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FREE RADICALS MEDICINE (X SHI, SECTION EDITOR)

Oxidative Stress: a Promising Target for Chemoprevention

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Abstract Cancer is a leading cause of death worldwide, and treating advanced stages of cancer remains clinically challenging. Epidemiological studies have shown that oxidants and free radicals induced DNA damage is one of the predominant causative factors for cancer pathogenesis. Hence, oxidants are attractive targets for chemoprevention as well as therapy. Dietary agents are known to exert an antioxidant property which is one of the most efficient preventive strategy in cancer progression. In this article, we highlight dietary agents can potentially target oxidative stress, in turn delaying, preventing, or treating cancer development. Some of these agents are currently in use in basic research, while some have been launched successfully into clinical trials.

Keywords Natural compounds · Anti-oxidants · Prevention · Cancer

Introduction

Despite great advancements in understanding the etiology and the molecular mechanisms underlying disease progression, cancer remains a leading cause of death worldwide and in the USA. Oxidative stress is a predominant causative factor in cancer development. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS), referred to as oxidants, are generated as byproducts of oxygen and nitrogen metabolism, respectively, in various normal metabolic pathways [1]. Production of oxidants in normal cells are tightly governed by enzymes in a controlled manner regulating several signaling pathways and functions including cell division, inflammation, immune autophagy, and stress response [2]. Any imbalance between free radicals (ROS, RNS) and antioxidants is the underlying basis of oxidative stress.

Dietary agents and supplements are major sources of antioxidants and are solely aimed at protecting aerobic organisms from the toxic effects of free radicals and oxidants. Antioxidants neutralize oxidative stress, either enzymatically (vitamins C or E or β-carotene) or non-enzymatically (superoxide dismutase [SOD], catalase [CAT], or glutathione peroxidase) to protect the organelles. Several epidemiological studies have demonstrated that changes in lifestyle and dietary habits could prevent or reduce cancer incidence [3]. Therefore, this review article aims to highlight the potential roles of dietary agents exerting antioxidant properties that may impede cancer progression (Fig. 1).

Molecular Function of Oxidative Stress

Carcinogenesis is a process that includes transforming a normal cell into a cancerous cell. It is a multistep process broadly involving either an aberrant expression of proto-oncogenes or downregulation of tumor suppressor genes. Over decades, studies have shown that cancer cells produce elevated levels of superoxide or H_2O_2, leading to oxidative stress that significantly aids in the transformation of healthy cells to tumor cells. The molecular pathways involved in an oxidative response include PI3K/AKT, PKC, STATs, AP-1, Ras/Raf/MAP kinase, ERK, NF-κB, Nrf2, VEGF, and JNK signaling by regulating cell-cycle progression, survival, invasion, and metastasis of cancer cells (Table 1). These studies not only highlight the significance of ROS and free radicals in regulating cancer, but also delineate how ROS is targeted through various dietary agents.

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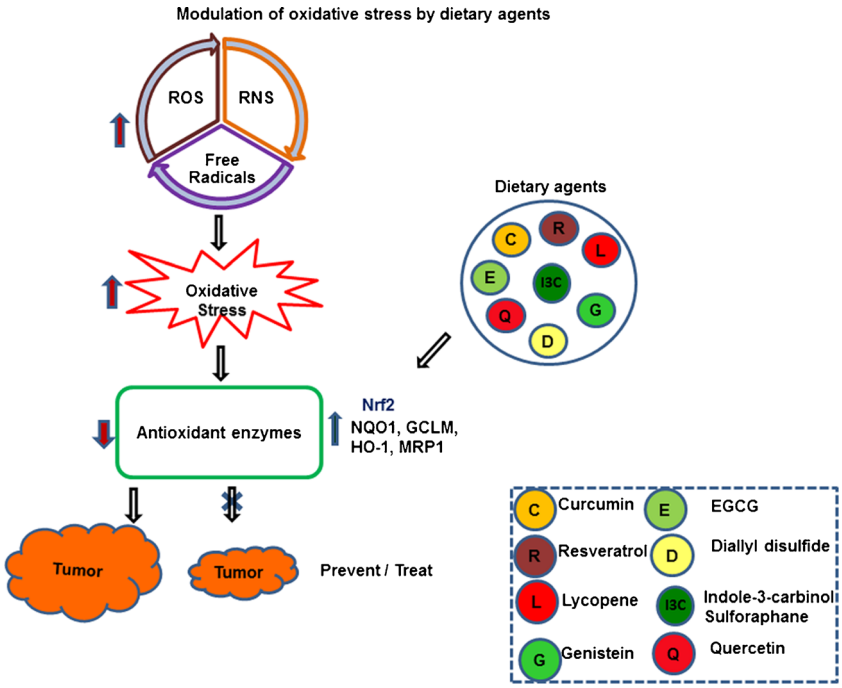

