



REVIEW

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Emerging insights of nutraceuticals as anticancer

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ABSTRACT

Among the most prevalent and feared diseases concerning individuals worldwide is cancer, which has multiple pathophysiological components. Over the past few years, nutraceuticals have garnered substantial interest as potential agents against cancer owing to their diverse array of bioactive compounds and limited adverse effects. This review endeavors to present a comprehensive perspective on the growing understanding of nutraceuticals' role as promising adjuncts or alternatives in cancer treatment. The focus of this review is on illuminating the anticancer attributes found in a variety of nutraceuticals, such as polyphenols, flavonoids, carotenoids, and other bioactive compounds. Due to their nutritional value and therapeutic potential against malignant cells, several nutraceuticals have recently attracted a lot of fascination. These bioactive compounds are capable of killing cancerous cells without damaging normal cells. In conclusion, this review sheds light on the emerging insights into nutraceuticals' anticancer properties and their potential as valuable components of integrative cancer therapy. Although significant progress has been made, further investigation is warranted to fully harness the therapeutic potential of these natural compounds and enhance their clinical application in the fight against cancer.

1. Introduction

Nutraceuticals are natural compounds that, along with having a nutritional role, impart health benefits as well. They possess health-nurturing, disease-healing, or disease-preventing effects; therefore, other than as a source of nutrition, they are also used as medicines (Kalra, 2003; Nasri et al., 2014). Stephen De Felice, MD, the founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, first used the phrase "nutraceutical" in 1989 (Balachandran & Govindarajan, 2005). They are known as dietary supplements, and in terms of nutrition, they include both nutrients (like proteins, carbohydrates, vitamins, lipids, and amino acids) and non-nutrients (such as enzymes, probiotics, and prebiotics) (Mathur et al., 2015). One of the primary causes of death, cancer leads to approximately three hundred thousand fatalities each year. In the United States, it accounts for roughly 25% of all deaths. The most common illness categories are malignancies of the colon, breast, and lungs (Salami et al., 2013). Cancer development begins as a result of cell function impairment. Numerous epigenetic and genetic alterations within the cell are the cause of cancer. It is challenging to assess each etiological factor, although a suggestion can be given that the interaction of multiple risk factors, including ranges of exogenous and endogenous environmental factors along with individual components, including genetic predisposition, is what contributes most to the progression of cancer. Numerous scientific studies are being conducted to treat this fatal illness (Arora & Jaglan, 2016). Current studies suggest the use of some plant-based agents in the molecular and cellular processes underlying tumor progression. The objective of this paper is to

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examine how nutraceuticals are used in both cancer treatment and prevention. From various studies, it has been estimated that, through appropriate nutrition and lifestyle changes alone, approximately one-third of all cancer deaths can be prevented. Patients with cancer frequently use nutritional supplements, and several studies conducted over the last few years have provided various affirmations about the usefulness of nutraceuticals as anti-cancer agents. Several *in vivo* and *in vitro* studies independently verified that nutraceuticals show antineoplastic features and hold other health benefits. In the area of cancer research, nutraceuticals are gaining much attention because of their relatively non-toxic behavior and pleiotropic effects. The mechanisms involved in the prevention of cancer by nutraceuticals include inhibition of cell proliferation and differentiation, suppression of efflux transporters like P-glycoprotein, breast cancer resistance protein, multidrug resistance protein, or reducing the toxicity of chemotherapeutic drugs. Most of the nutraceuticals studied for cancer prevention around the world have very low aqueous solubility and permeability, resulting in poor bioavailability in individuals. The few variables that may be responsible for the low bioavailability of nutraceuticals include controlled release from the food matrix, the formation of insoluble complexes with other ingredients in the gastrointestinal system, or biotransformation in the gastrointestinal tract (GIT).

