Targeting specific cell signaling transduction pathways by dietary and medicinal phytochemicals in cancer chemoprevention

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Abstract:

Natural phytochemicals derived from dietary sources or medicinal plants have gained significant recognition in the potential management of several human clinical conditions. Much research has also been geared towards the evaluation of plant extracts as effective prophylactic agents since they can act on specific and/or multiple molecular and cellular targets. Plants have been an abundant source of highly effective phytochemicals which offer great potential in the fight against cancer by inhibiting the process of carcinogenesis through the upregulation of cytoprotective genes that encode for carcinogen detoxifying enzymes and antioxidant enzymes. The mechanistic insight into chemoprevention further includes induction of cell cycle arrest and apoptosis or inhibition of signal transduction pathways mainly the mitogen-activated protein kinases (MAPK), protein kinases C (PKC), phosphoinositide 3-kinase (PI3K), glycogen synthase kinase (GSK) which lead to abnormal cyclooxygenase-2 (COX-2), activator protein-1 (AP-1), nuclear factor-kappaB (NF-κB) and c-myc expression. Effectiveness of chemopreventive agents reflects their ability to counteract certain upstream signals that leads to genotoxic damage, redox imbalances and other forms of cellular stress. Targeting malfunctioning molecules along the disrupted signal transduction pathway in cancer represent a rational strategy in chemoprevention. NF-κB and AP-1 provide mechanistic links between inflammation and cancer, and moreover regulate tumor angiogenesis and invasiveness, indicating that signaling pathways that mediate their activation provide attractive targets for new chemotherapeutic approaches. Thus cell signaling cascades and their interacting factors have become important targets of chemoprevention and phenolic phytochemicals and plant extracts seem to be promising in this endeavor.

Keywords: Phenolics | Plant extracts | Chemoprevention | MAP kinases | Transcription factors | Phase II detoxifying enzymes

Article:

1. Introduction

Cancer development is a multifactorial and multistage process consisting of three distinct phases: initiation, promotion and progression phases. Epigenetic changes in particular, aberrant promoter hypermethylation associated with inappropriate gene silencing contribute significantly to the initiation and progression of human cancer (Jones and Baylin, 2002). While current clinical therapies including radiation, chemotherapy, immunosuppression and surgery are limited as indicated by the high morbidity and mortality rate from cancer, there is an imperative need for new treatment modalities. Chemoprevention which involves the use of pharmacological, dietary biofactors, phytochemicals and even whole plant extracts to prevent, arrest or reverse the cellular and molecular processes of carcinogenesis has been proposed due to its multiple intervention strategies. In addition, epidemiological and experimental studies highlight the protective roles of dietary phytochemicals including sulforaphane, resveratrol, genistein, curcumin, epigallocatechin-3-gallate (EGCG), gingerol, diallyl sulfide, brassinin and caffeic acid phenyl ester for the control and containment of carcinogenesis (Arai et al., 2000, Bettuzzi et al., 2006, Chan et al., 2009, Kale et al., 2008, Knekt et al., 1997, Kundu and Surh, 2005, Surh, 2003). Plant-derived phytochemicals as well have played a dominant therapeutic role in the treatment of human ailments and plant extracts continue to play a major role in all forms of modern day pharmaceutical care. Research has also been directed towards the use of total plant extracts mainly because of the synergistic effects of the cocktail of plant metabolites and the multiple points of intervention in chemoprevention. The preventive mechanisms of tumor promotion by natural phytochemicals range from the inhibition of genotoxic effects, increased antioxidant and anti-inflammatory activity, inhibition of proteases and cell proliferation, protection of intercellular communications to modulation of apoptosis and signal transduction pathways (Chen and Kong, 2005, De Flora and Ferguson, 2005, Holmes-McNary and Baldwin, 2000, Hwang et al., 2005, Shimizu et al., 2005, Yu and Kensler, 2005, Aruoma et al., 2005, Soobrattee et al., 2006). However, well-controlled randomized clinical trials are warranted to ascertain the chemopreventive efficacy of these phytochemicals. Recent progress in understanding the molecular changes that underlie cancer development offer the prospect of specifically targeting malfunctioning molecules and pathways to achieve more effective and rational cancer therapy. This paper reviews the potential targets of chemoprevention and also emphasizes the important role of plant extracts and plant-derived phytochemicals primarily of polyphenolics in targeting disrupted cell signaling transduction pathways in carcinogenesis.

1.1. Regulation of nuclear factor-E2 related factor 2 (Nrf2) via the antioxidant/electrophile response element (ARE/EpRE)

A successful strategy for halting cancer development is to modulate by pharmacological or nutritional means the levels of biotransformation enzymes that promote the elimination of endogenous and environmental carcinogens (Owuor and Kong, 2002, Yu and Kensler, 2005). Under physiological conditions, these enzymes are expressed constitutively at relatively low levels and the expression levels can be enhanced in response to several classes of compounds in particular coumarins, diterpenes, indoles, curcumin, sulforaphane, isothiocyanates, (−)-epigallocatechin gallate and plant extracts in particular *Syzygium formosanum* and *Millettia pulchra var microphylla* (Chen and Kong, 2004, Chen and Kong, 2005, Kelloff et al., 2000, Lee et al., 2006, Na et al., 2008). These compounds can induce the phase I and II detoxifying

enzymes, however major interest is focused on inducers of phase II detoxifying enzymes for the biotransformation and elimination of potential carcinogens. The natural chemopreventive compounds serve as transcriptional activators for the expression of glutathione S-transferase, NAD(P)H:quinone oxidoreductase (NQO), heme oxygenase 1 (HO 1), γ-glutamylcysteine synthetase (γGCS) and antioxidant enzymes via the antioxidant/electrophile response element (ARE/EpRE) (Eggler et al., 2008, Owuor and Kong, 2002). The ARE/EpRE has been proposed to be pivotal in the regulation of the cellular defense system and has been described as an important target for achieving chemoprevention.

The induction effects of phase II detoxifying agents by natural phytochemicals are mediated in part through the activation of Nrf2 signaling pathways. Several intracellular signal transduction pathways, mitogen-activated protein kinases (MAPKs), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K) and RNA dependent protein kinase (PKR)-like endoplasmic reticulum kinase (PERK) can activate the KEAP 1–Nrf2 complex. Nrf2 interacts with KEAP 1, an actin binding cytosolic protein that sequesters the Nrf2 in the cytoplasm and targets it for proteasomal degradation. Activation of the KEAP 1–Nrf2 complex leads to the release of Nrf2 in the cytosol with the subsequent translocation of the latter to the nucleus which results in an increase in the transcriptional activity of ARE-regulated genes (Fig. 1) (Yu and Kensler, 2005). Subsequently, Nrf2 heterodimerizes with members of the small Maf protein family which bind to the ARE sequence in the promoter regions of many genes encoding cytoprotective enzymes. While the mechanism remains unclear how the PI3K signaling pathways can activate the KEAP 1–Nrf2 complex, experimental studies have shown that PKC and PERK phosphorylate the Ser40 in the KEAP 1-interacting Neh2 domain of the Nrf2 protein that results in release of the nuclear factor (Cullinan et al., 2003, Huang et al., 2000, Huang et al., 2002). MAPKs can affect Nrf2 function through the transcriptional co-activators such as p300, peroxisome proliferator-activated receptor (PPAR)-binding protein or cAMP response element-binding protein (CREB) binding protein (Misra et al., 2002, Shen et al., 2004).

