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Modulation of Inflammatory Genes by Natural Dietary Bioactive Compounds

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Several epidemiologic studies have shown that chronic inflammation predisposes individuals to various types of cancer. Many cancers arise from sites of infection, chronic irritation, and inflammation. Conversely, an oncogenic change induces an inflammatory microenvironment that promotes the development of tumors. Natural bioactive compounds in dietary plant products including fruits, vegetables, grains, legumes, tea, and wine are claimed to help prevent cancer, degenerative diseases, and chronic and acute inflammation. Modern methods in cell and molecular biology allow us to understand the interactions of different natural bioactive compounds with basic mechanisms of inflammatory response. The molecular pathways of this cancer-related inflammation are now unraveled. Natural bioactive compounds exert anti-inflammatory activity by modulating pro-inflammatory gene expressions have shown promising chemopreventive activity. This review summarizes current knowledge on natural bioactive compounds that act through the signaling pathways and modulate inflammatory gene expressions, thus providing evidence for these substances in cancer chemopreventive action.

KEYWORDS: Natural bioactive compounds; inflammatory microenvironment; chemoprevention; inflammation; nutraceuticals

INTRODUCTION

The food we consume affects our bodies beyond just providing essential nutrition and minerals. Many natural dietary bioactive compounds have established pharmacological effects and/or can significantly alter activity of therapeutic agents by modulating biochemical pathways (*1*). Health implications of food−gene interaction, commonly referred to as nutrigenomics (*2*), have attracted mounting interest of researchers, physicians, and dietitians (*3*, *4*). Excessive inflammation is considered to be a critical factor in many human diseases and conditions, including obesity, cardiovascular diseases, neurodegenerative diseases, diabetes, aging, and cancer. Inflammation is a complex process, involving numerous mediators of cellular and plasma origins. Chronic inflammations and infections lead to up-regulation of a series of enzyme and signaling proteins in affected tissues and cells. Among inflammatory cells, polymorphonuclear leukocytes are particularly adept at generating and releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as $^{\bullet}O_2^-$ (superoxide anion), $^{\bullet}OH$ (hydroxyl radical), H_2O_2 (hydrogen peroxide), nitric oxide (NO), and $^1O_2$ (singlet oxygen). The excessively produced ROS can injure cellular biomolecules such as nucleic acids, proteins, carbohydrates, and lipids, causing cellular and tissue damage, which in turn augments the state of inflammation. In a setting of chronic inflammation, the persistent tissue damage and cell proliferation, as well as the enrichment of ROS and reactive carbonyl species (RCS), contribute to a cancer-prone microenvironment (*5*). Among the pro-inflammatory enzymes, the inducible forms of nitric oxide synthase (iNOS) and cyclooxygenase (COX) are responsible for increasing the levels on NO and prostaglandin E_2 (PGE_2). They are known to be involved in various chronic diseases, including cancer (*6*). In response to tissue injury or inflammatory stimulants, inflammatory and immune cells invade the affected area and secrete large amounts of highly reactive chemicals and pro-inflammatory cytokines to eliminate foreign pathogens or recruit a wide range of immune cells. These inflammatory chemicals also attack normal tissues surrounding the infected tissue, resulting in oxidative DNA damage, gene mutation, and cell proliferation. In tumor tissue, these inflammatory cells and tumor cells also create an inflammatory microenvironment and a network of signaling molecules that not only promote proliferation, angiogenesis, invasion, and metastasis but also suppress the ability of the host antitumor immune responses by secretion of various immunosuppressive cytokines and chemokines (**Figure 1**). 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. Three critical steps in this process for several types of human cancer formation are initiation, promotion, and progression. Epidemiological studies have provided convincing evidence

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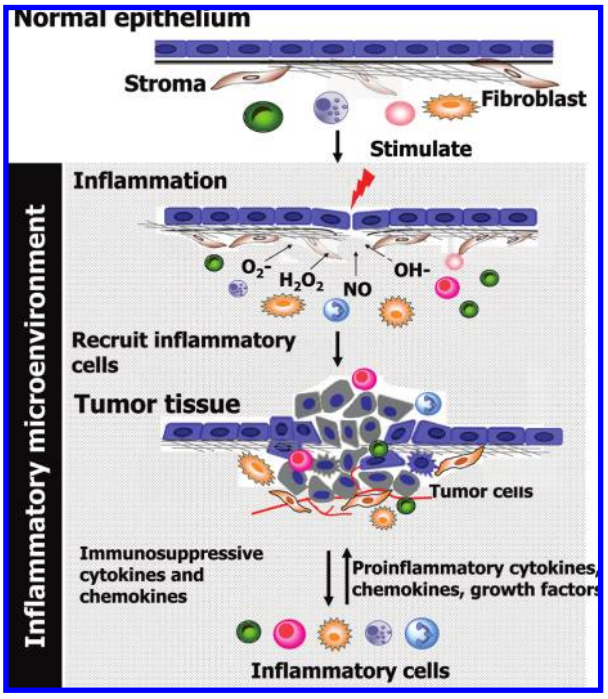

Figure 1. Role of inflammation in tumorigenesis. In response to tissue injury or inflammatory stimulation, the inflammatory and immune cells converge on the area and secrete large amounts of highly reactive chemicals and pro-inflammatory cytokines to eliminate foreign matters or recruit a wide range of immune cells. These inflammatory chemicals also attack normal tissue surrounding the infected tissue and result in oxidative DNA damage, gene mutation, and finally promote cell proliferation. In tumor tissue, these inflammatory cells and tumor cells also create an inflammatory microenvironment, and a network of signaling molecules not only promotes proliferation, angiogenesis, invasion, and metastasis but also suppresses the ability of the host antitumor immune responses by secretion of various immunosuppressive cytokines and chemokines.

that natural dietary compounds can modify this process. Laboratory research has further demonstrated the effectiveness of a number of natural bioactive compounds that have the ability to prevent and mitigate chronic diseases (*7*). Numerous studies in different cell lines and animal models suggest a protective role of natural dietary bioactive compounds against different types of cancer (*8*). At the same time, modulation of gene transcription by dietary compounds was found to be a viable anticancer strategy (*9*). Such promising research provides strong support for the future acceptance of natural bioactive compounds as chemopreventive agents. We suggest that cancer chemopreventive effects elicited by these natural bioactive compounds are due at least in part to the induction of cellular defense systems, including anti-inflammatory signaling pathways. The scope of the present review will focus on the molecular basis of the chemopreventive potential of natural bioactive compounds, with special emphasis on their effects on signaling molecules and pro-inflammatory gene expression as targets.

