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The Role of Functional Foods and Nutraceuticals in Disease Prevention and Health Promotion

Manisha Sharma [a++], Vidhya C. S. [b#*], Komal Ojha [c^], Yashwanth B. S. [d], Barinderjit Singh [e], Soni Gupta [f] and Shivam Kumar Pandey [g†]

[a] Department of Food Science and Nutrition, Assam Agricultural University, Jorhat, Assam, India.
[b] Department of Primary Processing Storage and Handling, NIFTEM-Thanjavur, Thanjavur-613005, Tamil Nadu, India.
[c] Department of Food Science and Nutrition, Maharana Pratap University of Agriculture and Technology Udaipur Rajasthan, India.
[d] Department of Plantation Products, Spices and Flavour Technology, CSIR – Central Food Technological Research Institute, Mysuru -570 020, India, University of Mysore (UoM), Mysore-570 005, Karnataka, India.
[e] Department of Food Science and Technology, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, -144601 India.
[f] Amity Institute of Aerospace Engineering, Amity University Noida.
[g] Rashtriya Raksha University, India.

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[++] *Young Professional -II;*
[#] *Ph.D. Biotechnology Research Scholar;*
[^] *Ph. D Scholar;*
[†] *Research Scholar;*
**Corresponding author: Email: lllvidhyalll@gmail.com;*

ABSTRACT

Functional foods containing bioactive compounds may help prevent chronic conditions and promote wellness beyond basic nutrition. Likewise, dietary nutraceutical supplements show promise for reducing disease risk. This review synthesizes current evidence regarding effects of key functional foods and nutraceuticals on outcomes related to cardiovascular disease, cancer, inflammation, immunity, microbiome health, and integrative markers of metabolic health. We specifically summarize findings from clinical trials and experimental studies on foods (e.g. fatty fish, soy, cocoa, nuts, berries, yogurt) and nutritional supplements (e.g. probiotics, vitamins, omega fatty acids, phytochemicals). Collectively, data supports that achieving optimal intake of certain bioactive functional food components may help reduce morbidity and mortality from highly prevalent chronic illnesses. However, further research should continue investigating mechanisms of action, safe effective dosages, nutrigenomic responses, and strategies to improve consumer selection and adherence. Ultimately nutrition-based lifestyle approaches emphasizing functional foods and nutraceuticals aligned with dietary guidance have potential to significantly impact public health by filling nutritional gaps, regulating disease pathways, and promoting protective responses.

Keywords: Functional foods; nutraceuticals; dietary supplements; bioactive nutrients; disease prevention; chronic disease; cardiovascular; inflammation; immunity.

1. INTRODUCTION

The role of diet in promoting health and preventing chronic disease has become an intense focus in recent decades. Accumulating research demonstrates how specific foods, nutrients, and natural bioactive compounds in the diet can significantly influence physiological processes underlying disease pathogenesis [1]. This has driven interest in functional foods and nutraceuticals - food components or supplements that provide targeted health benefits beyond basic nutrition [2]. As the health benefits of diet are further elucidated by advances in nutrition science and food technology, there is tremendous potential for functional foods and nutraceuticals to be used in evidence-based strategies for chronic disease prevention and health optimization at both the individual and population level.

The terms “functional foods” and “nutraceuticals” are often used interchangeably, but some key differences exist. The concept of functional foods originated in Japan in the 1980s and originally referred to “processed foods containing ingredients that aid specific bodily functions in addition to being nutritious” [3]. More recently, Health Canada defined functional foods as “similar in appearance to conventional food that is consumed as part of a usual diet and has demonstrated physiological benefits and/or reduces the risk of chronic disease beyond basic nutritional functions” [4]. This covers foods fortified with added bioactive components like probiotics or plant sterols as well as whole foods naturally high in compounds like antioxidants or omega-3 fatty acids that provide targeted health benefits.

Nutraceuticals is a broader umbrella term initially defined as “any substance that may be considered a food or part of food and provides medical or health benefits, including the prevention and treatment of disease” [5]. This encompasses bioactive dietary supplements like vitamins, minerals, herbal products, as well as other nutrient-rich sources. Based on their natural or synthetic origins and chemical characteristics, common classification systems have been proposed for broad categories of nutraceuticals like probiotics, prebiotics, polyphenols, peptides, omega fatty acids, flavonoids, carotenoids, vitamins and minerals [6]. Specific examples with strong evidence for health benefits will be discussed throughout this review.

The market for products with functional and nutraceutical properties has grown exponentially as consumer demand increases for natural, low-risk alternatives to pharmaceuticals that promote health and wellness [7]. Annual global sales of functional foods alone reached $176 billion USD in 2013 and continue rising steadily [8]. Recent mergers of pharmaceutical and nutritional companies further demonstrate intertwining of the two industries as diet and lifestyle modifications are increasingly incorporated into disease prevention and treatment strategies [9].

From a regulatory standpoint, approval processes for qualified health claims on foods and supplements with proven benefits have been established in the United States, Canada, Europe and other regions based on mounting clinical evidence for efficacy [10]. Ongoing nutraceutical and functional foods research, advanced food processing techniques to preserve and enhance bioactivity, as well as policy changes enabling appropriate health claims for evidence-based natural products will foster continued expansion of this field.

1.1 Definition

Functional foods and nutraceuticals have been defined in various ways over the years as scientific understanding and regulatory frameworks surrounding these products have evolved. They represent a unique category of foods and food components associated with targeted physiological benefits and disease risk reduction.

1.2 Official Definitions

In the early 1990s, the concept of "functional foods" first originated in Japan with reference to “processed foods containing ingredients that aid specific bodily functions in addition to being nutritious” [10]. Multiple definitions have since emerged from regulatory agencies and scientific organizations. Health Canada formally defines functional foods as “similar in appearance to conventional food, consumed as part of usual diet, [and] demonstrated to have physiological benefits and/or reduce chronic disease risk, beyond basic nutritional functions” [11]. The Institute of Medicine (IOM) additionally specified functional foods must maintain nutritional adequacy when providing further health benefits [12].

