ROS

REVIEW ARTICLES

Regulation of Oxidative Stress by Different Naturally Occurring Polyphenolic Compounds: An Emerging Anticancer Therapeutic Approach

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ABSTRACT | Oxidative stress is a critical factor for the development of cancer via inducing DNA mutations, damage, and genome instability. Different signaling pathways associated with the progression of cancer can modulate the intracellular level of reactive oxygen species (ROS). The level of intracellular ROS is usually high in cancer cells compared to different normal cell types due to abnormal functionality of different genes and perturbed metabolic activity facilitating extensive cellular proliferation. Among a few therapeutic options practiced recently, chemotherapy is the most effective so far. Despite its antitumor efficacy, treatment procedures of chemotherapy have several major side effects and this provokes the scientists for developing novel therapeutic option with minimum toxicity. Different naturally occurring polyphenolic compounds exhibit potential anti-oxidative, anti-inflammatory, and pro-apoptotic effect in several anticancer studies. The use of different polyphenolic compounds to target the redox status of the cell is a very promising strategy. These pleotropic polyphenolic compounds have been widely documented to modulate different signaling pathways in cancer cells either directly or indirectly. In this comprehensive review, we have summarized the anti-proliferative and pro-apoptotic properties of different polyphenolic compounds in various in vitro and in vivo cancer models.

KEYWORDS | Anticancer; Antioxidants; Oxidative stress; Polyphenols; Reactive oxygen species

ABBREVIATIONS | COX, cyclooxygenase; EGCG, epigallocatechin gallate; EGFR, epidermal growth factor receptor; GSH, reduced glutathione; Mgf, mangiferin; Qu, quercetin; ROS, reactive oxygen species

CONTENTS

1. INTRODUCTION

Most of us are unaware of the fact that the life-supporting gas, oxygen, though mostly seems to be a blessing but sometimes it turns out to be a curse to mankind. Oxygen is the determining factor for our survival because the essential action of breathing won't be possible without it [1]. This simple act of respiration leads to the production of highly reactive species, termed as free radicals. The presence of one or more unpaired electrons in these oxygen-containing free radicals contributes to their high reactivity. These free radicals being greatly reactive, swiftly interact with other important molecules of the body and lead to the development of a wide range of diseases, and the underlying causal phenomenon is oxidative damage to these biomolecules [2]. Vital cellular biomolecules such as protein, lipid, and DNA fall prey to these free radicals whereby the latter steal electrons from the former and become stabilized, in turn destabilizing these cellular component molecules. Next, these biological demolitions continue as these destabilized biomolecules trigger a large chain of highly reactive reactions to make themselves stable by pursuing and stealing electrons from other molecules, and as such, the damage continues to aggravate [3]. The free radicals are naturally produced by the body, but certain external factors hugely contribute to their excess production [4]. Some of these factors are exposure to ultraviolet (UV) rays, pollutions, unhealthy food habits, excessive exercise, medications, and smoking, among others. However, not all free radicals are detrimental to the body, as some are useful in killing foreign invaders (pathogens or microbes) [2].

Antioxidants are molecules that combat or nullify oxidative stress by defending the body against free radicals [5]. The endogenous molecules naturally produced by the body having anti-oxidative property can be both enzymatic and non-enzymatic [6]. The antioxidant enzymes include superoxide dismutase, catalase, peroxiredoxins, glutathione reductase, and glutathione peroxidases, among many others. The non-enzymatic electron donators include glutathione and NAD(P)H [7]. Unfortunately, these endogenous antioxidants are not sufficient to neutralize the excess load of free radicals during oxidative stress [8]. Thus, a persistent supply of exogenous antioxidants is of utmost importance as they can repair damaged molecules owing to their property of hydrogen donation and chelation of free radical production [9]. Plant-derived natural molecules are the most important external source of antioxidants. They are of different types obtained from various plants and have been reported to show protection against a wide range of diseases not only by neutralizing reactive oxygen species (ROS), but also by modulating different signaling cascades altered by ROS [10–12].

2. REACTIVE OXYGEN SPECIES AND OXIDATIVE STRESS

Free radicals containing oxygen are the most important group of notorious reactive molecules collectively termed as ROS. Few common examples include $OH^{\bullet}$ (hydroxyl radical), $O_2^{\bullet -}$ (superoxide radical), and H_2O_2 (hydrogen peroxide) [13–15]. In normal condition, healthy cells have a well-balanced redox status by carefully controlling the amount of ROS [16]. Mitochondria are the primary site of ROS production apart from the cytoplasm. The complexes I and III of the electron transport chain of mitochondria produce the maximum amount of ROS. In this electron transport chain, when one electron from NADH is transferred to the oxygen molecule, it gets reduced to $O_2^{\bullet -}$ which, via the catalysis of superoxide dismutase, can get converted to H_2O_2. This H_2O_2, in turn, gives rise to the highly reactive $OH^{\bullet}$ via Fenton reaction. Enzymes like nitric oxide synthase (NOS) produces free radicals such as nitric oxide (NO) and $O_2^{\bullet -}$, which react with each other to generate peroxynitrite ($ONOO^-$) [17]. Some other important enzymes participating in the production of

ROS are lipoxygenase, cyclooxygenases, xanthine oxidase, and cytochrome P450 enzyme families [18]. Common exogenous sources of ROS generation include environmental stresses like hypoxia, ionization, and UV radiation [19].

