Chemopreventive effects of natural dietary compounds on cancer development

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Chemoprevention, a relatively new and promising strategy to prevent cancer, is defined as the use of natural dietary compounds and/or synthetic substances to block, inhibit, reverse, or retard the process of carcinogenesis. The chemopreventive effects elicited by these natural dietary compounds are believed to include antioxidative, anti-inflammatory activity, induction of phase II enzymes, apoptosis, and cell cycle arrest. Many mechanisms have been shown to account for the anticarcinogenic actions of natural dietary compounds; attention has recently been focused on intracellular-signaling cascades as common molecular targets for various chemopreventive natural dietary compounds. In this *critical review*, we will summarize current knowledge on natural dietary compounds that act through the signaling pathways and modulate gene expression to induce detoxifying enzymes, programmed cell death, anti-inflammatory, and anti-proliferative effects, thus providing evidence for these substances in cancer chemopreventive action (128 references).

1. Generalized chemoprotective mechanisms

Cancer development, a dynamic and long-term process, involves many complex factors with a stepwise progression that ultimately leads to metastasis, an uncontrolled spreading and growth of cancerous cells throughout the body. The three critical steps in this process for several types of human cancer formation are initiation, promotion and progression. Epidemiological studies have provided convincing evidence that natural dietary compounds can modify this process. Laboratory research has further demonstrated the effectiveness of a number of bioactive dietary components that have the ability to prevent cancer and other chronic diseases.[1] Such promising research provides strong support for the future acceptance of natural dietary compounds as chemopreventive agents. We suggest that cancer chemopreventive effects elicited by these natural dietary compounds are due at least in part to the induction of cellular defence systems, including the detoxifying and antioxidant enzymes system as well as the inhibition of anti-inflammatory and anti-cell growth signaling pathways culminating in apoptosis and/or cell cycle arrest. The scope of the present critical review will focus on the molecular basis of chemopreventive potential of natural dietary compounds, with special emphasis on their effects on cellular signaling molecules as targets.

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1.1 Antioxidative activity

There are multiple lines of evidence from both laboratory and clinical studies that support that oxidative stress imposed by reactive oxygen species (ROS) plays a crucial role in the pathophysiology associated with atherosclerosis, neurodegenerative diseases, and all stages of carcinogenesis.[2]

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Oxidative stress is created when there is an imbalance between the generation of ROS and their removal, resulting in potential cell damage. These ROS include free radicals such as hydroxyl radical, peroxy radical, superoxide anion radical, and other reactive species, such as hydrogen peroxide and singlet oxygen, generated as a result of naturally occurring processes (*e.g.*, mitochondrial electron transport, exercise), environmental stimuli (*e.g.*, ionizing radiation from the sun), environmental pollutants, changed atmospheric conditions (*e.g.*, hypoxia), and lifestyle stressors (*e.g.*, cigarette smoke and excess alcohol consumption). However, increasing evidence in both clinical and experimental studies suggests a role for various reactive carbonyl species (RCS)[3] produced during lipid peroxidation (mainly of α,β-unsaturated aldehydes), or generated as a consequence of the reaction of reducing sugars, such as glyoxal and methylglyoxal, or their oxidation products with lysine residues of protein. Most of the biological effects of intermediate RCS are attributed to their capacity to react with the nucleophilic sites of proteins, forming advanced lipoxidation end products (ALEs) and advanced glycation end-products (AGEs) (Fig. 1). High glucose concentration in physiological systems leads to the generation of stable AGE adducts. Both RCS and AGEs have been shown to have a strong relationship with ROS. Recent data indicated that antioxidants such as tea polyphenols and certain flavonoids had marked inhibitory effects on ROS and AGE formation.[4] Defence mechanisms to remove the ROS include enzymes such as superoxide dismutase, catalase, glutathione peroxidase and antioxidants, which can exist endogenously in the body or be consumed from natural dietary sources (Fig. 1). Oxidative damage can occur to macromolecules such as proteins, DNA and lipids. DNA base alterations, strand breakage and mutations are problems that are usually associated with free radical attacks on DNA. In studies, it has been shown that this damage can be stopped, reduced and even reversed with antioxidant supplementation. Antioxidant protection from damage due to free radicals is vital for the integrity of cellular structures and macromolecules.[1] ROS can interfere with normal cellular signaling cascades by influencing the activation or expression of transcription factors and upstream kinases, modulated by antioxidative phenolic phytochemicals (Fig. 1).

1.2 Anti-inflammatory activity

Inflammation is a physiological process in response to tissue damage resulting from microbial pathogen infection, chemical irritation, and/or wounding. It has been known that inflammation is causally linked to carcinogenesis and acts as a driving force in premalignant and malignant transformation of cells.[5] There is now growing evidence supporting that chronic inflammation may lead to malignancies of different organs including skin, stomach, colon, breast, prostate and pancreas.[5] The initial inflammation involves the recruitment of a wide range of immune cells to inflamed sites and the release of various proinflammatory cytokines and other agents. In a setting of chronic inflammation, the persistent tissue damage and cell proliferation, as well as the enrichment of ROS and RCS, contribute to a cancer-prone microenvironment.[1] With

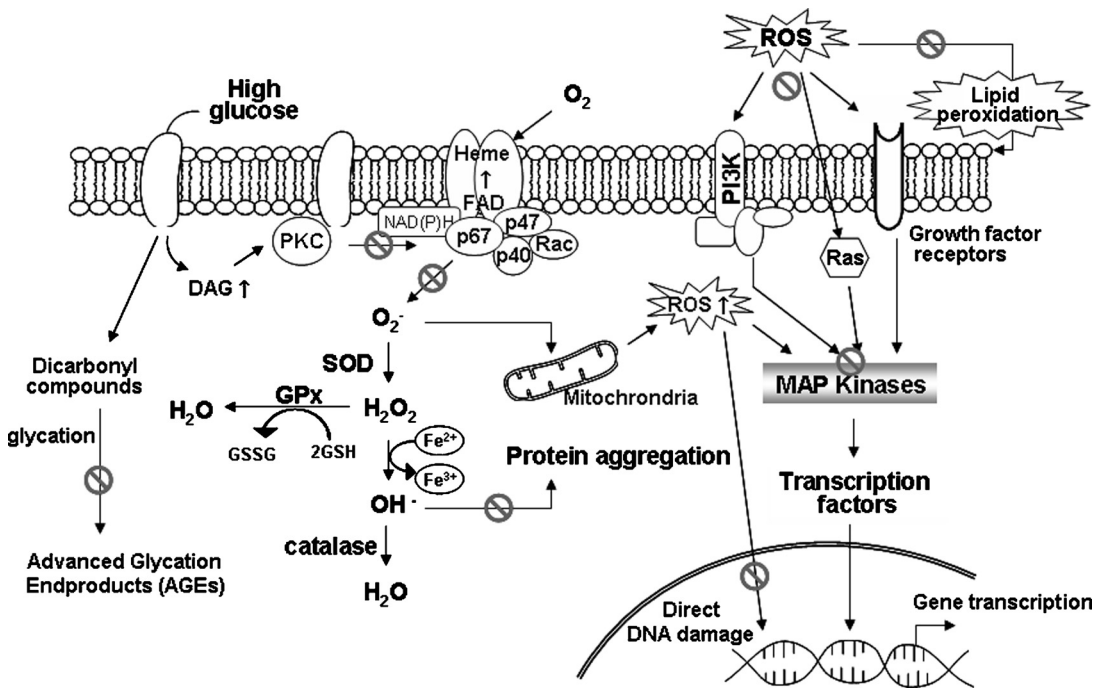


Fig. 1 Possible mechanisms of ROS production, oxidative damage and targets for food bioactive compounds. In mammalian cells, the ROS are generated during irradiation, metal-catalyzed reactions, enzymatic reactions and mitochondria-catalyzed electron transport reactions. These ROS result in direct DNA damage, protein aggregation and lipid peroxidation and lead to oxidative stress-associated signaling and gene expression involved in carcinogenesis. ROS are highly enriched with antioxidants including glutathione (GSH) and enzymes, such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx). The dietary antioxidants are direct scavengers for ROS, and also induction of endogenous antioxidative enzymes may reduce oxidative stress-mediated processes. The various protective mechanisms are marked with a ⊘.

