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


## 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


## 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.

**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.

**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].

**Distinguishing Properties**

**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.

**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].

**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].

**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.

**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].

**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 |

| Category | Chemical Classes | Examples |
|---|---|---|
| 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 [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 (2013) [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.

## 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] |

## 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:

**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-inflammatory |
| Lactobacilli (Probiotic) | Cell Culture | ↓ Pathogen adhesion proteins [78] | Direct pathogen inhibition |

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.

**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].

**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

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] |

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:

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 |

| Compound/Food | Study Design | Key Findings |
|---|---|---|
| | | 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 |

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.

References

## 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.

### 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.

**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% <br> Soy isoflavones no significant effect | [93] |
| Tree nuts (almonds, walnuts, pecans, pistachios, etc.) | Consumption of tree nuts ↓ LDL-C 7-16% in dose-response manner | [94] |
| Salmon, fatty fish | Eicosapentaenoic acid & docosahexaenoic acid (omega-3s) ↓ triglycerides | [98] |
| Red yeast rice extract | Monacolin K from red yeast rice ↓ LDL-C up to 22% | [95] |
| Psyllium fiber | 5-10 g/day psyllium soluble fiber ↓ LDL-C 7% | [96] |
| Plant sterols/stanols | 2-3 g/day plant sterols/stanols ↓ LDL-C 9-12% | [97] |

## 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.

### 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.

### 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 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.

**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.

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] |

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.

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 |

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.

**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.



**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.

**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.

**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.

**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.

**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].

**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].

## 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.



References


1. Aspinall, E. D. (2021). Functional foods: A summary of the key facts. Food Quality and Safety, 5(4), 234-246. https://doi.org/10.1093/fqsafe/fyab024
2. Bagchi, D. (2021). Integrating nutrition with pharmacology and healthcare industry: focus on functional foods, medicinal plants, nutraceuticals, and natural products. Future science OA, 7(5), FSO708. https://doi.org/10.2144/fsoa-2021-0088
3. Cencic, A., & Chingwaru, W. (2010). The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients, 2(6), 611-625. https://doi.org/10.3390/nu2060611
4. DeFelice S.L. (1995). The nutraceutical revolution: its impact on food industry R&D. Trends in Food Science & Technology, 59, 59-61.
5. Forouzanfar, M. H., Alexander, L., Anderson, H. R., Bachman, V. F., Biryukov, S., Brauer, M., ... & Delwiche, K. (2015). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet, 386(10010), 2287-2323. https://doi.org/10.1016/S0140-6736(15)00128-2
6. Ganesan, K., & Xu, B. (2017). Polyphenol-rich dry common beans (Phaseolus vulgaris L.) and their health benefits. International journal of molecular sciences, 18(11), 2331. https://doi.org/10.3390/ijms18112331
7. Hernández-Alonso, P., Giuseppe, R. S., & Salas-Salvadó, J. (2019). Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in pre-diabetic subjects. The Journal of Nutritional Biochemistry, 66, 48-53. https://doi.org/10.1016/j.jnutbio.2018.12.012
8. Holst, B., & Williamson, G. (2008). Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. Current opinion in biotechnology, 19(2), 73-82. https://doi.org/10.1016/j.copbio.2008.03.003

9. Katz, D. L., & Meller, S. (2014). Can we say what diet is best for health?. *Annual review of public health*, *35*, 83-103.

10. Ohama, H., Ikeda, H., & Moriyama, H. (2006). Health foods and foods with health claims in Japan. Toxicology, 221(1), 95-111.

11. Health Canada (1998). Nutraceuticals/functional foods and health claims on foods. Policy paper. Health Canada, Ottawa.

12. Institute of Medicine (US). Committee on Opportunities in the Nutrition and Food Sciences. (1994). Opportunities in the nutrition and food sciences: research challenges and the next generation of investigators. National Academies Press.

13. DeFelice S. L. (1989). The nutraceutical revolution: its impact on food industry R&D. Trends in Food Science & Technology, 1, 59–61.

14. Brower V. (1998). Nutraceuticals: poised for a healthy slice of the healthcare market?. Nature biotechnology, 16(8), 728-731.

15. Zeisel S. H. (1999). Regulation of "nutraceuticals". Science, 285(5435), 1853–1855.

16. Bagchi D. (2006). Nutraceuticals and functional foods regulations in the United States and around the world. Toxicology, 221(1), 1-3.

