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Review Article

Exploring the Potential of Dietary Phytochemicals in Cancer Prevention: A Comprehensive Review

Sunny Rathee, Umesh K. Patil and Sanjay K. Jain*

Pharmaceutics Research Laboratory, Department of Pharmaceutical Sciences, Dr Harisingh Gour University, Sagar, MP, India

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Abstract

Cancer is a significant global health issue and a primary cause of death. Extensive research has led to the development of various anticancer medications, driven by an improved knowledge and comprehension of the molecular pathways involved in cancer growth. However, there is a need for new approaches to enhance the effectiveness of existing cancer therapies. Dietary phytochemicals have gained increasing attention due to their potential role in tumor prevention. These bioactive compounds derived from plants exhibit a wide range of beneficial effects on human health, including their ability to inhibit carcinogenesis and promote anticancer activities. Examples of dietary phytochemicals with promising properties include vitamin D, vitamin E, lycopene, fisetin, genistein, epigallocatechin gallate, crocetin, curcumin, cyanidins, and gingerol. These compounds often exert their effects by regulating interconnected molecular pathways associated with cancer development and progression. Some of these pathways include the apoptosis pathway, cyclooxygenase-2 pathway, ATP-dependent chromatin remodeling pathway, DNA methylation-epigenetic pathway, Hedgehog signaling pathway, signal transducer and activator of transcription protein-3 pathway, tumor angiogenesis inhibition pathway, and Wnt pathway. This comprehensive review aims to summarize the current knowledge on the role of dietary phytochemicals in tumor prevention, highlighting their mechanisms of action and potential therapeutic applications.

Introduction

Cancer is a global health concern affecting both developed and developing countries. In 2021, there were approximately 21 million new cancer cases reported worldwide, and it is projected that this number will rise to 27.6 million by 2030.[1] Despite its widespread prevalence, the treatment of cancer remains challenging, yielding only partially satisfactory outcomes. The current therapeutic options for cancer typically involve surgical removal of the tumor and radiation therapy to target the localized cancer cells. Systemic chemotherapy is often administered as a maintenance treatment after surgery and radiation.[2]

Chemotherapy relies on various drugs to combat cancer, including antimetabolites like methotrexate, DNA-interactive medications such as cisplatin and doxorubicin, antitubulin medications like taxanes, as well as hormone-based treatments. However, chemotherapy has notable drawbacks. These include the risk of cancer recurrence, the development of drug resistance, and adverse effects on healthy tissues that are not directly targeted, ultimately impacting the patient's quality of life.[3] For thousands of years, natural herbs have been utilized for their healing properties and preventive measures against various ailments. Plants, particularly those used in gourmet cuisine, offer a rich source of bioactive components. Among these components, plant-based phytochemicals and their derivatives have shown promise in enhancing the response rates and minimizing side effects in cancer patients. Extensive research has focused on dietary phytochemicals, shedding light on their chemical and biological functionalities that benefit human health. The underlying mechanisms by which dietary phytochemicals exert their effects have been thoroughly investigated, employing various *in vitro* methods such as cellular, molecular, and genomic trial systems, as well as *in vivo* approaches utilizing transgenic and knockout animal models.

Phytochemicals possess the ability to combat free radicals upon entry into cells, while also generating signals in response to chemi-

Keywords: Cancer prevention; Dietary phytochemicals; Bioactive compounds; Molecular Pathways; Molecular targets; Therapeutic applications.

Abbreviations: Akt, protein kinase B; Bcl-2, B cell lymphoma 2; CDK, cyclin-dependent kinase; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; JAK, Janus-activated kinase; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-E2, nuclear factor erythroid-2; NF-κB, nuclear factor-kappa B; Nrf2, NF-E2-related factor 2; PI3K, phosphatidylinositol-3-kinase; STAT, signal transducer and activator of transcription proteins; VEGF, vascular endothelial growth factor; VDR, vitamin D receptor.

***Correspondence to:** Sanjay K. Jain, Pharmaceutics Research Laboratory, Department of Pharmaceutical Sciences, Dr Harisingh Gour University, Sagar, MP 470003, India. ORCID: https://orcid.org/0000-0002-9241-3114. Tel: +91-7582-265457, E-mail: drskjainin@gmail.com

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cal or electrophilic stress. These signals activate proteins associated with diverse cellular signaling pathways, further contributing to their beneficial effects. The activation of the Nrf2-Keap1 complex, which involves the Kelch-like ECH-associated protein 1 (Keap1) and nuclear factor erythroid-2 (NF-E2)-related factor 2 (Nrf2), plays a crucial role in the following cellular defense mechanisms.[4] Consequently, these molecules work to safeguard healthy cells from reactive oxygen species (ROS), reactive nitrogen species, and potentially harmful metabolites of carcinogenic compounds. Furthermore, they exhibit various methods to inhibit the growth of preneoplastic or neoplastic cells, including the modulation of cytochrome c (Cyt c)/caspases organization, cell cycle arrest, and interference with the nuclear factor-kappa B (NF-κB), Janus kinase (JAK)-signal transducer, and signal transducer and activator of transcription protein (STAT) signaling pathways.[5–7] It is crucial to acknowledge that advanced or metastatic malignancies, characterized by significant genetic mutations, loss of heterozygosity, and epigenetic modifications, often exhibit high resistance to conventional cancer treatments such as chemotherapy and radiation therapy. Consequently, dietary phytochemicals alone may not be sufficient to elicit a response in such cases. In recent years, the pursuit of effective strategies for cancer prevention has led to a growing interest in the potential role of dietary phytochemicals. Several phytochemicals derived from edible plants have been reported to possess the ability to interfere with specific steps of the carcinogenic process. Numerous studies have demonstrated that phytochemicals can act as chemopreventive agents against human cancer by modulating the cancer cell cycle, inhibiting tumor growth, and inducing apoptosis.[8] Phytochemicals, naturally occurring compounds found in various plant-based foods, have garnered attention for their diverse biological activities and potential health benefits. Emerging research suggests that these compounds possess unique properties that may contribute to reducing the risk of cancer development and progression. By targeting crucial cellular processes and pathways involved in carcinogenesis, dietary phytochemicals hold promise as an intriguing avenue for bolstering cancer prevention efforts. This article delves into the compelling rationale behind investigating the impact of dietary phytochemicals on cancer prevention, highlighting key studies that provide insight into their mechanisms of action and their potential to revolutionize approaches to cancer risk reduction.

Dietary phytoconstituents used in cancer treatment

In the field of cancer research and treatment, scientists are continually exploring various compounds derived from plants that hold potential to prevent and combat cancer. These compounds, known as phytoconstituents, encompass a diverse range of substances found in fruits, vegetables, herbs, and other botanical sources. They exhibit bioactive properties that have garnered significant attention for their possible role in cancer prevention and treatment.

Flavonoids, phenolics, and other nonflavonoid polyphenols are prominent groups of phytoconstituents that have been extensively studied for their anticancer effects. These compounds are widely distributed in nature and can be obtained from various plant sources. They possess diverse molecular structures and mechanisms of action that contribute to their potential health benefits. Among the notable phytoconstituents, the role of mushroom-derived vitamin D in cancer treatment has gained considerable interest. Mushrooms, particularly certain types like shiitake and maitake, are a natural source of vitamin D, which has shown promise in inhibiting the growth of cancer cells and modulating immune responses.

Another phytoconstituent, vitamin E derived from plant oils, has demonstrated potential in cancer treatment. Vitamin E exhibits antioxidant properties that help protect cells from damage caused by free radicals. This natural compound has been studied for its ability to inhibit the growth of cancer cells and reduce the risk of certain cancers. Lycopene, a phytochemical abundant in tomatoes, has attracted attention for its potential in cancer prevention. Studies have suggested that lycopene possesses antioxidant properties and may help protect against various types of cancer, including prostate, lung, and stomach cancers. Fisetin, found in strawberries and apples, has shown promise as a potential cancer-preventive compound. This flavonoid exhibits antioxidant and anti-inflammatory effects and has been investigated for its ability to induce cell death in cancer cells and inhibit tumor growth. Genistein, derived from soybeans, has been extensively studied for its potential health benefits, including its role in cancer prevention. This isoflavone compound has been found to possess anti-inflammatory and antioxidant properties, as well as the ability to inhibit cancer cell proliferation and induce cell death. Epigallocatechin gallate (EGCG), a catechin found in green tea, has been the subject of numerous studies exploring its potential health effects, including cancer prevention. EGCG exhibits antioxidant and anti-inflammatory properties and has shown promise in inhibiting the growth of cancer cells and suppressing tumor formation. Crocetin, derived from saffron, has garnered attention for its potential therapeutic properties. Studies have suggested that crocetin possesses anticancer effects, including inhibiting the proliferation of cancer cells and inducing apoptosis. Curcumin, a compound found in turmeric, has been extensively investigated for its potential as an anticancer agent. Curcumin exhibits anti-inflammatory, antioxidant, and anticancer properties, and research has shown its ability to inhibit tumor growth, prevent metastasis, and induce cell death in various cancer types. Cyanidin, an antioxidant compound found in red berries, has been studied for its potential role in preventing cancer. Cyanidin exhibits antioxidant and anti-inflammatory properties that contribute to its potential cancer-preventive effects. Gingerol, a bioactive compound present in ginger, has been identified as a promising anticancer compound. Gingerol possesses antioxidant, anti-inflammatory, and anticancer properties, and research suggests its ability to inhibit cancer cell proliferation and induce cell death. A wide range of phytochemicals are employed in cancer treatment, and several of them will be explored in this discussion (Table 1).

