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Commentary

Molecular targets of dietary agents for prevention and therapy of cancer☆

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ARTICLE INFO

Keywords:
NF-κB
AP-1
MAP kinases
Apoptosis
Cell cycle
Cancer
Dietary agents

Abbreviations:
AP-1, activator protein-1
CAPE, caffeic acid phenethyl ester
Cdk, cyclin-dependent kinase
COX-2, cyclooxygenase-2
cPLA$_2$, phospholipase A
CSF, colony-stimulating factors
DIM, 1,1-bis(3′-indolyl)-1-(*p*-substituted phenyl) methanes
DMBA, dimethyl-benz(*a*) anthracene
EGF, epidermal growth factor
EGCG, epigallocatechin-3-gallate
Epo, erythropoietin
ERK, extracellular signal-regulated kinase
FGF, fibroblast growth factor

ABSTRACT

While fruits and vegetables are recommended for prevention of cancer and other diseases, their active ingredients (at the molecular level) and their mechanisms of action less well understood. Extensive research during the last half century has identified various molecular targets that can potentially be used not only for the prevention of cancer but also for treatment. However, lack of success with targeted monotherapy resulting from bypass mechanisms has forced researchers to employ either combination therapy or agents that interfere with multiple cell-signaling pathways. In this review, we present evidence that numerous agents identified from fruits and vegetables can interfere with several cell-signaling pathways. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), beta carotene (carrots), and dietary fiber. For instance, the cell-signaling pathways inhibited by curcumin alone include NF-κB, AP-1, STAT3, Akt, Bcl-2, Bcl-X_L, caspases, PARP, IKK, EGFR, HER2, JNK, MAPK, COX2, and 5-LOX. The active principle identified in fruit and vegetables and the molecular targets modulated may be the basis for how these dietary agents not only prevent but also treat cancer and other diseases. This work reaffirms what Hippocrates said 25 centuries ago, let food be thy medicine and medicine be thy food.

☆ Supported by the Clayton Foundation for Research (to BBA), Department of Defense US Army Breast Cancer Research Program grant (BC010610, to BBA), a PO1 grant (CA91844) from the National Institutes of Health on lung cancer chemoprevention (to BBA), a P50 Head and Neck Cancer SPORE grant from the National Institutes of Health (to BBA), Cancer Center Core Grant CA 16672, and Texas Southern University Seed Grant (to SS).

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0006-2952/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2006.02.009

HER2, human epidermal growth factor receptor 2
I-3-C, indole-3-carbinol
ICAM-1, intercellular adhesion molecule-1
IFN, interferon
IGF, insulin-like growth factor
IκBα, inhibitory kappa B alpha
IKK, IκBα kinase
IL-1, interleukin
iNOS, inducible nitric oxide synthase
JNK, c Jun N-terminal kinase
LPS, lipopolysaccharide
LOX, lipoxygenase
MMP, matrix metalloproteinase
MAPK, mitogen-activated protein kinases
NF-κB, nuclear factor-kappa B
PDK, pyruvate dehydrogenase kinase
PTK, protein tyrosine kinase
PKB, protein kinase B
p27KIP1, p27 kinase inhibitor protein 1
PDGF, platelet-derived growth factor
PARP, polyadenosine-5′-diphosphate-ribose polymerase
STAT, signal transducer and activator of transcription
TGF, transforming growth factor
THC, tetrahydrocurcumin
TNF, tumor necrosis factor
TPA, phorbol 12-O-tetradecanoate-13-acetate
TRE, TPA response elements
uPA, urokinase-type plasminogen activator
VEGF, vascular endothelial growth factor

1. Introduction

Epidemiological data accumulated over the last 50 years show a significant decrease in the death rate within the US due to heart, cerebrovascular, and infectious diseases; however, cancer-related mortality has remained unaltered since 1950 [1,2]. Despite a better understanding of the disease and the advent of modern technology and rationally targeted drugs, the incidence and cure rate of cancer have not improved.

One secret to improving cancer statistics seems to reside in the epidemiology of the disease. Epidemiology has revealed that certain cancers are more common among people of some cultures than others [3–6]. Cancers of the lung, colon, prostate and breast are very common in Western countries; they are not as prevalent in Eastern countries. Similarly, cancers of the head and neck and of the cervix are most common in India, whereas stomach cancer is most prevalent in Japan.

Studies indicate that migration from native to adopted country, however, exposes an individual to the same cancer risk and incidence as that of others living in the adopted country. Because human beings are 99.1% identical in their genetic sequence, these differences in incidence cannot be attributed to the variation in their DNA sequence. In fact, if one twin is identified with breast cancer, the chance that the second twin will be diagnosed with breast cancer is 20%, indicating that the contribution of faulty genes to the pathogenesis of cancer is minimum [7]. Instead, it is estimated that 75–85% of all chronic illnesses and diseases are linked to

lifestyle and cannot be explained by differences in genetic makeup [8]. For example, there is a positive association between fat and red meat and an inverse association between dietary fiber, fruit and vegetable intake with the development of colorectal adenomas [9]. Epidemiological studies have indicated that populations that consume food rich in fruits and vegetables have a lower incidence of cancers [10–12]. Review of results from 206 human epidemiologic studies and 22 animal studies has indicated an inverse relationship between consumption of vegetables and fruits and risk for cancers of the stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon [13].

Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers. The questions that remain to be answered are which component of these dietary agents is responsible for the anti-cancer effects and what is the mechanism by which they suppress cancer? Dietary agents consist of a wide variety of biologically active compounds that are ubiquitous in plants, many of which have been used in traditional medicines for thousands of years. As early as 2500 years ago, Hippocrates recognized and professed the importance of various foods both natural and those derived from human skill in the primary constitution of the person.

