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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 anti-oxidant 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.

Introduction

Despite great advancements in understanding the etiology–the molecular mechanisms underlying disease progression, cancer remains a leading cause of death worldwide and in the United States. 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 (Wolfle et al. 2014). Production of oxidants in normal cells are tightly regulated by enzymes in a controlled manner regulating several signaling pathways and functions including cell division, inflammation, immune autophagy, and stress response (Finkel 2011). Any imbalance between free radicals (ROS, RNS) and antioxidants is the underlying basis of oxidative stress.

Dietary agents and supplements are major sources of anti-oxidants and are solely aimed at protecting aerobic organisms from the toxic effects of free radicals and oxidants. Anti-oxidants 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 (Anand et al. 2008). Therefore, this review article aims to highlight the potential roles of dietary agents exerting antioxidant properties that may impede cancer progression (Fig. 1).

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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 down-regulation 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.

Dietary agents and anticancer effects

It has evidently been proven 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 anti-oxidants 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 U.S. Food and Drug Administration (FDA), studies have shown that consumption of curcumin is safe, even at higher doses, with no toxicity in animals (Sridhar et al. 2014) or humans (Lao et al. 2006). The exceptional therapeutic potential of curcumin as an anti-inflammatory, anti-oxidant, hypoglycemic, anti-angiogenic, pro-apoptotic, and anti-cancer agent has been extensively studied. As an anti-inflammatory agent, it inhibits production of NO and COX-2 as well as NF-kB activation (Bhaumik et al. 2000; Surh et al. 2001). It also scavenges ROS and decreases specificity protein transcription factors by targeting microRNAs (Gandhy et al. 2012). The possible therapeutic effects of curcumin on several diseases are mainly associated with inhibition of oxidative stress and its downstream mediators. Several studies have evidently shown that curcumin inhibits free radical formation (Jain et al. 2015), lipid peroxidation (Al-Rubaei et al. 2014), DNA damage (Tokac et al. 2013), and damage to cytochrome p450, but it induces glutathione-S-transferase (Koe et al. 2014).

It is well documented that curcumin's anti-cancer 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 and colorectal, pancreatic, breast, prostate, lung, head, and neck, in both animal models and humans (Devassy et al. 2015). 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 (Yao et al. 2015). In pancreatic B cells, curcumin attenuates palmitate-induced apoptosis through PI3K/AKT/Fox01 and mitochondrial survival pathways (Hao et al. 2015). 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 (Jain et al. 2015). Studies have also shown that curcumin down-regulates 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 (Sarkar et al. 2014).

An approximate daily intake of 60–100 mg of curcumin in adults has been reported in the Indian diet (Tayyem et al. 2006). 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 (Dhillon et al. 2008). 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 (Thangavel et al. 2015).

Resveratrol

Phytoestrogens are phenolic compounds that are naturally occurring bioactive food components with diverse chemopreventive properties including antioxidant and angiogenic activities (Cao et al. 2005; Siddiqui et al. 2015). 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 with all three stages of carcinogenesis (initiation, promotion, and progression). As a potent anti-oxidant, it plays a crucial role by regulating several antioxidant enzymes, including glutathione peroxidase, glutathione–*S*-transferase, and glutathione reductase (Yen et al. 2003). It also prevents low density lipoprotein oxidation (Frankel et al. 1993) and inhibits platelet aggregation (Olas et al. 2001).

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 anti-cancer effects in breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer as well as leukemia (Gali-Muhtasib et al. 2015). Activation of NF-κB due to changes in cytokine and ROS levels in various diseases, including cancer, has been decreased by resveratrol (Feitelson et al. 2015). The anti-cancer properties of resveratrol include apoptotic induction by modulating the levels of Fas and FasL (Gu et al. 2015), reducing surviving expressions of both of these and Wnt/β-catenin signaling pathways (Fukada et al. 2007), and inhibiting angiogenesis (Garvin et al. 2006). It's antioxidant activity prevents tumor formation resulting from DNA damage (Kalra et al. 2008).