Depending on where they originate from, nutrients like vitamins, dietary fiber, carotenoids, prebiotics, probiotics, and phenolics are classified as either dietary supplements or herbal bioactive compounds. With a market value of approximately USD 117 billion, nutraceuticals have a considerable global presence (Mathur et al., 2015). The idea that nutraceuticals made from medicinal herbs like garlic, ginger, soybeans, tea, propolis, and others are effective against cancer has been highlighted by several studies done on epidemiologic and animal models (Kuppusamy et al., 2014). The current study investigates the anticancer potential of various nutraceuticals.

2. Materials and methods

For the current review, several scientific databases, including Wiley, Web of Science, Google Scholar, Science Direct, PubMed, ACS Publications, Taylor & Francis, and Springer, were searched for relevant literature.

3. Nutraceuticals' effects against cancer

3.1. Fisetin

Fisetin is a dietary flavonoid obtained from numerous vegetables and fruits, including cucumbers. In the earlier study conducted on this flavanoid, it was revealed that fisetin can initiate the mitochondrial apoptotic pathway in malignant cells by modulating the expression of Bcl-2 metabolites. It is also observed that fisetin escalates the proapoptotic Bak protein levels in cancerous cells of the colon (Lall et al., 2016).

3.2. Carotenoids

According to recent studies, there is a strong link between carotene consumption and a reduced risk of cancer. A major class of secondary metabolites known as carotenoids exhibits a variety of therapeutic properties, including those that can improve skin tone and scavenge free radicals. They are potent enough to be used in cancer treatment, including the prevention of gastrointestinal and colon cancer (Arora & Jaglan, 2016).

3.3. Lycopene

Lycopene, a natural antioxidant of the carotenoid family acts as a precursor of β -carotene in tomatoes and is present in higher quantities in ripe tomatoes but can be obtained in less quantity in grapes, watermelon, apricot, papaya, etc (Min & Kwon, 2014). β -carotene and lycopene both can persuade apoptosis in prostate cancer cells and malignant lymphoblast cells (Arora & Jaglan, 2016).

3.4. Tea polyphenols

Tea contains several polyphenols, like epigallocatechin-3-gallate, which exhibit antitumor activities by targeting cellular signaling pathways in cancer. From various studies conducted earlier, it was revealed that epigallocatechin-3-gallate eliminated cancer stem cells in various types of cancer. In combination with a phosphodiesterase 3 inhibitor, epigallocatechin-3-gallate alleviates cancer stem cell properties by suppressing CD44 and FOXO3 in pancreatic cancer. In inflammatory breast cancer, epigallocatechin-3-gallate is reported to suppress cancer stem cells by inhibiting the formation of tumor spheres (Chen et al., 2005). Pan et al. (2016) revealed that epigallocatechin-3-gallate is responsible for inducing programmed cell death in human prostate carcinoma cells.

3.5. Vitamin C

The role of Vitamin C (L-ascorbic acid or ascorbate) as an anticancer compound has long been investigated. In the study conducted earlier by Chen et al. (2005), it was concluded that L-ascorbic acid possesses *in vitro* antineoplastic activity by inducing the formation of hydrogen peroxide (H_2O_2) and diminishing GSH levels intracellularly, which elevates chemotherapy-induced DNA damage to oxidative stress (Chen et al., 2005). Although two successive double-blind, placebo-controlled trials accomplished in the 1980s were unable to report any beneficial effect from oral ascorbate in advanced cancers, this may be due to restricted absorption through the gut or fast excretion through the kidney when given orally. Due to this, the drug may fail to produce tumoricidal concentrations in plasma, which can only be obtained through the intravenous administration route (Padayatty et al., 2004). A high dose of ascorbic acid was well tolerated, and when given orally in patients with terminal cancer, it resulted in sporadic disease stabilization (Das, 2015).

