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Review Article

Functional Foods and Cancer Prevention: Molecular Mechanisms, Clinical Evidence and Future Perspectives

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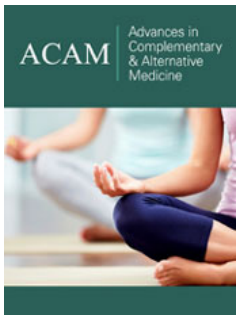

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Abstract

Cancer remains a leading cause of morbidity and mortality worldwide, emphasizing the need for effective and accessible preventive strategies. Although genetic susceptibility contributes to carcinogenesis, modifiable environmental and lifestyle factors, particularly diet, physical inactivity, obesity, tobacco use, and alcohol consumption, account for a substantial proportion of cancer risk. Functional foods are natural or minimally processed foods that provide health benefits beyond basic nutrition because of their biologically active constituents. These compounds include polyphenols, flavonoids, carotenoids, glucosinolates, organosulfur compounds, omega-3 fatty acids, dietary fiber, and probiotics. Experimental, epidemiological, and emerging clinical evidence suggests that functional foods may contribute to cancer prevention by reducing oxidative stress and chronic inflammation, enhancing DNA repair, regulating cell proliferation and apoptosis, inhibiting angiogenesis, modifying epigenetic processes, and supporting a healthy gut microbiome. Dietary patterns rich in these foods, including the Mediterranean diet and predominantly plant-based diets, have been associated with a reduced risk of several malignancies, particularly colorectal, breast, gastric, and prostate cancers. This narrative review summarizes current evidence on the relationship between functional foods and cancer prevention, with emphasis on molecular mechanisms, epidemiological and clinical findings, the gut microbiome, precision nutrition, and practical implications for healthcare professionals. Functional foods should not be considered substitutes for established cancer-prevention measures, screening, or treatment. Rather, they should be incorporated into comprehensive prevention strategies that include tobacco avoidance, healthy weight maintenance, regular physical activity, vaccination against oncogenic viruses, and guideline-recommended cancer screening.

Keywords: Functional foods; Cancer prevention; Bioactive compounds; Inflammation; Gut microbiome; Precision nutrition; Carcinogenesis; Inflammation; Apoptosis; Autophagy; Molecular pathways; Diet

Abbreviations: AMPK: AMP-Activated Protein Kinase; AP-1: Activator Protein-1; ATG: Autophagy-Related Protein; BAK: BCL-2 Antagonist/Killer; BAX: BCL-2-Associated X Protein; BCL: 2-B-Cell Lymphoma-2; BCL-XL: B-Cell Lymphoma-Extra Large; COX-2: Cyclooxygenase-2; DHA: Docosahexaenoic Acid; EGCG: Epigallocatechin-3-Gallate; EPA: Eicosapentaenoic Acid; ER: Estrogen Receptor; GPX: Glutathione Peroxidase; GSH: Glutathione; HDAC: Histone Deacetylase; HIF-1α: Hypoxia-Inducible Factor-1 Alpha; HO-1: Heme Oxygenase-1; IGF: Insulin-like Growth Factor; IKK: IκB Kinase; IL-1β: Interleukin-1 Beta; IL-6: Interleukin-6; Inos: Inducible Nitric Oxide Synthase; IκB: Inhibitor of Nuclear Factor-Kappa B; Keap1: Kelch-like ECH-Associated Protein 1; LC3: Microtubule-Associated Protein 1 Light Chain 3; LPS: Lpopolysaccharide; MAPK: Mitogen-Activated Protein Kinase; mTOR: Mechanistic Target of Rapamycin; NF-κB: Nuclear Factor-Kappa B; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2; PI3K: Phosphoinositide 3-Kinase; PKB/Akt: Protein Kinase B; RCT: Randomized Controlled Trial; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SCFAs: Short-Chain Fatty Acids; SIRT1: Sirtuin 1; SOD: Superoxide Dismutase; STAT3: Signal Transducer and Activator of Transcription 3; TNF-α: Tumor Necrosis Factor-Alpha; TRAIL: Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand; ULK1: Unc-51-Like Kinase 1; VEGF: Vascular Endothelial Growth Factor

Learning Objectives

Upon completion of this review, readers should be able to:

A. Define functional foods and distinguish them from dietary supplements and nutraceuticals.

B. Describe the major molecular mechanisms through which functional foods may influence carcinogenesis.

C. Identify the principal bioactive compounds found in commonly consumed functional foods.

D. Critically evaluate current clinical evidence supporting dietary interventions for cancer prevention.

E. Discuss the emerging role of the gut microbiome in mediating the relationship between diet and cancer risk.

F. Apply evidence-based nutritional recommendations in clinical practice while recognizing current limitations of the available literature.

Introduction

Cancer continues to represent one of the greatest global public health challenges of the twenty-first century. Although advances in molecular diagnostics, precision medicine, immunotherapy, and targeted therapies have significantly improved outcomes for many patients, the worldwide burden of cancer continues to rise owing to population growth, population aging, urbanization, and changes in lifestyle-related risk factors. Current estimates from the International Agency for Research on Cancer indicate that approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022. Demographic projections suggest that the annual number of new cancer cases could exceed 35 million by 2050, representing an increase of approximately 77% from 2022 levels [1]. Unlike many inherited disorders, most cancers develop through a complex interaction between genetic susceptibility and environmental exposures accumulated over many years. The multistep process of carcinogenesis involves sequential genetic and epigenetic alterations that ultimately result in sustained proliferative signaling, resistance to cell death, induction of angiogenesis, immune evasion, invasion, and metastasis [2]. Importantly, many of the biological processes underlying carcinogenesis are influenced by modifiable environmental and lifestyle factors, making cancer prevention an attainable public health goal.

