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Precise nutritional modulation of cancer biomarkers through the employment of functional foods and bioactive compounds

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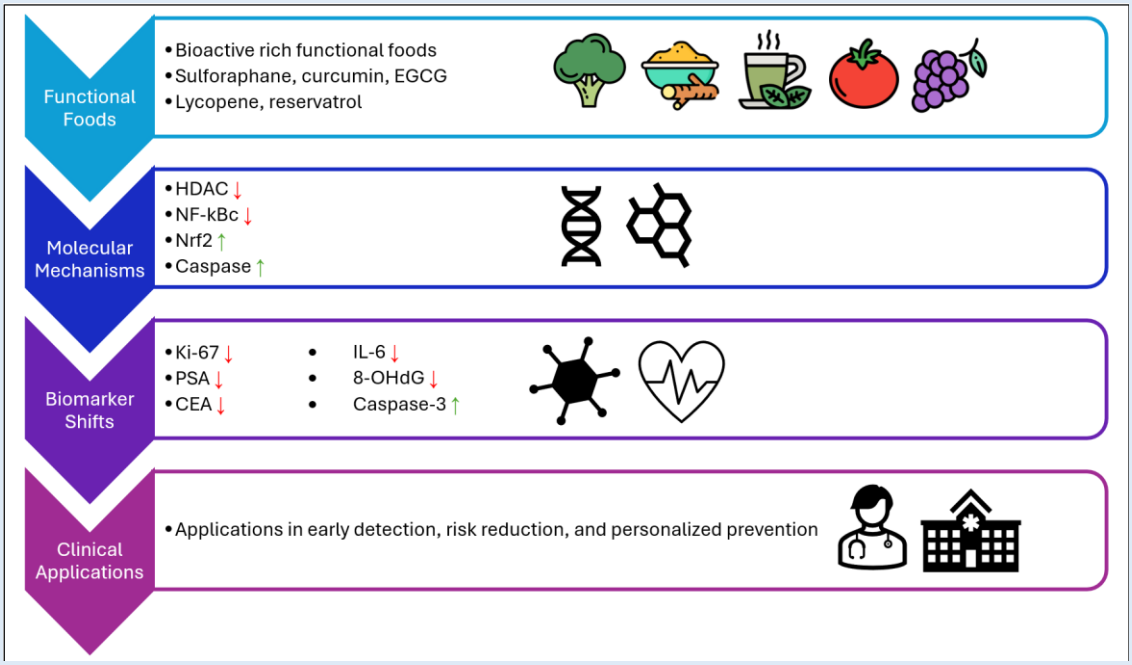
ABSTRACT

Cancer remains a leading cause of morbidity and mortality worldwide, prompting growing interest in preventive strategies that target early molecular changes. Functional foods (FFs), defined as bioactive-rich dietary components with health-promoting properties, have emerged as promising modulators of cancer-related biomarkers. This article reviews clinical and preclinical evidence on the influence of FFs and food bioactive compounds(FBCs)on key biomarkers, including HER2, Ki-67, PSA, and CEA, across various cancer types. Mechanistic insights reveal that these dietary compounds exert their effects through epigenetic modulation, anti-inflammatory signaling, reduction of oxidative stress, and regulation of apoptosis and the gut microbiome. Applications of these findings extend to biomarker-based early detection, dietary chemoprevention, and personalized nutrition strategies. However, limitations such as biomarker specificity, variable bioavailability, and a lack of long-term randomized trials continue to hinder clinical translation. Future directions emphasize the need for integrated omics approaches, development of multi-marker panels, and personalized dietary interventions supported by novel delivery systems. FFs hold significant promise in oncology, but rigorous, longitudinal studies are essential to validate their role in cancer prevention and precision medicine.

Novelty: This article uniquely synthesizes current clinical and preclinical evidence linking FFs and BCs to specific cancer-related biomarkers, while emphasizing mechanistic pathways and translational challenges. It further proposes integrated omics-based strategies and personalized nutrition approaches to enhance biomarker-guided cancer prevention, an area that remains underexplored in current literature.

Keywords: Functional foods, Bioactive Compounds, cancer biomarkers, chemoprevention, epigenetics, metabolomics, personalized nutrition, sulforaphane, bioavailability, dietary intervention, early detection.



Graphical Abstract: Precise nutritional modulation of cancer biomarkers

INTRODUCTION

FFs are defined as foods that provide health benefits beyond basic nutrition, often due to the presence of BCs such as polyphenols, flavonoids, carotenoids, and phytosterols. These BCs are increasingly recognized for their role in modulating physiological functions and reducing the risk of chronic diseases, including cancer [1–3]. As the field of nutritional science evolves, the potential of FFs to act not only as preventive agents but also as modulators of molecular and cellular processes relevant to disease progression is becoming increasingly evident [4–6].

