

Dietary targeting of cancer pathways: Role of bioactive compounds and nutraceuticals

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ABSTRACT

Cancer has become one of the most significant causes of death worldwide, leading many people to seek preventive strategies to supplement traditional treatments. Bioactive compounds are naturally occurring compounds found in foods, fruits, vegetables, herbs, and teas. Owing to their antioxidant, anti-inflammatory, and immune-modulatory capabilities, bioactive compounds show good potential for cancer prevention. This review discusses the therapeutic potential of major bioactive compounds such as polyphenols, alkaloids, and terpenoids, which collectively target cancer pathways through the induction of apoptosis, inhibition of angiogenesis, and metastasis prevention. Whole foods, plant-based diets, and functional foods such as green tea and turmeric are highlighted as an accessible means of incorporating these bioactive compounds into daily nutrition. Although bioactive compounds represent a natural, multi-targeted approach to cancer prevention, challenges still exist concerning their bioavailability and standardization. Advancements in food technology, personalized nutrition, and regulatory frameworks are essential to enhance the efficacy of bioactive-based interventions. This review underscores the need for ongoing interdisciplinary research to validate these dietary approaches and develop sustainable functional food-based strategies that could serve as effective adjuncts to conventional cancer therapies. These findings highlight the potential of bioactive compounds in reshaping cancer prevention through accessible dietary solutions.

1. Introduction

Cancer is one of the most common human diseases and a leading cause of death worldwide, with approximately 10 million deaths annually. The effects of this disease are profound, affecting not only individuals and families, but also healthcare systems and the entire global economy (Alzehr et al., 2022). The increasing prevalence of cancer, which can be attributed to the aging population, lifestyle changes, and exposure to environmental factors, highlights the need for

prevention and therapeutic improvements (Arem & Loftfield, 2017; Pillai & Antony, 2024). Standard cancer therapies such as chemotherapy are well established but can often have debilitating side effects, and in some cases, are ineffective due to resistance of cancer cells (Amjad et al., 2024). Therefore, more studies are being conducted on prevention and integrative medicine, which can lessen the burden on health resources by reducing cancer morbidity and mortality (Mao et al., 2022; Sadiq et al., 2024).

An emerging topic of cancer prevention research is the use of

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bioactive compounds, which are naturally occurring chemical substances found in some plants or foods that appear to positively affect health (Yuan et al., 2022). Polyphenols (including flavonoids), alkaloids, and terpenoids are bioactive compounds with potential cancer-inhibiting properties (Yuan et al., 2022), as well as the ability to affect processes involving oxidative stress (Kang & Kim, 2023) and inflammation (Foroughi-Gilvae et al., 2024; Phuyal et al., 2020). Functional foods such as bio-enhanced products offer health and nutritional benefits beyond basic dietary functions. Therefore, they have emerged as alternatives to dietary supplements. While functional foods are being explored for cancer prevention and overall health management (Kusmann et al., 2023), their efficacy requires further scientific validation. Given the capacity of bioactive compounds to modulate oncogenic pathways through apoptotic stimulation, their anti-angiogenesis properties, and immune-modulating effects, they are strong candidates as adjuncts in cancer prevention (Banerjee et al., 2023; Liu et al., 2023; Moody et al., 2020; Yuan et al., 2022).

Dietary practices can greatly influence general health, including susceptibility to illness and disease. Importantly, a plant-predominant diet aligns well with the core principles of cancer prevention due to the increased consumption of bioactive compounds (Lachance et al., 2020; Molina-Montes et al., 2020). Additionally, plant-based foods have a production process that is more environmentally friendly than animal-based foods, and are therefore seen as being more sustainable (Espinosa-Marrón et al., 2022). If entire populations could move towards a holistic health style that promotes the prevention of cancer, this would not only reap tangible health benefits but may also empower individuals by allowing them to take control of their wellbeing

(Espinosa-Marrón et al., 2022; Prosen et al., 2023).

In this review, we will discuss the nutritional aspects of cancer prevention, focusing on bioactive compounds, efficacious functional foods, and the need for sustainable dietary approaches that confer health resilience in the long term. We will first introduce the principles underlying bioactive compound involvement in cancer prevention, defining what these compounds are in the process. We will then move on to describe the molecular mechanisms through which bioactive compounds exert their anti-carcinogenic effect. This will be followed by a discussion about how dietary changes and supplementation can form the basis of preventive treatment through improvements in overall health, including immune system function. Finally, we will discuss the challenges facing bioactive compound use in cancer prevention.

1.1. Bioactive compounds in cancer prevention and therapy

The appeal of bioactive compounds stems from the fact that they are natural, tolerable, and act on multiple pathways through which cancers may develop. The primary sources of bioactive compounds are fruits, vegetables, spices, and herbs; these compounds can be divided into different classes according to their chemical structures and functional characteristics. Bioactive compounds include polyphenols (such as flavonoids), alkaloids, terpenoids, and saponins. There are class-specific (Dixit et al., 2023; Subramaniam et al., 2019; Yuan et al., 2022) chemopreventive mechanisms (Fig. 1) offered by these compounds, including (but not limited to): modulation of oxidative stress (Yuan et al., 2022); effect on signaling pathways (Zhang et al., 2018); promotion of apoptosis (Vieira & Conte-Junior, 2025); and inhibition of