Na et al. (2008) reported the activation of Nrf2 by EGCG in human mammary epithelial cells which resulted in the expression of glutamate–cysteine ligase, manganese superoxide dismutase and heme oxygenase 1 via the Akt and ERK 1/2 signaling pathways. Gao and Talalay (2004) reported the protective effect of sulforaphane against photooxidative damage in retinal pigment epithelial cells. The degree of protection was correlated with the potencies of sulforaphane to induce and elevate the level of glutathione and NAD(P)H:quinine oxidoreductase. In addition, another study indicated the prophylactic effect of sulforaphane via the upregulation of thioredoxin in mice retinal pigment epithelial cells (Tanito et al., 2005). The induction of ARE-dependent genes by chemopreventive phenolic agents including curcumin, isothiocyanates, catechins, quercetin has been widely discussed (Ferguson et al., 2004, Khan et al., 1992, Le Marchand, 2002, Valerio et al., 2001, Zhang, 2004). Indigenous plants from Taiwan, rich in phenolic acid, flavonoids, proanthocyanidins and tannins increased the promoter activity of heme oxygenase 1 thus accounting for the cytoprotective effects in rat aortic smooth muscle cells (Lee et al., 2006). Owuor and Kong (2002) have indicated that the chemopreventive compounds serve as transcriptional activators for the expression of glutathione S-transferase, NAD(P)H:quinone oxidoreductase (NQO), heme oxygenase 1 (HO 1), γ-glutamylcysteine synthetase (γGCS) and antioxidant enzymes via the antioxidant/electrophile response element (ARE/EpRE). In addition, antioxidative enzymes, anti-inflammatory genes and proteasomal subunits can be coordinately

upregulated via the Nrf2 pathway (Fig. 1). This intricate network of the proteasome system functions as the repair machinery that recognizes and degrades damaged proteins which are induced by ROS/RNS, thereby limiting the detrimental effects (Davis, 2001, Kwak et al., 2003). Nrf2-mediated responses appear to be regulated by multiple kinases, possibly at multiple residues of the Nrf2 protein.

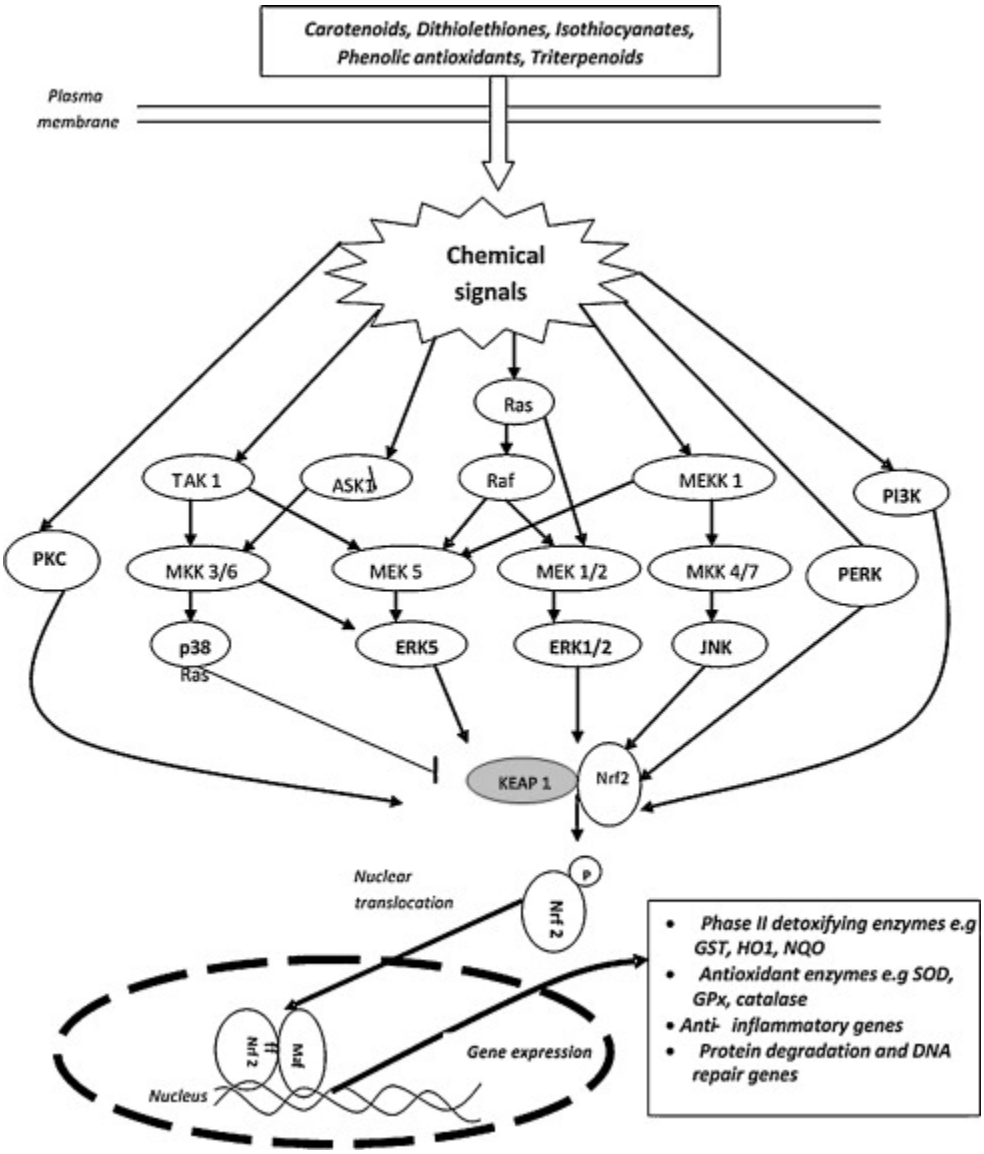

Figure 1. Regulation of the Nrf2-mediated pathways by natural phytochemicals, providing multiple modes of resistance to chemical induced carcinogenesis. Nrf2 is thethered in the cytoplasm by the KEAP 1 actin binding protein. The function and localization of Nrf2 is regulated by multiple upstream kinases (JNK, ERK, PKC, PERK, PI3K). Activation by these signaling pathways elicit positive influences on Nrf2 and subsequent translocation to the nucleus and binding to ARE sequences in the promoter regions of many genes encoding cytoprotective enzymes.