Oxidative stress is the phenomenon essentially resulting from an imbalance between the systemic manifestation and neutralization of free radicals and the ability of the body to easily detoxify the reactive intermediates through counteraction by antioxidants (both exogenous and endogenous) [20–22]. It occurs when the production of ROS is greater than its detoxification with the help of the first line of cellular antioxidant defense system (endogenous antioxidant enzymes and thiols) [23–25]. ROS take part in redox signaling by acting as cellular messengers. Hence, oxidative stress leads to the disruption of normal cellular signaling cascades and the onset of various diseases, including metabolic diseases (e.g., diabetes, obesity), cardiovascular disorders, hepatic pathophysiology, nephropathies, neurological diseases, and different types of cancer [26–28].

3. ROS AND CANCER-RELATED SIGNALING CASCADES

As of now, cancer is one of the most devastating diseases in the world affecting people of all age groups with more than 10 million new cases every year [29]. Occurrence of oxidative stress is one of the most critical conditions leading to the onset of tumur and its progression [30, 31]. In the late twentieth century, it was proved that transformation of the normal cells is linked with the intracellular ROS level. Scientists found out that administration of insulin elevates the intracellular ROS level and leads to the development of cancer. The exact role of ROS in cancer development and progression remains to be further defined [2, 32–34]. Prolonged inflammation is identified as one of the major causes associated with the oxidative stress phenomenon, and for the initiation of pre-neoplastic cellular growth [30, 35, 36].

In an inflamed tissue or lesion, a high level of oxidative species (ROS and reactive nitrogen species [RNS]) facilitates the recruitment and functioning of the immune cells, but after a longer period the reactive species overcome the cellular antioxidant defense and cause irreversible oxidative damage to the cellular biomolecules, i.e., proteins, lipids, and nucleic acids. This may be the possible cause of genetic and epigenetic modification, which leads to the non-equilibrium between the cellular redox status along with the oncogenic factors and tumor suppressor genes [37–41]. Moreover, different reports suggest that oxidative stress negatively modulates several cell proliferation-associated signaling cascade, such as epidermal growth factor receptor (EGFR) signaling pathway [42, 43]. ROS can also alter the expression of the tumor suppressor gene, p53, a crucial pro-apoptotic protein [44]. Furthermore, different key regulatory proteins, like the nuclear factor erythroid 2-related factor 2 (Nrf2), Ras/Raf, the mitogen-activated protein kinases (MAPKs) ERK1/2 and MEK, IκB kinase (IKK)/nuclear factor κ-B (NF-κB), phosphatidyl inositol 3-kinase (PI3K), phospholipase C, and protein kinase C, are significantly modulated by the accumulation of reactive species and occurrence of oxidative stress [28, 45–48]. In addition, ROS-mediated signaling pathways were found to interfere with many cellular activities, such as cell proliferation, cell cycle progression, energy metabolism, cell-cell adhesion, and cell motility, of the cancer cells [49, 50].

4. POLYPHENOLIC ANTIOXIDANTS AND CANCER CHEMOPREVENTION

In the plant kingdom, among various phytochemicals, the phenolic group of compounds constitutes the largest fleet with more than 8000 compounds divided into ten subgroups. Among the phenolic compounds, phenolic acids, flavonoids, stilbenes, and ligans are the most abundant ones [51, 52]. From a perspective of anticancer activity, various epidemiological studies suggest that diets rich in different naturally occurring phenolic antioxidants have a prophylactic role in lowering the risk of various types cancer and their progression [53–55]. These antioxidant molecules potentially affect the different inflammatory progression, cell proliferation, cell cycle arrest, induction of pro-apoptotic pathways, and related signaling cascades. It is known that the generation and accumulation of intracellular ROS stimulate mutagenesis and activate different pro-oncogenic activities, like cell proliferation [54, 56–58]. From this point of view, the antioxidants should prevent tumorigenesis. Here we have summarized

the mechanism of action of a few naturally occurring polyphenolic antioxidant compounds against cancer and other associated pathophysiological conditions.