Role of mushroom-derived vitamin D in cancer treatment

The synthesis of vitamin D in vertebrate species is known to occur in the skin upon exposure to ultraviolet B light.[9] Interestingly, mushrooms that have been exposed to light can also serve as a source of vitamin D. Vitamin D has been associated with breast cancer, colon cancer, ovarian cancer, and pancreatic cancer, either directly or indirectly.[10] The exact mechanism of action is still not fully understood, but the vitamin D receptor (VDR) appears to play a significant role in the treatment of various disorders.[11] Mutations in the VDR gene have been linked to an increased risk of breast cancer, suggesting that VDR may act as a mediator in breast cancer development and making it a potential target for cancer prevention.[3]

There are two physiologically significant forms of vitamin D: vitamin D2 (ergocalciferol) and vitamin D3. Vitamin D3 is produced in the skin after exposure to ultraviolet B light from the sun or other artificial sources.[12] Extensive research has shown that vitamin D plays a crucial role in cancer management. Polymorphisms in the VDR gene have been associated with an elevated risk of breast cancer. Studies using VDR knockout and wild-type mice

Table 1. Dietary phytoconstituents and their role in cancer prevention

S. no.	Phytoconstituent	Food Sources	Potential Role in Cancer
1.	Flavonoids	Various fruits, vegetables, and grains	Inhibition of cancer cell growth and proliferation, antioxidant and anti-inflammatory effects
2.	Phenolics and other Non-flavonoids	Various plant sources	Anticancer activity, inhibition of tumor growth, Apoptosis induction, and immune system modulation
3.	Mushroom-Derived vitamin D	Mushrooms, particularly Shiitake and maitake	Inhibition of cancer cell growth, modulation of Immune responses
4.	Plant Oil-Derived Vitamin E	Plant oils	Antioxidant properties, inhibition of cancer cell Growth, and reduced cancer risk
5.	Lycopene	Tomatoes	Antioxidant effects, protection against various cancers, including prostate, lung, and stomach cancers
6.	Fisetin	Strawberries and apples	Induction of cell death in cancer cells, inhibition of tumor growth
7.	Genistein	Soybeans	Anti-inflammatory and antioxidant effects, inhibition of cancer cell proliferation, and apoptosis
8.	Epigallocatechin Gallate (EGCG)	Green tea	Antioxidant and anti-inflammatory effects, Inhibition of cancer cell growth and tumor formation
9.	Crocetin	Saffron	Inhibition of cancer cell proliferation and induction of apoptosis
10.	Curcumin	Turmeric	Anti-inflammatory, antioxidant, and anticancer effects, inhibition of tumor growth, and metastasis
11.	Cyanidin	Red berries	Antioxidant and anti-inflammatory effects, potential cancer prevention
12.	Gingerol	Ginger	Antioxidant, anti-inflammatory, and anticancer properties, inhibition of cancer cell proliferation

EGCG, epigallocatechin gallate.

have demonstrated that low vitamin D intake or deletion of the VDR gene in prostate environments can increase the likelihood of early procarcinogenic events.[13] Furthermore, vitamin D3 is highly effective in reducing PTEN promoter methylation. It has also been linked to PTEN induction, down-regulation of DNA methyltransferase, and up-regulation of p21 following vitamin D3 treatments, suggesting a complex regulatory mechanism involving the DNA methylation machinery.[14]

The potential of plant oil-derived vitamin E in cancer treatment

Vitamin E, a fat-soluble antioxidant, is abundantly present in various food sources, including wheat germ oil, sunflower oil, and safflower oil. It encompasses a family of compounds known as tocopherols and tocotrienols.[15] Among these, α-tocopherol is considered the most bioactive form and exhibits its effects by inhibiting the formation of ROS.[16] Tocopherols and tocotrienols possess antioxidant properties that are believed to contribute to their potential antitumor activity.

In particular, tocotrienols have been found to exhibit superior bioactivity. *In vitro* studies have demonstrated that both tocopherols and tocotrienols possess antiproliferative, pro-apoptotic, and cyclooxygenase-2 (COX-2) inhibitory properties.[17] In 2022, Ranasinghe *et al.*[18] investigated the hypomethylated forms of tocotrienols and highlighted their significant *in vitro* and *in vivo* metabolism, as well as their effectiveness in cytoprotection, cancer prevention, and even chemotherapy activities. Furthermore, the use of vitamin E has been explored in mitigating the cytotoxic effects of cigarette smoke extract on mouse embryonic lung cells. This suggests the potential of vitamin E in preventing or reversing the detrimental impact of certain environmental factors. Overall, plant oil-derived vitamin E, with its various forms and antioxidant properties, holds promise in the realm of cancer treatment and prevention. Further research is warranted to fully elucidate its mechanisms of action and therapeutic applications.

In a recent comprehensive review by Wu *et al.*[19] published in 2020, the involvement of cellular signaling pathways, including NF-κB, STAT3, and COX-2, in inflammation and cancer was examined. Additionally, the impact of various vitamins on breast cancer risk was investigated. While the meta-analysis and meta-regression study revealed a significant decrease in breast cancer risk associated with dietary vitamin E, vitamin A, and total vitamin E intake, these results did not remain statistically significant when cohort study data was combined.

Tocotrienols, a subgroup of vitamin E compounds, have shown superior anticancer capabilities compared to tocopherols. This is attributed to their unsaturated isoprenoid side chain, which inhibits protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) activation, as well as blocking the ErbB2 pathway, known to promote pancreatic cancer cell growth.[5,6] Furthermore, tocotrienols have been observed to limit NF-κB activity in pancreatic cancer cell lines and specifically inhibit the HMG-CoA reductase pathway through posttranslational degradation. In cellular studies, tocotrienols have demonstrated the ability to decrease AKT and ERK MAP kinase activation, along with the downstream mediator ribosomal protein S6 kinase (RSK). By targeting critical cell survival and proliferative signaling pathways, such as those mediated by PI3-kinase/AKT and ERK/MAP kinases, tocotrienols effectively decrease apoptosis in pancreatic cancer cells.

To enhance the anticancer response, synergistic approaches involving the combination of tocotrienols with other drugs that exhibit complementary anticancer mechanisms have been explored. This includes the combination of tocotrienols with cancer chemo-

therapy, statins, receptor tyrosine kinase inhibitors, and COX-2 inhibitors. These strategies aim to optimize the therapeutic efficacy by leveraging the distinctive modes of action of each component. In conclusion, tocotrienols hold great promise as potent anticancer agents. Their unique molecular structure and ability to modulate critical signaling pathways contribute to their effectiveness in inhibiting cancer cell growth. Continued research and exploration of combination therapies involving tocotrienols are crucial for further understanding their full potential in cancer treatment.

Lycopene

Lycopene, a vibrant red pigment and phytochemical, is abundantly present in tomatoes, red carrots, watermelons, and red papayas.[20] Extensive research has highlighted the use of lycopene in the treatment of cancer specifically, prostate cancer and its remarkable antioxidant activity. While lycopene is poorly soluble in water, it readily dissolves in organic solvents. Its anticancer properties are attributed to the activation of cancer-fighting enzymes, particularly phase II detoxifying enzymes.[21]

The inhibitory effects on the growth of human cancer cells and their ability to suppress insulin-like growth factor-I have been well-documented. Various studies have extensively explored the role of lycopene in the prevention and treatment of endometrial cancer and other malignancies.[22] Lycopene has demonstrated inhibitory effects on breast cancer cells, endometrial cancer cells, prostate cancer cells, and colon cancer cells.

In animal studies, the administration of whole-dried tomato powder rich in lycopene to rats with xenografted prostate tumors resulted in slower tumor growth. This finding highlights the potential effectiveness of lycopene in managing prostate tumors.[23] It is important to note that further research is necessary to understand the mechanisms underlying lycopene's anticancer effects and to determine the optimal dosage for different types of cancer. Nevertheless, the promising findings thus far suggest that lycopene holds great potential as a valuable component in the fight against cancer.

In conclusion, lycopene, predominantly found in tomatoes, offers exciting prospects in the field of cancer treatment and prevention. Its potent antioxidant properties and impact on crucial cellular processes make it a compelling phytochemical. By incorporating lycopene-rich foods, like tomatoes, into one's diet, individuals can potentially harness the numerous health benefits associated with lycopene and contribute to their overall well-being.

Fisetin

Fisetin, a flavone present in various plants including *Acaciagreggii*, *Acacia berlandieri*, parrot trees, strawberries, apples, persimmons, grapes, onions, and cucumbers, has gained attention for its potential anti-aging, anti-inflammatory, and anticarcinogenesis properties.[24] Studies have demonstrated that fisetin modulates protein kinase and lipid kinase pathways, acts as a strong antioxidant, and exhibits protective effects against oxidative stress in human retinal pigment epithelial cells.[4,8] Moreover, fisetin has shown promising results in inhibiting signaling pathways involved in lung cancer and Wnt signaling, as well as reducing NF-κB levels.[25] With its ability to induce stress-induced cell death and reduce hydrogen peroxide-induced cell death, fisetin holds potential as a natural compound for cancer prevention and treatment.

Genistein

Genistein, a naturally occurring isoflavone found in various plants including lupine, fava beans, soybeans, kudzu, psoralea, fleminigiavestita, and coffee, offers a range of potential health benefits. With its anthelmintic and antioxidant properties, genistein has been shown to exhibit anti-angiogenic effects by inhibiting the growth of new blood vessels. Moreover, it has been found to have the potential to prevent uncontrolled cell growth associated with cancer. The primary mode of action of genistein is through the inhibition of enzymes that regulate cell division and cell survival, specifically targeting growth factors. Acting as a tyrosine kinase inhibitor, it also blocks DNA topoisomerase II activity.[26] Notably, genistein has demonstrated efficacy in the treatment of leukemia in both *in vitro* and *in vivo* studies.

In the context of breast cancer, genistein interacts with estrogen receptors (ERs). By competing with 17-estradiol (estrogen) for binding to the ER, genistein exhibits a higher affinity for the receptor. This mechanism has been found to modulate mammary cell proliferation, DNA replication, and cell division. It is important to note that genistein's effects on estrogen-dependent breast cancer can vary depending on the presence or absence of an estrogen antagonist. In some cases, genistein has been shown to accelerate the growth of certain ERs and the progression of estrogen-dependent breast cancer.[27] Understanding the potential benefits and complexities of genistein's interactions with ERs is crucial in harnessing its therapeutic potential for cancer prevention and treatment. Further research is warranted to elucidate the precise mechanisms and optimize their use in clinical settings.

EGCG

EGCG is a catechin and the most abundant polyphenol found in green tea. Scientific evidence suggests that EGCG may have therapeutic potential in the treatment of various types of cancers, including bladder, brain, prostate, and cervical malignancies. Studies conducted by Yang *et al.*[28] have investigated the molecular mechanisms and targets of tea components, including EGCG, in cancer prevention. One significant finding is that EGCG can bind to and inhibit the anti-apoptotic protein Bcl-xL, which is involved in the survival of both cancer cells and normal cells. This inhibition has been observed in multiple mechanistic studies. Furthermore, EGCG has demonstrated promising effects in preclinical studies. For instance, in mouse models with chemically induced colonic premalignant lesions, EGCG has been shown to reduce the development of such lesions.[29] Additionally, EGCG has been found to prevent hepatocyte growth factor-induced cell proliferation in colon cancer cells.

EGCG exerts its anticancer effects through the modulation of various cellular signaling pathways. It has been shown to inhibit mitogen-activated protein kinase (MAPK), cyclin-dependent kinases, growth factor-related cell signaling, activator protein 1, and NF-κB.[29] Moreover, EGCG has demonstrated inhibitory effects on topoisomerase I and matrix metalloproteinases, which are important factors involved in cancer progression. It is important to note that while the research on EGCG is promising, further studies are needed to determine the optimal dosage, formulation, and efficacy in humans. Additionally, the bioavailability of EGCG can be limited, which may affect its therapeutic potential. Nevertheless, EGCG from green tea shows potential as a natural compound for cancer treatment, and ongoing research aims to explore its full range of benefits.