1.2. Targeting the tumor microenvironment: inflammatory mediators and reactive oxygen/nitrogen species

Several reports have indicated the intrinsic link between cancer and inflammation (Balkwill and Mantovani, 2001, Palapattu et al., 2004, Schwartsburd, 2003). The inflammatory microenvironment of tumors is characterized by the presence of tumor-associated macrophages, tumor-infiltrating lymphocytes which produces a range of proinflammatory cytokines in particular the tumor necrosis factor (TNF), interleukins 1 and 6 (Il-1, Il-6), growth factors, chemokines like interleukin 8 (IL-8) and signal transducers and activators of transcription (STATs) (Balkwill and Mantovani, 2001, Klampfer, 2008). Cytokines and chemokines can promote cancer growth, invasion and metastasis by (i) inducing DNA damage by ROS/RNS, (ii) inhibiting the DNA repair mechanisms via ROS/RNS, (iii) the functional inactivation of the tumor suppressor genes mainly p53, (iv) autocrine/paracrine growth and survival factors for malignant cells, (v) induction of vascular permeability and activation of matrix metalloproteinases, (vi) modulation of cell to cell adhesion molecules, (vii) stimulation of angiogenesis by favoring the production of angiogenic factors (VEGF, bFGF, IL-8, MMP) (Balkwill and Mantovani, 2001, Coussens and Werb, 2002). The significant contribution of inflammatory processes in neoplasia has indicated the beneficial role of anti-inflammatory agents in cancer prevention. The intake of non-steroidal anti-inflammatory drugs (NSAIDs) correlated with a reduced incidence of oesophagus, colon and rectum, stomach cancer (Langman et al., 2000, Reddy et al., 1996, Steinbach et al., 2000). NSAIDs have shown undisputable promise as chemopreventive agents, however major concerns over their cardiovascular toxicity, gastrointestinal side effects, liver and renal adverse effects (Bresalier et al., 2005, Gupta and Eisen, 2009, Knights et al., 2009, Nussmeier et al., 2005, Solomon et al., 2005, Ulrich et al., 2006) have shifted interest on natural inflammatory agents that can reverse/and or halt the process of carcinogenesis with limited cytotoxicity (Table 2). The implication of inflammatory processes and oxidative stress on carcinogenesis indicate the therapeutic benefit of natural anti-inflammatory agents which exert their activity mostly through the antioxidative property.

Under normal physiological conditions, inflammation is associated with the production of diverse free radicals and oxidants that primarily combat and neutralize invading pathogens and foreign bodies and also destroy the infected host tissue. However chronic inflammation in cancer leads to the continuous production of ROS mainly superoxide radicals ($O_2^{\bullet -}$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), hypobromous acid (HOBr), hydroxyl radicals ($OH^{\bullet}$) and RNS like nitric oxide (NO) and nitrogen dioxide ($^{\bullet}NO_2$) (Ohshima et al., 2005). ROS and RNS not only can damage DNA and induce mutations, but also can participate in most carcinogenic processes by activating oncogene products and/or inactivating tumor-suppressor proteins (Eyfjord and Bodvarsdottir, 2005, Ohshima, 2003). In addition to direct DNA base modifications by ROS and RNS, base modifications can be induced by lipid peroxidation end-products (malondialdehyde, 4-hydroxynonenal, etc.) to form cyclic adducts (Singer and Bartsch, 1999) while lipid peroxides (LOOH) in the presence of heme iron, as in hemoglobin, can also induce strand breakage (Sawa et al., 1998) and form abasic sites (Kanazawa et al., 2000). ROS induced damage may be targeted towards proteins in the peptide backbone, and in various nucleophilic or redox-sensitive side chains (Marnett et al., 2003). Experimental studies have indicated a high level of ROS in particular H_2O_2 in several carcinomas including melanoma, neuroblastoma, colon carcinoma, ovarian carcinoma cell lines (Kondo et al., 1999, Toyokuni et al., 1995). The

H_2O_2 functions as a signaling molecule triggering signaling events that leads to transcriptional activation of cell proliferating genes. Thus an alternative approach is the scavenging of ROS by phenolic antioxidants that could short-circuit the signaling events and ultimately the expression of responsive genes that stimulate cancer cells. A number of studies have indicated that antioxidant rich plant-derived components and extracts can be considered as prophylactic agents in cancer. Plant extracts with high antioxidant index can mediate at least in part their anticarcinogenic effect by acting as free radical scavengers and metal chelators (Cheung and Tai, 2007, Ju et al., 2004, Kumar et al., 2007, Lee et al., 2004a, Lee et al., 2004b, Moongkarndi et al., 2004, Neergheen et al., 2006, Soobrattee et al., 2008) (Table 1).

Table 1. Plant extracts showing high *in vitro* antioxidant effectiveness as free radical scavengers with potentials as anticancer agents.

Family	Plant species	Antioxidant activity	References
Asteraceae	*Baccharis grisebachii*	Scavenger of superoxide radicals	Tapia et al. (2004)
Campanulaceae	*Platycodon grandiflorum* A. De Candolle	Inhibition of lipid peroxidation and scavenging of DPPH$^{\bullet}$	Lee et al., 2004a, Lee et al., 2004b
Ebenaceae	*Diospyros mellanida* *Diospyros revaughanii* *Diospyros neraudii*	Free radical scavenging activity against hypochlorous acid, hydroxyl radical, peroxyl radicals	Soobrattee et al. (2008)
Fabaceae	*Bauhinia racemosa*	Reduced lipid peroxidation and upregulated the antioxidant levels	Kumar et al. (2007)
	Acacia salicina	Scavenger of DPPH$^{\bullet}$ and inhibitor of superoxide radical production	Mansour et al. (2007)
Lamiaceae	*Rosmarinus officinalis*	Showed substantial trolox equivalent antioxidant activity	Cheung and Tai (2007)
Myrtaceae	*Syzygium commersonii* *Syzygium glomeratum* *Syzygium mauritianum* *Syzygium venosum* *Eugenia pollicina*	Potent scavenger of hypochlorous acid, hydroxyl radical, peroxyl radicals	Neergheen et al. (2006)

Damage to the biomolecules disrupt important metabolic pathways by inducing genetic alterations in genes involved in carcinogenesis (e.g. oncogenes and tumor-suppressor genes) or by epigenetic processes such as gene methylation, post-translational modifications of proteins and modification of gene expression patterns. Post-translational modification of various important proteins and enzymes associated with carcinogenesis by ROS and RNS may alter their functions (e.g. inhibition of tumor-suppressor gene products such as p53, proapoptotic enzymes such as caspases and DNA repair enzymes, etc. and activation of angiogenesis, telomerase, COX-2, metalloproteinase, DNA methyltransferase, etc.) (Ohshima et al., 2005).

The anti-inflammatory actions of these compounds can also rest on their ability to inhibit the cycloxygenase activity of COX-2 thereby decreasing the production of prostaglandins. COX-2 overexpression has been found in 90% of colorectal carcinomas and 40% of adenomas (Chapple et al., 2000, Eberhart, 1994, Kutchera et al., 1996, Wu, 2005) by possibly intervening through several mechanisms (Fig. 2). Prostaglandins in particular PGE_2 seems to have a key role in carcinogenesis as activation of several types of PGE_2 receptors triggers other signaling pathways, such as the epidermal growth factor receptor pathway (Han and Wu, 2005, Pai et al., 2002;). Furthermore, the genetic or pharmacological disruption of PGE_2 receptors reduces tumor formation in mouse models of colon carcinogenesis (Mutoh et al., 2002, Watanabe et al., 1999).

Therefore the suppression of prostaglandin synthesis through selective inhibition of COX-2 is another promising strategy in the identification and development of chemopreventive drugs.