Fruits and vegetables are excellent sources of fiber, vitamins, and minerals, but they also contain components like polyphenols, terpenes, alkaloids, and phenolics that may provide substantial health benefits beyond basic nutrition. Research over the last decade has shown that several micronutrients in fruits and vegetables reduce cancer (Table 1). The active components of dietary phytochemicals that most often appear to be protective against cancer are curcumin, genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, 6-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, dithiolthiones, isothiocyanates, indole-3-carbinol, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, Vitamin C, D-limonene, lutein, folic acid, beta carotene, selenium, Vitamin E, flavonoids, and dietary fiber (Figs. 1 and 2). These dietary agents are believed to suppress the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis as well, namely angiogenesis and metastasis (Fig. 3).

Tumorigenesis is a multistep process that can be activated by any of various environmental carcinogens (such as cigarette smoke, industrial emissions, gasoline vapors), inflammatory agents (such as tumor necrosis factor (TNF) and H_2O_2), and tumor promoters (such as phorbol esters and okadaic acid). These carcinogens are known to modulate the transcription factors (e.g., NF-κB, AP-1, STAT3), anti-apoptotic proteins (e.g., Akt, Bcl-2, Bcl-X_L), proapoptotic proteins (e.g., caspases, PARP), protein kinases (e.g., IKK, EGFR, HER2, JNK, MAPK), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), cell adhesion molecules, COX-2, and growth factor signaling pathways. This article reviews the current studies regarding the numerous pathways and molecular targets of dietary agents for not only prevention but also for therapy of cancers.

2. Molecular targets

2.1. *Nuclear factor-kappa B (NF-κB)*

NF-κB is a family of closely related protein dimers that bind to a common sequence motif in DNA called the κB site (for references see [14]). The identification of the p50 subunit (v-REL) of NF-κB as a member of the reticuloendotheliosis (REL) family of viruses provided the first evidence that NF-κB is linked to cancer. Under resting condition, the NF-κB dimers reside in the cytoplasm. NF-κB is activated by free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, γ-radiation, ultraviolet (UV) light, and X-rays. Upon activation, it is translocated to the nucleus, where it induces the expression of more than 200 genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance, and inflammation. Many of the target genes that are activated are critical to the establishment of the early and late stages of aggressive cancers, including expression of cyclin D1, apoptosis suppressor proteins such as Bcl-2 and Bcl-XL and those required for metastasis and angiogenesis, such as matrix metalloproteases (MMP) and vascular endothelial growth factor (VEGF).

Several dietary agents like curcumin [15], resveratrol [16], guggulsterone [17], ursolic acid [18], betulinic acid [19], emodin [20], gingerol [21], flavopiridol [22], zerumbone [23], evodiamine [24], indole-3-carbinol [25], elagic acid, anethole [26], green tea catechins [27], S-allyl cysteine [28], lycopene [29], and diosgenin [30] are natural chemopreventive agents that have been found to be potent inhibitors of NF-κB (Table 2). How these agents suppress NF-κB activation is becoming increasingly apparent. These inhibitors may block any one or more steps in the NF-κB signaling pathway such as the signals that activate the NF-κB signaling cascade, translocation of NF-κB into the nucleus, DNA binding of the dimers, or interactions with the basal transcriptional machinery.

A number of studies from our laboratory have shown that the spices derived from plants exert their anti-cancer effects through the suppression of NF-κB. Curcumin as well as various other curcuminoids from ginger family mediate their therapeutic effects by regulating the transcription factor NF-κB and NF-κB regulated gene products COX-2, cyclin D1, adhesion molecules, MMPs, inducible nitric oxide synthase, Bcl-2, Bcl-X_L and TNF [31]. Curcumin suppresses the TNF-induced activation of IKK that leads to the inhibition of TNF-dependent phosphorylation and degradation of IκBα and translocation of the p65 subunit. Curcumin also blocks phorbol ester- and hydrogen peroxide-mediated activation of NF-κB [15]. Guggulsterone suppresses NF-κB activation by suppressing the activation of IKK by interacting directly with the kinase [17]. In studies from our laboratory, resveratrol suppressed TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-κB and NF-κB-dependent reporter gene transcription. Suppression of TNF-induced NF-κB activation by resveratrol was not cell type specific and was observed in