Fig. 1 Modulation of oxidative stress by dietary agents. Oxidative stress induced by increased ROS, RNS, or free radicals reduces antioxidant production, thus triggering tumor growth. Activation of antioxidants (Nrf2, NQO1, GCLM, HO-1, and MRP1) by dietary agents inhibits oxidative stress, impeding cancer progression

Dietary Agents and Anticancer Effects

It has been evidently proved beyond doubt that foods and dietary supplements are powerful sources of antioxidants and that regular consumption of both fruits and vegetables can either prevent or reduce cancer risk. Over decades, research has highlighted a promising approach in cancer research by tapping the enormous potential of many herbal sources of antioxidants in combating oxidative stress, thus targeting cancer.

Curcumin

The well-known pleiotropic effect of curcumin with curcuminoid, the yellow pigment (turmeric), has been well documented for its traditional medicinal properties against various human ailments in both Chinese and Indian systems of medicine since ancient times. As a naturally occurring polyphenol isolated from the rhizome of *Curcuma longa*, curcumin (turmeric) has gained popularity because of its safety, low cost, and abundance. Approved by the US Food and Drug Administration (FDA), studies have shown that consumption of curcumin is safe, even at higher doses, with no toxicity in animals [4] or humans [5]. The exceptional therapeutic potential of curcumin as an anti-inflammatory, antioxidant, hypoglycemic, anti-angiogenic, pro-apoptotic, and anticancer agent has been extensively studied. As an anti-inflammatory agent, it inhibits production of NO and COX-2 as well as NF-kB activation [6, 7]. It also scavenges ROS and decreases specificity protein transcription factors by targeting microRNAs [8]. The possible therapeutic effects of curcumin on several diseases are mainly associated with

Table 1 Dietary compounds and major molecular targets

Dietary compound(s)	Molecular targets
Curcumin	NO, COX-2, NK-kB, MAPK, PI3K/AKT/Fox01/BRCA-1, H2AFX and PARP-1, hsp, Nrf2
Resveratrol	NF-κB/Wnt/β-catenin, Nrf2
Lycopene	IGBPs/PDGF/VEGF PI3K/AKT/PKB, Ras/Raf/MAP, cyclin D, c-myc Bcl-2, Bcl-XL, ERK/AKT, NF-κB, Nrf2
Epigallocatechin-3-gallate	Caspase activation, Bcl-2; NF-κB MAPK/TGF-β /EGFR/JAK/STAT; PI3K/AKT, Wnt/Notch, Nrf2
Quercetin	p53/ras protein/estrogen receptor/NF-κB, EGFR/PI3K/AKT/MAPKs; TRPM7, Nrf2
Diallyl disulfide	MAPKs and NF-κB/PI3K/AKT; p53/p21 and MEK-ERK, Nrf2
Genistein	NF-κB, VEGF, PDGF, EGF, IGF, JNK1, ERK/PI3K/AKT, Nrf2
Indole-3-carbinol and sulforaphane	Nrf2/ARE/Wnt/β-catenin

inhibition of oxidative stress and its downstream mediators. Several studies have evidently shown that curcumin inhibits free radical formation [9], lipid peroxidation [10], DNA damage [11], and damage to cytochrome p450, but induces glutathione-S-transferase [12].