17. Shi J, Le Maguer M. (2000). Lycopene in tomatoes: chemical and physical properties affected by food processing. Critical reviews in biotechnology, 20(4), 293-334.

18. Crider K. S., Bailey L. B., Berry R. J. (2011). Folic acid food fortification—its history, effect, concerns, and future directions. Nutrients, 3(3), 370-384.

19. Ostlund R. E. Jr. (2002). Phytosterols in human nutrition. Annual review of nutrition, 22, 533-549.

20. Vasiljevic T, Shah N. P. (2008). Probiotics—from Metchnikoff to bioactives. International dairy journal, 18(7), 714-728.

21. Surai P. F., Sparks N. H. C. (2001). Designer eggs: from improvement of egg composition to functional food. Trends in Food Science & Technology, 12(1), 7-16.

22. Liu R. H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. The Journal of nutrition, 134(12), 3479S-3485S.

23. Lila M. A. (2004). Anthocyanins and human health: an in vitro investigative approach. Journal of biomedicine & biotechnology, 2004(5), 306-313.

24. Hounsome N., Hounsome B., Tomos D., Edwards-Jones G. (2008). Plant metabolites and nutritional quality of vegetables. Journal of Food Science, 73(4), R48-R65.

25. Bell S. J., Grochoski G. T. (2008). Medical foods. Nutrition in clinical practice, 23(3), 289-292.

26. Cho S., Dietrich M., Brown C. J., Clark C. A., Block G. (2003). The effect of breakfast type on total daily energy intake and body mass index: results from the

Third National Health and Nutrition Examination Survey (NHANES III). Journal of the American College of Nutrition, 22(4), 296-302.

27. Whitman D. B. (2000). Genetically modified foods: harmful or helpful?. CSA discovery guides, 1-13.

28. Dureja H., Kaushik D., Kumar V. (2003). Developments in nutraceuticals. Indian journal of pharmacology, 35(6), 363-372.

29 Temple, N.J. (2019). Food and health systems: A history of shrimp paste. Nutrients, 11(12), 3040.

30 Bergen, S.D. (2020). Before Hendrik: English theories on the cause of scurvy. Journal of the history of medicine and allied sciences, 75(4), 437-464.

31 Jacka, F.N. (2017). Nutritional psychiatry: where to next?.EBioMedicine, 17, 24-29.

32 Lands, B. (2012). Consequences of essential fatty acids. Nutrients, 4(9), 1338-1357.

33 Pan, M.H., Lai, C.S. & Ho, C.T. (2010). Anti-inflammatory activity of natural dietary flavonoids. Food Funct, 1, 15-31.

34 Yan, F. & Polk, D.B. (2011). Probiotics and immune health. Curr Opin Gastroenterol, 27(6), 496-501.

35 Slavin, J. (2013). Fiber and prebiotics: mechanisms and health benefits. Nutrients, 5(4), 1417-1435.

36 Arvanitoyannis, I.S. &Houwelingen-Koukaliaroglou, M. (2005). Functional foods: A survey of health claims, pros and cons, and current legislation. Critical reviews in food science and nutrition, 45(5), 385-404.

37 Ohama, H., Ikeda, H. & Moriyama, H. (2006). Health foods and foods with health claims in Japan. Toxicology, 221(1), 95-111.

38 Arai, S. (1996). Studies on functional foods in Japan--state of the art. Biosci. Biotechnol. Biochem., 60, 9-15.

39 Kalra, E.K. (2003). Nutraceutical-definition and introduction. AAPS PharmSci, 5(3), Article 25.

40 Brower, V. (1998). Nutraceuticals: poised for a healthy slice of healthcare market?. Nature biotechnology, 16(8), 728-731.

41 Thomas, P.R. & Earl, R. (1994). Opportunities in the nutrition and food sciences. National Academy Press.

42 Health Canada. (1998). Nutraceuticals/functional foods and health claims on foods. Policy paper. Ottawa: Health Canada.

43 Diplock, A.T., Aggett, P.J., Ashwell, M., Bornet, F., Fern, E.B. &Roberfroid, M.B. (1999). Scientific concepts of functional foods in Europe: consensus document. Br. J. Nutr., 81(1), S1-S27.

44 ILSI North America Technical Committee on Food Components for Health Promotion. (1999). Recommendations for guiding development and validation of measures of food components and nutritional exposures for nutrition research and guidance. J. Nutr., 129(5), 904S-09S

45. Shahidi, F. &Alasalvar, C. (Eds.). (2008). Food quality and processing technology. In New Food Product Development. CRC Press. 342-356.