Table 1 – Molecular targets of dietary agents

Plant name	Active compound	Molecular target
Turmeric (*Curcuma longa*)	Curcumin, curcuminoids	↓NF-κB, ↓ AP-1, ↓Egr-1, ↓STAT1, ↓STAT3, ↓STAT5, ↑PPARγ, ↓EpRE, ↓CBP, ↓β-catenin, ↑Nrf2, ↑IKK, ↓EGFR, ↓HER2, ↓AKt, ↓Src, ↓JAK2, ↓TYK2, ↓JNK, ↓PKA, ↓PKC, ↓VCAM-1, ↓Bcl-2, ↓Bcl-XL, ↓ICAM-1, ↓TF, ↓AR/ARP, ↓p53, ↑MDR, ↓ELAM-1, ↓FTPase, ↑GST, ↑GSH-px, ↓uPA, ↑HO, ↓XOD, ↓cyclin D1, ↓5-LOX, ↓COX-2, ↓INOS, ↓MMP-9, ↓TNF, ↓IL-6, ↓IL-8, ↓IL-12
Grapes (*Vitis vinifera*)	Resveratrol	↓COX-2, ↓iNOS, ↓JNK, ↓MEK, ↓AP-1, ↓NF-κB, ↑P21 Cip1/WAF1, ↑p53, ↑Bax, ↑caspases, ↓survivin, ↓cyclin D1, ↓cyclin E, ↓Bcl-2, ↓Bcl-xL, ↓CIAP, ↓Egr-1, ↓PKC, ↓PKD, ↓casein kinase II, ↓5-LOX, ↓VEGF, ↓IL-1, ↓IL-6, ↓IL-8, ↓AR, ↓PSA, ↓CYP1A1, ↓TypeII-Ptdlns-4kinase, ↓Cdc2-tyr15[a], ↑HO-1, ↑Nrf2, ↓endothelin-1
Guggulu (*Commiphora mukul*)	Guggulsterone	↓NF-κB, ↓IAP1, ↓XIAP, ↓Bfl-1/A1, ↓Bcl-2, ↓cFLIP, ↓survivin, ↓cyclin D1, ↓c-Myc, ↓MMP-9, ↓COX-2, ↓VEGF, ↓BAR, ↓CYP7A1, ↓FXR, ↑CYP3A, ↓Cyp2b10
Pinecone ginger (*Zingiber zerumbet*)	Zerumbone	↓NF-κB, ↓IAP1, ↓XIAP, ↓Bfl-1/A1, ↓Bcl-2, ↓cFLIP, ↓survivin, ↓cyclin D1, ↓c-Myc, ↓MMP-9, ↓COX-2, ↓TRAF1
Aloe (*Aloe vera*)	Emodin	↓NF-κB, ↑HER-2/neu, ↑caspase-3, ↓AR, ↓MMP-9, ↑CYP1A1, ↑CYP1B1
Boswellia (Salai guggul) (*Boswellia serrata*)	Boswellic acids	↓NF-κB, ↑p42 MAPK, ↑p38 MAPK, ↓5-LOX, ↓survivin, ↓cyclin D1, ↓Bcl-2, ↓Bcl-xL, ↓CIAP
Cruciferous vegetables (*Brassica* sp.)	Sulforaphane, indole-3-carbinol	↓NF-κB, ↓survivin, ↓cyclin D1, ↓Bcl-2, ↓Bcl-xL, ↓CIAP ↓Cdc25, ↓Cdk1, ↓Bcl-2, ↓Bcl-xL
Quince (*Cydonia oblonga*)	Caffeoylquinic acids	↓IFN-γ, ↓IL-2, ↓ERK1/2, ↓AKT[a], ↓NF-κB, ↓NO, ↓iNOS
Rohitukine (*Dysoxylum binectrariferum*)	Flavopiridol	↓NF-κB, ↓COX-2, ↓cyclin D1, ↓MMP-9, ↓Bcl2
Coriander (*Coriandrum sativum*)	Linalool, monoterpenes	↓NF-κB, ↓AP-1, ↓JNK, ↓MAPK
Sweet Fennel (*Foeniculum vulgare*)	Anethole	↓NF-κB, ↓AP-1, ↓JNK, ↓MAPK
Ashwagandha (*Withania somnifera*)	Withonalides	↓NF-κB, ↓COX-2, ↓cyclin D1, ↓MMP-9, ↓survivin, ↓cyclin E, ↓Bcl-2, ↓Bcl-xL, ↓CIAP
Pomegranate (*Punica granatum*)	Ellagic acid	↓NF-κB, ↓COX-2, ↓cyclin D1, ↓MMP-9, ↓PDGF, ↓VEGF, ↑p21/WAF1, ↑p53
Soyabean (*Glycine max*)	Genistein	↓NF-κB, ↑caspase-12, ↑p21/WAF1, ↑glutathione peroxidase
Basil (*Ocimum sanctum*)	Ursolic acid	↓NF-κB, ↓COX-2, ↓cyclin D1, ↓MMP-9
Parthenium (*Tanacetum parthenium*)	Sesqiterpene lactones, parthenolides	↓NF-κB, ↑p53, ↑reactive oxygen species
Prunes and plums	Ursolic acid, oleanolic acid, triterpenoids	↓NF-κB, ↓COX-2, ↓cyclin D1, ↓MMP-9
Oleander (*Nerium oleander*)	Oleandrin	↓NF-κB, ↓AP-1, ↓JNK, ↓COX-2, ↓cyclin D1, ↓MMP-9
Tea (*Camellia sinensis*)	Flavonoids, catechins	↓NF-κB, ↓AP-1, ↓JNK, ↓COX-2, ↓cyclin D1, ↓MMP-9, ↑HO-1, ↓IL-6, ↓VEGF, ↓IGF, ↑p53, ↓Bcl-2, ↑p21/WAF1
Silymarin (*Silybum marianum* L.)	Silybinin	↓NF-κB, ↓AP-1, ↓JNK, ↓COX-2, ↓cyclin D1, ↓MMP-9
Citrus fruits, apple (*Citrus* sp.)	Quercetin	↓NF-κB, ↑Bax, ↓ Bcl-2, ↓cyclin D1, ↑caspase, ↑PARP, ↑Gadd 45
Red chilli (*Capsicum annum*)	Capsaicin	↓NF-κB, ↓survivin, ↓cyclin D1, ↓Bcl-2, ↓Bcl-xL, ↓CIAP, ↓Cdc25, ↓Cdk1, ↓Bcl-2, ↓Bcl-xL
Cloves (*Eugenia caryophyllus*)	Eugenol, isoeugenol	↓NF-κB
Cardamon (*Elettaria cardamomum*)	Limonene	↓COX-2, ↓iNOS
Ginger (*Zingiber officinale*)	Gingerol, paradol	↓TNF, ↓NF-κB, ↓AP-1, ↓COX-2, ↓ODC, ↓iNOS, ↓p38MAPK, ↓HIF, ↓VEGF, ↑caspase-3, ↓Bcl2
Galanga (*Alpinia officinarum*)	Yakuchinone A&B	↓COX2, ↓ iNOS, ↓NF-κB, ↓adhesion molecules, ↓TNF, ↓AP-1, ↓5-HETE
Kokum (*Garcinia indica*)	Garcinol	↓NF-κB, ↓COX-2, ↓iNOS, ↓HAT
Licorice (*Glycyrrhiza echinata*)	Dibenzoylmethane	↓COX2, ↓ LOX, ↓HIF, ↓VEGF

References, please visit Pub Med (http://www.ncbi.nih.gov/entrez/query.fcgi). NF-κB, nuclear factor kappa B; NO, nitric oxide; PGE, prostaglandin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; IL, interleukin; MAP, mitogen-activated protein; TNF, tumor necrosis factor; BAR, bile acid receptor; FXR, farnesoid X receptor; CYP7A1, cholesterol 7alpha-hydroxylase; CYP, cytochrome p450; HO, heme oxygenase; Nrf, NF-E2-related factor; Ptdlns, phosphatidylinositol; IAP, inhibitor-of-apoptosis protein; PKC, protein kinase C; PKD, protein kinase D; LOX, lipoxygenase; VEGF, vascular endothelial growth factor; AR, androgen receptor; PSA, prostate-specific antigen; ICAM, intercellular cell adhesion molecules; TF, tissue factor; MDR, multidrug resistance; Ftase, farnesyl-protein transferase; GST, glutathione S-transferase; GST-px, glutathione peroxidase; XOD, xanthine oxidase; TNF, tumor necrosis factor; MMP, matrix metalloprotease; STAT, signal transducers and activators of transcription.

