobacillus* sp., *Lb. brevis*	Sorghum
Koko	*Lb. fermentum*, *Lb. salivarius*	Millet
Mahewu	*Lb. bulgaricus*, *Lb. brevis*	Maize
Mawe	*Lb. fermentum*, *Lb. brevis*, *Lb. salivarius*, *Sacch. cerevisiae*	Maize
Ngari	*Lactococcus lactis* subsp. *cremoris*, *Lactococcus plantarum*, *Enterococcus faecium*, *Lb. fructosus*, *Lb. amylophilus*, *Lb. coryniformis* subsp. *torquens*, and *Lb. plantarum*	Fish
Ogi	*Lb. plantarum*, *Lb. fermentum*, *Leuc. mesenteroides*, and *Sacch. cerevisiae*	Maize
Sauerkraut	*Leuc. mesenteroides*, *Lactococcus lactis*, LAB	Cabbage
Som-fug	LAB	Fish
Tarhana	*Streptococcus thermophilus, Lb. bulgaricus*, *Lb. plantarum*	Parboiled wheat meal and yogurt
Tempeh	LAB, *Lb. plantarum*	Soybean
Uji	LAB	Maize, sorghum cassava, finger millet

Source: Rivera-Espinoza and Gallardo-Navarro 2010. Reproduced with permission of Elsevier.

probiotic with a readily available substrate for fermentation, resulting in a better microbial balance in the colon, which can provide protective effects against colonic carcinogenesis.

Several leading food companies such as Nestlé, DANONE Group, Kraft Foods, Unilever, PepsiCo, Coca-Cola, and Heinz are devoting part of their portfolios to the “Health and Wellness” market. While treating disease remains the primary pursuit of the pharmaceutical industry, some pharmaceutical companies such as Novartis Consumer Health have shown some interest in developing functional and nutraceutical foods. They are attracted to this portfolio due to the relatively shorter development times and lower product development costs compared to pharmaceutical products and their extensive experience in organizing clinical trials to back up health claims of a specific product (Siró et al. 2008). Some food industries such as DSM and ADM are also developing stronger links with pharmaceutical companies.

Becel pro-activ® is produced by Unilever as a functional variety of Becel® margarine with plant sterols. In light of this, Becel pro-activ® holds an EFSA-approved claim for cholesterol-lowering effects. Benecol® is a brand of products from the Finnish company Raisio Group, which also produces yogurts, spreads, yogurt drinks, cream cheese spreads, milk and soy drinks, bread, and oatmeal formulated with camelina oil as a source of PUFAs. Camelina oil contains ~57.4% of PUFAs with 38% as ALA (ω-3) and 17% LA (ω-6) (Health Canada 2010). Benecol®, Promise activ®, and HeartRight® contain 0.85, 1.0, and 1.7 g per tablespoon plant sterols, respectively. Blue Band Goede Start is another product from Unilever. It is a white bread fortified with fiber, prebiotic (inulin), vitamins (B1, B3, and B6), and minerals (iron and zinc).

Balade ™ light butter is a low-cholesterol butter (5 mg per teaspoon) made by removing about 90% of milk fat cholesterol by crystalline β-cyclodextrin (cyclic oligomers of glucose, sugar molecule bound in a ring). Beta-cyclodextrin has a hydrophobic core and a hydrophilic outside. Due to the bulkiness and hydrophobicity of cholesterol, it easily lodges inside the cyclodextrin ring and is then removed (Rodal et al. 1994; Alonso et al. 2009; dos Santos et al. 2011). Other spreads such as Olivio, Country Crock Omega Plus (or Plus Light), Promise, Land O’Lakes Margarine, Fleischmann’s, I Can’t Believe It’s Not Butter! Mediterranean Light, and Earth Balance all claim to contain ω-3 (due to the presence of ALA from the vegetable oils used).

Largo® is a fortified juice produced in Estonia. It contains functional ingredients such as inulin, l-carnitine, vitamins, calcium, and magnesium. Other examples of functional drinks include cholesterol-lowering drinks (made with a combination of ω-3 and soybean), “eye health” drinks (made with lutein), or “bone health” drinks (made with calcium and inulin). Beta-glucans have been used to produce low-fat ice creams and yogurts. BioGaia® currently produces infant formula, colic drops, chewable tablets, lozenges, chewing gums, and drops with specially added active live cultures of *Lactobacillus reuteri Protectis*.

