

Anti-Inflammatory Plant Natural Products for Cancer Therapy

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Abstract

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 Much of the current research in cancer therapeutics is aimed at developing drugs or vaccines to target key molecules for combating tumor cell growth, metastasis, proliferation, or changes in the associated stromal microenvironment. Studies on a wide spectrum of plant secondary metabolites extractable as natural products from fruits, vegetables, teas, spices, and traditional medicinal herbs show that these plant natural products can act as potent anti-inflammatory, antioxidant or anticancer agents. The recent advances in genomics and metabolomics have enabled biologists to better investigate the potential use of immunomodulatory natural products for treatment or control of various cancerous diseases. The cancer preventive or protective activities of the various immunomodulatory natural products lie in their effects on cellular defenses including detoxifying and antioxidant enzyme systems, and the induction of anti-inflammatory and antitumor or antimetastasis responses, often by targeting specific key transcription factors like nuclear factor kappa B (NF- κ B), activator protein (AP-1), signal transducers and activators of transcription (STAT) and others. This review presents recent findings and hypotheses on the molecular mechanisms through which various inflammatory activities are linked to tumorigenic processes and the specific immunomodulatory natural products that may suppress inflammation and the associated tumor progression and metastasis both *in vitro* and *in vivo*. In addition to tumor cells *per se*, the various associated roles of myeloid-derived suppressor cells, stromal fibroblasts, myofibroblasts, and inflammatory immune cells, and the possible effects of phytomedicines on these cells in the tumor microenvironment will be discussed.

Abbreviations

▼
 AKT: v-akt murine thymoma viral oncogene homolog
 AOM: azoxymethane
 AP-1: activator protein-1
 ARE: antioxidant response element
 CDC: cell division control
 CDK: cyclin-dependent kinase
 c-FLIP: cellular FLICE inhibitory protein
 COX: cyclooxygenase
 CREB: cAMP response element-binding
 CSF: colony-stimulating factor
 DMBA: dimethylbenz[*a*]anthracene
 EGCG: epigallocatechin gallate
 EGF: endothelial growth factor
 EGFR: epidermal growth factor receptor
 ERK: extracellular signal-regulated kinases
 FGF: fibroblast growth factor
 G-CSF: granulocyte colony stimulating factor
 GM-CSF: granulocyte macrophage colony-stimulating factor
 GST: glutathione-S-transferases
 HIF: hypoxia inducible factor
 HPETEs: hydroperoxyeicosatetraenoic acids
 I3C: indole-3-carbinol
 IAP: inhibitors of apoptosis
 iNOS: inducible nitric oxide synthase
 JAK: Janus kinase
 JNK: c-Jun NH₂-terminal kinase
 LOX: lipooxygenase
 LPS: lipopolysaccharide
 MAPK: mitogen-activated protein kinases
 MDSCs: myeloid-derived suppressor cells
 MMPs: matrix metalloproteinases
 NF- κ B: nuclear factor kappa B
 Nrf2: nuclear factor [erythroid-derived 2]-related factor
 PARP: poly(ADP-ribose) polymerase
 PDGF: platelet-derived growth factor
 PEITC: phenylethyl isothiocyanate
 PI3K: phosphoinositide 3-kinases

ROS: reactive oxygen species
 STAT: signal transducers and activators of transcription
 TNF- α : tumor necrosis factor-alpha
 TPA: 12-O-tetradecanoylphorbol 13-acetate

TRAIL: tumor necrosis factor-related apoptosis-inducing ligand
 VEGF: vascular endothelial growth factor

Introduction

Recent epidemiological and experimental animal studies strongly suggest that there is a strong link between increased consumption of fruits, vegetables, and certain spices and decreased cancer risk. These foods contain molecules with preventive or protective effects against carcinogenesis caused by irradiation or various endogenous (physiological) and exogenous (environmental or pathogenic) carcinogenic compounds or metabolites [1–4]. The stages of cancer progression have been extensively studied for decades, and carcinogenesis is now recognized as a very dynamic, multifactorial and long-term developmental process, which involves a series of complex factors and signaling systems. The stepwise development of cancer from initiation and promotion is followed by the progression phase, eventually culminating in metastasis that leads to uncontrolled spread of a cancer throughout the body. Although the initiation and promotion steps are evidently important, an increasing body of evidence now suggests that inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation. It is now also becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, cell survival, and migration [5–7]. Robert A. Weinberg of the Massachusetts Institute of Technology, highlighted this changing emphasis in a revision of his leading textbook, *The Biology of Cancer*, noting that “the connection between inflammation and cancer has moved to center stage in the research arena” [8]. Several pro-inflammatory gene products have been identified, which act in concert to mediate a critical role in suppression of apoptosis, proliferation, angiogenesis, invasion, and tumor metastasis. Among these gene products are tumor necrosis factor-alpha (TNF- α) and other members of its superfamily, interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, IL-18, chemokines (e.g., Mip-3 α , CXCL12), matrix metalloproteinases-9 (MMP-9), vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX). The expression of these genes is mainly regulated by the transcription factor NF- κ B, which is constitutively active in most tumors and is readily induced by various chemical carcinogens (e.g., cigarette tars and nicotine), tumor promoters, carcinogenic viral proteins, chemotherapeutic agents, and γ -irradiation [1,9]. Recently, immunologists have observed another class of immunosuppressive cell in cancer patients, the myeloid-derived suppressor cells (MDSCs), a heterogeneous cellular population containing macrophages, granulocytes, immature dendritic cells, and early myeloid precursors [10]. MDSCs, produced under the influence of VEGF, IL-1 β , and other factors which then migrate into the tumor environment, can inhibit immune responses to the tumor in a number of ways. These include blocking the activities of several types of cells (e.g., dendritic cells) needed for immune responses and converting type 1 macrophages to type 2 [11]. Generally, tumor cells are able to co-opt some of the signaling molecules of the innate immune system, such as cytokines, chemokines, and their receptors, for invasion, migration, and metastasis in the host. The profile of cytokines and chemokines persisting at an inflammatory

site is now also known to be very important for the development of chronic disease. Many of the above-mentioned cytokines and chemokines promote inflammation, suggesting that MDSCs may be at least partly responsible for mediating the carcinogenic effects of such inflammation. These insights are fostering new anti-inflammatory therapeutic approaches to the development of anticancer drugs [11–13].

Naturally occurring anti-inflammatory or immunomodulatory plant metabolites, used as single phytochemicals or as crude or fractionated extracts have chemopreventive or therapeutic effects on various cancers, by inducing or suppressing specific cellular inflammatory activities and the associated molecular signaling pathways. Currently, most immunomodulatory agents that are also antitumorigenic belong to two classes, (a) blocking agents, which inhibit the tumor initiation step by preventing carcinogen activation, and (b) suppressing agents, which inhibit tumor cell proliferation during the promotion and metastasis steps of tumorigenesis [14, 15]. Extensive epidemiological and animal studies have clearly demonstrated that a diet rich in fruits, vegetables, cereal grains, and spices decreases the rate or risk of cancer growth and metastasis [16–18]. Importantly, recent laboratory and preclinical studies have indicated that many of the cellular networks and molecular signaling pathways that act at different stages of carcinogenesis are associated with immune system regulation and inflammatory activities, providing a rationale for the use of immunomodulatory phytochemicals. The immunomodulatory or anti-inflammation effects of these natural products are dependent on dosage, target cell or tissue types and the time course of treatment [19–21]. The differential effects of phytochemicals in tumor cells versus normal cells may be due to different abilities to induce specific apoptotic pathways, modify the levels of major metabolic enzymes, or induce detoxifying enzymes and tumor suppressor genes in different cells [22]. This review discusses recent developments and hypotheses in research on the cancer chemopreventive or chemotherapeutic effects of anti-inflammatory plant natural products, including their effects on signaling pathways or key networks in inflammatory cells.