5. ANTICANCER ACTIVITY OF DIFFERENT NATURALLY OCCURRING POLYPHENOLIC COMPOUNDS

5.1. Curcumin

Dried rhizomes from *Curcuma longa L*. (family of *Zingiberaceae*) are the main source of turmeric from which curcumin is extracted. Curcumin, which is chemically recognized as diferuloylmethane ($C_{21}H_{20}O_6$), is the major curcuminoid found in turmeric. *Curcuma longa* grows naturally throughout the tropical countries, mainly in Southeast Asia. From ancient to modern times, curcumin has been used as a traditional medicinal agent in many parts of Southeast Asia for the treatment of several common diseases, like stomach upset, arthritis, heart disease, Alzheimer's disease, diabetes, and cancer [40, 59–61]. Despite the low bioavailability due to its low intestinal absorption and quick clearance from the physiological system, numerous studies have recommended that even low levels of curcumin can be enough for its anticancer activity. Besides, several other strategies, like preparations of liposomes, nanoparticles, micelles, and phospholipid complexes are being used to enhance its bioavailability [62].

Due to its anti-inflammatory, antioxidant, immunomodulatory, pro-apoptotic, and anti-angiogenic properties, curcumin inhibited tumorigenesis. Different lines of evidence indicated that curcumin may be used as a chemopreventive agent by modulating different cell signaling pathways. Curcumin has been shown to cause cytotoxicity and induce apoptosis in different in vitro and in vivo models [63]. Curcumin inhibited ROS formation as well as different ROS markers, like glutathione peroxidase and superoxide dismutase in a dose- and time-dependent manner [64]. It is an extremely pleiotropic molecule that changes numerous targets, like kinases (e.g., EGFR, ERK, JAK, and AAPK), cytokines (e.g., TNFs, ILs, MIPs, and MCPs), the transcription factors (e.g., NF-κB, STAT3, AP-1, Nrf-2, PPAR-γ, and HIF-1), receptors (e.g., HER-2, IL-8, and CXCR-4), growth factors (e.g., EGFs, NGFs, HGFs, and PDGFs), and enzymes (e.g., MMPs, GST, and iNOS) [65, 66]. In cancer growth and progression, the involvement of multiple cell signaling molecules creates complexities. Thus, curcumin like a multi-targeting drug may be more beneficial than the mono-targeting drugs. Treatment with 20 μM curcumin significantly increases the expression of MMP-9 and reduces the lung metastasis of ENU1564 cells (mouse mammary gland adenocarcinoma) [67]. Curcumin (100 ng/ml) in HC11 cells causes adverse effects to normal mammary epithelial cells and it has a specific effect on signal transduction in mammary epithelium. In the mouse colon carcinoma cell line (HCT116), curcumin enhanced the efficacy of oxaliplatin without affecting its activity [68].

COX-2 overexpression has been reported in different types of cancer. Curcumin inhibits the transcription of COX-2 which in turn reduces its inflammatory activity. In a study with human cervical cancer cells, it was found that downregulation of COX-2 induces nitric oxide synthase (iNOS) and cyclin D [62]. In an in vivo study of pancreatic carcinoma in nude mice, a reduction by 70% in tumour size on a diet rich in curcumin was demonstrated through downregulation of iNOS, COX-2, and upregulation of p21 [69]. Curcumin and some of its derivatives also inhibit COX-1 transcription. In in vitro studies of human mammary epithelial carcinoma cells, B-lymphoma cells, and prostate cancer cells, curcumin induces apoptosis. Apoptosis is induced by upregulation of p53 expression at the G2 cell cycle phase, and mitochondria also release cytochrome c in this process. The p53-dependent apoptosis was also reported in the colon, bladder, breast, neuron, ovary, and lung cancers [70]. However, in colorectal cancer, both p53-dependent and p53-independent G2/M phase arrest was observed [71]. Curcumin also arrests normal epithelial cells at the G0 phase of the cell cycle by downregulating cyclin D1 along with Cdk4/Cdk6 and upregulating the inhibitory protein p21Waf-1 [72]. Curcumin induces apoptosis in the pharynx and nasopharyngeal cancer cells via the caspase-3-dependent pathway [73]. It also helps in the progression of caspase-3-mediated cleavage of beta-catenin and reduces beta-catenin/Tcf-Lef trans-activation ability for c-Myc and cyclin D1. Curcumin also triggers activation of caspase-7 and caspase-9 and induces poly-ADP-ribose polymerase breakdown through the downregulation of NF-κB in different myeloma cells. In addition, it inhibits the activation

of EGFR and the activity of some other nuclear receptors involved in cellular proliferation. Its inhibitory effects on COX-2 and cyclin D1 is mediated trough NF-κB, which in turn limits tumor cell growth [73].

Curcumin treatment shows great promise as a therapeutic agent. Its beneficial role is being investigated in human clinical trials under different conditions, like multiple myeloma, myelodysplastic syndrome, pancreatic cancer, and colon cancer. Curcumin was also reported to protect against several chemotherapeutic side effects in many studies. Its exposure has been shown to alleviate oxidative stress in PC12 cells exposed to cisplatin [74]. Besides, this unique molecule has been used for a long period as a "herbal general medicine" to relieve discomfort and inflammation associated with different infectious as well as autoimmune diseases [10]. These properties also appear to help this multi-functional molecule to act as a potent anticancer drug. All these beneficial effects of curcumin are summarized in **Figure 1**.

