Cancer Chemoprevention by Dietary Phytochemicals: Promises and Pitfalls

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Abstract: Research over the past decade has provided convincing evidence to support the premise that phytochemicals from the diet offer protection against cancer risk. A large number of dietary phytochemicals have been demonstrated to exhibit anticancer activities by interfering with multiple signaling pathways aberrant in cancer. These agents target a plethora of cellular molecules and molecular pathways including xenobiotic-metabolizing enzymes, reactive oxygen species, inflammation, cell cycle, apoptosis, invasion, angiogenesis, transcription factors, and protein kinases. In addition, dietary phytochemicals also synergize with conventional chemotherapy and radiotherapy. Thus naturally derived phytochemicals could play an important role in cancer chemoprevention and therapy owing to multitargeted mechanistic action and lack of substantial toxicity. However, more rationally designed novel clinical trials are required to translate the preclinical findings into tangible clinical benefits.

Keywords: Chemoprevention, dietary agents, molecular targets, multitargeted prevention, phytochemicals.

INTRODUCTION

Cancer, a multifactorial disease, is a major cause of morbidity and mortality worldwide, accounting for 7.6 million deaths annually [1]. Carcinogenesis is a multistep process involving three discernible stages, initiation, promotion, and progression [2]. Environmental factors play a key role in carcinogenesis in addition to genetic susceptibility and epigenetic modifications. Human exposure to chemicals in the environment is the most critical factor in malignant transformation [3]. The quintessential traits of cancer cells, namely self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion, and metastasis collectively dictate the transformation of a normal cell to a malignant phenotype [4]. The sequential accumulation of mutations that occurs during carcinogenesis presents considerable opportunities for clinical interventions to prevent cancer initiation and treat preneoplastic conditions.

THE CONCEPT OF CHEMOPREVENTION

Cancer chemoprevention refers to the use of synthetic or natural agents to reverse, suppress, or prevent either the initiation phase of carcinogenesis, or the progression of neoplastic cells to cancer [5]. Thus chemoprevention envisages the multistep and multifocal nature of carcinogenesis as well as aberrations in multiple molecular pathways. Based on the stage at which the intervention is conducted, chemoprevention is classified into three complementary levels: primary, secondary, and tertiary chemoprevention. While primary chemoprevention is undertaken in high-risk individuals, secondary chemoprevention targets individuals with pre-malignant lesions, and tertiary chemoprevention is aimed to prevent secondary forms of cancer in patients already treated for a primary cancer [6]. The major goal of cancer prevention is to reduce the risk of cancer in the early stages.

Classification of Chemopreventive Agents

Watternberg [7] categorized chemopreventive agents into three classes: i) *inhibitors of carcinogen formation* that prevent the formation of carcinogens from precursor substances, ii) *blocking agents* that inhibit carcinogen-induced mutations by preventing metabolic activation of carcinogens, enhancing detoxification systems, or by trapping reactive oxygen species (ROS) before they interact with critical target sites, and iii) *suppressing agents* that prevent tumor progression by influencing cell proliferation, differentiation, senescence and/or apoptosis. A large number of phytochemicals inhibit carcinogenesis by one or more of these mechanisms [8]. Chemopreventive agents have also been found to increase the efficacy of conventional chemotherapeutic agents [9, 10].

Sources of Chemopreventive Agents

Several potential chemopreventive agents have been identified from microbial, marine, and plant sources. Many microbial products predominate among the agents developed by the Division of Cancer Treatment and Diagnosis (National Cancer Institute, National Institutes of Health) such as rapamycin, and cyclosporin A. The first anticancer product derived from marine sources to enter clinical trials was didemnin B, a cyclic depsipeptide isolated from the tunicate *Tridemnum solidum*. The vinca alkaloids, vinblastine and vincristine, taxanes, and silymarin are classic examples of plant-derived anticancer agents. In addition, plant-derived agents such as flavopiridol, and homoharringtonine have entered clinical trials for anticancer evaluation [11]. A wide

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range of dietary constituents has also been found to protect against neoplastic transformation [12].

Dietary Phytochemicals

Epidemiological studies have demonstrated an inverse correlation between high intake of fruits, and vegetables, and the risk of cancer. The Mediterranean diet rich in tomatoes and olive oil has been suggested to be responsible for the lower incidence of cancer in that region [13, 14]. Enhanced consumption of garlic was found to be associated with decreased risk of cancer at different sites [15]. The anticancer effects of tea polyphenols have been amply demonstrated in cancer cell lines, and in experimental as well as epidemiological studies [16-19].

The health benefits of dietary agents have been attributed to the constituent phytochemicals and more than 1000 different phytochemicals belonging to diverse structural and functional chemical classes have been identified to display potential chemopreventive activities. These include curcumin, a major constituent of turmeric; resveratrol, a phytoalexin found in grapes; genistein, a phytoesterone component of soy beans; 6-gingerol, a phenolic substance found in ginger; polyphenols and (-)-epigallocatechin gallate (EGCG) in green and black tea; indole-3-carbinol (I-3-C), a compound found in broccoli, cabbage, and brussel sprouts; lycopene, the red pigment in tomatoes; diallyltrisuphide (DATS) and diallyldisulphide (DADS), organosulphur constituents of garlic; and anthocyanins and flavonoid constituents of pomegranate [20, 21]. Table **1** lists some dietary phytochemicals with anticancer properties.