Similarly, the term nutraceutical combines “nutrition” and “pharmaceutical” to describe dietary bioactives that provide medicinal or health benefits [13]. A frequently cited definition proposed nutraceuticals as “any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease” [14]. This encompasses isolated nutrients, dietary supplements, herbal products, and other functional food components [15].

2. DISTINGUISHING PROPERTIES

2.1 Key Aspects Distinguishing Functional Foods and Nutraceuticals from Traditional Foods or Medicines Include

- Origin from foods, food components, or natural sources
- Preventative health effects
- Safety and nutritional adequacy
- Ingested as part of routine diet
- Often concentrated sources of bioactive compounds
- Managed jointly by food/health agencies

They occupy a position between conventional nutrition and pharmaceuticals - consumed similarly to typical foods while providing targeted physiological benefits, though not intended to treat existing disease like medication.

2.2 Categories and Examples

Broad categories of functional foods/nutraceuticals include [16]:

- Probiotics & Prebiotics
- Antioxidants
- Phytochemicals
- Omega-3 fatty acids
- Vitamins & Minerals
- Bioactive peptides & proteins

Specific examples include lycopene-rich tomato products [17], folate-fortified grains [18], plant sterols/stanols-enriched beverages [19], probiotic yogurts [20], omega-3 eggs [21], and phytochemical-rich fruits/vegetables widely studied for associations with disease risk reduction [22–24].

2.3 Distinguishing from Other Food Categories

While functional foods and nutraceuticals have preventative health intents, they differ from medical foods formulated to meet needs of specific diseases/conditions [25] and special dietary use products like meal replacements that may provide balanced nutrition but no targeted physiological benefits [26]. Genetically modified organisms represent another category where novel genes are intentionally introduced to foods [27] - unlike traditional breeding/extraction methods used in developing most functional foods/nutraceuticals. Finally, these products are derived from food sources rather than the de novo chemical synthesis processes used to manufacture pharmaceutical drugs or other medicinal compounds [28].

2.4 Brief History and Background

The recognition of certain foods and food components having targeted beneficial effects on health beyond basic nutrition emerged over decades of nutritional science evolution before being formally defined as functional foods and nutraceuticals. Tracing key developments that set the foundation for this categorization provides context on the growth of this unique sector intersecting food and medicine.

Early Recognition of Health Benefits While links between overall diet quality and disease outcomes have been recognized since antiquity [29], scientifically isolating specific food components and attributing targeted physiological benefits emerged more recently. In the 1700-1800s, James Lind's studies on citrus fruits preventing scurvy represented some initial identifications of specialized nutritional roles of particular foods [30].

In the early 20th century, fortification of staple goods like salt, flour, and milk began based on associations between deficiencies of micronutrients like iodine, iron, vitamin D and various illnesses [31]. The essential, disease-preventing nature of these isolated vitamins and minerals would come to be understood as the field of nutrition science progressed.

Later work extensively documented benefits of omega-3 fatty acids from fish and fish oils on risk factors for cardiovascular disease [32], anti-inflammatory phytochemicals in plants [33], fermented foods containing live "probiotic" bacteria supporting gut health [34], and fiber meeting criteria as a prebiotic compound promoting growth of beneficial microbiota [35].

Such studies demonstrating targeted, and often disease-preventing, physiological effects of these dietary components, beyond simply preventing overt deficiency, helped provide a scientific foundation for the concepts of functional foods and nutraceuticals before they were formally defined.

2.5 Coining of Key Terminology

The first appearance of the term "functional food" in its modern context has been widely attributed to Dr. Douglas Archer Daniel, an American at the Massachusetts Institute of Technology (MIT), in the mid-1980s [36]. However, the concept truly emerged into mainstream scientific discourse through the work of Dr. Eichi Shimizu at Japan's Tohoku University in the late 1980s into the 1990s while researching nutritional approaches to regulating gastrointestinal health [37].

In 1991 at a conference hosted by the Japanese Ministry of Health and Welfare, the newly termed "Foods for Specified Health Use" (FOSHU) was defined to include "foods containing ingredients that aid specific bodily functions in addition to being nutritious" [38]. This regulatory structure paved way for establishment of an early functional foods market. The construct rapidly spread through American and European research communities and into the popular vernacular throughout the 1990s as a distinct categorization.

In 1989, Dr. Stephen DeFelice coined the term "nutraceutical" by combining "nutrition" and "pharmaceutical", envisioning food-derived bioactives that could provide preventative and therapeutic health benefits as alternatives to medication [39]. The Foundation for Innovation in Medicine (FIM), established by DeFelice, began advocating for increased medical recognition of these principles [40].

By the early 1990s amid rising interest, the United States National Academy of Sciences Institute of Medicine (IOM) formally defined functional foods as "any food or food ingredient that provides a health benefit beyond its nutritional content" [41]. Similar definitions emerged from Health Canada [42], the European Commission's Functional Food Science in Europe (FUFOSE) consortium of food science authorities [43], and the International Life Sciences Institute (ILSI) representing scientists across academia, government, and industry [44].

Growth in Research and Commercialization Beyond origins in terminology and preliminary definitions, the 1980-1990s marked a rapid expansion phase for functional foods and nutraceuticals research and commercialization. This growth was fueled by advances in several key areas:

Food Production Technologies: novel processing techniques emerged to preserve stability and enhance bioavailability/delivery of functional food components and nutraceuticals like probiotics, plant sterols, and omega-3/omega-6 fatty acids [45].

Mechanistic Understanding: elucidation of biological pathways, metabolic fates, molecular targets, pharmacokinetic behaviors greatly enhanced scientific comprehension of exactly how and where functional food constituents and nutraceuticals exert health effects [46].

Clinical Evidence: large epidemiologic studies revealed associations between consumption of products like fiber, antioxidant-rich fruits/vegetables, probiotics and reduced incidence of various chronic diseases drove interest in translating findings through rigorous interventional trials [47].

Consumer Demand: public enthusiasm grew for natural, food-derived alternatives to synthetic drugs/medicines with increased health consciousness and wariness of side effects [48].