5.2. Genistein

Genistein is an effective phytoestrogen which can bind equally to both alpha and beta estrogen receptors and control the divergent intracellular signaling pathways of estrogen. Genistein was first isolated by Perkin and Newbury from *Genista tinctoria* (a leguminous plant, usually known as Dyer's Broom) in 1899. In 1928, Baker and Robinson first chemically synthesised this compound. This plant-derived flavonoid exhibits maximum antioxidant action among isoflavones. Soybean and soy products are the richest source of it. In multiple studies of Asian and Western populations, soybean was found as a rich diet to be advantageous in terms of chemoprevention. However, Asian population take more soya food than Western population and that may be the cause of less incidence of certain cancer in that area [75].

Genistein is capable of inducing apoptosis in the human cervical cancer cell line (HeLa) by inducing activation of caspase-9 and caspase-3, and decreasing the mitochondrial membrane potential which in turn increases oxidative stress. Genistein is the mostly studied soy isoflavone which has been accepted as an anticancer agent by the United Stated National Cancer Institute (NCI) in 1995 [76]. Different studies suggest that genistein inhibits cancer cell proliferation and metastasis and induces DNA fragmentation. Genistein changes multiple important signaling pathways related to apoptosis and cell proliferation [75]. The estrogen receptor-mediated signaling cascade is also attenuated in different types of cancer. In vitro and in vivo studies indicate that genistein causes selective cytotoxicity to different cancerous cells than normal cells [77]. Cancerous cell gene expression studies reveal that genistein inhibits angiogenesis and protein kinases and also blocks cell cycle progression at G2-M check point. It also increases the melanin production and tyrosinase activity in some specific cancer tissues and is capable of inhibiting the activation of NF-κB-mediated signaling cascade, which bring stability between cell death and survival [78]. This phenomenon made genistein a perfect anticancer compound in prostate cancer as it reverses epigenetic causes related to the cancer. As genistein is a phytoestrogen, it can prevent hormone-linked metastatic malignancies such as breast cancer. It mimics estrogen and interacts with estrogen receptor present in the cancer cell line. In this way genistein prohibits proliferation in different cancer cell lines with different ERα/ERβ ratios which are a predictive indicator for various cancers [79]. Genistein treatment of MCF-7 and normal HBF4a cells holdups the cell cycle at G0/G1 stage, without inducing apoptosis [80].

Genistein was reported to down-regulate hedgehog-Gli 1 signaling cascade, and this way it eliminates breast cancer stem cells and stem-like cells. Genistein can control the growth of colorectal cancer progression by suppressing the undesirable effect of EGFR via changing the activity of FOXO3 [81]. It modulates the inhibitor of IGF-IR and PI3K-AKT signaling pathways and also the apoptosis-related genes. It is also found capable of inhibiting cancer development and progression by interfering with the Wnt/β-catenin signaling pathway [75]. Genistein treatment of Caco-2 cells arrests cell cycle at G2/M phase and also significantly downregulates cyclin B1 and serine/threonine protein kinase 2 expression. Genistein inhibits the activity of DNA topoisomerase II in HCT 116 human colon carcinoma cell line as well as suppresses prostate cancer cell growth by modulating different genes related to DNA hypermethylation, and reactivating MGMT, p16INK4α and RAR-β genes due to gene silencing by methylation. It is also capable of sensitizing chemotherapeutic agents like docetaxel and selenium [82]. In prostate cancer progression, Wnt and Notch signal