The concept of chemoprevention by dietary phytochemicals is gaining increasing attention because of their chemical diversity, structural complexity, inherent biologic activity, affordability, easy availability, and lack of substantial toxic effects. Most importantly, phytochemicals protect against different types of cancer due to their ability to modulate a plethora of signal transduction pathways [12, 21, 22].

MOLECULAR TARGETS OF CHEMOPREVENTIVE AGENTS

Numerous cellular molecules and multiple signaling pathways have been identified as potential targets of chemopreventive agents. These include xenobiotic-metabolizing enzymes (XME); ROS generation and signaling; cyclooxygenase-2 (COX-2) and lipooxygenase (LOX) pathways; transcription factors; proteins involved in cell cycle, apoptosis, invasion, and angiogenesis; and enzymes involved in epigenetic modifications [20, 21].

Carcinogen Activation/Detoxification Enzymes

The probability that a carcinogen will reach a target cell and cause DNA damage is largely dependent upon the balance between carcinogen activation catalyzed by phase I cytochrome P450 (CYP) enzymes, and detoxification accomplished by phase II enzymes such as glutathione S-transferases. Ligand binding of the carcinogen to aryl hydrocarbon receptor (AhR) results in the nuclear translocation and dimerization of AhR and induction of CYP enzymes. Dietary phytochemicals including curcumin, EGCG, and resveratrol exert their chemopreventive activity by imparing nuclear translocation and dimerization of AhR, and decreasing the activities of phase I enzymes, while simultaneously increasing the activities of phase II enzymes through the activation of nuclear factor-erythroid2-related-factor-2 (Nrf2) signaling pathway [23-25].

ROS Scavenging and Anti-Inflammatory Effects

ROS produced by xenobiotic metabolism or inflammatory processes can damage DNA eventually leading to neoplastic transformation [26, 27]. Antioxidants that scavenge ROS protect against carcinogenesis by one or a combination of the following mechanisms: inhibition of procarcinogen activation, carcinogen inactivation, blocking DNA adduct formation, enhancing DNA repair enzymes, inhibition of cell proliferation, invasion, and angiogenesis, upregulating gap junctional communication, reducing protooncogene activation and mutant p53 expression, apoptosis induction, and modulation of transcription factors and proteins involved in tumor progression [12, 14, 15, 28]. Many phytochemicals function as potent antioxidants and inhibit the proinflammatory mediators COX-2 and LOX by suppressing the transcription factors NF-κB and activator protein-1 (AP-1) and by inhibiting nitric oxide synthase induction [27-29].

Cell Proliferation and Cell Cycle Arrest

Proliferation and cell cycle progression are prime targets of several chemopreventive phytochemicals [30]. Dietary phytochemicals have been demonstrated to block cell proliferation by inhibiting signal transducing protein kinases and polyamine biosynthesis, induce cell cycle arrest at G0/G1 and G2/M phase, upregulate cyclin-dependent kinase (CDK) inhibitors such as $p21^{Cip1/waf1}$ and downregulate cyclins, and CDKs [21, 31-33].

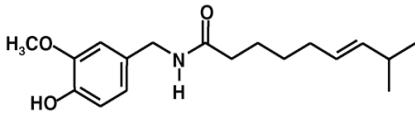
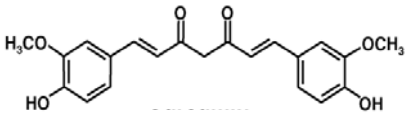
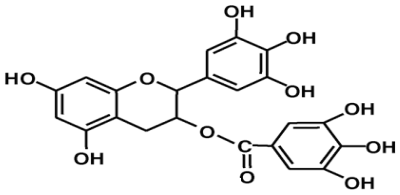
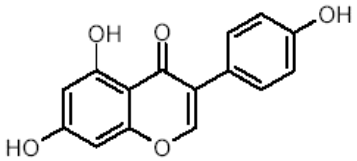
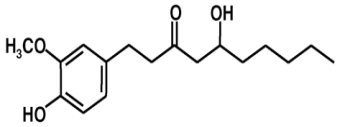
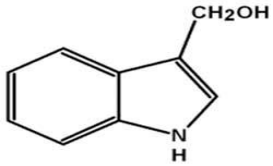
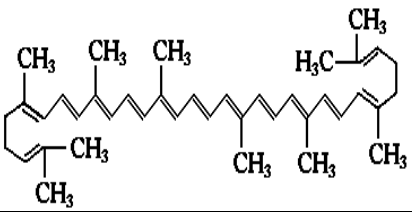
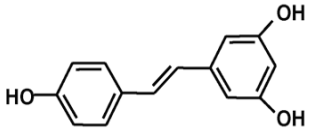
Apoptosis Induction