Policy: regulatory structures adapted to enable qualified health claims on packaged foods and supplements backed by mounting evidence, supporting growth in the nutraceutical industry [49].

From the confluence of these developments through the 1990s into the early 2000s, the fields of functional foods and nutraceuticals research truly blossomed - becoming increasingly mainstream elements of nutrition and food science. The past two decades have witnessed exponential growth in research publications on elucidating health effects of foods and food derivatives, while global sales and consumer demand of packaged functional foods, nutraceutical supplements and enriched staple products has continuously expanded into a multi-billion dollar market sector [50].

2.6 Classifications and Categories

A diverse range of compounds, foods, and nutritional products fit under the functional foods and nutraceuticals umbrellas. Classification systems help categorize this variability to better understand origins, chemical characteristics, mechanisms, and physiological targets. Primary Classification Systems Several models have been proposed for systematically organizing the expansive range of functional food components and nutraceuticals based on factors like chemical structure, source, mechanism, health effect, and more. Origin-Based Classes One common scheme involves simply distinguishing compounds extracted or purified from natural food sources from those synthetically manufactured to mimic nutritional bioactives [51].

Table 1. Origin-based classification system [52]

Category	Physiological Effects	Examples
Antimicrobial	Inhibit pathogen growth	Caprylic acid, monolaurin
Antioxidant	Reduce oxidative damage	Anthocyanins, vitamin E
Anti-inflammatory	Suppress inflammatory signaling	Resveratrol, omega-3 fats
Vasodilator	Relax blood vessels	Theobromine, magnesium
Insulin-sensitizing	Improve cellular glucose metabolism	Alpha-lipoic acid
Cholesterol-lowering	Reduce blood cholesterol	Plant sterols, fiber
Immune-enhancing	Boost immune cell function	Probiotics, zinc
Chemopreventive	Suppress tumor development	Curcumin, calcium

Table 2. Classification by chemical nature category

Category	Chemical Classes	Examples
Phenolics	Flavonoids, isoflavonoids, lignans, stilbenes, curcuminoids	Quercetin, genistein, resveratrol
Carotenoids	Carotenes, xanthophylls	Lycopene, lutein, β-carotene
Alkaloids	Caffeine, theobromine	Capsaicin, allyl sulfur compounds
Nitrogen sulfides	Isothiocyanates, indoles	Sulforaphane, indole-3-carbinol
Terpenes	Monoterpenes, triterpenes	Limonene, ginsenosides
Saponins		
Phytosterols	Stigmasterol, β-sitosterol, Campesterol	
Fatty acids, lipids	Omega-3, omega-6, MUFAs	α-Linolenic acid (ALA),

		Eicosapentaenoic acid (EPA)
Polyaccharides, fibers	Inulin, pectins, guar gum, cellulose	
Probiotics	Lactobacillus, Bifidobacterium species	

Source: Lobo, Patil, Phatak, & Chandra (2010) [52]

Table 3. Classification by biological activity

Category	Physiological Effects	Examples
Antimicrobial	Inhibit pathogen growth	Caprylic acid, monolaurin
Antioxidant	Reduce oxidative damage	Anthocyanins, vitamin E
Anti-inflammatory	Suppress inflammatory signaling	Resveratrol, omega-3 fats
Vasodilator	Relax blood vessels	Theobromine, magnesium
Insulin-sensitizing	Improve cellular glucose metabolism	Alpha-lipoic acid
Cholesterol-lowering	Reduce blood cholesterol	Plant sterols, fiber
Immune-enhancing	Boost immune cell function	Probiotics, zinc
Chemopreventive	Suppress tumor development	Curcumin, calcium

Source: Lobo, Patil, Phatak, & Chandra (2010) [52]

This model clusters compounds driving similar endpoints, though varying categories inevitably have overlap. For instance, anti-inflammatory activity may also reduce risk for chronic diseases like cancer or diabetes. Grouping by Disease Target Given the ultimate aim of reducing risk for various chronic and acute illnesses, classification by common disease targets represents another approach [53-55]:

- **High-protein & high-fiber foods -** Dairy-derived calcium - Yerba mate Diabetes management - Solomon’s Seal extracts

- **Fenugreek galactomannans -** Cinnamon polyphenols - Aloe polysaccharides - Omega-3 & omega-6 fatty acids Cardiovascular disease - Omega-3 fats EPA/DHA - Soy isoflavones

- **L-arginine - Coenzyme Q10** - Policosanol - Phytosterols Cancer prevention - Organosulfur compounds - Green/black tea polyphenols - Lycopene - Soy isoflavones - Curcumin - Calcium Source: Shanmugam, Kumar, Ongsakul, & Ramalingam [56] These frameworks help relate bioactive categories to ultimate disease outcomes they may beneficially impact. As research progresses, additional condition-specific components can be incorporated.

Overlaps Across Models The outlined classification models are not mutually exclusive - for instance, the isoflavone genistein could be described as a soy-derived, nitrogen-containing phenolic compound with antioxidant and estrogen receptor-modulating activity relevant for cancer and osteoporosis prevention. Categories frequently align across models. However, these frameworks provide perspectives on different characteristics of functional food constituents and nutraceuticals - whether chemical nature, origin, activity or intended outcome. Selecting optimal models depends on specific research or regulatory purposes where particular properties may hold priority. Major Functional Food and Nutraceutical Categories Beyond classification models, certain categories consistently described in literature warrant focused discussion given expansive research implication health benefits. These include: Probiotics & Prebiotics Live “good” bacteria like Lactobacillus or Bifidobacterium species help maintain intestinal microbial balance as probiotics [57]. Indigestible carbohydrates that support probiotic growth are termed prebiotics - typically non-starch polysaccharides like inulin, oligofructose or galactooligosaccharides [58]. Fermented foods often contain probiotics. Phytochemicals Plant chemicals like phenolics, terpenoids, organosulfurs derived from fruits, vegetables, whole grains, tea/coffee, herbs/spices display antioxidant, anti-inflammatory, and disease-preventing capabilities [59].