Among modifiable risk factors, nutrition occupies a unique position because dietary exposures occur continuously throughout life. Unlike pharmacologic interventions, dietary modification can simultaneously influence multiple biological pathways while providing additional cardiovascular, metabolic, and immunological benefits. The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) conclude that a substantial proportion of cancers could potentially be prevented through healthy lifestyle practices, including appropriate dietary choices, maintenance of a healthy body weight, regular physical activity, avoidance of tobacco products, and limitation or avoidance of alcohol consumption [3]. These estimates underscore the considerable potential of dietary and lifestyle interventions to reduce the global cancer burden. Historically, nutrition research focused primarily on preventing classical deficiency diseases such as scurvy, pellagra, rickets, and beriberi. During the latter half of the twentieth century, however, scientific interest shifted toward understanding how specific dietary components influence chronic diseases, including cardiovascular disease, diabetes mellitus, neurodegenerative disorders, and cancer. This paradigm shift gave rise to the concept of functional foods-foods that have been satisfactorily demonstrated to beneficially affect one or more physiological functions beyond the provision of adequate nutrition, in a manner relevant to improved health or reduced disease risk [4].

Unlike isolated pharmaceutical agents that frequently target a limited number of molecular pathways, functional foods contain complex mixtures of bioactive compounds capable of acting additively or synergistically across numerous signaling networks. Fruits, vegetables, whole grains, legumes, nuts, seeds, herbs, spices, fermented foods, and certain marine products contain numerous naturally occurring bioactive compounds, including polyphenols, carotenoids, glucosinolates, organosulfur compounds, phytosterols, terpenoids, dietary fibers, and omega-3 fatty acids. These compounds may contribute to antioxidant defense, immune regulation, modulation of inflammatory signaling, xenobiotic metabolism, and maintenance of cellular homeostasis [5]. One of the most compelling aspects of functional foods is their potential ability to influence multiple stages of carcinogenesis. Experimental studies have demonstrated that dietary bioactive compounds can reduce oxidative DNA damage, inhibit activation of Nuclear Factor-Kappa B (NF-κB), suppress Cyclooxygenase-2 (COX-2) expression, activate nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant and detoxification responses, and modulate interactions between inflammatory and cytoprotective signaling pathways [5,6].

Other reported effects include promotion of apoptosis through intrinsic and extrinsic pathways, inhibition of vascular endothelial growth factor-mediated angiogenesis, regulation of cell-cycle progression, and suppression of invasion and metastasis [5,6]. Dietary phytochemicals may also modulate epigenetic mechanisms, including DNA methylation, histone modification, chromatin remodeling, and microRNA expression [5,7]. Collectively, these observations suggest that nutritional exposures may influence multiple biological processes involved in both the initiation and progression of malignant disease. Recent advances in microbiome research have further expanded the understanding of diet-cancer interactions. The gastrointestinal tract contains trillions of microorganisms that collectively influence immune function, metabolism, inflammatory signaling, epithelial integrity, and the biotransformation of dietary and host-derived compounds. Dietary fiber, polyphenols, fermented foods, and other functional food components can substantially alter microbial composition and metabolic activity. Conversely, microbial metabolism can influence the bioavailability and biological activity of numerous dietary compounds, creating a complex bidirectional relationship between diet, the microbiome, and the host [8]. The production of beneficial microbial metabolites, particularly short-chain fatty acids such as acetate, propionate, and butyrate, has emerged as an important mechanism linking diet with colorectal health.

Butyrate, which is produced through bacterial fermentation of dietary fiber, serves as a principal energy source for normal colonocytes, contributes to maintenance of the intestinal epithelial

barrier, regulates inflammatory and immune responses, and may inhibit histone deacetylase activity in malignant colonocytes. These effects may influence cellular proliferation, differentiation, apoptosis, and colorectal tumor development [9]. Nevertheless, the biological effects of microbial metabolites depend on their concentration, location, host metabolic state, microbial ecology, and the molecular characteristics of the target tissue. Despite growing enthusiasm surrounding functional foods, important challenges remain. Much of the mechanistic evidence originates from cell-culture and animal studies employing concentrations of isolated compounds that may not be achievable through normal dietary intake. The absorption, metabolism, tissue distribution, and elimination of many phytochemicals also differ substantially between experimental models and humans. Furthermore, human nutritional research is inherently complex because dietary exposures occur over decades and are influenced by genetic, environmental, behavioral, cultural, and socioeconomic factors. Isolating the independent effects of individual foods or phytochemicals is therefore difficult, and randomized controlled trials evaluating dietary interventions frequently produce heterogeneous results. Differences in intervention composition, dosage, duration, adherence, baseline nutritional status, cancer type, genetic background, microbiome composition, and measured outcomes may contribute to inconsistencies across studies.

In addition, a bioactive compound may produce markedly different effects when consumed as part of a whole food than when administered as a highly concentrated supplement. Consequently, current cancer-prevention guidelines emphasize overall dietary patterns rather than reliance on individual functional foods or dietary supplements. Recommended patterns generally prioritize vegetables, fruits, legumes, and whole grains while limiting red and processed meats, sugar-sweetened beverages, highly processed foods, and alcohol. These recommendations are integrated with maintenance of a healthy body weight and regular physical activity [3,10]. This whole-diet approach recognizes that foods are consumed in combination and that long-term interactions among nutrients, bioactive compounds, energy balance, physical activity, and the intestinal microbiome may be more biologically relevant than the effects of any single dietary constituent. An additional consideration is the increasing public interest in complementary and integrative medicine. Patients frequently inquire about botanical products, herbal supplements, concentrated phytochemicals, and functional foods as potential strategies for cancer prevention or as adjuncts to conventional cancer therapy. Healthcare professionals must therefore possess a sound understanding of both the potential benefits and limitations of these interventions. Evidence-based counseling should distinguish between food-based dietary strategies supported by epidemiological and clinical evidence and high-dose supplements for which efficacy, safety, pharmacokinetics, and herb-drug interactions may be uncertain.

Functional foods should not be regarded as substitutes for established cancer-prevention measures, including tobacco avoidance, vaccination against oncogenic infections, appropriate cancer screening, maintenance of healthy body weight, regular physical activity, and adherence to evidence-based medical recommendations. Rather, they should be considered components of comprehensive dietary and lifestyle patterns that may contribute to risk reduction through cumulative and complementary biological effects. This review examines the current scientific understanding of functional foods in cancer prevention, integrating findings from molecular biology, nutritional epidemiology, clinical research, and emerging microbiome science. Emphasis is placed on biologically plausible mechanisms, the strength of clinical evidence, practical implications for patient counseling, and future directions in precision nutrition and integrative oncology. Through a comprehensive evaluation of the available literature, this review aims to provide physicians, medical students, researchers, and allied healthcare professionals with an evidence-based framework for understanding the role of functional foods within contemporary cancer-prevention strategies.