Cancer remains one of the leading causes of death globally, accounting for nearly 10 million deaths in 2020 alone, with numbers projected to rise in the coming decades [7]. The growing burden of cancer has intensified interest in non-pharmacological strategies for prevention, including diet-based interventions. Epidemiological and clinical studies suggest that regular consumption of certain FFs can reduce the incidence of specific cancers, potentially through mechanisms involving oxidative stress reduction, inflammation modulation, and cell cycle regulation [8–10]. Recent investigations have particularly focused on how dietary components may influence biomarkers associated with cancer initiation and progression [11–13].

Traditional cancer biomarkers, such as carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), and cancer antigen 125 (CA-125), are typically used for diagnosis, prognosis, and monitoring treatment response. However, these markers often become detectable only in advanced stages of disease, limiting their utility in early detection [14–16]. This has led researchers to explore whether BCs from FFs can induce earlier, subtler changes in biomarker expression or even uncover new, more sensitive biomarkers [17–19]. Such interactions may pave the way for non-invasive screening tools that integrate dietary patterns with biomarker surveillance, potentially shifting cancer management toward prevention and early intervention.

This review explores the current evidence on how FFs and their BCS interact with cancer-associated biomarkers. By examining molecular pathways, clinical findings, and emerging research, we aim to evaluate the potential of functional food-derived compounds in enhancing the early detection and prevention of cancer through modulation of biomarkers.

Research Strategy: A thorough review of available literature was conducted on publishing platforms such as PubMed and the Functional Food Center / Food Science Publisher journal database, to examine the methodology of how FFs impact biomarkers associated with cancer, alongside the capacity of FFs to detect and mange cancer potentially.

Utilized keywords include “functional foods”, “cancer”, “cancer biomarkers”, “bioactive compounds”, “colorectal cancer and diet”, “prostate cancer and phytochemicals”, “breast cancer and bioactives”, “lung cancer and nutrition”, “pancreatic cancer and natural compounds”, “DNA methylation”, “HDAC inhibition”, “histone acetylation”, “NF-kB inhibition”, “Nrf2 pathway”, “PD-l1 regulation”, “epigenetic modulation by diet”, “tumor suppressor gene reactivation”, “polyphenols”, “antioxidants and cancer”, “lycopene”, “epigallocatechin gallate”, “oxidative stress”, “apoptosis induction”, “sulforaphane”, and “biomarkers of dietary intake”. The literature spans the time frame from 2002 to 2025, covering over two decades of research.

Among the selected articles, the inclusion criteria prioritized original research articles (including clinical trials, cohort studies, case-control studies, in vitro and in vivo experimental studies), systematic reviews and meta-analyses, human studies, or studies on relevant animal models, as well as publications in peer-reviewed journals. The chosen studies required the involvement of FFs, BCs, or phytochemicals in assessing molecular or epigenetic mechanisms linked to cancer prevention. The results of each study were needed to illustrate cancer incidence, progression, survival, or recurrence, alongside measurements of biomarker levels related to oxidative stress, inflammation, apoptosis, or epigenetic modulation. The studies also necessitate the inclusion of relevant molecular pathways (such as NF-kB, HDAC, or DNA methylation) and how they were modulated, alongside pertinent information on the safety, bioavailability, or efficacy of FFs or BCs.

The exclusion criteria included editorials, commentaries, or conference abstracts without complete experimental data, non-peer-reviewed sources, and case reports with anecdotal evidence. Studies that focused on synthetic drugs without functional food components were excluded, alongside studies not involving dietary intake or supplementation of bioactive compounds. Studies without relevant cancer-related endpoints or mechanistic biomarkers were also excluded, along with studies lacking a transparent methodology.

Overview of Cancer Biomarkers: Diagnostic biomarkers, such as prostate-specific antigen (PSA), cancer antigen 125 (CA-125), and carcinoembryonic antigen (CEA), are essential tools for the initial detection of cancer. Dietary, such as curcumin (found in turmeric) and epigallocatechin gallate (EGCG), found in green tea, have demonstrated the ability to modulate these markers at both transcriptional and post-translational levels. For instance, EGCG has been shown to downregulate PSA secretion in prostate cancer cells through androgen receptor repression, while curcumin reduces CEA expression by impairing NF-κB–mediated gene transcription [20-22]. These changes are detectable in the in-patient serum and provide a foundation for research into dietary interventions that could lower diagnostic biomarker levels to clinical diagnosis.

Prognostic biomarkers, including HER2 overexpression in breast cancer and p53 mutations across multiple tumor types, carry significant implications for disease progression and patient outcomes. Resveratrol has been found to both degrade HER2 protein via proteasomal pathways and enhance acetylation of wild-type p53 by inhibiting HDACs, leading to the stabilization of p53 and an improved apoptotic response [23,24]. This modulation of prognostic markers at the protein expression and functional level suggests that sustained consumption of stilbene compounds may improve prognostic biomarker profiles and potentially delay disease progression.