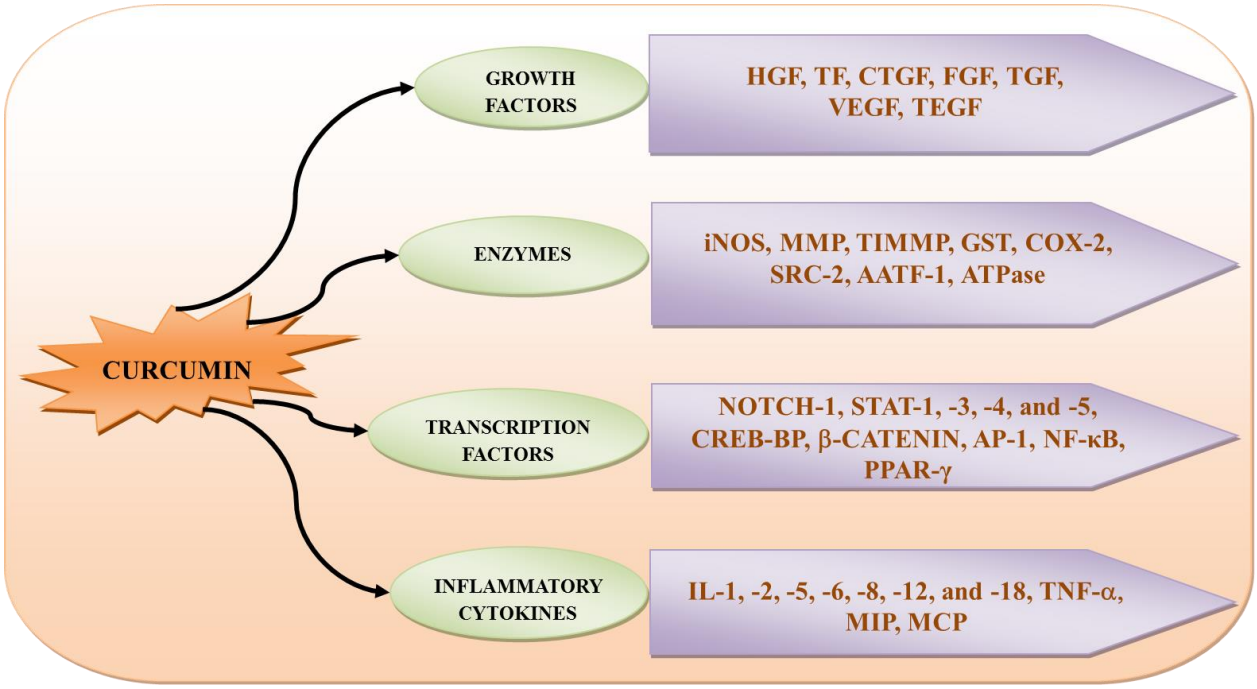

FIGURE 1. Different signaling molecules, like growth factors, enzymes, transcription factors, and inflammatory cytokines, regulated by curcumin to inhibit the progression of cancer development. See text (Section 5.1) for detailed description.

ing cascades are markedly altered. Different negative regulators of the Wnt pathway (e.g., SOX7, APC, SFRP1, and DKK3) were reported to be hypermethylated in prostate cancer. Genistein also controls Wnt inhibitory factor 1 (WIF1) expression which in turn decreases tumor development that is also hypermethylated in the case of prostate cancer [75]. Genistein induces cell-cycle arrest of prostate cancer cell lines in G2/M check point by increasing the expression of BRCA1, BARD1, BUB1, AURKB, CHEK2, and MAD2L1, and induces apoptosis by upregulating GZMB, DFFA, TNF, BIRC3, BCL10, and BIRC7 genes [79].

5.3. Mangiferin

In recent years, different xanthones become important in pharmacological research due to their biological properties. Among them, mangiferin (Mgf, 1,3,6,7-tetrahydroxyxanthone-C2-b-D-glucoside), which is chemically a C-glucosylxanthone, is gaining importance. Mgf can be extracted from the stem bark and leaves of *Mangifera indica*. Mgf possesses a catechol moiety which is pharmacologically well-known due to its antioxidant character and ROS-scavenging activity on $ONOO^-$ and $OH^\bullet$ [11].

Chronic inflammation is believed to be the major contributor to the progression of tumorigenesis and metastasis. One of the most studied and critical pro-inflammatory factor is tumor necrosis factor (TNF) and it is reported that TNF induces intracellular ROS formation. It causes the oxidation of intracellular glutathione which activates different pro-apoptotic transcription factors and caspases. Mgf inhibits inflammation-related molecules, such as NF-κB, IκBα, IL-6, IL-8, JAK1/2, STAT3, CXCR4, XIAP, AKT, MAPK, TNF, ICAM1, and COX2 as well as inhibits metastasis (**Figure 2**) [7, 8, 24].

Mgf also possesses anti-angiogenic properties as it downregulates VEGF, FGF, and TNFα, which in turn inhibit tumor growth [83]. Mgf acts as an apoptosis inducer as it downregulates Bcl-xL and Bcl-2 and upregulates several proapoptotic caspases. Suppression of NF-κB activation by Mgf also induces