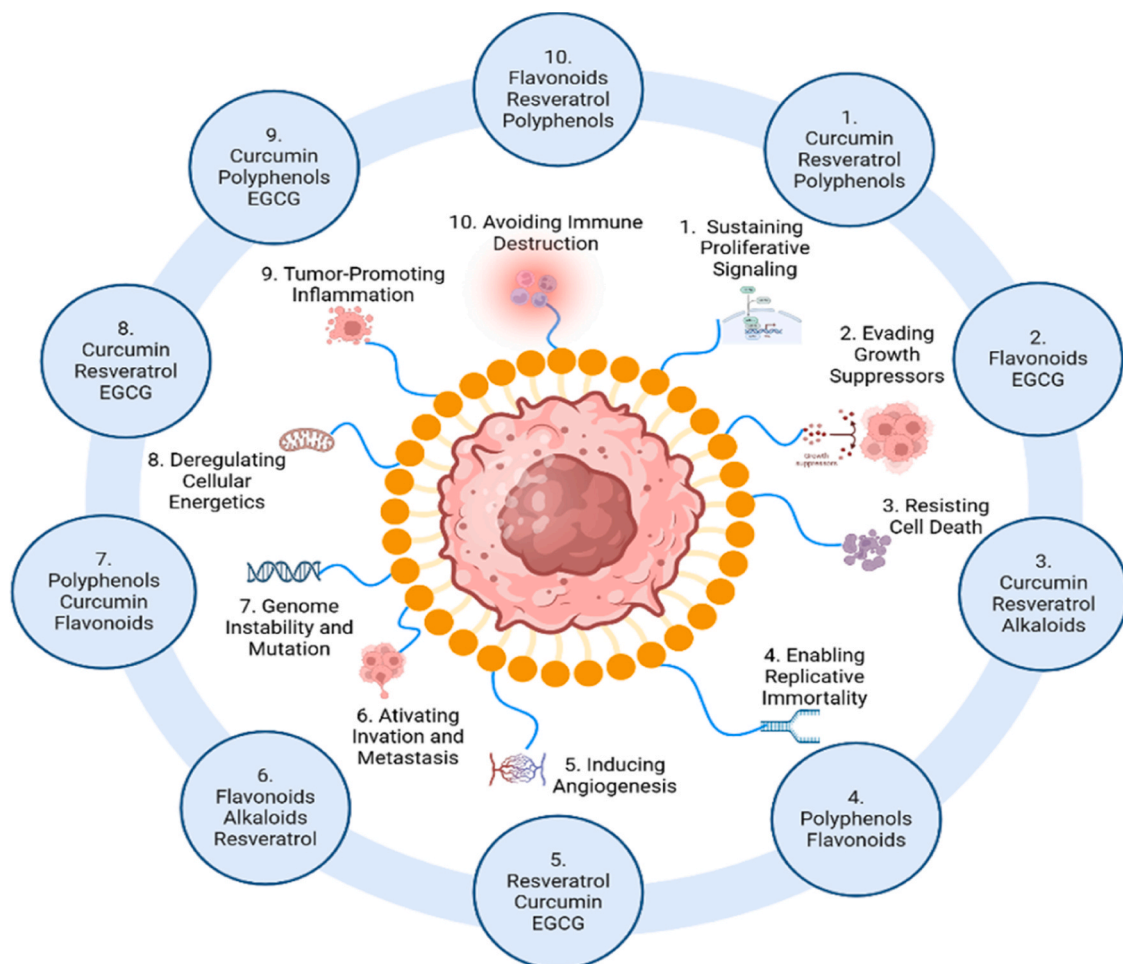


Fig. 1. The Hallmarks of Cancer in relation to bioactive compounds. (Figure designed with biorender.com).

angiogenesis (Kumar Subbaraj et al., 2021). This wide variety of activities renders bioactive compounds of potential importance not just in the prevention of cancer, but also for adjunctive use in conjunction with conventional therapies. Owing to their natural tolerance and often low toxicity, they are a sustainable alternative to synthetic drugs, particularly for preventive use.

1.2. Bioactive compounds: classifications and sources

Polyphenols. This group of compounds includes phenolic acids, flavonoids, and non-flavonoids; they are predominantly found in fruits (such as berries and grapes), vegetables, and tea. Among phytochemicals (bioactive compounds found specifically in plants) polyphenols such as resveratrol and quercetin possess remarkable antioxidant activity; this is thought to mitigate the genome destabilizing effects of free radicals such as reactive oxygen species (ROS), thereby preventing neoplastic transformation (Atuahene et al., 2023; Foroughi-Gilvae et al., 2024; Sadiq et al., 2024). The activity of flavonoids ranges from immune modulation and disruption of cell membranes to antioxidant activity. Compounds such as kaempferol and ginsenosides are used for inhibiting inflammation and modulation of immune function as well as for inhibition of carcinogenesis (Pillai & Antony, 2024; Sadiq et al., 2024).

Alkaloids. These bioactive compounds and their derivatives are enriched in plant-derived beverages such as coffee, as well as poppy plants (among others), and their derivatives, such as vincristine and berberine, induce cell cycle arrest and/or induction of apoptosis. This class of bioactive compound already plays a crucial role in chemotherapy, as several standard cancer treatment drugs are derived from them (Kusmann et al., 2023; Shenoy & Abdul Salam, 2024).

Terpenoids. This class of bioactive compounds are present in many herbs, spices, and essential oils. Terpenes such as limonene and lutein are recognized for their anti-inflammatory and antioxidant properties. Molecules within these compounds contribute to cancer prevention by blocking angiogenesis and downregulating inflammation in the tumor microenvironment, which would otherwise facilitate cancer development (Foroughi-Gilvae et al., 2024; Golonko et al., 2024).

To summarize the diversity of the bioactive compounds and their dietary sources, Table 1 provides a comprehensive overview of the primary classes, their sources, and key mechanisms involved in cancer prevention.

This table highlights the major classes of bioactive compounds, their primary dietary sources, examples of compounds, and mechanisms by which they contribute to cancer prevention.

2. Mechanisms of cancer prevention by bioactive compounds

Bioactive molecules affect multiple cancer pathways and cellular processes involved in tumor initiation, progression, and metastasis (Subramaniam et al., 2019). Notable mechanisms include antioxidant activity, modulation of inflammatory pathways, induction of apoptosis, and inhibition of angiogenesis (Asma et al., 2022). Unlike

treatment-specific compounds, bioactive compounds tend to affect these processes more broadly, making cancer prevention and management more holistic. To appreciate how bioactive compounds function in an anti-carcinogenic capacity, we have first considered their involvement in the Hallmarks of Cancer, which are key biological principles that encompass the complex phenotypes of cancer (Hanahan, 2022).