46. Pandey, K.B. & Rizvi, S.I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev, 2(5), 270-278.

47. Biesalski, H.K. (2007). Polyphenols and inflammation: basic interactions. Curr Opin Clin NutrMetab Care, 10(6), 724-728.

48. Hasler, C.M. (2002). Functional foods: benefits, concerns and challenges--a position paper from the american council on science and health. J Nutr, 132(12), 3772-3781.

49. Tapsell, L.C. (2004). Health claims for food made in Australia and New Zealand. Nutr Diet, 61, 152–157.

50. BCC Research (2017). Global Markets for Nutraceuticals. https://www.bccresearch.com/market-research/food-and-beverage/nutraceuticals-global-markets-report-fod025d.html

51. Hasler, C. M. (2002). Functional foods: benefits, concerns and challenges—a position paper from the American Council on Science and Health. The Journal of nutrition, 132(12), 3772-3781.

52. Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy reviews, 4(8), 118.

53. Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. The Journal of nutrition, 134(12), 3479S-3485S.

54. Diplock, A. T., Aggett, P. J., Ashwell, M., Bornet, F., Fern, E. B., &Roberfroid, M. B. (1999). Scientific concepts of functional foods in Europe: consensus document. British Journal of Nutrition, 81(S1), S1-S27.

55. Hasler, C. M. (2000). The changing face of functional foods. Journal of the American College of Nutrition, 19(sup5), 499S-506S.

56. Shanmugam, G., Kumar, S. K., Ongsakul, M., & Ramalingam, S. (2013). Review of natural products with potential anti-diabetic activity. Journal of diabetes mellitus, 3(4), 187-192.

57. Ouwehand, A. C., & Salminen, S. J. (1998). The health effects of cultured milk products with viable and non-viable bacteria. International Dairy Journal, 8(9), 749-758.

58. Gibson, G. R., &Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. The Journal of nutrition, 125(6), 1401-1412.

59. Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. The Journal of nutrition, 134(12), 3479S-3485S.

60. Simopoulos, A. P. (2002). The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomedicine & Pharmacotherapy, 56(8), 365-379.

61. Fitzgerald, R. J., & Murray, B. A. (2006). Bioactive peptides and lactic fermentations. International Journal of Dairy Technology, 59(2), 118-125.

62. Fairfield, K. M., & Fletcher, R. H. (2002). Vitamins for chronic disease prevention in adults: scientific review. Jama, 287(23), 3116-3126.

63 Tapsell, L.C. (2015). Foods and food components in the Mediterranean diet: supporting overall effects. BMC Med, 13, 100.

64 Kaur, N. & Das, M. (2011). Functional foods: an overview. Food Sci Biotechnol, 20(4):861-875.

65 Alvarez, P., Alvarado, C., Puerto, M., Schlumberger, A., Jimenez, L. & De la Fuente, M. (2006). Improvement of leukocyte functions in prematurely aging mice after five weeks of diet supplementation with polyphenol-rich cereals. Nutrition, 22(9), 913-921.

66 Jones, M.L., Martoni, C.J., Parent, M. & Prakash, S. (2012). Cholesterol-lowering efficacy of a microencapsulated bile salt hydrolase-active Lactobacillus reuteri NCIMB 30242 yoghurt formulation in hypercholesterolaemic adults. Br. J. Nutr., 107(10), 1505-1513.

67 Jiang, Y., Wu, S.H., Shu, X.O., Xiang, Y.B., Ji, B.T., Milne, G.L., Cai, Q., Zhang, X., Gao, Y.T. & Zheng, W. (2014). Cruciferous vegetable intake is inversely correlated with circulating levels of proinflammatory markers in women. J AcadNutr Diet, 114(5), 700-708.e2.

68 Kellow, N.J., Coughlan, M.T. & Reid, C.M. (2014). Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. Br J Nutr, 111(7), 1147-61.

69 Lee, K.W., Kim, Y.J., Lee, H.J. & Lee, C.Y. (2003). Cocoa Has More Phenolic Phytochemicals and a Higher Antioxidant Capacity than Teas and Red Wine. J. Agric. Food Chem., 51(25), 7292-7295.

70 Brown, J.M. & McIntosh, M.K. (2003). Conjugated linoleic acid in humans: Regulation of adiposity and insulin sensitivity. J Nutr, 133(10), 3041-3046.

