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Cancer Prevention with Promising Natural Products: Mechanisms of Action and Molecular Targets

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Abstract

Cancer is the second leading cause of death worldwide. There is greater need for more effective and less toxic therapeutic and preventive strategies. Natural products are becoming an important research area for novel and bioactive molecules for drug discovery. Phytochemicals and dietary compounds have been used for the treatment of cancer throughout history due to their safety, low toxicity, and general availability. Many active phytochemicals are in human clinical trials. Studies have indicated that daily consumption of dietary phytochemicals have cancer protective effects against carcinogens. They can inhibit, delay, or reverse carcinogenesis by inducing detoxifying and antioxidant enzymes systems, regulating inflammatory and proliferative signaling pathways, and inducing cell cycle arrest and apoptosis. Epidemiological studies have also revealed that high dietary intakes of fruits and vegetables reduce the risk of cancer. This review discusses potential natural cancer preventive compounds, their molecular targets, and their mechanisms of actions.

Keywords

Chemoprevention; Phytochemicals; Activator protein-1; Nuclear factor (NF)- κ B; Cyclooxygenase (COX)-2; Apoptosis; Cell cycle arrest; Angiogenesis; Oxidative stress; Curcumin; (-)-epigallocatechin-3-gallate; Resveratrol; Isothiocyanates

INTRODUCTION

Cancer is one of the leading causes of death worldwide and the incidence is on the rise in both developing and developed countries. Cancer prevention may be more effective and less costly because cancer is closely associated with lifestyle factors [1]. Natural products have been used for the treatment of various diseases and are becoming an important research area for drug discovery. These products, especially phytochemicals have been extensively studied and have exhibited anti-carcinogenic activities by interfering with the initiation, development and progression of cancer through the modulation of various mechanisms including cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis [2].

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

Many successful anti-cancer drugs now available are phytochemicals or their analogues [3], and some are in human clinical trials [4].

Phytochemicals obtained from vegetables, fruits, spices, teas, herbs, and medicinal plants, such as flavanoids, carotenoids, phenolic compounds, and terpenoids, have been extensively investigated for their anti-cancer activities due to their safety, low toxicity, and general availability [1, 5]. It has been estimated that more than two-third of human cancers could be prevented through appropriate lifestyle modification including dietary habits [6]. Recent studies have indicated that a high intake of fruit and vegetables is associated with a decreased risk of human malignancies, including colon, breast, lung, laryngeal, pancreatic, bladder, stomach, esophageal, and oral cancers [5, 7]. Population studies also suggest that a reduced risk of cancer is associated with a high consumption of vegetables and fruits.

Chemoprevention, a means of cancer control by which the occurrence of the disease can be entirely prevented, slowed down, or reversed by use of nontoxic natural or synthetic products, has emerged as a promising and pragmatic medical approach to reduce the risk of cancer. This concept is gaining increasing attention because it is a cost-effective alternative to cancer treatment [1, 8]. Cancer treatment with commercially available synthetic chemotherapeutic agents is limited because of their severe side effects. Various plant products have been reported to possess substantial chemopreventive properties [8]. Approximately, 20% of cancer incidents are preventable by consuming more vegetables and fruits and may potentially prevent approximately 200,000 cancer-related deaths annually [1].

Carcinogenesis is a multi-step process (Fig. 1) which begins with initiation followed by promotion and progression that involve a series of epigenetic and genetic alterations affecting oncogenes and tumor suppressor genes [9]. Tumor initiation is a rapid and irreversible process. This process involves an initial uptake of or exposure to a carcinogenic agent including a distribution of this agent to organs and tissues where metabolic activation and detoxification can occur. Finally this agent and its possible metabolic derivatives covalently interact with target-cell DNA, leading to genotoxic damage [10]. Phytochemicals can prevent these multi-step processes by exerting anti-inflammatory and anti-oxidative stress effects which are mediated by integrated Nrf2, NF- κ B, and AP-1 signaling pathways [9]. Many of the antioxidant compounds present in foods of plant origin protect against genotoxicity and other cancer-initiating or -promoting processes [11].

In this review we focus on (a) the usefulness of some promising phytochemicals (Fig. 2), including curcumin, resveratrol, epigallocatechin gallate (EGCG), apigenin, quercetin, genistein, lycopene, ursolic acid, isothiocyanates, and perillyl alcohol, and (b) their mechanism of actions as well as molecular targets (Fig. 3 & Table 1), such as antioxidant properties, inhibition of cell cycle, induction of apoptosis, regulation of angiogenesis, inhibition of cyclooxygenase (COX)-2, signal transducers and activator of transcription 3 (STAT3) inhibition, and down-regulation of nuclear factor-kappaB (NF- κ B), activator protein-1, and mitogen-activated protein kinases (MAPKs).

CURCUMIN

Curcumin (diferuloylmethane), a yellow pigment belongs to the class of polyphenols present in the rhizomes of turmeric (*Curcuma longa* L.), is used in cooking in India and other regions of Asia. It is also used as a cosmetic and in some medical preparations. It has a long history as herbal remedy for a variety of diseases and has been used in Indian and Chinese traditional medicine since 700 AD [12]. Curcumin has been demonstrated to have a wide spectrum of pharmacological properties. Multiple therapeutic activities of curcumin have also been considered to be associated with its antioxidant and anti-inflammatory properties. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) [13]. Curcumin likely exerts its inhibitory effect on cancer development by several mechanisms such as inhibition of carcinogen activation and stimulation of carcinogen detoxification, prevention of oxidative DNA damage, and its capacity to reduce inflammation [8]. Studies revealed that curcumin mediates its anti-inflammatory effects through the downregulation of inflammatory transcription factors (such as NF- κ B), enzymes (such as COX-2 and 5 LOX) and cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6) [14]. Curcumin has also been shown to be beneficial in all 3 stages of carcinogenesis. Much of its beneficial effect is found to be due to its inhibition of the transcription factor NF- κ B and subsequent inhibition of proinflammatory pathways [15]. Curcumin has the potential to inhibit the NF- κ B and AP-1, the major transcription factors that regulate inflammation, cell proliferation, differentiation and even apoptosis. It has promising chemopreventive and therapeutic potential for various cancers including leukemia, lymphoma and cancers of the gastrointestinal tract, genitourinary system, breast, ovary, head and neck, lung and skin [16]. It has also shown to affect a variety of other key players involved in carcinogenesis, such as cyclooxygenase-2, matrix metalloproteinases 2 and 9, and tumor necrosis factor α -induced vascular cell adhesion molecules [17].

Curcumin inhibits pancreatic tumor growth through mitotic catastrophe by increasing the expression of RNA binding protein CUGBP2, thereby inhibiting the translation of COX-2 and VEGF mRNA [18]. It enhances the effect of cisplatin in suppression of head and neck squamous cell carcinoma via inhibition of IKK β protein of the NF- κ B pathway [19]. Curcumin induces cell cycle arrest at the G2/M phase by decreasing the Cdc2 expression [20]. It inhibits cell proliferation, tumor growth, invasion and *in vivo* metastasis, and stabilizes the expression of the tumor suppressor Pcdcd4 in colorectal cancer [21]. It has been shown to protect against skin, oral, intestinal, and colon carcinogenesis and also to suppress angiogenesis and metastasis in a variety animal tumor models. It also inhibits the proliferation of cancer cells by arresting them in the various phases of the cell cycle and by inducing apoptosis. Curcumin has a capability to inhibit carcinogen bioactivation via suppression of specific cytochrome P450 isozymes, as well as to induce the activity or expression of phase II carcinogen detoxifying enzymes [8]. Combination of phenethyl isothiocyanate and curcumin caused suppression of epidermal growth factor (EGF) receptor phosphorylation and inhibition of EGF-induced phosphorylation of Akt and induction of phosphatidylinositol 3-kinase (PI3K) in PC-3 cells [22]. Menon *et al* first reported that curcumin inhibits the invasion of B16F10 cells by suppressing MMP-2, thereby inhibiting

lung metastasis in an animal model [23]. It has also been shown to suppress the production of cytokines such as interferon- γ (IFN- γ), interleukins, and tumor necrosis factor- α (TNF- α); to inhibit the inducible nitric oxide synthase (iNOS); and to suppress the activation of NF- κ B [24, 25]. Curcumin-induced inactivation of NF- κ B DNA-binding activity was potentially mediated by Notch-1 signaling pathway [26]. Curcumin regulates tumor cell growth through multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK) [27]. Curcumin also inhibited migration of Colo205 cells through the inhibition of NF- κ B and the down-regulation of COX-2 and MMP-2 expression [28]. Curcumin upregulated the expression of TRAIL-R1/DR4, TRAIL-R2/DR5, Bax, Bak, p21/WAF1, and p27/KIP1, and inhibited the activation of NF- κ B and its gene products in xenografted tumors [29]. Curcumin suppressed the expression of human epidermal growth factor receptor (HER) 2 and the activity of p21-activated kinase (PAK) 1, a downstream protein of EGFR, to inhibit the proliferation and invasion of gastric cancer cells [30]. Curcumin induces caspase-3-mediated cleavage of β -catenin, leading to inactivation of Wnt/ β -catenin signaling in HCT116 intestinal cancer cells [31].

RESVERATROL

Resveratrol (trans-3,5,4'-trihydroxystilbene), a naturally occurring phytoalexin, is found at a high concentration in the skin of red grapes and red wine. Resveratrol is known to have antioxidant, anti-inflammatory and antiproliferative effects on a variety of cancer cells *in vitro* and in various animal models [32]. It effectively scavenges superoxide, hydroxyl, and peroxynitrite radicals generated from enzymatic and nonenzymatic systems and affords protection against DNA damage caused by these ROS [33, 34]. Resveratrol has been identified as an effective candidate for cancer chemoprevention based on its striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression [35]. It potentiates antitumor activity by regulating multiple cell-signaling molecules, including drug transporters, cell survival proteins, cell proliferative proteins, and members of the NF- κ B and STAT3 signaling pathways [36]. The resveratrol-induced apoptosis was mediated by activation of caspases-9 and -3 and a change in the Bax/Bcl-2 ratio. It regulated the expressions of cyclin D1, E, and Cdk4 as well as cyclin D1/Cdk4 kinase activity in LNCaP cells [37]. It enhanced TRAIL-induced apoptosis through G1 cell cycle arrest and survivin depletion [38]. It can inhibit the activation of p38 MAPK, p53 and p21WAF1 pathway in tumor cells [39]. It has been shown to inhibit COX-2 activity [40], and tumor angiogenesis by regulating MMP-2 and MMP-9 [41, 42]. The inhibition of NF- κ B and MMP-9 activities by resveratrol in breast cancer cells blocks their migratory potentials [43]. It is well documented that resveratrol can suppress proliferation and invasion as well as induce apoptosis in a wide variety of tumor cell types [42]. Resveratrol suppressed NF- κ B-regulated gene products (COX-2, MMP-3, MMP-9, and VEGF), inhibited anti-apoptosis (Bcl-2, and Bcl-xL) [44]. It can block IL-1-induced activation of NF- κ B leading to inhibition of proliferation, S-phase arrest, and induces apoptosis [45]. Resveratrol has been shown to inhibit TNF α -mediated MMP-9 expression in HepG2 cells by downregulation of

the NF- κ B signaling pathway [46]. Extensive *in vitro* studies revealed multiple intracellular targets of resveratrol, which affect cell growth, inflammation, apoptosis, angiogenesis, and invasion and metastasis [47]. Resveratrol has been shown to inhibit the phosphatidylinositol-3 kinase (PI-3K)/AKT and the MAPK pathways, two key survival cascades that are frequently aberrantly activated in human cancers [48, 49]. It has been found to inhibit Mammalian target of rapamycin (mTOR) which is a central controller of cell growth, proliferation, metabolism and angiogenesis [50]. Resveratrol suppressed AP-1 activity by the inhibition of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK)1 > ERK1/2 signaling [51]. It also regulated the expression of IAPs and Bax, and decreased Akt phosphorylation in PC-3 cells, leading to increased caspase activation and apoptosis [52]. Resveratrol activates MAPK at low concentrations, but at higher concentrations it can inhibit this signal transducing kinase in cancer cells [53]. It inhibited nuclear expression of the AP-1 component proteins, in TPA stimulated mouse skin [54]. It has been shown to inhibit the migration and decrease the focal adhesion kinase (FAK) activity in MDAMB231 cells [55].