INFLAMMATORY PATHWAYS AS POTENTIAL TARGETS FOR NATURAL DIETARY BIOACTIVE COMPOUNDS

Inflammation is a multifaceted process that engages molecular and cellular mechanisms, resulting in widespread physiological changes. The initial inflammation involves the recruitment of a wide range of immune cells to inflamed sites and the release of various pro-inflammatory cytokines and other agents (*7*). This adaptive response evolved as a general reaction to a variety of stimuli and conditions, including infection and injuries (*10*), and the controlled acute inflammatory response is an essential part of the host's defense system. In sharp contrast with acute inflammation, systemic chronic inflammation, which is not apparently triggered by infection or injury, is strongly associated with a wide variety of diseases, including cancer, type 2 diabetes, and cardiovascular diseases. Chronic inflammation is linked to the malfunction of tissues and is believed to be functionally unrelated to tissue repair or to organism defense. It is well-established that inflammatory processes contribute to pathophysiology of cancer development and progression (*11*). The intrinsic pathway and the extrinsic pathway connect inflammation and cancer (*6*). The extrinsic pathway is driven by pre-existing conditions in the specific anatomical location, for example, inflammation, infection, or injury, that increase the probability of neoplasia. In contrast, the intrinsic pathway is triggered by genetic events, including activation of various types of oncogenes and the inactivation of tumor-suppressor genes. Both pathways converge, resulting in the activation of inflammatory signaling pathways (*6*). The network of inflammatory pathways includes, besides cytokines and chemokines, a variety of transcription factors and enzymes that should be recognized for their critical regulatory functions during this complicated process (**Figure 2**). Key molecular players linking cancer and inflammation include signal transducers and activators of transcriptions (STATs), nuclear factor-κB (NF-κB), nuclear factor of activated T-cells (NFAT), activator protein-1 (AP-1), CCAAT-enhancer binding protein (C/EBP), cAMP response element binding protein/p300 (CBP/p300), and activator transcription factor (ATF) (*12*). It has been recently recognized that NF-κB, the central coordinator of innate and adaptive immune responses, also plays a critical role in cancer development and progression (*13*). Activated NF-κB often facilitates transcription of numerous genes, including iNOS, COX-2, interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α), 5-lipoxygenase (5-LOX), hypoxia inducible factor-1α (HIF-1α), and vascular endothelial growth factor (VEGF), 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. These kinases can be activated through phosphorylation by upstream kinases, including NFκB-inducing kinase, mitogen-activated protein kinase (MAPK), and protein kinase C (PKC) (*14*). In addition, many studies have confirmed the cytokine function in the induction of transcription activity of NFκB through Janus kinase (JAK), extracellular signal-regulated protein kinase 1/2 (Erk1/2) (p42/44), p38 MAPK, Ras, and phosphoinositide-3 kinase (PI3K)/Akt pathways (*15*). NF-κB provides a mechanistic link between inflammation and cancer and is a major factor controlling the ability of both preneoplastic and malignant cells to resist apoptosis-based tumor surveillance mechanisms (*13*). Recent studies revealed that constitutive activation of STATs, 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 VEGF and its immune evasion. An understanding of molecular mechanisms linking inflammation and cancers is beneficial for the development of efficacious prevention and treatment of inflammation-associated tumorigenesis. Growing evidence clearly demonstrates that inflammatory pathways are critical targets in cancer treatment and prevention (*11*). Many natural bioactive compounds have been reported to interfere with the initiation, promotion/progression, and invasion/metastasis of cancer through control of intracellular signaling cascades of

inflammation process progresses (**Figure 2**) (*7*). There is growing research on the effects of plant-derived compounds on the attenuation of pro-inflammatory gene expression (*2*).