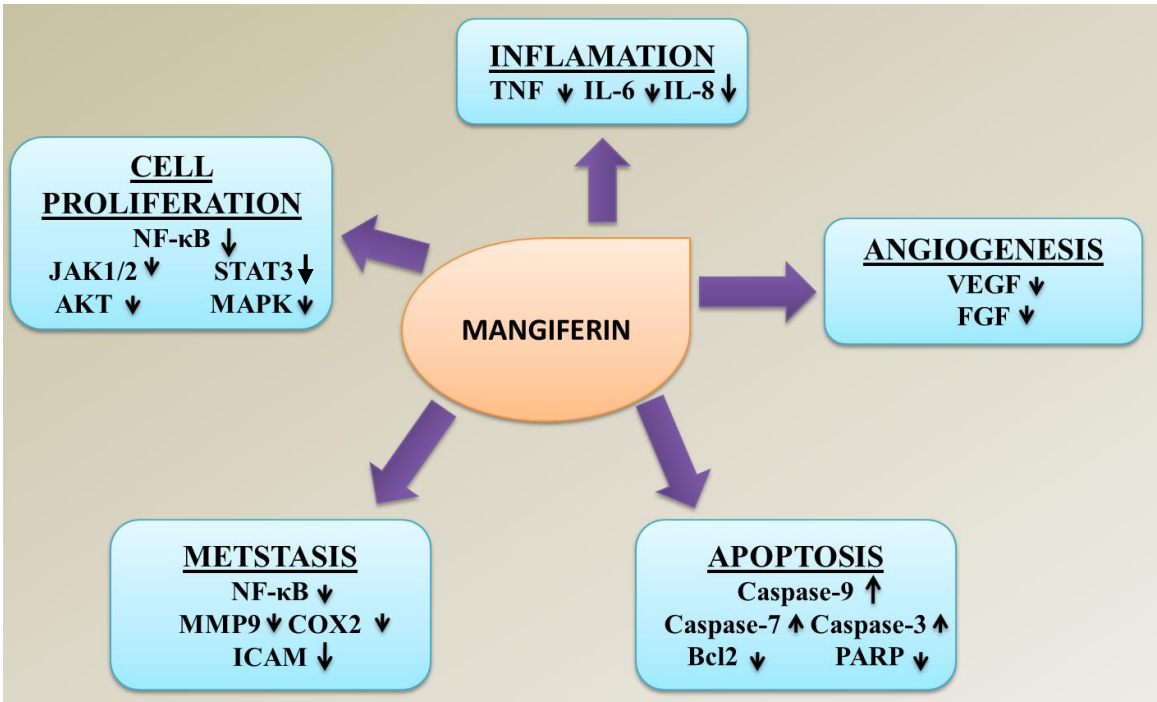

FIGURE 2. Schematic representation of the different molecular targets regulated by mangiferin. See text (Section 5.3) for detailed description.

apoptosis (**Figure 2**). Mgf disrupts the mitochondrial membrane potential which also helps induce apoptosis of cancer cells. Mgf can behave as a successful chemopreventive agent in breast cancer as it inhibits the β-catenin activation pathway. It is capable of delaying S-phase and can arrest cancer cells in G2/M phase which leads to apoptosis. In breast cancer cells, Mgf downregulates cdc2-cyclin B1 signaling cascade-mediated cell cycle arrest. In K562 human leukemia cells, Mgf dose and time dependently inhibits telomerase activity and promotes apoptosis by upregulating Fas genes [84].

Optimal health benefits of Mgf cannot completely be achieved due to its water insolubility and low oral bioavailability which is 1.2% in rats. Mgf is found to be effective on breast cancer, leukemia, multiple myeloma, hepatocellular carcinoma, skin cancer, prostate cancer, and ovarian cancer. Detailed study and clinical trials are needed to determine the possible mechanism in different types of cancer to fully utilize its therapeutic potential. Due to its low bioavailability and water-insolubility, future studies on novel delivery system are required to establish it as a multi-target drug [11].

5.4. Quercetin

Quercetin (3,30,40,5,7-pentahydroxyflavone, Qu) is a naturally-occurring dietary flavonol compound which shows numerous biological and pharmacological effects, including antioxidant, chelation, anti-carcinogenic, cardioprotective, bacteriostatic, and secretary properties. It is present in different daily foods, like vegetables, fruits, seeds, nuts, tea, and red wine. Qu selectively increases intracellular ROS levels and induces apoptosis. It can create free radical-mediated apoptosis through different cell signaling pathways like ROS/AMPKα1/ASK1/p38 and the AMPKα1/COX2 signaling pathways. Increasing amount of ROS formation activates AMPKα1 and ASK1. AMPKα1 and ASK1, in turn, activate p38 and increase different caspases. Qu also regulates COX-2 expression via AMPKα1 and induces apoptosis [85].

Qu decreases intracellular level of reduced glutathione (GSH), and lower level of GSH changes rate of ROS metabolism. Prolonged exposure of Qu decreases H_2O_2 and GSH content in U937 monoblastic and CEM lymphocytic cell lines. Qu and ROS react with each other and produce toxic semiquinone and quinone molecules. These species favorably react with GSH in a dose-dependent manner. Decrease of GSH creates mitochondrial depolarization which in turn induces apoptosis [86]. Qu activates mitochondria-dependent apoptosis by decreasing mitochondrial membrane potential and inducing release of cytochrome c to the cytosol, thereby leading to the activation of caspase-3 and caspase-7. Qu selectively induces apoptosis in cancer cells by regulating different signaling pathways. It upregulates Bax and Bak and downregulates Bcl-2 and Bcl-xL protein expression. This helps in creation of BAX multimerization in the mitochondrial membrane. Cleavage of procaspase 9 and of PARP also occurs simultaneously [87]. Qu inhibits the cell survival and proliferation pathway (PI3K/Akt pathway). It decreases enzymatic PI3K action without altering p85 or p110 subunit levels. Death receptor-dependent apoptotic pathway is also induced by Qu [88]. Death receptor-5 (DR-5) is found to be unregulated after Qu treatment in prostate cancer and hepatoma cells. DR-5 belongs to the TNF family and it is also activated by TNF-related apoptosis-inducing ligand (TRAIL). Caspase-8 inhibitors like c-FLIP are found to be downregulated along with upregulation of DR5, which in turn initiates Qu-induced apoptosis via TRAIL. The pro-apoptotic consequence due to Qu administration downregulates the heat shock protein (Hsp)-90 expression in a caspase-dependent manner [89].