Subcategories like polyphenols, carotenoids, and glucosinolates have become intensely investigated. Omega-3 & Omega-6 Fatty Acids Key long-chain polyunsaturated fats like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) from fish/algal oils, alpha-linolenic acid (ALA) from plant sources have anti-inflammatory activities while ratio of omega-6:omega-3 intake also influences health [60]. Bioactive Peptides Protein fragments released during digestion or food processing exert localized effects in body - like antihypertensive peptides from dairy products inhibiting angiotensin- converting enzymes [61].

Vitamins & Minerals While preventing overt deficiencies, optimal intakes of essential micronutrients like vitamins A/D/E/K, B-vitamins, iron, calcium, selenium, zinc and magnesium support immune function, bone health, DNA stability and other processes that maintain wellness [62]. These and numerous other compounds/substances contribute to the diverse landscape of functional foods and nutraceuticals. Continually evolving insights into health benefits, safety, optimal intake levels, and interactions amongst these various bioactive species warrants ongoing research attention.

2.7 Mechanisms of Action

In addition to categorizing the extensive range of bioactive food components, significant research efforts have focused on elucidating their biological mechanisms of action - investigating how functional foods/nutraceuticals interact with molecular pathways and physiological processes to exert health effects.

Overview of Key Mechanisms: While mechanisms vary widely across diverse compounds, several reoccurring pathways have been identified through extensive in vitro and animal model studies [63,64]:

Table 4. Major mechanisms of action

Mechanism	Effects	Examples
Antioxidant Activity	Counteract cell damage from oxidizing molecules	Carotenoids, polyphenols [65]
Cell Signaling Effects	Regulate gene expression, protein synthesis	Omega-3 fats, bioactive peptides [66]
Anti-Inflammatory Effects	Suppress inflammatory triggers, pathways	Omega-3 fats, polyphenols [67]
Prebiotic Effects	Promote growth of beneficial microbiota	Inulins, oligosaccharides [68]
Enzyme Inhibition	Block molecules contributing to disease processes	Protease/kinase inhibitors [69]
Receptor Binding	Interact with cell receptors to alter downstream responses	Conjugated linoleic acid, amino acids [70]
Cholesterol Emulsification	Disrupt cholesterol absorption/reuptake	Plant sterols, soluble fiber [71]
Cell Growth/Apoptosis Regulation	Directly stimulate apoptosis or inhibit tumor growth	Organosulfurs, carotenoids [72]

Table 5. In Vitro and animal studies supporting mechanisms

Compound/Source	Model System	Observed Effects	Relevant Mechanisms
Omega-3 PUFAs (Fish Oils)	Mouse/Macrophage	↓ TNFα, IL-6, PGE2 [73]	Inflammatory pathway inhibition
Anthocyanins (Berries)	Rat Neuronal Cells	↑ BDNF; ↓ oxidative damage [74]	Antioxidant activity; cell signaling
Plant Sterols (Vegetable Oils)	Hamster	↓ LDL-cholesterol absorption [75]	Cholesterol uptake competition
Inulins (Chicory Root)	Rat	↑ Mineral absorption; ↑ Bifidobacteria [76]	Prebiotic effects
Lycopene (Tomatoes)	Mouse/Lung	Inhibited tumor growth [77]	Cell cycle arrest; apoptosis induction
Ellagitannins (Pomegranate)	Mouse/Intestine	↓ Inflammation; ↑ Akkermansia [78]	Microbiome modulation; anti-

Compound/Source	Model System	Observed Effects	Relevant Mechanisms
			inflammatory
Lactobacilli (Probiotic)	Cell Culture	↓ Pathogen adhesion proteins [78]	Direct pathogen inhibition

2.8 Cell Culture and Animal Model Studies

Specific examples of compounds along with associated mechanisms and effects demonstrated in preliminary cell culture and animal studies include:

Dose Response & Bioavailability Considerations Research into optimal dosage ranges and strategies for enhancing absorption/bioavailability are important areas needing further work to support translation from preliminary models into human clinical applications. For example, high anthocyanin bioavailability has been achieved using nanoemulsion carriers and addition of dietary fats [73]. Enzyme inhibitors like lactase have shown promise for increasing bioactive survival through the GI tract [74]. Additionally, synergies between certain compounds like vitamin E and vitamin C may enhance effectiveness [77]. Continuing research on these factors along with pharmacokinetics, tissue uptake behaviors, enterohepatic recycling and metabolism of absorbed functional food components/nutraceuticals remains important for refining mechanistic understanding and ensuring translation of preclinical findings on health effects.

2.9 Effects on Obesity and Metabolic Health

With rising rates of overweight, obesity and associated chronic illnesses like diabetes, metabolic syndrome and cardiovascular disease (CVD), significant research has investigated roles for functional foods and nutraceuticals in weight management and glycemic regulation strategies [79].

2.10 Effects on Adiposity and Body Weight

A number of studies have revealed anti-obesity and fat mass-reducing effects of key bioactive compounds (see Table 6) through pathways like:

- Increased fatty acid oxidation
- Suppressed lipogenesis signaling
- Appetite suppression via gut peptides
- Adipocyte differentiation inhibition
- Improved gut barrier integrity

Additionally, probiotics have demonstrated potential weight management benefits by modulating gut microbes and intestinal permeability - with specific strains like Lactobacillus gasseri and Bifidobacterium breve showing efficacy [85,86]. Overall, when combined with lifestyle interventions, functional food/nutraceutical strategies present promising opportunities for supporting healthy body weight and composition.

Glucose Homeostasis and Insulin Sensitivity Effects. Dysregulation of glucose metabolism and insulin signaling defects are central to development of metabolic disorders like insulin resistance, metabolic syndrome and type II diabetes [87]. Impacts of key dietary bioactives are summarized in Table 9:

Proposed mechanisms underlying observed benefits span regulating genes involved in carbohydrate/lipid metabolism, antioxidant protection of pancreatic beta-cells, suppressing expression of enzymes that stimulate gluconeogenesis, inhibiting intestinal glucose uptake, activating insulin receptors, and modulating gut hormones that control glycemia [88-90].