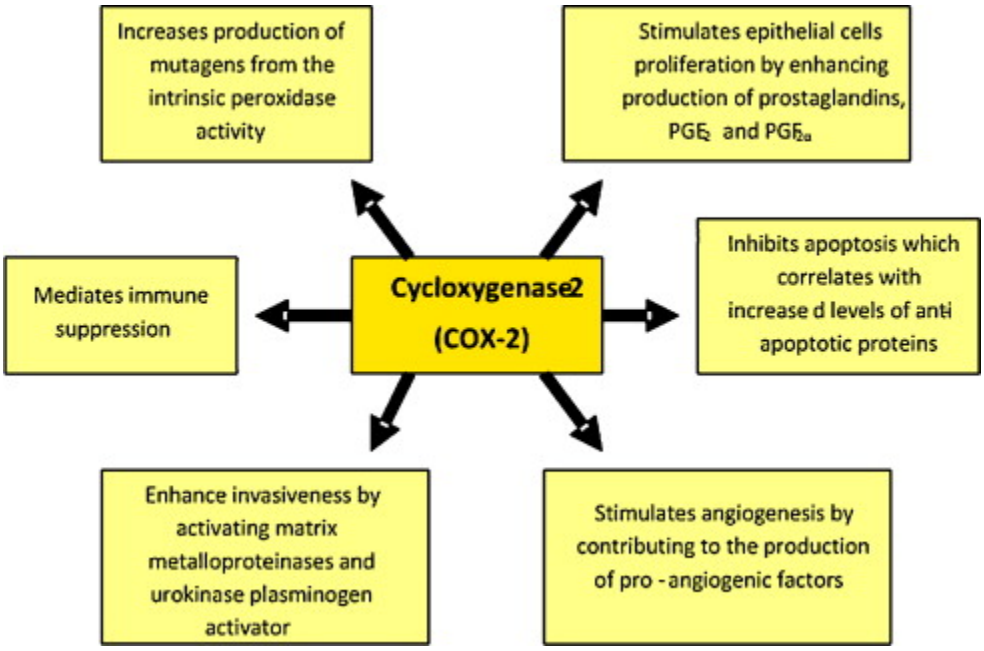

Figure 2. Key role of COX-2 in tumorigenesis.

A wide array of phenolic substances, particularly those present in dietary and/or medicinal plants in particular genistein, gingerol, capsaicin, EGCG, resveratrol and whole plant extracts in particular *Sutherlandia frutescens*, *Harpagophytum procumbens* and *Platycodon grandiflorum* (Ahn et al., 2005, Cavin et al., 2005, Kundu et al., 2005, Ye et al., 2004) have been reported to selectively inhibit the COX 2 expression (Table 1, Table 2). *S. fructescens* and *H. procumbens* have been shown to inhibit TPA and lipopolysaccharide induced COX-2 expression in human mammary epithelial cells and mouse fibroblast L929 cell lines respectively via the inhibition of DNA binding of AP-1 and NF-κB (Na et al. ,2004; Jang et al., 2003). Both extracts have also been reported to strongly inhibit the kinase activity of ERK which result in the inactivation of transcription factors AP-1 and CREB known to regulate COX-2 expression in mouse skin (Kundu et al., 2005). Chicory extract and EGCG, a green tea derived polyphenol produced a marked inhibition of PGE_2 production in human colon carcinoma HT 29 cells which correlated to the inhibition of COX-2 expression mediated by the inhibition of NF-κB and AMP-activated protein kinase respectively (Cavin et al., 2005, Hwang et al., 2007). Therefore the control of COX-2 expression by plant phytochemicals constitutes a promising avenue for chemoprevention.

Table 2. List of anti-inflammatory phytochemicals with putative chemopreventive potential *in vitro* and *in vivo*.

Phytochemical compound	Potential target	Putative sites of blockade by anti-inflammatory phytochemical	Reference
(+)-Epigallocatechin gallate Capsaicin Curcumin Caffeic acid phenyl ester (CAPE) Resveratrol Soybean saponins	Proinflammatory mediators	Downregulate proinflammatory mediators e.g. TNF-α, IL-8, PGE_2	Yang et al. (1998), Park et al. (2004), Abe et al. (1999), Trompezinski et al. (2003), Wheeler et al. (2004), Martinez and Moreno (2000), Michaluart et al. (1999), Matsuda et al. (2000), Onoda and Inano (2000), Kang et al. (2005)
Resveratrol, gingerol, CAPE curcumin, capsaicin, EGCG, soybean saponins, yakuchinones, ginsenosides	Proinflammatory enzymes COX-2	Downregulate the expression of COX-2 mRNA transcripts	Kang et al. (2005), Martinez and Moreno (2000), Murakami et al. (2003), Michaluart et al. (1999), Kim et al., 2004b, Kim et al., 2004c, Li et al. (2002), Yadav et al. (2003)
		Prevent mobilization of arachidonic acid and decrease PGE_2 production	Lee et al., 2004a, Lee et al., 2004b, Martinez and Moreno (2000)
Capsaicin, CAPE	Proinflammatory enzymes iNOS	Decrease the transcriptional activity of iNOS and reduce $NO^{\bullet}$ production	Chen et al. (2003), Song et al. (2002)
Resveratrol, gingerol, capsaicin, ginsenosides	Nf-κB, AP-1, β-catenin	Blocking phosphorylation and degradation of IκBα	Cho et al. (2002), Tsai et al. (1999), Kim et al., 2004a, Kim et al., 2004b, Han et al. (2001), Lee et al., 2004a, Lee et al., 2004b
		Suppressing phosphorylation and nuclear translocation of p65	
		Blocking the activation of IKKα	
		Downregulate β-catenin	Manna et al. (2000) Adhami et al. (2003)
Yakuchinones, ginsenosides	Protein kinases	Blocking ERK phosphorylation	Yadav et al. (2003), Lee et al., 2004a, Lee et al., 2004b

1.3. Targeting apoptotic regulatory pathways

Apoptosis or programmed cell death has long been described as a key strategy for the elimination of neoplastic cells. This process is an important regulator of physiological growth control and regulation of tissue homeostasis in embryonic, fetal and adult tissues (Herr and Debatin, 2001). Apoptosis is characterized by typical morphological and biochemical hallmarks including cell shrinkage, chromatin condensation, nuclear DNA fragmentation, membrane blebbing and the formation of apoptotic bodies (Hengartner, 2000). Apoptosis can be triggered by two major pathways: (i) at the plasma membrane upon ligation of the death receptor (extrinsic pathway) and (ii) at the mitochondria (intrinsic pathway) (Hengartner, 2000). The stimulation of death receptors of the tumor necrosis factor (TNF) receptor superfamily such as CD95 (APO-1/Fas) or TNF-related apoptosis-inducing ligand (TRAIL) receptors results in activation of the initiator caspase-8, which can propagate the apoptosis signal by direct cleavage of downstream effector caspases such as caspase-3 (Ashkenazi and Dixit, 1999). Ligation of the death receptors by their cognate ligands or agonistic antibodies results in receptor trimerization, clustering of the

receptors' death domains and recruitment of the adaptor molecules such as FADD through homophillic interaction mediated by the death domain (Fulda and Debatin, 2004, Kischkel et al., 1995, Barnhart et al., 2003). FADD in turn recruits caspase-8 to the activated receptor to form the death-inducing signaling complex (DISC) and oligomerization of caspase-8 upon DISC formation drives its activation through self-cleavage.