Predictive and pharmacodynamic biomarkers, such as PD-L1 expression, are increasingly relevant in the context of immune checkpoint therapies. In vitro studies have revealed that curcumin and EGCG attenuate PD-L1 levels in various carcinoma lines by inhibiting STAT3 and NF-κB signaling [25-26]. Suppression of PD-L1 leads to reduced tumor cell proliferation and increased apoptosis, which may augment responses to PD-1/PD-L1 blockade and serve as early markers of therapeutic efficacy. These findings support the inclusion of dietary BCs in biomarker-driven treatment strategies.

While not cancer-specific, inflammatory biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6), are mechanistically linked to tumor-promoting inflammation. Curcumin suppresses IL-6 and CRP levels by inhibiting the IL-6/ERK/NF-κB axis, with complementary reductions observed in TNF-α and TGF-β in both preclinical and clinical studies [27-29]. These biomarker changes are quantifiable via immunoassays and serve as sensitive indicators of dietary modulation of systemic inflammation, a known driver of carcinogenesis.

Oxidative stress markers, such as malondialdehyde (MDA) and 8-hydroxy-2’-deoxyguanosine (8-OHdG), although not unique to cancer, reflect damage to lipids and DNA, respectively. EGCG supplementation has been repeatedly shown to reduce urinary MDA and 8-OHdG levels by 20–40%, while enhancing OGG1-mediated DNA repair mechanisms in smokers and animal models [30-32]. These reductions highlight the antioxidant capacities of green tea polyphenols and position MDA and 8-OHdG as potential biomarkers for early chemoprevention trials.

Proliferation and apoptosis indicators, including Ki-67, Bcl-2, and caspases, offer insight into tumoral growth dynamics. EGCG reduces Ki-67 and Bcl-2, while increasing Bax and activating the caspase cascade, effects corroborated in melanoma and thyroid carcinoma models [33-35]. Similarly, curcumin decreases Ki-67 and Bcl-2 via STAT3 inhibition and triggers caspase-8–mediated apoptosis in lung cancer cells [36-37]. Such pathways are measurable through immunohistochemistry and provide mechanistically relevant endpoints for dietary intervention studies.

Epigenetic and genetic modifications, particularly HDAC activity and DNA methylation, are critical regulatory layers amenable to functional food modulation. Resveratrol acts as a pan-HDAC inhibitor, reducing HDAC2 expression by ~50% and elevating histone acetylation at tumor suppressor promoters [38]. It also induces significant promoter demethylation across multiple genes via DNMT1 inhibition within 48- hours in breast cancer models [39-40]. These epigenomic shifts are quantifiable through chromatin immunoprecipitation and methylation assays, making them viable biomarkers for dietary interventions that affect epigenetics.

Functional Foods and their Bioactive Compounds: The anticancer potential of FFs lies not only in nutrient content but also in their capacity to modulate molecular pathways and biomarkers associated with tumorigenesis [41-43].

Sulforaphane, a phytochemical abundant in cruciferous vegetables like broccoli, induces phase II detoxifying enzymes via Nrf2 activation and promotes apoptosis through caspase-3 activation. It downregulates HDAC activity, leading to histone acetylation changes and decreased expression of proliferation markers such as Ki-67 in colon and breast cancer models [44-46].

Curcumin, derived from turmeric, exerts anticancer effects by inhibiting NF-κB and STAT3 signaling, resulting in reduced expression of inflammatory cytokines (IL-6, TNF-α), proliferation markers (Ki-67, Bcl-2), and increased caspase–8–mediated apoptosis. Curcumin also exhibits epigenetic activity by inhibiting HDACs and DNMTs, thereby altering DNA methylation and histone acetylation in tumor suppressor genes [42, 47- 48].

Epigallocatechin-3-gallate (EGCG), the primary catechin in green tea, targets PI3K/Akt and mitochondrial pathways to decrease proliferation markers (Ki-67), downregulate Bcl-2, upregulate Bax, and activate caspase-3/-7/-9. It simultaneously reduces oxidative stress biomarkers (MDA, 8-OHdG) by enhancing OGG1-mediated DNA repair and inducing Nrf2-dependent antioxidant genes [49-51].

Resveratrol, found in grapes and berries, functions as a multitarget epigenetic modulator by inhibiting HDACs and DNMTs, leading to histone acetylation and promoter demethylation of tumor suppressor genes such as p21 and p16. It downregulates HER2, promotes p53 acetylation, and inhibits proliferation through STAT3 inhibition, while also activating caspase-mediated apoptosis [20, 52-53].

Lycopene, the predominant carotenoid in tomatoes, exhibits anticancer activity through antioxidant and anti-inflammatory mechanisms. It scavenges reactive oxygen species, reduces oxidative biomarkers such as MDA, and downregulates the IGF-1 and NF-κB pathways. It also inhibits proliferation by reducing IGF-1 signaling and cyclin D1 expression and induces apoptosis via caspase-9 activation [54-56].