APIGENIN

Apigenin, a naturally occurring plant flavone, abundantly present in common fruits and vegetables, possesses anti-oxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory, anti-growth, and anti-progression properties [56]. Apigenin is effective in carcinogenesis. Topical application of apigenin inhibited dimethyl benzanthracene-induced skin tumors [57], and also diminished UV-induced cancer incidence and increased tumor free survival experiment [58]. Previous studies demonstrated that apigenin promotes metal chelation, scavenges free radicals, and stimulates phase II detoxification enzymes in cell culture and in *in vivo* tumor models [59]. It has been shown to increase the intracellular concentration of glutathione, enhancing the endogenous defense against oxidative stress [60]. In PC-3 tumor model, treatment with apigenin resulted in 32% and 51% inhibition in tumor growth [57]. The proposed mechanism of anti-tumor activity by apigenin was upregulation of WAF1/p21, KIP1/p27, INK4a/p16, and down-modulation of the protein expression of cyclins D1, D2, E and cyclin-dependent kinases (cdk) [61]. Apigenin has been shown to inhibit the proliferation of human prostate cancer cells by regulating MAPK, PI3K-Akt pathways [62]. It inhibited the LPS-induced cyclooxygenase-2 and nitric oxide synthase-2 activity and expression in mouse macrophages [63]. Apigenin induced G2/M phase cell cycle arrest and reduced the levels of cyclin A, cyclin B, phosphorylated forms of cdc2 and cdc25 in pancreatic cancer cell lines [64]. It also induced growth-inhibition and G2/M phase arrest in two p53-mutant cancer cell lines, HT-29 and MG63. These effects were associated with a marked increase in the protein expression of p21/WAF1 [65]. Previous studies have shown that topical application of apigenin prior to UV irradiation prevents UV-induced tumorigenesis in mice by inhibiting the cell cycle machinery and cyclin-dependent kinases (cdk) [58, 66]. Apigenin has shown promise in inhibiting tumor cell invasion and metastases by regulating protease production [67]. It inhibited lung tumor metastasis in B16-BL6 murine melanoma metastasis model [68]. Apigenin has been shown to be markedly effective against human leukemia cells [69]. It inhibits HIF-1 α , GLUT-1, VEGF mRNA, and protein expression in pancreatic cancer cells in both normoxic and hypoxic conditions [70].

Apigenin is a strong inhibitor of ornithine decarboxylase, an enzyme that plays a major role in tumor promotion [57]. Apigenin inhibits the TPA-dependent increase in c-jun and c-fos gene expression and tumor promotion in mouse skin. It also suppresses the TPA-mediated COX-2 expression by blocking Akt signal transduction and arachidonic acid release in HaCaT cells [71]. It has been shown to inhibit proteasome activity and induce apoptosis in human breast cancer MDA-MB-231 cells [72]. Apigenin is a well-known inhibitor of protein-tyrosine kinases and has been shown to block peroxisome proliferation regulated kinase (ERK), a MAPK in isolated hepatocytes [73].

QUERCETIN

Quercetin is a dietary flavonoid abundant in variety of foods including apples, berries, brassica vegetables, grapes, onions, shallots, tea, and tomatoes, as well as many seeds, nuts, barks, and leaves [74]. It usually occurs as *O*-glycosides, with D-glucose as the most frequent sugar residue. More than 170 different quercetin glycosides have been identified [75]. Among polyphenols, quercetin is one of the most potent antioxidants, as demonstrated in different studies [76, 77]. It has been shown to inhibit oxidative species generating enzymes such as xanthine oxidase (XOD), lipoxygenase (LOX) and NADPH oxidase [78]. It is a potent anticancer agent, exhibiting different activities such as cell cycle regulation, interaction with type II estrogen binding sites, and tyrosine kinase inhibition [79]. Intravenous administration of quercetin inhibited the lymphocyte tyrosine kinase in cancer patients and it is the first tyrosine kinase inhibiting compound tested in a human phase I trial [80]. Studies have revealed that this flavonoid is capable of inhibiting LPS induced inflammation in macrophages [81]. Quercetin could inhibit the gene expression of TNF- α via modulation of NF- κ B in human peripheral blood mononuclear cells [82]. It inhibited the growth of multiple cancer cell lines by mitochondrial mediated apoptotic pathway [83]. It has been shown that quercetin reduced the expression of ErbB2 and ErbB3 proteins [84], and potentiated AMPK activation and p53-dependent apoptotic cell death in HT-29 colon cancer cells [85]. Chemopreventive properties of quercetin have been demonstrated in various animal models [86–89], and has been subjected to a Phase I clinical trial in cancer patients [80].

Previous study has shown that quercetin can induce cell cycle arrest at late G1 phase in human leukemic T-cells [90]. Quercetin increased the therapeutic efficacy of cisplatin both *in vivo* and *in vitro* [91] and also enhanced the cytotoxic effect of radiation on rat hepatoma cells [92]. It also caused pronounced apoptosis in both transformed and primary leukemia cells but not in normal blood peripheral mononuclear cells. Quercetin-induced apoptosis was accompanied by Mcl-1 downregulation and Bax conformational change and mitochondrial translocation that triggered cytochrome c release [93]. Quercetin modulates UVB-induced c-Fos expression through activation of p38 and cAMP-responsive element binding protein (CREB) [94]. It enhances the expression of p53, caspase-3,-9, cytochrome c in MDA-MB-231 cells [95]. It has been shown to regulate the expression of oncogenes (H-ras, c-myc and K-ras) and anti-oncogenes (p53) [96], cell cycle control protein (p21WAF1 and p27KIP1) [97], and inhibit different tyrosine and serine–threonine kinases associated with cell survival pathways (MAPK, AKT/PKB) [98]. Robaszekiewicz *et al.* studied the effect of quercetin on A-549 cells proliferation. They found that quercetin acts as both antioxidant

and pro-oxidant depending upon the concentration used. Quercetin at lower concentration enhanced the cancer cell proliferation whereas at higher concentrations showed the concentration dependent cytotoxicity [99]. Previous study has shown that quercetin can prevent metal induced tumorigenesis by inhibiting oxidative DNA damage [100]. It has also been shown to regulate several signal transduction pathways involving MEK/ERK and Nrf2/keap1, which are involved in the processes of inflammation and carcinogenesis [101]. Treatment of quercetin down-regulated the antiapoptotic proteins Bcl-2 and Bcl-xL and also up-regulated the proapoptotic proteins Bax and caspase-3 in prostatic PC-3 carcinoma cells [102]. Quercitrin blocked TPA-induced neoplastic transformation in JB6 P+ cells. Pretreatment of JB6 cells with quercitrin down-regulated transactivation of AP-1 and NF- κ B induced by UVB or TPA. [103], Wang *et al.*, reported that quercetin could activate autophagy in gastric cancer cells by regulating of Akt-mTOR and hypoxia-induced factor 1 α (HIF-1 α) signaling. This was further confirmed in animal model [104]. Previous studies revealed that quercetin can inhibit production of heat shock proteins in several cancers, including breast cancer [105], leukemia [106], and colon cancer [107]. Quercetin has been shown to induce estrogen-induced carcinogenesis in animal models [108, 109].

(-)-EPIGALLOCATECHIN-3-GALLATE

(-)-Epigallocatechin-3-gallate (EGCG) is the most abundant catechin, representing ~16.5 wt % of the water extractable fraction of green tea leaves [110]. EGCG is a strong anti-oxidant and it has been demonstrated to inhibit carcinogen-induced oxidative stress [111]. EGCG has been shown to inhibit NF- κ B activity, MAPK pathway, AP-1 activity, and EGFR-mediated downstream signaling pathways [112]. Previous studies have revealed that EGCG suppressed Akt activation in both colon cancer cell lines and *in vivo* mouse models [112, 113]. Topical application of EGCG to the skin has been shown to decrease the incidence of UVB induced skin cancer in SKH-1 mice [114]. EGCG inhibited the expression and activation of MMPs [115–117] and also increased the expression of the tissue inhibitor of MMPs (TIMP1 and TIMP2) [116], indicating its anti-invasive potential. EGCG combined with taxane showed an increase in the expression of apoptotic genes such as p53, p73, p21, and caspase-3 in *in vitro* and also in tumor model [118]. It can inhibit the VEGF expression and angiogenesis induced by interleukin-6 (IL-6) in gastric cancer [119]. EGCG treatment increased the levels of E-cadherin on the cell plasma membrane and suppressed the expression of nuclear β -catenin, c-Myc, phospho-Akt, and phospho-Erk in the tumors [120]. It inhibited cell proliferation and induced apoptosis in various types of cancer cells by inhibiting the activation of the epidermal growth factor receptor (EGFR) family of RTKs [121]. EGCG induced apoptosis in gastric cancer cell lines by down-regulating survivin expression [122].

Regulation of angiogenesis is one of the possible mechanisms by which EGCG can inhibit cancer progression [123]. EGCG inhibits IL-6-induced VEGF expression and angiogenesis via suppressing Stat3 activity in gastric cancer [119]. EGCG abolishes the activation of FAK and suppresses more than 50% of cell proliferation without evidence of apoptosis analyzed by PARP cleavage [124]. EGCG inhibits cell proliferation and AKT phosphorylation at Ser473 in MDA-MB-231 and A549 cells [125]. It has been shown to inhibit the activities of a variety of enzymes. Xu *et al.* reported the chemopreventive effect of EGCG on N-methyl-

N'-nitro-N-nitrosoguanidine (MNNG)-induced gastrointestinal cancer in rats [126]. It inhibited the phosphorylation of JNK, JUN, MEK1, MEK2, ERK1, ERK2, and ELK1 (Ets-like protein 1) in JB6 epidermal cell lines [127]. EGCG inhibits HGF-induced tumor growth and invasion in oral cancer [128]. It inhibited AZ521 cell proliferation by preventing β -catenin oncogenic signaling through proteasomal degradation of p68 [129]. EGCG treatment caused dose-dependent cell growth inhibition, cell cycle arrest at the G(0)/G(1) phase, and DNA fragmentation in HT-1080 cells [130]. EGCG showed significant reduction in tumor volume, proliferation, angiogenesis and metastasis and induction in apoptosis, and growth arrest in pancreatic cancer cells. EGCG also inhibited circulating endothelial growth factor receptor 2 (VEGF-R2) positive endothelial cells derived from xenografted mice. Tumor samples from EGCG treated mice showed significantly reduced ERK activity; and enhanced p38 and JNK activities [131].