Blocking Mechanisms of Anti-Inflammatory Plant Natural Products

The initiation of carcinogenesis can be blocked by anti-inflammatory plant natural products through several different mechanisms. These include prevention of reaction oxygen species (ROS) attack on DNA, alteration of the metabolism of precarcinogens by phase-I drug metabolizing enzymes (so they can no longer be converted to carcinogenic species), excretion of reactive metabolites from the cell by a secondary line of defense that involves phase-II conjugating enzymes [glucuronidases, glutathione-S-transferases (GST) and sulfotransferases], inhibition of uptake of toxic materials into cells, and enhancement of DNA repair. In addition to these specific effects, many anti-inflammatory plant natural products have strong antioxidant effects, either as general antioxidants or free radical scavengers, or by reducing redox imbalance following glutathione depletion. Some natural

products work by activating protective enzymes (e.g., glutathione peroxidase, superoxide dismutases, heme oxygenases) by targeting the transcription factor nuclear factor [Erythroid-derived 2]-related factor (Nrf2), which activates an antioxidant defense response by an antioxidant response element (ARE) [23, 24]. An effective antioxidant defense response in the face of a mild redox stress seems to be cytoprotective for normal or untransformed cells, probably because it can successfully counteract the genotoxic damage resulting from oxidative and electrophilic stress, and detoxifies excessive ROS [4]. Some of these anti-inflammatory plant secondary metabolites with high antioxidant activities, for example, resveratrol (a polyphenol from grapes), genistein (an isoflavone in soybean), quercetin (a flavonol in vegetables and fruits), shikonin (a naphthoquinone from *Lithospermum erythrorhizon*) and others are presented in **Table 1**. Blocking the initial genetic modification step of carcinogenesis by the consumption of various anti-inflammatory plant natural products helps to prevent the development of primary tumors [4, 25].

Paradoxically, some immunomodulatory plant natural products, such as epigallocatechin gallate (EGCG) in green tea, the polyphenol curcumin in turmeric and ascorbic acid in fruits, can act as both oxidants and antioxidants [4, 25]. Significant blockade and modulation of the phase I and phase II enzymes in human liver cancer cells by quercetin [26] and resveratrol [27] can be observed as either antioxidant or prooxidant activities under different experimental/physiological conditions and cancer cell types. Curcumin possesses potent anti-inflammatory activities and is a strong activator of Nrf2-protein and detoxifying heme-oxygenases in human cells [28]. Shikonin has strong antioxidant and anti-inflammatory activities via inhibition of TNF- α , granulocyte macrophage colony-stimulating factor (GM-CSF) [29, 30], presumably also via phase-II enzymes. EGCG and sulforaphane from cruciferous vegetables induce Nrf2 transcription factor, and eventually activate the antioxidant defense enzymes by ARE [31].

The Suppression Mechanisms of Anti-Inflammatory Plant Natural Products

▼ Growth suppression of tumor cells can be observed either as the induction of cell cycle arrest, which slows down inappropriate or uncontrolled cell division, or as the induction of apoptosis in stressed cells. Some anti-inflammatory plant natural products have been found to be very effective regulators of the cell cycle of tumor cells at an early stage by targeting specific cell signaling molecules, leading to apoptosis or cellular senescence. Other plant secondary metabolites can act at later stages of tumorigenesis by inhibition of angiogenesis or prevention of tumor invasion and metastasis [32–34]. Many anti-inflammatory plant natural products have molecular signaling targets that can be potentially employed for treatment of cancers. A main feature of a number of anti-inflammatory plant natural products (e.g., EGCG, curcumin, lycopene, gingerol and resveratrol) is their action on the suppression of EGFR and the subsequent downregulation of expression of various other key signaling molecules such as STAT-1, -3, NF- κ B, AKT, Bcl-2 in the nucleus and/or cytoplasm, which eventually induces apoptosis of target cells. The signaling network diagram (**Fig. 1**) summarizes all these recent findings and specific categories of these interactions are discussed below.

Cell cycle

Effective disruption of cell cycle progression and division of tumor cells by antitumor agents is very important for inhibition of cancer growth. The anti-cell cycle effects of several anti-inflammatory plant natural products have been extensively studied. Indole-3-carbinol (I3C) induces G₀-G₁ cell cycle arrest in breast cancer cells through downregulation of cyclin-dependent kinase 6 (CDK6); it upregulates the CDK inhibitors p21 and p27 [35]. Proanthocyanidins from grape seed produce a marked reduction in expression of CDK2, CDK4, and CDK6, and of cyclins D1, D2, and E in human epidermoid carcinoma (A431) cells [36]. Resveratrol causes cell cycle arrest mainly by upregulating the expression of p21, p27, and p16 and downregulating cyclin D1, E, CDK2, CDK4, and CDK7 in human colon carcinoma cells [37]. Amooranin (AMR), a novel triterpenoid from *Amoora rohituka* suppresses G₂/M phase and inhibits the growth of MCF-7 and MDA-468 breast cancer cells [38], while geraniol (an isoprenoid) inhibits CDK2 expression in human pancreatic adenocarcinoma cells, apparently mediated by a p21/p27-dependent pathway [39]. Curcumin induces G₀/G₁ and/or G₂/M phase cell cycle arrest, upregulates CDK inhibitors such as p21/Cip1/waf1 and p27Kip1, and downregulates cyclin B1 and cell division control 2 (CDC2) in immortalized human umbilical vein endothelial (ECV304) cells [40]. Similarly, EGCG induces cell cycle arrest by upregulation of p21/Cip1/waf1 and p27Kip1 and the subsequent downregulation of cyclin D1, cyclin E, CDK2 and CDK4 in human prostate carcinoma cells [41].

Cell survival and proliferation

Elevated signaling from mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinases (PI3K), protein kinase B (PKB), AP-1 and NF- κ B often favors cell survival and proliferation. Most of the key molecular targets in these pathways have been found to be overexpressed or constitutively upregulated in a variety of cancers, strongly suggesting that inhibition of these molecular targets can induce tumor cells to undergo apoptosis. Sulforaphane, an isothiocyanate from many crucifers, can suppress the phosphorylation of c-Jun NH₂-terminal kinase (JNK), extracellular signal-regulated kinases (ERK) and v-akt murine thymoma viral oncogene homolog (AKT) of gastrointestinal cancers and inhibit tumor growth [42]. Proanthocyanidins from grape seeds suppress NF- κ B of human epidermoid carcinoma A431 cells by downregulation of NF- κ B/p65 and IKK α , and inhibit the degradation of I κ B α protein, which is a regulator of NF- κ B [36]. Proanthocyanidins also inhibit the constitutive activation of MAPK proteins and decrease the phosphorylation of AKT in A431 cells [36]. EGCG inhibits the PI3K/AKT signaling pathways, thereby inducing apoptosis by suppressing Bcl-2 family protein expression and increasing Bax protein expression in T24 human bladder cancer cells [43]. Phenylethyl isothiocyanate (PEITC), another component of cruciferous vegetables, potently inhibits NF- κ B by inhibiting IKK α / β signaling pathways in human prostate cancer cells [44]. Curcumin was suggested to mediate therapeutic effects in test animals by regulating the transcription factor NF- κ B and NF- κ B-regulated gene products such as cyclin D1, Bcl-2, Bcl- χ L, and TNF- α [45]. Curcumin suppresses TNF- α induced IKK α which leads to the inhibition of TNF-dependent phosphorylation and degradation of I κ B α protein and thus can suppress the activation of NF- κ B [46]. Curcumin also suppresses the activation of 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced activator protein (AP-1) in HL-60 cells [47] and prostate cancer cells [48]. Genistein, an isoflavone from soybean, significantly suppresses human

Table 1 Dietary source, mechanism of action and molecular targets of natural compounds.