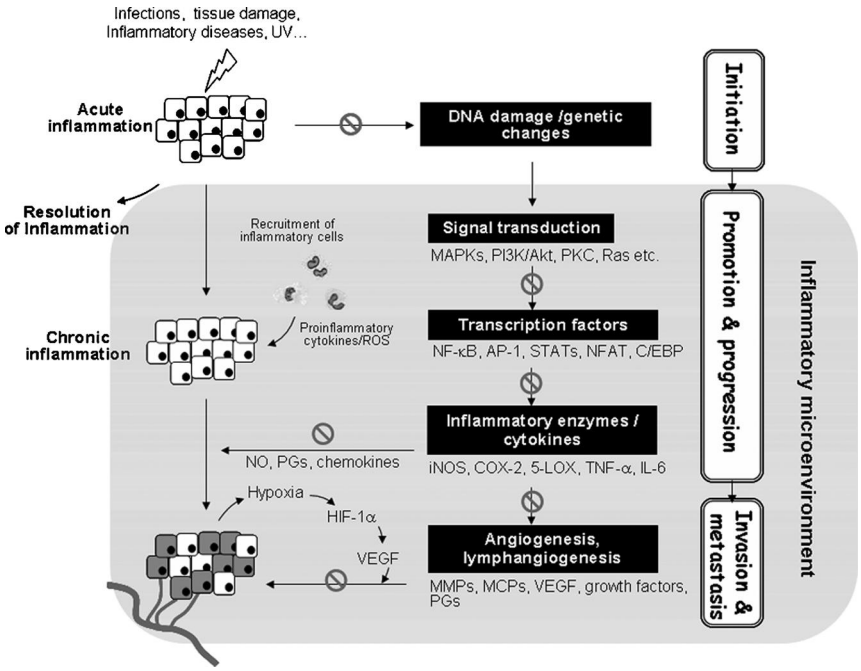


Fig. 2 Mechanisms for the association between inflammation and cancer development. Tissue damage caused by viruses, bacteria, radiation and carcinogens results in inflammation. While acute inflammation usually counteracts cancer development as a defence response, chronic inflammation promotes cancer development. During chronic inflammation, inflammatory cells are recruited to the damaged tissues and induce DNA damage in proliferating cells bearing survival advantages and that ultimately contribute to malignant transformation. These inflammatory cells also create an inflammatory microenvironment and a network of signaling molecules which promote in proliferation, angiogenesis, invasion, and metastasis. Several dietary agents act through avoiding the causes of tissue damage, inhibition of signaling pathways, inhibition of oxidant-generating enzymes and mediators of inflammation, scavenging reactive oxygen and nitrogen species generated by inflammatory cells, and modulation of angiogenesis and metastasis.

such a generalized model, several transcription factors and enzymes, besides cytokines and chemokines, should be taken into extensive consideration for their critical regulatory functions during this complicated process (Fig. 2). Recently, light has been shed on NF-κB, AP-1, STATs, NFAT, and C/EBP.[6] Activated NF-κB often facilitates transcription of numerous genes, including iNOS, COX-2, 5-LOX, TNF-α, HIF-α, and IL-6, resulting in inflammation and tumorigenesis. Activation of NF-κB is induced by a cascade of events leading to the activation of inhibitor κB (IκB) kinases (IKKs), which in turn phosphorylates IκB. The subsequent ubiquitination and proteasomal degradation of IκB leaves NF-κB free to translocate to the nucleus.[5] These kinases can be activated through phosphorylation by upstream kinases, including NF-κB-inducing kinase, mitogen-activated protein kinase, and protein kinase C[5]. In addition, many studies have confirmed the cytokine function in the induction of transcription activity of NF-κB through Erk1/2 (p42/44), p38 MAPK, Ras, and PI3K/Akt pathways.[7] Recent studies revealed that constitutive activation of STATs (signal transducers and activators of transcriptions), particularly STAT3, is found in a number of primary human epithelial tumors and cancer cell lines. Persistently active STAT3 induces tumor angiogenesis by up-regulation of vascular endothelial growth factor (VEGF) and its immune evasion.[5] Many natural dietary compounds have been reported to interfere at the initiation, promotion–progression, and invasion–metastasis of cancer through controlling intracellular-signaling cascades of inflammation progresses (Fig. 2).

1.3 Phase 2 enzyme induction

Several ligand-activated transcription factors regulate natural dietary compound induction of phase II enzymes, including non-receptor-, nuclear factor-erythroid 2-related factor 2 (Nrf2) and CCAAT/enhancer-binding protein β (C/EBPβ) and receptor-mediated pathways, the aryl hydrocarbon (AhR) and pregnane and xenobiotic receptors (PXR; or steroid and xenobiotic receptor, SXR).[8] The AhR is maintained in a cytoplasmic complex with heat shock and other chaperone proteins. Once bound to ligand, it enters the nucleus, separates from the chaperones, and complexes with the AhR nuclear translocator protein to induce transcription *via* binding to xenobiotic response elements (XRE) in promoters of target genes.[9] PXR is a nuclear hormone receptor that plays a key role in cholesterol and hormone homeostasis.[10] On binding of a small hydrophobic ligand, the PXR interacts with the retinoid-X receptor to induce gene transcription.[10] Under basal conditions, Nrf2 is sequestered in the cytoplasm *via* the cytoskeletal actin-binding protein, Kelch-like ECH-associating protein 1 (Keap1), which targets Nrf2 for proteasomal degradation.[11] Recent reports indicated that Nrf2 phosphorylation may disrupt the Keap1/Nrf2 complex through mitogen-activated protein kinase (MAPK), p38, extracellular-regulated kinase (ERK1/2), and c-Jun N-terminal kinase (JNK1), protein kinase C (PKC) and phosphatidylinositol-3 kinase (PI3K) pathways, freeing Nrf2 to enter the nucleus and induce gene expression of phase II enzyme[11] (Fig. 3). These

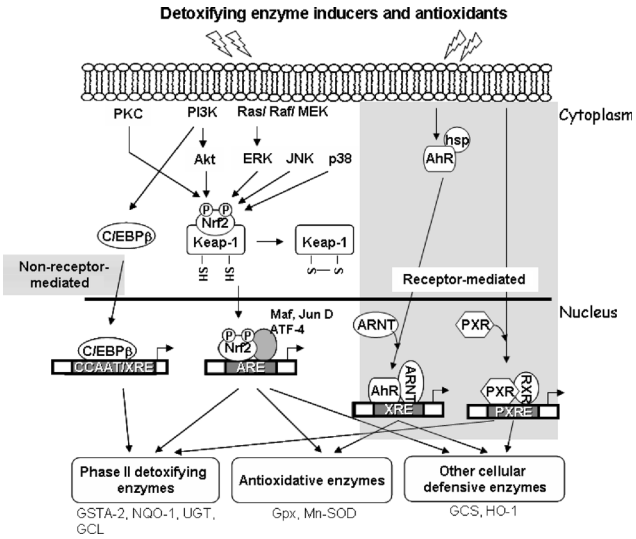


Fig. 3 Proposed pathways of activation of detoxifying enzymes. The antioxidants and phytochemicals activate diverse upstream kinase signaling and lead to activation of transcription factors such as Nrf2, AhR and PXR and increase phase II, antioxidative, and other cellular defensive enzyme expressions. Theses detoxifying enzymes may lead to detoxification of carcinogens, reduce free radicals and ROS, and remove or repair oxidatively-damaged proteins.

genes encode enzymes such as glutathione S-transferase (GST), glutathione peroxidase, NAD(P)H;quinone oxidoreductase (NQO), γ-glutamylcysteine synthetase, and heme oxygenase-1 (HO-1). Many basic leucine zipper transcription factors include Nrf, Jun, Fos, Fra, Maf, and the Ah receptor.

One successful strategy for cancer chemoprevention is modulation of drug metabolizing enzymes, leading to a facilitated elimination of endogenous and environmental carcinogens. The procarcinogenic metabolism can be altered by natural dietary compounds by inhibiting phase I drug metabolizing enzymes (cytochrome P450) or increasing the activity or modulating the gene expression of phase II conjugating-enzymes.

1.4 Apoptosis

Apoptosis, a form of programmed cell death, plays a critical role in both development and tissue homeostasis. It involves the concerted action of a number of intracellular signaling pathways, including members of the caspase family of cysteine proteases, stored in most cells as zymogens or procaspases. This distinguishes the apoptotic process from other forms of cell death, such as autophagy, oncosis, and necrosis.[1] Typically, apoptosis is also a gene-directed form of cell death with well-characterized morphological and biochemical features, which is characterized by cell shrinkage, membrane blebbing, chromatin condensation and formation of a DNA ladder with multiple fragments caused by internucleosomal DNA cleavage. Proteolytic cleavage of procaspases is an important step leading to caspase activation, which in turn is amplified by the cleavage and activation of other downstream caspases in the apoptosis cascade.[1,12] The two main apoptotic pathways, the death receptor (extrinsic) and mitochondrial (intrinsic) pathway, are activated by caspase-8 and caspase-9, respectively (Fig. 4). First, the interaction of a cell surface receptor, such as Fas, TNFR, DR3, DR4, or DR5, with their ligands occurs. Activation of death receptors (Fas) by cross-linking with their natural ligands (Fas ligand) induces receptor clustering and formation of a death-inducing signaling complex (DISC). The complex recruits procaspase-8 *via* the adaptor molecule Fas associated death domain protein (FADD), resulting in the activation of caspase-8. Activated caspase-8 directly cleaves and activates caspase-3, which in turn cleaves other caspases. Caspase-8 is recruited as a death-inducing signaling complex only when death receptors such as Fas or the tumor necrosis factor receptor bind to specific multimeric ligands. Second is the participation of mitochondria, which for most forms of apoptosis, is a response to cellular stress, loss of survival factors, and developmental cues.[1,12] Caspase-9 is activated when cytochrome *c* is released into the cytoplasm from the mitochondrial intermembranous space. Activated caspase-8 and caspase-9 activate executioner caspases, including caspase-3, which in turn cleave a number of cellular proteins that include structural proteins, nuclear proteins, cytoskeletal proteins, and signaling molecules.[12] Moreover, the mitochondrial pathway is regulated by the Bcl-2 family of proteins, including anti-apoptotic proteins, such as Bcl-2 and Bcl-X_L and pro-apoptotic proteins such as Bad, Bid, Bim, Bax, and Bak1. In recent studies, the endoplasmic reticulum (ER), as a third subcellular compartment containing caspases, was implicated in apoptotic execution induced by ER stress.[13] The ER stress-induced cell death modulator, a CCAAT/enhancer-binding protein (CEBP) homology protein GADD153, known as CHOP, is a member of the CEBP family of transcription factors. Expressed at low levels in proliferating cells, it is strongly induced in response to stresses that result in growth arrest or cellular death, including oxidant injury, DNA damaging agents such as peroxynitrite, UV radiation, anticancer chemotherapy, and ER stress.[13] Recent studies suggest that GADD153 plays a central role in apoptosis-induction by overexpression of GADD153 of vector-transfected cells, including the dephosphorylation of the pro-apoptotic protein Bad and down-regulation of Bcl-2 expression. Although caspase activation is a critical event in the induction of apoptosis, mammalian cells in a certain circumstance can undergo caspase-independent apoptosis that is mediated by the disruption of the mitochondrial membrane potential and the translocation of apoptosis-inducing factor (AIF) and endonuclease G to the nucleus where they induce chromatin condensation and/or large-scale DNA fragmentation. Recently, ciglitazone, a synthetic PPARγ, induced caspase-independent apoptosis through p38 MAP kinase-dependent AIF nuclear translocation in epithelial cells.[14] In contrast to necrosis, no inflammatory reaction results upon apoptosis.