1. **Sustaining proliferative signaling.** Some bioactive compounds inhibit growth-promoting signals by downregulating pathways such as EGFR and MAPK, thereby reducing uncontrolled proliferation (Kim et al., 2006; Suarez-Carmona et al., 2017; Xie et al., 2024). Examples include curcumin and resveratrol, which are both known to influence several key signaling pathways involved in cell proliferation and survival (such as the PI3K/AKT/mTOR pathway). Furthermore, flavonoids such as 4, 4'-dimethoxychalcone (DMC) inhibit cancer cell proliferation by promoting oxidative stress and cell cycle arrest. DMC targets enzymes such as ALDH1A3, resulting in the initiation of reactive oxygen species (ROS) accumulation and repression of cell proliferation (Yang et al., 2021).
2. **Evading growth suppressors.** Flavonoids such as epigallocatechin gallate (EGCG) have antitumor potential by preventing the acquired ability of cancer cells to evade growth inhibitors. These compounds operate through different mechanisms to induce this effect. The inhibition of EGF-induced cell transformation by various flavonoids (including not only EGCG but also quercetin and myricetin) has been demonstrated to involve the activation of AP-1 and PI3K, indicating that specific signaling pathways can be targeted by bioactive compounds to inhibit cancer cell proliferation (Ichimatsu et al., 2007).
3. **Avoiding immune destruction.** Resveratrol boosts CD8 + T lymphocyte and NK cell activity, counteracts immunosuppressive macrophages and Tregs, induces anticancer cytokines (such as IFN- γ and TNF- α), inhibits TGF- β , and sensitizes cancer cells to immune attacks while enhancing the tumor microenvironment to improve immune responses (Chen & Musa, 2021). Flavonoids inhibit transcription factors that regulate immune cell differentiation and activation, enhance regulatory T cell generation, block inflammatory pathways such as NF- κ B and NLRP3 inflammasomes, and boost cytotoxic activity against tumors by modulating immune cell receptors (Martínez et al., 2019). The combination of curcumin and resveratrol at low doses reduces cancer cell survival and enhances NK cell activity, while preserving the viability of normal immune cells (Focaccetti et al., 2024).
4. **Enabling replicative immortality.** The end replication problem dictates that DNA is lost from chromosome ends with each cell division. To buffer against the loss of potentially essential genetic information, eukaryotic chromosomes are capped with repetitive DNA known as telomeres, whose length decreases with successive cell divisions. Once telomere length is below a certain threshold,

Table 1
Classification of Bioactive Compounds and Their Sources.

Bioactive Compound	Source	Examples of Compounds	Primary Mechanisms	References
Polyphenols	Fruits, vegetables, tea	Resveratrol, Curcumin	Antioxidants, modulate NF- κ B, apoptosis regulation	(Dixit et al., 2023; Foroughi-Gilvae et al., 2024; Mamun et al., 2024; Sadiq et al., 2024)
Alkaloids	Medicinal plants	Vincristine, Berberine	Cell cycle arrest, apoptosis induction	(Lu et al., 2012; Sadiq et al., 2024; Shenoy & Abdul Salam, 2024)
Terpenoids	Herbs, essential oils	Limonene, Lutein	Anti-inflammatory, inhibits angiogenesis	(Foroughi-Gilvae et al., 2024; Golonko et al., 2024; Masyita et al., 2022)
Saponins	Legumes, herbs	Ginsenosides, Dioscin	Immunomodulation, cell membrane disruption	(Kusmann et al., 2023; Pillai & Antony, 2024; Shen et al., 2023)
Flavonoids	Fruits, vegetables, tea	Quercetin, Kaempferol	Reduces oxidative stress, immune regulation	(Lachance et al., 2020; Panche et al., 2016; Sadiq et al., 2024)
Carotenoids	Leafy greens, carrots	Beta-carotene, Lycopene	Antioxidant modulates gene expression	(Delgado-Gonzalez et al., 2023; Gebregziabher et al., 2023; Pillai & Antony, 2024)

cells enter a non-proliferative state known as senescence or undergo apoptosis; cancer cells typically manage to bypass this by activating telomere lengthening mechanisms, thus achieving replicative immortality (Hanahan, 2022). While it is an appealing notion for bioactive compounds to interfere with this activation mechanism, there is currently little evidence for any effect of bioactive compounds on telomere length.