Influence of Bioactive Compounds on Biomarkers: Evidence from Clinical and Preclinical Studies. Multiple clinical and preclinical studies have been conducted, illustrating the impact of various FFsBCs on biomarkers used for cancer detection. Several forms of cancer, such as breast cancer, prostate cancer, and colorectal cancer have been the focus of these studies.

Breast Cancer: BCs, specifically cruciferous vegetable derivatives such as sulforaphane, modulate key biomarkers associated with breast carcinoma progression, including HER2, Ki-67, HDAC activity, and estrogen receptor signaling. In vitro and preclinical experiments have repeatedly demonstrated that sulforaphane inhibits global HDAC activity across diverse breast cancer cell lines (e.g., MDA-MB-231, MCF-7), concomitantly decreasing expression of oncogenic receptors such as HER2 and ERα and activating apoptotic pathways [57-59]. Clinical evidence in women scheduled for breast biopsy further confirms that sulforaphane supplementation reduces peripheral blood mononuclear cell (PBMC) HDAC activity and Ki-67 expression in benign breast tissue. However, changes in malignant tissue may be less pronounced [60-62].

For instance, a randomized placebo-controlled clinical trial involving 54 women showed that short-term (2-4 weeks) sulforaphane intake resulted in a significant reduction in Ki-67 and HDAC3 levels in benign breast tissue, suggesting proliferation blockade at an early stage of disease [60]. Preclinical studies extend these findings by demonstrating that sulforaphane downregulates

HDAC6, leading to the induction of autophagy in triple-negative breast cancer xenografts [59]. Collectively, these data suggest that sulforaphane can target multiple biomarkers, particularly Ki-67 and HDAC activity, supporting its potential role in breast cancer prevention and adjunctive therapy.

Prostate Cancer: The consumption of cruciferous vegetables or their bioactive metabolites, particularly sulforaphane, has been consistently linked to the modulation of prostate-specific antigen (PSA) and androgen receptor (AR) expression, as well as inflammatory cytokine profiles. A meta-analysis encapsulating over 70 000 cases revealed that higher cruciferous vegetable intake correlates with reduced prostate cancer incidence (RR 0.87 per highest versus lowest intake) [63]. Mechanistically, sulforaphane upregulates phase II detoxification enzymes (e.g., NQO1), and decreases AR expression while inhibiting inflammatory signaling in prostate tissue [64–66].

In the ESCAPE randomized dietary trial, men undergoing active surveillance who consumed a glucoraphanin-rich broccoli intervention for one year exhibited stable PSA levels and distinct transcriptomic changes indicative of enhanced detoxification and reduced inflammation, without adverse metabolic effects [64,65]. Another interventional study in men with biochemical recurrence after prostatectomy demonstrated that sulforaphane tablets (10 mg/day) slowed PSA doubling compared with a placebo, indicating a tangible biomarker response [66]. Observational data further reinforce these findings: higher intake of cruciferous vegetables after diagnosis was inversely linked to progression risk [67].

Colorectal Cancer: Functional food components, notably polyphenols, influence colorectal cancer biomarkers including carcinoembryonic antigen (CEA), Wnt/β-catenin signaling, and markers of oxidative stress and inflammation. Polyphenols, such as epigallocatechin-3-gallate and curcumin, exert antioxidative effects, attenuating 8-oxo-dG formation, downregulating NF-κB and COX-2 expression, and restoring Wnt pathway regulation in preclinical models [68–70].

Although direct human trials remain limited, several small-scale interventions have reported decreased oxidative DNA damage and reduced inflammatory cytokine expression (e.g., IL-6, TNF-α) following dietary polyphenol supplementation. These shifts are often accompanied by modest reductions in serum CEA levels [71,72]. Collectively, this supports a role for polyphenol-rich FFs in modulating colorectal cancer progression at the molecular biomarker level.

Lung, Pancreatic, and Other Cancers: Emerging data indicate that BCs may modulate biomarkers in less commonly studied cancers, though the evidence base remains preliminary. For instance, sulforaphane has been shown to suppress metastatic signaling pathways (e.g., RAF/MEK/ERK) in triple-negative breast models, and early experimental data suggest similar effects in pancreatic neoplasia. Likewise, polyphenols and isothiocyanates have been shown to have potential in downregulating KRAS and NF-κB signaling in lung cancer cells in vitro [73–75]. Nonetheless, clinical corroboration is currently insufficient, underscoring the need for further targeted trials across diverse tumor types.

Table 1 summarizes the impact of BCs on cancer-related biomarkers, including evidence from clinical and preclinical trials.