Crocetin

Saffron, derived from the dried stigmas of the *Crocus sativus* L. plant, has gained attention as a potential herbal ingredient for cancer treatment, particularly hepatocellular carcinoma. Extensive studies have investigated saffron and its ethanolic extracts in various cancer types, including lung cancer, pancreatic cancer, skin

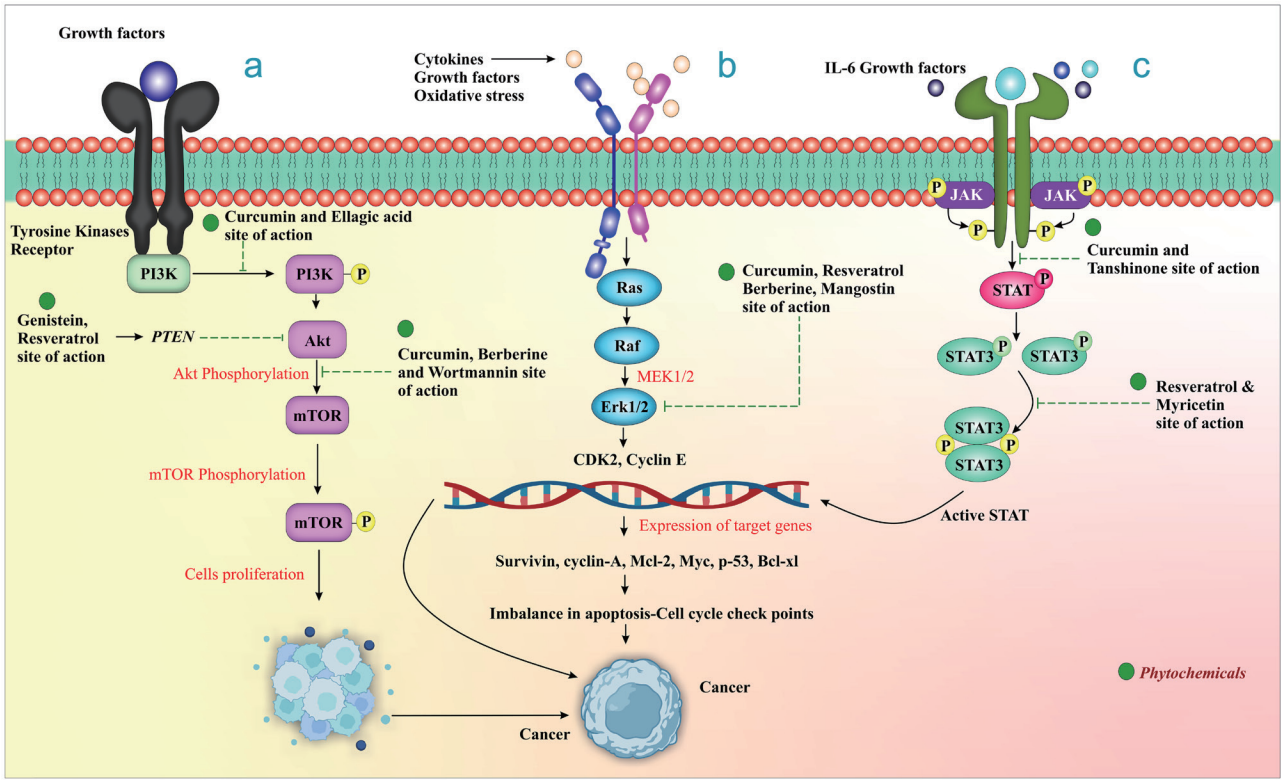

Fig. 1. Mechanism underlying the anticancer potentials of some lead dietary phytochemicals. (a) PI3K/Akt/mTOR pathway in cancer. (b) Ras Raf pathway. (c) STAT3 pathway. Akt, protein kinase B; CDK, Cyclin-dependent kinase; EGCG, epigallocatechin gallate; Erk, extracellular signal-regulated kinases; JAK, janus-activated kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma; Ras, rat sarcoma; STAT3, signal transducer and activator of transcription.

carcinoma, colorectal cancer, and breast cancer. One of the key components of saffron, crocetin, has shown promising effects in inhibiting the growth of cancer cells through multiple mechanisms. It has been found to prevent the production of nucleic acids, boost the immune system, trigger apoptosis (programmed cell death), and block the signaling of growth factors.[30] Additionally, crocetin effectively inhibits the release of nitric oxide, reduces the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1, and decreases intracellular ROS. It also activates NF-κB, a transcription factor involved in immune response and inflammation, while blocking the effects of lipopolysaccharide (LPS). These findings suggest that crocetin from saffron has the potential to be an effective therapeutic agent in cancer treatment. However, further research is needed to fully understand its mechanisms of action, optimal dosage, and potential side effects. Clinical studies are also required to evaluate its efficacy and safety in human cancer patients. In conclusion, saffron, particularly its constituent crocetin, holds promise as a natural herbal ingredient for cancer treatment. Its ability to inhibit cancer cell growth, modulate the immune response, and reduce inflammation highlights its potential therapeutic value. Nevertheless, more research is necessary to establish its effectiveness and ensure its safe use in clinical settings.

Curcumin

Turmeric, a spice derived from the *Curcuma longa* L. plant and a member of the ginger family, has been used for centuries in Indian traditional medicine. Within turmeric, curcumin has garnered significant interest for its potential anticancer properties, particularly in lung metastases, colon cancer, and breast cancer.[31] Researchers studying cancer have been intrigued by curcumin's ability to induce apoptosis selectively in cancer cells without harming healthy cells. One of its mechanisms involves interfering with NF-κB, a protein associated with inflammation and cancer.

Curcumin has also shown promise as a novel mammalian target of rapamycin (mTOR) inhibitor by separating Raptor from mTOR and inhibiting mTOR complex I.[29] It exerts its effects through the regulation of various cell signaling pathways involved in cell proliferation (e.g., cyclin D1, c-myc), cell survival [e.g., B cell lymphoma 2 (Bcl-2), Bcl-xL, cFLIP, XIAP, c-IAP1], caspase activation (e.g., caspase-8, 3, 9), tumor suppression (e.g., p53, p21), death receptor (e.g., DR4, DR5), and key signaling molecules (e.g., JNK, Akt, AMPK). Curcumin also exhibits anti-invasive properties by suppressing COX-2 and MMP-2 expression, modulating EGFR gene expression, and inhibiting cell growth through Akt/mTOR signaling, ultimately preventing p65 cell invasion (Fig. 1). Moreover, curcumin has demonstrated anti-inflammatory effects. It increases IL-10 levels in the mucosa of individuals with inflammatory bowel disease, inhibits the activation of p38 MAPK, and decreases IL-1β and matrix metalloproteinase-3. Furthermore, studies have shown that curcumin possesses antioxidant properties, contributing to its overall potential as an anticancer agent.

In clinical trials, curcumin is nontoxic to human subjects even at high oral doses of up to 12 g/day. However, the outcomes have been inconsistent, as the efficacy of curcumin in certain clinical

settings has been disputed. For example, the initial clinical trial failed to demonstrate cognitive decline improvement, possibly due to unexpected results in the placebo group. Nevertheless, the overall potential of curcumin as an anticancer compound and its multifaceted properties warrant further research and exploration.

In conclusion, curcumin, the bioactive compound found in turmeric, exhibits promising anticancer properties through its effects on various signaling pathways involved in cell survival, proliferation, and inflammation. While more studies are needed to determine its clinical efficacy and optimal dosage, curcumin holds great potential as a natural anticancer agent. Its widespread availability and low toxicity make it an attractive avenue for further investigation in cancer prevention and treatment strategies. The mechanism underlying the anticancer potentials of some lead phytochemicals, i.e.phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway in cancer is shown in Figure 1.

Cyanidin

Cyanidin is a natural compound that can be extracted from various red berries, such as grapes, blackberries, cranberries, and raspberries, as well as red vegetables like red cabbage and red onions. It possesses potent antioxidant and free radical scavenging properties, which have been associated with a potential reduction in the risk of cancer development. Studies have indicated that cyanidin can inhibit the proliferation of colon cancer cells and suppress the expression of genes involved in the production of iNOS and COX-2 enzymes.[32] Another investigation demonstrated that cyanidin-3-glucoside (C3G) blocked the activation of the Fyn kinase signaling pathway. It also attenuates the activation of AP-1 and NF-B, as well as the phosphorylation of MEK, MKK4, Akt, and MAPKs, suggesting its chemopreventive potential.[33] In breast cancer cells exposed to ethanol, C3G was found to inhibit the activation of the ErbB2/cSrc/FAK pathway, potentially reducing the risk of metastasis.[33]

Moreover, cyanidin and its derivatives have demonstrated significant anti-proliferative effects and induced cell death in a highly tumorigenic rat esophagus cell line. However, their effects were not observed in a moderately tumorigenic line (RE-149).[3] Cyanidin has also been shown to inhibit COX-2 expression and PGE2 secretion caused by UVB radiation in epidermal skin cells. This effect is mediated through the inhibition of NF-B and AP-1, which are regulated by MAPK signaling pathways. Cyanidin's targets for inhibiting UVB-induced COX-2 expression include MKK-4, MEK1, and Raf-1.[34] In terms of drug interactions, cyanidin and its derivatives have been identified as potential inhibitors of BCRP (breast cancer resistance protein) while showing minimal effects on multidrug resistance protein 1 (MDR1). Cyanidin-3-galactoside and cyanidin-3-glucoside, specifically, are substrates of BCRP.[34] It is important to note that further research is required to fully understand the mechanisms and potential therapeutic applications of cyanidin in cancer prevention and treatment. Nevertheless, the antioxidant and anti-proliferative properties of cyanidin make it a promising compound for exploring its role in reducing the risk of cancer and promoting overall health.

Gingerol

Gingerol, the compound responsible for the characteristic spicy flavor of ginger, has gained attention for its potential anticancer properties. Several studies have explored the medicinal applications of gingerol and highlighted its antioxidant, anti-inflammatory, and antitumor-promoting activities.[35] In a recent 2021 review by Bischoff *et al.,*[35] the mechanisms underlying the use of gingerol as a medicinal agent were outlined. Gingerol has been found to reduce the expression of iNOS and TNF-α by inhibiting IB phosphorylation and preventing the nuclear translocation of NF-B. This indicates its potential to modulate inflammatory responses. Moreover, gingerol has demonstrated the ability to induce apoptosis in leukemia cells through the mitochondrial pathway. Treatment with gingerol resulted in significantly higher levels of ROS compared with control groups, leading to apoptosis.

In addition to its apoptotic effects, gingerol and its derivative, 6-shogaol, have shown anti-invasive properties against human hepatocarcinoma cells. These compounds exert their effects by controlling the expression of MMP-9 and TIMP-1, which are involved in the invasive behavior of cancer cells. Furthermore, 6-shogaol has been found to regulate urokinase-type plasminogen activity, further contributing to its anti-invasive effects.[31] While gingerol holds promise as an anticancer agent, further research is needed to fully understand its mechanisms of action and its potential applications in cancer treatment. Nonetheless, the antioxidant, anti-inflammatory, and antitumor properties of gingerol make it an intriguing compound worthy of exploration in the field of cancer research.