ISOTHIOCYANATES

Isothiocyanates (ITCs) are electrophilic compounds that play a major role in potential chemopreventive effects associated with high intake of cruciferous vegetables such as watercress, brussel sprouts, broccoli, cabbage, horseradish, radish, and turnip [132]. Cruciferous vegetables have been widely accepted as potential diet components that may decrease the risk of cancer [133]. Epidemiological studies show that dietary intake of ITCs is associated with reduced risk of certain human cancers [134]. ITCs display anticarcinogenic activity by reducing the activation of carcinogens and increase their detoxification. They have been shown to inhibit the carcinogen-activating cytochrome P450 mono-oxygenases and also induce carcinogen-detoxifying phase 2 enzymes [135]. They exhibit anti-tumor activity by regulating multiple pathways including apoptosis, MAPK signaling, oxidative stress, and cell cycle progression [136]. They also inhibited the growth and proliferation of several types of cancer cells, such as prostate cancer [137], breast cancer [138], lung cancer [139], cervical cancer [140], leukaemia [141], and colorectal cancer [142].

ITCs have been divided into six dietary isothiocyanates (ITCs), allyl isothiocyanate (AITC), benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), sulforaphane (SFN), erucin (ERN), and iberin (IBN) based on biological activities [143]. PEITC and SFN are two of the most widely investigated isothiocyanates from the crucifers, which are highly effective in reducing the risk of cancer, induced by carcinogens in animals as well as cell culture models [144]. PEITC suppressed prostate cancer progression by induction of autophagic cell death [145]. They induced cervical cancer cell apoptosis by stimulating DR4 and DR5 through the inactivation of ERK and MEK [146]. They also have been shown to induce G2/M phase arrest and apoptosis in human prostate cancer DU 145 Cell [147].

PEITC induces apoptosis in human osteogenic sarcoma U-2 OS cells through ROS, caspase-3, and NO signaling pathways [148]. Recent studies have revealed that ITCs is able to inhibit the metastasis potential of human hepatoma cells [149], colon cancer cells [150], and breast cancer cells [151]. Previous studies reported that BITC and PEITC inhibited the metastasis potential of highly metastatic lung cancer cells by inducing apoptosis and cell cycle arrest, via targeting the MAPK/AP-1 pathway [152]. PEITC also inhibited the

migration and invasion of human gastric cells by regulating the extracellular signal-regulated kinases 1/2 (ERK1/2), protein kinase C (PKC), and nuclear factor-kappaB (NF- κ B) signaling pathways [153]. AITC has been shown to decrease the proliferation and viability of human brain malignant glioma GBM 8401 cells in a dose-dependent manner [154].

Shan *et al.* evaluated the protective effect of SFN on human vascular endothelial cells against lipopolysaccharide-induced inflammatory damage. Treatment of SFN inhibited the expression of COX-2, and iNOS and also suppressed the phosphorylation of ERK1/2, JNK, and p38 activated by lipopolysaccharide [155]. SFN has been shown to inhibit the interleukin-6 (IL-6)-inducible activation of STAT3, which is an oncogenic transcription factor activated in many human malignancies, including prostate cancer [156]. It activates NF-E2 related factor-2 (Nrf2), a well-known chemopreventive target and activates the Nrf2-regulated cytoprotective signaling pathway [157]. Treatment with SFN induced apoptosis in B16F-10, a highly metastatic melanoma cells by activating caspases 3,-9, Bax, p53 and downregulating Bcl-2, caspase-8, Bid, and NF- κ B [158]. It reduced the G1 phase cell distribution and also down regulated the phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2), and induced apoptosis in HCT116 cells [159]. Sulforaphane induces down-regulation of β -catenin in human cervical carcinoma HeLa and hepatocarcinoma HepG2 cells [160].

GENISTEIN

Genistein is an isoflavone compound, found in soy bean and related products such as tofu, soy milk and soy sauce [161], and is a promising cancer chemotherapeutic agent [162]. Treatment of genestein has shown to inhibit the growth of many different cancer cell lines by increasing apoptosis, inducing cell cycle delays, and modulating intracellular signaling pathways [162]. It inhibited tumor growth in mouse models of breast, prostate and skin cancers [163, 164]. Recent studies have demonstrated that genistein inhibited EGF-induced proliferation in colon cancer cells via regulating the PI3K/Akt pathway [165], and also induced apoptosis and cell cycle arrest at G(2)/M phase [166]. Li *et al.* showed that treatment of genestein enhanced the apoptotic effect of chemotherapy drugs in H460, a lung cancer cell line, through the inactivation of NF- κ B [167]. Genistein induced cell cycle arrest and apoptosis in breast cancer cells [168], and also modulated BRCA1 expression *in vitro* [169] and *in vivo* [170]. Laboratory investigations demonstrated that the growth inhibitory effects of genestein were linked to the inhibition of PI3K, leading to the inhibition of Akt, and eventual inhibition of NF- κ B [10, 167, 171]. Treatment of genestein can inhibit β -catenin-mediated WNT signaling through increasing sFRP2 gene expression by demethylating its silenced promoter in colon cancer cell line DLD-1 [172]. It has the potential to stimulate breast cancer cell death through mobilizing endogenous copper ions and generation of reactive oxygen species (ROS) [6].

Genistein has been shown to decrease the synthesis of prostaglandins in several normal and malignant cells [173–175]. In the cell culture experiments, genistein decreased cyclooxygenase-2 (COX-2) mRNA and protein expression in both human PCa cell lines (LNCaP and PC-3) and primary prostate epithelial cells and increased 15-hydroxyprostaglandin dehydrogenase (15-PGDH) mRNA levels in primary prostate cells

[176]. Treatment with genistein combined with prostate tumor irradiation significantly enhanced inhibition of prostate tumor growth and increased mouse survival in metastatic orthotopic PC-3 xenograft tumor model [177, 178]. It also inhibited the activation of NF- κ B DNA binding activity and upregulation of APE1/Ref-1 induced by radiation *in vitro* and in PC-3 prostate tumors *in vivo* [178, 179]. Genistein is a potent antiangiogenic agent which can inhibit VEGF-induced endothelial cell activation by decreasing protein tyrosine kinase (PTK) activity and MAPK activation [180]. It also decreased the activation of JNK and p38, induced by VEGF [180]. Genistein promotes the tissue-plasminogen activator (tPA) activity in human cervical cancer cells (HeLa S3) and in human umbilical vein endothelial cells (HUVEC) [181]. It has been demonstrated that genistein could inhibit osteolytic bone metastases, suppress bone resorption, increase bone mass and improve bone microstructure in bone metastases of breast cancer [172]. It has the potential to inhibit NF- κ B activation and modulate inflammatory pathways [179, 182, 183]. It also induces apoptosis via NF- κ B dependent and independent pathways [184]. Pretreatment with this isoflavone inhibited Src/STAT3/HIF-1 α activation by radiation and nuclear translocation of HIF-1 α [185].

URSOLIC ACID

Ursolic acid (UA) is a pentacyclic triterpene compound widely found in food, medicinal herbs, apple peel and is able to exhibit a wide range of pharmacological functions, including antioxidant, anti-tumor, and anti-inflammatory activities [186], and is also one of the most promising chemopreventive agents. Ursolic acid can inhibit the activities of DNA polymerase and DNA topoisomerase and decrease the rate of cell proliferation [187]. Ursolic acid attenuated oxidative stress-mediated hepatocellular carcinoma induction by diethylnitrosamine in male Wistar rats [188]. It also decreased the production of pro-inflammatory markers including COX-2, iNOS, TNF- α , IL-1 β , IL-2, and IL-6 in LPS-treated mouse brain [186]. Treatment with UA suppressed TPA-mediated induction of COX-2 protein and synthesis of PGE2 in human mammary epithelial cells. It also inhibited TPA-mediated activation of protein kinase C, extracellular signal regulated kinase 1/2 (ERK1/2), c-Jun NH2-terminal kinase 1/2 (JNK1/2), and p38 mitogen-activated protein kinase (MAPK) [189]. Ursolic acid potentiates its anti-tumor effects through suppression of NF- κ B and STAT3 pathways in prostate cancer [190]. Harmand *et al.* reported the apoptotic potential of ursolic acid in HaCat derived keratinocyte cell line. Treatment with UA decreased the viability of HaCat cells in a concentration- and time-dependent manner. In addition, cell cycle analysis revealed that UA treated HaCat cells were blocked predominantly in G1 phase [191]. It also has been found to inhibit the proliferation of MCF-7 cells followed by a significant decrease in CyclinD1/CDK4 expression, which can be regulated by FoxM1 [192].

Ursolic acid potentiates TRAIL-induced apoptosis through activation of ROS and JNK-mediated up-regulation of death receptors and down-regulation of decoy receptor 2 (DcR2) and cell survival proteins [193]. It has been shown to induce apoptosis in highly metastatic melanoma cell line, B16F-10 by activating cells p53 and caspase-3 gene expressions and inhibiting the NF- κ B mediated activation of bcl-2 [194]. Ursolic acid inhibits the invasion and metastasis of various cancers such as ovarian carcinoma [195], prostate [196, 197], and breast [198], probably through inhibiting the activity of gelatinase and the expressions of

MMP-2 and MMP-9 [180, 197], suppressing CXCR4 expression [196], and modulating c-Jun N-terminal kinase, Akt and mammalian target of rapamycin signalling [198]. It potentiates antiangiogenic activity by regulating VEGF, TIMP-1, MMP-2 and MMP-9 [199]. Shanmugam *et al.* investigated the effect of ursolic acid (UA) on NF- κ B and STAT3 signaling pathways in both androgen-independent (DU145) and androgen-dependent (LNCaP) prostate cancer cell lines. They found that UA inhibited constitutive and TNF- α -induced activation of NF- κ B in DU145 and LNCaP cells in a dose-dependent manner. This suppression was mediated through the inhibition of constitutive and TNF- α -induced I κ B kinase (IKK) activation, phosphorylation of I κ B α and p65, and NF- κ B-dependent reporter activity. Moreover, UA suppressed both constitutive and inducible STAT3 activation concomitant with upstream kinases (Src and JAK2) [190]. Ursolic acid can regulate key steps of angiogenesis *in vitro*, including endothelial cell proliferation, migration, and differentiation [200]. Raphael and Kuttan, investigated the effect of UA on the cell-mediated immune response in metastatic tumor-bearing C57BL/6 mice. They found that intraperitoneal administration of UA (50 μ moles/Kg body) increased natural killer cell activity (NK-activity) and enhanced the antibody dependent cell mediated cytotoxicity (ADCC) in metastatic tumor-bearing animals [201].

LYCOPENE

Lycopene is a most potent antioxidant carotenoid pigment, found in tomatoes, fruits, and vegetables such as red carrots, guava, watermelons, and papayas. High consumption of tomatoes and tomato products containing lycopene has been shown to decrease the risk of cancer [202]. The chemopreventive potential of lycopene can be contributed to its strong antioxidant activity [203]. Epidemiological studies have shown that dietary intake of lycopene is inversely correlated with the risk of many cancers including prostate [204], lung [205], colon [206], leukemia [207] and liver [208]. Lycopene prevents carcinogenesis by interfering with various cell signalling pathways. It regulates the cell cycle progression mainly in the G0/G1 phase via down-regulation of cell cycle regulatory proteins, including cyclin D1, cyclin E, and cyclin-dependent kinases (CDK) 2 and 4 in breast and prostate cancer cell lines [209–211]. A phase II randomized clinical trial of lycopene supplementation before radical prostatectomy showed that lycopene supplementation could decrease the growth of prostate cancer [212]. In another phase II trial combination of lycopene with soy isoflavones more strongly stabilized serum prostate-specific antigen (PSA) levels than lycopene alone in men with prostate cancer [213].