METHODS FOR INFLAMMATORY GENE ASSAY

Gene expression assays are used to assess the ability of natural products to regulate gene functions. The mode of action of natural bioactive compounds in modulating gene expression could include DNA repair, binding to transcription factor, DNA methylation, and turnover of regulatory proteins (*2*). A variety of methods can be used for evaluation of the expression level of genes in inflammatory pathways. The core methodology is based on measuring levels of mRNA. Traditional methods of quantifying mRNA levels include Northern analysis, in situ hybridization, ribonuclease (RNase) protection assay, and reverse transcription polymerase chain reaction (RT-PCR). Developed in the late 1970s, Northern analysis remains a standard method for the detection and quantification of mRNA levels. It is the preferred method for determining transcript size and for detecting alternatively spliced transcripts. Northern blot provides a direct relative comparison of message abundance between samples on a single membrane. The limitations of this method include relatively low sensitivity (*16*) and rapid decline of the data quality if RNA samples are even slightly degraded. The RNase protection assay shows higher specificity than Northern analysis and is most useful for mapping transcript initiation and termination (*17*). This assay could be used to study the expression of up to 12 mRNAs in a given sample. However, general sensitivity of the RNase protection assay is relatively low. RT-PCR is the most sensitive technique for mRNA detection and quantification, with the conversion of RNA to a complementary DNA (cDNA) template by the enzyme reverse transcriptase (*18*). Recently, real-time PCR has become one of the most widely used methods for measuring gene expression, overcoming the limitations of traditional quantification methods. This method uses fluorescent molecules to monitor PCR products accumulated during each cycle of the PCR reaction (*19*). Real-time PCR not only provides a faster and more sensitive technique to detect mRNA levels, but also increases the dynamic range of detection and reduces contaminations and no-post PCR processing. Lately, quantitative-PCR (qPCR) array systems are gaining popularity. The qPCR array is a set of optimized real-time PCR primer assays on up to 384-well plates. This reliable and sensitive gene expression profiling technology is broadly used for analyzing a panel of genes in signal transduction pathways. In addition, microarray technology is a practical method to assay large numbers of gene expressions at the same time. It consists of thousands of microscopic spots of DNA oligonucleotides that can be a short section of genes or part of conserved sequence of genes that are used as probes to hybridize a target DNA, cDNA, or mRNA under high-stringency conditions on a glass slide or membrane (*20*). So far, DNA microarray is widely used in molecular biology, medicine, and microbiological diagnostics. The gene regulation in eukaryotic cells is a complex process. There are numerous transcription factors and coactivators involved in regulating gene expression through the formation of multiprotein complexes and contribution to specific gene regulation events. The chromatin immunoprecipitation (ChIP) technique is important for studying protein−gene interactions in the promoter region and the cross-talk of various transcription factors in regulating diverse cellular processes. This technique involves the cross-linking of protein−protein and protein−DNA with formaldehyde, fragmentation, immunoprecipitation (IP) using a specific antibody, and identification of the immunoprecipitated DNA by PCR amplification

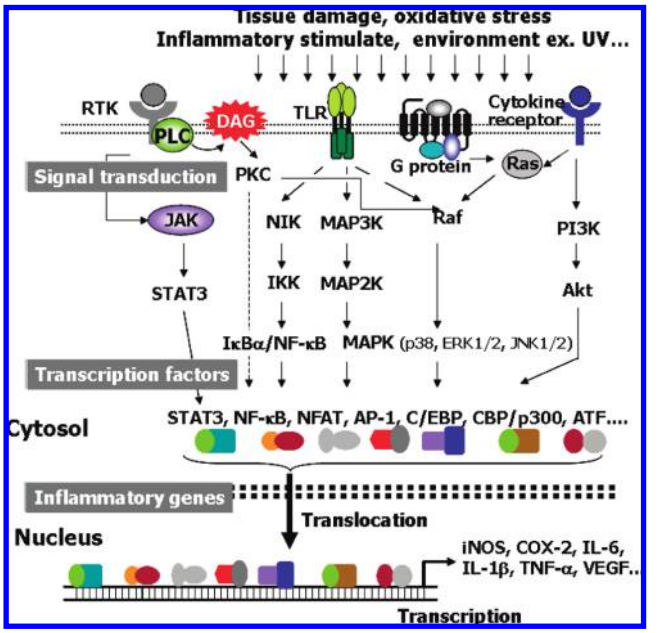

Figure 2. Multiple signaling pathways in regulating inflammatory gene expression. Tissue damage, oxidative stress, inflammatory stimulation, and environmental stimulation trigger the cellular signal transduction via ligand and receptor binding [receptor tyrosine kinase (RTK), Toll-like receptor (TLR), and cytokine receptor], leading to receptor phosphorylation and conformational change in protein structure. Receptor-mediated inflammatory signals recruit several adaptor proteins and result in activation of downstream MAPK. These stimuli also induce activation of phospholipase C (PLC) and activate small G protein to yield downstream second messenger diacylglycerol (DAG), an activator of PKC. These intracellular molecules amplify signaling transduction cascade through phosphorylation of transcription factors, lead to activation, and translocate to the nucleus involved in the inflammatory response modulating pro-inflammatory gene expression.

(*21*). Recently, several modifications of the ChIP technique have been published and successfully enhance its utility (*22*).

ANTI-INFLAMMATORY ACTIVITY OF NATURAL BIOACTIVE COMPOUNDS

Anti-inflammatory activity of natural bioactive compounds is attracting growing interest among researchers and physicians. This interest is inspired both by broad recognition of the ethnomedical observation of how inflammation is treated with commonly cultivated and harvested wild plants (*23*, *24*) and by advances in anti-inflammatory screening methods (*25*, *26*). Many natural bioactive compounds in fruits and vegetables with potent anti-inflammatory properties have been noted as plausible approaches for clinical cancer prevention trials. These compounds can be categorized into several classes. The molecular mechanisms underlying the modulating expression of inflammatory genes by selected natural dietary compounds (**Figure 3**) are described below.

Flavonoids. Flavonoids are ubiquitous in plants; almost all plant tissues are able to synthesize flavonoids. They can be classified into seven groups: flavones, flavonols, flavanones, flavanonols, flavanols, isoflavones, and anthocyanidins (**Table 1**). In general, the leaves, flowers, fruits, or the plants themselves contain flavonoid glycosides, whereas the woody tissues contain aglycones, and the seeds may contain both. Studies reported that isoflavone powders as well as isoflavone standard genistein were effective in inhibiting LPS-induced inflammation (*27*). Apigenin, present in parsley and celery, has been found to block pro-inflammatory cytokines and HIFα, VEGF, and COX-2 expression