Mechanism of action of various dietary phytochemicals

Dietary phytochemicals have emerged as influential orchestrators in the intricate molecular dance that dictates the fate of tumorigenic events. Their remarkable abilities to modulate key molecular pathways reveal their profound impact on cancer development and progression. Through intricate mechanisms, these phytochemicals exert their influence on critical pathways such as COX-2, ATM-dependent chromatin remodeling, Hedgehog pathway, STAT3, DNA methylation and epigenetic regulation, Wnt pathway, and tumor angiogenesis, collectively redefining the boundaries of cancer prevention strategies. The COX-2 pathway, known for its role in inflammation and tumorigenesis, becomes a focal point for dietary phytochemicals. These compounds exhibit an innate ability to inhibit COX-2 expression, dampening the inflammatory cascade that fuels cancer development. Furthermore, their engagement with the ATM-dependent chromatin remodeling pathway intricately restructures the chromatin landscape, curbing genetic anomalies and fortifying DNA integrity. The Hedgehog pathway, a regulator of cellular proliferation and differentiation, succumbs to the strategic influences of phytochemicals. These natural agents skillfully disrupt the pathway's aberrant activation, thwarting uncontrolled cell growth and hindering tumorigenesis at its inception. Meanwhile, the STAT3 pathway, a conductor of cellular signaling and survival, falls under the spell of dietary phytochemicals. These compounds intercede to inhibit aberrant STAT3 activation, stifling cancer cell survival and proliferation. The epigenetic realm, governed by DNA methylation and chromatin modifications, finds its equilibrium altered by dietary phytochemicals. These compounds engage in a delicate dance with DNA methyltransferases, inhibiting hypermethylation events that can drive tumor formation. This dynamic interplay extends to the Wnt pathway, a regulator of cell fate determination, where phytochemicals emerge as influential choreographers, orchestrating a symphony that directs cell differentiation away from tumorigenic paths. In the complex tapestry of tumorigenic events, angiogenesis assumes paramount importance. Dietary phytochemicals, even the vigilant guardians, intervene in the tumor angiogenesis process. Their potency is reflected in their ability to disrupt angiogenic signaling pathways, quelling the formation of new blood vessels that sustain growing tumors.

Table 2. Dietary phytochemical mechanisms for cancer prevention and treatment

S no.	Pathways	Mechanism of cancer prevention and disease treatment	Examples of dietary phytochemicals
1.	Apoptosis induction	Dietary phytochemicals activate pro-apoptotic pathways, triggering programmed cell death in cancer cells. They modulate apoptotic regulators, disrupting the balance between pro- and anti-apoptotic proteins, thereby promoting cell death.	Curcumin, resveratrol
2.	COX-2 inhibition	Dietary phytochemicals inhibit the activity of COX-2 enzyme, reducing the production of inflammatory mediators and prostaglandins. This curtails chronic inflammation, a hallmark of cancer development.	Curcumin, quercetin, resveratrol
3.	ATM-dependent chromatin remodeling	Phytochemicals influence the ATM pathway, promoting DNA repair and stability through chromatin remodeling. This mitigates genetic anomalies and reinforces genome integrity.	Sulforaphane, EGCG
4.	Hedgehog pathway modulation	Dietary compounds disrupt the Hedgehog signaling pathway, hindering its abnormal activation. This curbs uncontrolled cell proliferation and differentiation, characteristic of cancer cells.	Curcumin, resveratrol, EGCG
5.	STAT3 pathway suppression	Phytochemicals inhibit the STAT3 pathway, curbing its oncogenic signaling that promotes cell survival, proliferation, and immune evasion.	Curcumin, quercetin, EGCG
6.	DNA methylation and epigenetic regulation	Dietary phytochemicals influence DNA methylation patterns, modulating gene expression through epigenetic mechanisms. This controls the expression of genes involved in tumorigenesis.	Curcumin, EGCG, sulforaphane
7.	Wnt pathway modulation	Phytochemicals modulate the Wnt pathway, striking a balance between its activity for normal cellular functions and its avoidance of cancer-promoting roles.	EGCG, curcumin
8.	Tumor angiogenesis inhibition	Dietary compounds hinder the process of tumor angiogenesis by targeting signaling pathways that support the formation of new blood vessels to feed growing tumors.	Resveratrol, curcumin, green tea polyphenols, quercetin

ATM, ataxia telangiectasia mutated; COX-2, cyclooxygenase-2; DNA, deoxyribonucleic acid; EGCG, epigallocatechin gallate; STAT3, signal transducer and activator of transcription 3; Wnt, wingless-related integration site.

This multifaceted intervention strikes at the heart of tumorigenic nourishment. Collectively, the comprehensive influence of dietary phytochemicals on molecular pathways intricately links their role in the prevention of tumorigenic events. As we continue to unravel the complexity of cancer development, these phytochemicals stand as dynamic protagonists, navigating the intricate pathways of cellular transformation and steering them toward a trajectory of prevention. Their influence extends far beyond the plate, shaping a landscape where the synergy between science and nature paves the way for innovative cancer prevention strategies. The dietary phytochemical mechanisms for cancer prevention and treatment are summarized in Table 2.

Dietary phytochemicals inducing apoptosis mechanism

Inducing apoptosis, or programmed cell death, is an essential mechanism for controlling cell growth and preventing the development and progression of cancer. Several of the dietary phytoconstituents mentioned above have been found to induce apoptosis in cancer cells through various mechanisms. Here are some examples: Curcumin, derived from turmeric, has been extensively studied for its ability to induce apoptosis in cancer cells. It can modulate multiple signaling pathways involved in cell survival and apoptosis, including the activation of caspases, which are key enzymes responsible for initiating the apoptotic process. Curcumin also affects the expression of pro-apoptotic and anti-apoptotic proteins, leading to the induction of apoptosis in cancer cells.

Fisetin, found in strawberries and apples, has been shown to induce apoptosis in various cancer cell lines. It activates caspases and promotes DNA fragmentation, both of which are characteristic features of apoptotic cell death. Fisetin also modulates multiple signaling pathways, including the PI3K/Akt and NF-κB pathways, to induce apoptosis and inhibit cancer cell survival.

Genistein, derived from soybeans, has been found to induce apoptosis in cancer cells through various mechanisms. It can regulate the expression of proteins involved in apoptosis, including Bcl-2 family members, caspases, and death receptors. Genistein also inhibits signaling pathways that promote cell survival, such as the PI3K/Akt pathway, leading to the induction of apoptosis in cancer cells.

Curcumin, fisetin, and genistein, along with other dietary phytoconstituents, have also been found to modulate the expression of pro-apoptotic and anti-apoptotic proteins, regulate the release of apoptotic factors from mitochondria, and activate caspases, thereby initiating the apoptotic cascade. Dietary phytochemicals inducing apoptosis mechanisms are described in Figure 2.

Role of COX-2 and dietary phytochemicals in cellular processes

COX-2 is an enzyme that plays a significant role in various cellular processes, including inflammation, cell proliferation, and angiogenesis. Dysregulation of COX-2 has been implicated in the development and progression of cancer. Several dietary phytoconstituents mentioned above have been found to modulate the activity of COX-2 and its associated cellular processes.[36] Here are some examples: Curcumin, derived from turmeric, has been shown to inhibit the activity of COX-2. It exerts its anti-inflammatory effects by suppressing the expression of COX-2 and reducing the production of pro-inflammatory prostaglandins. Curcumin's inhibition of COX-2 contributes to its potential in preventing chronic inflammation, which is closely linked to cancer development. Gingerol, present in ginger, has also been found to inhibit COX-2 activity.

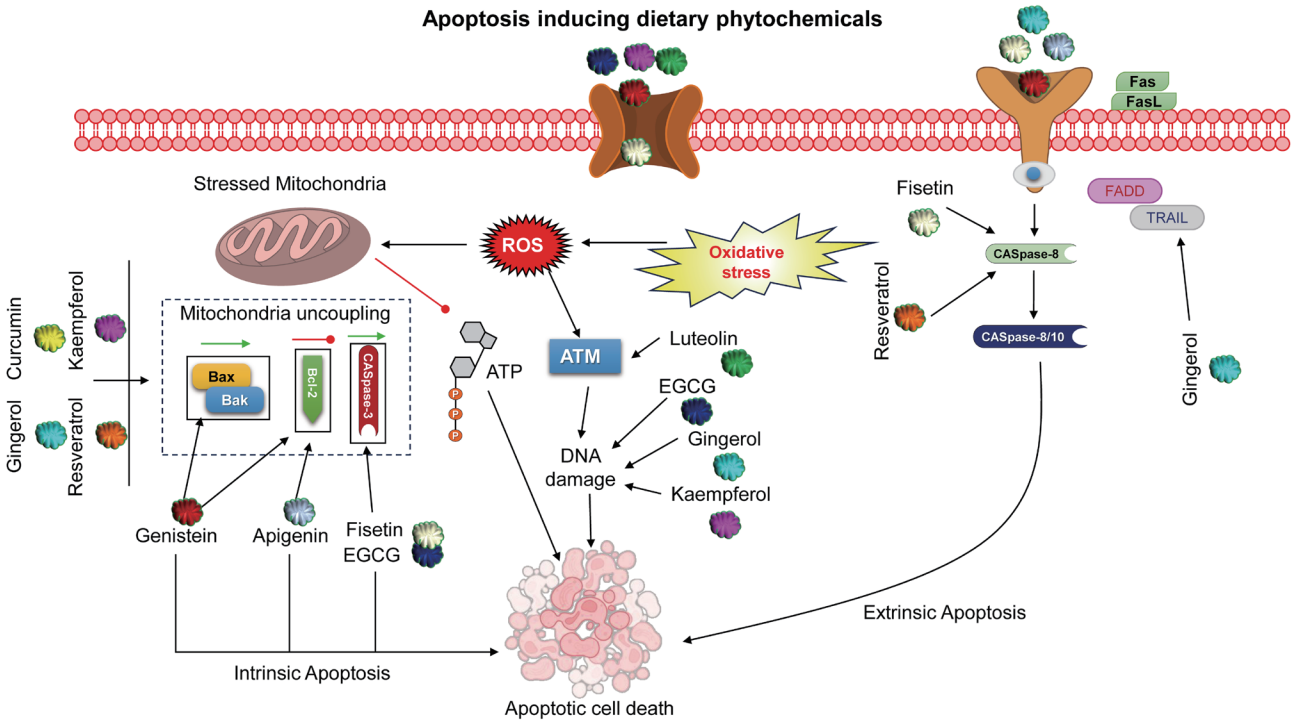

Fig. 2. Dietary phytochemicals inducing apoptosis mechanism. ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; Caspase 8, cysteine-aspartic acid protease 8; EGCG, epigallocatechin gallate; FADD, Fas-associated death domain; FASL, Fas ligand; ROS, reactive oxygen species; TRAIL, Tumor necrosis factor–related apoptosis-inducing ligand.