It has been reported that lycopene is able to modulate MAPK signalling in breast cancer cells [214] and is also able to regulate NF- κ B activation by inhibiting ROS production [215]. Lycopene effectively inhibited the HMG-CoA reductase expression and cell growth and inactivated the Ras activation in prostate PC-3, colon HCT-116, HT-29 and lung BEN cancer cells [215]. Scolastici *et al.* studied the antimutagenic potential of lycopene and showed its inhibitory effect on DNA damage induced either directly by hydrogen peroxide (H₂O₂) or indirectly by n-nitrosodiethylamine (DEN) in HepG2 cells [216]. The most important target of lycopene has been found to be IGF-1 receptor signaling. This signaling regulates the downstream Ras/MAPK and PI3K/Akt signalling pathway, leading to the blockade of cell cycle progression and finally apoptosis [217].

PERILLYL ALCOHOL (POH)

The monoterpene perillyl alcohol is a natural product from cherries, lavender, and other plants [218]. Perillyl alcohol (POH) has chemopreventive activity against rat liver cancer [219] and it inhibits the proliferation of cultured human colon carcinoma cells [220]. It exhibits chemotherapeutic activity against chemically induced rat mammary tumors with little toxicity to the host [221–223]. Perillyl alcohol has been shown to induce regression of 81% of small mammary carcinomas and up to 75% of advanced mammary carcinomas initiated by 7,12-dimethylbenz(a) anthracene (DMBA) in the Wistar rat. Dietary POH was more potent than monoterpene limonene at inducing tumor regression [221]. The chemopreventive activity of POH during the promotion phase of liver carcinogenesis is associated with a marked increase in tumor cell death by apoptosis, or programmed cell death [219]. Chaudhary *et al.*, investigated the chemopreventive effect of perillyl alcohol on DMBA-initiated and 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumorigenesis and its possible mechanisms of action in Swiss albino mice [224]. Pretreatment of POH modulated the activities of catalase, glutathione reductase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione contents on TPA-induced skin edema. Perillyl alcohol also suppressed the Ras/Raf/ERK pathway and induced apoptosis [224].

Perillyl alcohol has been shown to inhibit the growth and proliferation of various cancers [225–227]. It induced cell cycle arrest and apoptosis by upregulating the expression of bax, bid, and p21^{waf1}, and also by downregulating cyclinD and cdk2 expression [226]. In a combination treatment, POH and methyl jasmonate blocked cells at the G0/G1 phase of the cell cycle and induced forced apoptosis by the addition of cisplatin in breast cancer cells. Furthermore, POH and methyl jasmonate treatment activated tumor necrosis factor receptor 1 and this was further increased by the addition of cisplatin [228]. Yeruva *et al.* investigated the effects of POH and its metabolite perillic acid (PA) on the proliferation of non small cell lung cancer (NSCLC, A549, and H520) cells and found that both POH and PA elicited dose-dependent cytotoxicity, and induced cell cycle arrest and apoptosis with increasing expression of bax, p21 and caspase-3 activity in both the cell lines. Perillyl alcohol and PA in a combination treatment were also sensitized the cells to cisplatin and radiation in a dose-dependent manner [229].

MOLECULAR TARGETS FOR NATURAL CHEMOPREVENTIVE AGENTS

Regulation of Reactive Oxygen Species (ROS)

Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, so-called oxidants, and their elimination by protective mechanisms, referred to as anti-oxidative systems [230]. Generation of ROS and the corresponding response to oxidative stress are the key factors in the pathogenesis of several human diseases including cancer [231]. There are several studies indicating the relationship between ROS and tumor progression [232–234]. Epidemiological and laboratory studies together indicate that a high consumption of antioxidant-rich fruits and vegetables can reduce the risk of cancer [235–237]. The mitochondria, the cellular membrane oxidases, such as NADPH oxidase, nitric oxide synthase and myeloperoxidase are major sources of ROS. The byproducts associated

with the metabolism of arachidonic acid by cyclooxygenase, lipoxygenase, and cytochrome P450 monooxygenase also result in the production of ROS [238]. The ROS produced in the body include superoxide (O_2^-), hydroxyl (OH^-), hydroperoxyl (HOO^-), peroxy (ROO^-), and alkoxy (RO^-) radicals, and the reactive nitrogen species (RNS) include nitric oxide (NO^-) and the peroxynitrite anion ($ONOO^-$) [231]. Many tumor promoters generate ROS, and the involvement of ROS –particularly hydrogen peroxide (H_2O_2) – in tumor promotion is supported by both *in vivo* and *in vitro* studies [232, 239]. ROS are also known to play a significant role in the promotion stage of carcinogenesis. Vitamins and phenolic phytochemicals are among the most prevalent antioxidants in fruits and vegetables and are considered to prevent ROS-mediated carcinogenicity [231].

Curcumin has antioxidant activity against free radicals and also increases the activity of antioxidant enzymes [240]. Incubation with curcumin resulted in enhanced cellular resistance to oxidative damage [241]. Previous investigation has shown that curcumin prevents lipid peroxidation and DNA strand breakage [242]. Curcumin has been shown to induce phase II detoxifying enzymes (glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and catalase) and enhance the body's natural antioxidant system, leading to detoxification of mutagens and carcinogens [243]. Antioxidant effects of curcumin are 10-fold more potent than ascorbic acid or resveratrol [244]. Curcumin has been found to increase hepatic GSH, SOD, GPx, GR, GST, and CAT activities in paracetamol-treated rats [245]. It also down regulates nitric oxide formation, a key element in inflammation and possibly in the process of carcinogenesis [246, 247]. Curcumin increased heme oxygenase activity in vascular endothelial cells both in normoxic and hypoxic conditions. This function is important in curcumin-mediated cytoprotection against oxidative stress [241].

Resveratrol is a nutraceutical with well-known antioxidant activity [248]. Pinteá *et al.* studied the protective effect of resveratrol against hydrogen peroxide induced oxidative stress in cultured human RPE cells. They found that it has no cytotoxic effect at concentrations of 25–100 μ M in culture media, but showed a protective effect against hydrogen peroxide-induced cytotoxicity. Pretreatment with resveratrol induced a significant, dose-dependent increase of superoxide dismutase, glutathione peroxidase, and catalase activities. Moreover, it also enhanced the level of reduced glutathione under both basal and oxidative stress conditions [249]. Spanier *et al.* have reported that protective effects of resveratrol against oxidative injury is attributed to the upregulation of endogenous cellular antioxidant systems rather than the direct scavenging activity of ROS [250].

EGCG, isolated from green tea, displays several biological and pharmacological properties, antioxidant actions, iron-chelating capabilities, attenuation of lipid peroxidation due to various forms of radicals, and is thought to act as an antioxidant in biological systems [251]. It has also been found to protect and rescue PC12 cells against amyloid β -induced neurotoxicity in a dose dependent manner [252, 253]. In another study, oral supplementation of EGCG significantly decreased the levels of lipid peroxidation and protein carbonyl content in aged rats, possibly by enhancing the GSH redox status and both enzymic and non-enzymic antioxidants status [254]. Laboratory study revealed that EGCG has biphasic action and also acts as prooxidant depending on the concentration and cellular environment [255].

However, at lower concentrations, EGCG has been found to protect cells against the detrimental effects of oxidative stress [253].

Apigenin plays a role in cancer chemoprevention and cancer chemotherapy. It has been found to inhibit lipid peroxidation and protects antioxidant system in N-nitrosodiethylamine administered animals [256]. Apigenin has been found to scavenge free radicals and stimulates phase II detoxification enzymes in culture and tumor model [59]. It also has been shown to increase the level of intracellular glutathione and increase the endogenous defense against oxidative stress [60]. Ursolic acid remarkably inhibited the ethanol-induced oxidative stress in the liver and heart by decreasing lipid peroxidation products (thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides, and conjugated dienes) by enhancing the activities of antioxidant enzymes (superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione S-transferase) [257, 258].

Several studies have indicated that lycopene is an effective antioxidant and free radical scavenger [259]. Lycopene possess high number of conjugated double bonds, exhibits higher singlet oxygen quenching ability compared to β -carotene or α -tocopherol [260]. It has been shown to inactivate hydrogen peroxide and nitrogen dioxide [261, 262]. Dietary intake of lycopene significantly reduced lipid and protein oxidation and demonstrated a protective effect against azoxymethane (AOM)-induced colonic preneoplastic lesions [263]. Laboratory studies have shown that lycopene is able to protect lymphocytes against NO_2 -induced membrane damage and cell death twice as efficiently as β -carotene [261, 264].

REGULATION OF NUCLEAR FACTOR (NF)- κ B ACTIVATION

Nuclear factor (NF)- κ B, one of the most investigated transcription factors, has been found to control multiple cellular processes in cancer including inflammation, transformation, proliferation, angiogenesis, invasion, metastasis, chemoresistance, and radioresistance [265]. Vertebrate Rel/NF- κ B transcription factors include RelA, RelB, c-Rel, p50/p105 and p52/p100 [266]. They exist as homo or heterodimers, which bind to DNA target sites (κ B sites) to influence gene expression. The most common dimer is a p50-RelA heterodimer, specifically called NF- κ B. In most normal cells, they are retained in the cytoplasm as an inactive complex through the direct binding of I κ B inhibitor. Various signals, including many cytokines, can cause degradation of the I κ B protein and the resulting in translocation of the active Rel/NF- κ B complex into the nucleus [267–269]. Continuous activation of NF- κ B factors is also emerging as a hallmark of various types of solid tumors, including breast [270], ovarian [271], colon [272], pancreatic [273], thyroid [274], bladder [275], and prostate, carcinomas [276], as well as in melanomas [277]. Helbig *et al.* have demonstrated that NF- κ B regulates the motility of breast cancer cells by directly upregulating the expression of the chemokine receptor CXCR4 [278]. The regulation of apoptotic response by NF- κ B supports a role in oncogenesis and also in the resistance of tumor cells to chemotherapy [269]. This transcription factor controls the expression of gene products linked with invasion, angiogenesis, and metastasis of cancer [279].

NF- κ B stimulates VEGF, proteolytic enzymes such as MMPs, urokinase plasminogen activator (uPA), and cell adhesion molecules such as ICAM-1 [267]. NF- κ B regulates the

expression of growth factors, cytokines and other factors involved in stress responses, cell proliferation and cell cycle progression [267, 280, 281]. The ability of tumor cells to evade immune surveillance is another contributing factor to tumor progression. The patients with renal cell carcinoma (RCC) showed impaired T-cell signaling as a result of defective NF- κ B activation [282]. Therefore, drugs that could inhibit NF- κ B activity are found to be useful in cancer chemotherapy and treatment [283].

Curcumin exhibits several pharmacological properties in humans and experimental colitis through inhibition of NF- κ B transcription factor in inflammation 9 [284–286]. Curcumin blocked I κ B alpha phosphorylation and degradation, leading to abrogation of NF- κ B activation [287]. It has been shown to down regulate NF- κ B and inhibit IKB kinase, suppressing proliferation and inducing apoptosis [288]. Shishodia *et al.* studied the effect of curcumin on Human mantle cell lymphoma. Their study has shown that treatment of curcumin suppressed NF- κ B activation and also downregulated the expression of this transcription factor regulated gene products (Bcl-2, Bcl-XL, cyclin D1, COX-2, TNF, IL-6, RANK, and RANKL) leading to cell cycle arrest, suppression of proliferation and induction of apoptosis in Human mantle cell lymphoma (MCL) [289]. Curcumin is known to exert anti-inflammatory effects by interrupting NF- κ B signaling at multiple levels. Collet and Campbell, have shown that curcumin induces sustained activation of JNK, which promotes apoptosis in human HCT116 colon cancer cells [290]. Curcumin inhibits inducible NF- κ B activation and suppresses cancer cell proliferation in oral cancer [291], leukemia and multiple myeloma [292], breast cancer [293], ovarian cancer [294], pancreatic cancer [295], bladder cancer [296], and prostate cancer [297]. Curcumin sensitizes human cancer cells to cell-killing agents through NF- κ B pathway. In human pancreatic cancer, the curcumin combination therapy with TNF-related apoptosis inducing ligand (TRAIL) suggests that inhibition of NF- κ B stimulates TRAIL-induced apoptosis [298].