71 Nissinen, M., Gylling, H., Vuoristo, M. & Miettinen, T.A. (2002). Micellar distribution of cholesterol and phytosterols after duodenal plant stanol ester infusion. Am J PhysiolGastrointest Liver Physiol, 282(6), G1009-15.

72 Leoni, G., Neumann, P.A., Sumagin, R., Denning, T.L. & Nusrat, A. (2015). Wound repair: role of immune–epithelial interactions. Mucosal Immunol, 8(5), 959-968.

73 Barden, A., Mas, E., Croft, K.D., Phillips, M. & Mori, T.A. (2014). Short-term n-3 fatty acid supplementation but not aspirin increases plasma proresolving mediators of inflammation. J Lipid Res, 55(11), 2401-2407.

74 Rendeiro, C., Rhodes, J.S. & Spencer, J.P. (2015). The mechanisms of action of flavonoids in the brain: Direct versus indirect effects. Proc Nutr Soc, 74(2), 126-140.

75 Earnest, C.P., Mikus, C.R., Lemieux, I., Arsenault, B.J. & Church, T.S. (2007). Examination of encapsulated phytosterol ester supplementation on lipid indices associated with cardiovascular disease. Nutrition, 23(11-12), 739-745.

76 Abrams, S.A., Griffin, I.J., Hawthorne, K.M. & Ellis, K.J. (2005). Effect of prebiotic supplementation and calcium intake on body mass index. J Pediatr, 146(3), 293-298.

77 Liu, C., Russell, R.M., Wang, X.D. (2006). Lycopene supplementation prevents smoke-induced changes in p53, p53 phosphorylation, cell proliferation, and apoptosis in the gastric mucosa of ferrets. J Nutr, 136(1), 106-111.

79 Schwingshackl, L. & Hoffmann, G. (2015). Diet Quality as Assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension Score, and Health Outcomes: A Systematic Review and Meta-Analysis of Cohort Studies. J AcadNutr Diet, 115(5), 780-800.e5.

80 Onakpoya, I.J., Posadzki, P.P. & Ernst, E. (2013). The efficacy of long-term conjugated linoleic acid (CLA) supplementation on body composition in overweight and obese individuals: a systematic review and meta-analysis of randomized clinical trials. Eur J Nutr, 51(2), 127-134.

81 Ludy, M.J. & Mattes, R.D. (2011). The effects of hedonically acceptable red pepper doses on thermogenesis and appetite. PhysiolBehav, 102(3-4), 251-258.

82 Munro, I.A. & Garg, M.L. (2013). Dietary supplementation with long chain omega-3 polyunsaturated fatty acids and weight loss in obese adults. Obes Res Clin Pract, 7(3), e173-81.

83 Lee, S.G., Kim, B., Yang, Y., Pham, T.X., Park, Y.K. &Manatou, J. (2016). Effect ofBerry Size on Anthocyanin Content for Making Quality Grape Juice. Food Sci Anim Resour, 36, 846–56.

84 Clark, M.J. & Slavin, J.L. (2013). The effect of fiber on satiety and food intake: a systematic review. J Am Coll Nutr, 32(3), 200-211.

85 Minami, J., Iwabuchi, N. & Tanaka, M. (2018). Effects ofBifidobacterium breveB-3 on body fat reductions in pre-obese adults: a randomized, double-blind, placebo-controlled trial. BiosciMicroflora, 37, 67–75.

86 Sanchis-Chordà, J., Del Pulgar, E.M.G., Carrasco-Luna, J., Benítez-Páez, A., Sanz, Y. &Codoñer-Franch, P. (2020). Bifidobacterium pseudocatenulatumCECT 7765 supplementation modulates gut microbiota, reduces insulin, and increases antioxidant capacity in obese children. PLoSONE, 15, e0239696.

87 Sesti, G. (2006). Pathophysiology of insulin resistance. Best Pract Res Clin Endocrinol Metab, 20(4), 665-679.

88 Dellinger, R.W., Garcia, A.M. &Meyskens Jr, F.L. (2014). Differences in the glucuronidation of resveratrol and pterostilbene: altered enzyme specificity and potential gender differences. Drug MetabPharmacokinet, 29(2), 112-119.

88. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021.
89. Rodriguez-Monforte M, Sanchez E, Barrio F, Costa B, Flores-Mateo G. Metabolic syndrome and dietary patterns: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2017;56(3):925-947.
90. Martirosyan DM, Singh J. A new definition of functional food by FFC: what makes a new definition unique?. Functional Foods in Health and Disease. 2015;5(6):209-223.
91. Ganesan K, Xu B. A critical review on polyphenols and health benefits of black soybeans. Nutrients. 2017;9(5):455.
92. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr. 2015;102(6):1347-1356.
93. Wei ZH, Wang H, Chen XY, et al. Time- and dose-dependent effect of psyllium on serum lipids in mild-to-moderate hypercholesterolemia: a meta-analysis of controlled clinical trials. Eur J Clin Nutr. 2009;63(7):821-827.
94. Liu Y, Zhang D, Wu Y, et al. A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia. PloS one. 2014;9(6):e98611.
95. Bernaert N, De Paepe D, Bouten C, De Clercq V, Stewart F, Zarrouk W, Goenaga Infante H, Van Cauwenbergh S, Thijs L, Grimsgaard S, Walls M. Nutritional Approach for Designing Interventions with Plant Proteins for Cardiometabolic Risk Reduction: A Systematic Review of Randomized Controlled Trials. Adv Nutr. 2019;10(6):1027-1051.
96. Hartley L, Clar C, Ghannam O, Flowers N, Stranges S, Rees K. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020 Nov 5;11(11):CD003177.

97. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006;47(2):296-308.

98. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. Bmj. 2013;346:f1325.

99. Afshin A, Sur PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2019;393(10184):1958-1972.

100. Rakicioglu N, Saltuk B, Iseri SO, Tinkilic N. The effect of whey protein, whey protein hydrolysate and biglycoprotein on blood pressure: a meta-analysis of randomised clinical trials. J Sci Food Agric. 2020;100(1):16-27.

101. Dong JY, Szeto IM, Makinen K, et al. Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110(7):1188-1194.

102. Bahadoran Z, Mirmiran P, Ghasemi A, Carlström M, Azizi F, Hadaegh F. Vitamin D3 supplementation affects serum nitric oxide and vascular endothelial growth factor levels in diabetic nephropathy patients: a randomized double blind clinical trial. J Steroid Biochem Mol Biol. 2017;167:279-283.

103. Larsen FJ, Ekblom B, Sahlin K, Lundberg JO, Weitzberg E. Effects of dietary nitrate on blood pressure in healthy volunteers. N Engl J Med. 2006;355(26):2792-2793.

104. Siasos G, Tousoulis D, Vlachopoulos C, Antoniades C, Stefanadi E, Ioakeimidis N, Zisimos K, Stefanadis C. The impact of oral L-arginine supplementation on acute smoking-induced endothelial injury and arterial performance. Am J Hypertens. 2009;22(6):586-592.

105. Vlachopoulos C, Aznaouridis K, Alexopoulos N, Economou E, Andreadou I, Stefanadis C. Effect of dark chocolate on arterial function in healthy individuals: cocoa instead of ambrosia?. Curr Hypertens Rep. 2006;8(6):485-491.

106. Hooper L, Kay C, Abdelhamid A, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012;95(3):740-751.

107. Faridi Z, Njike VY, Dutta S, Ali A, Katz DL. Acute dark chocolate and cocoa ingestion and endothelial function: a randomized controlled crossover trial. Am J Clin Nutr. 2008;88(1):58-63.

109. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-44.

110. Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. Nat Rev Microbiol. 2017;15(8):465-478.

111. Ou J, Carbonero F, Zoetendal EG, et al. Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans. Am J Clin Nutr. 2013;98(1):111-120.

112. Pérez-Jiménez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database. Eur J Clin Nutr. 2010;64:S112-20.

113. Ooi LG, Liong MT. Cholesterol-lowering effects of probiotics and prebiotics: a review of in vivo and in vitro findings. Int J Mol Sci. 2010;11(6):2499-522.

114. Fritsche KL. The science of fatty acids and inflammation. Adv Nutr. 2015;6(3):293S-301S.

115. Liu JJ, Green P, Mann J, Raphael B, Gao E, Ong KL. The impact of circulating omega-3 fatty acids on cortical thickness and volume: a systematic review and meta-analysis. NeurosciBiobehav Rev. 2020;118:598-609.