It suppresses the expression of COX-2 and inhibits the production of prostaglandins, thereby exerting anti-inflammatory effects. Gingerol's ability to modulate COX-2 activity may contribute to its potential to reduce inflammation-associated cancer risk.

Resveratrol, found in grapes and red wine, has been shown to downregulate the expression of COX-2. By inhibiting COX-2, resveratrol can reduce inflammation and inhibit the proliferation of cancer cells. It has also been reported to suppress the production of prostaglandins, thereby attenuating inflammation-induced cancer progression. It is important to note that the regulation of COX-2 by dietary phytoconstituents is complex and can involve multiple molecular mechanisms. These phytochemicals may interfere with the expression of COX-2 at the transcriptional level, inhibit its enzymatic activity, or modulate signaling pathways associated with COX-2 expression. By targeting COX-2, these phytoconstituents have the potential to influence cellular processes involved in cancer development and progression.[37] However, it is crucial to consider that the impact of dietary phytoconstituents on COX-2 activity may vary depending on factors such as concentration, bioavailability, and interactions with other cellular components.[38]

Mechanism, function, and influence of dietary phytoconstituents on ATP-dependent chromatin remodeling

ATP-dependent chromatin remodeling plays a crucial role in regulating gene expression and chromatin structure, and several dietary phytoconstituents have been found to modulate this process. Here, we will discuss the mechanism of ATP-dependent chromatin remodeling and the potential influence of dietary phytoconstituents on this process.[39] As mentioned earlier, ATP-dependent chromatin remodeling complexes contain ATPase subunits that utilize the energy from ATP hydrolysis to remodel chromatin structure. These complexes can slide, evict, or reposition nucleosomes, thereby altering the accessibility of DNA to transcription factors and other regulatory proteins.[40]

Certain dietary phytoconstituents have been shown to affect ATP-dependent chromatin remodeling. For example, curcumin, derived from turmeric, has been found to influence chromatin remodeling processes. It has been reported to inhibit the activity of ATP-dependent chromatin remodeling complexes, leading to altered chromatin structure and gene expression patterns. By modulating chromatin remodeling, curcumin can potentially impact cellular processes involved in cancer development and other diseases.

Resveratrol, found in grapes and red wine, is another dietary phytoconstituent that has been associated with ATP-dependent chromatin remodeling. Resveratrol has been reported to activate certain ATP-dependent chromatin remodeling complexes, leading to changes in chromatin structure and gene expression. These effects may contribute to the potential health benefits of resveratrol, including its anti-inflammatory and anticancer properties.[41]

It is important to note that the influence of dietary phytoconstituents on ATP-dependent chromatin remodeling is still an area of active research, and the specific mechanisms by which these phytochemicals modulate this process are not yet fully understood. The effects may vary depending on the concentration, bioavailability, and interactions with other cellular components.

Moreover, the impact of dietary phytoconstituents on ATP-dependent chromatin remodeling is likely to be context-specific, influenced by the specific cell type, genetic background, and the presence of other co-factors or regulatory molecules. Further research is needed to unravel the precise mechanisms and functional implications of dietary phytoconstituents on ATP-dependent chromatin remodeling and to better understand their potential roles in

health and disease.[42]

In summary, ATP-dependent chromatin remodeling is a vital mechanism that allows cells to modulate chromatin structure, making it more accessible for DNA repair processes. By utilizing ATP hydrolysis, chromatin remodeling complexes play a crucial role in maintaining genome integrity and facilitating DNA repair. The understanding of the genetics, genomes, and mechanisms underlying ATP-dependent chromatin remodeling has been extensively reviewed.[42]

Influence of dietary phytoconstituents on DNA methylation and epigenetic regulation

DNA methylation is an epigenetic modification that plays a crucial role in gene expression regulation and cellular processes.[43] It involves the addition of a methyl group to the DNA molecule, typically occurring at cytosine residues in a CpG dinucleotide context. DNA methylation patterns can be influenced by various factors, including environmental exposure and dietary components. In recent years, several dietary phytoconstituents have gained attention for their potential role in modulating DNA methylation and epigenetic regulation, particularly in the context of cancer prevention and treatment.

Mushroom-derived vitamin D has been studied for its potential in cancer treatment. Vitamin D has been found to regulate DNA methylation patterns, influencing the expression of genes involved in cellular processes and immune function. By modulating DNA methylation, vitamin D may contribute to the regulation of cancer-related pathways and exert anticancer effects.

Plant oil-derived vitamin E has been investigated for its potential in cancer treatment. Vitamin E compounds have been shown to modulate DNA methylation patterns and gene expression, potentially influencing cellular processes associated with cancer development and progression.

Lycopene, a phytochemical abundant in tomatoes, has been studied for its cancer-prevention properties. Lycopene has been reported to affect DNA methylation patterns, potentially modulating the expression of genes involved in cell cycle control, apoptosis, and DNA repair.

Fisetin, found in strawberries and apples, has shown potential in cancer prevention. It has been found to influence DNA methylation patterns and modulate the expression of genes involved in cell cycle regulation and apoptosis, suggesting its role in cancer prevention.

Genistein, derived from soybeans, has been investigated for its potential health benefits and cancer prevention properties. Genistein has been shown to affect DNA methylation patterns and gene expression, potentially regulating pathways involved in cancer development and progression.

Epigallocatechin gallate (EGCG), a major catechin found in green tea, has been extensively studied for its potential health effects, including cancer prevention. EGCG has been reported to modulate DNA methylation patterns, affecting the expression of genes involved in cell cycle regulation, apoptosis, and DNA repair. Crocetin, a compound found in saffron, has shown potential as a therapeutic compound. It has been found to modulate DNA methylation patterns, potentially influencing genes involved in inflammation, cell proliferation, and apoptosis. Curcumin, derived from turmeric, has been extensively studied for its potential as an anticancer compound. Curcumin has been reported to influence DNA methylation patterns, regulating the expression of genes involved in cell cycle control, apoptosis, and inflammation.

Cyanidin, an antioxidant compound found in red berries, has been associated with potential health benefits. While its impact on DNA methylation is less explored, its antioxidant properties may contribute to overall cellular health and potentially influence epigenetic processes.

Gingerol, present in ginger, has shown promise as an anticancer compound. While its specific effects on DNA methylation are not extensively studied, its anti-inflammatory and antioxidant properties may have indirect effects on epigenetic regulation.[44]

In summary, DNA methylation and epigenetic regulation are crucial mechanisms in gene expression control and cellular processes. Several dietary phytoconstituents, including those mentioned above, have been found to modulate DNA methylation patterns and influence gene expression. Understanding the role of these dietary phytoconstituents in epigenetic regulation provides insights into their potential for cancer prevention and treatment strategies.[45]

Effect of dietary phytoconstituents on the Hedgehog signaling pathway

The Hedgehog signaling pathway is a highly conserved and essential signaling pathway involved in various cellular processes during development and tissue homeostasis. Dysregulation of this pathway has been associated with the development of several cancers. Alongside the understanding of the Hedgehog pathway, there is growing interest in the potential role of dietary phytoconstituents in modulating its activity for cancer prevention and treatment.[46]

The Hedgehog pathway is initiated by the binding of Hedgehog ligands (Sonic, Indian, or Desert Hedgehog) to their receptor, Patched (PTCH1), relieving its inhibition on the transmembrane protein Smoothened (SMO). Activation of SMO triggers a series of downstream events leading to the activation of the glioma-associated oncogene (GLI) transcription factors. Activated GLI proteins translocate to the nucleus, where they modulate the expression of target genes involved in cell proliferation, differentiation, and survival.

Mushroom-derived vitamin D has been investigated for its role in cancer treatment. Vitamin D has been shown to interact with the Hedgehog pathway by modulating the expression of GLI proteins and inhibiting their transcriptional activity. This interaction suggests that vitamin D may exert anticancer effects by interfering with Hedgehog signaling. Plant oil-derived vitamin E has also been studied for its potential in cancer treatment. Vitamin E compounds have been reported to influence the Hedgehog pathway by regulating the expression of Hedgehog ligands and downstream target genes. These effects suggest that vitamin E may play a role in modulating the Hedgehog pathway's activity and its associated cellular processes.

Lycopene, a phytochemical found abundantly in tomatoes, has shown promise in cancer prevention. Studies have suggested that lycopene can inhibit the activation of the Hedgehog pathway by suppressing the expression of Hedgehog ligands and downstream target genes. This inhibition may contribute to the anticancer effects attributed to lycopene. Fisetin, derived from strawberries and apples, has demonstrated potential in cancer prevention. It has been found to inhibit the Hedgehog pathway by targeting SMO and GLI proteins, leading to the suppression of Hedgehog signaling and its downstream effects on cell proliferation and survival. Genistein, a phytoestrogen present in soybeans, has been investigated for its potential health benefits and cancer prevention properties. Genistein has been reported to inhibit the Hedgehog pathway by suppressing the expression of Hedgehog ligands and downstream target genes. This inhibition suggests a potential role for genistein

in modulating the Hedgehog pathway and its associated cellular processes.

Epigallocatechin gallate (EGCG), a major catechin found in green tea, has been extensively studied for its potential health effects, including cancer prevention. EGCG has been reported to inhibit the Hedgehog pathway by targeting SMO and GLI proteins, thereby modulating Hedgehog signaling and its downstream effects on cell growth and survival.Crocetin, a compound found in saffron, has demonstrated potential as a therapeutic compound. Although its interaction with the Hedgehog pathway is not extensively studied, crocetin has shown inhibitory effects on Hedgehog signaling-related proteins, suggesting its potential involvement in modulating this pathway. Curcumin, derived from turmeric, has shown promise as an anticancer compound. Curcumin has been reported to inhibit the Hedgehog pathway by suppressing the expression of Hedgehog ligands and downstream target genes. These effects suggest that curcumin may interfere with the Hedgehog pathway's activity, contributing to its anticancer properties.[7]

Relationship between dietary phytochemicals and STAT3 pathway

The JAK-STAT pathway plays a crucial role in various cellular processes, including cell growth, differentiation, immune responses, and inflammation. While the specific involvement of the JAK-STAT pathway may vary among different dietary phytoconstituents, several of them have been found to modulate this signaling pathway, thereby influencing cancer prevention and treatment.

Genistein, derived from soybeans, has been shown to affect the JAK-STAT pathway. It can inhibit the activation of STAT proteins, which are key components of the pathway. By inhibiting the JAK-STAT signaling cascade, genistein can interfere with the growth and survival of cancer cells.

Curcumin, found in turmeric, also affects the JAK-STAT pathway. It has been found to inhibit the activation of JAK and STAT proteins, thereby reducing the proliferation and survival of cancer cells. Curcumin's ability to modulate this pathway contributes to its potential anticancer effects.