Group	Compound	Dietary source	Mechanism of action	Molecular targets	Reference
Isothiocyanates	Sulforaphane, Phenethyl isothiocyanate, Benzyl isothiocyanate	cruciferous vegetables (all Brassicaceae), cabbage, broccoli, turnips, cauliflower, brussels sprouts, kale, mustard, cress, etc.	anti-inflammation, anti-proliferation, activation of caspases, inhibition of angiogenesis	AKT, NF- κ B, AP-1, Bcl2, survivin, cyclin D, CDK, p53, Bax, COX-2, iNOS, VEGF, MMP-2/-9	[58, 91, 135, 155, 156]
Proanthocyanidins	Proanthocyanidins A2, -B1, -C1.	cocoa, berries, beans, nuts, wine	antioxidant, cell cycle arrest, anti-inflammation	MAPK, PI3K/AKT, NF- κ B, MMP-2, -9, AP-1, iNOS, COX-2	[15, 157–159]
Flavonoids	Quercetin	onion, broccoli, apples and berries	anti-inflammatory and apoptosis	iNOS, COX-2, AKT, caspases	[160, 161]
	Apigenin	celery and parsley	cell cycle arrest and apoptosis	CDK, caspases, Bax, p53, p21	[162, 163]
	Tangeretin	citrus peel	anti-inflammatory and cell cycle arrest	ERK, AKT, NF- κ B, AP-1, cyclin D1, CDK, iNOS, COX-2	[92, 164]
	Epigallocatechin-gallate (EGCG)	tea	antioxidant, antimutagenesis, antiproliferation, antiangiogenesis, anti-inflammation	EGFR, AKT, NF- κ B, cyclin D1, VEGF, COX-2, AP-1, MMP-2/-9, Bcl-2, Bax, IL-12	[60, 62, 130, 165, 166]
	Genistein	soybeans, red clover	antiproliferation, antioxidant, antiangiogenesis, anti-inflammation	caspases, ASK-1, AKT, NF- κ B, survivin, Bcl-2, Bax, STAT-3/-5, CDK, VEGF	[72, 167, 168]
	Delpinidin	pomegranate, strawberry	apoptosis, antioxidant, antiangiogenesis	AP-1, NF- κ B, C/EBP δ , MMP-2/-9, VEGF, caspases, Bcl-2, Bax	[74, 169]
Flavonolignans	Silibinin	milk thistle	anti-inflammation, cell cycle arrest, apoptosis	STAT-3, NF- κ B, JNK, CDK, iNOS, COX-2, MAPK, AKT, Bax, Bcl-2	[21, 170]
Carotenoids	Zeaxanthin	peas, cabbage, orange	antioxidant, anti-inflammation, apoptosis	iNOS, COX-2, AKT, Bax, Bcl-2, caspases	[171, 172]
	Lycopene	tomato, orange, papaya	antiproliferation, antioxidant, antiangiogenesis, anti-inflammation, immunomodulator	Bcl-2, Bcl-xL, Bax, p53, caspases, cyclin D1, AKT, NF- κ B, MMP-9, BAD, Sp-1, cytochrome c, IGF-BP3, PCNA	[173–175]
	β -Carotene	carrots, pumpkin, green leafy vegetables, red palm oil	antioxidant, anti-inflammation, apoptosis	AKT, NF- κ B, iNOS, COX-2, caspases, Bax, Bcl-2, GSH	[176, 177]
	Lutein	spinach	antiangiogenesis, antioxidant, apoptosis	VEGF, AP-1, NF- κ B, C/EBP δ , MMP-2/-9, caspases, Bcl-2, Bax	[178]
	Terpenoids	Geraniol, limonene	citrus, cherries, grapes	apoptosis, cell cycle arrest, anti-inflammation, antiangiogenesis	TNF- α , Bcl-2, Bcl-xL, Bax, p53, caspases, cyclin D1, CDK, p21, p27, VEGF
Polyphenols	Curcumin	turmeric	antiproliferation, antioxidant, anti-inflammation, antiangiogenesis, immunomodulation	AKT, EGFR, Her2, NF- κ B, IGF-1R, Bcl-2, COX-2, ERK, AP-1, VEGF, MMP-2/-9, p53, p21, Bax, STAT-3/-5, survivin, iNOS	[68, 108, 180]
	Resveratrol	grapes	antiproliferation, antioxidant, anti-inflammation, antiangiogenesis	NF- κ B, iNOS, COX-2, STAT-3, p53, survivin, p53, p21, Bax, SOD, catalase, GSH, cyclin D1, CDK, VEGF	[181, 182]
	6-Gingerol	ginger	antioxidant, anti-inflammation, antiproliferation, antiangiogenesis	GSK-3 β , MMP-2/-9, VEGF, NF- κ B, AP-1, COX-2, iNOS, Bax, Bcl-2, CDK, cyclin D1, cytochrome c, caspases	[132, 183]
Glucosinolate	Indole-3-carbinol	cruciferous vegetables	antiproliferation, antiangiogenesis	NF- κ B, PI3K, AKT, Bcl-2, Bax, Bcl-xL, caspases, TRAIL, cFLIP, IAP	[184, 185] <i>continued</i>

Table 1 Continued

Group	Compound	Dietary source	Mechanism of action	Molecular targets	Reference
Organosulfur compounds	Allicin, diallyl sulfide (DAS), S-allylcysteine	garlic and onion	antiproliferation, anti-angiogenesis, anti-inflammation, immunomodulation	JNK, caspases, PARP, Bax, Bcl-2, VEGF, p38, cytochrome c, p53	[186]
n-3 Polyunsaturated fatty acids (PUFAs)		sunflower oil, corn oil, safflower oil, olive oil	apoptosis, anti-inflammation, cell cycle arrest	NF- κ B, Bax, Bcl-2, STAT-3, Fas/FasL, Ras, ERK 1/2, p53, cyclin D1, CDK, COX-2	[187]