Table 1. Functional Foods and Their Effects on Cancer-Related Biomarkers

Cancer Type	Functional Food / Bioactive	Targeted Biomarkers / Pathways	Type of Evidence	Key Findings	Source
Breast cancer	Sulforaphane (cruciferous vegetables)	HER2, Ki-67, HDAC activity, ERα	In vitro, preclinical, clinical	Lowered HER2 and ERα expression; lowered HDAC and Ki-67; higher apoptosis; autophagy induction in TNBC cells	[57-62]
Breast cancer	Sulforaphane (cruciferous vegetables)	HDAC3, HDAC6	Randomized controlled trial	Lowered HDAC3 and Ki-67 in benign breast tissue after sulforaphane supplementation (2-4 weeks)	[60]
Prostate cancer	Sulforaphane (cruciferous vegetables)	PSA, AR, inflammatory cytokines (IL-6, TNF-α), NQO1	Meta analysis, clinical trials	Lowered AR and PSA; higher detox enzyme activity; lower inflammatory gene expression; PSA doubling time increased	[63-67]
Prostate cancer	Broccoli (glucoraphanin-rich)	Transcriptome-wide inflammation/detox markers	ESCAPE RCT, observational studies	Stable PSA, beneficial gene expression changes, inverse correlation with recurrence risk	[64-66]
Colorectal cancer	Polyphenols (EGCG, curcumin)	CEA, Wnt/β-catenin, 8-oxo-dG, NF-κB, COX-2, IL-6, TNF-α	Preclinical, small-scale human trials	↓ CEA, ↓ oxidative DNA damage, ↓ IL-6/TNF-α; Wnt signaling normalization; EGCG & curcumin reduce ROS and inflammatory mediators, improve Wnt pathway balance	[68-72]
Lung, pancreatic, and other cancers	Sulforaphane, isothiocyanates, polyphenols	RAF/MEK/ERK, KRAS, NF-κB	In vitro, early experimental	Suppressed metastasis-related pathways in TNBC and lung cancer; modulated KRAS/NF-κB signaling	[73-75]

Mechanisms of Action Linking Functional Foods to Biomarker Modulation: BCs influence cancer-related biomarkers through multiple molecular pathways. This section outlines key mechanistic categories, including epigenetic modulation, anti-inflammatory signaling, oxidative stress reduction, regulation of the cell cycle and apoptosis, and microbiome-mediated effects.

Epigenetic Modulation: HDAC Inhibition & DNA Methylation Changes: BCs such as sulforaphane and polyphenols alter epigenetic regulators including histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), leading to changes in chromatin structure and gene expression. Sulforaphane inhibits HDAC activity in breast, prostate, and colon cancer cells, reactivating tumor suppressor genes and suppressing oncogene expression [76–78]. It also promotes the demethylation of gene promoters, such as Nrf2, thereby restoring the activation of antioxidative genes [79]. Dietary polyphenols, such as quercetin, similarly reduce DNMT and HDAC activities, thereby decreasing global DNA methylation and enhancing the transcription of tumor suppressors via histone acetyltransferase (HAT) activation [80,81].

Anti-inflammatory Pathways: NF-κB, IL-6, and TNF-α Downregulation: Many functional food components suppress pro-inflammatory signaling pathways central to tumor progression. Polyphenols (e.g., curcumin, luteolin) inhibit NF-κB activation, thereby reducing downstream cytokines IL-6 and TNF-α and dampening inflammatory gene transcription [82–84]. In vivo, dietary anthocyanins and phenolics decrease serum levels of IL-6 and TNF-α and suppress NF-κB-mediated COX-2 expression in tumor-bearing models [83, 85]. Sulforaphane also interferes with NF-κB DNA binding,

exerting anti-inflammatory and anticancer effects, particularly in pancreatic cancer models [86].

Oxidative Stress Reduction: ROS Scavenging & Nrf2 Activation: FFs enhance endogenous antioxidant defenses. Sulforaphane, polyphenols, and flavones activate the Nrf2/ARE pathway, leading to the transcription of cytoprotective enzymes (e.g., NQO1, HO-1, GPx) that lower ROS levels and prevent oxidative DNA damage [79, 87]. Flavones the activation of oxidative stress–linked biomarkers. Luteolin further potentiates Nrf2 activity, reinforcing antioxidant protection and mitigating the activation of oxidative stress–linked biomarkers [88]. These effects counteract oxidative stress that promotes tumorigenesis and inflammatory signaling.

Cell Cycle & Apoptosis: Bcl-2, Caspases & Tumor Suppressor Activation: BCs promote cancer cell apoptosis by modulating Bcl-2 through the regulation of Bcl-2 family proteins and caspase cascades. Luteolin and sulforaphane downregulate anti-apoptotic Bcl-2/Bcl-xL, upregulate Bax, and increase caspase-3 and caspase-9 activation in cancer cells, leading to programmed cell death [83,84,89]. These molecular changes result in cell cycle arrest at the G0/G1 phase and suppression of the proliferative biomarker Ki-67, reinforcing the anti-proliferative effects.