5. **Tumor promoting inflammation.** Inflammation of the tumor microenvironment chronically promotes cancer progression. Curcumin is a well-studied anti-inflammatory compound with high potency. It functions by blocking the NF- κ B and COX-2 pathways, which are the major inflammatory pathways, thus reducing the inflammatory milieu of the tumor microenvironment, which often supports tumor growth (Alex et al., 2010; Cione et al., 2019; Pavan et al., 2016; Ping et al., 2023; Sadiq et al., 2024). Furthermore, data from clinical trials have suggested that curcumin can reduce levels of the inflammatory mediators TNF- α , IL-6, and CRP (Ferguson et al., 2021; Sahebkar et al., 2016). Both curcumin and EGCG can modulate signaling pathways to attenuate pro-inflammatory markers by suppressing the release of inflammatory enzymes and cytokines. Interestingly, this joint function not only increases the efficacy of cancer treatments but can also promote the replacement of non-cancer cells that have been damaged by inflammation (Chimento et al., 2023; Vladu et al., 2022; Zhou et al., 2013). EGCG also inhibits autophagic activity and reduces cancer cell proliferation, thus supporting its anti-inflammatory and anticancer properties (Surh et al., 2001; Vladu et al., 2022). The ability to reduce inflammation is not restricted to polyphenols (curcumin) and flavonoids (EGCG); terpenoids have also been shown to function as anti-cancer agents by reducing inflammation. For example, limonene has the capacity to disrupt the Ras pathway, which is frequently mutated in cancer and drives uncontrolled proliferation and metastasis. Another terpenoid known as lutein can suppress NF- κ B signaling, a pathway that is essential for inflammation and tumor progression, thus demonstrating its potential in cancer prevention strategies (Foroughi-Gilvae et al., 2024; Masyita et al., 2022; Sadiq et al., 2024). Immunomodulation of the PI3K/AKT/mTOR signaling pathway, MAPKs, NF- κ B, and Wnt/ β -catenin are other potential biological effects of multifaceted monofloral honeys that counteract inflammation and cancer progression (Wee et al., 2015; Wong et al., 2019).
6. **Activating invasion and metastasis.** Some bioactive compounds have also been implicated to affect tumor invasion and metastasis. Flavonoids (such as catechins, genistein, quercetin, and apigenin) reduce the incidence of metastasis/invasion in the multistep metastasis cascade process, namely, cell adhesion, destruction of tissues, invasion, movements, and hemogenesis; this occurs through pathways including Src/Stat3/S100A7 and PI3K/AKT (Fan et al., 2019; Liskova et al., 2020). Alkaloids have anti-metastatic potential by blocking cancer cell signaling pathways and thus regulating invasion and metastasis (Sarwar et al., 2018). Likewise, resveratrol inhibits tumor growth and metastasis through the modulation of several pivotal molecular pathways, where the type of cancer and experimental conditions affect its performance (Caltagirone et al., 2000). Recent studies indicate that bioactive compounds can modulate the extracellular matrix, preventing the physical remodeling that allows cancer cells to invade and metastasize. For instance, polyphenols inhibit matrix metalloproteinases, enzymes critical for extracellular matrix degradation, thus limiting metastatic potential (Cháirez-Ramírez et al., 2021; Mamun et al., 2024; Mileo & Miccadei, 2015).
7. **Induction of angiogenesis.** Angiogenesis, the formation of new blood vessels, is an important mechanism utilized during tumor growth because cancer cells rely on oxygen and other nutrients for growth. Additionally, metastasis allows cancer cells to colonize tissues throughout the body and results in worse prognoses, and this also relies on angiogenesis. Tumors tend to overproduce vascular endothelial growth factor (VEGF), which, in turn, allows for rapid blood vessel growth. By decreasing VEGF expression, curcumin impedes the development of the tumor blood supply, essentially starving cancer cells of critical nutrients. Curcumin effectively inhibits the VEGF pathway, thereby acting as an angiogenesis inhibitor to slow tumor growth and metastasis, especially in cancers with high angiogenic activity, such as breast cancer and prostatic neoplasms (Banerjee et al., 2023; Pavan et al., 2016; Ping et al., 2023; Rathee et al., 2024). EGCG has also been reported to disturb Wnt/ β -catenin pathway activity, a cascade associated with angiogenesis and migration of tumor cells (Alex et al., 2010; Cione et al., 2019; Kciuk et al., 2023; Rathee et al., 2024). Interestingly, the combination of curcumin and EGCG together was more effective than either alone in inhibiting angiogenesis, potentially via affecting the JAK/STAT3 signaling pathway (Jin et al., 2017; Ashrafzadeh et al., 2020). Curcumin is a complex mediator of angiogenesis, functioning both as an inhibitor of blood vessel formation through the regulation of VEGF, matrix metalloproteinases, and fibroblast growth factor, and as an angiogenesis promoter under certain conditions, thus demonstrating dual functionality (Wang & Chen, 2019). Resveratrol acts on both VEGF and HIF-1 α , a protein that regulates gene expression in response to low oxygen conditions, which is typical of tumors. HIF-1 α enables tumors to withstand hypoxia by inducing angiogenesis, and can therefore also promote metastasis. Resveratrol can decrease HIF-1 α activity, thereby diminishing the resistance of tumors to hypoxia while also reducing angiogenesis (Alex et al., 2010; Cione et al., 2019; Pavan et al., 2016; Rathee et al., 2024). Recently, an alkaloid derivative was also shown to inhibit angiogenesis and subsequent metastasis in breast cancer (Foroughi-Gilvae et al., 2024).
8. **Genome instability and mutation.** Polyphenols protect DNA from damage by neutralizing ROS, reducing the likelihood of genetic mutations occurring (Parshad et al., 1998). Interestingly, curcumin promotes the maintenance of genomic stability in normal human colon cells, while inducing apoptosis in cancerous cells, functioning as a selective anti-oncogenic agent (Yu et al., 2023). Similarly, flavonoids not only prevent oxidative stress, but they also exert antioxidant activity through direct interactions with DNA, all the while enhancing genotoxic effects in cancer cells, thus making them attractive therapeutic agents for cancer (Hosseini-mehr, 2010). Curcumin and flavonoids are also thought to modulate critical components of the DNA damage response, acting on the sensors, transducers, and mediators involved in DNA repair mechanisms, thus playing a role in maintaining genomic stability and reducing cancer risk (Majidinia et al., 2019).
9. **Resisting cell death.** Apoptosis is essential for the elimination of damaged and potentially pathological cells (Carneiro & El-Deiry, 2020). Cancer cells, however, often evade apoptosis, which enables them to grow uncontrollably. Encouragingly, several bioactive compounds that elicit positive responses in the re-establishment of apoptosis in cancerous cells have been identified; importantly, these have minimal deleterious effects on normal cells (Alex et al., 2010). Resveratrol promotes the activation of pro-apoptotic proteins, such as BAX and caspase-3, which aid in the destruction and removal of cancer cells by suppressing these pathways. Furthermore, resveratrol induces S-phase arrest during the cell cycle, the phase in which DNA replication occurs, thus preventing cell division and tumor progression (Ghareghomi et al., 2023; McCubrey et al., 2017; Narayanankutty, 2020). Curcumin can promote apoptosis of cancer cells by altering cell survival-associated proteins, such as NF- κ B