[a] Indicates phosphorylation.

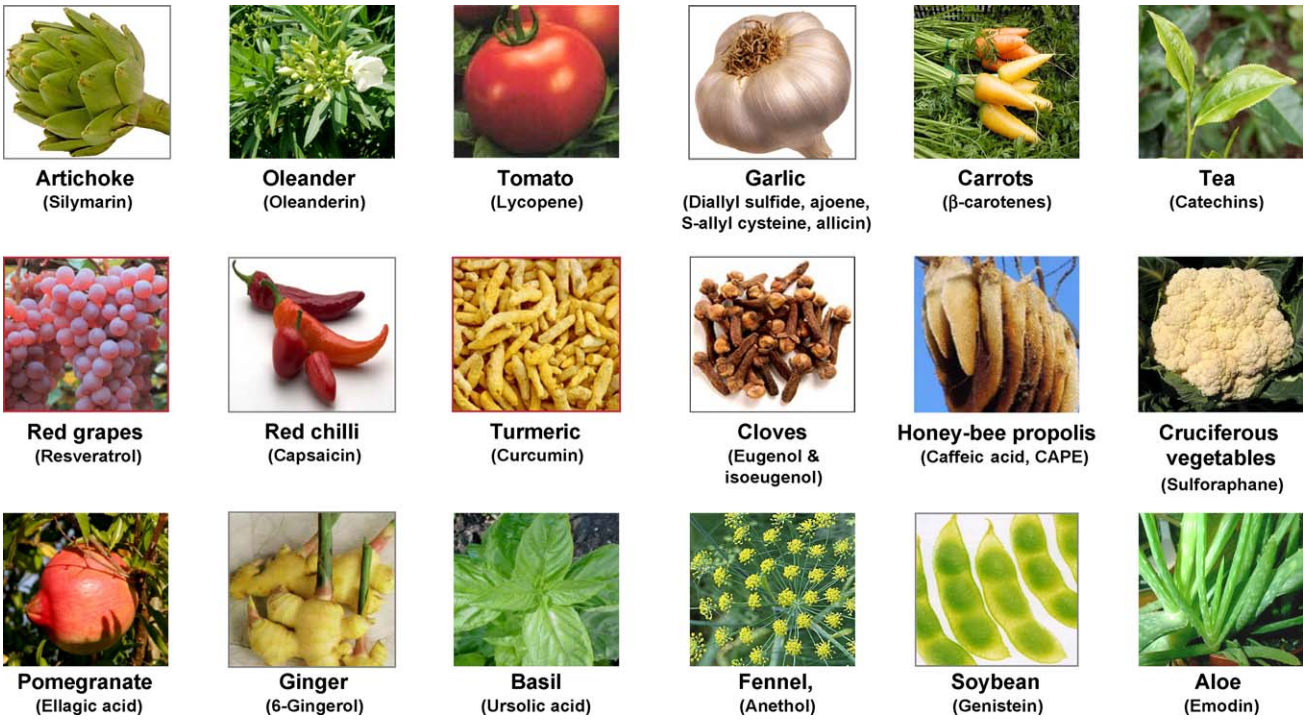


Fig. 1 – Dietary agents with anti-cancer properties.