Identification of agents that target molecules that play a crucial role in apoptosis regulation has evolved as a new paradigm in anticancer drug development [34]. Phytochemicals induce apoptosis via multiple mechanisms including activation of death receptor signaling, altered expression of the Bcl-2 family proteins that control mitochondrial release of cytochrome *c*, downregulation of the expression of anti-apoptotic Bcl-2, and inhibitors of apoptosis proteins (IAPs), upregulation of proapoptotic Bax, cytochrome *c*, activation of the caspase cascade, and poly(ADP-ribose) polymerase (PARP) cleavage [27,34,35]. Curcumin, EGCG, and lycopene were found to induce apoptosis through p53-dependent Bax induction, and inhibit cell cycle progression by upregulating $p21^{waf1/Cip1}$ and $p27^{Kip1}$ CDK inhibitors [36-39].

Angiogenesis Inhibition

Suppression of angiogenesis that plays a key role in tumor growth, progression, and metastasis is an attractive strategy for halting the process of carcinogenesis [40]. Curcumin inhibits epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), and nontyrosine kinase receptors such as Src and focal adhesion kinase that are responsible for

Table 1. Some Dietary Phytochemicals with Anticancer Activity

Phytochemical	Dietary Source	Structure
Capsaicin	Red chilli	
Curcumin	Turmeric	
DADS and DATS	Garlic	
EGCG	Tea	
Genistein	Soy beans	
6-Gingerol	Ginger	
Indole-3-carbinol	Broccoli, cabbage	
Lycopene	Tomato	
Resveratrol	Grapes	

the induction of angiogenic genes [41]. Resveratrol abrogates VEGF-mediated tyrosine phosphorylation of vascular endothelial cadherins and β-catenin, and prevents cytokine-induced vascular leakage [42].

Wnt Signaling

β-Catenin, a multifunctional protein, and a component of the Wnt signaling pathway, activates genes whose products are involved in cell cycle regulation, cell adhesion, and cellular development [43]. Curcumin downregulates Wnt signaling through degradation of β-catenin by caspases or by blocking nuclear translocation of β-catenin [44]. Isoflavones inhibit Wnt signaling by enhancing the expression of glycogen synthase kinase-3β (GSK-3β), binding of GSK-3β to β-catenin, increasing phosphorylation of β-catenin, and attenuating Wnt-induced proliferation and inhibition of Wnt target genes [45,46]. Fig. (**1**) illustrates the modulation of Wnt signaling by chemopreventive phytochemicals.

Modulation of Transcription Factors and Signaling Kinases

Several dietary phytochemicals have been identified to target upstream signaling kinases and downstream transcription factor activities. Strategies that target the transcription factor NF-κB that regulates the transcription of over 400 genes involved in the control of cell proliferation, cell cycle, apoptosis, invasion, metastasis, and angiogenesis are considered central in designing effective anticancer agents for therapy [47, 48]. Phytochemicals with proven chemopreventive efficacy such as curcumin and resveratrol inhibit NF-κB signaling by preventing NF-κB activation, blocking the phosphorylation and proteasomal degradation of inhibitory kappaB (IκB) thereby preventing nuclear translocation of NF-κB [47-50]. Akt inactivation is a key event in suppression of NF-κB signaling by curcumin and genistein [51, 52]. Fig. (**2**) shows the modulation of NF-κB signaling by chemopreventive phytochemicals.

Phytochemicals such as curcumin and resveratrol suppress activation of AP-1, a transcription factor that promotes cell proliferation [49, 50]. Proteasomal degradation of Kelch-like ECH-associated protein 1 (Keap1), that sequesters the transcription factor Nrf2 leads to nuclear translocation of Nrf2 and activation of phase II enzymes [53]. Fig. (**3**) illustrates the mechanism of phase II enzyme activation by phytochemicals via disruption of the Nrf2-Keap1 complex, and nuclear translocation of Nrf2.

Dietary phytochemicals suppress activation of signal transducers and activators of transcription (STAT) in tumor cells by inhibiting STAT phosphorylation, and consequent nuclear translocation, cell survival, and apoptosis evasion [54]. Curcumin, and EGCG modulate mitogen activated protein kinase (MAPK) cascade either by inhibiting the activation of extracellular signal regulated kinase (ERK), c-Jun NH_2-terminal kinase (JNK) or by downregulating the expression of MAPK [55, 56].