A recent study suggests that MAPKs, including stress-activated protein kinases such as c-Jun NH2-terminal kinases (JNK) and p38, play important roles in triggering apoptosis in response to various cellular stressors such as oxidative stress. The phosphorylation of Bcl-2 has been described as an important step from microtubule damage to apoptosis. Furthermore, Bid is believed to be relatively inactive in the cytosol until activated by proteolytic cleavage by caspase-8.

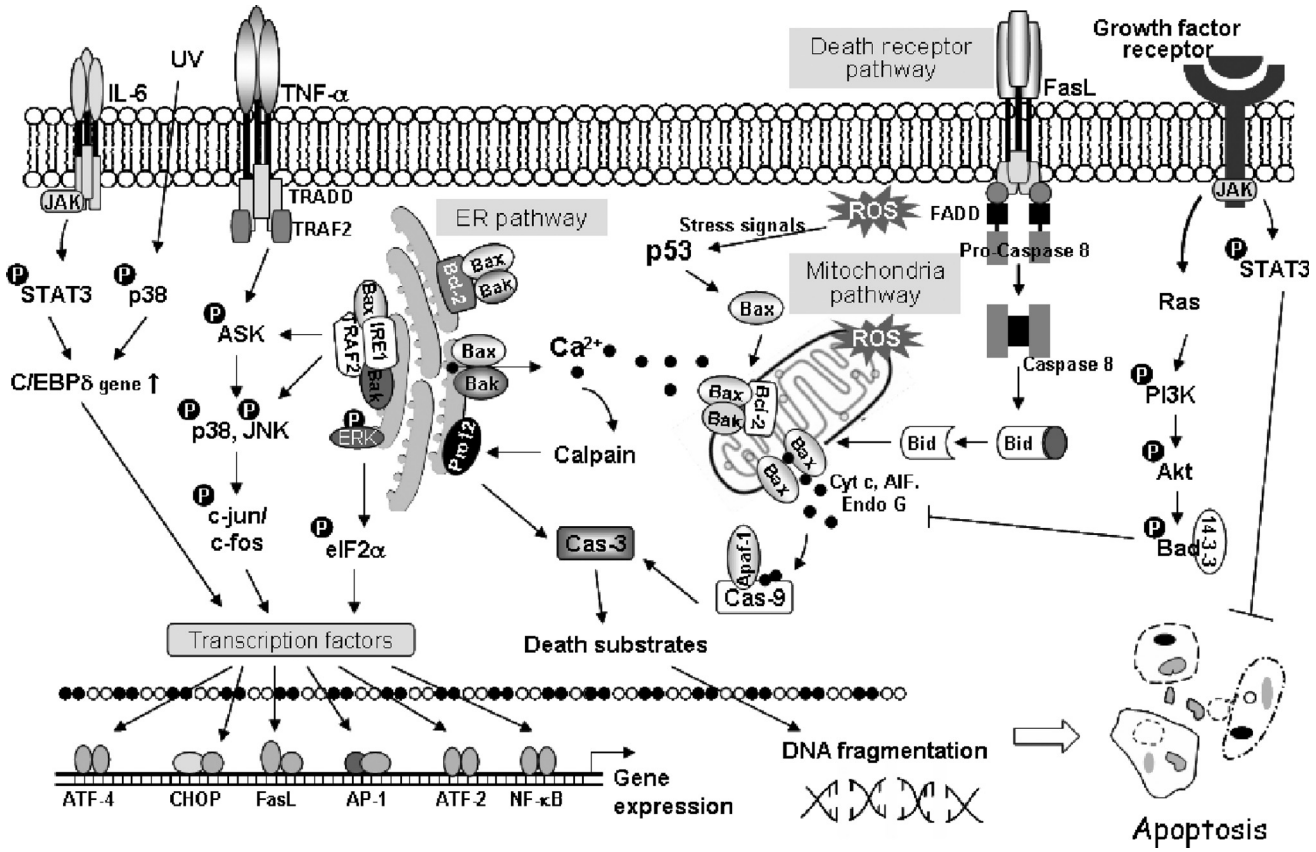


Fig. 4 Signaling and molecular pathway of apoptosis in mammalian cells. In the death receptor pathway, death receptors interact with their ligands and recruit adaptor protein and initiator procaspases-8. Active initiator caspase-8 activates the effector caspase-3 to induce apoptosis or to initiate degradation of Bid and to yield cytochrome *c* release from mitochondria. The mitochondrial pathway involves release of cytochrome *c* and other mitochondrial molecules such as AIF and endo G, thereby forming the apoptosome which activates caspase-9 and is capable of proteolytically processing caspase-3 to induce apoptosis. The mitochondrial permeability also interacts with the Bcl-2 family of proteins. In the ER pathway, cytoplasmic Ca^{2+} concentration, as a result of ER stress, results in the activation of caspase-12, activation of JNK signaling and transcriptional induction of CHOP/GADD153. ROS and other signals activated by natural dietary compounds could regulate the cellular signaling and pro-apoptotic molecules to trigger apoptosis.

However, the apoptotic pathways in which Bid plays a role are not yet fully characterized. Recent studies suggest that Bid is phosphorylated by DNA-damage kinase ATM (ataxia t elangiectasia mutated) and may play an important role for S phase arrest.[15] Therefore, apoptosis induction may be considered one of the important targets in a preventive approach against cancer at the moment by reversion of the conversion of a normal cell to a malignant one. It is now apparent that many natural dietary compounds for human consumption can also preferentially inhibit the growth of tumor cells by targeting one or more signaling intermediates leading to induction of apoptosis.

1.5 Cell cycle arrest

In cancer, normal cell growth and behaviour is lost and there are alterations in the regulation of the cell cycle, which is tightly controlled in normal cells by checkpoints and can become activated due to DNA damage, exogenous stress signals, and defects during the replication of DNA or failure of chromosomes to attach to the mitotic spindle. The loss of this regulation is the hallmark of cancer. The cell cycle consists of four phases (G1, S, G2 and M). Several proteins are known to regulate the timing of the events in the cell cycle. The C/EBP family of transcription factors plays an important role in controlling cell proliferation and differentiation.[16] The eukaryotic cell cycle is regulated through the sequential activation and inactivation of cyclin-dependent kinases (Cdks) that drive cell cycle progression through phosphorylation and dephosphorylation of several regulatory proteins.[16] In normal cells, Cdks exist predominantly in quaternary complexes consisting of a Cdk, a cyclin, a proliferating cell nuclear antigen (PCNA), and a 21 kDa protein (p21). Cdk activation requires cyclin binding and phosphorylation of conserved threonine residues by Cdk-activating kinase (CAK). The activated Cdk–cyclin complexes can be changed to an inactive state by phosphorylation of a conserved threonine–tyrosine pair or binding to Cdk inhibitory subunits (CKIs). Progression from the G1 to the S phase in mammalian cells is regulated by the accumulation of cyclins D, E, and A, which bind to and activate different Cdk catalytic subunits. The activation of Cdk4–cyclin D and/or Cdk6–cyclin D complex is necessary for the transition from the early to the mid G1 phase. Transition through mid G1 to the S phase is regulated by activation of the Cdk2–cyclin E complex. Progression through the late G1 to

the S phase also requires the presence of the Cdk2–cyclin A complex. The retinoblastoma tumor suppressor protein (Rb) is a critical target protein that is phosphorylated *via* these Cdk–cyclin complexes. Rb controls gene expression mediated by a family of heterodimeric transcriptional regulators, collectively termed the E2F, which can transactivate genes whose products are important for transition from the G1 to the S phase.[17] Phosphorylation of Rb frees these regulators, enabling them to transactivate the target genes. Therefore, the hypophosphorylated forms of Rb are predominantly found in the G0–G1 phase, but the hyperphosphorylated forms of Rb are required during the S and G2–M phases[17] (Fig. 5).