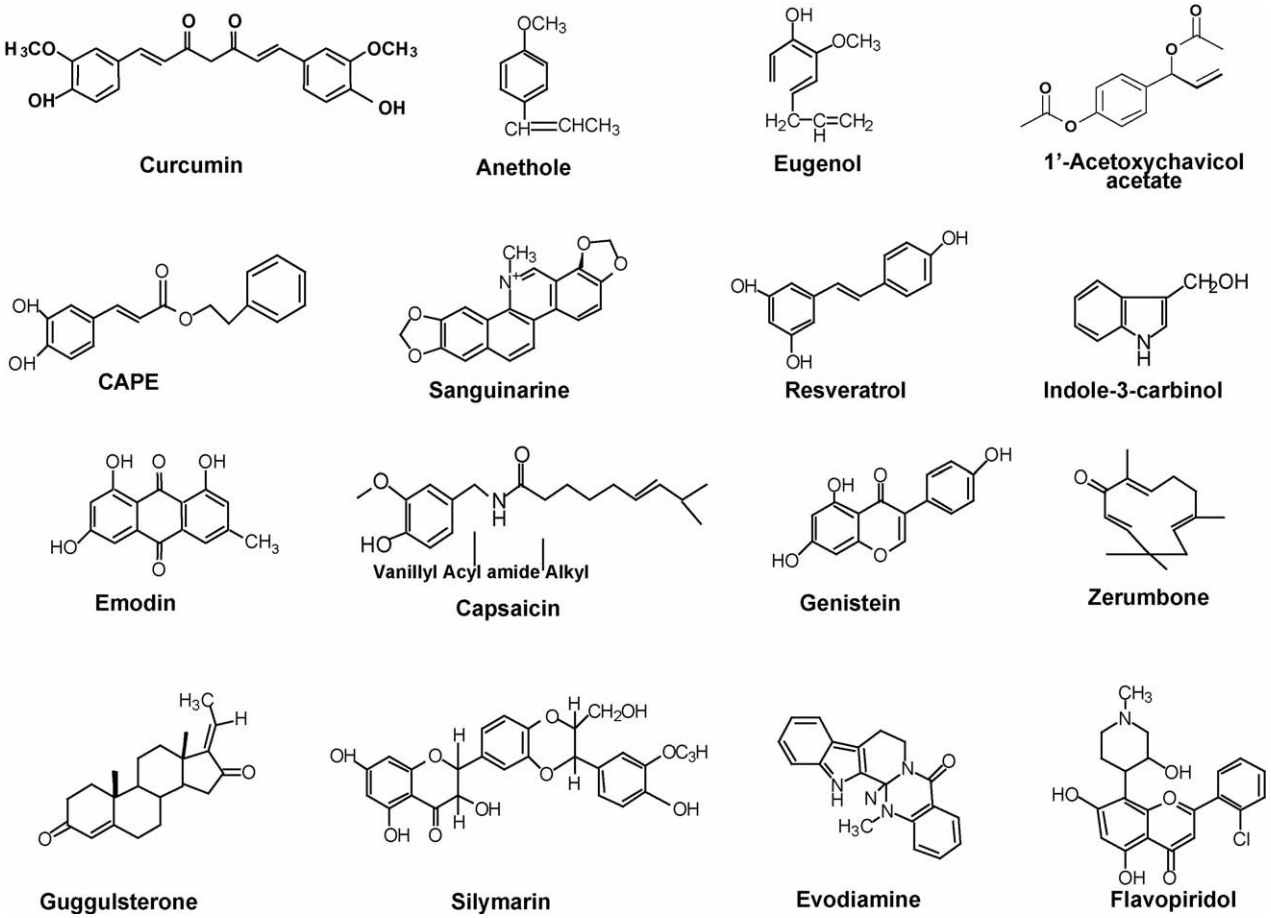
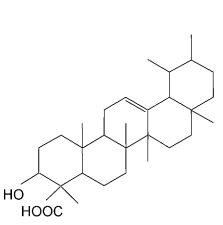
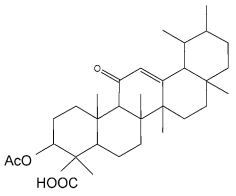


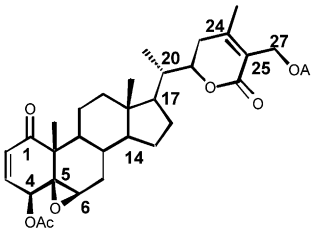
Fig. 2 – Chemical structures of dietary compounds.



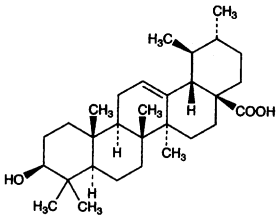
beta-boswellic acid (BA)



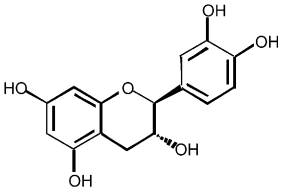
Acetyl-11-keto-b-boswellic acid (AKBA)



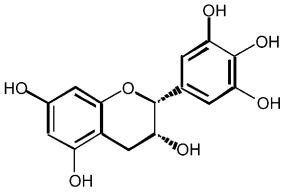
Withanolide



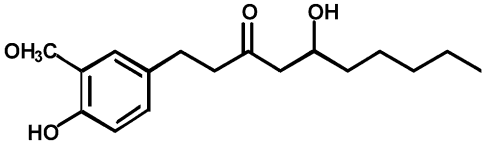
Ursolic acid



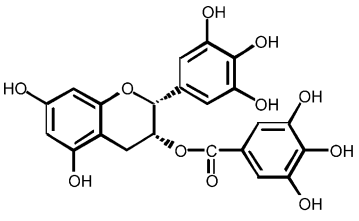
(-)-Catechin



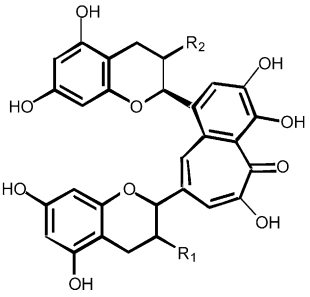
(-)-Epigallocatechin



[6]-Gingerol



(-)-Epigallocatechin-3-gallate



	R_1	R_2
Theaflavin	OH	OH
Theaflavin-3-gallate	Gallate	OH
Theaflavin-3'-gallate	OH	Gallate
Theaflavin-3,3'-digallate	Gallate	Gallate

Fig. 2. (Continued).

myeloid (U-937), lymphoid (Jurkat) and epithelial (HeLa and H4) cells. The molecule also blocked NF-κB activation induced by various carcinogens and tumor promoters including PMA, LPS, H_2O_2, okadaic acid, and ceramide [16]. Caffeic acid phenethyl ester (CAPE) has been shown to suppress NF-κB activation by suppressing the binding of p50–p65 complex directly to the DNA [32], whereas both sanguinarine and emodin act by blocking the degradation of IκBα. The alkaloid sanguinarine can prevent phosphorylation and degradation of IκBα in response to TNFα, phorbol ester, IL-1 or okadaic acid stimulation [33]. Similar to sanguinarine, emodin inhibits TNF-dependent IκBα degradation [20]. Based on its ability to inhibit other kinases, emodin may act directly on the IKK complex to block phosphorylation of IκBα. Yang et al. found that the green tea polyphenol, EGCG, suppresses NF-κB activation by inhibiting IKK activity [27], as do various other chemopreventive dietary agents. Some act by suppressing IκBα degradation and p65 translocation or NF-κB–DNA binding activity. Thus, one of the probable mechanisms by which dietary agents exercise their anti-tumor properties is through the suppression of the NF-κB signaling pathway.