Functional Foods and Bioactive Compounds

Functional foods: Definition and classification

The concept of functional foods has evolved considerably over the past three decades, reflecting advances in nutritional science, molecular biology, and preventive medicine. Unlike conventional foods that primarily provide energy and essential nutrients, functional foods are defined as foods that confer physiological benefits beyond basic nutritional requirements, thereby contributing to health promotion and disease prevention. Although no universally accepted definition exists, the International Food Information Council (IFIC) describes functional foods as foods that provide health benefits beyond basic nutrition due to the presence of biologically active components. Similarly, the International Life Sciences Institute (ILSI) defines a functional food as one that has been satisfactorily demonstrated to beneficially affect one or more target functions in the body, beyond adequate nutritional effects, in a manner relevant to improved health or reduced disease risk [11,12].

The concept originated in Japan during the 1980s with the introduction of Foods for Specified Health Uses (FOSHU), a regulatory framework recognizing foods with scientifically substantiated health benefits. Since then, functional foods have become an integral component of preventive healthcare strategies worldwide, particularly in the context of chronic non-communicable diseases, including cardiovascular disease, diabetes, neurodegenerative disorders, and cancer [13]. Cancer prevention represents one of the most extensively investigated applications of functional foods. Epidemiological studies consistently demonstrate that dietary patterns characterized by abundant fruits, vegetables, legumes, whole grains, nuts, and fermented foods are associated with lower incidence of several malignancies, including colorectal, gastric, breast, prostate, and lung cancers [14,15]. While individual nutrients undoubtedly contribute to these protective effects, growing evidence suggests that complex interactions among multiple bioactive compounds within whole foods produce synergistic biological activities that cannot be replicated by isolated supplements alone. Functional foods can be broadly categorized into several groups.

Naturally functional foods include fruits, vegetables, whole grains, legumes, nuts, seeds, herbs, spices, mushrooms, and fermented foods that naturally contain high concentrations of bioactive phytochemicals. Fortified foods are conventional foods supplemented with vitamins, minerals, probiotics, or other beneficial constituents. Enriched foods contain increased concentrations of naturally occurring compounds through agricultural or technological interventions, whereas enhanced foods are produced by modifying animal feeding practices or cultivation techniques to increase beneficial nutrients such as omega-3 fatty acids. Fermented functional foods constitute another important category because microbial fermentation generates novel bioactive metabolites while improving nutrient bioavailability [16]. Unlike dietary supplements, which generally provide isolated nutrients or phytochemicals in concentrated forms, functional foods deliver complex mixtures of biologically active compounds within their natural food matrix. This distinction is increasingly recognized as clinically important because food matrices influence digestion, absorption, metabolism, gut microbial interactions, and ultimately biological efficacy [17]. Consequently, current dietary recommendations emphasize whole-food dietary patterns rather than isolated supplementation for long-term cancer prevention.

Major bioactive compounds in functional foods

The anticancer properties of functional foods are largely attributed to diverse bioactive compounds that modulate multiple molecular pathways involved in carcinogenesis. These naturally occurring phytochemicals exhibit antioxidant, anti-inflammatory, immunomodulatory, antiproliferative, antiangiogenic, and epigenetic regulatory activities that collectively contribute to cancer prevention.

Polyphenols: Polyphenols constitute one of the largest families of plant-derived bioactive compounds, encompassing more than 8,000 identified molecules. Major subclasses include flavonoids, phenolic acids, stilbenes, lignans, tannins, and anthocyanins. Rich dietary sources include berries, grapes, apples, cocoa, coffee, tea, olive oil, and numerous herbs and spices [18].

Polyphenols exert pleiotropic biological effects. Rather than acting solely as direct antioxidants, they regulate intracellular signaling pathways involved in oxidative stress, inflammation, apoptosis, autophagy, mitochondrial function, and immune surveillance. Curcumin, Epigallocatechin Gallate (EGCG), quercetin, resveratrol, and anthocyanins have received particular attention because of their ability to inhibit NF-κB activation, suppress STAT3 signaling, activate Nrf2-mediated antioxidant responses, and modulate PI3K/Akt and MAPK pathways [19,20].

Carotenoids: Carotenoids are naturally occurring lipid-soluble pigments responsible for the red, orange, and yellow coloration of many fruits and vegetables. Important dietary carotenoids include β-carotene, lycopene, lutein, zeaxanthin, and astaxanthin. Lycopene, found predominantly in tomatoes and tomato products, has demonstrated antioxidant and antiproliferative effects and may influence several signaling processes relevant to cancer development [21]. β-Carotene serves as a precursor of vitamin A and contributes to several physiological functions. However, randomized clinical trials have demonstrated that high-dose β-carotene supplementation can increase lung-cancer risk among smokers, highlighting the complexity of translating the effects of carotenoid-rich foods into isolated high-dose supplements [22].

Organosulfur Compounds: Garlic, onions, leeks, shallots, and cruciferous vegetables provide abundant sulfur-containing phytochemicals with recognized anticancer activities. Garlic-derived organosulfur compounds, including allicin, diallyl sulfide, diallyl disulfide, and S-allyl cysteine, inhibit carcinogen activation, promote apoptosis, suppress angiogenesis, and reduce chronic inflammation [23]. Cruciferous vegetables contain glucosinolates, which are converted by the enzyme myrosinase into biologically active isothiocyanates and indoles following plant tissue disruption. Sulforaphane, one of the best-characterized isothiocyanates, activates phase II detoxification enzymes, enhances antioxidant defense through Nrf2 activation, suppresses histone deacetylases, and selectively targets cancer stem cells in experimental models [24,25].