Recent studies show that Cdk regulation involves a diverse family of proteins, termed the CKIs (Cdk inhibitors), that bind and inactivate Cdk–cyclin complexes. In mammalian cells CKIs fall into two classes: (1) p21 (Cip1/Waf1/Cap20/Sdi1/Pic1), p27 (Kip1), and p57 (Kip2) are related proteins with a preference for Cdk2– and Cdk4–cyclin complexes; (2) p16INK4, p15INK4B, p18INK4C and p19INK4D are closely related CKIs specific for Cdk4– and Cdk6–cyclin complexes. The majority of *in vivo* studies suggest that the inhibitory effect of p21 is largely exerted during the G1 phase of the cell cycle, with preferential binding to Cdk4- and Cdk2-containing complexes, and that it either inhibits their kinase activities or prevents their activation by CAK. In addition, the regulation of p21 is largely dependent on the presence of functional p53, a transcriptional regulator that mediates cell cycle arrest following DNA damage (since it requires gene transcription, and it also involves the p53 activating ATM, ATR, and Chk2), senescence, hypoxia, and oncogene activation.[18]

In addition p21, p53-dependent transcriptional regulation of 14-3-3σ, Cdc25C, and GADD45 has been proposed to mediate cell growth arrest.[18] These effects probably play a role in the ability of p53 to act as a tumor suppressor, and a number of natural dietary compounds have been shown to exert their antitumorigenic activity through p53-dependent mechanisms.[19] The induction of cell cycle arrest and/or apoptosis is considered to be a promising chemopreventive strategy.

2. Chemopreventive natural dietary compounds

Chemoprevention through the consumption of natural dietary compounds such as resveratrol from grapes, lycopene from tomatoes, and genistein from soy products may reduce both morbidity and mortality from cancer.[20] The foods and herbs that possess anticancer activity include garlic, soybeans, cabbage, ginger, licorice, onions, flax, turmeric, cruciferous vegetables, tomatoes, peppers, brown rice, wheat and the umbelliferous vegetables such as carrots, celery and parsley. Natural products and their isolated constituents have been shown to possess strong chemopreventive activity in animal models.[20] The effects of nutraceuticals on apoptotic pathways, signaling pathways, and/or different targets in cancer mean that they could be helpful starting points in the design and development of novel cancer preventive agents.

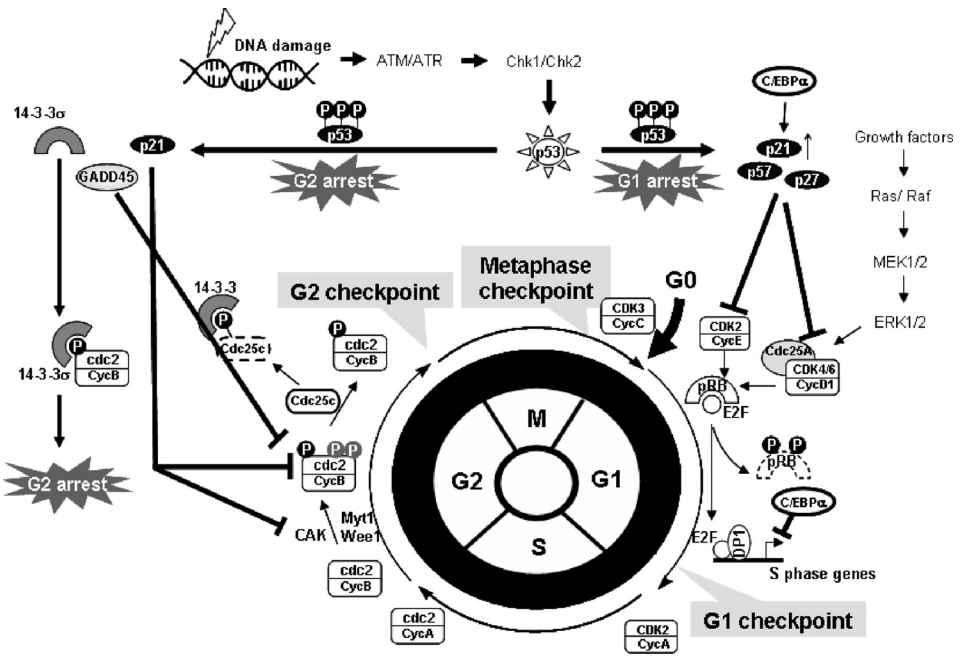


Fig. 5 Current understanding of the mammalian cell cycle. The cell cycle is broadly divided into four phases (G1, S, G2 and M) culminating in cell duplication. Each phase of the cell cycle is regulated by a different complement of CDK–cyclin complexes. In response to growth factor stimulation, Rb is phosphorylated by the G1 CDKs and results in release of E2F, allowing the expression of genes that are required for S phase progression. Activation of ATM/ATR by DNA damage results in the activation of checkpoint and signal transduction pathways that induce cell cycle arrest at the G1/S, S and G2/M phases. 14-3-3 proteins function at several key points in the G2/M-transition by binding to regulatory proteins and modulating their function. C/EBPα is a particularly potent regulator of cell cycle exit as a component of the p53-regulated growth arrest response. Many dietary phytochemicals have been shown to modulate cell cycle regulators including cyclin-dependent kinases and their inhibitors, CKIs, cyclins, p53, Rb proteins, E2Fs, check-point kinases, ATM/ATR and control G1/S and G2/M check-point transitions in cell cycle progression.

Many natural dietary compounds in fruits and vegetables have been isolated and have demonstrated health-promoting properties. They can be categorized into several classes. The molecular mechanisms underlying the chemopreventive effects of selected natural dietary compounds are described below.

2.1 Carotenoids

Carotenoids are natural, fat-soluble pigments that provide bright coloration to plants and animals. They also act as antioxidants, and some of them possess vitamin A activity. One defining characteristic of carotenoids is the chemical structure of their backbone molecule, a 40-carbon polyene chain, derived from isoprene. The polyene backbone consists of conjugated double bonds, which allows the carotenoids to take up excess energy from other molecules through a non-radiative energy transfer mechanism.[21] This characteristic may be responsible for the antioxidant activity seen in biological carotenoids, as it has the ability to quench singlet oxygen.

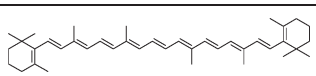
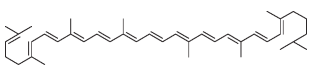
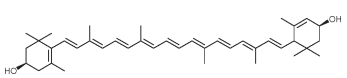
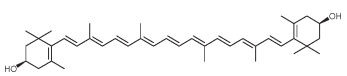
β-Carotene (Table 1) is the most common carotenoid in food and the most potent of the provitamin A carotenoids. β-Carotene is known for its many health promoting characteristics such as enhancement of the immune system by improved activity and changes in immune cell numbers, and decreased risk of degenerative diseases such as cancer, cardiovascular diseases, age-related macular degeneration and cataract formation.[22] β-Carotene is primarily found in red palm oil, palm fruits, leafy green vegetables, carrots, sweet potatoes, mature squashes, pumpkin, mangoes and papayas.

Epidemiological and animal studies support the hypothesis that β-carotene can prevent cancer in humans.[23] In contrast, chemoprevention trials with β-carotene either alone or in combination with vitamin A or vitamin E actually increased the incidence of lung cancer in high risk groups of humans.[24] Other *in vitro* and *in vivo* studies have shown that while β-carotene itself may be anticarcinogenic, its oxidized products may facilitate carcinogenesis, thus providing an explanation for the chemoprevention trial results.

Additionally, β-carotene is believed to have antioxidant activity, inhibit 4-(methylnitrosamino)-1-(3-pyridyl)-1-;butanone (NNK)-induced lung carcinogenesis,[25] and improve cell viability through induced Phase 2 enzyme.[26] It has been shown to exhibit radical-trapping behavior only at partial pressures of oxygen substantially less than that of normal air.[27] Such low oxygen partial pressures are found in most tissues under physiological conditions. At higher oxygen pressure, it loses the antioxidant activity and shows a pro-oxidant effect.[27]

Lycopene, a carotenoid found in tomato, watermelon, papaya, apricot, and orange and pink grapefruit, has antioxidant and anticancer activities. About 80% of dietary lycopene is from tomatoes and tomato-related products. The bioavailability of lycopene is rather poor, but it is improved by thermal processing.[28] Numerous studies have suggested reduced risk of prostate cancer from the consumption of processed tomato