2.2. *Activator protein-1 (AP-1)*

AP-1 was originally identified by its binding to a DNA sequence in the SV40 enhancer [34]. This complex consists of either homo- or heterodimers of the members of the JUN and FOS family of proteins [35]. Many stimuli, most notably serum, growth factors, and oncoproteins, are potent inducers of AP-1 activity; it is also induced by TNF and Interleukin 1 (IL-1), as well as by a variety of environmental stresses, such as UV radiation [35]. AP-1 activation is linked to growth regulation, cell transformation, inflammation, and innate immune response. AP-1 has been implicated in regulation of genes involved in apoptosis and proliferation and may promote cell proliferation by activating the *cyclin D1* gene, and repressing tumor-suppressor genes, such as p53, p21cip1/waf1 and p16. Most important, AP-1 can promote the transition of tumor cells from an epithelial to mesenchymal morphology, which is one of the early steps in tumor metastasis. Expression of genes such as MMP and uPA especially promotes angiogenesis and invasive growth of cancer cells. These oncogenic properties of AP-1 are primarily dictated by the dimer composition of the AP-1 family proteins and their post-transcriptional and translational modifications [35].

Several phytochemicals such as green tea catechins [36], quercetin [37], resveratrol [16], curcumin [38,39], capsaicin [40], oleandrin [41], anethole [26], and beta-lapachone, [42] have been shown to suppress the AP-1 activation process. EGCG and theaflavins inhibit TPA- and epidermal growth factor-induced transformation of JB6 mouse epidermal cells [36]. This finding correlates with the inhibition of AP-1 DNA binding and transcriptional activity. The inhibition of AP-1 activity by

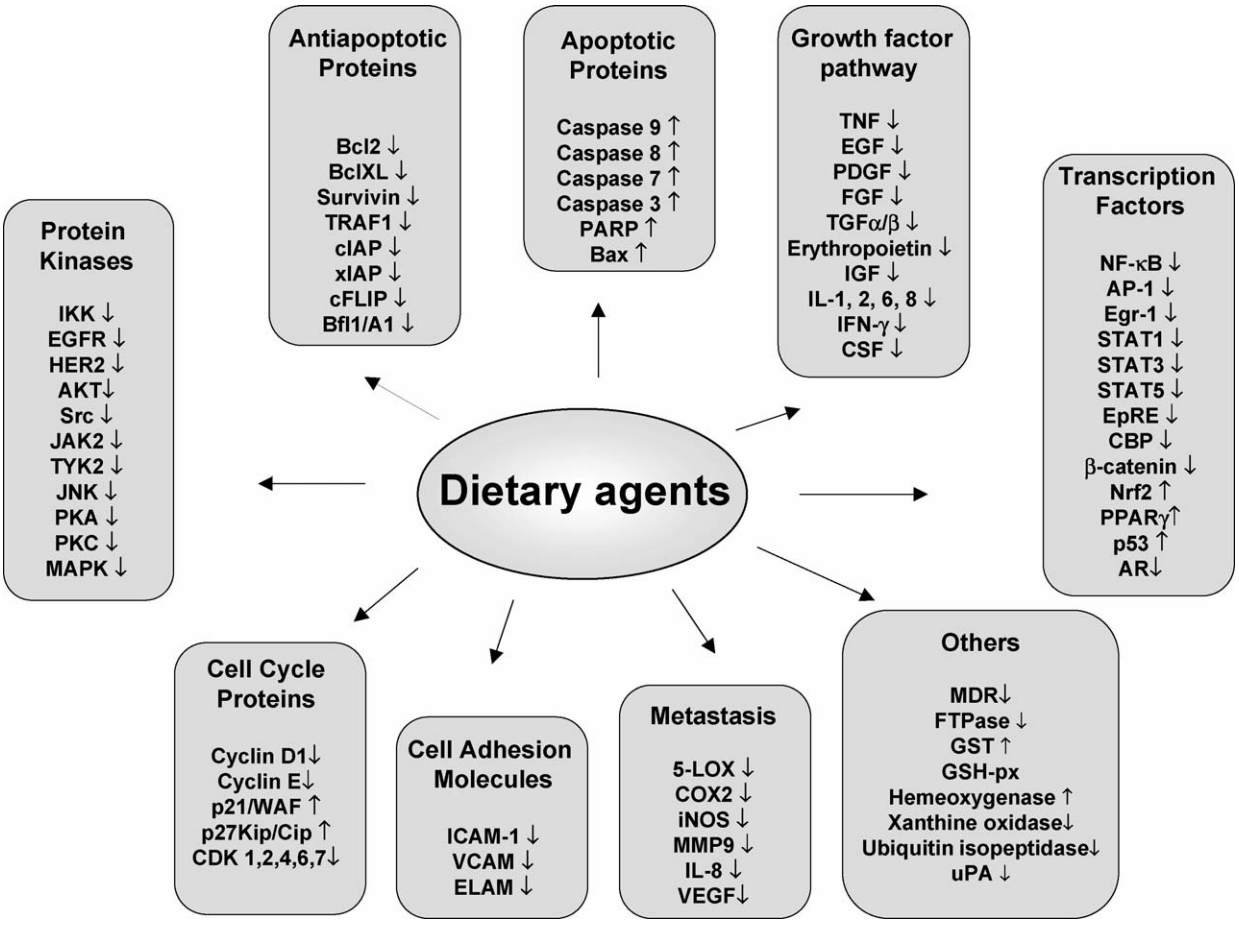


Fig. 3 – Molecular targets of dietary agents.

EGCG was associated with inhibition of JNK activation but not ERK activation. Interestingly, in another study where EGCG blocked the UVB-induced c-Fos activation in a human keratinocyte cell line HaCaT [43], inhibition of p38 activation was suggested as the major mechanism underlying the effects of EGCG. The role of MAPK pathways in the regulation of AP-1 activity by EGCG has been further investigated [44]. Treatment of Ha-ras-transformed human bronchial cells with EGCG has been shown to inhibit c-Jun and ERK1/2 phosphorylation as well as the phosphorylation of ELK1 and MEK1/2 [45]. In contrast to these reports, EGCG has been shown to markedly increase AP-1 factor-associated responses through a MAPK signaling mechanism in normal human keratinocytes, suggesting that the signaling mechanism of EGCG action could be markedly different in different cell types [46]. Lagarrigue et al. showed that the flavonoid quercetin could inhibit the transformation of the rat liver epithelial cell line overexpressing c-Fos, suggesting that regulation of c-Fos/AP-1 complexes might be involved in the antitransforming mechanism of quercetin [37]. Pretreatment of RAW 264.7 macrophages with quercetin blocked LPS-induced TNF transcription. This effect of quercetin was mediated by inhibiting the phosphorylation and activation of JNK/stress-activated protein kinase, by suppressing AP-1 DNA binding, and by down-regulating TNF transcription [47].