It is well documented that curcumin's anticancer properties make it feasible in preclinical trials to modulate multiple cell-signaling pathways through mitigation or prevention of many different types of cancers, including multiple myeloma, colorectal, pancreatic, breast, prostate, lung, head & neck, in both animal models and humans [13]. In lung cancer, curcumin induces apoptosis accompanied by changes in intracellular oxidative stress-related enzymes and also by phosphorylation and activation of the mitogen-activated protein kinase signaling pathway factors c-Jun N-terminal kinase, p38, and extracellular signal-regulated kinase [14]. In pancreatic B cells, curcumin attenuates palmitate-induced apoptosis through PI3K/AKT/Fox01 and mitochondrial survival pathways [15]. A decrease in ROS with a concomitant increase in various antioxidant and DNA repair genes, such as BRCA-1, H2AFX, and PARP-1, were observed after curcumin treatment [9]. Studies have also shown that curcumin downregulates heat shock proteins and histone deacetylation in tumor cells under oxidative stress. It also induces apoptosis by modulating apoptosis-related proteins and also arrests the cell cycle by inhibiting tumor markers [16].

An approximate daily intake of 60–100 mg of curcumin in adults has been reported in the Indian diet [17]. Based on dietary intake, dosages as high as 12 g/day during the first 3 months of treatment are in phase I, II, and III clinical trials [18]. In several studies using curcumin on multiple molecular targets, it has been demonstrated that cancer therapy is limited because of curcumin's poor stability and bio-availability resulting from its increased oxidative degradation. However, a recent study has clearly shown that an encapsulation of curcumin as a redox nanoparticle rapidly scavenges the free radicals and ROS by overcoming the oxidative degradation, thus making it more potential than curcumin alone in cancer therapy [19].

Resveratrol

Phytoestrogens are phenolic compounds that are naturally occurring bioactive food components with diverse chemopreventive properties including antioxidant and angiogenic activities [20, 21]. Of the various classes of phytoestrogens, resveratrol (trans-3,4′,5-trihydroxystilbene), found in varying concentrations in many plants such as grapes, berries, and nuts, has evidently showed that it interferes at all the three stages of carcinogenesis (initiation, promotion, and progression). As a potent antioxidant, it plays a crucial role by regulating several antioxidant enzymes, including glutathione peroxidase, glutathione–*S*-transferase, and glutathione reductase [22]. It also prevents low density lipoprotein oxidation [23] and inhibits platelet aggregation [24].

While the effects of resveratrol on cancer are at this time uncertain, numerous studies have clearly highlighted its beneficial effects, such as cardiovascular and cancer preventive properties. In vitro findings in several labs have shown its anticancer effects in breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer as well as leukemia [25]. Activation of NF-κB due to changes in cytokine and ROS levels in various diseases, including cancer, has been decreased by resveratrol [26]. The anticancer properties of resveratrol include apoptotic induction by modulating the levels of Fas and FasL [27], reducing surviving expressions of both of these and Wnt/β-catenin signaling pathways [28], and inhibiting angiogenesis [29]. Resveratrol's antioxidant activity prevents tumor formation resulting from DNA damage [30].

As a chemopreventive agent, resveratrol has a dual role; it is anti-apoptotic and pro-apoptotic, and these diverse health benefits are enabled in a dose-dependent manner. Low doses maintain protection from various types of diseases; however, higher doses have been shown to inhibit tumor growth [31]. It is rapidly absorbed and metabolized and is safe in long-term administration against several pathological conditions. Although many studies have highlighted the potential therapeutic effects of resveratrol on various diseases, including cancer, whether it targets both survival and apoptotic signaling pathways needs to be ascertained through clinical trials.

Lycopene

Lycopene is a naturally occurring carotenoid that gives red color to fruits and vegetables. Predominantly rich in tomatoes (0.9 to 92.7 mg/100 g) and tomato-based products (51 to 59.7 mg/100 g), more than 80 % of total lycopene intake in the Western diet is through these sources.