Table 1 Chemopreventive mechanisms of major carotenoids

Group	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Carotenoids	β-Carotene		Red palm oil, carrots, pumpkin and leafy green vegetables	• Inhibits NNK-induced lung carcinogenesis	25
				• Reduces 8-OHdG concentration and increases antioxidative ability in the skin and liver of UVB-irradiated Osteogenic Disorder Shionogi (ODS) rats	26
				• Improves the cell viability, and increases catalase activities and GSH levels in hepatocytes from chronically ethanol-fed rats	27
	Lycopene		Tomatoes, watermelon, papaya and orange	• Against γ-radiation induced DNA damage, lipid peroxidation	29
				• Induces apoptosis during experimental gastric carcinogenesis	30
				• Inhibits lung squamous metaplasia and induces apoptosis in cigarette smoke-exposed ferrets	30
				• Reduces the incidence of ACF in AOM-induced colon carcinogenesis model	31
	Lutein		Spinach and kale	• Protects against UV light irradiation-induced lipid peroxidation	32
				• Inhibits mouse mammary tumor growth by regulating angiogenesis and apoptosis	33
	Zeaxanthin		Squash, peas, cabbage and orange	• Reduces oxidative stress-induced apoptosis in photoreceptors and enhances photoreceptor differentiation	34
				• Protects against UV light irradiation-induced lipid peroxidation	32

products. Consistently, a lower risk of a variety of cancers and cardiovascular disease has been associated with the higher consumption of tomato-based products. Although, the beneficial health effects of lycopene are thought to be due to its antioxidant properties,[29] evidence is accumulating to suggest other mechanisms of action, such as the induction of apoptosis in smoke-induced lung carcinogenesis[30] and the inhibition of azoxymethane (AOM)-induced colon carcinogenesis.[31] Lycopene is the most abundant carotenoid in human plasma, which may imply its elevated level of importance in the human body compared with other carotenoids, such as β-carotene and lutein. Lutein and its isomer, zeaxanthin, are yellow pigments that belong to the classes of non-provitamin A carotenoids (Table 1). Unlike other carotenoids, hydroxyl groups are substituted on the ring structures at the end of the conjugated double bond chains of lutein and zeaxanthin; therefore, they are also called oxycarotenoids or xanthophylls. Lutein is naturally occurring and found predominantly in dark green, leafy vegetables such as spinach and kale. Zeaxanthin gives corn its yellow color. Lutein and zeaxanthin protect from UV light irradiation-induced lipid peroxidation,[32] inhibit tumor growth in mouse mammary tumor cells[33] and reduce oxidative stress-induced apoptosis in rat photoreceptor cells.[34]

2.2 Flavonoids

Flavonoids are ubiquitous in plants; almost all plant tissues are able to synthesize flavonoids. There are also a wide variety of types—at least 2000 naturally occurring flavonoids. They can be classified into seven groups: flavones, flavanones, flavonols, flavanonols, isoflavones, flavanols (catechins) and anthocyanidins (Table 2). In general, the leaves, flowers, fruits, or the plant itself, contain flavonoid glycosides, while the woody tissues contain aglycones, and the seeds may contain both.

Quercetin is found typically in grapes, wine, tea, onions, apples, and leafy green vegetables, and it has been shown to be a potent antioxidant and anti-inflammatory agent that protects the blood vessels, the cell, and its structures from the harmful effects produced by free radicals. Quercetin also exhibits potential antioxidant activity, modulates phase I and phase II enzymes,[35] induces apoptosis in human breast cancer MDA-mB-435 cells,[36] and inhibits AOM-induced colorectal carcinogenesis.[37] The anti-inflammatory mechanism of action of quercetin is believed to be through the inhibition of lipoxygenase, cyclooxygenase, and PKC, resulting in a reduction of the production of pro-inflammatory oxylipin mediators.[38] Kaempferol, present in broccoli and tea, causes G2/M arrest and induces apoptosis in human oesophageal adenocarcinoma cells,[39] and inhibits STAT1 and NF-κB activation in activated macrophages.[40] Apigenin, present in parsley and celery, evokes its inhibitory effect on carcinogenesis through the induction of apoptosis and cell cycle arrest in pancreatic cancer cells.[41,42]

Tangeretin (5,6,7,8,4′-pentamethoxyflavone) belongs to the polymethoxylated flavones and is abundant in citrus peels.[43] Tangeretin plays an important role in every stage of cancer development. It blocks the xenobiotic cancer initiation stage by modulating hepatic phase I and phase II enzymes. It is also able to block cancer promotional stages in various ways such as the modulation of the cell cycle and ERK regulation pathway,[43,44] the inhibition of cancer cell growth through apoptosis, and the suppression of IL-1β-induced cyclooxygenase (COX)-2 expression.[43,45] Compared to hydroxylated flavonoids, methoxylation increases hydrophobicity of the molecules, which facilitates cell membrane uptake and *in vivo* bioavailability. Based on all these properties, tangeretin and other related polymethoxylated flavones seem to hold promise in dietary strategies to reduce risk of cancer and other human chronic diseases. In our laboratory, we have demonstrated that 5-hydroxy-3,6,7,8,3′, 4′-hexamethoxyflavone, in citrus, exerts its chemopreventive activity through the induction of apoptosis in human leukemia HL-60 cells and inhibition of inflammation.[46,47]

Green tea catechins have been the most-studied health-promoting flavonoids in recent years. Tea is one of the most widely consumed beverages in the world. More than 300 different kinds of tea are produced from the leaves of *Camellia sinensis* by different manufacturing processes. Generally they are divided into three types: green tea (non-fermented), oolong tea (semi-fermented), and black tea (fermented). Experimental and epidemiological studies have linked the consumption of tea to reduced risk of cancer. These effects have been attributed to the polyphenolic compounds in tea.[48] Catechins are the most abundant polyphenols in green tea. A typical cup of brewed green tea contains, by dry weight, 30–40% catechins, including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). EGCG is the most abundant catechin in green tea. The main pigments in black tea are theaflavins and thearubigins, which are formed by enzymatic oxidation and polymerization of catechins during fermentation. It is known that theaflavins make important contributions to the properties of black tea, such as color, taste and mouthfeel.[48]

Green tea and its constituents have been extensively studied both *in vitro* and in animal models of carcinogenesis.[49] Numerous potential mechanisms have been proposed for the cancer preventive activity of tea and tea constituents based on studies with cancer cell lines. *In vitro*, tea polyphenols, especially EC and EGCG, have been shown to cause growth inhibition and induce apoptosis in a number of human tumor cell lines including melanoma, breast cancer, lung cancer, leukemia and colon cancer.[48,50] EGCG treatment suppresses NADPH oxidase, modulates Nrf2-mediated antioxidant and detoxifying enzyme, and inhibits AOM-induced carcinogenesis and tumor growth.[51,52] The relative importance of any of these mechanisms *in vivo* remains to be determined.

Naringenin, a flavanone present in orange peel, is believed to contribute to the activation of phase II detoxifying enzymes, protect against UVB-induced apoptosis in immortalized p53-mutant human keratinocyte HaCaT cells, and induce apoptosis in various cancer cells.[53]

Cyanidin, an anthocyanidin present in cherries and strawberries, exhibited a significant decrease in CCl_4-induced lipid and protein peroxidation and induced G2/M arrest and apoptosis in U937 cells.[54,55] Delphinidin, an anthocyanidin present in dark fruit, is believed to contribute to the inhibition of COX-2 expression by blocking MAPK signaling and NF-κB, AP-1 and C/EBPδ nuclear translocation.[56] Delphinidin treatment resulted in protection from UVB-mediated oxidative stress and apoptosis in mouse skin.[57]

Table 2 The classes, individual compounds, dietary sources of commonly occurring flavonoids and their chemopreventive activities

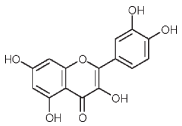
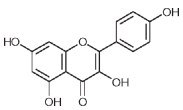
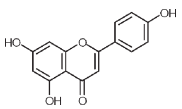
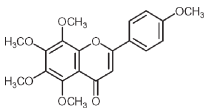
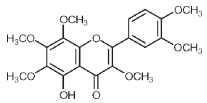
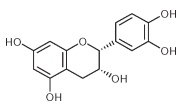
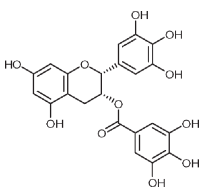
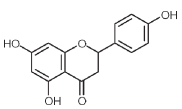
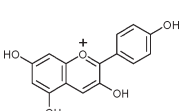
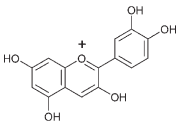
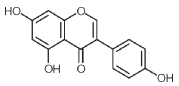
Group	Class	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Flavonoids	Flavonols	Quercetin		Onion, broccoli, apples and berries	• Modulates phase I and phase II enzyme expression in hepatocytes	35
					• Inhibits proinflammatory mediator release, intracellular calcium influx and PKC θ signaling	38
					• Induces apoptosis in a human breast cancer MDA-MB-435 cell xenograft model	36
					• Inhibits azoxymethane-induced colorectal carcinogenesis in F344 rats	37
		Kaempferol		Broccoli and tea	• Causes G2/M arrest and induced apoptosis	39
					• Inhibits STAT-1 and NF-κB activation in activated macrophages	40
	Flavones	Apigenin		Parsley and celery	• Induces apoptosis in a human breast cancer cell xenograft model	41
					• Induces cell cycle arrest by modulation of MAPK and PI3K	41,42
		Tangeretin		Citrus peels	• Induces cell cycle arrest in human colorectal carcinoma cells	43
					• Inhibits extracellular-signal-regulated kinase (ERK) phosphorylation	44
					• Suppresses IL-1β-induced cyclooxygenase (COX)-2 expression	45
		5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone		Citrus peels	• Induces apoptosis through ROS production in human leukemia cells	46
					• Inhibits phorbol ester-induced skin inflammation and tumor promotion	47
	Flavanols (catechins)	Epicatechin (EC)		Tea	• Against tamoxifen-induced liver injury in rats	48
					• Induces cell cycle arrest and apoptosis in various cancer cells	50
					• Reduces lipid peroxidation and streptozotocin-induced diabetes in rats	49
		Epigallocatechin-3-gallate (EGCG)		Tea	• Suppresses NADPH oxidase expression and ROS generation	51
					• Modulation of Nrf2-mediated antioxidant and detoxifying enzymes	51
					• Inhibits colorectal ACF formation in an azoxymethane carcinogenesis model	52
					• Inhibits tumor growth by reducing VEGF production and angiogenesis and STAT3 signaling	52
	Flavanones	Naringenin		Orange peel	• Activation of phase II detoxifying enzymes	53
					• Against UVB-induced apoptosis and enhances the removal of cyclobutane pyrimidine dimers in human keratinocytes	53
	Anthocyanidins	Cyanidin		Cherries and strawberries	• Decreases CCL_4-induced lipid and protein (carbonyl) peroxidation	54,55
					• Induces G2/M arrest and apoptosis in U937 leukemia cells	55