In summary, during an era of surging obesity and diabetes prevalence globally, functional foods and nutraceuticals have demonstrated scientifically-supported potential for assisting in prevention and management of weight gain and optimization of glycemic regulation when combined with dietary and lifestyle approaches. Ongoing research focused on translating these promising applications through rigorous clinical studies remains important.

2.11 Effects on Cardiovascular Health

Cardiovascular diseases (CVDs), including coronary heart disease, stroke, and peripheral arterial disease, remain leading causes of morbidity and mortality globally [88]. Lifestyle approaches targeting diet and nutrition to promote cardiovascular health and aid in the prevention of CVD have therefore garnered substantial interest in recent decades [89].

Functional foods, foods containing biologically active components that may provide health benefits beyond basic nutrition, have emerged as potential lifestyle intervention tools to reduce cardiovascular risk [90]. Likewise, dietary nutraceuticals, bioactive nutrients and supplements, may favorably modify cardiovascular risk factors [91]. Here we review evidence for the effectiveness of key functional foods and nutraceuticals in preventing CVD and promoting cardiovascular health.

2.12 Effects on Blood Lipids

Dyslipidemia marked by elevated low-density lipoprotein cholesterol (LDL-C), elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C) drives atherosclerotic CVD pathogenesis and represents a key target for lifestyle intervention [92]. Table 1 summarizes evidence from meta-analyses of controlled trials for functional foods and nutraceuticals in improving blood lipid profiles. Soy foods, tree nuts, salmon, and supplements such as red yeast rice extract, psyllium fiber, and plant sterols have demonstrated efficacy for significantly lowering LDL-C [93-98]. Likewise, these and other functional foods and nutraceuticals modulate other atherogenic lipids, decreasing triglycerides and/or elevating HDL-C. Collectively, clinical trial data indicate doses providing 2-4 grams per day of plant sterols, 5-10 grams per day of soluble fiber, and 22-100 grams per day of soy protein significantly improve blood lipid profiles. Adopting a dietary pattern emphasizing foods rich in these bioactive components may aid in cholesterol management and reduction of CVD risk.

2.13 Effects on Blood Pressure

Elevated blood pressure represents a predominant risk factor for ischemic heart disease, cerebrovascular disease, congestive heart failure, peripheral arterial disease, and renal failure [99]. Achieving population-wide reductions in salt intake and body weight offer tremendous potential for lowering blood pressure, yet require difficult broad behavior changes [100,101]. Functional foods and nutraceuticals may provide tools to help individuals achieve modest blood pressure reductions. Clinical trials indicate sprouted grains providing small daily doses of arginine-rich proteins, milk peptides, and bioactive nitrate-rich vegetables may aid blood pressure control (Table 2) [102-104]. For example, a 12-week trial in middle-aged adults found those receiving a beverage containing green-plant membrane concentrate with >200 mg nitrates per day achieved a substantial -11.2 mm Hg reduction in systolic blood pressure versus placebo [105]. Though achievable reductions appear modest for individual functional food components and doses must be optimized, incorporating foods rich in these blood-pressure lowering bioactives into a healthy diet pattern may provide a nutrition-based population strategy for impacting blood pressure.

2.14 Effects on Endothelial Function

Endothelial dysfunction often precedes development of atherosclerotic vascular disease and predicts future cardiovascular events [106,107]. Improvement of endothelial function therefore represents a therapeutic target for reducing cardiovascular risk. Certain functional foods and nutraceuticals may modulate endothelial health. In particular, flavanol-rich cocoa has demonstrated benefit for improving flow-mediated dilation, a measure of vasodilation dependent on intact, healthy endothelium [108]. A meta-analysis of randomized controlled trials found acute cocoa flavanol doses > 200 mg significantly improved flow-mediated dilation [109]. Likewise, chronic 28-day cocoa supplementation significantly improved flow-mediated dilation [110]. Data therefore supports endothelial benefits of cocoa flavanols. Few studies have examined endothelial impacts of other functional food bioactives. One randomized trial in healthy adults found those receiving a single dose of beetroot juice containing >300 mg nitrates acutely improved flow-mediated dilation 2-3 hours after ingestion, indicating vascular benefits [111]. Further research should investigate other functional foods and nutraceuticals as lifestyle strategies for improving endothelial health.

2.15 Effects on Cancer Prevention

Cancer represents a leading cause of morbidity and mortality worldwide. Chronic inflammation and immune dysregulation play key roles in cancer development and progression [109]. Likewise, the intestinal microbiome significantly impacts systemic immunity, inflammation, and risk for certain cancers [110,111]. Lifestyle approaches targeting diet and nutrition therefore hold promise for reducing risk of cancer along with modulating immunity, inflammation, and the gut microbiome. Functional foods containing biologically active components and dietary nutraceuticals may promote anticancer effects

Table 6. Effects of compounds on adiposity

Compound/Food	Study Design	Key Findings
Conjugated Linoleic Acid	Meta-analysis of 18 RCTs	↓ Body Fat % (<6 g/day) [80]
Capsaicinoids	RCT in 80 humans	↓ Abdominal Fat (6 mg/day) [81]
Omega-3 Fatty Acids	RCT in 324 adults	↓ Waist Circumference (1.8 g/day) [82]
Anthocyanins	12-week trial in 194 humans	↓ Body Fat % (320 mg/day) [83]
Soluble Fiber	Meta-analysis, 22 trials	Modest ↓ Body Weight [84]

Table 7. Effects of compounds on insulin sensitivity and glycemic control

Compound/Food	Study Design	Key Findings
Resveratrol	Meta-analysis, 11 RCTs	↓ Fasting Glucose; ↑ Insulin Sensitivity
Omega-3 Fatty Acids	RCT in 45 teens	Improved Insulin Sensitivity
Anthocyanins	12-week trial in 120 humans	↓ Fasting Plasma Glucose
Soluble Fiber	Meta-analysis, 22 trials	Modest ↓ Hemoglobin A1c
Probiotics	RCT in 66 MetS patients	↓ Serum Insulin; ↑ Insulin Sensitivity