Dietary Fiber and Short-Chain Fatty Acids: Dietary fiber has emerged as an important component of cancer prevention through its effects on gastrointestinal physiology and the gut microbiome. Fermentable fibers undergo bacterial metabolism within the colon, producing Short-Chain Fatty Acids (SCFAs), particularly acetate, propionate, and butyrate [26]. Butyrate serves as a major energy source for normal colonocytes while also functioning as a histone deacetylase inhibitor, thereby influencing gene expression, immune regulation, inflammation, epithelial-barrier integrity, and pathways involved in apoptosis [26]. Large prospective studies and meta-analyses have demonstrated inverse associations between dietary fiber intake and colorectal cancer risk [26,27].

Omega-3 Fatty Acids: Long-chain omega-3 polyunsaturated fatty acids, particularly Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), are obtained primarily from fatty fish, marine oils, algae, and fortified foods. These fatty acids have been widely investigated for their potential anti-inflammatory and cancer-preventive effects. However, clinical evidence for cancer prevention remains inconclusive. A large systematic review and meta-analysis of randomized controlled trials found that increasing long-chain omega-3 intake had little or no effect on overall cancer incidence or cancer mortality [28]. These findings suggest that, although omega-3 fatty acids may have important biological effects, current evidence does not support a clear cancer-preventive benefit from omega-3 supplementation alone.

Probiotics and Prebiotics: The intestinal microbiome plays an important role in host immunity, inflammation, and metabolism. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Certain fermented foods may contain live microorganisms, although not all fermented foods meet the scientific definition of a probiotic [29]. Prebiotic and fiber-rich foods can influence the gut microbiome and microbial metabolism, including the production of short-chain fatty acids. Emerging evidence also suggests that diet and gut microbial composition may influence responses to cancer

immunotherapy. In patients with melanoma receiving immune-checkpoint inhibitors, higher dietary fiber intake was associated with improved treatment outcomes, highlighting a potential interaction among diet, the microbiome, and antitumor immunity [30].

Major functional foods with potential roles in cancer prevention

Among naturally occurring functional foods, cruciferous vegetables-including broccoli, Brussels sprouts, cabbage, kale, cauliflower, and bok choy-have received considerable attention for their potential role in cancer prevention. These vegetables are rich in glucosinolates, which are metabolized to biologically active compounds such as isothiocyanates and indoles, including sulforaphane and indole-3-carbinol. Experimental and epidemiologic studies suggest that these compounds may influence carcinogen metabolism, cellular antioxidant defenses, inflammation, apoptosis, and other pathways involved in carcinogenesis [31]. Berries represent another extensively investigated group of functional foods because of their high concentrations of polyphenols, particularly anthocyanins and other flavonoids. Blueberries, strawberries, raspberries, blackberries, cranberries, and other berries have demonstrated antioxidant and anti-inflammatory properties and can influence cellular proliferation, apoptosis, cell-cycle regulation, and angiogenesis in experimental cancer models.

Preclinical studies and limited human investigations suggest potential beneficial effects particularly in colorectal cancer prevention, although additional clinical studies are needed [32]. Green tea has long been consumed throughout Asia and is a rich dietary source of catechins, particularly Epigallocatechin-3-Gallate (EGCG). Experimental studies demonstrate that green-tea polyphenols can influence tumor-cell proliferation, oxidative stress, inflammation, angiogenesis, and metastatic signaling. Epidemiological studies have reported possible protective associations for several cancer types, although findings remain inconsistent across populations and cancer sites [33]. Turmeric *(Curcuma longa)* occupies a unique position at the intersection of traditional medicine and modern biomedical research. Curcumin, its principal polyphenolic constituent, has demonstrated broad anticancer activity in preclinical models through modulation of multiple signaling pathways. However, poor oral bioavailability resulting from limited absorption, rapid metabolism, and systemic elimination has restricted its clinical translation.

Consequently, several strategies-including nanoparticle formulations, liposomal delivery, phospholipid complexes, and bioavailability-enhancing adjuvants-have been investigated to improve systemic exposure [34]. Soybeans and soy-derived foods contain isoflavones, including genistein and daidzein, which interact with estrogen receptors and have historically raised concerns regarding their use in hormone-dependent cancers. However, accumulating clinical and epidemiological evidence indicates that moderate consumption of soy foods is generally safe for breast cancer survivors and may be associated with favorable outcomes, including reduced recurrence and cancer-specific mortality, even among women with estrogen receptor-positive disease [35]. Collectively, these functional foods illustrate the complexity of dietary cancer prevention. Rather than acting through a single mechanism, they influence numerous interconnected biological pathways, emphasizing the importance of whole-food dietary patterns over reductionist approaches focusing on individual nutrients.

Future perspectives: Precision nutrition, multi-omics, and personalized functional food strategies

The field of functional foods is increasingly moving from generalized dietary recommendations toward precision nutrition. Individuals can respond differently to the same foods because of variations in genetics, metabolism, lifestyle, and gut microbiome composition [36-40]. Precision nutrition seeks to integrate these factors with emerging technologies such as genomics, metabolomics, microbiome profiling, and systems biology to better predict individual responses to dietary interventions [36,37]. The gut microbiome is likely to be particularly important in this individualized response. Intestinal microorganisms metabolize dietary components, including polyphenols, into bioactive metabolites that may differ substantially among individuals because of variations in microbial composition and function [38-42]. Dietary fiber is similarly fermented by gut microorganisms to produce short-chain fatty acids such as acetate, propionate, and butyrate, which influence intestinal and metabolic homeostasis [39,43,44]. Together, these advances suggest that the future of functional-food research may involve combining dietary information with genetic, metabolic, and microbiome profiles rather than assuming that a single dietary intervention will produce the same biological response in every person [36-40,45]. Such approaches may ultimately support more individualized and evidence-based strategies for cancer prevention.

Multi-Omics, clinical translation, and dietary patterns: Advances in multi-omics and systems biology are improving our ability to understand complex biological responses to diet. Integration of genomic, transcriptomic, proteomic, and metabolomic information may help identify molecular patterns associated with disease risk and individual biological responses [46,47]. Artificial intelligence may further assist in analyzing these complex datasets and contribute to more individualized approaches to prevention and health care [48]. Translation into clinical practice, however, remains challenging. Nutritional studies vary considerably in dietary assessment, participant characteristics, intervention duration, adherence, and measured outcomes, while observational studies remain vulnerable to measurement error and residual confounding [49,50]. Bioavailability is another important consideration, particularly for dietary polyphenols, whose absorption and metabolism can vary substantially [51].