Table 2 (*continued*)

Group	Class	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
		Delphinidin		Dark fruits	• Inhibits COX-2 expression by blocking MAPK signaling and NF-κB, AP-1 and C/EBPδ nuclear translocation	56
					• Against UVB-mediated oxidative stress and apoptosis in mouse skin	57
	Isoflavonoids	Genistein		Soybean	• Induces apoptosis by activation of calpain-caspase and ASK-1 signaling	58
					• Inhibits tyrosine phosphorylation of C/EBPδ.	59

Health benefits of soybean and its products have been recognized in recent years. Genistein , which is an isoflavone, is considered to be the main nutraceutical in soybeans. As a phytoestrogen, genistein lacks estrogenic activity and exhibits anti-estrogenic activity. Genistein induced apoptosis by activation of calpain-caspase and the ASK-1 signaling pathway in human breast cancer MCF-7 cells.[58]

Genistein has been shown, through *in vitro* studies, to inhibit the growth of various types of cancer cells, especially those that are hormone-dependent. The mechanisms of action include the inhibition of many enzymes involved in tumor growth and development, and the induction of apoptosis.[59] There is also evidence of antioxidant activity and scavenging activity of hydrogen peroxide by genistein.

2.3 Proanthocyanidins and flavonolignans

Proanthocyanidins are synonymous with condensed tannins and are found in fruits, berries, beans, nuts, cocoa and wine.[60] The abundance of proanthocyanidins in plants makes them an important part of the human diet.[60] Proanthocyanidins are oligomers or polymers of flavan-3-ols and these units are linked mainly through C4→C8 bonds. This linkage is called a B-type linkage. An additional ether bond between C2→C7, resulting in the double linkage of the flavan-3-ol units is called an A-type linkage.[60] Table 3 shows the chemical structures of the most common dimers A_2, B_1, as well as trimers C_1.

Proanthocyanidins A_2 treatment modulated antioxidant enzyme expression and decreased UVB-induced skin tumors.[61] Proanthocyanidins inhibited mitogenic and survival-signaling *in vitro* and tumor growth *in vivo*.[62] Proanthocyanidins also inhibited carrageenan-induced paw edema in rats and suppressed LPS-induced inflammation.[63] In addition, proanthocyanidins altered oxidative stress, genomic integrity, and cell death and induced antioxidant activity, which contributed to its anticarcinogenesis and antitumorigenesis.[64,65]

Silymarin is a phytochemical isolated from the milk thistle plant *Silybum marianum*. Silymarin is the collective term for a mixture of seven flavonolignans. Silibinin is the best-documented of the flavonolignans in displaying health-beneficial effects. Silibinin was reported to inhibit the activation of STAT3 and tumor xenograft growth, inhibiting proliferation and promoting cell cycle arrest.[66,67] More recently, silibinin has been found to inhibit inflammation and angiogenesis in SKH-1 hairless mice and protect from photocarcinogenesis by modulation of cell cycle regulators, MAPK and Akt signaling pathways.[68,69]

2.4 Other polyphenolic compounds

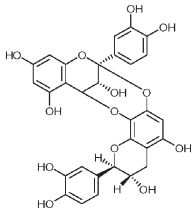
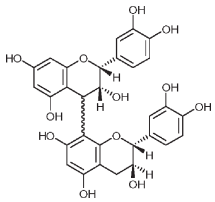
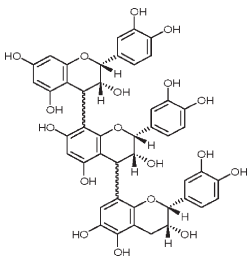
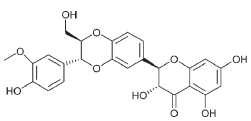
Besides flavonoids, there exist many polyphenolic compounds in food, particularly fruits, vegetables and spices. Table 4 shows the health benefits of some of these compounds.

The dried rhizome of the plant *Curcuma linga* Linn., has been used for centuries as a naturally occurring medicine for the treatment of topical inflammation and other diseases. The major pigment in powdered rhizome, commonly known as turmeric spice, was identified as curcumin. Several laboratories have shown that curcumin and/or turmeric have potent anti-inflammatory activity.[70] Curcumin has also been reported to induce HO-1 expression and inhibit cytokine secretion.[71] In another study, curcumin increased nuclear translocation of Nrf2 and modulated phase II enzyme expression.[72] Curcumin has also been demonstrated to decrease TPA-induced PKC translocation involved in antitumor promotion.[73] Besides being a powerful antioxidant and anti-inflammatory agent, the most interesting property of curcumin is its anticarcinogenic power, which relies on decreasing cell proliferation of cancer cells by inducing apoptosis.[74] Several *in vitro* and some *in vivo* studies have demonstrated that curcumin is very effective at inducing apoptosis in several types of cancer cells.[70]

Gingerols are the main pungent components of the rhizome of *Zingiber officinale*, which belongs to the ginger family *Zingiberaceae*. Common ginger has been used as a folk medicine for thousands of years. 6-Gingerol is the most studied gingerol in anticarcinogenic research and has been shown to be a potent chemopreventive agent in both *in vitro* and *in vivo* models.[75] 6-Gingerol was reported to prevent peroxynitrite-induced oxidation and inhibit growth and secretion of angiogenic factors.[76] More recently, 6-gingerol has been found to induce apoptosis and inhibit metastasis, VEGF-induced cell proliferation and angiogenesis in human colorectal and breast cancer cells.[77,78] Gingerols are sensitive to heat. During drying or thermal processing gingerols either dehydrate to the corresponding shogaols or are degraded by a retro-aldol reaction to zingerone and the corresponding aldehyde.[79]

6-Shogaol was reported to reduce chronic inflammatory response by lowering VCAM-1 in the blood and infiltration of leukocytes.[80] 6-Shogaol also induced apoptosis in cultured human hepatoma cells.[81] In our laboratory, 6-shogaol caused apoptotic

Table 3 Proposed chemopreventive mechanisms of proanthocyanidins (PAs) and flavonolignans[a]

Group	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Proanthocyanidins	Proanthocyanidins A_2		Fruits, berries, beans, nuts, cocoa and wine	• Modulates the expression of the antioxidant enzyme genes	61
				• Inhibits lipid oxidation and protects the membrane against the attack of oxidants	61
	Proanthocyanidins B_1			• Inhibits the growth of A431-xenografts in mice by suppressing PI3K/Akt survival signaling	62
				• Inhibits carrageenan-induced paw edema in rats through oxygen free radical scavenging, anti-lipid peroxidation	63
				• Suppresses nitric oxide production in LPS-stimulated macrophage cells	63
	Proanthocyanidins C_1			• Inhibits DMN-induced liver carcinogenesis and tumorigenesis by selectively altering oxidative stress, genomic integrity and inducing apoptosis	64
				• Increases pancreatic glutathione (GSH) levels and inhibits lipid peroxidation in alloxan-induced diabetes in rats	65
Flavonolignans	Silibinin		Milk thistle	• Inhibits activation of STAT3 in DU145 cells and inhibits human bladder tumor xenograft growth	67
				• Inhibits proliferation and promotes cell cycle arrest	66
				• Inhibits inflammatory and angiogenesis in SKH-1 hairless mice	68
				• Against photocarcinogenesis by modulation of cell cycle regulators, MAPK and Akt signaling	69

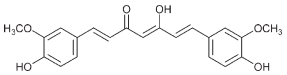
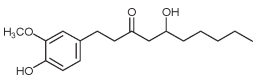
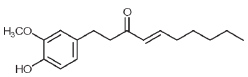
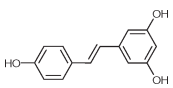
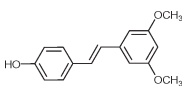
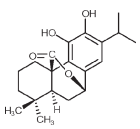
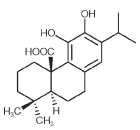
[a] Oligomeric and polymeric flavan-3-ols are better known as proanthocyanidins (PAs) or condensed tannins. PAs with uncommon structures are found as minor components in many plant foods. However, considering all of the available literature and more recent studies, the indication is that PAs, in mixture form, are more likely anticarcinogenic in humans and many animal models.

death in human colorectal carcinoma cells through generation of ROS, marked activation of caspases, and expression of GADD153.[82]