EGCG, a catechin present in green tea, has been shown to inhibit the JAK-STAT pathway in cancer cells. It can suppress the activation of STAT proteins, leading to the inhibition of tumor cell growth and the induction of apoptosis. Furthermore, the JAK-STAT pathway has been implicated in the anti-inflammatory effects of certain dietary phytoconstituents. Compounds such as gingerol from ginger and resveratrol from grapes have been shown to inhibit the activation of the JAK-STAT pathway, thereby reducing inflammation and potentially influencing cancer development and progression. It is important to note that the modulation of the JAK-STAT pathway by dietary phytoconstituents may vary depending on the specific compound, cancer type, and cellular context.[7]

Inhibition of tumor angiogenesis by dietary phytoconstituents

Tumor angiogenesis, the formation of new blood vessels to supply nutrients and oxygen to cancer cells, is a critical process for tumor growth and metastasis. Inhibiting tumor angiogenesis has emerged as a promising therapeutic strategy in cancer treatment. Interestingly, several dietary phytoconstituents have been investigated for their potential to modulate tumor angiogenesis and thereby play a role in cancer prevention and treatment.

Mushroom-derived vitamin D has been studied for its potential role in cancer treatment, including its influence on tumor angiogenesis. Vitamin D has been found to affect the expression of angiogenesis-related factors, such as vascular endothelial growth factor (VEGF), which plays a key role in promoting the growth of blood vessels. By regulating angiogenic factors, vitamin D may help inhibit tumor angiogenesis and hinder cancer progression.[47] Plant oil-derived vitamin E has also been explored for its anticancer properties, including its potential to inhibit tumor angiogenesis. Vitamin E compounds have been shown to modulate the expression of angiogenic factors and inhibit the proliferation of endothelial cells, which are essential for the formation of new blood vessels. These effects suggest that vitamin E may contribute to the inhibition of tumor angiogenesis and limit cancer growth.

Lycopene, a phytochemical abundant in tomatoes, has been investigated for its cancer-preventive effects. Studies have suggested that lycopene can inhibit angiogenesis by suppressing the expression of VEGF and other angiogenic factors. This anti-angiogenic activity of lycopene may contribute to its potential in preventing cancer development and progression.

Fisetin, found in strawberries and apples, has shown promise in cancer prevention, including its effects on tumor angiogenesis. Fisetin has been reported to inhibit the expression of angiogenic factors and disrupt the signaling pathways involved in angiogenesis. These effects indicate that fisetin may possess anti-angiogenic properties, which could be valuable in suppressing tumor growth and metastasis.

Genistein, derived from soybeans, has been extensively studied for its potential health benefits and cancer prevention properties. Genistein has been shown to inhibit tumor angiogenesis by interfering with the signaling pathways involved in angiogenesis and modulating the expression of angiogenic factors. These anti-angiogenic effects of genistein contribute to its potential in preventing and treating cancer.

Epigallocatechin gallate (EGCG), a major catechin found in green tea, has been widely studied for its health effects, including its anticancer properties. EGCG has been reported to inhibit angiogenesis by targeting key signaling pathways and suppressing the expression of angiogenic factors. This anti-angiogenic activity may contribute to the cancer-preventive effects of EGCG.

Crocetin, a compound found in saffron, has demonstrated potential as a therapeutic compound in cancer treatment. While its specific effects on tumor angiogenesis are less explored, crocetin has shown inhibitory effects on angiogenic factors and neovascularization processes, indicating its potential role in suppressing tumor angiogenesis.

Curcumin, derived from turmeric, has been extensively studied for its anticancer properties. Curcumin has been reported to inhibit tumor angiogenesis by targeting multiple signaling pathways involved in angiogenesis and modulating the expression of angiogenic factors. These effects contribute to curcumin's potential as an anti-angiogenic agent in cancer prevention and treatment.

Cyanidin, an antioxidant compound found in red berries, and gingerol, present in ginger, have shown promising anticancer properties. While their specific effects on tumor angiogenesis are not extensively studied, their antioxidant and anti-inflammatory properties may indirectly influence angiogenic processes and contribute to overall anticancer effects.[48]

Role of the Wnt pathway in cellular processes and influence of dietary phytoconstituents

The intricate interplay between dietary phytochemicals and the Wnt pathway in the context of cancer prevention warrants further clarification, as it stands as a pivotal regulatory mechanism that shapes the landscape of tumorigenesis. The Wnt pathway, known for its role in cell proliferation, differentiation, and embryonic de-

velopment, emerges as a central protagonist in the broader narrative of dietary phytochemicals' influence on cancer prevention. Dietary phytochemicals exhibit a remarkable capacity to engage with the Wnt pathway, both as mediators and as correctors of its activity. Numerous studies have described their ability to modulate the expression of key components within the Wnt pathway, steering it away from the tumorigenic course. For instance, certain phytochemicals have been shown to inhibit the aberrant activation of Wnt signaling, which is frequently implicated in the uncontrolled proliferation of cancer cells. By curbing the excessive signaling cascade, dietary phytochemicals intervene in the cellular decision-making process, preventing cells from adopting a cancer-promoting identity. Moreover, the relationship between dietary phytochemicals and the Wnt pathway extends beyond mere inhibition. Phytochemicals often exhibit a dual role, not only dampening the overactive pathway but also fostering the activation of the canonical Wnt signaling when required for normal cellular functions, such as tissue regeneration. This nuanced modulation highlights the exquisite adaptability of dietary compounds in ensuring the pathway's equilibrium and safeguarding against tumorigenic perturbations. In essence, dietary phytochemicals emerge as dynamic custodians of the Wnt pathway, engaging in a delicate dance that corrects imbalances while preserving its vital role in healthy cellular processes. By deciphering and elucidating this intricate relationship, researchers can provide a more comprehensive understanding of how dietary interventions may orchestrate cancer prevention through the strategic modulation of the Wnt pathway. Mushroom-derived vitamin D has been investigated for its potential in cancer treatment, and it has been shown to interact with the Wnt pathway. Studies have indicated that vitamin D can inhibit the activity of the Wnt pathway, thereby suppressing the proliferation and survival of cancer cells. This suggests that mushroom-derived vitamin D may exert its anticancer effects, at least in part, through the modulation of the Wnt signaling pathway.[49] Plant oil-derived vitamin E has also been explored for its anticancer properties, including its potential involvement in the Wnt pathway. While more research is needed, studies have suggested that vitamin E may modulate the activity of the Wnt pathway and its downstream signaling components. This modulation could potentially influence cell proliferation, differentiation, and apoptosis, all of which are regulated by the Wnt pathway. Lycopene, a phytochemical abundant in tomatoes, has been extensively studied for its potential in cancer prevention. It has been found that lycopene can inhibit the activation of the Wnt pathway by interfering with the expression of Wnt ligands and downstream target genes. This inhibition of the Wnt pathway may contribute to the anticancer effects attributed to lycopene. Fisetin, derived from strawberries and apples, has demonstrated potential in cancer prevention. Studies have suggested that fisetin can inhibit the Wnt pathway by modulating the expression and activity of Wnt ligands and their receptors. This inhibition may interfere with the proliferation and survival of cancer cells, thereby contributing to its potential as a cancer-preventive agent. Genistein, a phytoestrogen found in soybeans, has been extensively investigated for its potential health benefits and cancer prevention properties. It has been reported that genistein can modulate the Wnt pathway by affecting the expression and activity of Wnt ligands and their downstream targets. This modulation may contribute to the anticancer effects associated with genistein. EGCG, a major catechin found in green tea, has been widely studied for its health effects, including its potential role in cancer prevention. It has been reported that EGCG can inhibit the Wnt pathway by regulating the expression and activity of Wnt ligands and their receptors. This inhibition may interfere with the proliferation and survival of cancer cells, contributing to the potential cancer-preventive effects of EGCG. Crocetin, a compound found in saffron, has shown potential as a therapeutic compound in cancer treatment. While its specific effects on the Wnt pathway are less explored, crocetin has been reported to modulate the expression and activity of Wnt ligands and their downstream targets. This modulation may influence cell proliferation and differentiation, which are regulated by the Wnt pathway. Curcumin, derived from turmeric, has been extensively studied for its anticancer properties. It has been reported that curcumin can inhibit the Wnt pathway by interfering with the expression and activity of Wnt ligands and their downstream targets. This inhibition may contribute to the anticancer effects associated with curcumin. Cyanidin, an antioxidant compound found in red berries, and gingerol, present in ginger, have shown promising anticancer properties. While their specific effects on the Wnt pathway are not extensively studied, their antioxidant and anti-inflammatory properties may indirectly influence Wnt signaling and contribute to overall anticancer effects.[50] The role of Wnt pathway in cellular processes and influence of dietary phytoconstituents is described in Figure 3.

Future prospects

As we continue to unravel the complex interplay between dietary phytochemicals and cancer prevention, several avenues of research beckon for exploration. One promising avenue lies in personalized nutrition and tailored interventions. Harnessing the power of dietary phytochemicals may involve identifying individuals who could derive the most significant benefit from specific compounds based on their genetic makeup, lifestyle, and risk factors. Precision nutrition may provide a means to optimize the use of phytochemicals as a complementary approach to existing cancer prevention strategies, thereby reducing the global cancer burden. Furthermore, the development of innovative delivery systems for phytochemicals is a frontier that warrants attention. Formulations that enhance the bioavailability and stability of these compounds could open doors to more effective preventive strategies. Nanoencapsulation, targeted delivery, and controlled release technologies offer the potential to optimize the pharmacokinetics of phytochemicals, ensuring their presence and activity at the tumor site. Research in this direction could revolutionize the practical application of dietary phytochemicals in cancer prevention. In the era of '*omics*' technologies, integrating genomics, proteomics, metabolomics, and epigenomics into the study of dietary phytochemicals and cancer prevention presents an exciting opportunity. A systems biology approach could provide a comprehensive understanding of how phytochemicals interact with the intricate molecular networks underlying carcinogenesis. Unraveling the intricate web of interactions between phytochemicals and the host's biological systems may lead to the identification of novel targets and the development of multitargeted strategies for cancer prevention. Lastly, continued efforts in clinical research are essential to bridge the gap between preclinical findings and real-world applications. Well-designed clinical trials that assess the efficacy and safety of phytochemical-based interventions in diverse populations are critical. These trials should also explore potential synergistic effects with conventional therapies. By generating robust clinical evidence, we can move closer to the integration of dietary phytochemicals into standard cancer prevention and treatment protocols. In summary, the future of exploring dietary phytochemicals in cancer prevention is a dynamic and promising field. With advances in personalized nutri-