Caspases, a ubiquitous family of cysteine proteases play key roles both as upstream initiators and downstream effectors in apoptosis (Nicholson and Thornberry, 1997). This cascade leads to proteolytic cleavage of a variety of cytoplasmic and nuclear proteins, thereby favoring the prevalence of proapoptotic activities on antiapoptotic activities. The mitochondrial pathway is initiated by the release of apoptogenic factors such as cytochrome *c*, apoptosis-inducing factor (AIF), Smac/DIABLO, Omi/HtrA2, endonuclease G, caspase-2 or caspase-9 from the mitochondrial intermembrane space (Van Loo et al., 2002). The release of cytochrome *c* into the cytosol triggers caspase-3 activation through formation of the cytochrome *c*/Apaf-1/caspase-9-containing apoptosome complex, while Smac/DIABLO and Omi/HtrA2 promote caspase activation through neutralizing the inhibitory effects to inhibitor of apoptotic proteins (IAPs) (Van Loo et al., 2002, Du et al., 2000). The selective induction of apoptosis in malignant and premalignant cells indicate a protective mechanism of both chemoprevention and chemoptherapy in carcinogenesis while enhancement of apoptosis is considered as a double-edged sword because of its potential implication in neuronal cell death in degenerative diseases (D'Agostini et al., 2005).

Several mechanisms of apoptotic cell death have been proposed (Fulda and Debatin, 2004, Cummings et al., 2004). Chemoprevention by targeting key components of the apoptosis regulatory pathways which include the antiapoptotic Bcl-2 family of proteins, the inhibitors of apoptosis (IAPs) in particular XIAP, cIAP1, cIAP2, survivin, nuclear factor-κB (NF-κB), caspases, tyrosine kinases and key signaling routes (the PI-3K/PKB pathway, the Stat3/5 pathway and the MAPK pathway) (Hu et al., 2003, Juin et al., 2004, Lin and Karin, 2003, Nakshatri and Goulet, 2002, Orlowski and Baldwin, 2002, Reed, 2003, Schimmer et al., 2004, Stein and Waterfield, 2000, Workman, 2004) seems to be a rational approach in reducing the incidence of cancer. Bcl-2 or Bcl-X_L exert their antiapoptotic function, at least in part, by sequestering BH3 domain only proteins in stable mitochondrial complexes, thereby preventing activation and translocation of proapoptotic proteins Bax or Bak to mitochondria (Cory and Adams, 2002). In addition, Bcl-2 and Bcl-X_L block apoptosis by preventing cytochrome *c* release through a direct effect on mitochondrial channels such as the voltage-dependent anion channel (VDAC) or the permeability transition pore complex (PTPC) (Cheng et al., 2003). Thus the Bcl-2 and the bcl-X_L have emerged as a major new anticancer target.

Another attractive cancer therapy is to trigger apoptosis in tumor cells via the death receptors in particular the tumor necrosis factor (TNF) receptor superfamily which includes CD95 and TRAIL receptors (Fulda and Debatin, 2004). Signaling through the death receptors induces apoptosis and chemopreventive agents and drugs can upregulate CD95 receptors and CD95 ligands thereby stimulating the receptor pathway (Villunger et al., 1997). Moreover several anticancer agents have been reported to activate the CD95 pathway by modulating expression and recruitment of pro- or antiapoptotic components of the CD95 DISC to activated receptors (Fulda et al., 2001). Other modes of cell death including necrosis and autophagy (Leist and

Jaattela, 2001) can also be considered as interesting target for chemoprevention. Thus a better understanding of the diverse modes of cell death in cancer therapy will provide a molecular basis for new strategies targeting death pathways.

A wide range of putative cancer-chemopreventive plant extracts in particular *Glycyrrhiza uralensis*, *Sologrum nigrum*, *Pereskia bleo*, *Cratoxylum cochinchinense*, *Rhodiola rosea*, *Physalis peruviana*, *Betulla platyphylla* (Jo et al., 2005, Ju et al., 2004, Majewska et al., 2006, Tan et al., 2005, Tang et al., 2004, Wu et al., 2004) has been suggested to induce apoptosis in neoplastic cells (Table 3). The apoptotic effect of the ethanolic extract of *P. peruviana* in human HepG2 cells resulted from the collapse of the mitochondrial membrane permeability and depletion of glutathione (Wu et al., 2004). Several authors have indicated that plant extracts can induce apoptosis via multiple mechanisms in particular by triggering the CD95–CD95L signaling pathway, activating the caspases, decreasing the expression of Bcl-2 and cyclin D1, upregulating p21 and proapoptotic protein Bax and by the MAPK activation that results in p53 upregulation (Clement et al., 1998, Hu et al., 2002, She et al., 2001, She et al., 2002, Ju et al., 2004). Literature data has indicated that apoptosis can be induced by the multitude of bioactive constituents in the herbal extracts. Organosulfur compounds, phenolic acids, resveratrol, flavonoids have been shown to induce apoptosis in a number of cancer cell lines (Majewska et al., 2006, Son et al., 2003, Tan et al., 2005, Tang et al., 2004). Resveratrol produced a significant induction of p21 expression that resulted in cell cycle blockade at the S phase and apoptosis induction in MCF-7 breast cancer cells (Pozo-Guisado et al., 2002). In addition, organosulfur compounds including ajoene, diallyl trisulfide, diallyl disulfide induced apoptosis through increased cytochrome *c* release, activation of caspase-3 and -8 and a decrease in Bcl-2 protein activity in a range of human derived cells (Lea et al., 1999, Lund et al., 2001, Tilli et al., 2003, Sundaram and Milner, 1996, Xiao et al., 2004, Xiao and Singh, 2003). Recently Dave et al. (2005) showed that the isoflavone genistein prevented cancer by inducing apoptosis in target cell which coincided with increased PTEN expression both in vivo and in vitro. Another interesting target is the induction of TNF receptors mainly death receptor 4 (DR4) and death receptor 5 (DR5) which activate the apoptotic cascades. Curcumin enhanced TRAIL-induced apoptosis by significantly increasing DR5 expression both at its mRNA and protein levels (Jung et al., 2005). Moreover, Tsai et al. (2009) showed the in vivo efficacy of *Wedelia chinensis*, a common plant ingredient of Chinese herbal medicine in animals bearing a subcutaneous or orthotopic prostate cancer xenograft. The plant extract induced apoptosis selectively in androgen receptor-positive cancer cells and attenuated the growth of prostate tumors in nude mice implanted with a xenograft. These findings support the concept that inducers of apoptosis in neoplastic cells are of potential interest for rational drug design and several anticancer drugs that target apoptosis regulatory pathways are under clinical trials (Cummings et al., 2004).

Table 3. The chemoprotective effect of plant extracts and their mechanism of action in cancer cell lines.