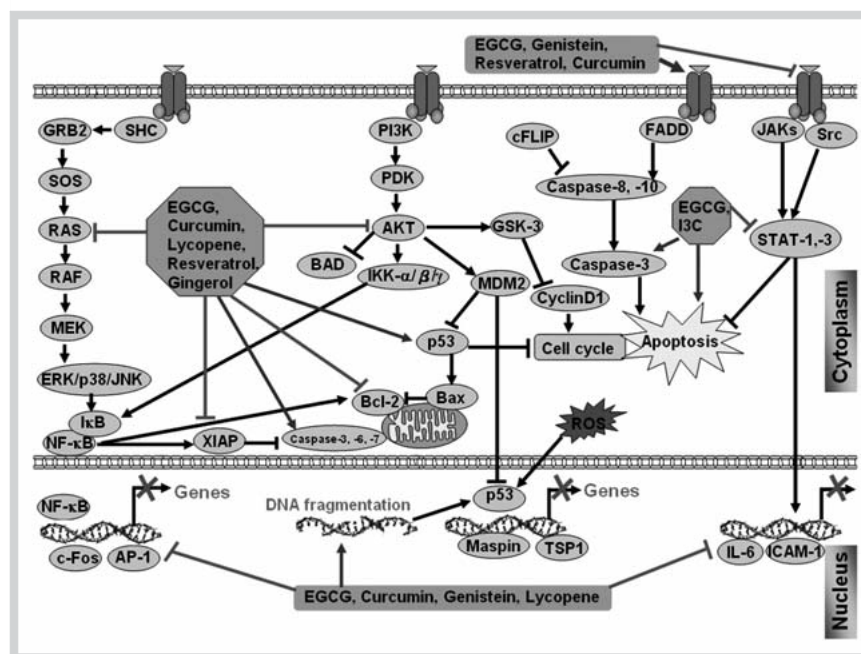


Fig. 1 Effects of different immunomodulatory plant natural products on activation and suppression of multiple cell signaling pathways. Multiple growth factor receptors (vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor receptor, fibroblast growth factor receptor) and their further downstream signaling pathways, Ras-MAPK (such as ERK/MAPK/JNK) pathways, the JAK-STAT pathways, the PI3K-AKT pathways, and transcription factors such as NF- κ B and AP-1 are suppressed by natural immunomodulatory plant natural products. Some natural products induce the tumor suppressor p53 and result in DNA fragmentation of cancer cells, with parallel high induction of reactive oxygen species (ROS) to further activate the tumor suppressor p53 and induction of cell cycle arrest and apoptosis.

bladder cancer growth and induces apoptosis through inhibition of the NF- κ B pathway [49]. [6]-Gingerol, a phenolic substance from ginger root (*Zingiber officinale*), inhibits epidermal growth factor-induced AP-1 activation and neoplastic transformation in mouse epidermal JB6 cells [50]. Capsaicin, the pungent component of hot chili (*Capsicum annuum*), suppresses TNF- α induced AP-1 activation in cultured human leukemia HL-60 cells, resulting in inhibition of cell survival and proliferation [51]. I3C inhibits the activation of AKT and NF- κ B of breast cancer cells, downregulates their specific target gene products including cyclin D1 and E, and induces apoptosis of breast cancer cells [52]. Resveratrol blocks NF- κ B activation and significantly inhibits the activities of MAPK/ERK kinase (MEK) and JNK and the binding efficiency of AP-1 to DNA in human lymphoma cells [53]. The inhibitory activities of various phytochemicals toward specific pro-inflammatory signaling activities collectively describe a relatively common molecular mechanism for their antitumor actions.

Apoptosis

Apoptosis is a specific, programmed mechanism of cell death that helps to regulate tissue homeostasis through the elimination of populations of potentially deleterious cells [54]. This activity involves the active participation of affected cells in a self-destructive

cascade that includes symptoms of membrane blebbing, shrinkage of cell and nuclear volume, chromatin condensation and endonuclease activation-mediated nuclear DNA fragmentation [55]. Many studies have suggested that various anti-inflammatory plant natural products (see Fig. 2a,b) may work by induction of apoptosis in cancer cells and subsequently suppress tumor growth. Resveratrol effectively induces apoptosis in rat and human cancer cells. The resveratrol-induced apoptosis in human cancer cells was reported mainly to result from an increase in caspase activity, upregulation of p53, Bax, and downregulation of Bcl-2, Bcl-XL, survivin and inhibitors of apoptosis (IAPs) in a variety of human cancers [56,57]. Benzyl isothiocyanate, yet another component of cruciferous vegetables, causes apoptosis by inducing DNA damage in human pancreatic cancer cells [58]. I3C, also abundant in cruciferous vegetables, induces apoptosis by significant downregulation of Bcl-2, Bcl-XL, IAP, X chromosome-linked IAP, and cellular FLICE inhibitory protein (c-FLIP) in human prostate cancer cells [59]. In treating pancreatic cells, EGCG invokes Bax oligomerization and depolarization of mitochondrial membranes to enhance release of cytochrome c into cytosol. EGCG also induces downregulation of X chromosome-linked IAP to facilitate cytochrome c-mediated downstream caspase activation [60]. In prostate cancer cells, EGCG treatment causes an activation of caspases-3, -7, and -9, followed by upregulation of Bax and downregulation of Bcl-2 proteins, eventually

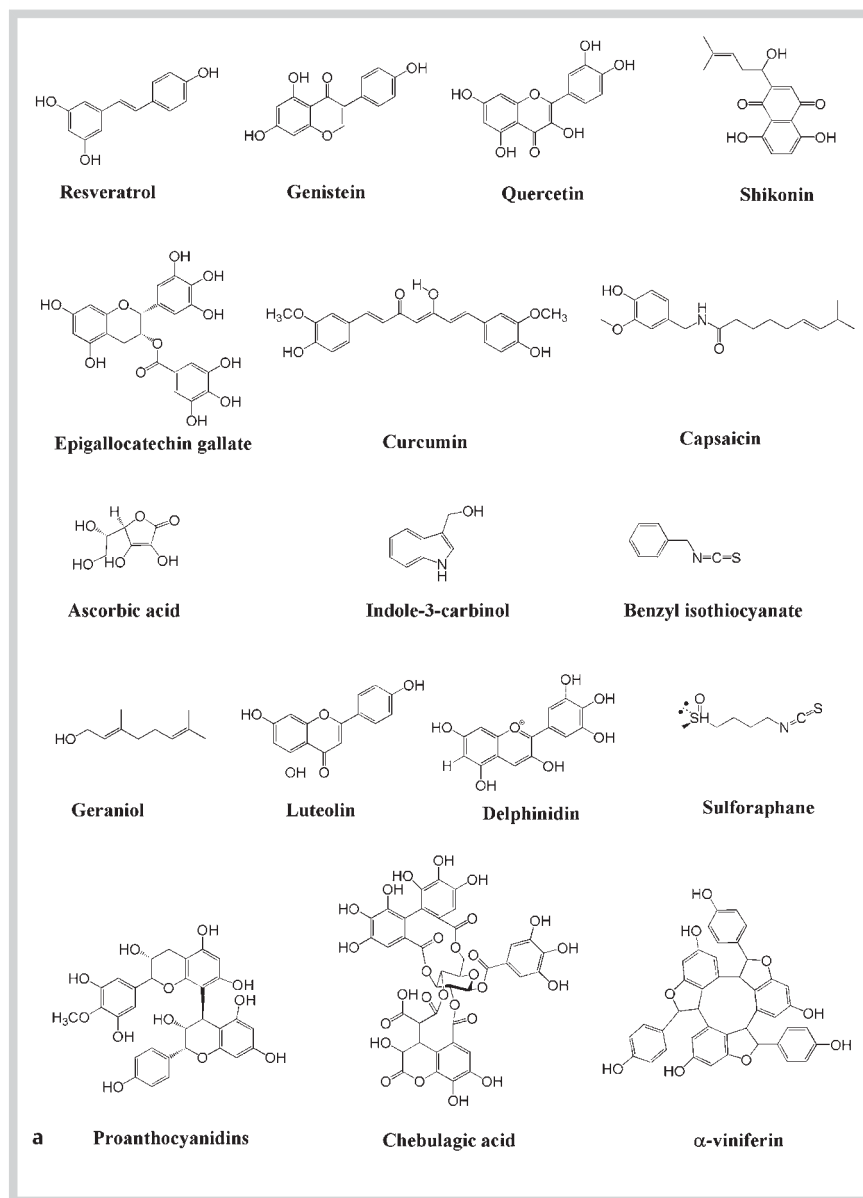


Fig. 2a Chemical structures of anti-inflammatory plant natural products.