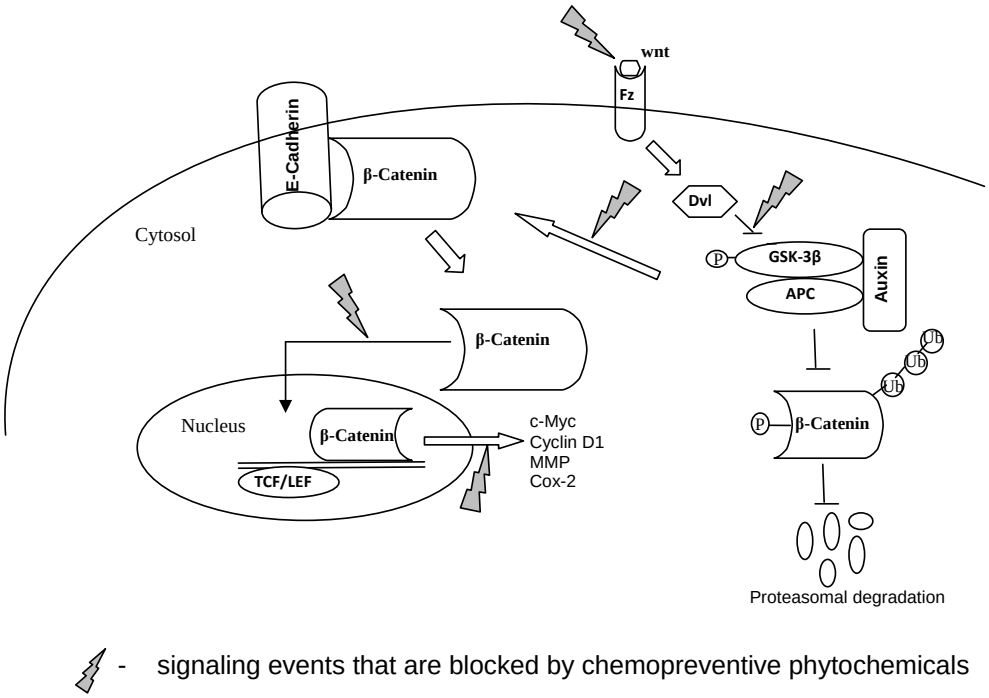


Fig. (1) Modulation of β-catenin mediated signaling by chemopreventive phytochemicals. Binding of Wnt to its frizzled receptor activates Dvl, leading to the inhibition of APC/Axin/GSK3β-mediated β-catenin degradation by E3 ubiquitin ligase. Phytochemicals block β-catenin-mediated signaling by blocking Wnt/Dvl-mediated inactivation of GSK3β, inhibiting nuclear translocation of β-catenin, and/or blocking the formation of β-catenin-TCF/LEF complex and transcriptional activation of target genes. APC, Adenomatous polyposis coli; Dvl, Dishevelled; Fz, Frizzled receptor; GSK3β, Glycogen synthase kinase-3β; LEF, Lymphoid enhancer factor; TCF, β-Catenin/T-cell transcription factor.

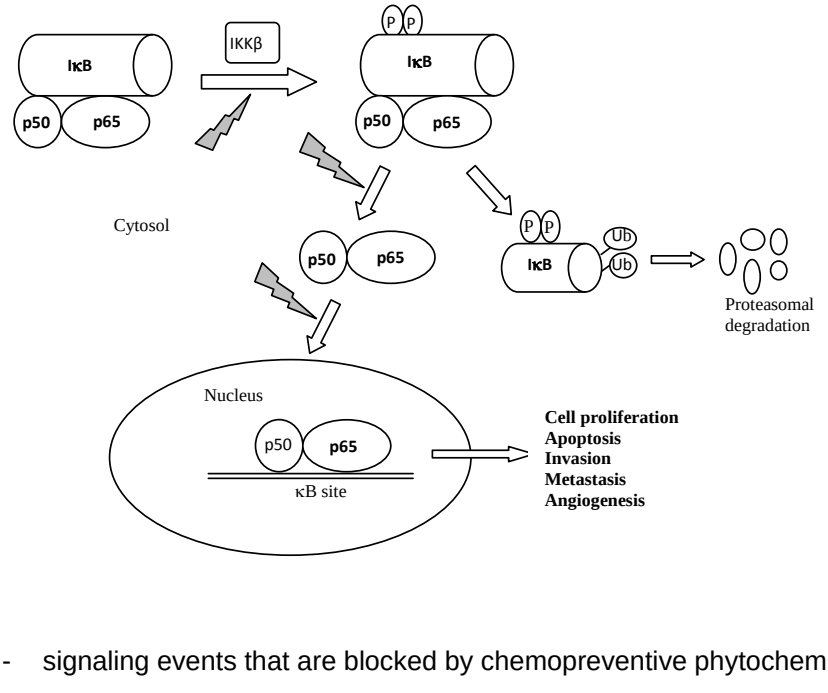


Fig. (2). Modulation of nuclear factor κB (NF-κB) signaling by phytochemicals. NF-κB exists in the cytoplasm as heterodimers complexed to IκB. Phosphorylation of IκB by IKKβ followed by polyubiquitination and proteasomal degradation releases NF-κB that translocates to the nucleus, binds to κB elements in the DNA, and transactivates downstream genes. Chemopreventive phytochemicals prevent NF-κB signaling by inhibiting I*κ*B phosphorylation, and blocking the nuclear translocation of NF-κB. IκB, Inhibitor of NF-κB; IKKβ, IκB kinase β.