Microbiome Interactions: Metabolite-Host Biomarker Crosstalk: Emerging research highlights how dietary BCs modulate the gut microbiome and its metabolites, impacting host biomarker regulation. For example, polyphenol-rich diets alter microbial composition, increasing the production of short-chain fatty acids (e.g., butyrate), which functions as an HDAC inhibitor and anti-inflammatory agent, thereby modulating biomarkers such as NF-κB and Nrf2 [90-91]. Glucosinolate metabolites from cruciferous vegetables undergo microbiome-mediated transformation, leading to bioactive isothiocyanates that influence epigenetic regulators and detoxification biomarkers [92]. While these pathways are less thoroughly characterized than others, they suggest a convergence of diet, microbiome, and systemic biomarker modulation.

Applications in Early Detection and Preventive Strategies: FFs and BCs have significant potential for early cancer detection and prevention by modulating non-invasive biomarkers measurable in urine, blood, or tissue. Clinical studies indicate that intake of sulforaphane-rich broccoli extracts increases urinary isothiocyanate levels, which correlate with reduced proliferation markers (e.g., Ki-67) in bronchial epithelium and reduced urinary toxicant burden in former smokers [93–95]. These findings support the feasibility of using urinary sulforaphane metabolites both to monitor dietary adherence and to serve as early indicators of tissue-level biomarker modulation in at-risk individuals [95]. Moreover, quantitative analysis of short-chain fatty acids (SCFAs) in feces or serum, especially butyrate, has emerged as a putative biomarker for colorectal cancer prevention, reflecting modulation of HDAC activity and immune regulation [96–98].

Chemoprevention trials in high-risk populations have demonstrated that sustained dietary intake of cruciferous vegetables or concentrated sulforaphane supplements elicits favorable biomarker responses. A randomized phase II trial in individuals with premalignant bronchial lesions demonstrated that daily sulforaphane supplementation over 12 months significantly decreased Ki-67 proliferation indices in lung tissue, accompanied by activated apoptotic markers [93]. Similarly, investigations in former smokers revealed enhanced detoxification enzyme activity and suppressed DNA damage in peripheral and pulmonary tissues after broccoli-derived supplement regimens [93,99]. These trials demonstrate the utility of FFsBCs as preventive interventions targeting

early molecular changes that precede malignant transformation.

Integrating dietary biomarker monitoring with conventional surveillance methods, such as imaging or genetic profiling, enhances early detection strategies. Urinary isothiocyanate levels can complement PSA monitoring in prostate screening, particularly when linked to GST polymorphisms impacting sulforaphane metabolism [100,101]. Likewise, quantitative SCFA profiling, coupled with fecal DNA testing, may refine colorectal cancer risk models by combining microbial metabolite signatures with genetic and epigenetic biomarkers [96,98]. Such layered surveillance approaches offer more sensitive and personalized risk stratification than conventional modalities alone.

Personalized nutrition harnesses biomarker-informed feedback to tailor dietary interventions. Interindividual variation in GST enzyme genotype alters sulforaphane metabolism and tissue biomarker responses, indicating that genetic screening (e.g., GSTT1*/GSTM1 null variants) could guide the dosing of cruciferous foods for optimal chemopreventive efficacy [101]. Additionally, individual gut microbiome composition—shaping isothiocyanate bioavailability and SCFA production—suggests the potential for microbiome profiling to inform targeted dietary strategies that maximize biomarker modulation [96,102]. Together, these approaches support a precision nutrition framework, where diet is customized based on biomarker outcomes to enhance prevention in genetically or environmentally predisposed individuals.

Limitations and Challenges: Functional food–induced biomarker changes are frequently constrained by limited specificity; many candidate markers, such as circulating carotenoids, vitamin C, or short-chain fatty acids, are not unique to cancer biology but instead reflect general nutritional status, inflammation, or lifestyle factors [103-105]. For example, dietary biomarkers such as plasma vitamin C or urinary flavanol metabolites can increase with increased fruit and vegetable intake, yet fail to distinguish between cancer prevention and improved general health [103,105]. Similarly, butyrate levels may increase with fiber-rich diets but do not exclusively indicate colorectal neoplasia prevention without context [104,106]. This nonspecificity complicates the interpretation of biomarker shifts following functional food interventions, limiting their diagnostic and predictive utility in oncology.

Bioavailability and metabolism of phytochemicals present critical hurdles in translating laboratory data to human outcomes. Many BCs, including curcumin and sulforaphane, exhibit low oral bioavailability and rapid systemic clearance, resulting in tissue exposures that are notably lower than those observed in vitro [107-109]. Genetic variations, such as those in the GSTM1 or GSTT1 enzymes, alongside individual differences in gut microbiota, further influence the absorption, metabolism, and excretion of these compounds, creating wide interindividual variability [108,110-111]. Consequently, the significant epigenetic or anti-inflammatory effects observed under controlled conditions are challenging to replicate in diverse human populations, undermining dose-response predictability based on biomarker responses.