Lycopene possesses significant antioxidant activity by quenching and inactivating the ROS [32]. Studies have shown that it prevents and reduces the risk of heart disease and several cancers including lung and prostate cancer [33, 34]. Both lycopene and its indirect effects play beneficial roles in preventing oxidative reactions that arise from the formation of nitrosamines [35]. It potentially targets the mechanisms involved in cell cycle arrest and apoptotic induction by abolishing growth factor receptor signaling pathways [36]. Studies have shown that it inhibits cancer cell growth by inhibiting ROS and by decreasing ERK expression [37].

A clinical trial involving a large population of prostate cancer patients undergoing radical prostatectomy with 4.2 years follow-up with lycopene supplementation have shown significantly smaller tumors [38]. Antioxidant properties and other signaling mechanisms of lycopene are primarily responsible for its therapeutic effects, targeting growth factors,

signaling pathways, antioxidant response element (ARE) regulation, cell cycles, apoptosis, cell invasion, and metastasis [39]. Findings on ethanolic extract of lycopene have shown that it triggers induction of phase II detoxification enzymes by activating ARE and its transcription factor nuclear factor E_2-related factor 2, thus enhancing its anti-tumorigenic effect [40].

Lycopene exerts its effects by regulating several growth factors and signaling pathways, including reduction of IGF-1 levels with enhanced IGBPs (breast, lung, colorectal, and prostate cancers) [41], PDGF [42], and VEGF [43]. At attainable concentrations, it modulates cancer progression by downregulating PI3K/AKT, and PKB and the kinase metabolic pathways of Ras, Raf, and MAP. It also targets the subsequent expression of genes involved in cell proliferation (cyclin D, Bcl-2, and Bcl-XL), cell cycles, apoptosis [44, 45], inflammation, angiogenesis, invasion, and metastasis [39]. Cell cycle progression is arrested by lycopene at phases G_0/G_1 and S by decreasing the expression of cyclin D and c-myc [46].

Many preclinical epidemiological studies have shown that lycopene at physiological concentrations arrests cell proliferation in gastric (ERK pathway), colon (AKT signaling), breast, and prostate (NF-κB) cancers [37], but further clinical trials are needed to explore all its potential therapeutic roles. Because of its free radical scavenging property, lycopene has been proven beyond doubt to be a natural potential antioxidant compound. Moreover, its multi-targeting effects allow it to remain a promising dietary agent for cancer therapy, attracting scientists for extensive research.

Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG), a polyphenol in green tea (*Camellia sinensis*) popularly consumed as a health-promoting beverage around the world, is another significant phytochemical. As a powerful antioxidant, anti-inflammatory, and anti-proliferative compound, it is the most potent of all catechins.

In recent years, the potential effects of green tea have been intensively studied in animal models, in vitro, and in human studies against many pathological conditions. Induction of antioxidant enzymes and phase II metabolism by ECGC has been highlighted in both animal and human models [47]. To a greater extent, it can inhibit tumorigenesis in the stomach, lungs, liver, breast, and colon during all three stages of cancer through multiple signaling pathways. The compound ginseng, found in green tea, has a synergistic effect with anticancer drugs in arresting colon cancer cell proliferation. These polyphenols inhibit cancer cell survival via several growth factor receptors. It has been shown that ECGC induces apoptosis via ROS-dependent mechanism [5] and caspase activation with altered Bcl-2 family member expression, decreasing NF-κB kinase activity and therefore reducing nitric oxide production along with up- or downregulation of a number of enzymes involved in MAPK, oncogenes, and tumor suppressor genes [48]. Enhanced expression of the genes responsible for TGF-β signaling, mediated by ROS, was evident following EGCG treatment [47]. Furthermore, several studies have proven that it also inhibits tumor growth mediated by multi-signaling pathways—EGFR, JNK, STAT, PI3K/AKT, Wnt, or Notch [49].