Manna *et al.* investigated the effect of resveratrol on NF- κ B activation induced by various inflammatory agents. They showed that resveratrol blocked TNF- α induced activation of NF- κ B in a dose- and time-dependent manner. Resveratrol also suppressed TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF- κ B. Suppression of TNF- α induced NF-kappaB activation by resveratrol was not restricted to myeloid cells (U-937); it was also observed in lymphoid (Jurkat) and epithelial (HeLa and H4) cells. Resveratrol also blocked the NF-kappaB activation induced by PMA, LPS, H₂O₂, okadaic acid, and ceramide [299]. Resveratrol suppressed phosphorylation and subsequent degradation of I κ B α , thereby inhibiting activation of NF- κ B in TPA-stimulated mouse skin [300].

Apigenin inhibits the transcriptional activity of NF- κ B in LPS-stimulated mouse macrophages. The classical proteasome-dependent degradation of the NF- κ B inhibitor I κ B alpha was observed in apigenin LPS-stimulated human monocytes [301]. Xu *et al.* demonstrated that treatment of apigenin potentiated the activation-induced cell death (AICD) by inhibiting NF- κ B activation and suppressing NF- κ B -regulated anti-apoptotic molecules, cFLIP, Bcl-x(L), Mcl-1, XIAP, and IAP, but not Bcl-2. Furthermore, it suppressed NF- κ B translocation to nucleus and inhibited I κ B- α phosphorylation and degradation in response to TCR stimulation in reactivated peripheral blood CD4 T cells, as

well as in leukemic Jurkat T cell lines [302]. Apigenin has been found to inhibit DNA binding and reduce nuclear levels of the p65 and p50 subunits of NF- κ B in human prostate carcinoma PC-3 cells. Apigenin blocked the I κ B degradation, I κ B- α phosphorylation along with significant decrease in IKK-alpha kinase activity.

Apigenin also inhibited TNF- α -induced activation of NF- κ B via the I κ B- α pathway, thereby sensitizing the cells to TNF- α -induced apoptosis. The inhibition of NF- κ B activation correlated with a decreased expression of NF- κ B -dependent reporter gene and suppressed expression of NF- κ B-regulated genes specifically, Bcl2, cyclin D1, COX-2, MMP-9, iNOS-2, and VEGF, which contribute to prostate cancer progression [303]. Afaq *et al.* evaluated the effect of EGCG on UVB-mediated modulation of the NF- κ B pathway. Treatment of normal human epidermal keratinocytes (NHEK) with EGCG (10–40 μ M) for 24 h resulted in a significant inhibition of UVB (40 mJ/cm²)-mediated degradation and phosphorylation of I κ B- α and activation of IKK- α , in a dose-dependent manner. Data suggest that EGCG protects against the adverse effects of UV radiation via modulations in NF- κ B pathway, and provide a molecular basis for the photochemopreventive effect of EGCG [304]. Pretreatment of normal human bronchial epithelial cells (NHBE) cells with EGCG suppressed CSC-induced phosphorylation of I κ B- α , and activation and nuclear translocation of NF- κ B /p65, which leads to the significant downregulation of NF- κ B -regulated proteins cyclin D1, MMP-9, IL-8, and iNOS [305]. Quercetin has been found to inhibit the NF- κ B and their downstream cascade including TNF- α and NO [306]. It binds to the NF- κ B in HepG2 cells [307]. Davis *et al.*, demonstrated that the soy isoflavone genistein inhibits the cell growth and induced apoptosis in human prostate cancer, LNCaP and PC3 cells by regulating NF- κ B [308]. Treatment with low doses of UA has been found to sensitize cancer cells to chemotherapeutic agents, taxol or cisplatin through suppressing NF- κ B [309].

INHIBITION OF ANGIOGENESIS

Angiogenesis is the development of new blood vessels from the pre-existing vascular beds. It is tightly regulated by a large number of proangiogenic and antiangiogenic factors, occurs in response to the increasing demand for nutrients and oxygen experienced by proliferating tumor cells. Angiogenesis plays a pivotal role in tumor growth, invasion, and metastasis [310]. Tumors cannot grow beyond a size of approximately 1–2mm without neovascularization [311]. The angiogenic process involves the activation, proliferation, and migration of endothelial cells toward angiogenic stimuli produced by the tumor [312]. The tumor cells induced secretion of angiogenesis factors which is commonly observed in most aggressive tumors. The process of angiogenesis is mediated by several pro-angiogenic molecules released by both tumor cells and host cells including endothelial cells, epithelial cells, mesothelial cells, and leucocytes [310]. These pro-angiogenic molecules bind to receptors on nearby blood vessels and induce the activation, proliferation, and migration of endothelial cells towards the tumor. Stimuli for the production of pro-angiogenic mediators include hypoxia, cytokines, and growth factors, as well as mutations in oncogenes and tumor suppressor genes [313].

Among various angiogenic factors, VEGF, fibroblast growth factor (FGF) family, interleukin-8 (IL-8), angiogenin, angiotropin, epidermal growth factor (EGF), platelet-derived endothelial cell growth factor (PD-ECGF), platelet derived growth factor (PDGF), fibrin, nicotinamide, transforming growth factor- α (TGF- α), TGF- β , and tumor necrosis factor- α (TNF- α) are important regulators [314]. Degradation of basement membrane is a crucial event in angiogenesis. Many proteases are capable of degrading extracellular matrix components. They are of three major groups: Serine proteases, Cathepsins, and Matrix metalloproteases (MMPs). Urokinase plasminogen activator is the most important member of the serine protease family involved in ECM degradation. It is secreted as an inactive, single chain precursor that requires binding to its cell membrane receptor for activation [313]. Members of this system, including uPA and its receptor (uPAR), are over expressed in several malignant tumors [315]. MMPs are a broad family of zinc-binding endopeptidases, which secreted in inactive proenzymatic forms. MMPs can be subdivided on the basis of preferential extracellular matrix substrate [316]. Among matrix metalloproteinases (MMPs), gelatinases such as MMP-2 and MMP-9 play a key role in degrading most ECM components surrounding tumor tissue [317].

There are several natural products which have been tested for their antiangiogenic potential [318]. Curcumin is found to be a potent angiogenesis inhibitor which downregulates various proangiogenic proteins such as vascular endothelial growth factor and basic fibroblast growth factor [319].

Previous studies have shown that curcumin inhibited vascular endothelial cell proliferation *in vitro* and capillary tube formation *in vivo* [288, 320, 321]. Curcumin has been shown to down-regulate the hypoxia-induced mRNA and the protein expression of VEGF, leading to suppression of hypoxia-stimulated angiogenesis [322]. Thaloor *et al.* studied the effect of curcumin on endothelial cell migration, attachment, and tube formation on matrigel. Curcumin treatment resulted in a dose-dependent inhibition of tube formation and metalloproteinase activities. It also inhibited angiogenesis in a s.c. matrigel plug model in mice [323].

Singh *et al.* investigated the antiangiogenic potential of EGCG, and found that treatment of EGCG inhibited the tube formation, migration and regulated MMPs [324]. Apigenin has been found to inhibit tumor angiogenesis by downregulating HIF-1 and VEGF expression in human ovarian cancer cells under normoxic condition [325]. Apigenin also suppressed the expression of erythropoietin mRNA, which is a typical hypoxia-inducible gene, via the degradation of HIF-1 α [326].

Genistein has been found to be the most potent angiogenesis inhibitor among the flavanoids compounds. Treatment with genistein caused a dose-dependent inhibition in the expression of VEGF, PDGF, uPA, and MMP-2 and 9, respectively. Furthermore, angiogenesis inhibitors-plasminogen activator inhibitor-1, endostatin, angiostatin, and thrombospondin-1 were also upregulated [327]. Igura *et al.*, studied the effect of resveratrol and quercetin on the inhibition of angiogenesis *in vitro*. They found that treatment of resveratrol and quercetin inhibited angiogenesis by inhibiting the migration and tube formation in bovine aorta endothelial (BAE) cells [328].

Antiangiogenic potential of UA in both *in vitro* and *in vivo* model was investigated. Treatment of ursolic acid inhibited the proliferation, migration, invasion, and tube formation in human umbilical vein endothelial cells (HUVEC). The levels of serum VEGF, NO, and proinflammatory cytokines were significantly reduced, whereas serum TIMP-1 and IL-2 levels were significantly elevated in UA treated animals compared with those in control animals. Gelatin zymographic analysis also showed the inhibitory effect of UA on the protein expression of matrix metalloproteinases MMP-2 and MMP-9 [199].

The PEITC treatment caused a decrease in survival of HUVECs in a concentration- and time-dependent manner. The tube formation and migration by HUVEC was also inhibited in the presence of PEITC at pharmacologically relevant concentrations. This effect has been associated with suppression of VEGF secretion, downregulation of VEGF receptor 2 protein levels, and inactivation of prosurvival serine-threonine kinase Akt [329]. Sulforaphane showed inhibitory effects on hypoxia-induced VEGF and VEGF receptor (flk-1) expression, and also two angiogenesis-associated transcription factors, HIF-1 α and c-Myc in HMEC-1 cells [330]. This compound also caused the inhibition of cell migration and capillary tube formation in HUVECs by regulating the MEK/ERK and PI3K/AKT pathways which synergistically induced FOXO transcriptional activity [331].

REGULATIN OF APOPTOSIS

Cancer is a disorder characterized by uncontrolled proliferation and reduced apoptosis. Apoptosis, a genetically programmed cell-suicide process, is vital for the proper development and functioning of multicellular organisms. It is characterized by typical morphological and biochemical hallmarks, including cell shrinkage, membrane blebbing, nuclear condensation, and fragmentation [332, 333]. Inducing apoptosis is an effective method of treating cancers. There are two major pathways, extrinsic and intrinsic, have been identified for the induction of apoptosis [334]. The most evident morphological signs of apoptosis are cellular shrinkage, membrane blebbing, nuclear condensation, and fragmentation, which are the final steps of consequential signaling cascades [335]. Apoptotic signaling pathways can also be divided into caspase-dependent and -independent or mitochondria-dependent and -independent pathways. Caspases are cysteine proteases and play a central role in the initiation and execution phases of apoptosis.

Activation of caspases is recognized as a key element in the apoptotic process [336]. They are of two types, initiator caspases (caspase 2, 8, 9 and 10), and effector or executioner caspases (caspase 3, 6 and 7). Initiator caspases transmit the death signal generated by the apoptotic stimulus to the effector caspases, which act to cleave the target proteins and thus produce the morphological features of apoptosis [337]. During apoptosis, the released cytochrome c from mitochondria triggers caspase-9 activation whereas ligation of death receptors on the plasma membrane activates caspase-8 [338]. p53 also called 'guardian of the genome', the first tumor suppressor gene involved in cell cycle regulation and induction of apoptosis. p53 can be activated by a variety of stimuli such as radiation and anticancer agents, leading to cell cycle arrest and/or apoptosis [339]. It has been found that; p53 is either mutated or overexpressed in most of the human tumors along with antiapoptotic gene bcl-2 that enhances tumor cell proliferation and metastasis [340].