leading to apoptosis [61]. EGCG treatment also results in down-regulation of anti-apoptotic protein Bcl-2 and upregulation of pro-apoptotic Bax in melanoma cells [62], and increased tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in hepatocellular carcinoma cell lines [63]. Luteolin, abundant in celery and green pepper, induces the expression of TRAIL and Bid, leading to cleavage and activation of caspases-8, -10, -9 and -3, and subsequent apoptosis in HeLa cells [64]. Apigenin, a flavonoid from parsley, celery and lettuce, induces apoptosis in monocytic and lymphocytic leukemia cell lines, and this was reported to be mediated by activation of caspase-9 and -3 and of PKC δ [65]. Curcumin induces apoptosis in human melanoma cells through activation of a Fas receptor/caspase-8 pathway [66], but paradoxically can inhibit the mitochondrial release of cytochrome *c* in human breast cancer cell lines [67]. Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome *c* from mitochondria [68]. The organosulfur compound diallyl sulfide, a natural immunomodulatory plant natural product from onion and garlic, induces apoptosis

via mitochondria-mediated cell death in prostate cancer cells, regulated by Bax/Bak but independent of Bcl-2 or Bcl- χ L [69]. Allicin induces apoptosis in human epithelial carcinoma cells, mediated by mitochondrial release of apoptosis inducing factor (AIF) [70]. Genistein, the soy isoflavone, decreases anti-apoptotic Bcl-2 protein and increases pro-apoptotic Bax protein, and leads to apoptosis of human gastric cancer cells [71]. In hepatocellular carcinoma cells, genistein treatment leads to activation of caspase-3, and -9, and cleavage of the caspase-3 substrate, poly (ADP-ribose) polymerase (PARP) [72] and enhanced TRAIL-induced apoptosis through inhibition of p38 MAPK [73]. Delphinidin, a flavonoid metabolite in depigmented fruits, activates caspases, increases Bax, Bid, and Bak levels, and decreases Bcl-2 and Bcl- χ L levels in immortalized human keratinocyte HaCaT cells [74].

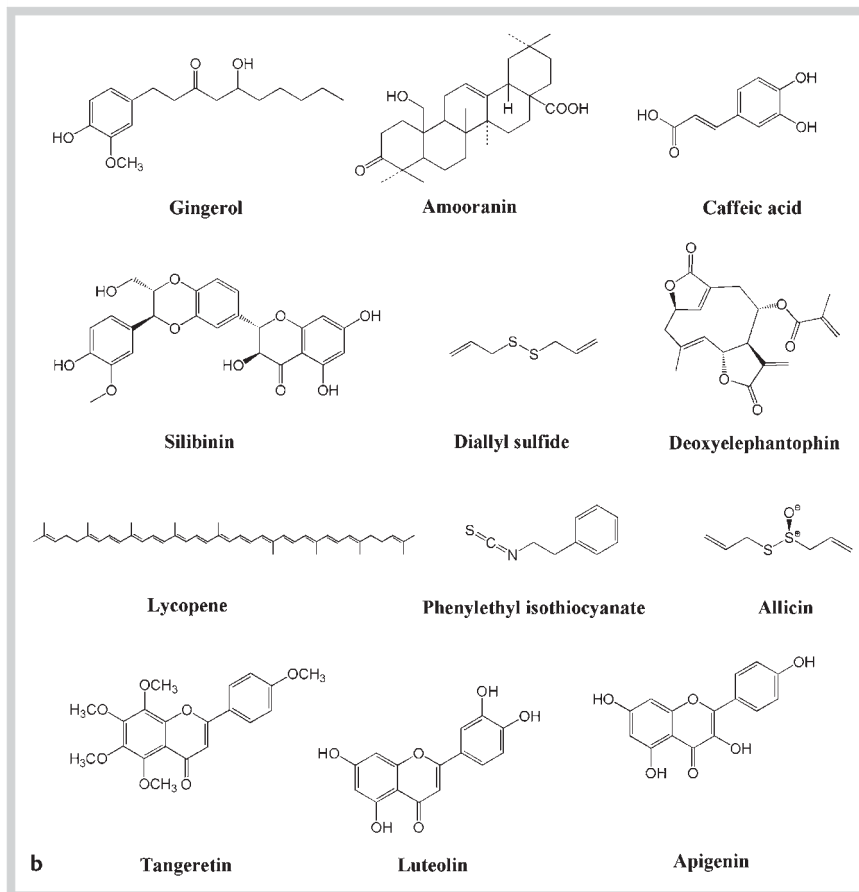


Fig. 2b Chemical structures of anti-inflammatory plant natural products.

Inflammation

Inflammation can be a host response to invading foreign pathogens, a reaction to tissue injury, or a response to a spectrum of physical, chemical, or biological stresses. Inflammatory responses are often induced by tissue wounding, and eventually lead to the restoration of normal structure and function of tissues by wound healing. A normal inflammatory response is generally self-limiting, and involves the eventual downregulation of expression of various pro-inflammatory proteins (some of the cytokines and chemokines) and increased expression of a group of anti-inflammatory proteins (other specific cytokines and chemokines) [75, 76]. NF- κ B, a key molecule for many inflammatory responses, is a dimeric transcription factor that is formed by the dimerization of specific proteins of the Rel family [77]. The activity of NF- κ B is fine tuned by various inflammatory stress or danger signals, and it is responsible for the hierarchical regulation of the expression of a spectrum of genes that encode inflammatory cytokines, chemokines, adhesion molecules, growth factors, and inducible enzymes such as COX-2 and inducible nitric oxide synthase (iNOS) [77, 78]. In addition to NF- κ B, another important inflammatory modulator that is being examined as a target in cancer is TNF- α , a growth factor or promoter for most tumor cells, now recognized to play a very important role in the maintenance of tumorigenesis [79]. Various immunomodulatory plant secondary metabolites such as EGCG, curcumin and resveratrol have been shown to decrease TNF- α production in tumor cells and thereby suppress tumor growth [80–82].