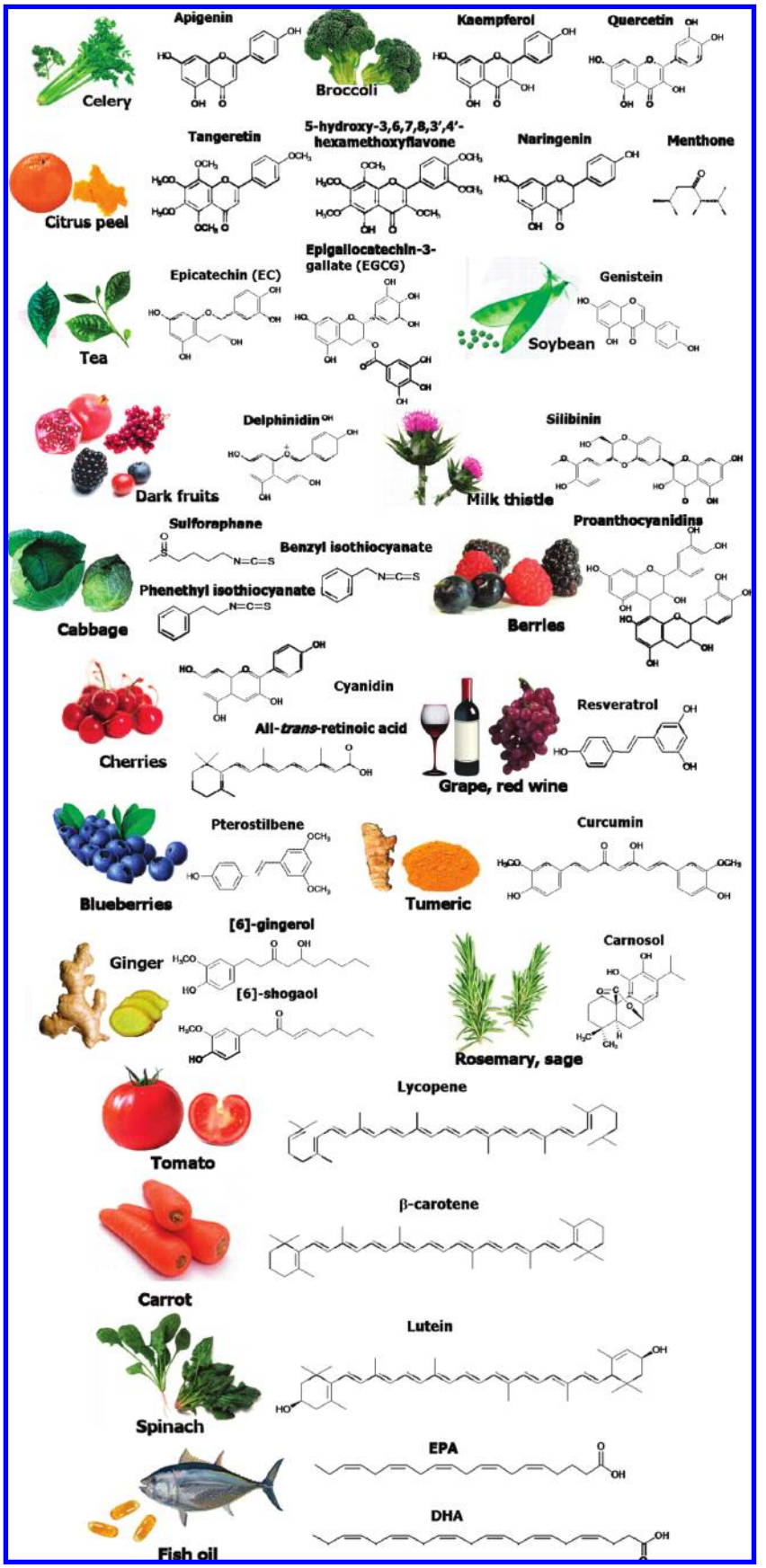

Figure 3. Representative natural dietary bioactive compounds and their sources.

through inhibition of NF-κB, PI3K/Akt, and ATF/cyclic AMP responsive element (CRE) signaling pathways (*28*−*30*). Numerous epidemiological and laboratory studies suggest that citrus flavonoids have become a particular interest because many of these flavonoids exhibit a broad spectrum of biological activities, including anticancer and anti-inflammation (*31*−*33*). Tangeretin

Table 1. Possible Mechanism of Flavonoids in Modulating Expression of Inflammatory Genes