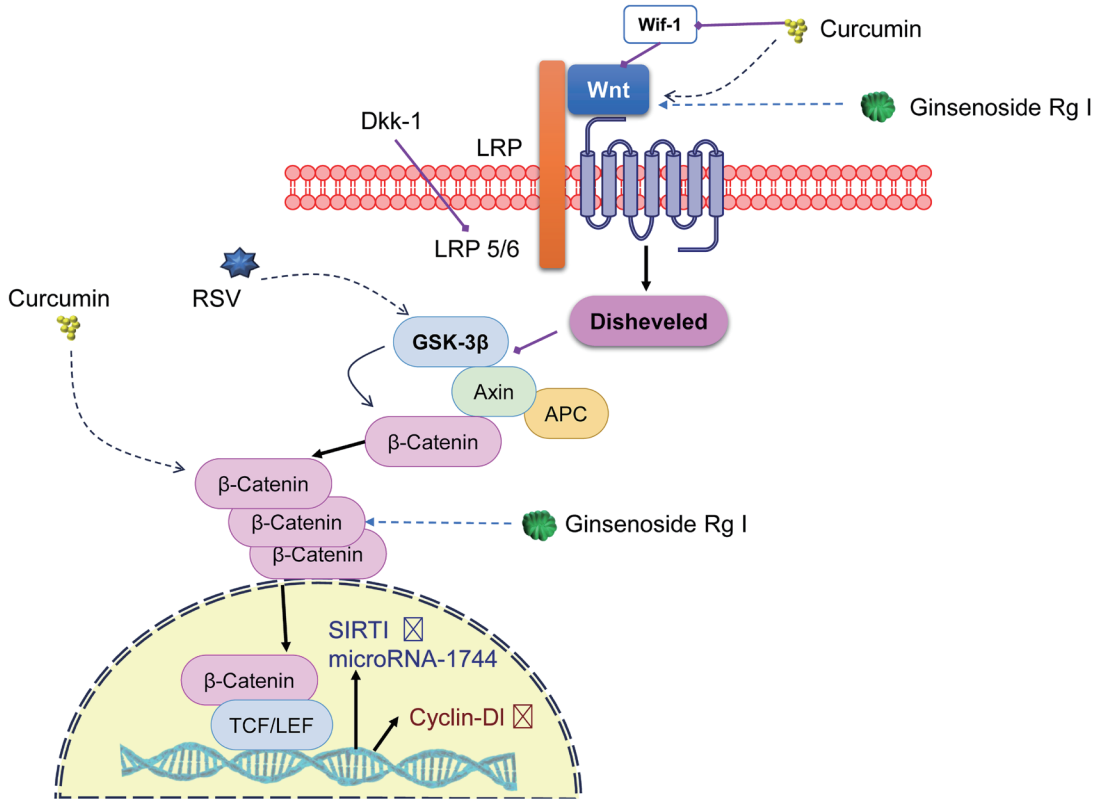

Fig. 3. Role of the Wnt pathway in cellular processes and influence of dietary phytoconstituents. APC, adenomatous polyposis coli; DKK-1, Dickkopf-1; GSK-3β, glycogen synthase kinase-3 beta; LEF, leflunomide; LRP, low-density lipoprotein receptor-related protein; RSV, resveratrol; SIRT1, silent information regulator-1; TCF, T-cell factor; Wif-1, Wnt inhibitory factor 1; Wnt, wingless/integrated related integration site.

tion, innovative delivery systems, 'omics' technologies, and robust clinical research, the potential for dietary phytochemicals to make a significant impact on reducing the global cancer burden is both tantalizing and within reach. As we continue to unearth the secrets of these natural compounds, we stand at the brink of a new era in the fight against cancer, offering hope to countless individuals worldwide.

Conclusion

In the realm of cancer prevention, the significance of dietary phytochemicals as potent allies cannot be overstated. The impressive array of mushroom-derived vitamin D, plant-derived vitamin E, lycopene, fisetin, genistin, epigallocatechin gallate, crocetin, curcumin, cynarin, and gingerol has emerged as a beacon of hope in the ongoing quest to thwart the development and progression of various cancers. The culmination of rigorous scientific research has unequivocally highlighted their exceptional potency, attributing their effectiveness to a multitude of mechanisms targeting cancer cells at their core. From halting uncontrolled cell growth to modulating inflammation and oxidative stress, these phytochemicals have proven their mettle in battling cancer through multifaceted approaches. As we stand at the intersection of scientific innovation and natural solutions, these findings resonate with a promise that extends beyond conventional paradigms, offering novel avenues for proactive cancer prevention strategies. The future holds the potential for harnessing the power of these dietary champions not only to enhance our understanding of cancer biology but also to empower individuals in taking charge of their health and well-being through informed dietary choices.

In conclusion, the discussed dietary phytoconstituents have shown promising potential in cancer prevention and treatment through various mechanisms of action. These phytochemicals, including mushroom-derived vitamin D, plant oil-derived vitamin E, lycopene, fisetin, genistein, EGCG, crocetin, curcumin, cyanidin, and gingerol, have been investigated for their effects on different pathways and cellular processes involved in cancer development and progression. The Wnt signaling pathway, a crucial pathway involved in embryonic development and cell proliferation, has been implicated in cancer when dysregulated. Several of the mentioned dietary phytoconstituents have been found to modulate the Wnt pathway. Mushroom-derived vitamin D, for example, has been shown to inhibit the activity of the Wnt pathway, suppressing the proliferation and survival of cancer cells. Plant oil-derived vitamin E has been reported to modulate the Wnt pathway and its downstream signaling components, potentially influencing cell proliferation, differentiation, and apoptosis. Lycopene, abundantly found in tomatoes, has been studied for its ability to inhibit the activation of the Wnt pathway by interfering with the expression of Wnt ligands and downstream target genes. Fisetin from strawberries and apples has also demonstrated inhibitory effects on the Wnt pathway by modulating the expression and activity of Wnt ligands and receptors. Genistein from soybeans and EGCG from green tea have been investigated for their effects on the Wnt pathway, with studies suggesting their ability to affect the expression and activity of Wnt ligands and downstream targets. These phytochemicals

may contribute to their anticancer effects through the modulation of the Wnt pathway. Crocetin from saffron and curcumin from turmeric have shown potential as anticancer compounds. Although their specific effects on the Wnt pathway are less explored, they have been reported to interfere with the expression and activity of Wnt ligands and downstream targets, potentially influencing cell proliferation and differentiation. Additionally, cyanidin from red berries and gingerol from ginger, while less studied for their effects on the Wnt pathway, possess antioxidant and anti-inflammatory properties, which may indirectly influence Wnt signaling and contribute to their overall anticancer effects.

Despite the promising potential of dietary phytochemicals in revolutionizing cancer prevention strategies, significant obstacles continue to impede their widespread adoption. A prevailing resistance rooted in several factors hampers the seamless integration of these natural compounds into mainstream healthcare practices. A key challenge lies in the intricate complexities of translating laboratory findings to real-world scenarios, with concerns about standardized dosages and optimal delivery methods often clouding the path forward. Additionally, the lack of comprehensive clinical trials and robust long-term studies raises skepticism regarding the efficacy and safety of phytochemical interventions. Moreover, the dominance of conventional medical approaches and the hesitance to deviate from established norms perpetuates reluctance toward embracing alternative preventive measures. Furthermore, the influence of commercial interests and the marketing of pharmaceutical solutions can overshadow the potential of dietary interventions, fostering a climate where natural solutions are viewed with skepticism. As we navigate these barriers, a holistic approach that amalgamates rigorous scientific scrutiny, education, and cultural shifts is essential to surmounting the resistance and fostering a broader understanding of the transformative role that dietary phytochemicals can play in the realm of cancer prevention.

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Conflict of interest

The authors declare that they have no conflict of interests.

Author contributions

Contributed to the study concept and design (SR, UKP, SKJ), drafted the manuscript (SR), critically revised the manuscript (UKP, SKJ), and provided supervision throughout the study (SKJ). All authors made significant contributions to this review article and have approved the final manuscript.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71(1):7–33. doi:10.3322/caac.21654, PMID:33433946.

[2] Schmidt DR, Patel R, Kirsch DG, Lewis CA, Vander Heiden MG, Locasale JW. Metabolomics in cancer research and emerging applications in clinical oncology. CA Cancer J Clin 2021;71(4):333–358. doi:10.3322/caac.21670, PMID:33982817.

[3] Blasiak J, Chojnacki J, Pawlowska E, Jablkowska A, Chojnacki C. Vitamin D May Protect against Breast Cancer through the Regulation of Long Noncoding RNAs by VDR Signaling. Int J Mol Sci 2022;23(6):3189. doi:10.3390/ijms23063189, PMID:35328609.

[4] Rivera-Pérez J, Martínez-Rosas M, Conde-Castañón CA, Toscano-Garibay JD, Ruiz-Pérez NJ, Flores PL, *et al*. Epigallocatechin 3-Gallate Has a Neuroprotective Effect in Retinas of Rabbits with Ischemia/Reperfusion through the Activation of Nrf2/HO-1. Int J Mol Sci 2020;21(10):3716. doi:10.3390/ijms21103716, PMID:32466215.

[5] Jiang Q. Natural forms of vitamin E and metabolites-regulation of cancer cell death and underlying mechanisms. IUBMB Life 2019;71(4):495–506. doi:10.1002/iub.1978, PMID:30548200.

[6] Tan B, Huang Y, Zhang B, Lin N. The effect of ibrutinib on radiosensitivity in pancreatic cancer cells by targeting EGFR/AKT/mTOR signaling pathway. Biomed Pharmacother 2020;128:110133. doi:10.1016/j.biopha.2020.110133, PMID:32447207.

[7] Mohan CD, Rangappa S, Preetham HD, Chandra Nayaka S, Gupta VK, Basappa S, *et al*. Targeting STAT3 signaling pathway in cancer by agents derived from Mother Nature. Semin Cancer Biol 2022;80:157–182. doi:10.1016/j.semcancer.2020.03.016, PMID:32325172.

[8] Imran M, Saeed F, Gilani SA, Shariati MA, Imran A, Afzaal M, *et al*. Fisetin: An anticancer perspective. Food Sci Nutr 2021;9(1):3–16. doi:10.1002/fsn3.1872, PMID:33473265.

[9] Hanel A, Carlberg C. Vitamin D and evolution: Pharmacologic implications. BiochemPharmacol 2020;173:113595. doi:10.1016/j.bcp.2019.07.024, PMID:31377232.

[10] Camara AB, Brandao IA. The Role of Vitamin D and Sunlight Incidence in Cancer. Anticancer Agents Med Chem 2019;19(11):1418–1436. doi:10.2174/1389557519666190312123212, PMID:30864510.

[11] Zmijewski MA, Carlberg C. Vitamin D receptor(s): In the nucleus but also at membranes? Exp Dermatol 2020;29(9):876–884. doi:10.1111/exd.14147, PMID:32654294.

[12] Bigman G. Vitamin D metabolites, D(3) and D(2), and their independent associations with depression symptoms among adults in the United States. NutrNeurosci 2022;25(4):648–656. doi:10.1080/1028415X.2020.1794422, PMID:32684140.