In some cervical cancer cells, Qu reacts with estrogen receptor α (ER-α) and induces cytotoxicity. ER-α-P38/mitogen-activated protein kinase cell signaling cascade induces apoptosis after Qu administration. Qu comparatively favors the binding to estrogen receptor β (ER-β) than ER-α. At more than 50 μM concentration, Qu binds ER-β receptor and induces apoptosis [90]. ER-β increases intracellular pH by altering Na^+/H^+ exchanger and initiates Bax-mediated mitochondria-dependent apoptosis. Qu treatment reduces Hsp90 levels in the cells and dose dependently increases caspase-3 and caspase-9. Thus, Qu can act towards different anticancer therapeutic targets and definitely represents its candidature for being a fascinating tool in the field of oncology. Dietary intake of Qu can easily avoid drug resistance and realize selectivity of treatment without affecting normal cells [89].

5.5. Resveratrol

Resveratrol (trans-3,5,4′-trihydroxy-trans-stilbene) is a non-flavonoid antioxidant available in peanuts and grapes. It inhibits cancer formation, progression, angiogenesis, and metastasis. Resveratrol also possesses anti-inflammatory activity by modulating different pro-inflammatory pathways. As it is a lipophilic compound, absorption and bioavailability of resveratrol are expected to be increased by lipid-rich diet. But bioavailability and absorption of resveratrol in red wine consumed by humans were found to be independent of the lipid-rich meal [91].

Although resveratrol exhibits low bioavailability, it possesses anticancer activity and it is also accumulated in tumor cells. In mouse xenograft models of human SH-SY5Y, NGP, and SK-N-AS neuroblastoma cell lines, 50 μM concentration of resveratrol induces cell death [92]. Cancer progression of estrogen positive breast cancer cell lines like MCF-7 and estrogen negative cell lines like MDA-MB-231 was found to be inhibited by 1 μM resveratrol [93]. Resveratrol treatment of 10 mg/kg body weight for 2 days minimized cancer cell progression in cancer-bearing nude mice. Exposure to 100 μM resveratrol for 48 hours also induced cell death in DLD1 and HT29 human colorectal cancer cell lines [94]. In a study with TRAMP (transgenic adenocarcinoma mouse prostate) mice, resveratrol suppressed prostate cancer progression. It was also found to inhibit cancer progression and metastasis in pancreatic cancer, lung cancer, and human multiple myeloma. In most of the studies, it was indicated that resveratrol induces apoptosis via different cell signaling pathways. In a human neuroblastoma cell line, resveratrol decreases mitochondrial membrane potential which in turn stimulates release of cytochrome c and subsequent activation of pro-apoptotic caspase 3 and 9 [95]. It also arrests prostate cancer cell cycles at G0/G1 by reducing expression of different cell cycle growth factors. In T-cell acute lymphoblastic leukemia cells, resveratrol upregulates different pro-apoptotic proteins like Bax, p53, and $p21^{waf}$ and downregulates different anti-apoptotic proteins like BclxL, Bcl-2, cyclin D1, and TNF receptor-associated factor [96]. Resveratrol also inhibits