Despite promising short-term interventions, the field lacks robust longitudinal data linking FFs, biomarker modulation, and cancer outcomes. Most randomized controlled trials to date are of limited duration (often <12 months), focus on surrogate biochemical endpoints (e.g., Ki-67 or PSA), operate with small sample sizes, and are insufficient to evaluate cancer incidence or progression [112-114]. There have been few large-scale, long-term RCTs that integrate dietary interventions with multi-omics biomarker panels and clinical endpoints due to high costs, logistical complexity, and ethical considerations [113,115]. Without such longitudinal evidence, claims regarding the efficacy of FFs and BCs in cancer prevention remain provisional, highlighting the

pressing need for multi-year, adequately powered clinical trials to validate biomarker-guided dietary strategies.

Functional Food Science: Bridging Bioactive Compounds, Biomarkers, and Cancer Management: This review highlights the significant potential of FFs and their constituent BCs in modulating cancer-associated biomarkers, offering new avenues for early detection and prevention. This area of inquiry is intrinsically linked to functional food science, an interdisciplinary field to understanding how food components provide health benefits beyond basic nutrition. Functional food science aims to identify, characterize, and validate the biological activities of these compounds, translating complex molecular interactions into practical dietary strategies [116-117]. It provides the scientific backbone for classifying foods that can significantly impact health beyond basic nutritional value [117-118].

Functional food science explores how specific v, such as polyphenols, carotenoids, and various plant extracts, interact with cellular pathways involved in carcinogenesis and tumor progression [118,119]. This extends to their influence on biomarkers of inflammation, oxidative stress, cellular proliferation, and even genetic stability, all of which are critical indicators in cancer development and progression [119,120]. Studies in this field demonstrate how certain functional ingredients can exert anti-inflammatory and antioxidant activities, which are essential to mitigating cellular damage that often precedes cancer [118, 121]. By systematically investigating these interactions, functional food science provides the evidentiary basis for developing food products specifically designed to exert beneficial effects on health, including a reduction in cancer risk [116, 119, 122].

Ultimately, the rigorous methodologies employed in functional food research enable the creation of functional food products that can directly target cancer-associated biomarkers. This offers a proactive approach to prevention by mitigating risk factors and holds promise for supporting early detection efforts through measurable changes in these biomarkers. The continuous pursuit of understanding how dietary patterns affect disease outcomes, particularly through the regulation of inflammatory and oxidative stress signaling pathways, underpins this field [120,123]. Embracing FFs and their BCs within a robust scientific framework offers a sustainable, accessible, and complementary strategy in the ongoing fight against cancer, underscoring the critical role of food in maintaining optimal health and potentially shifting the paradigm towards dietary interventions in cancer care [115,122].

Future Directions: Future research should focus on developing comprehensive diet-responsive biomarker panels that integrate multiple molecular changes induced by FFs. Instead of relying on single biomarkers, multiplex panels combining epigenetic, inflammatory, oxidative, and microbiome-derived markers could offer greater specificity and sensitivity in early detection or monitoring dietary interventions. For example, combined measurement of promoter methylation patterns (e.g., Nrf2 or GSTP1), serum IL-6/TNF-α levels, urinary isothiocyanates, and plasma short-chain fatty acids has been proposed as a robust signature of cruciferous vegetable intake and chemopreventive activity [123-125]. Validating such multi-marker panels in pilot human studies would represent a significant advancement in the development of precision nutrition biomarkers [126].

The integration of multi-omics platforms, including metabolomics, proteomics, and transcriptomics, will be essential for elucidating the mechanistic pathways linking functional food compounds to biomarker modulation in cancer prevention. Untargeted metabolomic profiling has already revealed novel bioactive metabolites and metabolic shifts following dietary interventions with sulforaphane and polyphenols [127-129]. Likewise, proteomic analyses have detected changes in key signaling networks, such as those regulated by NF-κB and Nrf2, in response to dietary bioactives [128,130]. The harmonization of these omics layers in cohort studies can

enable systems-level modeling of diet–biomarker–disease interactions, accelerating identification of actionable targets.

Conducting large-scale, population-based trials that deliver functional food interventions tailored to individual genetics and microbiome composition represents a key next step. Randomized trials with crossover designs incorporating GST polymorphisms or microbiome stratification have demonstrated differential biomarker responses to sulforaphane intake [131-133]. Scaling these designs to diverse populations—with longitudinal follow-up for cancer incidence or progression—could clarify which individuals benefit most from specific dietary strategies and enable the development of personalized public health recommendations. Digital health tools for monitoring dietary adherence and real-time biomarker feedback will further enhance trial precision and scalability [132,134].

Advances in novel delivery systems, such as nanoparticle formulations, liposomal encapsulation, and prodrug design, offer promising solutions for the bioavailability challenges inherent to dietary bioactives. For instance, curcumin-loaded nanoparticles improve plasma half-life and tumor tissue penetration in animal models, yielding more pronounced biomarker responses than unformulated compounds [135-137]. Similarly, glucoraphanin embedded in sustained-release matrices has demonstrated enhanced systemic exposure and more robust induction of detoxification enzymes in human pilot studies [138-140]. Future trials should evaluate these technologies in the context of chemoprevention, assessing both pharmacokinetic improvements and downstream biomarker and clinical outcomes.