Curcumin has been shown to induce apoptosis in many types of cancer cell lines [341–343]. Previous studies have demonstrated that curcumin induces apoptosis through a mechanism of downregulating ornithine decarboxylase and along a ROS dependent mitochondria-mediated pathway in human acute promyelocytic leukemia HL-60 cells [344]. Curcumin treatment resulted in cleavage of caspase-3 and poly adenosine diphosphate-ribose polymerase. It also increased the cellular levels of apoptotic Bcl-XL protein and a decreased the cellular content of antiapoptotic protein Bcl-2 [345]. Wu *et al.*, studied the effect of curcumin on human non-small cell lung cancer NCI-H460 cells. They have shown that curcumin induces apoptosis in NCI-H460 cells in a dose-dependent manner. Curcumin treatment upregulated BAX and BAD and down regulated BCL-2, BCL-XL and XIAP. It also has been shown that increase the reactive oxygen species (ROS), intracellular Ca (2+) and endoplasmic reticulum (ER) stress in NCI-H460 cells after exposure to curcumin [346]. It has been suggested that production of reactive oxygen intermediates the release of cytochrome c causing tumor cell apoptosis as a result of curcumin treatment [347]. Curcumin is also able to induce mitochondrial abnormalities and promote p53-dependent apoptosis and the activation of caspase-8 and caspase-3 [348–350].

Resveratrol-treatment inhibited the constitutive expression of phosphatidylinositol 3'-kinase (PI3K) and phosphorylated (active) Akt in human prostate carcinoma LNCaP cells. It also down regulated the level of anti apoptotic protein Bcl-2 and up regulated the proapoptotic members of the Bcl-2 family such as Bax, Bak, Bid, and Bad [351]. Resveratrol activate intracellular Notch-1 and restore wild-type p53 expression in glioblastoma cells. Significant de-phosphorylation of Akt, increased Bax expression and decreased Bcl-2 expression and cleavage of caspase-3 were also observed in resveratrol-induced apoptosis in glioblastoma cells [352].

EGCG inhibited the growth of anaplastic thyroid carcinoma cells in a dose-dependent manner. Treatment of EGCG has been shown to suppress the phosphorylation of EGFR, ERK1/2, JNK, and p38. These changes were correlated with increased p21 and reduced cyclin B1/CDK1 expression. Furthermore, it increased the accumulation of sub-G1 cell, activated caspase-3 and cleaved PARP [353]. Lim and Cha studied the *in vitro* cytotoxic effect of EGCG against human laryngeal epidermoid carcinoma Hep2 cells. EGCG-treatment increased the p53 level in the cells, with a corresponding decrease in Bcl-2 and Bid protein levels as well as an increase in the Bax level. EGCG also induced the cytoplasmic release of cytochrome c from the mitochondria accompanied by a decreased mitochondrial membrane potential, and subsequently upregulated translocation of apoptosis-inducing factor (AIF) and endonuclease G (EndoG) into the nucleus during the apoptotic process [353].

Treatment with apigenin inhibited the proliferation of MDA-MB-453 human breast cancer cells in a dose- and time-dependent manner. Apigenin activated caspase-9 and -3, accompanied by the cleavage of caspases-6, -7, and -8 [354]. Wang *et al.* reported that the apoptotic rate was significantly increased in tumor cells treated with ursolic acid both *in vitro* and *in vivo*. Ursolic acid induced DNA fragmentation, upregulated caspase-3, -8, and -9 and down regulated expression of Bcl-2 in BGC-803 cells [355]. Ursolic acid at non-cytotoxic concentrations, upregulated the tumor suppressor gene p53 and caspase-3 and

down-regulated the anti-apoptotic gene Bcl-2 in B16F-10 melanoma cells [194]. Incubation of HepG2 cells with quercetin induced apoptosis by the activating caspase-3 and -9, but not caspase-8. Furthermore, this flavonoid decreased the Bcl-xL:Bcl-xS ratio and increased translocation of Bax to the mitochondrial membrane. It also inhibited the major survival signals, Akt and extracellular regulated kinase (ERK) in the same experiment [356].

REGULATION OF CYCLOOXYGENASE (COX)-2

Cyclooxygenase (COX) is a member of the prostaglandin synthase family of enzymes that plays an important role in the growth and progression of cancer. They are made up of two main types of enzymes, namely COX-1 and COX-2. COX-1 enzyme is constitutively expressed in normal circumstances, whereas COX-2, which is an inducible enzyme, has a major role in inflammatory response [357, 358]. COX-2 is overexpressed in inflammatory states which are induced by a variety of stimulators including cytokines, growth factors, as well as tumor promoters [359]. The specific function of COX-2 is the conversion of arachidonic acid to prostaglandin (PGE(2)), a major metabolite in inflammation. COX-2 has been found to be constitutively expressed in a number of cancers, colon [360, 361], prostate [362, 363] breast [364], where the expression of COX-2 is paralleled by a higher incidence of chemotherapy failure. A study showed that COX-2 was expressed in 24% of adenomas and in 56% of adenocarcinomas [365]. COX-2 protein inhibitors (i.e., NSAIDs and COXIBs) are not recommended for prolonged administration since they may cause severe side effects [366].

Curcumin is a potent inhibitor of COX-2. It inhibits COX-2 via NF- κ B downregulation, which is one of the major inducers of COX-2 promoter activation [367]. Celecoxib is a promising preventive drug but its long-term use causes adverse cardiovascular effects [368]. Curcumin in combination with celecoxib have been shown to inhibit colon cancer cell growth by suppressing COX-2 [369]. In another study, curcumin has been found to inhibit PMA-induced COX-2 mRNA and protein levels in H460 cells [370]. Wang *et al.* studied the effect of curcumin on deoxycholic acid (DCA) induced cell proliferation in human HT-29 colon cancer cell line and its underlying molecular mechanisms. They found that treatment of curcumin inhibited the cell proliferation by regulating COX-2 mRNA transcription, COX-2 protein expression, and PGE(2) synthesis induced by DCA in HT-29 cell line [371].

Resveratrol dose-dependently prevented both COX-2 induction and PGE(2) production in bFGF-stimulated fibroblasts [372]. Studies revealed that apigenin can inhibit the phorbol ester-induced COX-2 expression in the breast cancer cell lines (MCF-10A and MCF-7) [373] and human brain microvascular endothelial cells (HBMEC) [374]. Furthermore, apigenin suppressed the expression of COX-2 by decreasing the intracellular Ca(2+) level and inhibiting NF- κ B activation in human mast cell line (HMC-1) [375]. In another study EGCG has been found to inhibit COX-2, PGE(2), and IL-8 expression, induced by IL-1beta in human synovial fibroblasts [376], and the inhibition of COX-2 was associated with inhibition of NF- κ B translocation [377]. Genistein in combination with capsaicin exerts anti-inflammatory and anticarcinogenic properties through the modulation of COX-2 in TPA (12-O-tetradecanoylphorbol-13-acetate) -treated rat mammary glands or mammary cancer cell line [378].

INHIBITION OF SIGNAL TRANSDUCERS AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3)

STAT proteins were originally identified as being latent cytoplasmic transcription factors, which were only translocated to the nucleus upon Jak-mediated phosphorylation and dimerization following cytokine-induced activation of Jaks [379]. Constitutive activation of Stat proteins, notably of Stat3 and also Jak- Stat3 signalling pathway has been frequently observed in many primary human tumors [380, 381]. Dysregulated Stat3 has been associated with increased breast cancer cell proliferation, survival, and metastasis [382]. Abberent Stat3 promotes uncontrolled growth and survival through dysregulation of gene expression, including cyclin D1, c-Myc, Bcl-xL, Mcl-1, and survivin genes, thereby contributing to oncogenesis [380, 383, 384]. Constitutive activation of Stat3 signaling also confers resistance to apoptosis in human U266 myeloma cells [385], in breast cancer cells [382] and in other cells [386]. Inhibition of the Stat3 pathway has been shown to induce apoptosis in breast cancer cell lines [387]. Antiapoptotic proteins, such as Bcl-xL and Mcl-1, were shown to be up-regulated in multiple myeloma cells in which constitutive Stat3 activity was induced by IL-6 [385, 388].

Curcumin was shown to inhibit constitutive and IL-6-induced Stat3 activation in human multiple myeloma cells [389]. Stat3 was considered to be a master regulator in human glioma and essential for tumor cell survival and its ability to invade the normal brain [390]. Weissenberger *et al.* studied the effect of curcumin on Jak/Stat3 activity in glioma cell. Low dose of curcumin treatment inhibited Jak1,2/Stat3 tyrosine-phosphorylation in a dose-dependent fashion. Curcumin downregulated transcription of the Stat3 target genes c-Myc, MMP-9, Snail, and Twist, and of the proliferation marker Ki67. It has also been shown to inhibit cell proliferation by inducing a G2/M phase arrest [391]. Treatment of cancer cells with curcumin induced a dose- and time-dependent decrease of constitutive IL-6 expression and IL-6-induced Stat3 phosphorylation in ovarian and endometrial cancer cells. Stat3 activation was found to be reversible and was returned to control levels 24 h after curcumin removal [392].

Epigallocatechin-3-gallate inhibits growth and angiogenesis of gastric cancer by inhibiting VEGF and Stat3 activation [393]. It blocked Stat3 phosphorylation (Tyr705 and Ser727) and thereby inhibited the collagen production and proliferation in keloid fibroblasts cells [394]. EGCG also markedly inhibited the activation of Stat3 in YCU-H891 (carcinoma of the hypopharynx) cells [395] and BT-474 (human breast cancer *cell*) cells [396]. Apigenin inhibited Stat3 phosphorylation following exposure to hypoxia. Interestingly, Stat3 inhibition is correlated with VEGF expression [397]. Previous study has shown that luteolin inhibited phosphorylation of STAT3 and inhibited the expression of cyclin D1, survivin, Bcl-x(L), and VEGF [398].

Resveratrol has been found to regulate interleukin (IL)-6-induced ICAM-1 gene expression by attenuating Stat3 phosphorylation [399]. Resveratrol promotes differentiation and apoptosis of medulloblastoma cells by suppressing Stat3 signaling and a range of cancer-associated gene expression [400]. Yang *et al.*, reported that resveratrol can reduce *in vivo* tumorigenicity and enhance the sensitivity of glioblastoma tumor initiating cells (GBM-TIC)

to radiotherapies through the Stat3 pathway [401]. Quercetin inhibited Cu(2+)-oxidized LDL-induced endothelial apoptosis through modulating Jak2-Stat3 pathways [402]. *In vitro* treatment of activated T cells with quercetin blocked IL-12-induced tyrosine phosphorylation of Jak2, Tyk2, Stat3, and Stat4, resulting in a decrease in IL-12-induced T cell proliferation and Th1 differentiation [403]. Pathak *et al.* showed that treatment of UA, inhibited both constitutive and IL-6-inducible Stat3 activation in a dose- and time-dependent manner in multiple myeloma cells [404].