For cancer prevention, these limitations support greater emphasis on whole foods and overall dietary patterns rather than isolated bioactive compounds. Whole foods contain multiple interacting nutrients and phytochemicals, and holistic dietary approaches may better reflect their combined biological effects [52]. Current cancer-prevention recommendations similarly

emphasize a dietary pattern rich in whole grains, vegetables, fruits, and legumes together with healthy body weight, regular physical activity, and limitation of alcohol [53]. Substantial interindividual variation in metabolic responses to identical foods further supports the development of personalized rather than uniform dietary recommendations [54,55]. Large-scale human studies have demonstrated that postprandial glucose, insulin, and lipid responses vary considerably among individuals and can be partly predicted using clinical, dietary, and microbiome characteristics [55].

The greatest preventive benefit is likely to arise when functional-food strategies are integrated with established clinical and public-health measures. Precision nutrition may eventually allow dietary recommendations to be tailored to genetic, metabolic, microbiome, environmental, and individual factors. However, such recommendations should remain grounded in the overall strength of clinical evidence rather than mechanistic findings alone. Growing attention is now focused on the molecular pathways through which functional-food bio actives may influence carcinogenesis, including oxidative stress, inflammation, apoptosis, autophagy, cell-cycle regulation, angiogenesis, epigenetic mechanisms, immune function, and cellular metabolism. Understanding these interconnected pathways is important for translating experimental and epidemiological findings into credible cancer-prevention strategies. The following section examines these major mechanisms.

Molecular Mechanisms of Cancer Prevention

Oxidative stress and antioxidant defense systems

Oxidative stress is widely recognized as one of the earliest and most fundamental biological processes contributing to carcinogenesis. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are continuously generated as by-products of normal cellular metabolism, particularly through mitochondrial oxidative phosphorylation, inflammatory responses, and enzymatic reactions involving NADPH oxidases, xanthine oxidase, and cytochrome P450 enzymes [54,55]. Under physiological conditions, endogenous antioxidant defense systems tightly regulate ROS production, allowing these reactive molecules to function as essential signaling mediators involved in cell proliferation, differentiation, immune responses, and apoptosis. However, persistent oxidative stress resulting from excessive ROS production or impaired antioxidant defenses leads to oxidative damage of DNA, proteins, lipids, and cellular organelles, thereby promoting genomic instability, mutagenesis, chronic inflammation, and ultimately malignant transformation [56-58].

Accumulating evidence indicates that oxidative DNA damage represents one of the earliest molecular events in tumor initiation. ROS readily oxidize nucleotide bases, producing lesions such as 8-Hydroxy-2'-Deoxyguanosine (8-OHdG), which can generate G:C to T:A transversion mutations if not efficiently repaired by base excision repair pathways [59]. Similar oxidative modifications affect mitochondrial DNA, which possesses limited repair capacity compared with nuclear DNA, leading to mitochondrial dysfunction, further ROS generation, and a self-perpetuating cycle of oxidative injury [60]. Lipid peroxidation products including Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE) also form DNA adducts and interfere with normal cellular signaling pathways that regulate proliferation and apoptosis [61]. Beyond direct DNA damage, oxidative stress also influences multiple oncogenic signaling pathways. At moderate concentrations, ROS can function as signaling molecules that modulate transcription factors and signaling pathways including NF-κB, AP-1, HIF-1α, Wnt/β-catenin, PI3K/Akt, and MAPK cascades [54,55,62,63].

Activation of these pathways can promote cellular proliferation and survival, angiogenesis, epithelial-mesenchymal transition, invasion, and metastatic progression [55,62,64]. Conversely, excessively high ROS concentrations may induce irreversible oxidative injury and activate intrinsic apoptotic pathways. This dual role explains why cancer cells often maintain ROS concentrations that are sufficiently elevated to stimulate growth while simultaneously enhancing antioxidant defense mechanisms to avoid cytotoxicity [64,65]. Cells have evolved sophisticated endogenous antioxidant systems to maintain redox homeostasis. Major enzymatic defenses include superoxide dismutases (SOD1, SOD2, and SOD3), catalase, Glutathione Peroxidases (GPXs), glutathione reductase, and the thioredoxin-thioredoxin reductase and peroxiredoxin systems [62,65]. Additional stress-responsive enzymes, including Heme Oxygenase-1 (HO-1), contribute to cellular protection against oxidative injury. These systems function in concert with nonenzymatic antioxidants such as glutathione, coenzyme Q10, uric acid, bilirubin, and dietary antioxidants including vitamins C and E to regulate cellular redox balance and limit oxidative damage.

Glutathione is particularly important in maintaining intracellular redox homeostasis. In addition to serving as an electron donor for glutathione peroxidases during peroxide detoxification, glutathione participates in the regulation of protein thiol redox states and numerous redox-sensitive signaling processes [65]. Among the molecular regulators of antioxidant defense, nuclear factor erythroid 2-related factor 2 (Nrf2) has emerged as a master transcriptional regulator of cellular redox homeostasis. Under basal conditions, Nrf2 remains bound to Kelch-like ECH-associated protein 1 (Keap1), which promotes its ubiquitination and proteasomal degradation [66]. During oxidative stress, critical cysteine residues within Keap1 become oxidized, permitting Nrf2 stabilization, nuclear translocation, and binding to antioxidant response elements (AREs) within promoter regions of cytoprotective genes [66]. Nrf2 activation subsequently induces transcription of numerous detoxification enzymes including glutathione S-transferases, NAD(P)H quinone oxidoreductase-1 (NQO1), heme oxygenase-1, glutamate-cysteine ligase, thioredoxin reductase, and multiple phase II detoxification enzymes [66].