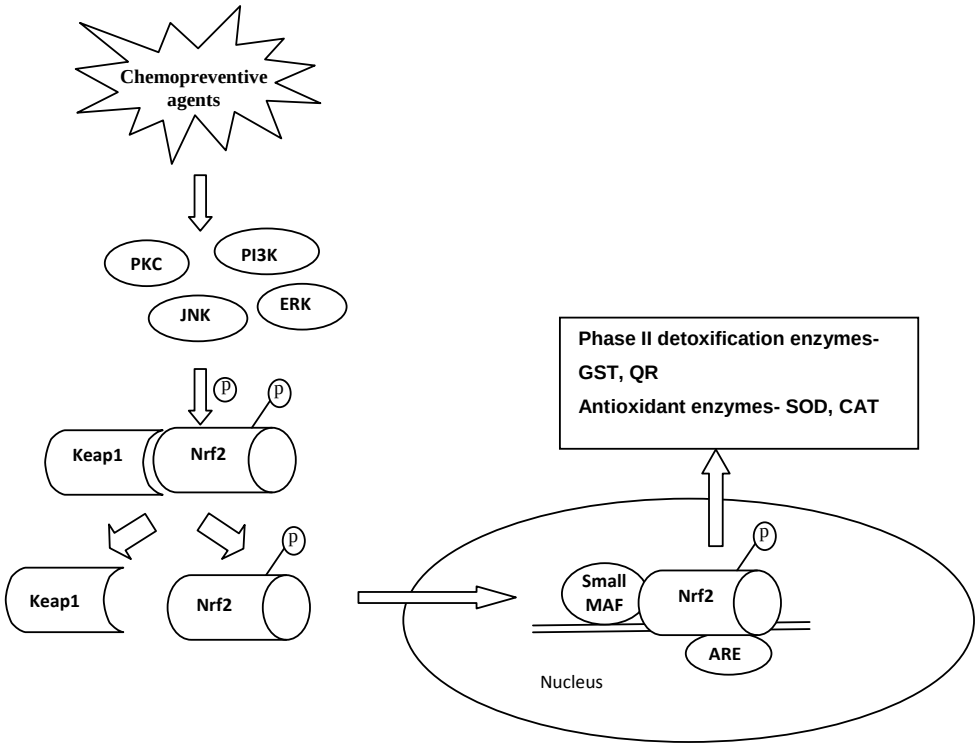


Fig. (3). Activation of antioxidant and phase II detoxification enzymes through Nrf2-Keap1 pathway by chemopreventive phytochemicals. Nrf2 is sequestered in the cytoplasm by the Keap1 actin binding protein. Chemopreventive agents activate upstream kinases dissociating Nrf2 from Keap1. Free Nrf2 translocates to the nucleus, heterodimerizes with small Maf proteins and binds to ARE sequences in the promoter regions, transactivating genes encoding antioxidant and phase II detoxification enzymes. ARE, Antioxidant response element; ERK, Extracellular signal-regulated protein kinase; JNK, c-Jun NH_2-terminal kinase; Keap1, Kelch-like ECH associating protein 1; Nrf2, Nuclear factor erythroid–2-related factor 2; PKC, Protein kinase C; PI3K, Phosphatidylinositol-3-kinase.

Epigenetic Alterations

DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs) play a central role as key regulators of chromatin structure and transcriptional activity. While HAT activity is associated with transcriptionally active chromatin, DNMTs and HDACs cause gene silencing. An altered balance of DNA methylation and histone acetylation/deacetylation contributes to neoplastic transformation [57]. Inhibitors of HDAC that have a broad spectrum of anticancer effects such as growth arrest, differentiation, and apoptosis have attracted recent attention as potential anticancer agents [58]. HDAC inhibitors although unselective, have shown promising results in clinical trials in acute leukemia and breast cancer [59,60].

MULTITARGETED CHEMOPREVENTION

Accumulating evidence suggests that several dietary phytochemicals act through multiple mechanisms including interaction with receptors, modulation of signal transduction pathways and genes involved in the control of cell proliferation, cell cycle, apoptosis, and transcription regulation to exert their antitumor and chemotherapeutic effects. Based on the molecular evidence of multitargeted chemoprevention, several phytochemicals have entered clinical trials [61-63].

Curcumin

Curcumin exerts its pleiotropic mode of chemopreventive action by downregulating transcription factors and signaling cascades. Curcumin inhibits IκB kinase complex (IKK) activity, NF-κB activation and expression of NF-κB target genes [36, 49]. Curcumin shows inhibitory effects on Akt and MAPK signaling and attenuates Wnt signaling by downregulating Frizzled-1 (Wnt receptor) and p300, a positive regulator of the Wnt/β-catenin pathway [44, 51, 55]. Curcumin has also been demonstrated to inhibit angiogenesis, induce p53-and caspase-mediated apoptosis, and downregulate the expression of proliferation, antiapoptotic, and metastatic genes [36,41,51]. Curcumin is a potent agent for the inhibition of carcinogenesis and tumor progression in animal models [64, 65]. Curcumin analogs have evolved as a new class of antiandrogenic agents based on their ability to control androgen receptor-mediated prostate cancer growth [66].