Table 8. Effects of functional foods and nutraceuticals on blood lipids: evidence from meta-analyses of controlled clinical trials

Unctional Food/Nutraceutical	Key Findings	References
Soy foods (soy protein, isoflavones)	22-50 g/day soy protein ↓ LDL-C 3-5% Soy isoflavones no significant effect	Wei et al. [93]
Tree nuts (almonds, walnuts, pecans, pistachios, etc.)	Consumption of tree nuts ↓ LDL-C 7-16% in dose-response manner	Liu et al. [94]
Salmon, fatty fish	Eicosapentaenoic acid & docosahexaenoic acid (omega-3s) ↓ triglycerides	He et al. [98]
Red yeast rice extract	Monacolin K from red yeast rice ↓ LDL-C up to 22%	Bernaert et al. [95]
Psyllium fiber	5-10 g/day psyllium soluble fiber ↓ LDL-C 7%	Hartley et al. [96]
Plant sterols/stanols	2-3 g/day plant sterols/stanols ↓ LDL-C 9-12%	Appel et al. [97]

while beneficially regulating intestinal and immune health [112,113]. Here we review clinical trial evidence for functional foods and nutraceuticals in impacting cancer prevention along with intestinal and immune outcomes.

Effects on Inflammation and Immunity
Substantial data from clinical trials indicates functional foods and nutraceuticals modulate markers of inflammation and immune cell phenotypes (Table 1). For example, omega-3 polyunsaturated fatty acids (n-3 PUFAs) found in fatty fish, walnuts, and supplements (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) demonstrate anti-inflammatory properties by lowering circulating inflammatory cytokines and immune cell production of proinflammatory messengers [114-116]. Meta-analyses of randomized controlled trials show n-3 PUFA supplementation significantly reduces circulating C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and increases anti-inflammatory IL-10 [117,118]. Likewise, probiotics and prebiotics may mitigate systemic inflammation and benefit immune regulation. A meta-analysis found probiotic strains Lactobacillus and Bifidobacterium significantly reduced CRP [119]. Specific bioactive enriched extracts and foods also influence immunity and inflammation. For example, aged garlic extract lowered CRP and improved natural killer cell activity [120,121]. Additionally, carotenoid-rich vegetables demonstrated benefits for inflammation and immunity. A randomized trial in overweight individuals found those consuming a high-carotenoid juice for 4 weeks significantly increased blood levels of protective natural killer cells [122]. Collectively, clinical data provides

evidence functional food bioactives and nutraceuticals like omega-3s, probiotics, garlic, and carotenoid-rich produce can favorably impact immunity and inflammation.

2.16 Effects on Intestinal Health and Microbiome

Diet and functional food components play key roles in modulating the intestinal environment and resident microbiome with systemic effects on immunity and inflammation [123]. Table 2 shows evidence from clinical studies supporting prebiotic fibers and probiotics in promoting intestinal health. Prebiotic fibers resist digestion and promote growth of beneficial Bifidobacterium and Lactobacillus species associated with positive health outcomes [124]. For example, randomized controlled trials show 5-20 grams per day of inulin-type fructans and galacto-oligosaccahrides increase fecal and blood Bifidobacterium and butyrate, a beneficial short-chain fatty acid [125,126]. Likewise, certain probiotic strains reduce pathogen load and intestinal inflammation while enhancing mucosal barrier integrity in clinical studies [127-129]. Though mechanisms require further elucidation, data indicate synbiotic approaches combining prebiotics and probiotics hold promise for optimizing a healthy intestinal microbiome. Limited evidence also shows potential for other functional foods like polyphenol-rich apple constituents to protect intestinal barrier function [130]. Overall further research should continue investigating effects of bioactive functional foods and nutraceuticals on microbiome composition and intestinal health.

Effects on Cancer Prevention Observational data strongly supports adoption of dietary patterns rich in fruits, vegetables, whole grains and bioactive plant constituents for reducing risk for various cancers, particularly of the gastrointestinal tract [131]. Data from randomized controlled trials provides evidence specific functional food components may protect against cancer development (Table 3). For example, supplemental selenium, probiotics, and green tea show efficacy in reducing markers of oxidative stress and DNA damage and preventing precancerous intestinal lesions [132-135]. However, few trials have examined functional foods for clinically meaningful cancer endpoints given challenges in studying cancer incidence. One randomized placebo-controlled trial in high-risk individuals found daily supplementation with selenium, vitamin E, vitamin C, β-carotene, and zinc for 7-12 years significantly lowered risk of gastric cancer, particularly in Helicobacter pylori-infected individuals [136]. Overall clinical data supports anticancer potential for specific functional foods and nutraceuticals, but additional rigorous trials are needed investigating bioactive doses and additive/synergistic effects of combinations on clinically relevant cancer outcomes.

Conclusions A growing body of clinical research provides evidence for functional foods and nutraceuticals in beneficially impacting cancer prevention along with inflammation, immunity, intestinal health, and the microbiome. Specifically, bioactive components like omega-3s, probiotics, prebiotics, selenium, garlic, green tea, and carotenoid-rich plant foods demonstrate efficacy in modulating these outcomes. Both further mechanistic studies and long-term trials examining clinically meaningful endpoints are warranted to better define optimal bioactive doses, characterize additive/synergistic effects of combinations, and develop functional food-based dietary recommendations focused on reducing cancer and chronic disease risk.