Functional foods and dietary phytochemicals are increasingly recognized as modulators of Nrf2 signaling. Sulforaphane, an isothiocyanate abundant in broccoli sprouts and other cruciferous vegetables, is among the best-characterized naturally occurring Nrf2 activators [66,67]. As an electrophilic compound, sulforaphane modifies reactive cysteine residues within Keap1, particularly

Cys151, thereby disrupting Keap1-mediated repression of Nrf2 and promoting transcription of antioxidant and cytoprotective enzymes [66,68]. Experimental studies have shown that curcumin can enhance endogenous antioxidant defenses, including glutathione-related pathways, superoxide dismutase, and catalase activity, while reducing lipid peroxidation and other indices of oxidative stress [69]. Likewise, Epigallocatechin-3-Gallate (EGCG), the principal catechin in green tea, can modulate Nrf2-dependent antioxidant responses and influence cancer-related signaling pathways, including MAPK and PI3K/Akt [70]. Resveratrol, a polyphenolic compound abundant in grapes, berries, and peanuts, also exhibits substantial antioxidant properties through activation of sirtuin-1 (SIRT1), AMP-Activated Protein Kinase (AMPK), and Nrf2 signaling pathways [71].

These effects improve mitochondrial function, reduce mitochondrial ROS generation, and enhance cellular resistance to oxidative injury. In addition, resveratrol suppresses NADPH oxidase activity while increasing endogenous antioxidant enzyme expression, thereby limiting oxidative DNA damage associated with chronic inflammation [71]. Carotenoids, including lycopene, lutein, zeaxanthin, β-carotene, and astaxanthin, function primarily as singlet oxygen quenchers and lipid-soluble free radical scavengers. Lycopene, particularly abundant in tomatoes, has demonstrated the ability to reduce oxidative DNA damage, inhibit insulin-like growth factor signaling, and suppress proliferation in prostate, breast, and gastrointestinal cancers [72]. Similarly, anthocyanins present in berries, purple grapes, black rice, and colored vegetables reduce intracellular ROS accumulation while activating endogenous antioxidant enzymes and preserving mitochondrial integrity [73].

The relationship between antioxidants and cancer prevention, however, is considerably more complex than originally appreciated. While diets naturally rich in antioxidant-containing fruits and vegetables consistently demonstrate inverse associations with cancer risk, randomized clinical trials evaluating isolated antioxidant supplements have produced inconsistent or occasionally adverse findings. Large intervention studies involving high-dose β-carotene supplementation unexpectedly demonstrated increased lung cancer incidence among smokers, suggesting that excessive supplementation may alter physiological redox signaling or exhibit pro-oxidant effects under specific conditions [74]. Similarly, the SELECT trial demonstrated an increased risk of prostate cancer among men receiving vitamin E supplementation [75]. These observations emphasize that the health effects associated with whole-food dietary patterns cannot necessarily be reproduced by administering isolated micronutrients at pharmacological doses and may instead reflect complex interactions among multiple nutrients and phytochemicals within foods.

Inflammation and pro-inflammatory signaling

Chronic, unresolved inflammation is a major biological link between environmental exposures, metabolic dysfunction, tissue injury, and carcinogenesis. In contrast to acute inflammation, which is generally self-limiting and supports tissue repair, persistent inflammatory signaling creates a microenvironment characterized by oxidative stress, genomic instability, abnormal cell proliferation, angiogenesis, immune suppression, and resistance to apoptosis. Inflammatory cells may also release reactive oxygen and nitrogen species that damage DNA and promote mutagenic changes in neighboring epithelial cells. Consequently, inflammation is now regarded as both an enabling characteristic and an important driver of malignant transformation [76,77]. Nuclear Factor Kappa B (NF-κB) is one of the central transcriptional regulators connecting inflammation with cancer. Activation of the canonical NF-κB pathway promotes the expression of inflammatory cytokines, chemokines, cyclooxygenase-2, inducible nitric oxide synthase, anti-apoptotic proteins, adhesion molecules, and angiogenic mediators.

Persistent NF-κB activity can therefore support tumor-cell survival while recruiting inflammatory and immunosuppressive cells into the developing tumor microenvironment [76,78]. Other relevant pathways include signal transducer and activator of transcription 3 (STAT3), activator protein-1, mitogen-activated protein kinases, and the NLRP3 inflammasome. Interleukin-6-mediated STAT3 activation is particularly important because it promotes proliferation, stemness, epithelial-mesenchymal transition, angiogenesis, and resistance to immune-mediated elimination [79]. Functional foods may influence inflammatory networks through diverse bioactive constituents, including polyphenols, carotenoids, organosulfur compounds, omega-3 fatty acids, fermentable fiber, and microbiota-derived metabolites. Among these, dietary phytochemicals such as curcumin, resveratrol, EGCG, quercetin, and sulforaphane have been shown in experimental models to modulate inflammatory signaling pathways, including NF-κB, MAPK, and STAT3, and to influence the production of pro-inflammatory mediators [80-82].

Curcumin, for example, can suppress IKK-mediated NF-κB activation and reduce the expression of inflammatory mediators including TNF-α, IL-6, COX-2, and inducible nitric oxide synthase [81]. Sulforaphane can similarly inhibit IKK/NF-κB signaling and, in some cancer models, suppress STAT3 activation [82,83]. Resveratrol and other polyphenols also influence inflammatory signaling through pathways that include NF-κB, AMPK, and sirtuin-dependent mechanisms [80,83]. Marine omega-3 fatty acids, particularly Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), can alter membrane lipid composition and reduce the production of arachidonic acid-derived inflammatory eicosanoids. EPA and DHA also serve as precursors for specialized pro-resolving mediators, including resolvins, protectins, and maresins, which actively promote the resolution of inflammation rather than simply inhibiting its initiation [84]. Dietary fiber may influence inflammatory processes through microbial fermentation and the production of short-chain fatty acids, particularly butyrate.

Butyrate can support intestinal epithelial-barrier function, influence regulatory T-cell differentiation, inhibit histone deacetylases, and suppress selected inflammatory signaling pathways within the colon [85,86]. These findings suggest that functional foods should be considered as part of an overall dietary pattern rather than as individual anti-inflammatory treatments. Diets rich in plant foods, fiber, healthy fats, herbs, spices, and

fermented foods may help reduce chronic inflammation through several biological pathways and may therefore influence processes involved in cancer development. However, many laboratory studies use concentrations of bioactive compounds that are much higher than those normally obtained from food. For this reason, applying these findings to clinical practice requires careful consideration of how these compounds are absorbed and metabolized, how they interact with the food matrix, the dose and duration of intake, and differences among individuals.