Resveratrol has been shown to inhibit the activity of AP-1 as demonstrated by several studies. We have found that resveratrol inhibits TNF-dependent AP-1 activation in U-937 cells, and that pretreatment with resveratrol strongly attenuates TNF-activated JNK and MEK kinases [16]. Curcumin has been shown to suppress the activation of TPA-induced AP-1 in HL-60 cells and Raji cells [38,39]. Curcumin treatment also suppresses constitutive AP-1 activity in the prostate cancer cell lines LNCaP, PC-3, and DU145 [48,49]. Inhibition of AP-1 transcriptional activity by curcumin also correlated with inhibition of Lewis lung carcinoma invasion in an orthotopic implantation model [50]. More recently, curcumin was reported to suppress LPS-induced cyclooxygenase-2 gene expression by inhibiting AP-1 DNA binding in BV2 microglial cells [51]. These results suggest that chemopreventive agents specifically targeting AP-1 or its activating kinases could be promising agents for the treatment of several cancers.

2.3. *Cell cycle*

Several proteins are known to regulate the timing of the events in the cell cycle. The loss of this regulation is the hallmark of cancer. Major control switches of the cell cycle are the cyclins and the cyclin-dependent kinases. Cyclin D1, a component subunit of cyclin-dependent kinase (Cdk)-4 and Cdk6, is a

Table 2 – Natural products from plants that inhibit NF-κB activation pathway

Compound	Source	Botanical name
Polyphenols		
Apigenin	Plant seeds and vegetables	*Scutellaria* spp. (include in Chinese herbal mixture, PCSPES, Huang-Qi; Qingkailing; Shuanghuanglian, etc.); *Cirisium* spp.; *Crotalaria* spp.; *Quercus nutgall*; *Matricaria recutita*; *Saussurea medusa*; *Lantana montevidensis* Briq.
Baicalein and its derivatives (includes baicalein, wogonin 6-methoxy-baicalein)	Skullcap	*Scutellaria* spp. (include in Chinese herbal mixture, PCSPES, Huang-Qi; Qingkailing; Shuanghuanglian, etc.); *Scutellaria lateriflora* L.
Blueberry and berry mix	Blueberry, black currant, raspberry, strawberry Eggpl	*Rubus* spp.; *Vaccinum* spp.; *Vaccinium corymbosum* L.; *Vaccinium myrtillus*; *Fragaria ananassal*; *Solanum melongena*
Bakuchiol (drupanol)		*Psoralea corylifolia*
Cannabinol		*Cannabis* spp.
Capsaicinoids (include capsaicin and analogues)	Pepper, red chilli	*Capsaicum* spp.; *Euphorbia* spp.; *C. annum*; *C. frutens*
Carnosol	Rosemary	*Rosmarinus officinalis*
Catechin and theaflavins (include (−)-epicatechin, 3-epicatechin-3-gallate)	Green and black teas, berries, spotted knapweed, shea, cocoa, carob, grape	*C. sinensis*; *Centarea maculosa* Lam; *Vitellaria paradoxa*; *Theobroma cacao*; *Polygonum cuspidatum*
Ellagic acid	Avocado, red berries, grapes, strawberries, raspberries	*Perxea americana*; *P. mill*; *Physalis polygonum*; *Cuspidatum* root; *F. ananassa*; *Rubus idaeus*
Emodin	Aloe vera, cassia obtusifolia, kidachi aloe	*Polygonum* spp.; *Cassia obtusifolia* Moghat; *Glossostemon bruguieri*; *Rheum* spp.; *Rhubarb*; *Astertataricus*; *Radix rhei*; *Hovenia aceae*; *Polygonum emodin*; *Leguminosae*; *Aloe arborescens* var.
Gallic acid	Guava, geraniaceae	*Psidium guajava*; *L. rodium glaucophyllum*; *Melaleuca quinquenervia*
Genistein	Soybeans, chickpea, kudzu root	*Pueraria labata radix*; *Cicer arietinum*; *Desmodium uncinatum*; *G. max*
Kaempferol	Tomato	*Lycopersicon esculentum*; *Ginkgo biloba*
Luteolin	Tea, fruits and vegetables	*Scutellaria* spp.
Purpurogallin	Black tea	*Piper nigrum*; *Quercus* sp. nutgall
Rocaglamides		*Aglaia* spp.
Sanggenon C	Mulberry	*Morus* spp.
Silymarin (includes silybin, silibinin, silidian, silychrist)	Milk thistle, artichokes, wild artichokes	*Cynara scolymus*; *S. marianum*
Yakuchinones A and B		*Alpinia oxyphylla*
Terpenes		
Anethol and analogues (eugenol, bis-eugenol, isoeugenol, anetholdithiolthione)	Broccoli, anise, cloves cashew	*Brassica oleracea italica*; *Illicum verum*; *Ocimum selloi*; *Benth syzygium aromaticum*; *Anacardium occidentale*; *Hibiscus sabdariffa*
Artemisinin extract (Qinghaosu)		*Artemisia annua*
Avicins (include avicins D and G)		*Acasia victoriae*
Azadirachtin	Neem tree	*Azadirachta indica* A.
β-Carotene	Carrot, citrus fruits, pumpkin	*Daucus carota sativus*; *Citrus unshiu marc*; *Curcurbita moschata*
β-Cryptoxanthin	Orange, berries	*Carcica papaya* L. Physalis
Betulinic acid	Birch tree, almond hulls	*Betula* spp.; *Betula alba*; *Quisqualis fructus*; *Coussarea paniculata*; *Alangium lamarckii*
G. biloba extract		*G. biloba*
Glycyrrhizin	Licorice root	*Glycyrrhiza glabra*; *Glycyrrhiza radix*; *Glycyrrhiza uralensis*
Limonene	Lemon, sweet orange, grapefruit	*Citrus limon*; *Citrus paradisi*; *Citrusaurantium*
Lutein	Tomato	*L. esculentum*
Lycopene	Tomato	*L. esculentum*
Parthenolide	Feverfew	*T. parthenium* and *T. larvatum*; *Michelia champaca*; *Talauma ovat*; *Magnolia grandiflora*; *Artemisia myriantha*