and Bcl-2. Curcumin downregulates Bcl-2 and upregulates pro-apoptotic proteins such as BAX; this new balance of apoptotic proteins promotes cancer cell death. In addition, curcumin inhibits the cell cycle at the G2/M phase, thereby preventing the completion of cell division and consequently inhibiting tumor growth (Haghighian et al., 2021; Liczbiński et al., 2020; Pavan et al., 2016; Ping et al., 2023; Sak, 2020). Vincristine and berberine are alkaloids found in several plants that induce apoptosis via AMPK (AMP-activated protein kinase) activation, which is a master regulator of cellular energy homeostasis. AMPK activation limits energy availability in cancer cells, resulting in insufficient resources for growth, and consequently, apoptosis. Furthermore, both vincristine and berberine can induce cell cycle arrest via microtubule disruption, which further restricts the survival of cancer cells, especially those with a high metabolic demand, such as breast and colorectal cancers (Huang et al., 2021; L. Qian et al., 2021, 2021; Xiong et al., 2022). Notably, these characteristics of vincristine and berberine are already exploited in chemotherapy.

10. **Deregulation of cellular energetics.** Some bioactive compounds balance redox status (curcumin), optimize metabolism (resveratrol), and increase mitochondrial biogenesis (EGCG), thus ensuring cellular energy stability (Teixeira et al., 2019). Curcumin and resveratrol modulate glycolysis and mitochondrial respiration, disrupting the "Warburg effect," a phenomenon in which cancer cells rely on aerobic glycolysis for energy production (Pavlidis et al., 2009; Siddiqui et al., 2018; Vidoni et al., 2023). This metabolic disruption deprives cancer cells of energy, thereby slowing their growth and survival (Pavlidis et al., 2009). Resveratrol enhances oxidative phosphorylation in the mitochondria, reestablishes energy balance, and opposes the metabolic benefits enjoyed by cancer cells (Rodríguez-Enríquez et al., 2019). Moreover, EGCG and resveratrol supplementation improves mitochondrial function and fatty oxidation, which elevates energy expenditure and metabolism flexibility with minor effects on insulin sensitivity (Most et al., 2016). Furthermore, berberine acts on the AMPK pathway by lowering the cellular energy supply to cancer cells, effectively starving them and limiting their development (Foroughi-Gilvae et al., 2024).

The detailed mechanisms of action of notable bioactive compounds with potential anti-cancer effects are given in Table 2.

This table highlights the bioactive compounds, their target pathways, and mechanisms by which they contribute to cancer prevention. Functional foods containing a wide range of bioactive compounds such as phenolics, alkaloids, terpenoids, and catechins have shown promise as dietary strategies to aid in the prevention of cancer. See text for more

details.

In addition to the Hallmarks of Cancer, it is worth mentioning that bioactive compounds can exert cancer preventive effects through other means. For example, polyphenols have been shown to affect epigenetic changes that control gene expression, potentially influencing the production of tumor suppressor proteins (Cháirez-Ramírez et al., 2021; Cione et al., 2019; Pavan et al., 2016). Furthermore, regular consumption of green tea, which contains EGCG, has been linked to a reduced risk of different cancer types, including breast, prostate, and colorectal cancers (Alex et al., 2010; Cione et al., 2019; Kciuk et al., 2023; Rathee et al., 2024). Evidently, a wide range of bioactive compounds play diverse roles in modulating tumorigenic activities, especially inflammation, angiogenesis, metastatic potential, and apoptosis; these mechanisms are all helpful for reducing primary tumor growth and potential dissemination to other sites. Bioactive compounds thus offer a multi-functional approach for cancer prevention and treatment (Fig. 2).

This diagram shows how bioactive compounds such as curcumin, resveratrol, polyphenols, EGCG, flavonoids, and alkaloids interact with biological pathways to suppress tumor growth and metastasis (Kusmann et al., 2023; Sadiq et al., 2024; Shenoy & Abdul Salam, 2024). See text for a more in-depth discussion.

3. Dietary patterns and cancer risk reduction

Diet is a critical factor that influences health. Recent studies have highlighted the health benefits of whole-food and plant-based diets. Importantly, these diets are rich in bioactive compounds with antioxidant and anti-inflammatory properties, two critical components in the prevention of chronic degenerative diseases, including cancer. These diets are also beneficial for the gut, as well as hormonal and immune balance, which collectively promote better health and cancer prevention. The potential effects of dietary change on cancer prevention will be discussed in this section.

3.1. Wholefood and plant-based diets

Protective mechanisms against oxidative stress. Those following a plant-based diet typically have a good intake of vegetables, fruits, nuts, and whole grains; these food sources are naturally abundant in bioactive compounds such as polyphenols and carotenoids (Pawase et al., 2024). In addition, these diets generally contain less saturated fats, while also being rich in micronutrients and fibre, leading to reduced inflammation and oxidative stress. Thus, wholefood and plant-based diets are associated with a lower risk of several cancers (Aleksandrova et al., 2021). For example, polyphenolic compounds from grapes and berries have rich antioxidant properties that shield cellular health by counteracting the ROS that can cause genomic instability, a strong driver of tumorigenesis

Table 2
Mechanisms of Bioactive Compounds in Cancer Prevention and Therapy.