Hypothesis: Based on the current synthesis of clinical and preclinical evidence, we hypothesize that targeted dietary interventions utilizing FFs rich in BCs can modulate cancer-associated biomarkers in a manner that is both predictive and preventative. Specifically, we propose that sustained intake of select FF constituents, such as sulforaphane, curcumin, EGCG [141], and resveratrol[142], can elicit measurable shifts in molecular biomarkers related to inflammation, oxidative stress, epigenetic regulation, and tumor cell proliferation. These shifts may occur at subclinical stages and therefore hold promise as early indicators of cancer risk modulation.

Curcumin has demonstrated anti-inflammatory and antioxidant effects in chronic conditions and cancer-like diseases, including improved biomarker profiles in streptozotocin-induced diabetic models and the modulation of inflammatory cytokines [141].

Furthermore, we propose that integrating functional food interventions with biomarker-based monitoring, particularly within a personalized nutrition framework, may enable real-time tracking of disease susceptibility and therapeutic responsiveness. This approach would benefit from the development of multi-biomarker panels informed by metabolomic, proteomic, and epigenomic data to capture the complex, systemic effects of dietary bioactives. Such a model would not only advance our understanding of diet–cancer interactions but could also contribute to stratified prevention strategies tailored to individual risk profiles.

Future research should aim to validate this hypothesis through longitudinal, controlled human trials that incorporate FF interventions alongside multi-omics biomarker monitoring. The ultimate goal is to determine whether diet-driven biomarker modulation can serve as a valuable tool in personalized cancer prevention and early detection paradigms.

In future research, the assessment of sulforaphane, as a functional food ingredient should adhere to a comprehensive, multi-phase evaluation process, such as the framework developed by the Functional Food Center. This model includes defined benchmarks for demonstrating both the biological effectiveness and the structural integrity of potential functional food products [143–144].

CONCLUSION

FFs present a compelling avenue for modulating cancer-related biomarkers, offering molecular-level effects that span epigenetic regulation, inflammation, oxidative

stress, and immune signaling. A growing body of preclinical and clinical evidence supports their ability to influence key biomarkers associated with carcinogenesis, including Ki-67, PSA, CEA, and HDAC activity, among others. These effects not only suggest therapeutic potential but also highlight the role of FFs and BCsin early detection, monitoring, and cancer prevention strategies.

Importantly, functional food–induced biomarker shifts have demonstrated value as non-invasive indicators of physiological response, dietary adherence, and potential risk modification in high-risk populations. When insights into the complex interactions between nutrition, gene expression, and cancer-related pathways. In parallel, emerging technologies in biomarker detection and delivery systems are helping to address long-standing challenges related to specificity and bioavailability.

Despite this progress, the translation of functional food research into clinical practice remains constrained by variability in individual response, limited long-term data, and insufficient integration with personalized medicine frameworks. To fully realize their clinical utility, future studies must adopt more rigorous designs (such as incorporating stratified cohorts, multi-omics analyses, and extended follow-up) to validate the preventive and diagnostic relevance of diet-modulated biomarkers. Personalized nutrition approaches, grounded in genetic and microbiome profiling, will be essential for tailoring functional food interventions and ensuring their effective implementation in cancer prevention and care.

List of Abbreviations: Akt: protein kinase B, Bcl-2: B-cell lymphoma 2, Bax: Bcl-2-associated X protein, BCs: Bioactive compounds, CA-125: cancer antigen 125, CEA: carcinoembryonic antigen, CRP: C-reactive protein, DNMT: DNA (cytosine-5)-methyltransferase, DNMT1: DNA methyltransferase 1, EGCG: epigallocatechin-3-gallate, ERK: extracellular signal-regulated kinase, FFs: functional foods, HDAC: histone deacetylase, HDAC2: histone deacetylase 2, HER2: human epidermal growth factor receptor 2, IGF-1: insulin-like growth factor 1, IL-6: interleukin-6, Ki-67: proliferation-associated nuclear antigen Ki-67, MDA: malondialdehyde, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, Nrf2: nuclear factor erythroid 2–related factor 2, OGG1: 8-oxoguanine DNA glycosylase, p16: cyclin-dependent kinase inhibitor 2A, p21: cyclin-dependent kinase inhibitor 1A, p53: tumor protein 53, PD-1: programmed death-1, PD-L1: programmed death-ligand 1, PI3K: phosphoinositide 3-kinase, PSA: prostate-specific antigen, STAT3: signal transducer and activator of transcription 3, TGF-β: transforming growth factor-beta, TNF-α: tumor necrosis factor-alpha, and 8-OHdG: 8-hydroxy-2′-deoxyguanosine.

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