REGULATING MITOGEN-ACTIVATED PROTEIN KINASES (MAPKs) PATHWAY

Mitogen-activated protein kinases (MAPKs), comprising a family of serine and threonine kinases of ERK, JNK, and p38, play an important role in the transmission of cell signals through transduction systems to cell nucleus, where they influence the expression of genes that regulate important cellular processes such as cell growth, differentiation, proliferation, survival, migration, and apoptosis [405, 406]. Components of these pathways are mutated or aberrantly expressed in human cancer (e.g., Ras, B-Raf, PI3K, PTEN, Akt) [407]. The Raf/MEK/ERK pathway has a major role in the regulation of apoptosis by the post-translational phosphorylation of apoptotic regulatory molecules including Bad, caspase 9, and Bcl-2 [408]. This pathway also contributes to chemotherapeutic drug resistance as ectopic activation of Raf induces resistance to doxorubicin and paclitaxel in breast cancer cells, and also B-Raf has been found to be mutated in various malignancies including melanoma, thyroid and breast cancer [409]. Similar to other MAPKs, p38 is activated by MAP kinase kinases (MAPKKs/MKKs) with MKK3 and MKK6 being the two main upstream MAPKKs [410]. p38 stimulates a number of downstream substrates, including MAP kinase-activated protein kinase-2 (MAPKAPK-2/MK2), transcription factor-2 (ATF-2), mitogen- and stress-activated kinase (MSK), and p53 [411–413].

Curcumin caused a down-regulation of enhancer of zeste homolog 2 (EZH2) genes through stimulation of three major members of the mitogen-activated protein kinase (MAPK) pathway: c-Jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and p38 kinase in MDA-MB-435 human breast cancer cells [414]. Weir *et al.* reported that curcumin induced apoptosis in cisplatin-resistant human ovarian cancer cells by modulating p38 and Akt [415]. Curcumin also has been shown to suppress the PMA-induced phosphorylation of ERK, JNK, and p38 MAP kinase in human astrogloma cells [416].

Resveratrol has been found to activate MAP kinases pathways and induce apoptosis in human breast cancer cells MCF-7 [417]. Dietary supplementation of resveratrol attenuated chronic colonic inflammation in mice. Treatment of resveratrol reduced prostaglandin E synthase-1 (PGES-1), COX-2, and iNOS proteins expression, via downregulation of p38, a mitogen-activated protein kinase (MAPK) signal pathway in chronic dextran sulphate sodium (DSS)-induced colitis mice model [418].

Noh *et al.* found that apigenin could inhibit PMA-induced phosphorylation of p38, which was involved in the down-regulation of the expression of MMP-9 at mRNA levels. Furthermore, the treatment of p38 MAPK inhibitors (SB203580) to Caski cells caused the

reduction of MMP-9 expression [419]. Apigenin treatment caused increased phosphorylation of ERK1/2 and JNK1/2 and this sustained activation resulted in decreased ELK-1 phosphorylation and c-FOS expression, leading to inhibition cell survival in human prostate cancer cells [420].

Treatment of EGCG significantly inhibited the phosphorylation of p38 and c-Jun N-terminal kinase (JNK), NF- κ B, and AP-1 transcriptional activities in human corneal epithelial cells [421]. In another study, EGCG inhibited Ang II-induced endothelial stress fiber formation and hyperpermeability via inactivation of p38 MAPK/HSP27 pathway [422]. Quercitrin blocked TPA-induced neoplastic transformation in JB6 P+ cells. Pretreatment of JB6 cells with quercitrin down-regulated transactivation of AP-1 and NF- κ B induced by UVB or TPA through the inhibition of MAPKs phosphorylation, including ERKs and p38 kinase and the inhibition of JNKs [103]. Ursolic acid inhibited the proliferation and induced apoptosis in HT-29 colon cancer cells by inhibiting the EGFR/MAPK pathway. Treatment with UA suppressed the phosphorylation of EGFR, ERK1/2, p38 MAPK, and JNK, which is well correlated with its growth inhibitory effect [423].

REGULATION OF CELL CYCLE

Cell growth and proliferation are highly regulated events in normal cells, and dysregulation of cell cycle can lead to uncontrolled proliferation and contribute to the malignant phenotype of tumor cells [421]. Cancer cells are characterized by a failure of cell cycle control which results in their over proliferation. Cell cycle checkpoints play pivotal roles in the regulation of critical events, including DNA replication, cellular proliferation, cellular differentiation, and apoptosis [424]. Cell cycle control is a highly regulated process that involves the modulation of cell cycle regulatory proteins, including cyclins (cyclin A, B, Ds, or E); cyclin-dependent kinases (CDKs) (CDK 1, 2, 4, or 6); and CDK inhibitors, such as p21WAF1, p27KIP1, p53, and phosphorylated retinoblastoma (pRb) [425]. Many phytochemicals have been shown to regulate the cell cycle proteins, leading to the inhibition of cancer cell proliferation. In addition, cell cycle checkpoints, such as G1/S and G2/M, are also important targets in cell cycle control [426]. Studies showed that apoptosis was accompanied by a reduction in the number of cells in G0/G1 and an increase in the number of G2/M-phase cells, indicating a cell cycle arrest in G2/M phase [427–429].

Lu *et al.* investigated the curcumin induced DNA damage, S and G2/M phase arrest in the colorectal carcinoma HCT116 cells [430]. In another study curcumin induced successive G(1)/S and G(2)/M phase arrest accompanied by down-regulation of cyclin D1, cdc2 and cyclin B1 in HOS cells [431]. Treatment of quercetin caused G2/M arrest in human esophageal squamous cell carcinoma cell line through up-regulation of p73 and p21waf1 and subsequent down-regulation of cyclin B1, both at the mRNA and protein levels [432]. Resveratrol (100 μ mol/L) induced cell cycle block and accumulation of cells at the G0–G1 phase by 48 h in PANC-1 cells. In AsPC-1 cells, resveratrol caused cell cycle arrest and induced depletion of cells in the S and G2-M phases of the cell cycle [433].

In vitro study showed that EGCG down-regulated cell cyclereLATED proteins such as cyclin B1 and CDK1, whereas p21 was up-regulated in ARO cells [353]. Apigenin remarkably

inhibited Huh7 cell proliferation and induced cell cycle arrest at G2/M phase and an increased rate of apoptosis [434]. In another study, apigenin blocked the proliferation of two types of leukemia through cell-cycle arrest in G(2)/M phase (myeloid HL60) and G(0)/G(1) phase for (erythroid TF1 cells) [435].

Isothiocyanates induced G(2)/M cell cycle arrest accompanied by mitotic phosphorylation of histone H3 in multiple myeloma [436]. PEITC induced a dose-dependent decrease in cell viability through induction of cell apoptosis and cell cycle arrest in the G(2)/M phase of DU 145 cells. The induction of G(2)/M phase arrest was mediated by the increase of p53 and WEE1 [147].

REGULATION OF ACTIVATOR PROTEIN-1

Activator protein-1 (AP-1) is a transcription factor that regulates genes involved in carcinogenesis, cell proliferation, and progression of benign tumors to malignancy and in metastasis. It is formed by dimerization of activated c-Jun, and c-FOS [437, 438]. When AP-1 is activated, it binds to TPA response elements (TRE) or cAMP response element (CRE) in the promoter region of the target genes [439]. There is a close relationship between c-fos over-expression and tumor development. Furthermore, inactivation or suppression of c-jun leads to the development of papillomas and liver tumors [440]. JNK and p38 MAPK phosphorylation enhances the activity of c-Jun and ATF2 proteins, which in turn activate AP-1 target genes [441]. AP-1 has been found to induce COX-2, uPA, c-Fos, MMP-9, cyclin D1, VEGF [442], and this transcription factor is recognized as a molecular target of many antioxidant and chemopreventive compounds [443]. Inhibition of AP-1 has been shown to block tumor promotion, transformation, progression, and invasion [444].

Curcumin effectively blocks AP-1 and NF- κ B signaling pathways and enhances apoptosis in many cancer cell lines [445]. Curcumin also has been reported to inhibit the activation of AP-1 induced by tumor promoters by direct interaction with the AP-1 DNA-binding motif and to inhibit C-Jun N-terminal kinase (JNK) activation by carcinogens [389, 442]. Resveratrol inhibited the c-Fos [446] and suppressed AP-1 DNA binding affinity [54], via MEK1 > ERK1/2 signaling [51]. Treatment of EGCG inhibited phosphorylation of the MAPKs p38, JNK and AP-1 transcriptional activity in human corneal epithelial cells [421]. Electrophoretic mobility shift assay revealed that EGCG inhibits binding of AP-1 proteins to its response elements in synovial fibroblast [447]. Nair *et al.*, showed that treatment of SULF in combination with EGCG attenuated AP-1 activity in PC-3 cells [448].

Previous study showed that treatment of apigenin inhibited c-Fos / AP-1 activity by regulating and Janus kinase 2 (JAK2) / signal transducer and activator of transcription 1/2 (STAT1/2) pathways in interleukin-1 β -treated articular chondrocytes [449]. Hwang *et al.* investigated the protective effects of apigenin and luteolin on immortalized human keratinocytes (HaCaT) against UVA damage, and found that treatment of both flavanoids inhibited UVA-induced collagenolytic MMP-1 production by interfering with Ca(2+)-dependent MAPKs and AP-1 signaling [450]. Li *et al.* showed that Ras/MAPK/AP-1 signalling pathway is involved in genistein induced G2/M cell cycle arrest in MDA-MB-231 breast cancer cells [451].

CONCLUSION

Natural products are a rich source of cancer chemotherapy drugs, and primarily target rapidly proliferating tumor cells. Chemoprevention by edible phytochemicals is of great interest and is considered to be an inexpensive, readily applicable, acceptable, and accessible approach to cancer control and management. Several phytochemicals are in preclinical or clinical trials for cancer chemoprevention. Epidemiological studies have shown that high dietary consumption of vegetables and fruits reduced the risk of cancer. Severe toxicity is the major drawback in conventional radiotherapy and chemotherapy. Both methods exert toxic side effects, such as nausea, vomiting, mucosal ulceration, alopecia, pulmonary fibrosis, cardiac, and hepatic toxicity. Use of natural compounds as an adjunct to chemotherapy and radiation may reduce treatment toxicities as well as increase the therapeutic index. Studies showed that phytochemicals, including curcumin, resveratrol, epigallocatechin gallate, apigenin, quercetin, genistein, lycopene, ursolic acid, isothiocyanates, and perillyl alcohol exerted anticancer effects by multiple signal transduction pathways. They inhibited the reactive oxygen species production, NF- κ B activation, angiogenesis, AP-1 and COX-2; regulated Stat3 and MAPKs pathway; and induced cell cycle arrest and apoptosis; in various experimental models. Based on these available evidences, it can be concluded that the daily consumption of fruits and vegetables rich in above discussed components could be beneficial for the cancer prevention. The better strategy to identify the compounds for cancer prevention is through mechanism based investigation. The understanding of molecular mechanism of a specific plant derived compound against a particular type of cancer will leads to the invention of novel drug and drug targets for therapeutic intervention.

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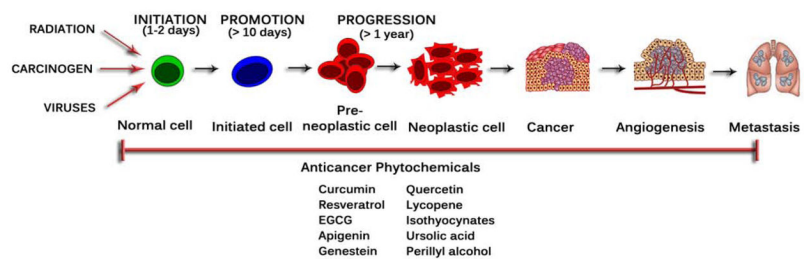


Fig. (1).
Multi-step process in carcinogenesis.