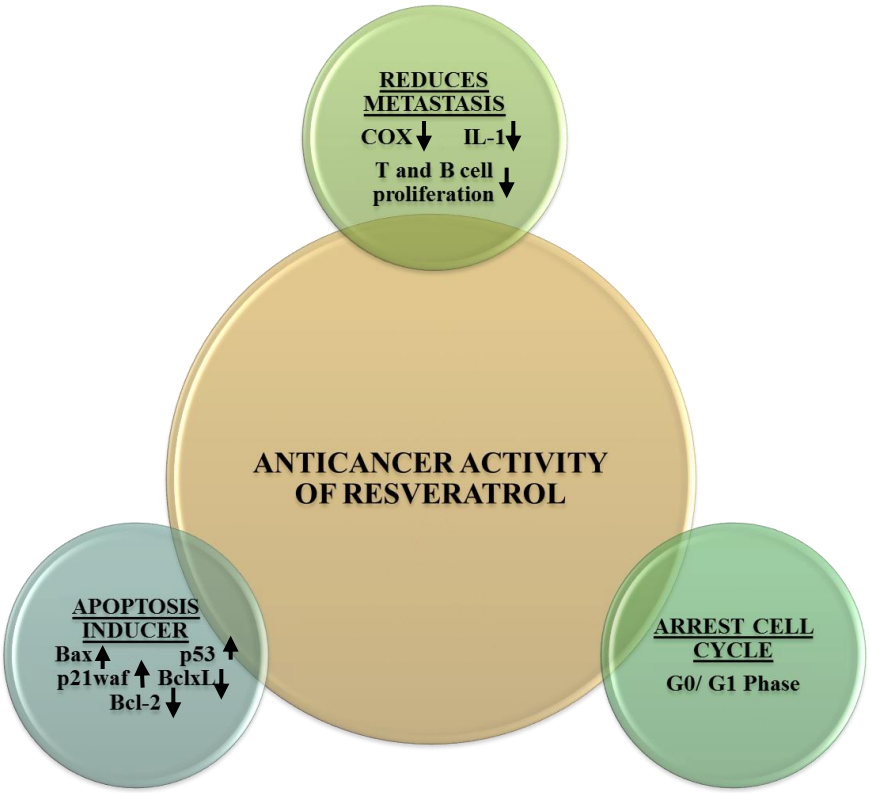

FIGURE 3. Anticancer activity of resveratrol. These regulatory molecules shown in the scheme are described as possible targets for chemoprevention. See text (Section 5.5) for detailed description.

PI3K/Akt pathway and is found to inhibit protein kinase B and activate forkhead proteins (FOXO3a) in human breast cancer cells. FOXO3a is an important transcription factor for occurrence of apoptosis as it activates different apoptotic genes. FOXO3a is also found to be involved in cell differentiation, cell cycle arrest, DNA repair, and angiogenesis [97]. In myeloma cells, resveratrol was found to inhibit the expression of NF-κB-mediated pro-apoptotic genes [98].

In prostate cancer cells, which are not androgen sensitive, resveratrol increases cellular ROS production which in turn decreases anti-apoptotic gene expressions and increases pro-apoptotic gene expression as well as TRAIL expression. Dietary inoculation of resveratrol in prostate cancer reduces cell proliferation and expression of tumor suppressor estrogen receptor-β (ER-β) [99]. In non-melanoma skin cancer, resveratrol downregulates the expression of Cdk 2, 4 and 6, cyclins D1 and D2, and PCNA, but p21WAF1/CIP1 was found to be upregulated [100]. Anti-apoptotic proteins like surviving and tumor progression markers like COX-2 and ornithine decarboxylase are also inhibited by resveratrol. In melanoma cell lines, resveratrol inhibits progression of cancer cells and induces apoptosis [101]. However, further studies and detail clinical trials need to be performed to establish resveratrol as a potent anticancer and chemotherapeutic drug, and such investigation is currently in progress. Resveratrol-induced beneficial effects in protecting against cancer are presented in **Figure 3**.

5.6. Catechins

Green tea contains several antioxidants, collectively known as catechins. Green tea extract contains four types of catechins (epicatechin, epigallocatechin,

gallate, and epigallocatechin gallate [EGCG]). Catechins are found to be beneficial against different diseases like cancer, Alzheimer's disease, Parkinson's disease, diabetes, and obesity. Recent research indicates that EGCG, chemically known as [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate, is the principle catechin in green tea which may be the key player for its health benefits [102]. In vivo, in vitro, clinical, and epidemiological studies demonstrate its antitumor and antioxidant properties. In different studies, it is also found to be capable of blocking tumor progression and suppressing metastasis.

EGCG inactivates NF-κB which is overexpressed in cancer cells due to oxidative stress [103]. EGCG induces apoptosis by inactivating NF-κB after increasing degradation of IκB due to phosphorylation. EGCG also downregulates expression of CDK2, CDK4, CDK6, cyclin D1, and cyclin E which subsequently leads to cell cycle arrest and apoptosis [104]. EGCG also upregulates different pro-apoptotic proteins along with caspase-3 and alleviates p53 protein and leads to apoptosis [105].

6. CONCLUSION

This review has discussed different aspects of targeting oxidative stress-associated signaling cascades in developing an effective therapeutic option against cancer. In recent times, best possible combination therapy is used to combat cancer. Depending upon the tumor size and the type of the cancer, specific strategies are used either by increasing the intracellular ROS level to induce toxicity or by using antioxidants to scavenge free radicals and induce different pleotropic signaling cascades. In the last two decades, different polyphenolic antioxidant molecules present in the daily diet has shown significant chemopreventive effects. However, very little is known about the definite connection between the pathogenesis of cancer and dietary intake of antioxidant-rich food. As discussed in this review, the toxicity of these dietary anti-oxidants is found to be critically depending upon the dose and intracellular chemical environment. In conclusion, better understanding is required of the possible signaling interactions suppressing oncogenic factors and inducing tumor suppressor proteins before any therapeutic use of these polyphenols in treating cancer.

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