Resveratrol (3,5,4′-trihydroxystilbene) is a compound found mainly in the skin of grapes, peanuts and mulberries, and is believed to bring about disease resistance in plants.[83] The epidemiologic finding of an inverse relationship between consumption of red wine and mortality rates from cardiovascular disease and certain cancers has been called the "French paradox". The growth-inhibitory effects of resveratrol are mediated through induction of apoptosis and cell cycle arrest in both rat and human cancer cells. Resveratrol-induced apoptosis has been repeatedly reported to be accompanied by increased caspase activity, up-regulation of p53, Bax, and down-regulation of Bcl-2, Bcl-X_L, survivin, and cIAPs in a variety of human cancers. Resveratrol caused cell cycle arrest *via* up-regulation of p21, p27, p16, and down-regulation of cyclin D1, cyclin E, Cdk2, Cdk4, Cdk7 in human colon carcinoma cells.[84] Resveratrol has also been shown to induce GSH synthesis through activation of Nrf2.[85] Furthermore, resveratrol induced S phase arrest through the ATM/ATR-Chk1/2-Cdc25C pathway.[86] Resveratrol treatment induced apoptosis in DMBA/TPA induced mouse skin tumorigenesis through the mitochondrial pathway.[87] On the other hand, *in vitro* and animal experiments have shown that it exhibits many ;biological effects, such as protection against atherosclerosis, antioxidant activity, inhibition of platelet aggregation, and antimutagenic and anticarcinogenic properties.[83,88]

Pterostilbene (*trans*-3,5-dimethoxy-4′-hydroxystilbene), a dimethyl ether analogue of resveratrol, was found to be as effective as resveratrol in preventing carcinogen-induced preneoplastic lesions in a mouse mammary culture model and inhibited metastatic growth of melanoma cells to the liver.[89] Pterostilbene, isolated from *Vaccinium* barriers, together with resveratrol, suppressed aberrant crypt foci

Table 4 Suggested mechanisms of chemopreventive effects induced by other polyphenolic compounds

Group	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Other polyphenolic compounds	Curcumin		Turmeric	• Induces HO-1 expression through the activation of PKCα, PKCδ/ERK1/2, p38α pathway and inhibits cytokine secretion	71
				• Increases Nrf2 protein and modulates phase II enzyme expression in B(a)P-treated mice	72
				• Decreases TPA-induced protein kinase C translocation and effects TPA-induced molecular alterations in mouse skin	73
				• Inhibits NF-κB and STAT3 signaling and induces apoptosis	74
				• Reduces the production of PMA-induced lipid peroxidation and 8-OHdG	73
	6-Gingerol		Ginger	• Prevents peroxynitrite-induced oxidation and nitration reactions	76
				• Inhibits growth and modulates secretion of angiogenic factors in ovarian cancer cells	76
				• Down-regulates PKCe, and GSK-3β pathways and induces cell growth arrest and apoptosis	77
				• Inhibits cell adhesion and invasion and decreases the activity of MMP-2 and MMP-9	78
				• Inhibits VEGF-induced cell proliferation and angiogenesis	78
	6-Shogaol		Ginger	• Reduces chronic inflammatory response by lowering VCAM-1 in the blood and infiltration of leukocytes	80
				• Induces apoptotic cell death of human hepatoma p53 mutant Mahlavu subline	81
				• Induces apoptosis *via* ROS production, caspase activation, and GADD 153 expression	92
	Resveratrol		Grapes, red wine	• Inhibits proliferation and induces apoptosis by down-regulation of STAT3 and NF-κB-regulated anti-apoptotic and cell survival genes	84
				• Induces glutathione synthesis by activation of Nrf2	85
				• Causes Cdc2-tyr15 phosphorylation *via* ATM/ATR-Chk1/2-Cdc25C pathway and induces cell cycle arrest	86
				• Induces apoptosis through mitochondrial pathways in DMBA/TPA induced mouse skin tumorigenesis	87
	Pterostilbene		Blueberries	• Induces cell cycle arrest and apoptosis in various cancer cells	91,92
				• Suppresses AOM-induced colonic cell proliferation and ACF formation	90
				• Decreases B16M-F10 cell adhesion and metastatic activity	89
	Carnosol		Rosemary, sage	• Induces HO-1 expression through the PI3K/Akt pathway and the Nrf2	95
				• Induces G2/M phase cell cycle arrest by alteration of cyclin B1 levels	96
				• Suppresses NO production and iNOS gene expression by inhibiting NF-κB activation	97
				• Inhibits the invasion of B16/F10 mouse melanoma cells by suppressing MMP-9 and down-regulating NF-κB and c-Jun	98
	Carnosic acid		Rosemary, sage	• Induces G2/M phase cell cycle arrest by alteration of cyclin A levels	96
				• Protects neurons from oxidative stress through activation of the Keap1/Nrf2 pathway	99
				• Inhibits migration by suppressing MMP-9 expression through down-regulation of NF-κB	94

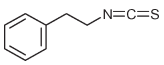
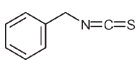
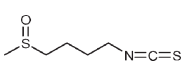
formation in the azoxymethane-induced colon carcinogenesis in rats.[90] Pterostilbene has been demonstrated to have a cancer chemopreventive activity similar to that of resveratrol and it is cytotoxic to a number of cancer cell lines.[91] Our recent report has shown that pterostilbene exhibited anticancer, anti-inflammatory, antioxidant and analgesic activity.[92,93]

Rosemary and sage leaves are commonly used as spices and flavoring agents. The dried leaf of the rosemary plant is one of the most widely used spices for food processing because it has a desirable flavor and high antioxidant activity. Several phenolic diterpenes with antioxidant activity, most notably carnosic acid, have been isolated from rosemary and sage leaves. Carnosic acid is not stable during processing and storage. It will first oxidize to form carnosol, which undergoes further oxidative transformation to form rosmanol.[94] PI3K/Akt, which is upstream of Nrf2, seems to be involved in carnosol induced HO-1 expression.[95,96] Carnosol also induced G2/M cell cycle arrest through altering the levels of cyclin A and cycle B1.[96] Carnosol also inhibited LPS-induced activation of p38 and p44/42 mitogen-activated protein kinase (MAPK) and IKK, and abrogated LPS-induced iNOS expression.[97] Moreover, carnosol inhibited invasion in B16/F10 melanoma cells, possibly through inhibition of NF-κB and c-Jun by blocking MMP-2 and MMP-9 activity.[98] It is interesting to note that both carnosol and rosmanol have antioxidant activity comparable to that of carnosic acid.[94] Besides antioxidant activity, carnosic acid has been shown to induce cell-growth arrest, activate the Keap1/Nrf2 pathway, and suppress the activation of NF-κB, which might contribute to its cytostatic and/or chemopreventive effects.[99]

2.5 Isothiocyanates

Compounds known as isothiocyanates and indoles are formed during the mastication of some cruciferous vegetables, which promotes thioglucosidase (myrosinase) hydrolysis of the precursor conjugates known as glucosinolates. The vegetables belonging to the *Brassica* genus, which include cabbage, broccoli, kale, turnips, cauliflower and Brussels sprouts, are the primary source of glucosinolates and related breakdown products. Studies have shown that animals treated with isothiocyanates such as phenethyl isothiocyanate, benzyl isothiocyanate and sulforaphane (4-methylsulfinylbutyl isothiocyanate) after carcinogen exposure, had reduced tumor incidence[100] (Table 5).

Table 5 Major isothiocyanates and their possible chemopreventive effects

Group	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Isothiocyanates	Phenethyl isothiocyanate		Cabbage, turnips, broccoli, kale, cauliflower, Brussels sprouts	• Reduces the number of polyps and inhibits growth of adenomas through increase of apoptosis in $Apc^{(Min/+)}$ mice	101
				• Inhibition of angiogenesis through suppression of VEGF and inactivation of Akt signaling	102
				• Inhibition of PC-3 xenograft growth by induction of Bax and Bid proteins	103
				• Inhibition of P450 2A6- and 2A13-mediated metabolisms	104
				• Inhibits malignant progression of lung adenomas induced by tobacco carcinogens in A/J mice	105
				• Induces cell cycle arrest by reduction of CDK1 and cdc25c	106
				• Activates ARE-mediated phase II enzyme gene expression by induction of JNK1- and Nrf2-pathways	107
	Benzyl isothiocyanate			• Induces DNA damage, causes G2/M cell cycle arrest and apoptosis	108
				• Inhibits TPA-induced oxidative stress through inhibition of NADPH oxidase and leukocyte infiltration	109
				• Inhibits TNF-α-induced MMP-9 secretion by down-regulation of NF-κB and AP-1	110
	Sulforaphane			• Induces expression of phase II detoxification genes through the Nrf2/ARE pathway	111
				• Inhibits the development of intestinal adenomas by down-regulating cell survival and growth-related signaling pathways	112
				• Reduces the number of polyps through suppressing MAPK signaling	113
				• Inhibits cytokine-dependent induction of iNOS in macrophages and against UV-induced skin carcinogenesis in SKH-1 hairless mice	114
				• Suppresses LPS-induced COX-2 expression, down-regulating NF-κB, C/EBP, CREB and AP-1	115

Phenethyl isothiocyanate treatment reduces the number of polyps in $Apc^{(Min/+)}$ mice.[101] It also inhibits angiogenesis through suppression of VEGF and inactivation of Akt signaling *in vitro* and *ex vivo*.[102] Phenethyl isothiocyanate induced apoptosis in PC-3 human prostate cancer cells through the mitochondrial-mediated pathway.[103] Phenethyl isothiocyanate also displayed inhibition of P450 2A6- and 2A13-mediated metabolisms and induction of apoptosis in lung adenoma formation induced by tobacco carcinogens in A/J mice, which might contribute to its chemoprevention of lung cancer.[104,105] Treatment of human prostate cancer PC-3 cells with phenethyl isothiocyanate also suppressed CDK1 activity and cell growth.[106] Exposure of HeLa cells to phenethyl isothiocyanate induces expression of phase II detoxifying enzymes through ARE by inducing JNK1- and Nrf2 pathways.[107]