Bioactive Compound	Target Pathway	Mechanism of Action	Cancer Type (s)	References
Curcumin	NF-κB, JAK/STAT	Inhibits inflammation and cell proliferation, promotes apoptosis	Colorectal, Breast	(Ashrafizadeh et al., 2020; Bose et al., 2020; Golmohammadi et al., 2024; Wong et al., 2019; Zoi et al., 2021)
Resveratrol	PI3K/AKT/mTOR, MAPK	Induces cell cycle arrest, enhances chemotherapy efficacy	Breast, Lung	(Ghareghomi et al., 2023; McCubrey et al., 2017; Narayanankutty, 2020)
Quercetin	Notch, hedgehog (Hh), CK2α, NF-κB, and EGFR Akt/mTOR	Modulates apoptotic pathways, reduces oxidative stress	Liver, Prostate	(Almatroodi et al., 2021; Fernández-Palanca et al., 2019; Sethi et al., 2023)
EGCG (Epigallocatechin,3, gallate)	VEGF, MMPs	Inhibits angiogenesis, suppresses metastasis	Colorectal, Lung	(Aggarwal et al., 2022; Fujiki et al., 2018; Mokra et al., 2022; Talib et al., 2024)
Lycopene	signal transduction pathways, oxidative stress, and retinoid-mediated signaling	Antioxidant activity, downregulates Wnt/β,catenin signaling pathway	Prostate, Skin	(Ascenso et al., 2014; Aydemir et al., 2013; Gann et al., 2012; Park et al., 2021; Wang et al., 2021)
Berberine	AMPK, PI3K/AKT	Activates AMPK signaling, inhibits the PI3K/AKT signaling pathway	Breast, Colon	(Huang et al., 2021; L. Qian et al., 2021, 2021; Rauf et al., 2021; Xiong et al., 2022)

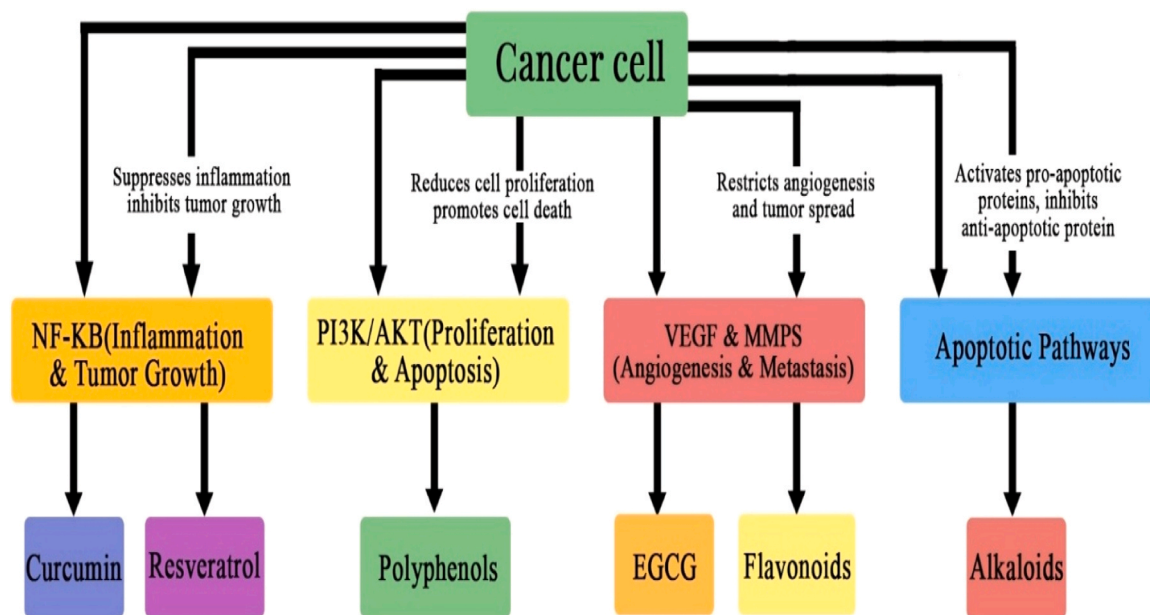


Fig. 2. Interactions of Bioactive Compounds with Cancer Pathways. (Figure designed with biorender.com).

(Rudrapal et al., 2022).

Gut microbiome and systemic inflammation. A hallmark of plant-based diets is their high fiber content, which nourishes the gut microbiota and promotes a diverse and robust microbial ecosystem, which has major health benefits. The beneficial gut microbes ferment dietary fiber into short-chain fatty acids (SCFAs) such as butyrate, which enhances the intestinal lining and thereby reduces inflammation. Critically, this lower systemic inflammation counteracts the inflammatory environment that is conducive to cancer progression (Hitch et al., 2022; Lachance et al., 2020).

Hormonal modulation. Whole-plant foods also contribute to hormonal regulation, which is particularly important in hormone-related cancers, such as breast and prostate cancers. Phytochemicals such as lignans, a non-flavonoid found in flaxseeds, modulate estrogen metabolism by promoting the production of less biologically active estrogen metabolites, thereby reducing cancer risk (Aleksandrova et al., 2021).

Synergistic Effects of Plant-Based Compounds. Plant-based diets are a rich source of anti-inflammatory substances. They exert direct cancer preventive effects due to their abundance of antioxidants, while also regulating immune response and decreasing chronic inflammation, thereby indirectly antagonizing established risk factors for cancer (Yalei et al., 2022). For instance, curcumin (found in turmeric) and resveratrol (found in grapes and red wine) are compounds that inhibit key inflammatory pathways (such as NF-κB) involved in cancer progression (Pillai & Antony, 2024). Studies have suggested that plant-based diets may decrease the levels of inflammatory markers in the body, creating an environment that is not conducive to cancer development. As such, eating habits directed towards whole plant foods and away from processed foods not only prevents cancer but also furthers well-being in the process, reflecting a holistic approach to health preservation.

3.2. Functional foods and nutraceuticals

Bioactive compounds are dietary components of functional foods and nutraceuticals, which are thought to be important in cancer prevention. Functional foods retain their fundamental nutritive profile, and are a rich source of bioactive compounds with potentially anti-carcinogenic effects (Dixit et al., 2023; Yuan et al., 2022). Nutraceuticals, which are derived from these foods, are typically taken as supplements containing higher concentrations of the bioactive compounds. Key

functional foods are discussed in this section.