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 (Mukherjee et al. 2010). 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/100g) and tomato-based products (51 to 59.7 mg/100g), 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 (Guder et al. 2014). Studies have shown that it prevents and reduces the risk of heart disease and several cancers including lung and prostate cancer (Arab, Steck 2000; Kim, Kim 2015). Both lycopene and its indirect effects play beneficial roles in preventing oxidative reactions that arise from the formation of nitrosamines (Yegin et al. 2015). It potentially targets the mechanisms involved in cell cycle arrest and apoptotic induction by abolishing growth factor receptor signaling pathways (Rao et al. 2006). Studies have shown that it inhibits cancer cell growth by inhibiting ROS and by decreasing ERK expression (Palozza et al. 2010).

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 smaller tumors (Kirsh et al. 2006). 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 (Trejo-Solis et al. 2013). 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 (Ben-Dor et al. 2005).

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) (Giovannucci et al. 1995), PDGF (Chan et al. 2009), and VEGF (Chen et al. 2012). At attainable concentrations, it modulates cancer progression by down-regulating 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 (Kolberg et al. 2015; Rotelli et al. 2015), inflammation, angiogenesis, invasion, and metastasis (Trejo-Solis et al. 2013). 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 (Ono et al. 2015).

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 (Palozza et al. 2010), 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 anti-oxidant 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 anti-oxidant, 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 (Lambert, Elias 2010). 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 anti-cancer drugs in arresting colon cancer cell proliferation. These polyphenols inhibits cancer cell survival via several growth factor receptors. It has been shown that ECGC induces apoptosis via an ROS-dependent mechanism (Lao et al. 2006) 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 down-regulation of a number of enzymes involved in MAPK, oncogenes, and tumor suppressor genes (Beltz et al. 2006). Enhanced expression of the genes responsible for TGF-B signaling, mediated by ROS, was evident following EGCG treatment (Lambert, Elias 2010). Furthermore, several studies have proven that it also inhibits tumor growth mediated by multi-signaling pathways - EGFR, JNK, STAT, PI3K/AKT, Wnt, or Notch (Ma et al. 2014).

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 (Khan, Mukhtar 2010). 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) (Fujiki et al. 1999). 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 (Erdogan 1972). These results clearly highlight that ECGC, used either alone or in synergistic treatment with other chemotherapy drugs, has great 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, immunemodulator, anti-atherogenic, anti-oxidant, anti-hypertensive, and anti-toxic (Boersma et al. 2002; Rani et al. 2015). Major plant sources of the flavonoid, a brilliant citron yellow pigment, include red onions, tomatoes (organic), honey, fruits, and leafy vegetables (Rani et al. 2015). Average daily intake is 30 mg in Western countries (Noroozi et al. 2000). Various effects of quercetin in the presence of low and high levels of reduced GSH has been clearly demonstrated to possess both anti-oxidant (low) and pro-oxidant (high) properties (Robaszkiewicz et al. 2007).

Quercetin, either alone or in combination, has significant anti-cancer effects by inducing cell death through apoptosis in leukemia, lung, hepatoma, oral, and colon cancer cell lines (Atashpour et al. 2015; Lee et al. 2015; Liu et al. 2015; Maurya, Vinayak 2015; Yuan et al. 2015; Refolo et al. 2015), inducing the apoptotic pathway, down-regulating mutant p53, inhibiting the ras protein, and targeting estrogen receptor binding capacity (Rani et al. 2015). The molecular mechanisms by which it exerts its therapeutic effects include inhibition of NF-κB (Zheng et al. 2014) and EGFR (Fridrich et al. 2008), 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 (Kim et al. 2014) and regulating Bcl-2 and Bax in breast cancers (Duo et al. 2012). A recent study has revealed that it also reverses tamoxifen resistance in breast cancer cells (Wang et al. 2015). 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 (Bulzomi et al. 2012).

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 (Gibellini et al. 2011). 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 (Calixto-Campos et al. 2015). However, further investigation is recommended. Its poor solubility in water is a hurdle that is improvised by combining it with either (polyethylene glycol) (Yuan et al. 2006) or sulfobutyl ether-7beta-cyclodextrin, augmenting its anti-cancer effects. These beneficial effects of quercetin make 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* (Milner 2006) and *in vitro*

(Huang et al. 2007). It has been shown that DADS scavenges free radicals and oxidants by stimulating the activities of GPX, glutathione reductase, and SOD (Yin et al. 2014).