Induction of apoptosis and elimination of damaged cells

Apoptosis is a tightly regulated form of programmed cell death that removes damaged, mutated, infected, or otherwise unnecessary cells while generally limiting inflammation in surrounding tissues [87]. Failure of apoptosis can allow genetically damaged cells to survive and continue proliferating, thereby facilitating the accumulation of additional abnormalities that contribute to malignant transformation [88]. Resistance to cell death is therefore recognized as one of the defining hallmarks of cancer [89]. Apoptosis occurs principally through the intrinsic mitochondrial pathway and the extrinsic death-receptor pathway. The intrinsic pathway is controlled by the balance between pro-apoptotic and anti-apoptotic members of the B-cell lymphoma-2 protein family. Cellular stress activates proteins such as BAX and BAK, leading to mitochondrial outer-membrane permeabilization, cytochrome-c release, apoptosome formation, caspase-9 activation, and subsequent activation of executioner caspases. The extrinsic pathway is initiated through receptors such as Fas, tumor necrosis factor-related apoptosis-inducing ligand receptors, and tumor necrosis factor receptors, culminating in caspase-8 activation. Cross-talk between these pathways determines whether a damaged cell undergoes repair, senescence, or irreversible death [90].

Several dietary bioactive compounds can influence apoptotic signaling in transformed cells. Curcumin has been reported to suppress anti-apoptotic proteins, including BCL-2, BCL-XL, survivin, and inhibitors of apoptosis, while promoting BAX/BAK activation, mitochondrial dysfunction, and caspase-dependent apoptosis [91]. Resveratrol can induce both p53-dependent and p53-independent apoptosis, alter the balance between pro- and anti-apoptotic BCL-2-family proteins, inhibit PI3K/Akt signaling, and promote mitochondrial cytochrome-c release and caspase activation [92,93]. EGCG may similarly promote apoptosis through modulation of death-receptor and receptor tyrosine kinase signaling and inhibition of survival pathways including PI3K/Akt and NF-κB [94]. Sulforaphane, an isothiocyanate derived from glucoraphanin in cruciferous vegetables, has demonstrated particularly broad effects on cell-cycle regulation and apoptosis. In experimental systems, sulforaphane can activate caspases, promote mitochondrial dysfunction in transformed cells, inhibit histone deacetylases, stabilize tumor-suppressor responses, and reduce the expression of proteins involved in proliferation and survival [95]. Other compounds, including genistein, quercetin, apigenin, indole-3-carbinol, diallyl sulfide, lycopene, and berry anthocyanins, have shown related effects across various cancer models.

An important proposed feature of dietary phytochemicals is their relative selectivity. Although these compounds may protect normal cells against oxidative injury at physiologically relevant exposures, higher local or intracellular concentrations may act as pro-oxidants in malignant cells, which frequently possess elevated basal oxidative stress. Additional reactive oxygen species can exceed the antioxidant capacity of cancer cells, disrupt mitochondrial function, and trigger apoptosis [96]. This biphasic action is highly dependent on dose, cellular context, oxygen tension, metal availability, metabolic phenotype, and the activity of antioxidant systems. The apoptosis-inducing effects of functional-food constituents are biologically plausible and well supported by cell-culture and animal studies. However, evidence that normal dietary exposure produces equivalent effects in human premalignant tissues is less conclusive. Future prevention trials should integrate tissue biomarkers, apoptotic indices, pharmacokinetics, and molecular stratification rather than relying exclusively on circulating compound levels or epidemiologic associations.

Regulation of autophagy

Autophagy is an evolutionarily conserved cellular process in which damaged proteins, dysfunctional organelles, and other cytoplasmic components are sequestered within autophagosomes and delivered to lysosomes for degradation. Basal autophagy contributes to cellular homeostasis by removing damaged cellular components, maintaining organelle quality, and limiting the accumulation of potentially harmful material. In this context, autophagy can function as a tumor-suppressive mechanism during the early stages of carcinogenesis [97]. The relationship between autophagy and cancer is nevertheless context dependent. During early carcinogenesis, autophagy may help suppress tumor development by maintaining cellular homeostasis and limiting the accumulation of damaged cellular components. Once a tumor is established, however, malignant cells may use autophagy as an adaptive survival mechanism during nutrient deprivation, hypoxia, oxidative and metabolic stress, detachment, and anticancer treatment. Thus, impaired autophagy may facilitate tumor initiation in some settings, whereas tumor-supportive autophagy may contribute to the survival and progression of established cancers [97,98].

Major regulators of autophagy include the AMP-Activated Protein Kinase (AMPK)-Mechanistic Target of Rapamycin (mTOR) axis, the ULK1 complex, Beclin-1 and the class III phosphatidylinositol 3-kinase complex, and multiple autophagy-related (ATG) proteins that regulate autophagosome formation, maturation, and lysosomal degradation [97]. Diet-derived compounds can modulate autophagy by influencing cellular energy status, oxidative stress, endoplasmic-reticulum stress, and nutrient-sensing pathways. Resveratrol can activate SIRT1 and AMPK while inhibiting mechanistic target of rapamycin (mTOR) signaling, thereby promoting autophagy under selected experimental conditions [98]. Curcumin may modulate autophagy through pathways involving AKT-mTOR, AMPK, Beclin-1, and microtubule-associated protein 1 light chain 3 (LC3) [99]. EGCG, quercetin, genistein, and sulforaphane have also been reported

to influence autophagy in experimental cancer models [99,100]. The biological outcome of autophagy induction varies according to cancer type, stage, genetic background, and degree of cellular stress. Moderate autophagy may allow damaged cells to recover, whereas sustained or dysregulated autophagy may contribute to autophagy-associated cell death or enhance sensitivity to apoptosis [97].