group	class	compound	dietary source	anti-inflammatory mechanisms	refs
flavonoids	flavones	apigenin	parsley and celery	inhibits HIF-1α and VEGF expression by blocking PI3K/Akt signaling blocks LPS-induced pro-inflammatory cytokines expression by inactivating NF-κB through the suppression of p65 phosphorylation inhibits UVB-induced CBP binding to the ATF/CRE of the COX-2 promoter	(*28*−*30*)
		tangeretin	citrus peels	inhibits LPS-induced NO production and suppresses IL-1β-induced COX-2 expression through inhibition of p38 MAPK, JNK, and AKT activation	(*34*, *91*)
		5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone	citrus peels	inhibits TPA-induced skin inflammation and tumor promotion by suppressing MAP kinase and PI3K/Akt pathway, phosphorylation and activation of NF-κB and STAT3	(*35*)
	flavonols	kaempferol	broccoli and tea	inhibits iNOS expression and NO production by suppressing STAT-1 and NF-κB activations in activated macrophages inhibits cytokine-induced expression of iNOS, COX-2, and adhesion molecules by blocking signaling of NF-κB and AP-1 in human endothelial cells	(*36*, *37*)
		quercetin	onion, broccoli, apples, and berries	inhibits cytokine-induced expression of iNOS, COX-2, and adhesion molecules by blocking signaling of NF-κB and AP-1 in human endothelial cells inhibits phorbol-12-myristate-13-acetate (PMA)-induced histamine release and expression of pro-inflammatory cytokines through inhibiting nuclear translocation, DNA binding and transcriptional activity of NF-κB in mast cells suppresses TNF-induced NF-κB and CBP/p300 recruitment to pro-inflammatory gene promoters and down-regulation of interferon-inducible protein-10 (IP-10) and macrophage inflammatory protein-2 (MIP-2) gene expression	(*37*−*39*)
	flavanones	naringenin	orange peel	inhibits LPS-induced IL-1β, TNF-α production by suppressing phosphorylation on serines 63 and 73 of Jun proto-oncogene-encoded AP-1 transcription factor inhibits iNOS protein and mRNA expression and also NO production through blocking activation of NF-κB	(*36*, *40*)
	flavanols (catechins)	epicatechin (EC)	tea	inhibits TPA-induced O_2 generation and nuclear translocation of p65 and subsequent DNA binding of NF-κB by blocking the degradation of IκBα	(*42*)
		epigallocatechin-3-gallate (EGCG)	tea	suppresses Akt phosphorylation as well as TNF activation of tumor necrosis factor receptor (TNFR)-1, which subsequently resulted in reduced MCP-1 production inhibits IL-1β-dependent pro-inflammatory signal transduction through mediated receptor-associated kinase (IRAK) degradation, IKK activation, and NF-κB signaling inhibits TPA-induced DNA binding of NF-κB and CBP by blocking activation of p38 MAPK	(*43*−*45*)
	isoflavonoids	genistein	soybean	reduces LPS-induced IL-6 cytokine production and affects NF-κB subcellular localization and DNA binding transcription down-regulates phytohemagglutinin (PHA)-induced activation of p42/44 and JNK	(*49*, *50*)
	anthocyanidins	cyanidin	cherry and strawberry	inhibits PDGF-induced VEGF expression by preventing activation of p38 MAPK and JNK inhibits LPS/IFN-γ-induced NO production and LPS-induced iNOS and COX-2 expression by suppressing the functional activation of NF-κB but not nuclear translocation inhibits UVB- and TPA-induced transactivation of NF-κB and AP-1 and expression of COX-2 and TNF-α through the inhibition of MAPK activity	(*51*−*53*, *92*)
		delphinidin	dark fruits	inhibits platelet-derived growth factor ligand/receptor (PDGF/PDGFR) signaling and activation of ERK1/2	(*54*)
flavonolignans		silibinin	milk thistle	inhibits LPS-induced IL-12 expression by down-regulation of MAPKs signaling and the nuclear translocation of the NF-κB p65 subunit inhibits UV-induced iNOS and COX-2 expression through decreasing phosphorylation and nuclear translocation of STAT3 and p65	(*57*, *58*)

belongs to the polymethoxylated flavones and is abundant in citrus peels. Tangeretin plays an important role in every stage of cancer development. It suppresses IL-1β-induced COX-2 expression through inhibition of p38 MAPK, c-Jun N-terminal kinase (JNK), and Akt activation (*34*). We have recently reported that 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone, in citrus peel, inhibits 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA)-induced skin inflammation and tumor promotion by suppressing MAPK and PI3K/Akt signaling pathway (*35*). Kaempferol, present in broccoli and tea, has been found to reduce the activity of inflammation-related genes such as iNOS and COX-2 by blocking signaling of STAT-1, NF-κB, and AP-1 in activated macrophages (*36*) and human endothelial cells (*37*). Quercetin, one of the ubiquitous plant secondary metabolites, is found typically in onions, broccoli, apples, grapes, wine, tea, and leafy green vegetables, and it has been shown to be a potent antioxidant and anti-inflammatory agent. The anti-inflammatory mechanism of quercetin is believed to inhibit the expression of pro-inflammatory cytokines in mast cells (*38*) and to suppress TNF-induced NF-κB and CBP/p300 recruitment to pro-inflammatory gene promoters (*39*). Naringenin, a flavanone present in oranges, is believed to inhibit LPS-induced IL-1β and TNF-α production (*40*) and inhibit iNOS protein and gene expression through blocking activation of NF-κB (*36*).

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. Numerous health benefits have been attributed to the polyphenolic compounds in tea (*41*). Catechins, the most abundant polyphenols in green tea, have been extensively studied in recent years. A typical cup of brewed green tea contains, by dry weight, 30−40% catechins, including epigallocatechin-3-gallate (EGCG),

Table 2. Possible Mechanisms of Isothiocyanates, Proanthocyanidins, and Terpenoids in Modulating Expression of Inflammatory Genes

group	compound	dietary source	anti-inflammatory mechanisms	refs
isothiocyanates	sulforaphane	cabbage, turnips, broccoli, kale, cauliflower, brussels sprouts	suppresses LPS-induced COX-2 expression, down-regulating NF-κB, C/EBP and AP-1 inhibits LPS-stimulated mRNA and protein expression of TNF-α, IL-1β, COX-2, and iNOS via activation of Nrf2 in mouse peritoneal macrophages	(*59*, *60*)
	phenethyl isothiocyanate		suppresses RANKL-induced degradation of IκBα, phosphorylation of p38 MAPK and ERK1/2, and expression NFAT in RAW264.7 macrophage reduces LPS-induced phosphorylation of IκBα and transcriptional activity of NF-κB	(*61*, *62*)
	benzyl isothiocyanate		decreases TPA-induced leukocyte infiltration and inhibits excessive superoxide generation in inflammatory leukocytes in mouse dermis	(*63*, *64*)
proanthocyanidins		fruits, berries, beans, nuts, cocoa, and wine	inhibits LPS-induced iNOS and COX-2 expression through blocking phosphorylation of IKK, degradation of IκBα, nuclear translocation, and DNA binding of NF-κB suppresses LPS-induced COX-2 expression via blocking MAPK-mediated activation of NF-κB, AP-1, and C/EBPδ	(*65*, *93*)
terpenoids	menthone	citrus fruits, cherries, spearmint, dill, caraway, apricots, and grapes	inhibits LPS-induced cytokine production through blocking phosphorylation of IκBα and translocation of NF-κB	(*68*)
	all-trans-retinoic acid		down-regulates Th2- and Th1-related chemokine expression via affecting c-Raf-MKK1/2-ERK/MAPK pathway inhibits IL-1-induced iNOS, COX-2, and chemokine production by down-regulation of AP-1 DNA binding activity	(*69*, *70*)

epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). In vivo, EC inhibited TPA-induced COX-2 expression through modulating NF-κB activation (*42*). Recent studies indicated that EC reduced monocyte chemoattractant protein-1 (MCP-1) production by suppressing Akt phosphorylation TNF-α in endothelial cells (*43*). EGCG is the most abundant catechin in green tea. EGCG treatment suppressed IL-1β-dependent pro-inflammatory signal transduction in epithelial cells (*44*) and inhibited TPA-induced activation of NF-κB and CRP in mouse skin (*45*). Theaflavins from black tea and theaflavin-3, 3′-digallate in particular were demonstrated to be effective anti-inflammatory agents. The beneficial anti-inflammatory effect was linked to theaflavins' ability to inhibit the activation of NF-κB by inhibiting the phosphorylation, subsequent degradation of IκBα, and suppression of expression of pro-inflammatory genes, including interferon-γ (IFN-γ), IL-12, TNF-α, and iNOS (*46*). Theaflavin also affects brain injury by blocking inflammation-related events, including overexpression of COX-2 and iNOS via down-regulation of STAT-1 phosphorylation (*47*). Recently theaflavin monogallate and theaflavin-3,3′-digallate were shown to modulate the regulators of G-protein signaling by selectively inducing the expression of regulator of G-protein signaling (RGS)-10 (*22*).

The health benefits of soybeans and their products have been recognized in recent years (*48*). Genistein, an isoflavone, is considered to be the main nutraceutical in soybeans. In the immune system, NF-κB is involved in the maturation of dendritic cells and is a critical mediator of inflammation progress, regulating the expression of a wide range of inflammation molecules. Genistein inhibited NF-κB-dependent gene expression in Toll-like receptor (TLR) 4-stimulated dendritic cells (*49*) and blocked the production of TNF-α and IL-1β in phytohemagglutinin-treated macrophages (*50*). Cyanidin, an anthocyanidin present in cherries and strawberries, exhibited a significant decrease in LPS-induced iNOS and COX-2 expression and platelet-derived growth factor ligand (PDGF)-induced VEGF expression in vascular smooth muscle cells (*51*, *52*). Cyanidin inhibited tumor promoter-induced carcinogenesis and tumor metastasis in vivo by modulating the expression of COX-2 and TNF-α (*53*). Delphinidin, an anthocyanidin present in dark fruits, is believed to contribute to anti-angiogenic activity by inhibiting activation of the PDGF-BB/PDGF receptor (PDGFR)-β in smooth muscle cells (*54*). Silymarin, a collective term for a mixture of seven flavonolignans from milk thistle (*Silybum marianum* (L.) Gaertn.), is included in the pharmacopoeia of many countries under the trademark Legalon or Hepatron and is often used as supportive therapy in food poisoning due to fungi and in chronic liver disorders (*55*). Growing interest in using silymarin in cancer treatment and prevention is linked to its anti-inflammatory properties (*56*). Out of the mixture, silibinin is the best-documented of the flavonolignans displaying beneficial effects. Silibinin was reported to inhibit UV-induced iNOS and COX-2 expression and to inhibit LPS-induced IL-12 expression by down-regulation of inflammatory-related signaling pathways (*57*, *58*).

Isothiocyanates, Proanthocyanidins, and Terpenoids. Compounds known as isothiocyanates are formed during the mastication of some cruciferous vegetables, a process that 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 sources of glucosinolates and related breakdown products. Phenethyl isothiocyanate treatment suppressed LPS-induced inflammation in mouse macrophages and inhibited COX-2 expression through modulation of multiple targets in the COX-2 gene promoter (*59*, *60*) (**Table 2**). Exposure of RAW 264.7 cells to phenethyl isothiocyanate suppressed the receptor for activation of NF-κB ligand (RANKL)-induced degradation of IκBα, phosphorylation of p38 MAPK and ERK1/2, and expression of NFAT (*61*). Phenethyl isothiocyanate also displayed inhibition of NF-κB-mediated inflammatory transduction pathways in the colon and/or colon cancer (*62*). Benzyl isothiocyanate was reported to decrease TPA-induced leukocyte infiltration and inhibit excessive superoxide generation in inflammatory leukocytes in mouse dermis (*63*, *64*). Topical application of benzyl isothiocyanate inhibited TPA-induced mouse skin inflammation (*64*). Proanthocyanidins have been shown to inhibit COX-2 expression in LPS-activated mouse macrophages (*65*). The proanthocyanidin

Table 3. Possible Mechanism of Other Polyphenolic Compounds in Modulating Expression of Inflammatory Genes

group	compound	dietary source	anti-inflammatory mechanisms	refs
other polyphenolic compounds	resveratrol	grape, red wine	modulates TPA-induced COX-2 expression by blocking MAPK signaling, inhibition of IKK activity, and activation of NF-κB and AP-1	(*71*−*73*, *94*)
			inhibits IL-6-induced ICAM-1 gene expression by interfering with Rac-mediated pathways via the attenuation of STAT3 phosphorylation	
			inhibits LPS-induced NF-κB and C/EBP-mediated inflammatory genes expression	
	pterostilbene	blueberries	inhibits LPS-induced activation of PI3K/Akt, extracellular signal-regulated kinase 1/2i and p38 MAPK and down-regulates inflammatory iNOS and COX-2 gene expression in murine RAW 264.7 macrophages cells	(*74*, *75*)
			inhibits TPA-induced expression and activity of COX-2, and iNOS through blocking translocation and DNA binding activity of NF-κB and AP-1 in mouse epidermis	
	curcumin	tumeric	decreases TPA-induced COX-2 expression by inhibiting of translocation and activity of PKC	(*76*, *77*)
			attenuates TNF-α-stimulated inflammatory cytokines production through modulating phosphorylation of p38 and JNK, as well as activation of STAT-3 and NF-κB	
	[6]-gingerol	ginger	inhibits TPA-induced COX-2 expression in mouse skin by blocking the activity of p38 and transcriptional activities of NF-κB signaling pathway	(*78*)
	[6]-shogaol	ginger	down-regulates inflammatory iNOS and COX-2 gene expression in macrophages by inhibiting the activation of NF-κB by interfering with the activation PI3K/Akt/IκB kinases and MAPK	(*79*)
	carnosol	rosemary, sage	suppresses LPS-induced p38 and p44/42 MAPK activation and suppresses the NO production and iNOS gene expression by inhibiting NF-κB activation in murine RAW 264.7 macrophages cells.	(*80*, *81*)
			decreases PMA-induced COX-2 expression by blocking PKC signaling and the binding of AP-1 to the CRE of the COX-2 promoter	

A2 in longan flower has potent antioxidative activity and delays LDL oxidation (*66*).