Diallyl disulfide prevents hemorrhagic cystitis by inhibiting oxidative damage and the MAPKs and NF-κB pathways (Kim et al. 2015). Possible protective anti-oxidant mechanisms are explained by various authors and include activation of Nrf2 pathways by inhibition of NF-κB activation, thus preventing hepatotoxicity (Lee et al. 2014). 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 (Koh et al. 2005).

As an effective anti-cancer 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 (Lin et al. 2008; Nagaraj et al. 2010; Lu et al. 2004). Epidemiologic studies have undoubtedly shown that the frequency of contracting gastric cancer is significantly reduced with increased consumption of garlic (Yi, Su 2013). Studies have also shown that it reduces PSA, a well-known prostate cancer biomarker (Gunadharini et al. 2006). Induction of apoptosis is related to the anti-proliferative effect of DADS mediated through the signaling pathways of EGFR, ERK, and PKM2 (Ma et al. 2014), p53, p21, and MEK-ERK (Yuan et al. 2015), and also by inducing cell cycle arrest.

These studies clearly show the multi-tasking effect of these organosulfur compounds. Modulating the cellular redox state, detoxify carcinogens, induce cell cycle arrest and apoptosis, and inhibit angiogenesis and cell invasion, underline DADS as a potent therapeutic agent because it has few toxic effects on healthy cells. Most *in vivo* and *in vitro* studies 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 anti-oxidant, anti-proliferative, and anti-carcinogenic properties, and it is more potent than daidzein. The anti-oxidant and anti-cancer 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 (Polkowski et al. 2004). A potent anti-oxidant, genistein results in elevated levels of anti-oxidant enzymes such as glutathione peroxidase, SOD, and glutathione reductase, increasing the scavenging of free radicals and reducing lipid peroxidation (Wei et al. 2015).

Several studies have clearly proven the differential effect of genistein as an estrogenic and anti-estrogenic, attributing to the treatment of hormone-related cancers (Banerjee et al. 2008). The average daily dietary intake of isoflavones is comparatively low in Western countries (2 mg) than in Asian countries (25–50 mg) (van Erp-Baart et al. 2003; Messina et

al. 2006), 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 anti-cancer properties through downregulating several molecular pathways – NF-kB, VEGF, PDGF, EGF, IGF, JNK1, ERK/PI3K/AKT (Varinska et al. 2015). *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 (Kim et al. 2005; Zhang et al. 2013; Wang et al. 2014; Ito et al. 2014). Based on epidemiological data, the role of isoflavone in gastric cancer is debatable because schools of thought differ (Hara et al. 2013; Koh et al. 2005). 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 (Seo et al. 2006). Besides concentration, soy intake also plays a crucial role in breast cancer because it is shown to be protective prior to puberty, reducing during adolescence, and tumorigenic pre-menopausal.

As a FDA-approved drug and in Phase I and II trials for the treatment of metastatic colorectal cancer, genistein has gained more importance (Spagnuolo et al. 2015). 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 anti-cancer drug. Nonetheless, it has thus far been shown to exert chemo-preventive effects and therefore is a promising anti-cancer 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 anti-cancer 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 (Krajka-Kuzniak et al. 2015). 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 (Wu et al. 2010). Numerous *in vitro, in vivo*, and human studies have shown its targeted ability to suppress cell proliferation in various cancer models [breast (Ebert et al. 2007), prostate (Traka et al. 2008), colon (Pappa et al. 2006), lung (Higdon et al. 2007), and leukemia (Ho et al. 2011)]. 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 (Fahey, Talalay 1999), and I3C reversed the cytotoxic effect of dexamethasone by blocking ROS overproduction and Nrf2 expression enhancement (Lin et

al. 2015). 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 anti-oxidants 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 anti-oxidants, 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 by products can help prevent cancer.