[13] Smolinski JB. Dietary Chemoprevention Studies in Preclinical Models of Prostate Cancer: Bioactive Lipids and Vitamin D[Dissertation]. Ohio: The Ohio State University; 2010.

[14] Boughanem H, Cabrera-Mulero A, Hernández-Alonso P, Clemente-Postigo M, Casanueva FF, Tinahones FJ, *et al*. Association between variation of circulating 25-OH vitamin D and methylation of secreted frizzled-related protein 2 in colorectal cancer. Clin Epigenetics 2020;12(1):83. doi:10.1186/s13148-020-00875-9, PMID:32517740.

[15] Aksoz E, Korkut O, Aksit D, Gokbulut C. Vitamin E (α, β, γ and δ tocopherol) levels in plant oils. Flavour Frag J 2020;35(5):504–510. doi:10.1002/ffj.3585.

[16] Rashidi B, Hoseini Z, Sahebkar A, Mirzaei H. Anti-Atherosclerotic Effects of Vitamins D and E in Suppression of Atherogenesis. J Cell Physiol 2017;232(11):2968–2976. doi:10.1002/jcp.25738, PMID:27966778.

[17] Zingg JM. Vitamin E: Regulatory Role on Signal Transduction. IUBMB Life 2019;71(4):456–478. doi:10.1002/iub.1986, PMID:30556637.

[18] Ranasinghe R, Mathai M, Zulli A. Revisiting the therapeutic potential of tocotrienol. Biofactors 2022;48(4):813–856. doi:10.1002/biof.1873, PMID:35719120.

[19] Wu JY, Chen YJ, Bai L, Liu YX, Fu XQ, Zhu PL, *et al*. Chrysoeriol ameliorates TPA-induced acute skin inflammation in mice and inhibits NF-κB and STAT3 pathways. Phytomedicine 2020;68:153173. doi:10.1016/j.phymed.2020.153173, PMID:31999977.

[20] Chauhan M, Garg V, Zia G, Dutt R. Potential role of phytochemicals of fruits and vegetables in human diet. Research J Pharm and Tech 2020;13(3):1587–1591. doi:10.5958/0974-360X.2020.00287.5.

[21] Roy M, Datta A. Fundamentals of phytochemicals. Cancer Genetics and Therapeutics: Focus on Phytochemicals. Springer; 2019:49–81. doi:10.1007/978-981-13-9471-3_3.

[22] Song X, Luo Y, Ma L, Hu X, Simal-Gandara J, Wang LS, *et al*. Recent trends and advances in the epidemiology, synergism, and delivery system of lycopene as an anticancer agent. Semin Cancer Biol 2021;73:331–346.

doi:10.1016/j.semcancer.2021.03.028, PMID:33794344.
[23] Moran NE, Thomas-Ahner JM, Wan L, Zuniga KE, Erdman JW, Clinton SK. Tomatoes, Lycopene, and Prostate Cancer: What Have We Learned from Experimental Models? J Nutr 2022;152(6):1381–1403. doi:10.1093/jn/nxac066, PMID:35278075.
[24] Kumar R, Kumar R, Khursheed R, Awasthi A, Khurana N, Singh SK, *et al*. Development and validation of RP-HPLC method for estimation of fisetin in rat plasma. South African Journal of Botany 2021;140:284–289. doi:10.1016/j.sajb.2020.05.010.
[25] Farooqi AA, Naureen H, Zahid R, Youssef L, Attar R, Xu B. Cancer chemopreventive role of fisetin: Regulation of cell signaling pathways in different cancers. Pharmacol Res 2021;172:105784. doi:10.1016/j.phrs.2021.105784, PMID:34302980.
[26] Nakai S, Fujita M, Kamei Y. Health Promotion Effects of Soy Isoflavones. J Nutr Sci Vitaminol (Tokyo) 2020;66(6):502–507. doi:10.3177/jnsv.66.502, PMID:33390391.
[27] Ghadimi D, Hemmati M, Karimi N, Khadive T. Soy Isoflavone Genistein Is a Potential Agent for Metabolic Syndrome Treatment: A Narrative Review. Journal of Advances in Medical and Biomedical Research 2020;28(127):64–75. doi:10.30699/jambs.28.127.64.
[28] Aggarwal V, Tuli HS, Tania M, Srivastava S, Ritzer EE, Pandey A, *et al*. Molecular mechanisms of action of epigallocatechin gallate in cancer: Recent trends and advancement. Semin Cancer Biol 2022;80:256–275. doi:10.1016/j.semcancer.2020.05.011, PMID:32461153.
[29] Zhang C, Sheng J, Li G, Zhao L, Wang Y, Yang W, *et al*. Effects of Berberine and Its Derivatives on Cancer: A Systems Pharmacology Review. Front Pharmacol 2019;10:1461. doi:10.3389/fphar.2019.01461, PMID:32009943.
[30] Veisi A, Akbari G, Mard SA, Badfar G, Zarezade V, Mirshekar MA. Role of crocin in several cancer cell lines: An updated review. Iran J Basic Med Sci 2020;23(1):3–12. doi:10.22038/IJBMS.2019.37821.8995, PMID:32405344.
[31] Lee JH, Kim YG, Choi P, Ham J, Park JG, Lee J. Antibiofilm and Antivirulence Activities of 6-Gingerol and 6-Shogaol Against Candida albicans Due to Hyphal Inhibition. Front Cell Infect Microbiol 2018;8:299. doi:10.3389/fcimb.2018.00299, PMID:30211127.
[32] Tan C, Kong Y, Tong Y, Deng H, Wang M, Zhao Y, *et al*. Anti-apoptotic effects of high hydrostatic pressure treated cyanidin-3-glucoside and blueberry pectin complexes on lipopolysaccharide-induced inflammation in Caco-2 cells. J Funct Foods 2021;86:104709. doi:10.1016/j.jff.2021.104709.
[33] Jeong H, Shin JY, Lee K, Lee SJ, Chong HJ, Jeong H, *et al*. Caffeoyl-Prolyl-Histidine Amide Inhibits Fyn and Alleviates Atopic Dermatitis-Like Phenotypes via Suppression of NF-κB Activation. Int J Mol Sci 2020;21(19):7160. doi:10.3390/ijms21197160, PMID:32998341.
[34] Manolescu BN, Oprea E, Mititelu M, Ruta LL, Farcasanu IC. Dietary Anthocyanins and Stroke: A Review of Pharmacokinetic and Pharmacodynamic Studies. Nutrients 2019;11(7):1479. doi:10.3390/nu11071479, PMID:31261786.
[35] Bischoff-Kont I, Fürst R. Benefits of Ginger and Its Constituent 6-Shogaol in Inhibiting Inflammatory Processes. Pharmaceuticals (Basel) 2021;14(6):571. doi:10.3390/ph14060571, PMID:34203813.
[36] Xu D, Cai J, Wan ZK, Gao H, Sun Y. Pathophysiological role of prostaglandin E synthases in liver diseases. Prostaglandins Other Lipid Mediat 2021;154:106552. doi:10.1016/j.prostaglandins.2021.106552, PMID:33930567.
[37] Berbecka M, Forma A, Baj J, Furtak-Niczyporuk M, Maciejewski R, Sitarz R. A Systematic Review of the Cyclooxygenase-2 (COX-2) Expression in Rectal Cancer Patients Treated with Preoperative Radiotherapy or Radiochemotherapy. J Clin Med 2021;10(19):4443. doi:10.3390/jcm10194443, PMID:34640461.
[38] Torun A, Enayat S, Sheraj I, Tunçer S, Ülgen DH, Banerjee S. Butyrate mediated regulation of RNA binding proteins in the post-transcriptional regulation of inflammatory gene expression. Cell Signal 2019;64:109410. doi:10.1016/j.cellsig.2019.109410, PMID:31487531.
[39] Chikhirzhina E, Starkova T, Beljajev A, Polyanichko A, Tomilin A. Functional Diversity of Non-Histone Chromosomal Protein HmgB1. Int J Mol Sci 2020;21(21):7948. doi:10.3390/ijms21217948, PMID:33114717.
[40] Banerjee S, Roy S. An insight into understanding the coupling between homologous recombination mediated DNA repair and chromatin remodeling mechanisms in plant genome: an update. Cell Cycle 2021;20(18):1760–1784. doi:10.1080/15384101.2021.1966584, PMID:34437813.
[41] Schier AC, Taatjes DJ. Structure and mechanism of the RNA polymerase II transcription machinery. Genes Dev 2020;34(7-8):465–488. doi:10.1101/gad.335679.119, PMID:32238450.
[42] López AJ, Hecking JK, White AO. The Emerging Role of ATP-Dependent Chromatin Remodeling in Memory and Substance Use Disorders. Int J Mol Sci 2020;21(18):6816. doi:10.3390/ijms21186816, PMID:32957495.
[43] Li S, Peng Y, Panchenko AR. DNA methylation: Precise modulation of chromatin structure and dynamics. CurrOpin Struct Biol 2022;75:102430. doi:10.1016/j.sbi.2022.102430, PMID:35914496.
[44] Greenberg MVC, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol 2019;20(10):590–607. doi:10.1038/s41580-019-0159-6, PMID:31399642.
[45] Pan ZX, Zhang XY, Chen SR, Li CZ. Upregulated exosomal miR-221/222 promotes cervical cancer via repressing methyl-CpG-binding domain protein 2. Eur Rev Med Pharmacol Sci 2019;23(9):3645–3653. doi:10.26355/eurrev_201905_17788, PMID:31114989.
[46] Bhateja P, Cherian M, Majumder S, Ramaswamy B. The Hedgehog Signaling Pathway: A Viable Target in Breast Cancer? Cancers (Basel) 2019;11(8):1126. doi:10.3390/cancers11081126, PMID:31394751.
[47] Jiang X, Wang J, Deng X, Xiong F, Zhang S, Gong Z, *et al*. The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res 2020;39(1):204. doi:10.1186/s13046-020-01709-5, PMID:32993787.
[48] Teleanu RI, Chircov C, Grumezescu AM, Teleanu DM. Tumor Angiogenesis and Anti-Angiogenic Strategies for Cancer Treatment. J Clin Med 2019;9(1):84. doi:10.3390/jcm9010084, PMID:31905724.
[49] Bugter JM, Fenderico N, Maurice MM. Mutations and mechanisms of WNT pathway tumour suppressors in cancer. Nat Rev Cancer 2021;21(1):5–21. doi:10.1038/s41568-020-00307-z, PMID:33097916.
[50] Houschyar KS, Tapking C, Borrelli MR, Popp D, Duscher D, Maan ZN, *et al*. Wnt Pathway in Bone Repair and Regeneration - What Do We Know So Far. Front Cell Dev Biol 2018;6:170. doi:10.3389/fcell.2018.00170, PMID:30666305.