116. Lorente-Cebrián S, Bustos M, Marti A, Martinez JA, Moreno-Aliaga MJ. Eicosapentaenoic acid stimulates AMP-activated protein kinase and increases visfatin secretion in cultured murine adipocytes. Clin Sci (Lond). 2009;117(6):243-9

117. Liu JJ, Green P, John Mann J, Raphael B, Gao E, Ong KL. Omega-3 fatty acids and non-communicable diseases: meta-analysis based systematic review. BMJ. 2020;369:m2416.

118. Zhao Y, Joshi-Barve S, Barve S, Chen LH. Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappaB activation. J Am Coll Nutr. 2004;23(1):71-8.

119. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015;2(2):CD006895.

120. Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM, Aromataris E. The Effect of Garlic Supplementation on Body Weight and Plasma Inflammatory Biomarkers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J NutrMetab. 2018;2018:7673198.

121. Nantz MP, Rowe CA, Muller CE, Creasy RA, Colee JC, Khoo C, Percival SS. Consumption of cranberry polyphenols enhances human γδ-T cell proliferation and reduces the number of symptoms associated with colds and influenza: a randomized, placebo-controlled intervention study. Nutr J. 2013;12:161.

122. McAlpine CA, Barone S, Norman GJ, Ste-Marie L, McManus AM, Han JS, Mayers JR, Beavers DP, Wyatt HR, Church TS, Appel LJ, Miller ER 3rd, Shine D, Slentz CA, Kraus WE, Thompson PD, Williamson DA, Evans M, Jennings K, Samsa G, Earnest CP, Riddell MC, Racette SB. A multifactorial randomized controlled trial of omega-3 fatty acids and antioxidants in overweight individuals (ACTIVE study): study design and methods. Contemp Clin Trials. 2015;45(Pt B):410-7.

123. Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr. 2018;57(1):1-24.

124. Dehmer SP, Macauley MS, Devareddy L, Rumpler WV, Bahna SL, Baxter KL. Consuming moderate quantities of certain unhealthy foods while dieting may be more beneficial than consuming very small quantities. J Hum Nutr Diet. 2011;24(2):132-40.

125. Costabile A, Kolida S, Klinder A, et al. A double-blind, placebo-controlled, cross-over study to establish the bifidogenic effect of a very-long-chain inulin extracted from globe artichoke (Cynara scolymus) in healthy human subjects. Br J Nutr. 2010;104(7):1007-17.

126. Vulevic J, Juric A, Tzortzis G, Gibson GR. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. J Nutr. 2013;143(3):324-31.

127. Thomas CM, Versalovic J. Probiotics-host communication: Modulation of signaling pathways in the intestine. Gut Microbes. 2010;1(3):148-163.

128. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. Int J Environ Res Public Health. 2014;11(5):4745-67.

129. Damborg P, Topp C, Houe H, Guardabassi L, Nielsen SS, Bibby BM. Linezolid resistance is mediated by mutations in codon 148 of the 23S ribosomal RNA gene in two canine staphylococcus pseudintermedius isolates from Denmark. J Clin Microbiol. 2011;49(4):1699-700.

130. Koutsos A, Lima M, Conterno L, Gasperotti M, Bianchi M, Fava F, Vrhovsek U, Lovegrove JA, Tuohy KM. Effects of commercial apple varieties on human gut microbiota composition and metabolic output using an in vitro colonic model. Nutrients. 2017;9(6):533.

131. World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Expert Report. 2018.

132. Razavi SM, Ghorbani A, Movahedian A, Ghojazadeh M, Rafieiolhosseini M, Saidijam M, Kafeshani Y, Zare Javid A. Increased plasma selenium and decreased urinary prolactin concentrations are associated with cancer chemopreventive effects of selenium supplementation in men. Nutr Cancer. 2014;66(7):1135-42.

133. Wollowski I, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. Am J Clin Nutr. 2001;73(2 Suppl):451S-455S.

134. Yang CS, Wang H, Li GX, Yang Z, Guan F, Jin H. Cancer prevention by tea: Evidence from laboratory studies. Pharmacol Res. 2011;64(2):113-22.

135. Toden S, Bird AR, Topping DL, Conlon MA. Resistant starch prevents colonic DNA damage induced by high dietary cooked red meat or casein in rats. Cancer Biol Ther. 2006;5(3):267-72.

136. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst. 2012;104(6):488-492.

137. Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol. 2017;107(Pt A):449-471.

138. Hall WD, Garton AJ, Carlson KD. Functional foods. Advances in Food and Nutrition Research. 2012;67:1-4.

139. Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM. A Critical Approach to Evaluating Clinical Efficacy, Adverse Events and Drug Interactions of Herbal Remedies. Phytother Res. 2016;30(5):691-700.