The terpenoids are a class of secondary metabolites from the common origin of mevalonate and isopentenyl pyrophosphate that are lipophilic in nature (*67*). Menthone suppressed LPS-induced IL-1β and TNF-α production by suppressing the NF-κB signaling pathway in HaCat cells (*68*). *all-trans*-Retinoic acid treatment resulted in inhibition of Th1- and Th2-related chemokine production via affecting c-Raf-MAPK kinase (MKK)1/2-ERK/MAPK signaling pathway in monocytes (*69*). Furthermore, *all-trans*-retinoic acid also suppressed IL-1-induced iNOS and COX-2 expression in human chondrocytes, which contributes to its anti-inflammatory activity (*70*).

Other Polyphenolic Compounds. Besides flavonoids, many other polyphenolic compounds in nature also show health-promoting effects in food (**Table 3**). One of the best researched is resveratrol, a compound found mainly in the skin of grapes, peanuts, mulberries, blueberries, and cranberries; most importantly, it is also found in red wines. Resveratrol was found to inhibit TPA-induced pro-inflammatory signaling pathways (*71*) and to inhibit COX-2 expression by blocking IKK activity in mouse skin (*72*). Resveratrol has also been shown to suppress IL-6-induced intercellular cell adhesion molecule-1 (ICAM-1) gene expression in endothelial cells (*73*). Pterostilbene, isolated from *Vaccinium* berries, has been shown to suppress LPS-induced iNOS and COX-2 expression in murine macrophages, which contributes to its anti-inflammatory activity (*74*). Pterostilbene was found to be as effective as resveratrol in inhibiting TPA-activated NFκB, AP-1, COX-2, and iNOS in mouse epidermis (*75*). The dried rhizome of the turmeric plant (*Curcuma longa* Linn.) has been used for centuries as a naturally occurring medicine for treatment of topical inflammation and other diseases. The major pigment in the 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. Curcumin has also been reported to attenuate TNF-α-stimulated inflammatory cytokine production through modulating phosphorylation of p38, JNK and activation of STAT-3 and NF-κB in human endothelial cells (*76*). Curcumin also suppressed TPA-induced COX-2 expression by inhibiting NF-κB translocation and PKC activity (*77*). Gingerols are the main pungent components of the rhizome ginger (*Zingiber officinale* Roscoe), which belongs to the ginger family Zingiberaceae. Common ginger has been used as a folk medicine for thousands of years. More recently, [6]-gingerol has been found to inhibit COX-2 expression by blocking the activation of p38 MAPK and NF-κB in TPA-stimulated mouse skin (*78*). We recently demonstrated that [6]-shogaol suppressed LPS-induced up-expression of iNOS and COX-2 by interfering with the activation of PI3K/Akt/IKK and MAPK in murine macrophages (*79*). Rosemary and sage leaves are commonly used as spices and flavoring agents. Carnosol, an antioxidant in rosemary, suppressed LPS-induced iNOS expression through down-regulating NF-κB in macrophages (*80*). Carnosol also inhibited COX-2 gene transcription by blocking PKC signaling and the binding of AP-1 to the CRE of the COX-2 promoter in human mammary epithelial cells (*81*).

Carotenoids and Omega-3 Polyunsaturated Fatty Acids. Carotenoids are natural, fat-soluble pigments that provide bright coloration to plants and animals (**Table 4**). Lycopene, a carotenoid found in tomatoes, watermelon, papaya, apricots, oranges, and pink grapefruit, has established anti-inflammatory activities. Lycopene was reported to reduce inflammatory response by lowering iNOS and COX-2 gene expression (*82*) and IL-12 production through blocking MAPK signaling and activation of NF-κB in murine dendritic cells (*83*). β-Carotene is primarily found in red palm oil, palm fruits, leafy green vegetables, carrots, sweet potatoes, mature squashes, pumpkins, mangoes, and papayas. β-Carotene is the most common carotenoid in food and the most potent of the provitamin A carotenoids. β-Carotene has been reported to inhibit LPS-induced iNOS, COX-2, and TNF-α expression by decreasing phosphorylation and degradation of IκBα and nuclear translocation of NF-κB in macrophages (*84*). Lutein, found predominantly in dark green, leafy vegetables such as spinach and kale, is a yellow pigment that belongs to the class of non-provitamin A carotenoids. Lutein treatment inhibited LPS- and H_2O_2-induced pro-inflammatory gene expression by decreasing the activity of PI3K and NF-κB inducing kinase (NIK) and phosphorylation of Akt in RAW 264.7 cells (*85*). Lutein has also been found to inhibit LPS-induced inflammatory cytokine signals and STAT3 phosphorylation in C57BL/6 mice (*86*).