3.6. Artemisinin and its derivatives

Das (2015) has established the antitumor effects of the antimalarial complex artemisinin *in vitro* and *in vivo*. The antitumor effect depends on multiple mechanisms, including inhibition of tumor angiogenesis, initiation of oxidative stress, alteration of calcium metabolism, etc. *Artemisia annua* is taken as a supplement by many cancer patients. A study performed by Jansen et al. (2011) in patients with associated cervix cancer has shown adequate tolerability and augmentation of symptoms with oral arteminol-RIn antimalarial dosages. Artemisinin-derived compounds are safe and they are still promising as antitumor agents (Jansen et al., 2011). For better defining the maximum tolerated dose, identifying effective antitumor dosages, and determining the best combinations with standard treatments in cancer patients, further studies are needed (Picotto et al., 2012).

3.7. Vitamin D and its derivatives

Calcium metabolism is regulated by the steroid hormone vitamin D (Mohr et al., 2014). Studies done by Picotto et al. (2012) and Trump

et al. (2004) on 25-dihydroxy vitamin D, which is an active metabolite of vitamin D, have shown both in vivo and in vitro anti-proliferative, pro-differentiation, and antiangiogenic effects. Additionally, patients with CRC and breast cancer exhibiting greater plasmatic levels of the vitamin D metabolite 25-hydroxycholecalciferol have shown improved survival rates (Jain et al., 2011; Maalmi et al., 2014). Even though the investigation of Jain et al. (2011) on single-agent calcitriol or its synthetic counterparts was unable to demonstrate any appreciable clinical activity (Beer et al., 2003), combinations of CT with high-dose calcitriol have also been investigated, and preliminary reports indicate that they increase response rates in prostate cancer and NSCLC (Scher et al., 2011). Disappointingly, negative results were also obtained in a phase III trial on patients with prostate cancer receiving high-dose calcitriol plus docetaxel. It was revealed that patients taking a combination of high-dose calcitriol and docetaxel lived less than patients receiving docetaxel alone (Muindi et al., 2009). In another study, when calcitriol was given in combination with gefitinib and dexamethasone, it did not show any effect in advanced solid tumors (Jain et al., 2011). Gross published results as yet manifest deficient antitumor activity and probable toxicities with high doses of calcitriol and related compounds. Due to these reasons, the extensive use of vitamin D or its derivatives, when given alone or in combination with standard treatments, should be discouraged, and further studies are needed (Tsai et al., 2016).

3.8. Quercetin

Quercetin, a dietary flavonoid obtained from various vegetables and fruits, is a dynamic anticancer agent that shows anticancer activity through the regulation of several signaling pathways. It also causes leukemogenic rearrangements by altering responses due to DNA damage via inhibition of the PI3K and Topo II pathways. Through several studies conducted on quercetin, it was concluded that quercetin can prevent epithelial-mesenchymal transition (EMT) via a deduction in the expression of N-cadherin in pancreatic cancer stem cells. However, quercetin was also able to reduce the expression of beta-catenin in cancer stem cells of the pancreas and repress self-renewal capacity. Another study conducted on quercetin demonstrated that quercetin targets cancer stem cells in the pancreas and is responsible for inhibiting proliferation by inducing apoptosis and retarding angiogenesis (Wang et al., 2014).

3.9. Phenethyl isothiocyanate

Several cruciferous vegetables resembling broccoli contain phenethyl isothiocyanate as a major constituent, and this phenethyl isothiocyanate is responsible for interfering with the multiplication of cervical cancer stem cells by increasing the utterance of death receptors 4 and 5 and cPARP (Upadhyaya et al., 2019). Phenethyl isothiocyanate has also been shown to increase stress due to oxidation and repress Sp1 expression in cervical cancer stem cells (Yun et al., 2017). In vivo, phenethyl isothiocyanate has been shown to repress cancer stem cell traits in NCCI embryonic cancerous cells (Koschorke et al., 2019). Phenethyl isothiocyanate has been shown to target the CSC compartment in HER2+ ovarian and breast cancer cells, resulting in hampering cell growth and tumor development (Erdogan et al., 2017).