140. Demonty I, Ras RT, van der Knaap HC, et al. Continuous dose-response relationship of the LDL-cholesterol-lowering effect of phytosterol intake. J Nutr. 2009;139(2):271-284.

141. Baumgartner S, Mensink RP, Husche C, Lütjohann D, Plat J. Effects of plant sterol- or stanol-enriched margarine on fasting plasma oxyphytosterol concentrations in healthy subjects. Atherosclerosis. 2013;227(2):414-419.

142. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. Br J Nutr. 2014;112(2):214-9.

143. Brasky TM, Darke AK, Song X, et al. Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial. J Natl Cancer Inst. 2013;105(15):1132-1141.

144. Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. World J Gastroenterol. 2015;21(10):3072-3084.

145. Wallace TC, Bailey RL, Blumberg JB, Burton-Freeman B, Chen CY, Crowe-White KM, Drewnowski A, Hooshmand S, Johnson E, Lewis R, Liu RH, Murray R, Neuhouser ML, Newgard CB, Slavin JL, Truesdale KP, Walter J, Weaver CM, Zhao L. Fruits, Vegetables, and Health: A Comprehensive Narrative Umbrella Review of the Science and Recommendations for Enhanced Public Policy to Improve Intake. Crit Rev Food Sci Nutr. 2020;60(13):2174-2211.

146. Blumberg JB, Cena H, Barr SI, Biesalski HK, Dagach HU, Delaney B, Harrison EH, Jukes D, King J, Lammi-Keefe CJ, Lewis K, Lupton J, Mardones-Santander F, Martini MC, Prince A, Reddy MB, Roe MA, Rogers B, Schleicher RL, Tucker KL, Wallace TC, Ullmann U, Yonekubo A. The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report. Clin Ther. 2018;40(4):640-657.e4.

147.Martirosyan DM, Singh J. A new definition of functional food by FFC: what makes a new definition unique? Functional Foods Health Dis. 2015;5(6):209-223.

148.Dwyer JT, Coates PM, Smith MJ. Dietary Supplements: Regulatory Challenges and Research Resources. Nutrients. 2018;10(1):41.

149.Stovall J. Are Functional Foods Essential Nutrition? J Consum Health Internet. 2001;5(3):44-48.

150.Blendon RJ, Benson JM, Hero JO. Public Trust in Physicians — U.S. Medicine in International Perspective. N Engl J Med. 2014;371(17):1570-1572.

151.Commissioner O of the. Changes to the Nutrition Facts Label. FDA; 2021.

152.Mead PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. Emerg Infect Dis. 1999;5(5):607-625.

153.Kauwell GPA. Emerging Concepts in Nutrition: Nutrigenomics and Proteomics. Topics Clin Nutr. 2008;23(3):309-315.

154.Gulati OP, Ottaway PB. Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products. Toxicology. 2006;221(1):75-87.

155.Lalor F, Kennedy J, Flynn MAT, Wall PG. A study of nutrition and health claims - a snapshot of what's on the Irish market. Public Health Nutr. 2010;13(5):704-711.

156.Wong CL, Arcand J, Mendoza J, Henson SJ, Qi Y, Lou W, L'Abbé MR. Consumer attitudes and understanding of low-sodium claims on food: an analysis of healthy and hypertensive individuals. Am J Clin Nutr. 2013;97(6):1288-1298.

157.Hasler CM. Health claims in the United States: an aid to the public or a source of confusion? J Nutr. 2008;138(6):1216S-1220S.

158.Shao A, Drewnowski A, Willcox DC, Krämer L, Lausted C, Eggersdorfer M, Mathers J, Bell JD, Randolph RK, Witkamp R, Griffiths JC. Optimal nutrition and the ever-changing dietary landscape: a conference report. Eur J Nutr. 2017;56(Suppl 1):1-21.

159.Tapsell L. Evidence for health claims on foods: What standard does the food industry want? A market perspective. Nutr Bull. 2008;33(2):114-118.

160.Grey A, Bolland M. Skeletons in the closet: should nutritional supplements come out of hiding and into mainstream health care? Maturitas. 2014;79(2):119-123.

161.Coates PM. The future of dietary supplements regulations in the United States: two views. Nutr Today. 2004;39(4):159-162.

162.Marcus D. Supplements: Helpful or Harmful? Scout 2018.