Escalating demand for conventional ingredients is putting pressure on prices, while demands for specific ingredients such as whole grains and gluten-free grains are also on the rise. Additionally, to help improve waste disposal in pursuance of corporate sustainability and growing regulatory pressure around waste disposal (Vriesmann et al. 2012), food manufactures such as Barry Callebaut have used valorization as a source of ingredients in food processing. Cocoa husks account for approximately 52–76% of the weight of the fruit (Donkoh et al. 1991). Barry Callebaut has filed several patents for various by-products that can be obtained from cocoa processing, such as fiber and antioxidants from cocoa shell/hull/husk, and to grind the shells into a powder for use as a cocoa replacer, fat bloom inhibitor, and ingredient in other foods. Kraft Foods filed a patent in 2005 for a method for extracting theobromine-enriched fractions and polyphenol-enriched fractions from cocoa shells. Tomato processing generates a large amount of waste made up of skins, seeds, and pulp (Kalogeropoulos et al. 2012). These three components account for about 10–30% of the total weight of tomato while the skins and seeds account for about 1–4% (Benakmoum et al. 2008). The by-products of tomato processing contain significantly lower amounts of lycopene, but increased amounts of tocopherol, polyphenol, β-carotene, terpenes, and sterols that seem to withstand industrial processing methods, and possess similar antioxidant activities to unprocessed tomatoes. Low-quality edible oil formulated with tomato skins enriched the oil with β-carotene and lycopene more than when tomato purée was used (Benakmoum et al. 2008).

While some information on these methods has been reported, detailed descriptions of several other emerging formulations is still at the developmental stage, with strong intellectual property positions. Some formulation and processing technologies' trends of interest include pressurized solvent extraction (PLE) and a variation of conventional solvent extraction using high temperatures (50–200°C) and pressures (1,450–2,175 psi); this maintains the solvent in the liquid state during the whole extraction procedure, and allows faster extraction by using lesser amounts of solvents, resulting in higher product yields. Increasing the temperature decreases the dielectric constant and polarity of a solvent; thus, by varying temperature, polar and non-polar compounds can be extracted. Due to the high temperatures employed, PLE is not suitable for thermolabile compounds. Water or other GRAS solvents, such as ethanol, can be used.

Gamma irradiation has been used to extend the shelf life of grape pomace and improve anthocyanin content (Ayed et al. 1999). Lower storage temperatures have been used to reduce isomerization and oxidation. Enzymatic liquefaction with pectinases and cellulases has been used to enhance the release of phenolics from apple pomace (Will et al. 2000), with improved juice yields for extended fields of application. In another interesting study, pulsed electric field (PEF) was used on tomato to induce a stress response that enhanced metabolic activity and accumulated secondary metabolites (Vallverdú-Queralta et al. 2013). The use of moderate-intensity pulsed electric field (MIPEF) made it possible to obtain tomato juices with high carotenoid content, while using high-intensity pulsed electric fields (HIPEF) helped to maintain higher contents of carotenoids (10–20%) during storage compared to thermally treated and untreated juices (Vallverdú-Queralta et al. 2013).

One of the critical parameters preventing the adoption of novel technologies and broad commercial implementation in specific applications has been technological/scale-up boundaries (Siró et al. 2008). Harmonizing regulatory processes across major international markets may also be beneficial to the success of functional foods and nutraceuticals at the global level.

1.5 Conclusion

Epidemiological and clinical studies across multiple geographical locations have generally shown neutral or beneficial effects of the consumption of certain types of foods on health and wellness and reduction of risk factors for certain diseases. Health-conscious consumers have developed an awareness and overall positive perception of functional foods and nutraceutical products derived from such food sources. Whereas much progress has been made in the last few decades in this market sector, there remains significant opportunity for further research and development. Substantiation of health claims, identification of new bioactives, robust processing technologies, and development of shelf-stable, tasty, and convenient products are examples of areas needing continued attention. Further innovation and introduction of products with well-substantiated health claims are therefore anticipated in the coming decades.

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