Autophagy also interacts extensively with inflammatory and immune pathways. Removal of damaged mitochondria can reduce mitochondrial reactive oxygen species and inflammasome activation, while autophagic processing can influence antigen presentation and immunogenic cell death [101]. For cancer prevention, one potentially important role of functional foods may be the maintenance of normal autophagic activity before malignant transformation. Energy balance, fasting-related signaling, physical activity, plant-derived bioactive compounds, and overall metabolic health may influence cellular housekeeping, mitochondrial quality control, and other processes involved in maintaining cellular homeostasis. However, autophagy should not be regarded as uniformly beneficial. In established malignancies, tumor cells may exploit autophagy as an adaptive survival mechanism during metabolic stress, hypoxia, and anticancer treatment. Thus, the potential preventive effects of modulating autophagy should be distinguished from its more complex and context-dependent role in established cancer.

Clinical Evidence, Gut Microbiome, Future Directions, and Conclusion

Clinical evidence supporting functional foods in cancer prevention

Although mechanistic studies provide strong biological plausibility for functional foods in cancer prevention, clinical evidence is more variable. Overall, the strongest evidence supports healthy dietary patterns rich in whole grains, vegetables, fruits, legumes, and other minimally processed plant foods rather than isolated bioactive compounds or supplements [102,103]. This may partly reflect the combined effects of fiber, micronutrients, phytochemicals, and other food components acting within the whole-food matrix.

Clinical trials of individual phytochemicals have produced mixed results. For example, despite promising preclinical findings, randomized trials of curcumin in familial adenomatous polyposis and green-tea extract for colorectal adenoma prevention did not demonstrate significant reductions in adenoma burden or recurrence [104,105]. These findings highlight the challenges of translating experimental effects into clinical benefit, including differences in dose, bioavailability, duration of exposure, and individual response.

Dietary fiber and whole grains have some of the strongest epidemiologic evidence, particularly for colorectal cancer prevention [102,106]. Collectively, current evidence favors incorporating functional foods within an overall healthy dietary pattern while remaining cautious about assuming that isolated nutraceutical supplements will reproduce the benefits associated with whole foods.

Gut microbiome: A Link between nutrition and cancer prevention

The gut microbiome is increasingly recognized as an important interface between diet and host biology and may influence cancer risk through metabolic, inflammatory, immune, and epigenetic pathways. Dietary components such as fiber and phytochemicals can modify microbial composition and undergo microbial metabolism to generate short-chain fatty acids and other bioactive metabolites that support intestinal barrier integrity, immune homeostasis, and anti-inflammatory signaling. Conversely, microbial dysbiosis may impair barrier function and increase exposure to pro-inflammatory microbial products such as bacterial Lipopolysaccharide (LPS), thereby promoting systemic inflammation and cellular stress, processes that may contribute to an environment favorable to carcinogenesis. Martins has highlighted the potential importance of LPS-mediated inflammatory toxicity in chronic disease, while Sharma and Martins described the close relationship among diet, microbial composition, host metabolism, and inflammatory.

Together, these observations support the broader concept that diet-induced alterations in the microbiome can influence biological pathways well beyond the gastrointestinal tract. Diet-microbiome interactions may also affect nutrient-responsive cellular regulatory pathways. Martins proposed a role for Sirtuin 1 (SIRT1) in linking nutrition with metabolic and inflammatory regulation and suggested that microbial products such as LPS may adversely influence SIRT1-related cellular functions. Because SIRT1 participates in cellular metabolism, stress responses, inflammation, and genomic regulation, preservation of these regulatory pathways provides an additional potential mechanism through which diet and the microbiome could influence pathways relevant to chronic disease and carcinogenesis.

Diet remains one of the most modifiable determinants of the gut microbiome. Human intervention studies demonstrate that high-fiber and fermented-food diets can alter microbial function, diversity, and immune responses, although considerable interindividual variability exists. The microbiome may also influence responses to cancer therapy, particularly immune-checkpoint inhibitors, creating growing interest in dietary and microbiome-directed strategies as components of precision oncology. However, differences in microbial composition among individuals, dietary exposures, study methods, and cancer types currently limit translation into standardized recommendations. Further clinical studies are needed to determine whether targeted dietary modification of the microbiome can meaningfully reduce cancer risk or improve therapeutic outcomes.

Future directions

Future progress in nutritional oncology will increasingly depend on precision nutrition approaches that integrate genomics, metabolomics, microbiome profiling, and artificial intelligence to better predict individual responses to dietary interventions. Key priorities include larger randomized clinical trials with meaningful cancer outcomes, improved standardization of functional-food

composition, validated biomarkers of dietary exposure and response, clearer dose-response relationships, and integration of microbiome and multi-omics data into clinical research. Addressing these gaps will improve the quality of evidence and help translate functional-food research into more individualized and clinically useful cancer-prevention strategies.

Conclusion

Functional foods represent a promising component of cancer-prevention strategies because dietary bioactive compounds can influence multiple interconnected biological processes. As discussed in this review, these compounds may modulate oxidative stress, chronic inflammation, apoptosis, autophagy, and related signaling pathways involved in cancer initiation and progression. Their effects are therefore better understood as pleiotropic actions across biological networks rather than as the result of a single molecular target. Current evidence supports dietary patterns rich in fruits, vegetables, legumes, whole grains, fermented foods, marine-derived nutrients, herbs, and spices as important components of a comprehensive approach to cancer prevention. Emerging research on the gut microbiome further suggests that microbial metabolism may serve as an important link between diet and host biology, creating new opportunities for more individualized nutritional strategies.

Additional mechanisms, including epigenetic regulation, immune surveillance, tumor metabolism, angiogenesis, and cancer stem-cell biology, may also contribute to the cancer-preventive effects of dietary bioactive compounds but were beyond the scope of this review. These areas remain important directions for future investigation. Despite substantial mechanistic and epidemiologic evidence, important gaps remain regarding optimal intake, bioavailability, individual variability, and long-term clinical effectiveness. Functional foods should therefore not be viewed as alternatives to established cancer-prevention measures, but as evidence-informed components of broader lifestyle-based prevention strategies. Continued integration of nutritional science, oncology, molecular biology, microbiome research, and precision nutrition may ultimately help translate these findings into more practical and individualized approaches to reducing cancer risk.

Conflict of Interest

The author declares no conflict of interest.

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