Table 4. Possible Mechanism of Carotenoids and Omega-3 Polyunsaturated Fatty Acids in Modulating Expression of Inflammatory Genes

group	compound	dietary source	anti-inflammatory mechanisms	refs
carotenoids	lycopene	tomatoes, watermelon, papaya, and orange	inhibits IFN-γ-induced iNOS and COX-2 gene expression by suppressing the activation of NF-κB, IRF-1, and STAT-1α in murine RAW 264.7 macrophages inhibits LPS-induced production of IL-12 through blocking MAPK signaling and activation of NF-κB	(*82*, *83*)
	β-carotene	red palm oil, carrots, pumpkin, and leafy green vegetables	inhibits LPS-induced iNOS, COX-2, and TNF-α expression by decreasing phosphorylation and degradation of IκBα as well as nuclear translocation of NF-κB	(*84*)
	lutein	spinach and kale	inhibits LPS- and H_2O_2-induced pro-inflammatory genes expression by decreasing in activity of PI3K and NIK, and phosphorylation of Akt in RAW264.7 macrophages inhibits LPS-induced inflammatory cytokine signals and STAT3 phosphorylation in C57BL/6 mice	(*85*, *86*)
omega-3 fatty acids	EPA	fish oils	decreases production of NO, expression of iNOS mRNA through suppression of DNA-binding activity of NF-κB inhibits the release of NO, PGE_2, IL-1β IL-6, and TNF-α and suppressing NF-κB activation by blocking the MAPKs and PI3K/Akt pathways in LPS-stimulated BV2 microglia	(*88*, *89*)
	DHA		decreases RANKL-induced pro-inflammatory cytokine production by inhibiting activation of c-fos, NF-κB, and p38 MAPK signaling	(*90*)

A number of experimental and clinical studies have described potential health benefits of omega-3 polyunsaturated fatty acids (PUFA) abundant in marine oil and also present in some plant seed oil. These fatty acids 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 (*87*). Pretreatment of EPA inhibited iNOS mRNA expression through suppression of DNA-binding activity of NF-κB (*88*). EPA was also reported to inhibit the release of NO, PGE_2, IL-1β, IL-6, and TNFα and to suppress NF-κB activation by blocking the MAPKs and PI3K/Akt pathways in LPS-stimulated BV2 microglia (*89*). DHA was reported to decrease RANKL-induced pro-inflammatory cytokine production by inhibiting activation of c-fos, NFκB, and p38 MAPK signaling pathways (*90*).

CONCLUSION

Modulation of inflammatory genes by natural dietary bioactive compounds plays an important role in the prevention, mitigation, and treatment of many diseases and conditions. In a fully developed malignancy, there are excess inflammatory cells in the tumor microenvironment. It is well-established that anti-inflammatory therapy is efficacious against early neoplastic progression and malignant conversion. As inflammation is deeply involved in complicated pathological processes associated with cancer development and progression, by effectively targeting pro-inflammatory-mediated signaling pathways it is possible to stop and even reverse tumorigenesis. It was recently suggested that the diverse effects of tea polyphenols mediated via G-signaling pathways may be attributable to their selective effects on regulator of G-binding protein signaling (RGS) family genes (*22*). Modulation by natural dietary bioactive compounds of signal transduction pathways linked to NF-κB, PI3K/Akt, MAPK, p38 MAPK, JNK, STAT3, and AP-1 is well-established (**Tables 1**−**3**). Natural bioactive compounds that target cancer-related inflammation also may revert a tumor-promoting inflammatory infiltrate and prevent inflammatory cells from migrating to the tumor site and tumor-promoting microenvironment. This potential for reversing tumor-supporting inflammation could be the beginning of an exciting new era for treatment of the inflammation associated with tumorigenesis. Additional extensive research on the effects of natural bioactive compounds on modulation of inflammatory signaling pathways and/or different targets in cancer would be helpful in the design and development of novel cancer-preventive agents.

Abbreviations Used

5-LOX 5-lipoxygenase
AP-1 activator protein-1
ATF activator transcription factor
C/EBP CCAAT-enhancer binding protein
CBP cAMP response element binding protein
cDNA complementary DNA
ChIP chromatin immunoprecipition
COX-2 cyclooxygenase-2
CRE cyclic AMP responsive element
DAG diacylglycerol
DHA docosahexaenoic acid
EC epicatechin
ECG epicatechin-3-gallate
EGC epigallocatechin
EGCG epigallocatechin-3-gallate
EPA eicosapentaenoic acid
ERK1/2 extracellular signal-regulated protein kinase 1/2
HIF-1α hypoxia inducible factor-1α
ICAM-1 intercellular cell adhesion molecule-1
IFN-γ interferon-γ
IKK IκB kinase
ILs interleukins
iNOS inducible nitric oxide synthase
IP immunoprecipitation
IP-10 interferon-inducible protein 10
IRAK interleukin-1 (IL-1) receptor-associated kinase
IκB inhibitor κB
JAK Janus kinase
JNK1/2 c-Jun N-terminal kinase
LPS lipopolysaccharide
MAPK mitogen-activated protein kinase
MCP-1 monocyte chemoattractant protein-1
MIP-2 macrophage inflammatory protein-2
MKK MAPK kinase
NFAT nuclear factor of activated T-cells
NF-κB nuclear factor-κB
NIK NF-κB inducing kinase
NO nitric oxide
PDGF platelet-derived growth factor ligand
PDGFR platelet-derived growth factor receptor
PGE_2 prostaglandin E_2
PHA phytohemagglutinin
PI3K phosphoinositide-3 ki.nase
PKC protein kinase C

PLCε phospholipase Cε
PMA phorbol-12-myristate-13-acetate
PUFA polyunsaturated fatty acid
RANKL
receptor for activation of NF-κB ligand
RCS reactive carbonyl species
RGS regulator of G-protein signaling
RNase ribonuclease
RNS reactive nitrogen species
ROS reactive oxygen species
RTK receptor tyrosine kinase
RT-PCR
reverse transcription Polymerase Chain Reaction
STAT3 signal transducer and activator of transcription 3
TLR Toll-like receptor
TNFR tumor necrosis factor receptor
TNF-α tumor necrosis factor-α
TPA 12-*O*-tetradecanoyl-phorbol-13-acetate
VEGF vascular endothelial growth factor

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