Table 9. Clinical evidence for selected prebiotics & probiotics in promoting intestinal health

Prebiotic/Probiotic	Clinical Evidence for Intestinal Health
Inulin	- Increased abundance of beneficial bacteria (Bifidobacteria) [Reference]
Fructo-oligosaccharides	- Improved gut microbial composition [Reference]
Lactobacillus rhamnosus	- Reduced symptoms of irritable bowel syndrome (IBS) [Reference]
Bifidobacterium breve	- Alleviated symptoms of diarrhea and gastrointestinal discomfort [Reference]
Saccharomyces boulardii	- Effective in preventing and treating antibiotic-associated diarrhea [Reference]
Galacto-oligosaccharides	- Enhanced growth of beneficial bacteria [Reference]

Table 10. Evidence for anticancer effects of selected functional foods/nutraceuticals from clinical trials

Functional Food/Nutraceutical	Anticancer Effects in Clinical Trials
Green Tea (Epigallocatechin gallate)	- Reduced risk of various cancers such as breast, prostate, and colorectal [Reference]
Turmeric (Curcumin)	- Inhibition of cancer cell growth and metastasis [Reference]
Garlic	- Potential preventive effects against stomach and colorectal cancers [Reference]
Berries (Blueberries, Strawberries)	- Antioxidant and anti-inflammatory properties; potential anticancer effects [Reference]
Cruciferous Vegetables (Broccoli, Cauliflower)	- Induction of detoxification enzymes; potential cancer preventive effects [Reference]
Resveratrol (Found in Red Grapes, Red Wine)	- In

2.17 Safety Considerations

While interest in utilizing functional foods and nutraceuticals for disease prevention continues growing, safety considerations merit attention [137]. Precise safety profiles depend upon the specific bioactive food component, source, dose, and target population [138]. Though serious adverse events appear relatively rare, mild-moderate gastrointestinal upset represents the most common side effect, particularly with high polyphenol doses [139]. Additionally, certain functional food-drug interactions may impact pharmacological therapy.

Safety concerns do exist for specific bioactive components. For example, though plant sterol/stanol enriched foods effectively lower cholesterol, questions remain whether they might negatively impact carotenoid absorption or promote development of non-alcoholic fatty liver disease [140,141]. However, a systematic review of over 80 clinical trials found no significant effects of plant sterols/stanols on fat-soluble vitamin levels [142]. Regarding fatty acids, a meta-analysis associated omega-3 fish oil supplementation with modestly increased prostate cancer risk, highlighting the need to establish safe upper limits [143]. Finally, select probiotic strains used in high doses could potentially trigger harmful immune responses in vulnerable subgroups [144]. While rare, these concerns illustrate need for further surveillance, especially with increasing consumer use.

Establishing definitively safe upper limits for bioactive functional food components and nutraceuticals remains challenging and will require continued rigorous study of long-term safety and potential adverse effects across populations. However, current evidence suggests most bioactives do not demonstrate adverse events when consumed in doses achievable from foods during typical diets. For example, clinical trials indicate flavonoid-rich fruit and vegetable intake equivalent to 8-10 servings daily are safe and beneficial [145].

Overall maintaining intake of functional food bioactives at recommended dietary allowance levels appears prudent based on current data [146]. Individuals taking medications or with underlying health conditions should consult health professionals regarding potential supplement-drug interactions along with precautions for specific medical diagnoses prior to significantly increasing functional food or nutraceutical intake beyond levels readily achieved from regular diets high in fruits, vegetables, whole grains, nuts, seeds, and yogurt.

2.18 Regulatory Landscape

The regulatory environment surrounding functional foods and nutraceuticals varies substantially worldwide, posing certain challenges but also opportunities to better define and support this growing category of lifestyle intervention tools for preventing chronic disease and promoting health [147]. Unlike pharmaceuticals, functional foods and dietary supplements do not undergo rigorous premarket evaluation of efficacy and safety by regulatory bodies like the Food and Drug Administration (FDA) or European Food Safety Authority (EFSA) [148]. Rather, regulations focus on monitoring safety and compliance once products reach consumer markets. These distinct regulatory frameworks result in adoption of functional foods and nutraceuticals in disease prevention ahead of definitive proof of efficacy and safety leading to scientific, policy, and messaging challenges [149].

In the United States, the Dietary Supplement Health and Education Act established special regulatory frameworks for dietary supplements separate from food or drug oversight by the FDA [150]. Manufacturers bear responsibility for marketing safe products meeting quality standards while the FDA monitors and acts against unsafe products following consumer complaints or reported adverse events. Unlike new pharmaceuticals, dietary supplements require no approval before reaching markets and limited premarket safety data [151]. The FDA maintains a registry of permitted dietary ingredients and can act to remove unsafe products from commerce, though resource constraints challenge active enforcement [152]. Because disease risk reduction or treatment claims would categorize a product legally as an unapproved drug, supplements may only make vague structure-function statements like "supports heart health" subject to warning letters from the FDA [153]. Similar policies govern functional foods which may only make approved health claims after submitting petitions demonstrating convincing scientific evidence [154]. Because no incentives exist like market exclusivity rights for pharmaceuticals, gathering costly trial data on functional foods poses financial disincentives for manufacturers. Ultimately, policies place responsibility heavily upon consumers for choosing safe, high-quality functional food and supplement products from amongst thousands with questionable efficacy data.

European Union regulations established by the EFSA also focus heavily on safety, quality, and labeling review rather than efficacy evaluation for functional foods or food supplements making premarket approval health claims [155]. Manufacturers submit dossiers supporting proposed health claims to the EFSA for review. After assessing strength and quality of evidence for cause-effect relationships between the food/constituent and health outcome, the EFSA approves or denies proposed claims [156]. Manufacturers may only market products making approved claims vetted for scientific substantiation by the EFSA. This centralized vetting aims to enhance consumer trust and consistency across the internal EU market. Similar regulatory frameworks apply in Canada, Brazil, Australia and elsewhere requiring review of evidence supporting marketing of products making specific health claims [157]. Ultimately these policies offer certain advantages but share overarching limitations present in the United States where products reach markets far faster than science establishes efficacy and safety.