3.10. Apigenin

Apigenin, which is a dietary flavonoid, is found to inhibit casein kinase 2 cancer cells of the cervical and SKOV3 cancer cells of the ovaries by suppressing the self-renewal capacity of sphere-forming cells (Yang et al., 2018). Erdogan et al. (2017) revealed in their study

that apigenin has been shown to inhibit prostate cancer stem cell migration and survival via the PI3K/Akt/NF- κ B signaling pathway. Furthermore, in CD44+ cancer stem cells of the prostate, apigenin has been shown to increase the sensitivity of cisplatin (Erdogan et al., 2017; Li et al., 2018). Li et al. (2018) established in their study that in TNBC cells, apigenin can induce the activation of YAP and TAZ activity, resulting in a reduction of stem cells in cancer.

3.11. Sulforaphane

Sulforaphane, a dietary compound found in cruciferous vegetables like broccoli, cauliflower, etc., targets stem cells of cancer in a range of human cancers to act as a chemoprotective agent. Sulforaphane was found to suppress cancer stem cells of the breast in a study conducted by Castro et al. (2019) by decreasing the quantity and size of mammospheres by downregulating the Wnt/beta-catenin pathway. The study of Li et al. (2013) revealed that sulforaphane helps restore miR-140 expression, minimize ALDH1 and SOX9 expression, and thus inhibit cancer stem cell formation in breast cancer.

3.12. Soy isoflavone

Soybean is a rich source of soy isoflavones, including lunasin, genistein, daidzein, and glycitein. In a study, it was demonstrated that isoflavone can modulate several signaling pathways like nuclear factor- κ B (NF- κ B) and Notch, etc., resulting in angiogenesis and metastasis (Sahin et al., 2019). Since most cases of breast cancer is hormone receptor-positive and soy isoflavones have anti-estrogenic attributes, Douglas et al. (2013) found that soy isoflavones can be utilized to treat breast cancer. In their study, Zhou et al. (2021) demonstrated that soy isoflavone genistein inhibits the arsenic-induced expression of HER2 phosphorylation, suppressing HER2 targets including ERK, STAT3, and AKT signaling pathways, and causing a reduction in the expression of the cancer stem cell marker CD44 in bladder epithelial cells.

3.13. Ellagic acid

Ellagic acid is a polyphenolic compound present in numerous seeds, nuts, and fruits, including black raspberries, strawberries, pomegranates, walnuts, raspberries, and almonds. Studies conducted by Nasri et al. (2014) have shown the chemoprotective effect of ellagic acid. Some studies conducted earlier also demonstrated that ellagic acid possesses anti-apoptotic, chemoprotective, and antineoplastic properties, due to which it can be further studied for different disorders, particularly cancer cell systems. Curcumin and ellagic acid in combination showed stronger antitumor effects than either compound alone. Additionally, it has been demonstrated that p53, a crucial apoptosis promoter, is restored to expression and function by both curcumin and ellagic acid (Kumar et al., 2016).

3.14. Withaferin-A

A steroidal lactone, withaferin-A, obtained from *Withania somnifera*, has been shown to reduce breast CSC fraction and mammosphere formation in SUM159 and MCF-7 breast cancer cells (Kim & Singh, 2014). Moreover, withaferin A also inhibits the fraction of cancer stem cells in breast tissue by suppressing FoxQ1 (Kim et al., 2021). In cancer cells of the pancreas, withaferin A was found to suppress the activity of the stem cell marker Nestin (Su et al., 2013). In a study conducted by Kakar et al. (2014), it was demonstrated that in ovarian cancer, withaferin A eliminates cancer

stem cells, resulting in suppression of growth and metastasis due to the downregulation of Notch-1, Hes-1, and Hey-1.

3.15. Resveratrol

It is a natural polyphenol derived from peanuts, red wine, pistachios, grapes, blueberries, cranberries, etc. It shows various anti-cancer effects by targeting cancer stem cells in different types of cancer. Through several studies conducted earlier, it was revealed that resveratrol can modulate DNA methylation in several genes involved in cancer. In a current study, resveratrol was found to restore the hypermethylated and hypomethylated states in oncogenic genes (Shin et al., 2020).