Plant extracts with bioactive components	Cell lines/animal models	Mechanism of action	Reference
Sutherlandia frutescens (Cancer bush) and *Harpagophylum procumbens* (Devil's claw)	Human mammary epithelial cells (MCF-10A) stimulated with TPA	Decreased COX-2 expression by inhibiting DNA binding of AP-1 and NF-κB.	Kundu et al. (2005), Na et al. (2004)
	ICR Mice (TPA induced COX-2 expression in mouse skin)	Inhibition of c-Fos expression and reduction of CREB DNA binding	
Trigonella foenum graecum	Wistar rats (DMBA-induced breast cancer)	Induction of apoptosis	Amin et al. (2005), Loo et al. (2004), Jo et al. (2005), Son et al. (2003), Tan et al. (2005), Tang et al. (2004), Ju et al. (2004)
Herbal extracts (ginseng and *Carthamus tinctorius*)	MDA-MB 231 human breast cancer cells		
Glycyrrhiza uralensis (Chinese licorice); *Solanum nigrum* L.	MCF-7 human breast cancer cells		
Pereskia bleo	T-47 D		
Cratoxylum cochinchinense	Jurkat T cells		
Bettula platyphylla var japonica	Human promyelocytic leukaemia (HL-60)		
Glycyrrhiza uralensis (Chinese licorice)	MCF-7 human breast cancer cells	G1 cell cycle arrest	Jo et al. (2005)
Ganoderma lucidum	PC-3 human prostate cancer cell line	Inhibit angiogenesis via the inactivation of AP-1 resulting in down-regulation of VEGF and TGF-β1	Stanley et al. (2005), Neto et al. (2006)
Vaccinium macrocarpon	DU-145 prostate tumor cell line	Decrease MMP-2 and MMP-9 expression	
Phellinus linteus; *Psyllium* extracts	WB rat liver epithelial cells	Modulation MAPK and downstream NF-κB and AP-1	Cho et al. (2002), Nakamura et al. (2004)

1.4. Cell cycle arrest in chemoprevention

Cell cycle arrest occurs in response to cellular stress through activation of signal transduction pathways commonly referred to as checkpoints (Hartwell and Weinert, 1989). The checkpoints are activated in the G1/S phase to prevent replication of damaged DNA or in the G2/M phase to prevent segregation of damaged chromosomes during mitosis. Checkpoints ensure completion of phase-specific events and help maintain genetic integrity (Hartwell and Weinert, 1989). Increasing experimental data suggest that cell cycle control, particularly at the G1/S and G2/M transitions, represent a major task for the cell to ensure an accurate cell division. The carcinogenic process often affect progression through the S phase by inducing changes in expression and/or activity of cell cycle regulators thus offering a potential target for chemoprevention. The ethanolic extract of Chinese licorice root *G. uralensis* and downregulated CDK 2 and cyclin E and subsequently induced G1 cell cycle arrest in MCF-7 human breast cancer cell (Jo et al., 2005). Similar observations were made using eupatilin from *Artemesia*

asiatica against MCF 10A-ras cells respectively (Kim et al., 2004b). This function can be attributed to the presence of secondary metabolites within the plant extract. A wide range of such phytochemicals have been reported to induce growth inhibition of cancer cells by interfering with their deregulated cell cycle progression through modulation of the expression and/or activities of key proteins including cyclin D1, cyclin B1, cdk2, cdc2, p53 and $p27^{kip1}$. For instance the antiproliferative activity of the natural phytoalexin resveratrol was shown to result from the concentration-dependent inhibition in the expression of regulators of the G1/S transition of the cell cycle in particular cyclin D1, CDK4 and cyclin E in the MDA-MB-231 human breast cancer cells. In a similar fashion to the effects reported for the G1/S transition, resveratrol inhibited the expression of the G2/M regulators cdc2 and cyclin B1 (Pozo-Guisado et al., 2002). In addition an increase in the concentration of resveratrol induced a progressive decrease in the kinase activity of cyclin D1/CDK4 and cyclin B1/cdc2 complexes (Pozo-Guisado et al., 2002). Quercetin on the other hand exerts its anti-tumor effect through blocking cell cycle progression at the G0/G1 interface, consistent with Cdk inhibition while myricetin inhibited Cdk2 (Cragg and Newman, 2005).

1.5. Angiogenesis: a potential target of chemoprevention

Angiogenesis, the process of new blood vessel growth play a major role in tumor growth and metastasis. Thus, suppression of abnormal angiogenesis may provide strategies for halting the process of carcinogenesis (Ferrara and Kerbel, 2005). Part of the attraction of this approach is the near universality of its potential application, as essentially all cancers require a subsequent blood supply for their growth and their spread (Sawyers, 2004). A great deal of evidence suggests the antiangiogenic properties of a number of naturally derived phytochemicals (Cao et al., 2002, Oak et al., 2005, Stoclet et al., 2004). Tumor cells can produce potent angiogenic factors such as vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) and fibroblast growth factor-2 (FGF-2), which switch on an angiogenic phenotype of the tumor implant (Cross and Claesson-Welsh, 2001). The underlying mechanisms of a switch of angiogenesis phenotype in tumors are complex and often require upregulation of angiogenic factors and simultaneous down regulation of angiogenesis inhibitors. Therefore intervention of the angiogenic process seems to be a powerful approach for cancer therapy. The mechanistic insights of antiangiogenic compounds involve the inhibition of matrix metalloproteinases which block the degradation of the endothelial basement membrane, thereby preventing capillary sprout formation. Several of the chemopreventive agents can also prevent the angiogenic ligand/receptor mediated signaling pathways.

Recent interest in extracts derived from food plants or medicinal herbs has gained significant recognition for their potential therapeutic uses in the inhibition of angiogenesis. The root extracts of *Withania somnifera* inhibited VEGF-induced angiogenesis in both the chickchorio-allantoic membrane and in mouse models (Mathur et al., 2006). Mechanistic insights into the potential effect of plant extracts included the modulation of MAPK and Akt signaling, inhibition of AP-1 activation, and the down-regulation of VEGF and TGF-β1 (Stanley et al., 2005) which is largely due to the active ingredients within the extracts. Thus the effects of flavonoids mainly luteolin, genistein, apigenin, quercetin, fisetin in suppressing the growth of tumor cells have been reported (Fotsis et al., 1995, Fotsis et al., 1997). For instance EGCG target tissue plasminogen activator (t-PA), which is one of the critical proteases that enable tumors to metastasize (Jankun et al.,

1997). Moreover EGCG was found to directly inhibit capillary endothelial cell proliferation at low concentrations pointing out that the latter is an important angiogenesis inhibitor (Cao and Cao, 1999). The targets of EGCG seem not only to be limited to endothelial cells and their inhibition of angiogenesis may result from the inhibition of MMP-2 and MMP-9, as well as urokinase plasminogen activator (u-PA) at higher concentrations while a downregulation of VEGF production in tumor cells and subsequent repression of AP-1, NF-κB and STAT 1 transcription factor pathways (Jung et al., 2001, Lin et al., 1999).

The major antiangiogenic mechanisms of the natural phytochemicals (resveratrol, genistein, diadzein, apigenin) involve the down regulation of the angiogenic factors (MMP-9 and VEGF) as well as the upregulation of tissue inhibitor metalloproteinases (TIMP)-1 which lead to reduction of tumor cell invasion and blood vessel growth (Brakenhielm et al., 2001, Huang et al., 1999, Tosetti et al., 2002). Another study showed the antiangiogenic effects of green tea extracts and its main catechin, EGCG in MDA-MB231 breast cancer cells and human umbilical vein endothelial cells. The extracts showed a significant decrease in VEGF peptide and this inhibition was regulated at the transcriptional level and accompanied by a significant decrease in VEGF promoter activity. The inhibition of VEGF formation correlated with the inhibition of protein kinase C and also c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1-responsive regions present in the human VEGF promoter may be involved in this inhibitory effect (Sartippour et al., 2002). In addition antioxidative effect of phytochemicals has recently been linked to antiangiogenesis. For instance, reduction of the oxidative stress by polyphenols leads to blockage of ROS formation and alterations in the cellular redox state, resulting in a reduced activation of transcription factors such as AP-1, p53 and NF-κB, which regulate the expression levels of the key angiogenic factors VEGF (Tosetti et al., 2002). This suggests the importance of antioxidant rich plant extracts (Table 1) or compounds in the management of angiogenesis as a key regulator in chemoprevention.