Resveratrol

Resveratrol mediates its anticancer effects by modulating XME, stimulating cell cycle arrest, suppressing nitric oxide synthase, and inducing apoptosis via ceramide activation, tubulin polymerization, upregulation of proapoptotic p53, Fas, and Bax, downregulation of antiapoptotic proteins, and caspase activation [67]. Resveratrol attenuates oxidative stress and suppresses the inflammatory cascade in diethylnitrosamine-initiated hepatocarcinogenesis [68, 69]. Abrogation of NF-κB signaling by resveratrol is mediated by blocking IκB kinase activity [48, 50, 69]. In addition, resveratrol blocks VEGF signaling and inhibits angiogenesis [42].

Tea Polyphenols

Both epidemiological and experimental studies support a positive role for tea consumption in preventing the risk of cancer [16, 70, 71]. The chemopreventive effects of tea have been attributed to its antioxidant activity, induction of detoxification enzymes, modulation of cell proliferation, differentiation, and apoptosis, and improvement in the function of intestinal bacterial flora [17, 37, 46]. Tea polyphenols blockade NF-κB, and MAPK signaling, and induce cell cycle arrest by upregulating p21, and p53, and inhibiting cyclins and CDKs [37, 56, 72]. Apoptosis induction occurs by decreasing the expression of Bcl-2 and IAPs, upregulating Bax and Bid, and caspase activation [37, 72, 73]. Black tea polyphenols ameliorate oxidative stress and inhibit tumor invasion and angiogenesis by modulating matrix metalloproteinases (MMPs), tissue inhibitors of MMPs, RECK, hypoxia inducible factor 1α, and VEGF [18, 72-74].

Isoflavones

The inhibitory effects of the isoflavones genistein, and I-3-C on tumor development and progression have been demonstrated to be mediated through the regulation of NF-κB/Notch/Akt/Wnt/androgen receptor signaling networks [30, 46]. Abrogation of NF-κB signaling appears to be the most important mechanism by which the isoflavones exert their chemopreventive effects. Genistein inhibited nuclear translocation of NF-κB and subsequent transactivation of NF-κB target genes in addition to modulation of IKK and IκB [52, 75]. Isoflavones inactivate Akt by phosphorylation, and inhibit Wnt and Notch signaling [45,76]. Genistein downregulated androgen receptor expression with decreased nuclear binding of the receptor to the androgen responsive element and reduced expression of prostate specific antigen (PSA) [46].

Lycopene

The anticancer properties of lycopene have been attributed predominantly to its antioxidant function [77]. Lycopene is reported to upregulate detoxification systems, induce gap-junctional communication, inhibit cell proliferation and cell cycle progression, and modulate Akt, MAPK, NF-κB and Wnt signaling [14, 38, 78, 79]. Lycopene was shown to downregulate the nuclear translocation of NF-κB and transactivation of the NF-κB target gene MMP-9 [80]. Lycopene also influences cancer cascades by modulating transcription by nuclear receptors, hormones, carcinogen metabolism, immune status, angiogenesis, and apoptosis [14, 38, 77-81].

Garlic

Garlic and its organosulfur constituents exert anticancer effects by enhancing carcinogen detoxification and immunity, ROS scavenging, suppressing proliferation, angiogenesis and inflammation, inducing apoptosis and DNA repair, and inhibiting angiogenesis [15]. These effects are mediated through the inhibition of hepatic CYP-mediated activation of NFκB, induction of drug-metabolizing enzymes, downregulation of cyclins, CDK, Bcl-2 and Bcl-xL, transcriptional activation of CDK inhibitors, Bax, Bad and p53, and inhibition of HDAC activity [15, 82, 83].

Neem Limonoids

Neem (*Azadirachta indica* A. Juss), a rich source of limonoids exhibits antioxidant, anti-inflammatory and anticar-

cinogenic effects [84]. Studies from our laboratory have demonstrated that the neem limonoids nimbolide and azadirachtin inhibit the growth of malignant cells *in vitro* and *in vivo* by targeting XME, cell proliferation, apoptosis, invasion, and angiogenesis [85-87].

COMBINATION CHEMOPREVENTION

Chemoprevention by a combination of dietary phytochemicals with distinct molecular mechanisms has received growing consideration as a means to achieve higher efficacy and potency with reduced toxicity and drug resistance. Dietary phytochemicals that influence different molecular targets within a specific pathway exert additive or synergistic effects on combination. For example, the synergistic interaction between quercetin that mediates cell cycle arrest at G1/S phase, and genistein that affects G2 and/or early M phase inhibits proliferation of ovarian carcinoma cells by modifying different stages in the cell cycle [88]. Curcumin in combination with quercetin induced tumor regression in a phase I clinical trial on patients with familial adenomatous polyposis [89].

A combination of EGCG, resveratrol, and gamma-tocotrienol at a suboptimal dose of 10 μM elicited synergism in suppressing cell proliferation, modulating gene expression, and enhancing antioxidant activity in MCF-7 cells [90]. EGCG in combination with genistein and quercetin suppressed the proliferation of prostate cancer cells by synergistically modulating the expression of the androgen receptor, p53, and quinone reductase [91]. In particular, combination regimens that use tea polyphenols as one of the constituents were found to be potentially effective in chemoprevention and chemotherapy trials [92, 93]. We have documented the combinatorial chemopreventive efficacy of lycopene with S-allylcysteine as well as black tea polyphenols with bovine milk lactoferrin [17, 82]. Dietary phytochemicals also exert additive or synergistic effects with pharmaceutical agents. Combination of olive oil with sulindac, an anti-inflammatory drug protects against colon cancer by regulating prostaglandin biosynthesis and apoptosis [94]. Combination of soy isoflavone with tamoxifen reduced mammary tumors by inhibiting oxidative DNA damage [95].