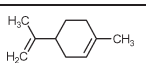
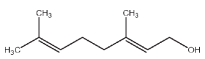
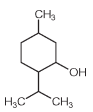
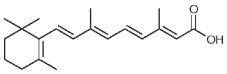
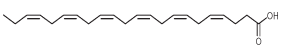
Benzyl isothiocyanate was reported to cause cell cycle arrest and apoptosis by inducing DNA damage in cancer cells.[108] Topical application of benzyl isothiocyanate inhibited TPA-induced mouse skin inflammation.[109] Benzyl isothiocyanate also inhibited TNF-α-induced MMP-9 secretion by down-regulation of NF-κB and AP-1.[110]

Sulforaphane has been shown to induce phase II detoxifying enzymes by altering nuclear Nrf2 levels.[111] Furthermore, dietary administration of $Apc^{(Min/+)}$ mice with sulforaphane inhibited the development of intestinal adenoma, inhibiting HIF-1α and c-Myc.[113] In addition, sulforaphane suppressed the phosphorylation of JNK, ERK, and Akt.[112] Sulforaphane also suppressed angiogenesis by inhibiting cytokine-induced iNOS expression and UV-induced skin carcinogenesis,[114] and suppressed LPS-induced COX-2 expression,[115] which contributes to its anticarcinogenesis and anti-inflammatory activities.

2.6 Terpenoids and omega-3 fatty acids

The terpenoids are a class of secondary metabolites from the common origin of mevalonate and isopentenyl pyrophosphate that are lipophilic in nature. They represent the largest and most diverse class of plant compounds. Chemically, terpenoids are usually cyclic unsaturated hydrocarbons, with different degrees of oxygen in the constituent groups attached to the basic isoprene skeleton.[116] Monoterpenes are non-nutrient natural dietary compounds of fruit, cherries, spearmint dill, caraway, apricots and grapes. The most investigated monoterpenes for chemoprevention are limonene, geraniol, menthol, carvone, carveol and perillyl alcohol. Limonene induced apoptosis through activation of the ERK and caspase-dependent mitochondrial death pathways in human leukemia cells.[117] Limonene treatment resulted in inhibition of tumor growth and metastasis through inhibiting VEGF and inducing apoptosis in human gastric cancer implanted in nude mice[118] (Table 6). Geraniol has been reported to inhibit cell proliferation through inhibiting CDK2 activity and the p21/p27-dependent pathway.[119] More recently, geraniol treatment of rats

Table 6 Structures of major terpenoids and omega-3 fatty acids and their target functions in chemoprevention

Group	Class	Compound	Structure	Dietary source	Chemopreventive mechanisms	Ref.
Terpenoids	Monoterpenes	Limonene		Citrus fruits, cherries, spearmint dill, caraway, apricots and grapes.	• Induces apoptosis through activation of the ERK and caspase-dependent mitochondrial death pathways	117
					• Inhibits tumor growth and metastasis through inhibiting VEGF and induced apoptosis	118
		Geraniol			• Inhibits cell proliferation through inhibiting CDK2 activity and the p21/p27-dependent pathway	119
					• Inhibits hepatocarcinogenesis by cell proliferation and DNA damage	120
		Menthol			• Induces cell death through Ca^{2+} production from both endoplasmic reticulum and Golgi compartments	121
					• Induces cytotoxicity through inhibiting gene expression of topoisomerases and promoting the gene expression of NF-κB	122
	Diterpenes	All-*trans*-retinoic acid			• Induces G1 arrest through hyperphosphorylation of Rb2/p130	123
					• Up-regulation of MnSOD by activation of the NF-κB pathway	124
					• Activation of the transcription factor C/EBPβ and up-regulates p21	125
					• Inhibits cell proliferation by inhibition of STAT3 signaling	126
Omega-3 fatty acids		EPA		Fish oils, golden algae oil	• Inhibits TNF-α-induced MMP-9 expression	127
		DHA			• Inhibits colorectal cancer growth by p53 dependent and independent pathways *in vitro* and *in vivo*	128

resulted in inhibition of HMG CoA reductase activity, which could contribute to its antihepatocarcinogenesis.[120]

Menthol, a secondary alcohol produced by the peppermint herb, *Mentha piperita*, is widely used in the food and pharmaceutical industries as a cooling/soothing compound and odorant. Menthol induced cell death *via* Ca^{2+} release from both the endoplasmic reticulum and Golgi compartments.[121] Furthermore, menthol also induced cytotoxicity in human gastric cancer cells by inhibiting the gene expression of topoisomerases.[122]

Diterpenes are defined by their biosynthetic origin from the C-20 precursor geranylgeraniol. The main component of this group is the retinoids, including retinol and all-*trans*-retinoic acid, which play fundamental roles in human vision. All-*trans*-retinoic acid induced G1 arrest in ovarian carcinoma cells through hyperphosphorylation of RB2/p130.[123] More recently, all-*trans*-retinoic acid treatment of a human neuroblastoma cell line resulted in up-regulation of MnSOD by activation of the NF-κB pathway.[124] All-*trans*-retinoic acid also induced leukemic cell differentiation by activation of C/EBPβ and up-regulation of p21.[125] Similarly, all-*trans*-retinoic acid inhibited cell proliferation and caused G1 cell cycle arrest by inhibition of the STAT3 signaling pathway.[126]

A number of experimental and clinical studies have described potential health benefits for omega-3 polyunsaturated fatty acids (PUFA), abundant in marine oil. They are therapeutically useful in various diseases such as inflammatory disease and in prostate and colon cancers. Studies with fish oil, which contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), showed that it has anti-inflammatory and anticancer properties (Table 6). Pretreatment of EPA inhibited TNF-α-induced MMP-9 expression through inhibition of p38 and Akt activation.[127] Dietary DHA significantly depressed the growth of human colon carcinoma *in vivo* and *in vitro* by p53 dependent and independent pathways.[128]

In addition to the aforementioned natural dietary compounds, capsaicin, caffeic acid phenethyl ester, indole-3-carbinol, silymarin and emodin have also been reported to suppress the activation of NF-κB and AP1, which might contribute to their chemopreventive effects.

Abbreviations

5-LOX	5-lipoxygenase
8-OHdG	8-hydroxy 2′-deoxyguanosine
ACF	aberrant crypt foci
AGEs	advanced glycation end products
ALEs	advanced lipoxidation end products
AhR	aryl hydrocarbon receptor
AIF	apoptosis-inducing factor
AOM	azoxymethane
AP-1	activator protein 1
ARE	antioxidant response element
ASK-1	apoptosis signal-regulating kinase 1
ATM	ataxia-telangiectasia mutated
ATR	ATM and Rad3-related
C/EBP	CCAAT/enhancer-binding protein
CAK	Cdk-activating kinase
CCl_4	carbon tetrachloride
CDK	cyclin-dependent kinases
CDKIs	cyclin-dependent kinase inhibitors
Chk	checkpoint kinase
CHOP	CCAAT/enhancer-binding protein (C/EBP) homology protein
CKIs	CDK inhibitors
COX-2	cyclooxygenase-2
CREB	cAMP response element-binding
DHA	docosahexaenoic acid
DISC	death inducing signaling complex
DMBA	7,12-dimethylbenz(*a*)anthracene
DMN	dimethylnitrosamine
EC	epicatechin
ECG	epicatechin-3-gallate
EGC	epigallocatechin
EGCG	epigallocatechin-3-gallate
endo G	endonuclease G
EPA	eicosapentaenoic acid
ER	endoplasmic reticulum
ERK1/2	extracellular signal-regulated protein kinase
FADD	Fas associated death domain protein
GADD153	growth arrest and DNA damage 153
GM-CSF	granulocyte-macrophage colony stimulating factor
GPx	glutathione peroxidase
GSH	glutathione
GSK-3β	glycogen synthase kinase-3β
GST	glutathione S-transferase
HDL	high-density lipoproteins
HIF	hypoxia inducible factor
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HO-1	heme oxygenase-1
IKKs	inhibitor κB (IκB) kinases
IL	interleukin
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase
Keap1	Kelch-like ECH-associating protein 1
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MMP	matrix metalloproteinase
NADPH	oxidase nicotinamide adenine dinucleotide phosphate-oxidase
NF-κB	nuclear factor-κB
NFAT	nuclear factor of activated T-cells
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NO	nitric oxide
NQO	NAD(P)H;quinine oxidoreductase
Nrf2	nuclear factor-erythroid 2-related factor 2
PCNA	proliferating cell nuclear antigen
PI3K	phosphatidylinositol-3 kinase
PKC	protein kinase C
PMA	phorbol myristate acetate
PXR	pregnane and xenobiotic receptors
Rb	retinoblastoma protein
RCS	reactive carbonyl species
ROS	reactive oxygen species
SOD	superoxide dismutase
STAT	signal transducers and activators of transcriptions

SXR	steroid and xenobiotic receptor
TIMP	tissue inhibitors of metalloproteinase
TNF-α	tumor necrosis factor α
TNFR	tumor necrosis factor receptor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
UV	ultraviolet
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
XRE	xenobiotic response elements

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