1.6. Upregulation of gap junctional intercellular communication (GJIC)

Another important target of chemoprevention involves the upregulation of gap junctional intercellular communication (GJIC). GJIC has been hypothesized to regulate growth, differentiation, apoptosis, wound healing and adaptive responses of differentiated cells (Loewenstein, 1990, Lucke et al., 1999, Wilson et al., 2000, Yamasaki and Naus, 1996). The gap junctions structure is transcribed and translated from a highly conserved family of genes coding for connexins which assembled into hexamers forming connexons which aligned with connexons of opposing contiguous cell membrane forming a channel for passive cytoplasmic diffusion of ions and other polarized and non-polarized molecules up to a molecular mass of 1 kDa which may set up gradients crucial in tissue growth and differentiation (Bruzzone et al., 1996, Kumar and Gilula, 1996). Data have shown that transfection of Cx32 or Cx43 gene into GJIC-defective and neoplastic cells resulted in GJIC restoration and reversion of the transformed phenotype (Omori et al., 1996, Rose et al., 1993) while dominant-negative mutant Cx43 transfected cell has been shown to inhibit GJIC and enhance tumorigenicity (Omori et al., 1996, Rose et al., 1993). Unlike the normal cells, neoplastic cells often elude this homeostatic control due to dysfunctional GJIC that could result mainly from non-expression of the connexin gene or from the non-functional connexin proteins due to a mutation, abnormal splicing of message or modification by oncogenes and chemical tumor promoters (Trosko and Ruch, 2003). Tumor cells are therefore

characterized by dysfunctional GJIC resulting in a lack of growth control by the inability to differentiate and by resistance to apoptosis (Hix et al., 2004).

Various tumor promoters and oncogenes downregulate GJIC (Matesic et al., 1994) while several dietary factors and medicinal extracts have been suggested to modulate GJIC by induction of various signal transducing systems which can prevent inhibition of GJIC and therefore suppress tumorigenesis (Nielsen et al., 2000, Sigler and Ruch, 1993). Restoration of GJIC by natural compounds including CAPE, resveratrol, epicatechin, carotenoids, apigenin, tangeretin, ginsenoside Rb_2 can be attributed to the upregulated expression of connexin 43 (CX43) protein and increased formation of Cx43 immunoreactive plaques in regions of the plasma membrane consistent with localization of gap junctions (Chaumontet et al., 1997, Hix et al., 2004, Na et al., 2000, Nielsen et al., 2000, Kang et al., 2000). The activation of ERK1/2 and p38 kinase has been suggested as a primary mechanism of GJIC inhibition by various tumor promoters (Cho et al., 2002). The intricate link between MAPK activation and inhibition of GJIC has been widely discussed (Cho et al., 2002), thus MAPK inhibitors are prospective therapeutic compounds against carcinogenesis. Plant extracts in particular *Phellinus linteus* and *Psyllium* extracts, have shown their efficacy in enhancing GJIC by targeting ERK1/2 and p38 kinase (Cho et al., 2002, Nakamura et al., 2004).

1.7. A unifying target: upstream kinases of intracellular signaling cascades and the downstream transcription factors

A wide range of cytoplasmic protein kinases is important in relaying the events during cell signal transduction. In carcinogenesis, exogenous and endogenous stimuli affect the cell signaling network leading to activation and/or repression of upstream kinases thereby transmitting signals to the downstream targets. Cancer is characterized by aberrant and disrupted intracellular signaling networks (Shaw and Cantley, 2006), thus targeted inhibition of the protein kinases represent a rational approach in cancer chemoprevention. Several natural compounds including curcumin, flavonoids, genistein, luteolin, resveratrol, isothiocyanates, catechins, terpenoids and herbal/medicinal extracts have been identified to target components of the signal transduction pathways (Aggarwal and Shishodia, 2006, Huang et al., 2007, Hwang et al., 2005, Kundu and Surh, 2004, Lee et al., 2006, Lin et al., 1999) This makes them ideal components in maintaining the proper transmission of signal from receptors to effectors. Upstream components of the cytoplasmic signaling networks include the family of proline-directed serine/threonine kinases also referred to as the MAPKs, PKC, PI3K, protein kinase B/Akt, GSK and inappropriate upregulation of the above mentioned protein kinases transmit mitogenic signals to transcription factors, co-activators and co-repressors that result in the expression of cell proliferating genes. These pathways in turn regulate GJIC, the process of angiogenesis and the apoptotic regulatory network.

Numerous intracellular signaling cascades converge with the activation of NF-κB, AP-1, c-myc, β-catenin which act independently or coordinately to regulate expression of target genes. These transcription factors mediate pleiotropic effects on cellular transformation and tumor promotion by transactivating several classes of target genes that have inflammatory, immunoregulatory, antiapoptotic and the cell cycle regulatory functions (Karin, 2006). Elevated levels of NF-κB have been detected in a number of human malignancies and the subsequent activation have been

shown to suppress apoptosis, induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance and inflammation (Aggarwal and Shishodia, 2006). Suppressing the activity of these transcription factors by phenolic rich extracts would be expected to thwart the ability of cancer cells to thrive. Thus experimental data support the idea that transcription factors are the prime molecular targets of chemopreventive phytochemicals (Bode and Dong, 2004). The overexpression of the transcription factor NF-κB involved in multiple survival signaling pathways upregulate antiapoptotic proteins (Bcl-X_L), XIAP and cIAP-2 suggesting NF-κB as a potential target for chemoprevention (Lin and Karin, 2003). Literature abounds in examples where plant extracts modulate the activation of protein kinases and transcription factors thereby interfering with carcinogenesis (Cavin et al., 2005, Kundu et al., 2005) (Table 3). These cytoprotective effects have been ascribed to the naturally occurring secondary metabolites and experimental data have shown that resveratrol, EGCG, curcumin, apigenin, 1,4-dihydroquinone, flavan-3-ol derivatives, procyanidins, terpenoids interfere with the activation of NF-κB and AP-1 (Jeong et al., 2004, Kundu and Surh, 2004, Ma et al., 2003). The molecular mechanisms involved the blockade of phosphorylation and degradation of IκBα, thereby preventing the subsequent nuclear translocation (Cho et al., 2002, Tsai et al., 1999). Inhibitory effects on cell signaling molecules namely the MAPKs, NIK, IKK has been attributed for the subsequent inactivation of the transcription factors. Oligonol, a formulation of catechin type oligomers successfully inhibited 12-O tetradecanoylphorbol-13-acetate (TPA) induced COX-2 expression by blocking the activation of NF-κB and C/EBP via modulation of MAP kinases thereby suppressing mouse skin carcinogenesis (Kundu et al., 2009). The gallotannin penta 1,2,3,4,6-O-galloyl β-d-glucose inhibited DU145 xenograft growth in an athymic mouse model by inhibiting the activity pSTAT3 which in turn inhibit the expression of genes involved in cell survival (Hu et al., 2008). The promising therapeutic effect of cancer-chemopreventive agents on protein kinases is also an important strategy for the prevention of angiogenesis since activation of mitogen-activated protein kinase (MAPK) stimulates expression of VEGF, a key factor in angiogenesis (Milanini-Mongiat et al., 2002). Moreover inhibition of protein kinases may enhance the apoptotic pathway and the elimination of neoplastic cells as discussed above.