Dietary Agents as Chemo and Radiosensitizers

Dietary phytochemicals function as chemosensitizers by several mechanisms. Genistein potentiates the apoptosis inducing effects of the chemotherapeutic drugs erlotinib and gemcitabine by inhibiting the activation of Akt and NF-κB and sensitizing tumor cells to EGFR blockade [96]. Flavopiridol, a semi-synthetic flavonoid promotes drug-induced apoptosis in breast and gastric cancer cells potentiating the cytotoxic effects of mitomycin C [97]. Curcumin potentiates the cytotoxicity of 5-fluorouracil and paclitaxel in prostate cancer cells by suppressing the constitutive activation of NF-κB [98].

Radiosensitization strategies using phytochemicals that specifically block prosurvival signaling pathways increase the efficacy of radiotherapy without adverse toxicity and side effects. Radiation therapy coupled with genistein administration inhibited primary prostate cancer growth and lymph node metastasis by inhibiting NF-κB activity, altering the expression of cell cycle regulatory proteins, and inducing cell cycle arrest at G2/M [99]. Curcumin exhibits radiosensitizing effects on prostate cancer cells by downregulating MDM2 oncogene through the PI3K/mTOR/ETS2 pathway [100].

PHYTOCHEMICALS IN CANCER THERAPY AND CLINICAL TRIALS

Several studies have demonstrated the chemotherapeutic potential of dietary phytochemicals. Lycopene supplements reduced tumor size and PSA level in localized prostate can-

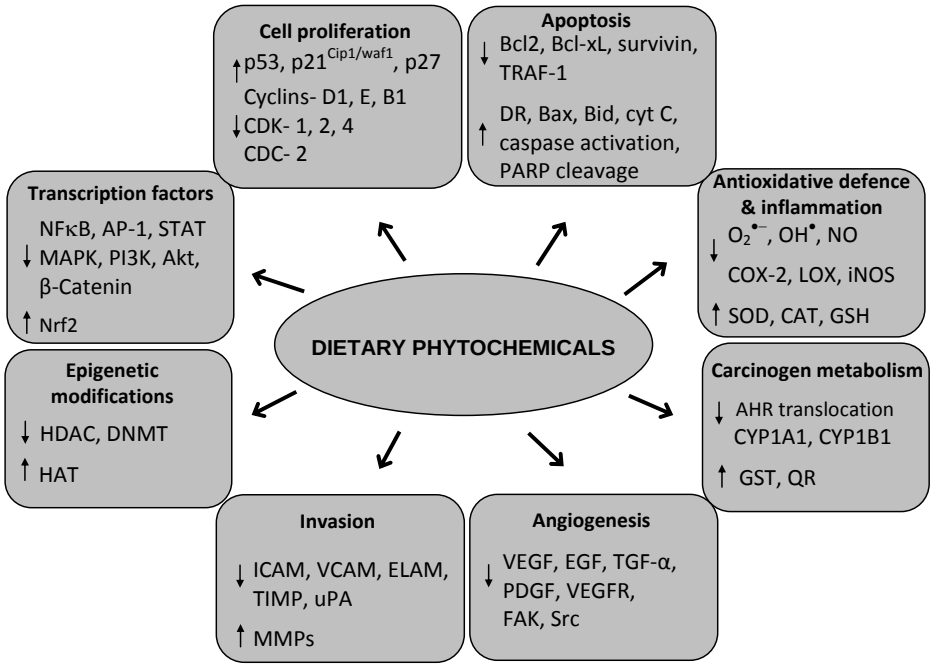


Fig. (4). Molecular targets of dietary phytochemicals.

cers with downregulation of androgen receptor nuclear translocation [101]. A phase II trial in patients with advanced pancreatic cancer revealed significant tumor regression in curcumin administered groups [61]. Several ongoing clinical trials are investigating the efficacy of curcumin in preventing cancer both alone and in combination with conventional chemotherapeutic agents [46].

Breast cancer patients who consumed more than five cups of green tea per day showed a lower recurrence rate and a longer disease-free period compared to those consuming fewer than four cups per day [102]. Consumption of green tea catechin capsules inhibited the progression of high-grade prostate intraepithelial neoplasia to cancer [103]. Yamamoto *et al.* [104] provided evidence to show that green tea polyphenols enhance the effectiveness of chemo/radiation therapy to promote cancer cell death while protecting normal cells.

The antiproliferative effects of resveratrol *in vitro* prompted preclinical testing in several animal tumor models for chemopreventive and chemotherapeutic effects as well as interventional clinical trials [105]. Resveratrol potentiates the effects of gemcitabine, a standard chemotherapeutic drug for prostate cancer through suppression of markers of proliferation, invasion, angiogenesis, and metastasis [106].