Studies emanating from various groups have highlighted that to a greater extent, ECGC prevents metastatic properties in various cancers, such as skin, prostate, liver, lung, breast, pancreatic, and other cancers; however, further studies will elucidate the protective effects of green tea against cancer metastasis [50]. A few clinical trials have also clearly demonstrated the anti-tumorigenic property of ECGC, showing delayed cancer onset followed by lower recurrence rates in breast cancer patients (stages I and II) [51]. The efficacy of green tea extracts, both in ointment and capsule forms, has further confirmed that ECGC is effective in treating cervical lesions, a beneficial therapy for HPV patients [52]. These results clearly highlight that ECGC, used either alone or in synergistic treatment with other chemotherapy drugs, has greater potential in cancer prevention and therapy, and it also explains its demanding roles in both phase II and III clinical trials.

Quercetin

Of the known bioflavonoids, quercetin (3,3′,4′,5,7-pentahydroxyflavone) has gained interest in research because of its several potential health effects as an anti-inflammatory, immune-modulator, anti-atherogenic, antioxidant, anti-hypertensive, and anti-toxic [53, 54]. Major plant sources of the flavonoid, a brilliant citron yellow pigment, include red onions, tomatoes (organic), honey, fruits, and leafy vegetables [54] with an average daily intake of 30 mg in Western countries [55]. Various effects of quercetin in the presence of low and high levels of reduced GSH have been clearly demonstrated to possess both antioxidant (low) and pro-oxidant (high) properties [56].

Quercetin, either alone or in combination, has significant anticancer effects by inducing cell death through apoptosis in leukemia, lung, hepatoma, oral, and colon cancer cell lines [57–62], inducing the apoptotic pathway, downregulating mutant p53, inhibiting the ras protein, and targeting estrogen receptor binding capacity [54]. The molecular mechanisms by which it exerts its therapeutic effects include inhibition of NF-κB [63] and EGFR [64], thus modulating the downstream PI3K/AKT pathway. Apoptotic induction is also evinced by the action of quercetin inhibiting MAPKs and transient receptor potential melastatin 7 (TRPM7) channels in gastric tumors [65] and regulating Bcl-2 and Bax in breast cancers [66]. A recent study has revealed that it also reverses tamoxifen resistance in breast cancer cells [67]. Another important mechanism is its ability to modulate estrogen receptors, thus

inducing apoptosis, which is ERα-dependent. Furthermore, it renders a protective dual role against E2-related cancers, especially in ERα- and ERβ-expressing organs [68].

As a well-known therapeutic dietary agent, quercetin also regulates cell cycle progression, targeting several factors, including p21, cyclin B, p27, CDK, and topoisomerase II, thus inducing cell cycle arrest either at the G_2/M or G_1/S stages or a location specific to tumor origin [69]. Recent studies have evidently shown that it reduces the production of hyperalgesic cytokines and oxidative stress and also activates the opioid-dependent analgesic pathway, thus making it a most relevant therapeutic option in treating cancer-associated pain [70]. However, further investigation is recommended. Its poor solubility in water is a hurdle which is improvised by combining it with either (polyethylene glycol) [71] or sulfobutyl ether-7beta-cyclodextrin, augmenting its anticancer effects. The above mentioned beneficial effects of quercetin makes it a potential cancer therapy.

Diallyl Disulfide

Diallyl disulfide (DADS; 4,5-dithia-1,7-octadiene), is a major organosulphur compound present in garlic and few allium plants. Recent studies have shown that the natural compound, allicin, has significant anti-mitotic effects both in vivo [72] and in vitro [73]. It has been shown that DADS scavenges free radicals and oxidants by stimulating the activities of GPX, glutathione reductase, and SOD [74].

Diallyl disulfide prevents hemorrhagic cystitis by inhibiting oxidative damage and the MAPKs and NF-κB pathways [75]. Possible protective antioxidant mechanisms are explained by various authors and include activation of Nrf2 pathways by inhibition of NF-κB activation, thus preventing hepatotoxicity [76]. Koh et al. reported the dose-dependent role of DADS on PC-12 cells, resulting in a neuroprotective effect at lower concentrations by activating PI3K and AKT and inhibiting GSK-3 activation, cytochrome-c release, caspase 3 activities, and PARP cleavage while it is cytotoxic at higher concentrations [77].