3.16. Eugenol

Eugenol, a natural compound present in various crude drugs like clove, cinnamon, etc., may act as a pro-oxidant and thus help in demolishing tumor cells. It is believed that eugenol acts by arresting the S-phase of the cell cycle, causing a reduction in inflammatory cytokine levels, which triggers apoptosis (Fangjun & Zhijia, 2018; Fathy et al., 2019). Pisano et al. (2007) demonstrated the antiproliferative activity of biphenyl (S)-6,60-dibromodehydrodieugenol via induction of apoptosis in their study. In the study conducted earlier by Hussain et al. (2011), it was revealed that eugenol inhibited cell proliferation when taken alone, however, when taken in combination with gemcitabine, it boosted treatment efficiency against HeLa cells, a human-derived cervical tumor cell line.

3.17. Garlic

Significant cancer cell-killing effects of garlic have been demonstrated through various in vitro studies (Charron et al., 2015). Phytoconstituents obtained from garlic have been shown to inhibit cancer at different stages by altering the activity of the epidermal growth factor receptor, protein kinase C, nitric oxide synthetase, nuclear factor-B, cell cycle, and peroxidation of lipids (Mondal et al., 2022). Preclinical studies provided several confirmations regarding the suppressing effects of garlic on different types of cancers, including pancreatic, gastric, colorectal, oral, breast, prostate, ovarian, and bone cancers. Various clinical studies supporting the therapeutic anticancer effects of garlic are also available (Charron et al., 2015; Khanum et al., 2004).

3.18. Sanguinarine

A natural agent, sanguinarine, obtained from the roots of *Sanguinaria canadensis*, was shown to be effective against lung CSCs (Prabhu et al., 2021). According to a different study, sanguinarine altered the characteristics of pancreatic CSCs by obstructing the Shh/Gli/Nanog pathway and elevating oxidative stress (Ma et al., 2017).

3.19. Caffeic acid

Caffeic acid is found to be effective as a potent anticancerous compound in treating various types of cancer in humans. Mechanisms involved in inducing therapeutic effects of caffeic acid include suppression of MMP-2 and -9, inhibition of NF-B, AP-1, etc. Several in vitro and in vivo examinations conducted previously indicate the role of caffeic acid as an anticancer agent (Alam et al., 2022; Tyszka-Czochara et al., 2017). Earlier studies conducted on caffeic acid revealed that it acts by normalizing the enhancement of reactive oxygen species levels and by altering mitochondrial

membrane potential in ME-180 and HeLa cancer cells (Kanimozi & Prasad, 2015).

3.20. Curcumin

An essential secondary metabolite of turmeric called curcumin has been extensively researched for its ability to fight cancer. Numerous molecular targets have been investigated to comprehend the basic mechanisms by which curcumin causes cell death in CRC (Ismail et al., 2019). According to earlier studies, mechanisms leading to apoptosis disruption are changes in the cytokines that regulate apoptosis (Guo et al., 2013). Findings from numerous studies revealed that curcumin can suppress the cell proliferation cycle and induce apoptosis to stop the growth and spread of malignancies or diminish their size (Duvoix et al., 2005; Prasad et al., 2014).

3.21. Oleuropein

Oleuropein, a polyphenolic compound obtained from the olive plant, is protective against cancer. Hamadi and Castellon (2005), through their study, concluded that oleuropein irreversibly bounds cancer cells and prevents motility due to cancerous transformation. Numerous studies have demonstrated oleuropein's efficacy against certain breast cancer cell lines. Sirianni et al. (2010) demonstrated, through their study, the role of oleuropein in inhibiting estradiol-dependent activation of extracellular managed kinase.

3.22. Acetylpoaranotin

Acetylpoaranotin, which is isolated from marine *Aspergillus* species, is a diketopiperazine disulfide. Different apoptotic assays confirm that in human colon cancer cells (HCT116), acetylpoaranotin can induce apoptosis. This compound is also found to inhibit tumor growth in vivo (Kuppasamy et al., 2014). Choi et al. (2011), through their study of the HCT 116 colon cancer cell line, demonstrated the molecular role of diketopiperazine disulfides in apoptosis.