The two most accessible inducible pro-inflammatory enzymes in cancer therapy are iNOS and COX-2. The expression of both COX-

2 and iNOS is tightly regulated, and may be readily induced by oxidative stress and certain inflammatory cytokines. They are thus suggested to play an important role in the promotion and progression of various cancers. In fact, the 5' promoter regions of both iNOS and COX-2 genes contain putative binding sites for the transcription factors NF- κ B and AP-1 [83, 84]. COX is an essential enzyme in arachidonic acid metabolism, which can be divided into the LOX or the COX pathways. The COX pathway leads to prostaglandin (PG) and thromboxane production, whereas the LOX pathway leads to synthesis of leukotrienes (LTs) and hydroperoxyeicosatetraenoic acids (HPETEs). There are two main enzymes in the COX pathway, COX-1 and COX-2, and of these, COX-2 plays the major role in inflammation, including activities associated with cell growth regulation, tissue remodeling and carcinogenesis [85]. Overexpression of COX-2 results in induction of pro-inflammatory PGs such as prostaglandin E2 (PGE2), anti-apoptotic Bcl-2 family proteins, E-cadherin, MMPs, and specific angiogenic factors, and activation of the antiapoptotic PI3K/AKT pathway [86, 87]. EGCG selectively inhibited the expression of COX-2 and cell growth in human prostate carcinoma cells [88]. It also downregulated COX-2 activity in TPA-stimulated human mammary MCF-10A cells *in vitro* [89]. The important anti-inflammatory curcumin inhibited COX-2 activities through suppression of NF- κ B activity via control of the NIK/IKK signaling complex in colon cancer cells [90]. Sulforaphane suppressed lipopolysaccharide (LPS)-induced COX-2 expression and downregulated NF- κ B, cAMP response element-binding (CREB) and AP-1 activities [91]. Tangeretin, a flavonoid in citrus peels, was reported to effectively suppress IL-1 β -induced COX-2 expression through inhibition of p38 MAPK and JNK, and activation of AKT in

human lung carcinoma cells [92]. Another flavonoid, delphinidin, abundant in dark fruits, significantly inhibited COX-2 expression by blocking MAPK signaling and NF- κ B, AP-1 and C/EBP δ nuclear translocation in LPS-stimulated murine macrophage RAW264.7 cells [93]. Similarly, the grape phytochemicals resveratrol and α -viniferin inhibited COX-2 activity and COX-2 mRNA transcription in the same cell type [94].

There are several reports that immunomodulatory plant natural products can specifically suppress 5-LOX activity. Curcumin inhibited the release of arachidonic acid, cytosolic phospholipase A2 (cPLA2) and 5-LOX in LPS-stimulated RAW cells and A23187-stimulated human colon cancer HT-29 cells [95]. EGCG can significantly suppress the 5-LOX-dependent metabolism of arachidonic acid in human colon mucosa and colon tumor tissues [96]. Chebulagic acid (CA), a natural antioxidant, showed potent anti-inflammatory effects in suppression of 5-LOX in stimulated macrophages [97]. Procyanidins from cocoa (*Theobroma cocoa*) significantly inhibited the activity of human 5-LOX, a key enzyme for synthesis of pro-inflammatory leukotrienes, and suppressed inflammatory activities [98].

A number of naturally-occurring inhibitors of iNOS are being evaluated in clinical trials for cancer prevention. Curcumin has been reported to exert strong inhibitory effects on iNOS and its upstream regulators. Low concentrations of curcumin inhibited NO production via suppression of iNOS mRNA transcription and protein expression in macrophages [99]. Similarly, EGCG was found to inhibit expression and catalytic activities of iNOS, reduce the DNA binding ability of NF- κ B and inhibit the transcriptional activity of AP-1 [1]. Phenylethyl isothiocyanate in winter cress showed a strong anti-inflammatory activity by reducing the level of iNOS mRNA in LPS-stimulated mouse RAW264.7 macrophages [100]. Gingerol of ginger inhibited nitric oxide synthesis in activated J774.1 mouse macrophages and prevented peroxynitrite-induced oxidation and nitration reactions in macrophages [101]. I3C from cruciferous vegetables reduced the level of iNOS in stimulated macrophages [102].

Signal Transducers and Activators of Transcription (STAT) Pathway

One of the key signal transduction pathways to the nucleus has been discovered through the study of transcriptional activation in response to interferon-gamma (IFN- γ) [103]. So far, cDNA genes encoding seven mammalian STAT family members (STAT1–7) have been cloned, and found to share some common structural elements. These STAT family members can be activated by phosphorylation through specific cytokine receptors, e.g., by Janus kinase (JAK), growth factor receptors and various G-protein-coupled receptors, which can lead to the dimerization and nuclear localization of targeted STAT proteins, resulting in binding to specific DNA elements and ultimately activating the transcription of specific targeted genes. Importantly, constitutive activation of STAT3 and STAT5 has been implicated in many solid tumors, especially lymphomas and leukemias, among others [104–106]. A number of anti-inflammatory plant secondary metabolites have been shown to suppress gene activation of members of the STAT family in tumor cells. Polyphenols from green tea inhibit STAT3 expression and prostate cancer growth and subsequently induce apoptosis of prostate cancer cells [107]. In Hodgkin's lymphoma cells, curcumin induces cell arrest and apoptosis in association with the inhibition of the constitutively

active NF- κ B and STAT3 pathways. Its expression in the human chronic myelogenous leukemia cell line K562 also induces a decrease of nuclear STAT3, -5a and -5b, without affecting either STAT1 expression or the phosphorylation states of STAT1, -3 or -5 [108]. Most interestingly, the decrease of nuclear STAT5a and -5b after curcumin treatment was accompanied by an increase of the truncated STAT5 isoforms, indicating that curcumin is able to induce the cleavage of STAT5 into its dominant negative variants lacking the STAT5 C-terminal region [109]. Resveratrol modulates IL-6-induced intercellular adhesion molecule-1 (ICAM-1) gene expression by suppressing STAT3 phosphorylation [110]. Luteolin, a flavonoid from celery and green pepper, promotes degradation of STAT3 in human hepatoma cells, leading to a downregulation of the targeted downstream gene products such as cyclin D1, survivin, and Bcl-xL [111]. Another flavonoid, kaempferol, found in broccoli and tea, significantly inhibits STAT1 and NF- κ B activation in LPS-activated murine macrophage J774 cells [112]. Silibinin, a flavonolignan in milk thistle extract, inhibits the activation of STAT3 in human bladder cancer DU145 cells and suppresses tumor growth both *in vitro* and *in vivo*. Silibinin robustly decreases the protein expression and nuclear localization of survivin, as well as its secretion from tumor into plasma in the mouse, but it also increases the levels of p53 and cleaved caspase-3 in test tumors [21]. Many of these findings suggest that immunomodulatory and anti-inflammatory plant natural products target the STAT-signaling pathways, and can result in effective suppression of tumor growth (● Fig. 1).

Growth factors and their receptors

Growth factors are proteins, steroids or other biochemical substances that can bind to specific receptors on the cell surface, and thereby, via a cascade signaling pathway or network, stimulate the proliferation and differentiation of targeted cells or tissues. Growth factors can act as signaling molecules between two different cell types, and are important for regulating a variety of cellular processes. A number of growth factor signaling molecules, such as fibroblast growth factor (FGF), endothelial growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), hepatoma-derived growth factor, hypoxia-inducible factor, VEGF, IL-1, IL-6, IL-8, IL-10, colony-stimulating factor (CSF), and transforming growth factor (TGF) play important roles in carcinogenesis and metastasis. Activation of abnormal growth factor signaling pathways leads to increased cell proliferation, differentiation, maturation, suppression of apoptotic signals, and invasion, and eventually leads to cancer cell metastasis. These molecular signaling pathways or networks can have a strong impact on primary tumorigenesis and metastasis. Many immunomodulatory plant natural products have quite specific effects on these various signaling pathways, and are thus being actively evaluated for use as anticancer and anti-inflammatory disease remedies [1, 9, 13, 29, 30].