As an effective anticancer agent, DADS inhibits growth and the metastatic potentials of various cancers, such as breast, gastric, leukemia, esophageal, squamous cell carcinoma, prostate, colorectal adenoma, uterine, lung, and skin cancers [78–80]. Epidemiologic studies have undoubtedly shown that the frequency of contracting gastric cancer is significantly reduced with increased consumption of garlic [81]. Studies have also shown that it reduces PSA, a well-known prostate cancer biomarker [82]. Induction of apoptosis is related to the anti-proliferative effect of DADS mediated through the signaling pathways of EGFR, ERK, and PKM2 [49], p53, p21, and MEK-ERK [62], and also by inducing cell cycle arrest.

These studies clearly show the multi-tasking effect of these organosulfur compounds. DADS as a potent thearapeutic agent, modulates the cellular redox state, detoxifies carcinogens, inducing cell cycle arrest, apoptosis and inhibit angiogenesis with minimal toxic effects on healthy cells. Most in vivo and in vitro studies have used this compound at higher concentrations; therefore, the feasibility of using such high concentrations in human clinical trials needs to be reviewed before it can be used for prevention or treatment of cancer.

Genistein

The predominant food sources of the phytoestrogens genistein and daidzein are soybeans and their by-products, lupin, chick peas, and other legumes. Present as β-glucoside, genistein is an isoflavone that exhibits antioxidant, anti-proliferative, and anti-carcinogenic properties, and it is more potent than daidzein. The antioxidant and anticancer effects as well as other pharmacological properties of genistein are brought about by free genistein aglycone, found after digestion of the glycosylated form of genistein in the small intestine [83]. As a potent antioxidant, genistein induces the antioxidant enzymes such as glutathione peroxidase, SOD, and glutathione reductase, which ehances the free radicals scanvenging and decreases lipid peroixiation [84].

Several studies have clearly proven the differential effect of genistein as an estrogenic and anti-estrogenic, attributing to the treatment of hormone-related cancers [85]. The average daily dietary intake of isoflavones are comparatively lower in Western countries (2 mg) than in Asian countries (25–50 mg) [86, 87], a causative factor of disparity observed in the frequency of breast and prostate cancers. Soybeans modulate carcinogenesis by targeting tumor initiation, proliferation, and progression. Genistein augments its anticancer properties through downregulating several molecular pathways—NF-kB, VEGF, PDGF, EGF, IGF, JNK1, ERK/PI3K/AKT [88]. In vivo and in vitro studies have proven the efficacy and synergistic effects of genistein in inhibiting cell proliferation and inducing apoptosis in liver, lung, colon, and prostate cancers [89–92]. Based on epidemiological data, the role of isoflavone in gastric cancer is debatable because schools of thought differ [77, 93]. The paradoxical effect of genistein is that it has an anti-tumorigenic effect at higher concentrations (>10 uM) in both estrogen receptor-positive and -negative breast cancer cells; however, at lower concentrations, it stimulates the proliferation of ER-positive breast cancer cell lines [94].

As a FDA-approved drug and in phase I and II trials for the treatment of metastatic colorectal cancer, genistein has gained more importance [95]. Although variations occur between the

epidemiologic in vitro and in vivo studies, more research and additional clinical trials are required to validate genistein as a potent anticancer drug. Nonetheless, it has thus far been shown to exert chemo-preventive effects and therefore is a promising anticancer agent.

Indole-3-Carbinol and Sulforaphane

Another natural compound, predominantly found in members of the Brassica genus (cabbage, radishes, cauliflower, broccoli, sprouts, and daikon), is glucosinolate. After consumption of glucosinolate, the active organosulfur compounds indole-3-carbinol (I3C) and sulforaphane, which possess anticancer properties, are formed. Both the phytochemicals have potent antioxidant, anti-carcinogenic, and anti-atherogenic properties; however, they increased the expression of genes encoding antioxidant enzymes (CAT, SOD, GR, and GPX) in hepatoma cells through Nrf2 and ARE signaling pathways [96]. Findings have also shown that the anti-tumorigenic effect of I3C is partly achieved by one of its major byproducts, diindolylmethane, which acts as an anti-angiogenic, inducing cell death.