3.23. Omega-3 fatty acids

Supplementation of "omega-3", a polyunsaturated fatty acid, has shown a reduction in the risk of tumor growth and metastasis. Both docosahexaenoic acid and eicosapentaenoic acid are effective against colon and breast cancer (Cockbain et al., 2012). The potential therapeutic value of fish oil supplements in the treatment of colon cancer has been assessed in several clinical investigations. These omega-3 fatty acids obtained from fish oil supplements are found to enhance apoptosis in cancer cells. In an earlier study conducted by Fasano and Uzzau (1997), it was demonstrated that these omega-3 fatty acids are effective in the initial stage of colon cancer. Omega-3 fatty acids diminish the proliferation of colonic cancer cells in the early stages of cancer and may help protect individuals from high-risk colon cancer.

3.24. Astaxanthin

Astaxanthin is a secondary metabolite produced by the single-celled green algae *Haematococcus pluvialis* and other marine animals. Astaxanthin is widely used to control colon ulcers (Yang et al., 2013). Prabhu et al. (2009) concluded from their study that astaxanthin markedly reduces colon carcinogenesis induced by 1,2-dimethylhydrazine. It shows a superior chemopreventive effect on cell proliferation and lipid peroxidation and eventually results in a reduction of histological lesions in a rat model.

3.25. Siphonaxanthin

Marine green alga *Codium fragile* is the main source of siphonaxanthin, which leads to apoptosis in human leukemia and colon cells (Ganesan et al., 2011). It is shown to suppress the proliferation of endothelial cells and have significant anti-cancerous activity by suppressing endothelial cell proliferation and HUVEC tube formation. In their study, Ganesan et al. (2010) revealed that siphonaxanthin causes caspase-3 activation and therefore induces apoptosis in HL-60 cells.

3.26. Pterostilbene

Pterostilbene is a stilbenoid phytochemical that structurally and biologically resembles resveratrol (Estrela et al., 2013). Additionally, its effectiveness in inhibiting the growth of colon cancer cells in humans is greater than that of resveratrol (Chiou et al., 2011). While results from the animal studies conducted on pterostilbene revealed that it inhibits the growth of breast and pancreatic cancer in xenotransplanted nude mice (Pan et al., 2014), pterostilbene may be utilized in the prevention and treatment of several forms of human cancer, according to in vitro and in vivo research (Wakimoto et al., 2017).

3.27. Luteolin

Luteolin is a flavonoid present in various plants, including herbs, vegetables, and fruits. It can be used in the treatment of many forms of human malignancies, including lung, prostate, colon, breast, and pancreatic cancers. Innumerable in vitro and in vivo investigations revealed that luteolin inhibits the growth of tumor cells, provides defense against cancer-causing agents, pauses the cell cycle, and instigates apoptosis via a variety of signaling pathways. Furthermore, luteolin has been shown to increase intracellular reactive oxygen species (ROS) levels in glioblastoma cells by causing dysfunction of mitochondria and a deadly stress response in the endoplasmic reticulum (Imran et al., 2019).

4. Conclusions

It is well known that synthetic anticancer drugs possess limited therapeutic activity. The current review emphasizes the potential of nutraceuticals, which are widely available in a diversity of vegetables, fruits, foods, and minerals and can be taken in addition to conventional treatment with anticancerous drugs for enhancing responses and adherence in cancer patients. It is well known that synthetic anticancer drugs possess limited therapeutic activity due to resistance, and these drugs are also well known for their serious side effects. However, given the lack of information on the bioavailability of natural compounds, more research and clinical trials are required to fully comprehend the actual value of nutraceuticals in the prevention and treatment of various cancers. But as we have little information about the bioavailability of natural compounds, further studies, and clinical trials are necessary to understand the factual value of nutraceuticals in the deterrence and management of different types of cancer.

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The authors confirm that there are no known conflicts of interest.

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Supplementary File

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