Proanthocyanidins in grapes reduce the UVB radiation-induced increase in levels of IL-10 in skin and enhance the expression of IL-12 in test skin [113]. EGCG inhibits both tumor cell growth and the activation of epidermal growth factor receptor (EGFR) and human EGFR-2 signaling pathways in human colon cancer cells [114]. EGCG also inhibits hypoxia- and serum-induced HIF-1 α protein accumulation and VEGF expression in human cervical carcinoma and hepatoma HepG2 cells [115], and inhibits the activation of HER-2/neu and downstream signaling pathways in human head, neck, and breast carcinoma cells [116]. Green tea catechins inhibit VEGF-induced angiogenesis *in vitro* through

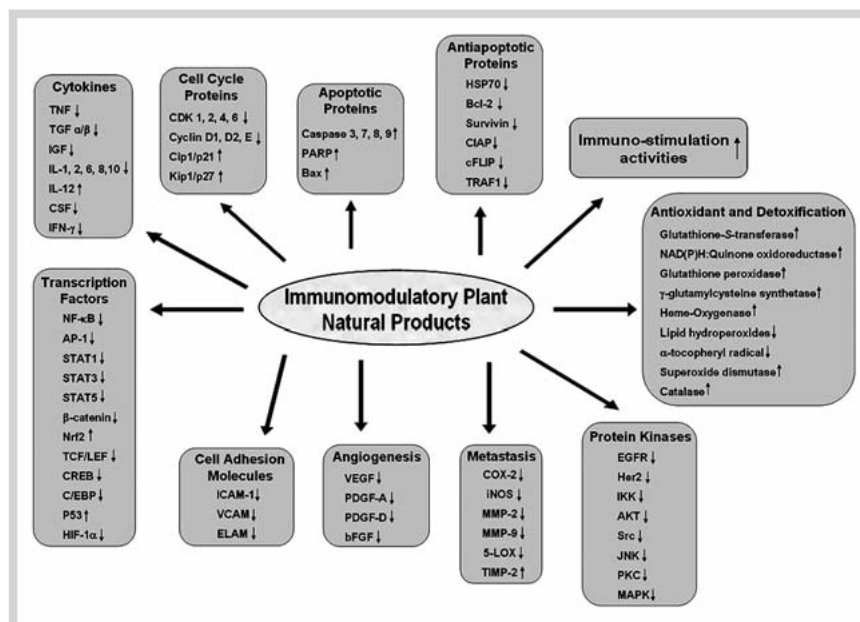


Fig. 3 Molecular targets of natural immunomodulatory plant natural products in prevention or therapy of cancers (modified from Aggarwal BB, Shishodia S. *Biochem Pharmacol* 2006; 7: 1397–1421) [9].

the suppression of VE-cadherin phosphorylation and inactivation of the AKT molecule [117]. Recently, we observed that shikonin from purple gromwell (*Lithospermum erythrorhizon*) suppresses LPS-induced TNF- α expression in human acute monocytic leukemia THP-1 cells, by the interesting route of blocking the pre-mRNA splicing activity mediated by the 3'-UTR element. Shikonin can also effectively inhibit transcriptional activity of TNF- α , GM-CSF and other inflammatory cytokine genes via interference with their promoter activities [30]. Curcumin inhibits the activation and expression of HER-2, HER-3, and EGFR in breast and colon cancer cells, and thus enhances apoptosis [118,119]. Lycopene from tomatoes markedly inhibits the migration of colorectal cancer cells, reduces the level of circulating insulin-like growth factor (IGF)-I [120] and traps platelet-derived growth factor (PDGF) [121]. The bioactive soybean component, genistein, effectively suppresses the activation of EGFR in human breast cancer cells and inhibited tumor cell proliferation [122].

Angiogenesis and metastasis

Angiogenesis is the process of forming a new blood supply from preexisting vessels in or near wound or tumor tissue, and is essential for the provision of sufficient essential nutrients and oxygen for tumor growth. Almost forty years ago, Dr. Judah Folkman of Harvard Medical School proposed the working hypotheses and principles that underlie contemporary research in tumor angiogenesis. His work showed that new vessels that formed at the tumor site were not inconsequential bystanders, but were absolutely required for the expansion of the tumor spheroid beyond a diameter of 1.2 mm, at which point the diffusion of nutrients in and waste products out becomes rate-limiting for tumor development [123]. Tumor angiogenesis and metastasis are meticulously regulated by the production of angiogenic stimulators, including members of the FGF, PDGF-A and -D and VEGF families (● Fig. 3). Tumor angiogenesis and cancer metastases are also intrinsically connected. Angiogenesis can facilitate tumor metastasis by providing an efficient route of exit for tumor cells to leave the primary site by entry into the bloodstream [124]. Metastasis is carefully regulated by the combined action of angiogenic factors, cyclooxygenases (like COX-2), and the MMPs that degrade

the basement membrane anchoring epithelial cells and pave the way for migration of cancer cells. Matrix metalloproteinases, including collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -7, -10) and elastases (MMP-12), are known to contribute to the various steps of metastasis [125,126]. Although angiogenesis and metastasis belong to the later stages of tumor growth and development, there is good evidence that several anti-inflammatory or immunomodulatory plant natural products may help to switch off angiogenesis and metastasis. For example, resveratrol inhibits VEGF-induced angiogenic effects in human umbilical vein endothelial cells and prevents activation of VE-cadherin and β -catenin [127]. Proanthocyanidins inhibit fibroblast-conditioned medium-induced expression of MMP-2 and MMP-9 in androgen-insensitive cells (DU145) as well as androgen-sensitive (LnCaP) human prostate carcinoma cells, and reduce the secretion of MMP-2 and MMP-9 by inhibition of MAPK phosphorylation and NF- κ B activation [128]. Another procyanidin extracted from Japanese quince fruit effectively inhibits MMP-2 and MMP-9 in human leukemia HL-60 cells [129]. EGCG inhibits tumor growth by reducing the VEGF level and angiogenesis in rat colon cancer [130]; it also suppresses the activities of MMP-2 and MMP-9 in the human fibrosarcoma HT1080 cell line [131]. The phytochemical 6-gingerol inhibits cell adhesion and invasion and decreases the activity of MMP-2 and MMP-9 in the human breast cancer line MDA-MB-231, and also inhibits VEGF-induced cell proliferation and angiogenesis [132]. Curcumin reduces the expression of MMP-2 and MMP-9 and reduces the degradation of extracellular matrix that forms the basis of the angiogenic switch, as well as targeting the non-receptor tyrosine kinases such as Src and FAK, thus inhibiting the downstream PI3K signaling network responsible for the induction of angiogenic and metastatic target genes as COX-2, VEGF and MMPs [133,134]. The PEITC from edible cruciferous vegetables inhibits the angiogenic features of human umbilical vein endothelial cells *in vitro*, apparently by suppression of VEGF secretion, the down-regulation of VEGF receptor 2 levels, and the inactivation of pro-survival serine-threonine kinase AKT. PEITC treatment also reduces the migration of PC-3 human prostate cancer cells, which correlates with an inactivation of AKT and the suppression for se-

cretion of VEGF, epidermal growth factor (EGF), and granulocyte colony-stimulating factor (G-CSF) [135].