Highlighting the anti-tumorigenic properties, both in vivo and in vitro studies have showed that I3C arrests the G_1 cell cycle and inhibits the growth of breast cancer cells through degradation of Cdc25A [97]. Numerous in vitro, in vivo, and human studies have shown its targeted ability to suppress cell proliferation in various cancer models (breast [98], prostate [99], colon [100], lung [101], and leukemia [102]). However, most therapeutic studies reveal that I3C is more potent for hormonal-dependent cancers such as breast and cervical cancer under in vivo conditions. Further studies have shown sulforaphane as a potent inducer of phase II detoxication enzymes [103], and I3C reversed the cytotoxic effect of dexamethasone by blocking ROS overproduction and Nrf2 expression enhancement [104]. Sulforaphane also has a therapeutic role in neurodegenerative disorders other than cancer (Wnt and β-catenin).

This clearly underscores the potential use of these organosulfur compounds as therapeutic agents against cancer and other diseases mediated through suppression of free radical production, induction of apoptosis, and regulation of various signaling pathways.

Conclusion

Studies have clearly shown that both lifestyle and types of dietary intake have a significant influence on preventing the cancer incidence by activating anti-inflammatory pathways. The rapid increase in cancer research over the decades has shed some light on identifying and targeting the molecular pathways in cancer treatment. With the availability of many therapeutic methods aiming toward cancer treatment, chemoprevention by potent dietary agents is of greater significance as it targets many signaling pathways. The studies highlight the importance of antioxidants as one of the potential tool in cancer prevention and treatment by scavenging the effects of free radicals and oxidants. Treatment with these dietary agents rich in antioxidants, either alone or in combination, focuses the beneficial effects of inhibiting cell proliferation, survival, invasion, and metastasis and inducing apoptosis. It may be noteworthy, that this article emphasizes only some of the predominant dietary compounds, although there are still a larger number compounds that are being explored. However, because of the differential effects of some of these compounds, further exploration is needed. It is highly imperative to have a better understanding of the possible roles of these compounds so that they can be used in safe and effective cancer therapies. Nevertheless, consumption of dietary agents and their byproducts can help prevent cancer.

AKT/PKC, Protein kinase C; AP-1, Activator Protein 1; ARE, Antioxidant response element; Bax, BCL2-associated X protein; Bcl-2, B cell lymphoma 2; Bcl-xl, B cell lymphoma-extra-large; BRCA-1, Breast cancer 1; CAT, Catalase; Cdc25A, Cell Division Cycle 25A; CDK, Cyclin-dependent kinase; COX-2, Cyclooxygenase; EGFR, epidermal growth factor receptor; Fas, cell-surface Fas receptor; FasL, Fas ligand; Fox01, Forkhead box protein O1; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, Glutathione; GSK-3, Glycogen Synthase Kinase 3; H2AFX, H2A histone family; IGBP, IGF binding protein; IGF-1, Insulin-like Growth Factor-1; JNK, Janus kinase; NF-κB, Nuclear factor-kappa B; NO, Nitric oxide; Nrf-2, Nuclear factor erythroid 2 [NF-E2]-related factor 2; PARP-1-, (Poly (ADP-Ribose) Polymerase 1; PDGF, Platelet-derived growth factor; PI3K, Phosphoinositide 3-kinase; PSA, Prostate specific antigen; Ras/Raf/MAP, kinase; ERK, Mitogen-activated protein kinase; SOD, Superoxide dismutase; STATs, Signal transducer and activator of transcription; TGF-β, Transforming growth factor-beta; VEGF, Vascular endothelial growth factor; Wnt, Wingless signaling in Drosophila

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Compliance with Ethical Standards

Conflict of Interest None.

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