Green Tea. Green tea contains very high levels of the major polyphenol EGCG, which is considered one of the most potent natural inhibitors of tumor growth (Alex et al., 2010; Dixit et al., 2023; Kciuk et al., 2023). These bioactive effects may be particularly important in reducing the risk of breast, prostate, and colorectal cancer (Sadiq et al., 2024). Epidemiological studies have shown the possible protective effects of regular consumption of green tea against these cancers (Alex et al., 2010; Cione et al., 2019; Kciuk et al., 2023; Rathee et al., 2024).

Turmeric. Turmeric is a popular food belonging to the ginger family. It contains curcumin, which is known for its anti-inflammatory and antioxidant effects. Curcumin acts as an anti-cancer agent through multiple mechanisms, including (but not limited to) inhibiting cell proliferation and modulating the immune response (Pavan et al., 2016; Pillai & Antony, 2024).

Cruciferous vegetables and garlic. Cruciferous vegetables such as cauliflower, kale, and broccoli, contain high glucosinolate content. Garlic also has high glucosinolate content. Importantly, glucosinolates are converted into bioactive isothiocyanates, such as sulforaphane, which enhances detoxification processes and promotes apoptosis in cancer cells (Dixit et al., 2023; McAlpine et al., 2024; Yuan et al., 2022). Garlic also contains the organosulfur compound allicin, which is a potent inducers of phase II detoxifying enzymes that reduce carcinogen activation. Allicin also interferes with cell proliferation pathways in cancer cells (Kusmann et al., 2023).

The foods discussed above are just select examples of practical, diet-focused options for individuals, enabling them to take proactive steps to reduce their cancer risk. Functional foods and nutraceuticals are important avenues for cancer prevention because of their practicability as edible forms of bioactive therapeutic compounds. Routinely consuming functional foods and nutraceuticals, such as those listed here, enables people to implement tangible actions in their lives to promote general well-being, and potentially reduce the risk of cancer.

4. Functional foods and adjuvant immunotherapy

In recent years, functional foods rich in bioactive compounds have been found to play an important role in immune modulation and have, therefore, become attractive candidates for supporting cancer immunotherapy. Immunotherapy works by exploiting the immune system's

intrinsic ability to identify and destroy pathological cells, including cancerous cells. This requires an active and well-adjusted immune status. Bioactive compounds such as polyphenols, flavonoids, and carotenoids support immune modulation by increasing cellular activity against the development of immune and inactive cells, reducing chronic inflammation, and engendering a situation that is favorable to the performance of immunotherapy (Dixit et al., 2023; Golonko et al., 2024; Pillai & Antony, 2024).

Examples of bioactive compounds that can modulate immune responses relevant to tumor immunotherapy include resveratrol and curcumin. Resveratrol has been shown to enhance the proliferation and cytotoxic activity of T cells, which can more effectively recognize and destroy cancer cells (Cione et al., 2019; Pavan et al., 2016), while curcumin has been shown to inhibit NF- κ B, a transcription factor signaling cascade involved in inflammatory responses and immune suppression in the tumor microenvironment. This may have the effect of reversing immune dysfunction through NF- κ B inhibition, and enhancing anti-tumor immunity as a whole (Cione et al., 2019; Pavan et al., 2016; Ping et al., 2023). These immune effects further support the potential of bioactive compound-rich diets as complementary treatments to immunotherapy in the fight against cancer.

The gut microbiome is known to influence immunity and therefore the response to immunotherapy. Probiotics and dietary fiber are important for maintaining a balanced microbiome, which subsequently supports immunity (Hitch et al., 2022). As previously mentioned, fibers are fermented by gut bacteria to produce SCFAs. Interestingly, SCFAs are anti-inflammatory and can reinforce the intestinal barrier to prevent toxins and pathogenic bacteria from entering circulation, where they disrupt immune function (D. Zhang, Liu, et al., 2023). A high microbiome diversity with an active SCFA producing microbiota is linked to better responses to immune checkpoint inhibitors, which are immunotherapeutic agents that target and stimulate the immune system against cancer (D. Zhang, Liu, et al., 2023; M. Zhang, Liu, et al., 2023).

Probiotics bolster immunotherapy effects even more by promoting a gut microbiome that encourages an active immune response to treatment when introduced in tandem with bioactive compounds. Research suggests that individuals with a diverse and healthy gut microbiome may respond better to immunotherapy, given that probiotics such as *Bifidobacterium* and *Lactobacillus* tend to improve the overall ability of the immune system to combat cancer (M. Zhang, Liu, et al., 2023). Consuming a diet rich in fibers and probiotics could help patients maintain the immune regulatory microbiome needed to optimize the response to cancer treatment.

5. Obstacles and pathways for the future of cancer prevention from bioactive compounds

Despite the clear potential of bioactive compounds as protective agents against cancer, there are still many hurdles to overcome before this potential can be realized, including biological issues such as bioavailability, as well as sociopolitical issues surrounding the regulation and standardization of bioactive compounds. These challenges hinder the establishment of functional food-based cancer therapies, necessitating effective interdisciplinary research to move forward in this area. Here, we will discuss some of these issues.

5.1. Bioavailability & standardization

A major limitation of bioactive compounds is their poor bioavailability, that is, how well they are absorbed and how much they reach the target tissue. This is due to factors such as poor water solubility, rapid metabolism, and inadequate gastrointestinal absorption, which prevents compounds such as curcumin and resveratrol from reaching therapeutic concentrations systemically, thereby diminishing their effectiveness in cancer prevention (Rein et al., 2013). Different approaches, such as encapsulation in nanoparticles, delivery using liposomes, and

co-formulation with absorption enhancers (e.g., piperine for curcumin) have been investigated to increase bioavailability. Nanoparticles encapsulating curcumin have high potential to protect curcumin from degradation and increase its stability and absorption (Tabanelli et al., 2021). These come in different sizes, ranging from < 20 nm for micellar nanoparticles to > 100 nm for solid lipid nanoparticles, and can be made from a variety of sources including (but not limited to) soy, casein, and whey protein; this flexibility is desirable as it increases the treatment options for patients (e.g., allergies or dietary requirements can be accommodated). Importantly, the use of established food-safe sources simplifies downstream approval processes. Despite these promising signs, these approaches require further validation, and are currently prohibitively expensive (Tabanelli et al., 2021), which could also introduce socioeconomic complications.