◉ **Fig. 3** summarizes the currently known cellular physiological and biochemical activities (e.g., protein kinases, cell cycle proteins, cell adhesion molecules), immunoregulation and pathogen defense activities (e.g., immunostimulation, cytokines, transcription factors), and anti-inflammatory and antitumor activities (e.g., apoptotic proteins, antiapoptotic proteins, antioxidant, detoxification, angiogenesis, metastasis) of the various immunomodulatory plant natural products. We believe that future studies will continue to provide useful information on immunomodulatory and chemopreventive activities for candidate anticancer phytomedicines.

In Vivo Studies on the Use of Anti-Inflammatory Plant Natural Products in Cancer Therapy

Many experimental animal model studies have supported the promise offered by the use of immunomodulatory or anti-inflammatory plants or their constituents to reduce growth or metastasis of primary tumors *in vivo*. We recently reported that caffeic acid (a phenolic compound present in many fruits and vegetables) suppressed UVB radiation-induced expression of IL-10 and the activation of mitogen-activated protein kinases in mouse skin [136], and that shikonin, extracted from a traditional Chinese medicinal herb, suppressed transcription of the pro-inflammatory cytokine TNF- α promoter (mRNA and protein) in mouse skin [29]. Recently we found that the germacranolide sesquiterpene lactone, deoxyelephantopin, identified from *Elephantopus scaber* L. (known as “Didancao” in Chinese medicine) shows significant antitumor growth effect on murine glioblastoma GL-261 cells (Kandan Aravindaram, unpublished data) and mammary adenocarcinoma TS/A cells in mice (Lie-Fen Shyur, unpublished data). Elsewhere, curcumin was shown to significantly inhibit AKT and NF- κ B signaling pathways, resulting in an inhibition of cell proliferation and induction of apoptosis in PC-3 prostate tumor xenografts in nude mice [137]. Frequent feeding of a 2% curcumin preparation produced a marked increase in apoptosis and a significant decrease in angiogenesis in nude mice bearing human prostate tumor LnCap cells [138]. Curcumin also inhibits the initiation and promotion of TPA-induced skin cancers in mice and dimethylbenz[*a*]anthracene (DMBA)-induced oral carcinogenesis in Syrian golden hamsters [139, 140], inhibits the azoxymethane (AOM)-induced colon tumors in male F344 rats, prevents tumor growth in C57BL/6J-Apc Min/+ mice, and inhibits growth of AOM-induced rat colon carcinogenesis by suppressing synthesis of prostaglandin (PG) and thromboxane (Tx) [141]. Genistein from soybeans inhibits prostate cancer cell growth by inducing G2/M cell cycle arrest and cell apoptosis, inhibiting the secretion of prostate-specific antigen (PSA), and increasing the effect of radiation treatment against prostate cancers *in vivo* in both orthotopic and metastatic models [142, 143]. Apigenin, a plant flavonoid, suppresses the expression of VEGF and hypoxia-inducible factor-1 (HIF-1) in tumor tissues of nude mice with xenografts of A549 human lung cancer cells [144].

Proanthocyanidins have been shown to act as potent antioxidants and free radical scavengers; they inhibit 4T1 murine mammary cancer cell growth in immunocompetent Balb/c mice, resulting in a significant increase in the survival rate of the tumor-bearing mice [145]. They also inhibit the metastasis of mammary carcinoma cells from the primary tumor site to the lungs in mice,

and inhibit growth of HT29 human colorectal tumors in athymic nude mice without any apparent toxicity [146]. Supplementing the diet with proanthocyanidins was found to effectively inhibit the incidence of DMBA-induced mammary tumors in Sprague-Dawley rats [147]. Luteolin, a flavonoid present at high levels in several green vegetables, significantly decreases colon cancer incidence and the number of tumor nodules per rat when administered at the initiation and the post-initiation stages of carcinogenesis [148]. Lycopene a natural antioxidant in tomatoes, oranges, papaya, and other fruits, reduces the incidence of lung adenocarcinoma in mice [149], and prevents leiomyoma of the oviduct in the Japanese quail [150]. Sulforaphane inhibits DMBA-induced skin tumorigenesis in C57BL/6 mice by the induction of antioxidant/phase II detoxification enzymes following their activation via the Nrf2 signaling pathway [151]. EGCG from green tea inhibits growth of 4T1 mouse mammary carcinoma and suppresses metastasis into the lung. It also reduces tumor blood vessel formation in estrogen receptor-negative breast cancers [152], reduces colorectal aberrant crypt foci (ACF) formation, and prevents oncogenic changes in dysplastic ACF in azoxymethane-treated F344 rats [130]. For almost all of the model studies described above, studies exist that seemingly contradict them in one way or another. However, decades of cancer research have led us to appreciate that each model has its own specific advantages and disadvantages. The basic aim of the use of animal models is to understand the causal relationship between human exposure to immunomodulatory plant natural products and cancer therapy.

Conclusions and Future Directions

A broad spectrum of immunomodulatory or anti-inflammatory plant natural products has been isolated from fruits, vegetables, spices and traditional herbal medicines. They have gained much attention over the last decade for consideration as cancer chemopreventive or therapeutic agents. Advances in cellular, biochemical and molecular biology techniques and experimental approaches using transcriptome, proteome, metabolome and bioinformatics analyses have provided useful new insights into cancer therapeutics, including the exploration of specific plant secondary metabolites as natural products to treat immune imbalances, cancer and inflammation-associated diseases. These plant secondary metabolites may exhibit considerable benefits over synthetic drug approaches as they offer an inexpensive, convenient, readily applicable and accessible health-care approach for prevention, control and management of these diseases. While the specific use of these phytochemicals as medicines, dietary supplements or “health food” ingredients would need concerted future systematic study, especially in terms of translational research rather than the current mechanistic mode, there is continued excitement about their potential. The continued emergence of new evidence for the specific anti-inflammatory and immunomodulatory effects of these plant natural products on cancer cell signaling and molecular target pathways has certainly provided much impetus for future research into their modes of action and their application in cancer prevention and treatment.

A key challenge to researchers is how to best make use of these anti-inflammatory plant natural products for prevention of specific cancers in different populations. The provision of personalized medicines (as advocated in traditional Chinese medicine practice), an awareness of the varying nutritional needs for dif-

ferent races or individuals, and the availability of modern Western medicine in less developed areas are all considerations for cancer treatment. Moreover, further development of these potent natural products is needed to improve the efficacy of targeted therapeutic strategies to win the battle against cancer in the long run. In addition to the regrettably few ongoing clinical trials involving single anti-inflammatory plant natural products with multiple activities [153, 154], combinational approaches using fractionated or crude plant extracts and multiple plant formulations certainly warrant further consideration. In the future, long-term systematic and epidemiological studies of human clinical or nutritional trials of foods with defined anti-inflammatory properties will be essential to gather good evidence of their anticancer potential. With the expected advances in our understanding of the specific signaling pathways, transcription factors and molecular target genes affected by anti-inflammatory or immunomodulatory plant compounds, these natural products offer great promise as anticancer therapeutics or chemopreventive health care agents for a better quality of life for all.

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