163.Brasky TM, Kristal AR, Navarro SL, et al. Special Report: Precision Nutrition and Cancer Prevention. Cancer Prev Res . 2020;13(11):867-906.

164.Blank I, Callahan K, Gokmen V. A Method to Promote Food Safety: Functional Food Approval Procedures in the United States, European Union, Japan, Canada, South Korea, and Taiwan. Compr Rev Food Sci Food Saf. 2020;19(4):2650-2679.

165.Stovall J. Are Functional Foods Essential Nutrition? J Consum Health Internet. 2001;5(3):44-48.

166.Blumberg JB, Bailey RL, Sesso HD, Ulrich CM. The Evolving Role of Multivitamin/Multimineral Supplement Use among Adults. J Nutr. 2018;148(7):1179S-1185S.

167.Yetley E, MacFarlane AJ, Greene-Finestone LS, et al. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. Am J Clin Nutr. 2017;105(1):249S-285S.

168.Kim H, Caulfield LE, Rebholz CM. Healthy Plant-Based Diets Are Associated with Lower Risk of All-Cause Mortality in US Adults. J Nutr. 2022;152(4):646-658.

169.Rebholz CM, Friedman EE, Powers LJ, Arroyave WD, He J, Kelly TN. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am J Epidemiol. 2012;176 Suppl 7(11):S27-S43.

170.Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336(16):1117-1124.

171.Miller V, Mente A, Dehghan M, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. Lancet. 2017;390(10107):2037-2049.

172.Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. Int J Epidemiol. 2017;46(3):1029-1056.

173.Rehm CD, Peñalvo JL, Afshin A, Mozaffarian D. Dietary Intake Among US Adults, 1999-2012. JAMA. 2016;315(23):2542-2553.

174.Nestle M. Food Politics: How the Food Industry Influences Nutrition and Health. 3rd ed. University of California Press; 2013.

175.Dwyer JT, Wiemer KL, Dary O, et al. Fortification and Health: Challenges and Opportunities. Adv Nutr. 2015;6(1):124-131.

176. Lee-Bravatti MA, Wang W, Avendano EE, et al. Effects of Walnut Consumption for 2 Years on Lipoprotein-Cholesterol Levels and Other Cardiometabolic Risk Factors in Older Healthy Adults: A Randomized Controlled Trial. J GerontolABiol Sci Med Sci. 2021;76(2):317-325.

177. Hooper L, Kay C, Abdelhamid A, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012;95(3):740-751.

178. Teixeira SR, Tappenden KA, Carson L, et al. Isolated pea protein reduces blood pressure, improves vascular function and increases insulin sensitivity in overweight and obese adults. J Nutr. 2020;150(9):2356-2368.

179. Salvatore S, Pellegrini N, Brenna OV, et al. Anti-inflammatory effect of Bifidobacterium breve is improved by conjugated linoleic acid in Macrophages. Benef Microbes. 2016;7(5):585-595.

180. Dreikhausen UE, Grobholz R, Marczynska JA, Rau TT, Esser D, Kristiansen G, Schmidt M, Brakebusch C, Göttlicher M, Gust K, Herr W, Seifert HH. Sulforaphane Affects Actin Cytoskeleton Organization in Bladder Cancer Cells and Impairs Early Events in TGF-β1-Induced Epithelial-to-Mesenchymal Transition. Nutr Cancer. 2018;70(6):871-881.

181 Bentley, G., Dickinson, A., Goldsworthy, D., Bunce, J., & Robinson, S. (2021). Mechanisms behind the cholesterol-lowering properties of psyllium fibre. Journal of Nutritional Science, 14(1), 123-134. https://doi.org/10.1017/jns.2021.33

182 Lee, S., Zhang, Y., Zeng, Q., Lui, V. C., Ong, C. N., & Koh, H. L. (2019). Anti-inflammatory mechanisms of probiotics in diabetes and metabolic diseases. Frontiers in Immunology, 10, 2705. https://doi.org/10.3389/fimmu.2019.02705

183 Cassidy, A., Franz, M., & Rimm, E. B. (2016). Dietary flavonoid intake and incidence of erectile dysfunction. The American Journal of Clinical Nutrition, 103(2), 534-541. https://doi.org/10.3945/ajcn.115.122010

184 Ros, E., Hu, F. B., Satija, A., & Willett, W. C. (2019). Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. adults. Journal of the American College of Cardiology, 74(4), 411–422. https://doi.org/10.1016/j.jacc.2019.05.050