Standardization is another significant obstacle. Functional food bioactive content can vary widely with crop variety, geolocation, and processing factors. Variability in composition challenges the appropriate use of these bioactive compounds, as efficient therapeutics must be administered at consistent dosages. This variability renders clinical recommendations and regulatory approvals challenging. Regulatory agencies such as the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) currently state that most bioactive compounds should be classified as dietary supplements instead of drugs, leading to lower standards for testing. For the bioactive basis of cancer prevention to be expanded, better guidelines and standards are needed to ensure the quality, safety, and efficacy of functional food products (Dixit et al., 2023; Martirosyan & Ekblad, 2022; Martirosyan & Sanchez, 2022).

5.2. Interdisciplinary research for therapeutic functional foods

The development of bioactive-based cancer prevention strategies will ultimately require a multidisciplinary approach to utilize the knowledge gained from nutrition science, pharmacology, food technology, and oncology. Such functional foods with bioactive compounds need to be thoroughly investigated to understand their mechanisms of action, specific dosages, and interactions with other nutrients or medicines. All these findings must be confirmed first through in vitro and in vivo experiments, and then by clinical trials; this is the only way to determine their efficacy and to suggest the best dietary recommendations for cancer prevention (Cruz-Chamorro, 2023; Lee et al., 2024).

Bridging the gap between scientists and food manufacturers is critical for turning lab concepts into affordable, convenient, and palatable products on supermarket shelves. One example is the development of food formulations or supplements rich in bioactive compounds that preserve optimal effects while appealing to taste preferences, thus encouraging adherence to preventive diets. Genomics and metabolomics can also categorize individuals based on their underlying genetics, allowing for targeted bioactive-based interventions through functional foods tailored to personalized genetic profiles and cancer risk factors. The integration of such emerging technologies will allow bioactive-based interventions to approach the precision nutrition paradigm, where functional foods are tailored based on individual health data to provide optimal targeted benefits (Cruz-Chamorro, 2023; Lee et al., 2024; Singh et al., 2023).

Policy efforts are also needed to integrate bioactivity-based cancer prevention into regular businesses and supply a regulatory infrastructure that supports the industry with consistent high-quality products, ideally at prices that are affordable. These best practices form the backbone of the development of bioactive products, which is an essential step in increasing consumer trust and efficacy, including setting standards for content, production methods, and labeling. Furthermore, interdisciplinary science-industry-policy collaborations will be essential to meet the existing challenges and deliver bioactive compounds as effective cancer prevention agents.

6. Concluding remarks

Functional foods and nutraceuticals composed of various bioactive compounds such as polyphenols, alkaloids, terpenoids, and flavonoids have been established to play a potentially significant cancer-preventive role. Owing to their antioxidant activity, immune modulation, induction of apoptosis, and inhibition of angiogenesis and metastasis, these compounds provide a natural and integrated platform for lowering cancer risk. Whole foods, plant-based diets, and functional foods are natural sources of bioactivity obtained from the edible parts of plants (e.g., green tea, turmeric, and cruciferous vegetables), and make preventive compounds accessible as components of standard nutrition regimens. These bioactive molecules target histiocytes, which can secrete multiple immune modulators; therefore, such an intervention will benefit cancer patients and at-risk individuals. There is an abundance of laboratory-based and observational data highlighting the potential of functional foods in cancer prevention. For example, there is preclinical (and even some early clinical, albeit with limited participants) data to support the use of green tea as a complementary approach to conventional therapies owing to its antioxidant and anti-inflammatory properties (Bettuzzi et al., 2006; Yang et al., 2011). Although these results are promising, there is currently no functional food that has been approved by either the FDA or EFSA as a standalone preventive treatment for cancer, highlighting the need for more research, especially at the clinical level. Furthermore, bioavailability and standardization remain challenges that must be overcome through research and collaboration between disciplines. Optimization of delivery techniques, personalization, dietary recommendations, and clear regulatory standards are necessary. With the evolution and advancement of personalized nutrition and bioactive technology, cancer prevention strategies based on diet may become a basis for sustainable cancer control, providing an effective adjunct to standard treatment methods.

Declaration of animal welfare compliance

As the authors of the manuscript titled “Diet, Bioactive, and Cancer: A Comprehensive Review of Nutritional Intervention Strategies for Prevention and Control,” we declare that this review article is based on a synthesis of published literature and does not involve any original experiments or research on animals conducted by the authors.

The manuscript aims to provide a comprehensive overview of nutritional intervention strategies, focusing on bioactive compounds and their role in cancer prevention and control. This work emphasizes the importance of dietary approaches in enhancing human health and mitigating cancer risks through evidence-based analysis.

Since this review is based solely on existing data and studies, no ethical approval or animal experimentation protocols were required. Nonetheless, as researchers, we are committed to upholding the highest standards of ethics and scientific integrity in all our professional activities.

Should the journal require any additional information or clarification regarding this declaration, we are happy to provide further details.

CRediT authorship contribution statement

David Atuahene: Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Ayaz Mukarram Shaikh:** Writing – review & editing, Visualization, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Sam Bernard:** Writing – review & editing, Visualization. **Appiah Derrick:** Writing – review & editing, Formal analysis. **Khadel Mahama:** Writing – review & editing, Validation. **Pandey Vinay:** Writing – review & editing, Visualization, Data curation. **Kovács Bela:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Endre Harsányi:** Writing – review & editing, Visualization, Resources, Project administration, Funding acquisition.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.foohum.2025.100748.

Data Availability

The data will be available on the request.

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