2.19 Challenges

While functional foods and dietary supplements hold promise supporting lifestyle chronic disease prevention, the existing regulatory environment poses certain challenges (Table 1). First, limitations in federal resources for oversight enables market proliferation of products with questionable quality control standards or unsubstantiated efficacy and safety claims [158]. Second, deficiencies in financial incentives for costly clinical trials and limitations on allowable health claims discourage investment in generating scientific evidence [159]. Third, variability in regional regulations leads to inconsistencies, consumer confusion, and regulatory gaps exploited by some manufacturers [160]. Finally lack of adequately defined product categories, criteria qualifying products as "functional foods", or requirements for demonstrating bioavailability of active food components creates ambiguity for manufacturers, regulators, healthcare providers and consumers [161]. Collectively these realities explain conflicting expert views on the appropriate role of functional foods and supplements in preventive health. While some cite promise for bioactives filling nutritional gaps, others argue unproven benefits cannot outweigh potential safety risks without stronger regulatory oversight and transparency [162,163]. Ultimately, addressing these inter-related challenges will require coordinated efforts improving regulatory efficiency, expanding scientific evidence, and better educating consumers.

2.20 Potential Policy Solutions

Establishing more robust regulatory frameworks better incentivizing science supporting responsible innovation requires balancing expanded oversight with retaining market access for functional foods and supplements showing promise through limited early stage trials. Potential policy solutions summarized in Table 2 include: 1) Expanding federal funding for functional food research and FDA authority over product advertising/claims; 2) Developing centralized review processes and databases for aggregating efficacy/safety data; 3) Implementing minimum bioavailability and bioactivity standards for qualifying products as “functional”; 4) Creating incentives like extended exclusivity for manufacturers generating clinical data supporting qualified health claims; and 5) Launching federal traceback audit systems and quality seals given to compliant products meeting purity/potency standards [164-168]. While questions remain regarding precise policy changes, enhancing regulatory efficiency, improving quality and safety standards, reducing misleading claims, and expanding incentives for research represent shared goals across functional food/nutraceutical stakeholders.

2.21 Future Directions

1) Expanding high-quality clinical trials establishing definitively safe ranges of intake for bioactive components, efficacy for disease prevention, and optimal food sources;
2) Developing defined categories and criteria for functional foods and supplements supported by science;
3) Creating financial incentives and public funding for research on functional foods given limitations of patents and exclusivity rights for natural products;
4) Improving regulatory coordination domestically and globally to enhance consistency, oversight efficiency, and transparency;
5) Establishing federal quality standards, testing processes, adverse event monitoring, and enforcement of marketing/health claims;
6) Optimizing consumer education campaigns regarding appropriate selections and use of functional food/supplements tailored to individual health histories;
7) Studying synergistic/additive effects of bioactive combinations across functional food groups;
8) Exploring impacts on health disparities and opportunities to improve prevention in at-risk communities facing elevated chronic disease rates; and
9) Monitoring ecological impacts of diversified sustainable agriculture required for supplying functional food and nutraceuticals supported by science [169-175]. Addressing these interdisciplinary areas through cooperative initiatives across public health agencies, legislative bodies, scientific funding organizations and stakeholders in the food/nutrition industries and farming communities will help guide responsible policies advancing dietary approaches leveraging functional foods in chronic disease prevention and health promotion.

3. RESULTS

1. Results from a randomized controlled trial found that participants receiving a daily walnut-enriched diet for 2 years significantly reduced LDL cholesterol compared to controls receiving an standard diet (8.82 mg/dL greater reduction, p=0.019) [176].
2. A meta-analysis of 11 clinical trials found that ingestion of cocoa flavanols in doses over 200mg acutely improved flow-mediated dilation of the brachial artery by 1.39% (95% CI 0.72–2.07), indicating enhanced endothelial function [177].
3. In a 4-week randomized controlled trial in 132 overweight and obese adults, consumption of a meal replacement shake providing 20g pea protein resulted in significantly greater reductions in systolic and diastolic blood pressure compared to the control shake without pea protein [178].
4. A randomized, placebo-controlled trial in 81 healthy adults found that daily consumption of a multispecies probiotic supplement for 4 weeks significantly decreased serum CRP levels compared to placebo, indicating reduction of systemic inflammation [179].
5. Intake of broccoli sprout powder providing glucosinolates and sulforaphane was associated with significant inhibition of bladder tumor growth compared to placebo in a small clinical trial in 20 bladder cancer patients awaiting surgery [180].

4. DISCUSSION

1. Daily supplementation with psyllium fiber was found to significantly lower LDL cholesterol by 5-10% in patients with hypercholesterolemia. Researchers hypothesize the viscosity and bile acid binding properties of psyllium fibers interfere with cholesterol absorption and synthesis in the gastrointestinal tract [181].
2. Multiple randomized controlled trials have reported Lactobacillus probiotic strains reduce systemic inflammation markers like CRP and cytokines in patients with diabetes and metabolic disease. Proposed mechanisms include modulation of gut

barrier function, improved insulin sensitivity, and interactions with inflammatory signaling pathways via microbial metabolites [182].

3. Higher intakes of anthocyanin-rich berries were associated with lower blood pressure in a longitudinal cohort study of over 50,000 women, suggesting berries may aid blood pressure regulation. Anthocyanins may induce vasodilation by increasing nitric oxide production and attenuating oxidative stress [183].
4. In interventional trials, diets enriched with plant-based unsaturated fatty acids like olive oil rapidly incorporate into cell membranes and tissue lipids, replacing saturated fats. This structural change beneficially alters membrane protein activity and downstream signaling related to inflammation in vascular and adipose tissues [184].

5. CONCLUSION

In conclusion, functional foods such as fatty fish, soy, nuts, seeds, beans, yogurt, cocoa, berries, tomatoes, and whole grains containing bioactive compounds plus dietary supplements providing vitamins, minerals, fiber, probiotics, omega-3s, or phytochemicals show efficacy in randomized controlled trials and experimental models for favorable impacts on integrative markers of metabolic health, inflammation, oxidative stress, vascular function, and even disease treatment outcomes. Achieving sufficient, consistent intake of these nutrients is challenging with standard diets alone, especially for those with increased requirements. Thus personalized functional food and nutraceutical strategies aligned with dietary guidance help promote homeostasis and resilience. While further research on mechanisms, optimal doses, combinations and long-term impacts is warranted, tailored approaches leveraging what science confirms regarding benefits of functional and bioactive components represent promising lifestyle prevention tools complementary to pharmaceutical approaches for combating highly prevalent chronic diseases to optimize population health.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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