2. Bioavailabilty and risk assessment of dietary polyphenols

Despite numerous reports on the beneficial effects of polyphenols against a wide-spectrum of degenerative disorders, knowledge pertaining to bioavailability, pharmacokinetics, disposition and metabolic fate in humans is limited. However a number of human and animal studies have indicated the presence of phenolic compounds in the plasma and in specific tissues (Table 4). It is well known that absorption of polyphenols mainly of aglycones and anthocyanidins begins in the stomach (Passamonti et al., 2003) while pharmacokinetic data points to the absorption of both the aglycones and galloylated forms of flavonoids from the small intestine (Spencer et al., 2000). In addition, the latter are metabolised to form methylated, glucuronidated or sulfated metabolites (Kay et al., 2005, Manach et al., 2005). A number of the polyphenolic classes in the main isoflavones, flavonols, flavanones, flavan-3-ols, phenolic acids and stilbenes have been shown to be absorbed sufficiently to exert their biological effects. The plasma kinetics of polyphenols differs among the polyphenolic classes depending on structural attributes with the maximum concentration being reached between 1.5 and 5.5 h depending on the site of intestinal absorption (Manach et al., 2005). Manach et al. (2005) reported that for the flavonoids-epicatechin and genistein, a dose of 50 mg would give rise to a maximum plasma concentration

from 0.4 μM (-epicatechin) to 2.5 μM (genistein). Almeida et al. (2009) reported the presence of trans-resveratrol in blood plasma of healthy adult volunteers following the administration of 25, 50, 100 or 150 mg trans-resveratrol, six times/day with mean peak plasma concentration being 3.89, 7.39, 23.1 and 63.8 ng/ml, 0.8–1.5 h postdose. The presence of phenolics constituents in the plasma and tissues can therefore improve the oxidant effects and prevents the disruption of cellular transduction pathways.

Table 4. Bioavailaibility studies of anthocyanin, flavonols, flavanones, flavonols and isoflavones containing foods. T_{max}: time to reach maximum concentration; bw: body weight; EGCG: epigallocatechin gallate; EGC: epigallocatechin; cyan-3-glc: cyanidin-3-glucoside.

Source	Class of phenolic or compound	No. of subjects	Dose	T_{max} plasma (h)	Plasma concentration (nmol/L)	Urinary excretion % of intake	Reference
Black currant juice	Anthocyanin	17	20 or 12 mg total anth/kg bw	0.75	32–107	0.045–0.072	Nielsen et al. (2003)
Red fruit extract (1.6 g)	Anthocyanin	12	2.7 mg cyan-3-glc/kg bw	1	29	–	Miyazawa et al. (1999)
Onions	Quercetin	5	186 mg quercetin eq	1.3–1.9	2180	1.11	Aziz et al. (1998)
Pure quercetin	Quercetin	12	0.14 mg/kg bw	0.5	150–420	2.9–7	Goldberg et al. (2003)
Buckwheat tea	Quercetin	12	200 mg quercetin eq	4.3	2.1	1	Graefe et al. (2001)
Orange juice	Flavanones	8	23 mg naringenin eq	5.5	0.64	1.1	Erlund et al. (2001)
Grapefruit juice	Flavanones	5	199 mg naringenin eq	4.8	5.99	30.2	Erlund et al. (2001)
Cocoa	Flavanols	6	1.53 mg/kg bw	2	1–1.5	–	Schramm et al. (2003)
Red wine (120 ml)	Flavanols	9	35 mg catechin	1.44	0.077	–	Bell et al. (2000)
Green tea extracts	Flavanols	8	2.8 mg EGCG/kg bw	1.6	0.17 EGCG	Trace amount	Lee et al. (1995)
Black tea	Flavanols	15	400 mg total catechins		0.02 EGCG; 0.14 EGC	0.14 EGCG; 0.14 EGC	Warden et al. (2001)
Soy beverage	Isoflavones	12	0.6 mg diadzein/kg bw	5.5	0.3	–	Shelnutt et al. (2002)

Diet rich in flavanols and procyanidins can improve oxidant defense although these effects can be tissue specific. For instance, ellagic acid following pomegranate juice intake was detected in the plasma of all the human subjects studied with a maximum concentration of 0.06 ± 0.01 μmol/L after 1 h while ellagic acid metabolites primarily total urolithin A and total urolithin B ranged between 0.14 and 0.01 μmol/L respectively at 6 h (Seeram et al., 2006). Another human intervention study showed the plasma pharmacokinetics of EGCG concentrations to range between 0.7 ± 0.4 and 0.5 ± 0.2 μmol/L after 2.5 h following intake of purified EGCG and green tea extract respectively. In addition the maximum plasma total flavanol (EGC, EC, EGCG, ECG) concentration after green tea extract intake was 3.2 μmol/L (Henning et al., 2005). Plasma epicatechin concentrations in Sprague–Dawley rats were also

increased in a dose-dependent fashion following cocoa intake (128–790 nM) (Orozco et al., 2003).

Plant extracts/food biofactors with pharmacologic doses of polyphenols can therefore find applications in chemoprevention, however bioavailability and pharmacokinetics are vital for the design and interpretation of intervention studies and toxicologic testing may be required to ensure safe levels of intake.

3. Conclusion

Data derived from cancer cell lines, animal and clinical studies have indicated the potential role of targeting the disrupted cell signaling transduction pathways to intercept the relay of signals to downstream transcription factors and co-activators resulting in neoplastic transformation and cell proliferation. Moreover induction of phase II detoxifying enzymes, scavenging of ROS/RNS and induction of apoptosis represent an important strategy for the prevention of carcinogenesis. Plant-derived phytochemcials and plant extracts have been widely reported for their antioxidant properties, anti-inflammatory activities, upregulation of detoxifying enzymes and activation and/or repression of signal transduction pathways (Table 1, Table 2). Several independent studies have reported the beneficial effects of plant-derived phytochemicals and these compounds are mostly responsible for the protective properties of plant extracts. The potential synergistic effects of the myriad components in a plant extract may account for the protective effects against carcinogenesis. In addition, mixtures of interacting compounds produced by the plants may provide important combination therapies that simultaneously affect multiple pharmacological targets and can achieve clinical efficacy beyond the reach of single compound-based drugs while at the same time reducing the potential toxicity since much lower doses are sufficient. However, particular attention is mandatory before the potential application of these phytoceuticals in the management of cancer primarily in terms of (i) optimal dose, (ii) toxicity of the phytochemicals, (iii) metabolic conversion into pro-oxidant and cytotoxic components, (iv) interference with endogenous metabolic pathways, (v) interaction with other chemicals from the diet or drugs, (vi) induction of carcinogen activating enzymes and (vii) effects on human intestinal microflora should be assessed (Hodek et al., 2009). The bioavailability concerns that arise can only be resolved by future clinical trials which in addition will advance our understanding of the efficacy and safety of many chemopreventive phytoceuticals/extracts with therapeutic potential. Thus finding alternative/complementary approach in the prevention and treatment of carcinogenesis is of utmost significance.

Conflict of interest

The authors declare that there are no conflicts of interest.

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