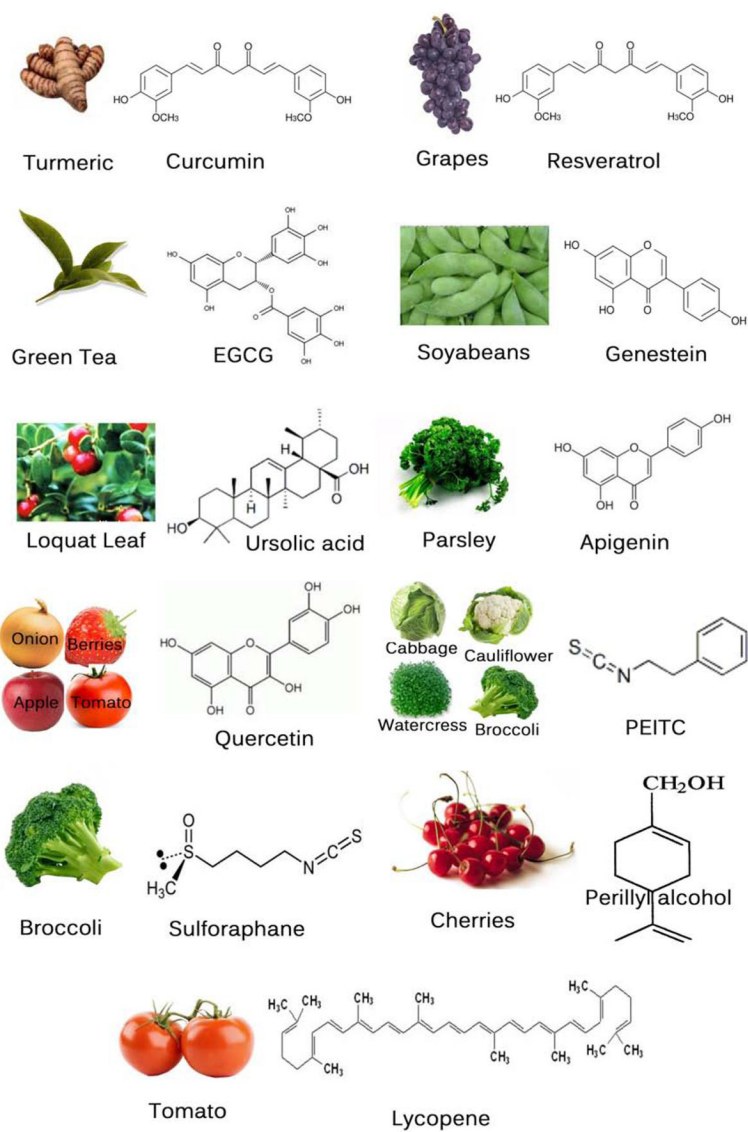


Fig. (2).
Chemical structures and sources of natural chemopreventive agents.

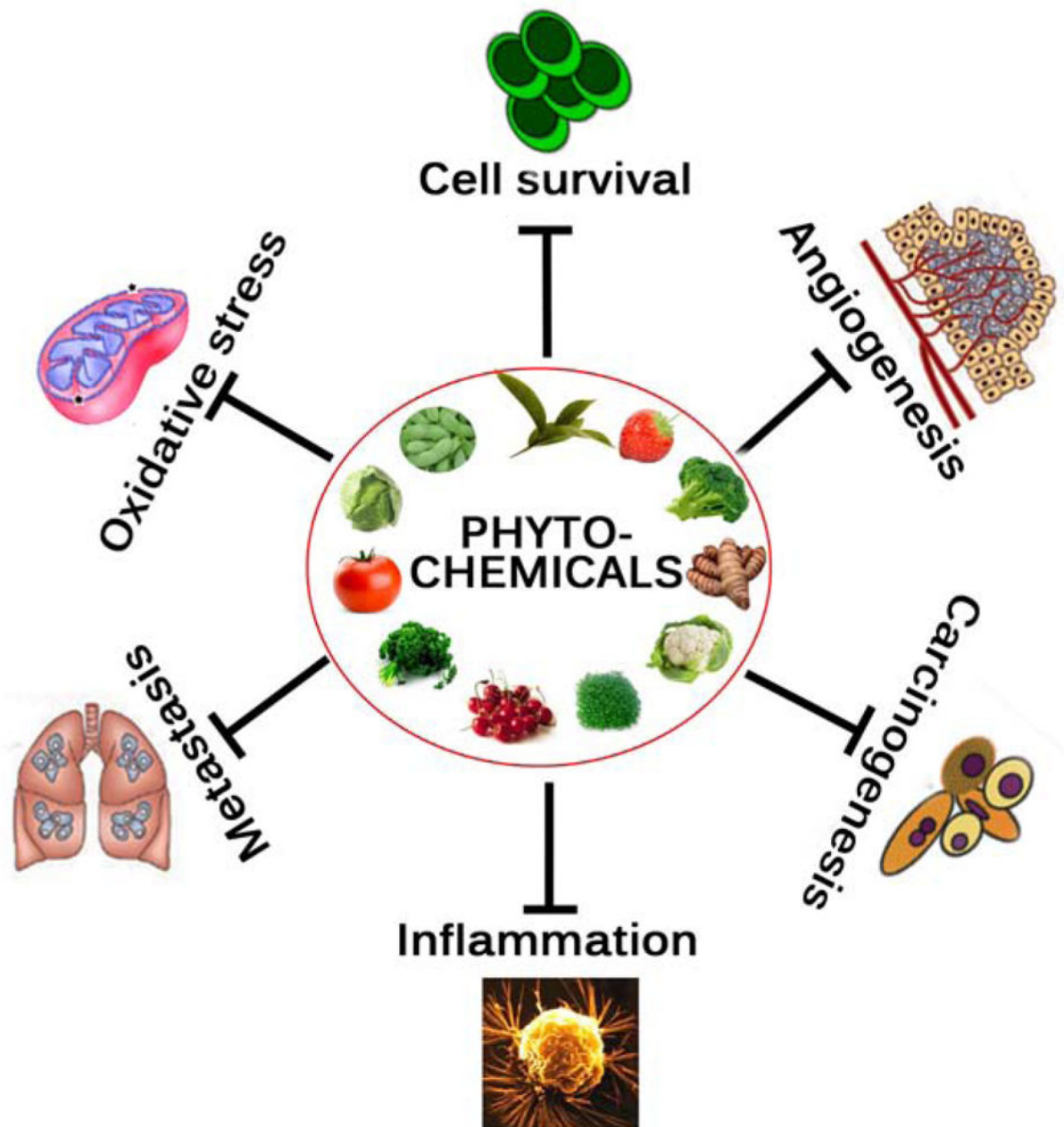


Fig. (3).
Targets of natural chemopreventive agents.

Table 1

Molecular Targets for Natural Chemopreventive Agents

Agent	Natural Source	Mechanism of Action	Molecular Targets
Curcumin	<i>Curcuma longa</i> (turmeric powder)	Anti-oxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiinflammation, antiangiogenesis.	EGFR, IGF-1R, AKT, NF- κ B, COX-2, LOX, ERK, AP-1, PI3K, VEGF, VEGFR1, MMP-2/9, p53, p21, Bax, iNOS, STAT3/5, TRAIL-R1/DR4, G2/M phase arrest, cyclin D1, c-myc, Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1, JNK.
Resveratrol	Red wine, grapes (mainly in the skin), mulberries, peanuts, vines, pines	Antioxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiangiogenesis, antiinflammation	SOD, catalase, glutathione, AKT, AP-1, NF- κ B, iNOS, COX-2, STAT3, survivin, p53, p21, BAX, BAK, MMP-2, MMP-9, Bcl-2, Bcl-xL, and Caspase-3.
EGCG	Camellia sinensis (green tea)	Antioxidant, anti-mutagenesis, anti-proliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiinflammation, antiangiogenesis.	p53, p73, p21, Bax, EGFR, AKT, NF- κ B, Bcl-2, cyclin D1, COX-2, VEGF, MMP-2/9, STAT3, ERK1/2, AP-1, IL-12,
Isothiocyanates	cruciferous vegetables, watercress, brussels sprouts, broccoli, cabbage, horseradish, radish	Anticarcinogenesis, Anti-oxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiinflammation, antiangiogenesis.	MEK, ERK1/2, PKC, COX-2, iNOS, JNK, p38, c-Jun and c-Fos
Quercetin	phytoalexin, skin of red grapes and red wine	Anticarcinogenesis, Anti-oxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiinflammation, antiangiogenesis.	MAPK, AKT, Bcl-2, Bax and caspase-3, mTOR
Genistein	Soybeans and soy products, red clover (<i>Trifolium pretense</i>), sicilian pistachio (<i>Pistacia vera</i>)	Antioxidant, antiproliferation, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis, antiangiogenesis, antiinflammation	AKT, NF- κ B, Bcl-2, survivin, cyclin D1, COX-2, MMP-2/9, p53, p21, GADD153, Bax, STAT3/5, ERK1/2, CDK1, AP-1, IGF-1R
Apigenin	Parsley, <i>Petroselinum crispum</i>	Anti-oxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis	MAPK, PI3K-AKT, NF- κ B, Bcl-2, cyclin D1, COX-2, MMP-2/9, ICAM-1, HIF-1, VEGF
Ursolic acid	Loquat leaf, apples, bilberries, cranberries	Anti-oxidant, antiproliferation, anticarcinogenesis, cell cycle arrest, apoptosis.	COX-2, iNOS, TNF- α , IL-1 β , IL-2 and IL-6, JNK1/2, MAPK, CyclinD1/CDK4.
Perillyl alcohol	cherries, lavender	Antioxidant, antiproliferation (growth inhibition, cell cycle arrest, apoptosis), antiangiogenesis, antiinflammation,	MAPK, AKT, bax, p21 and caspase-3
Lycopene	Tomatoes, guava, rosehip, watermelon, papaya, apricot and pink grapefruit; most abundant in red tomatoes	Antioxidant, antiproliferation (growth inhibition, cell cycle arrest, apoptosis), antiangiogenesis, antiinflammation, immunomodulator	Cyclin D1, Bcl-2, Bcl-xL, AKT, BAD, NF- κ B, MMP-9, Sp-1, IGF-BP3

Abbreviations: EGFR, epidermal growth factor receptor; EGCG, epigallocatechin-3-gallate; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; NF- κ B, nuclear factor- κ B; MMP-2/9, matrix metalloproteinases; IL-12, interleukin 12; Jun-N-terminal kinase; iNOS, inducible nitric oxide synthase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; COX-2, cyclo-oxygenase-2; VEGF, vascular endothelial growth factor; VEGFR1, vascular endothelial growth factor receptor 1; TNF- α , tumor necrosis factor- α ; JNK, Jun-N-terminal kinase; CDK, cyclin-dependent kinase; ERK, extracellular signal-regulated kinase; SOD, superoxide dismutase; mTOR, mammalian target of rapamycin; DR, death receptor; PAFR, platelet activating factor receptor; NO, nitric oxide; eNOS, endothelial nitric oxide synthase. ICAM-1 intercellular adhesion molecule 1; Mcl-1 myeloid cell leukemia 1; XIAP, X-chromosome-linked IAP; Bax Bcl-2-associated X protein, Bcl-2 B cell lymphoma 2; AP-1 activator protein 1; IGF-BP3, insulin-like growth factor binding protein 3.