A soy rich diet inhibited pulmonary metastasis of melanoma cells in C57Bl/6 mice [107]. High intake of genistein was found to be associated with decreased risk of recurrence of colorectal adenoma [108]. In a phase II clinical trial, prostate cancer patients receiving the soy isoflavone supplement Novasoy™ containing genistein, diadzein and glycitin showed a decrease in the rate of rise in serum PSA [109]. The isoflavone genistein enhanced the antitumor activity of chemotherapeutic agents by attenuating NF-κB activation and NF-κB signaling [110].

FAILURES AND PITFALLS OF CHEMOPREVENTIVE PHYTOCHEMICALS

The increasing acceptability of phytochemicals as cancer chemopreventive agents in recent years may be attributed to their high potency, low toxicity, relative safety compared to synthetic anticancer agents, and the fact that they are not perceived as medicine. However, the nontoxic therapeutic effects are not substantiated by clinical trials. Furthermore, the evidence for chemopreventive properties of a phytochemical is generally based on *in vitro* tests in cell lines or in animal tumor models using doses several orders of magnitude higher than the physiological concentrations obtainable from a normal diet. Such high concentrations may in fact be toxic in humans. Long-term administration of phytochemicals, which are also xenobiotics must therefore be monitored with caution and the risk-benefit weighed before treatment. In addition to their beneficial effects, phytochemicals may display toxicity *per se* or by metabolic conversion to intermediates that are cytotoxic, interfere with endogenous metabolic pathways, interact with other xenobiotics and affect the human intestinal microflora [111].

Interactions of chemopreventive agents with XME can cause adverse side effects. Some chemopreventive agents function as CYP inducers, whereas others inhibit CYPs. While CYP inducers enhance the carcinogenicity of procarcinogens, CYP inhibitors can cause accumulation of cytotoxic compounds, impaired metabolism of endogenous compounds, or fatal drug-inhibitor interactions, resulting in overdose or loss of the therapeutic effect of drugs. Although phase II reactions cause detoxification, these can also result in the formation of highly reactive carbenium or nitrenium cations that covalently bind to proteins and nucleic acids [112]. In addition, the transcription factor Nrf2 has been reported to enhance the resistance of cancer cells to chemotherapeutic drugs [113].

Although studies on the adverse effects have not been extensively documented in literature, detrimental effects have been reported for some phytochemicals. Cancer prevention trials have provided evidence for an unexpected increase in the risk of lung cancer and colorectal adenomas in high-risk individuals supplemented with β-carotene [114, 115]. Increased consumption of cruciferous vegetables is recognized to cause hormonal imbalance and increase breast cancer risk by stimulating estradiol hydroxylation and conversion to catechols [116, 117].

Flavonoids present in fruits, vegetables, and beverages that display potent anticancer properties have also been reported to function as mutagens, pro-oxidants, and inhibitors of drug-metabolizing enzymes [118]. The isoflavone genistein that protects against hormone-dependent cancers, decreases fertility and causes sexual dysfunction in experimental animals in high doses [119].

Thus high consumption of dietary phytochemicals should be considered with caution taking into account their dosage regimes, toxicity, metabolic conversion, transport mechanisms, tissue availability, synergistic interaction with drugs, and interference with key enzymes, receptors, metabolic pathways, and normal human microflora.

TARGETED DELIVERY

Targeted delivery of phytochemicals through advanced modalities such as multi-functional gold nanoparticles and liposome-encapsulation has gained importance in recent years as these methods could increase bioavailability, reduce first-pass metabolic degradation, and enhance therapeutic efficacy with low to minimal side effects. Multi-functional gold nanoparticles are highly stable and versatile scaffolds for the delivery of phytochemicals due to their unique size, and physicochemical properties. Liposomes have been used as carriers for drugs and chemopreventive agents due to high biocompatibility, cell-specific targeting and controlled release [120, 121]. Gold nanoparticles and liposome encapsulation of curcumin, EGCG, DATS, and deguelin have shown increased biological efficacy in model systems [122-125].

CONCLUSIONS AND FUTURE PERSPECTIVES

With increasing knowledge of the molecular heterogeneity of tumors and aberrations in multiple signaling pathways that characterize neoplastic transformation, the current focus of chemoprevention research is on identifying agents that are capable of targeting multiple cellular molecules and signaling pathways involved in carcinogenesis. However, the complexity of signaling networks, synergistic, additive, or an-

tagonistic effects on different cell types, concentration of the phytochemical, unidentified crosstalk with other signaling molecules are major hurdles for the extrapolation of results obtained *in vitro* to humans. Unraveling the synergistic interactions of phytochemicals and their effects on humans would help substantially in achieving success in chemoprevention by dietary phytochemicals. The identification of molecularly targeted phytochemicals that are promising in "convergent" trials designed to include patients with preneoplastic lesions and early stage cancers as well as end stage disease will facilitate the development of rational, effective, and safe drugs for cancer chemoprevention in future.

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