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Abbreviations

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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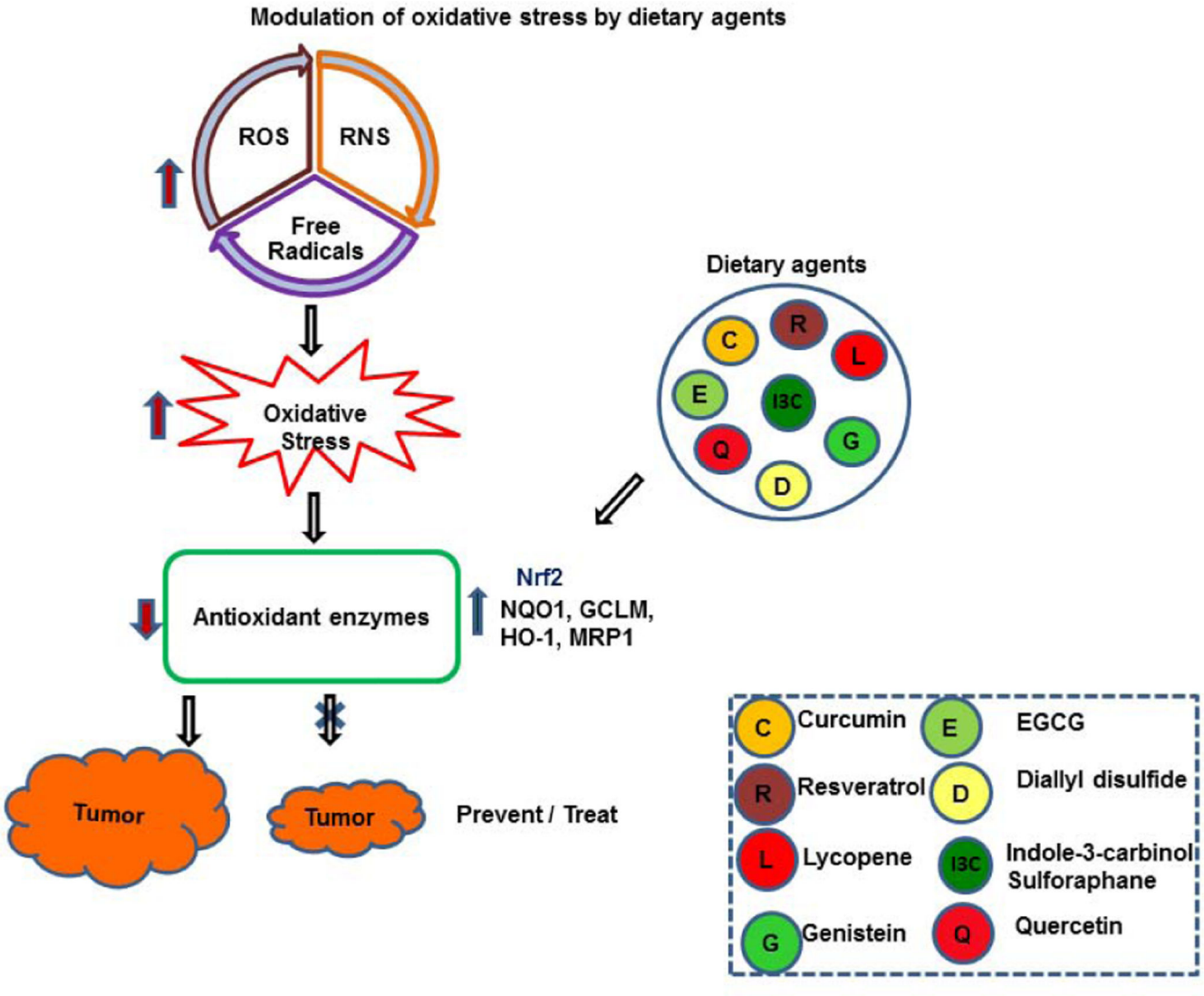

Fig. 1. Modulation of oxidative stress by dietary agents

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.

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
Resveratrol	NF-κB / Wnt/β-catenin
Lycopene	IGBPs/PDGF/VEGF PI3K/AKT/PKB, Ras/Raf/MAP, cyclin D, c-myc Bcl-2, Bcl-XL, ERK/AKT, NF-κB
Epigallocatechin-3-gallate	Caspase activation, Bcl-2; NF-κB MAPK/TGF-B/ EGFR / JAK/STAT; PI3K/AKT, Wnt/Notch
Quercetin	p53 / ras protein/ estrogen receptor/ NF-κB, EGFR/ PI3K/AKT/ MAPKs;TRPM7
Diallyl disulfide	MAPKs and NF-κB/ PI3K/AKT; p53/p21 and MEK-ERK
Genistein	NF-κB, VEGF, PDGF, EGF, IGF, JNK1, ERK/PI3K/AKT
Indole-3-carbinol and Sulforaphane	Nrf2/ARE/ Wnt/β-Catenin