Table 2 (*Continued*)

Compound	Source	Botanical name
Ursolic acid	Basil, salvia, rosemary, berries	*Rosemainus officinalis*; *O. sanctum*; *Aronia melanocarpa*; *Oxycoccus quadripetalus*; *Origanum majorana*; *Diospyros melanoxylon*; *Salvia przewalskii* Maxim
Withanolides		*Withania sominifera*
Alkaloids		
Conophylline		*Tabernaemontana* spp.; *Ervatamia microphylla*
Cucurbitacin	Cucurbitaceae	*Cucurbita andreana*; *Trichosanthes kirilowii*; *Elaeocarpus mastersii*
Higenamine	Ranunculaceae, lianas	*Aconitum japonicum*; *Argemone mexicana*; *Gnetum parvifolium*
Mahanimbine	Rutaceous	*Murraya koenigii*; *Clausena dunniana*; *Murraya siamensis*
Mahanine	Rutaceous	*M. koenigii*; *Micromelum minutum*
Morphine and its analogues (include KT 90 and sanguinarine)		*Rapaver* spp.; *Opium poppy*
Piperine	Black pepper	*Garcinia xanthochymu*; *Piper longum*
Flavonoids		
Cirsimaritin	Basil, sage, rosemary	*O. sanctum*; *Salvia officinalis*; *Rosemaribus officinalis*
Flavopiridol		*Dysoxylum binectariferum*
Hesperidine	Oranges	*Gamellia sinensis* O.Ktze.
Morin	Almond	*P. guajava* L.; *Prunus dulcis* (Mill.)
Nobiletin	Citrus	*C. u. marc*
Pycnogenol	Citrus fruit	*Citrus retirulata*; *Pinus maritima*
Persenone A	Tomato, avocado	*L. esculentum*; *Persea americana* P. Mil
Phenolics		
Ethyl gallate	Grapes, tea, red maple	*Paeonia* spp.; *Sophora japonica*; *Acerrubrum*; *Haematoxylon campechianum*; *V. vinifera*; *V. paradoxa*; *Camellia senensis*
Gingerol	Ginger	*Z. officinale* Roscoe
Morellin	Indica fruit	*Garcinia purpurea*; *Garcinia hanburyi*
Rosemarinic acid	Rosemary, sage	*R. officinalis*; *Saliva officinalis*
Others		
Allicin (allyl-thiosulfinate)	Garlic	*Allium sativum*
Allixin (phytoalexin)	Garlic	*A. sativum* Linn
Aucubin (iridoid glycoside)	Algae	*Eucommia* spp.; *Veronica* spp.; *Vitex* spp.; *Globularia* spp.
Calagualine (saponin)		*Polypodium* spp.
CAPE (caffeic acid phenethyl ester)	Honey bee propolis	*Apis mellifera capensis*
Diallyl sulfide	Garlic, Chinese leek	*A. sativum*
Flavokavine	Kava kava	*Piper methysticum*
Garcinol and its analogue (polyisoprenylated benzophenone)	Indica fruit, African plant	*A. sativum* Linn; *Garcinia huillensis*; *G. purpurea*
Indole-3-carbinol (indole)	Onions, cabbage, Brassicaceae	*Allium cepa*; *B. o. capita*; *Brassica genus*
Lapachone (benzo[*a*]phenazine)	Indian ginseng, lapacha tree, trunkwood	*Tabebuia avellanedae* genus; *Tabebuia heptaphylla*
Plumbagin (naphthoquinone)		*Plumbago zeylanica*
Resveratrol and analogues e.g. picetannol (stilbene)	Grapes, cranberries, etc.	*P. cuspidatum*; *Veratrum* spp.
Rotenone (benzopyranone)		*Derris* spp.
Sulforaphane (glucosinolate)	Broccoli, cauliflower	*B. o. italica*; *B. o. italica*
1′-Acetoxychavicol acetate	Ginger family	*Languas galanga*
α-Lipoic acid	Asparagus, wheat, potato	
Aged garlic extract; garlic	Garlic	*A. sativum*
Cirsilineol	Basil, Verbenaceae, thyme	*O. sanctum*; *L. montevidensis* Briq.; *Thymus vulgaris*
Isothymonin	Basil	*O. sanctum*
Trans-asarone	Carrot	*Daucus carota* L.
S-Allylcysteine	Allium	*A. sativum*
Procyanidin	Apple, grape, pear	*Braeburn cultivar*; *Vitis vinfera* L.; *Prunus perisicol*
Vitamin C	Fruits and vegetables	
Vitamin E	Plant seeds and vegetables	

rate-limiting factor in progression of cells through the first gap (G1) phase of the cell cycle [52]. Dysregulation of the cell cycle check points and overexpression of growth-promoting cell cycle factors such as cyclin D1 and cyclin-dependent kinases (CDK) are associated with tumorigenesis [53]. Several dietary agents including curcumin [54], resveratrol [55], genistein [56], dietary isothiocyanates [57], apigenin [58], and silibinin [59] have been shown to block the deregulated cell cycle in cancers.

Cyclin D1 has been shown to be overexpressed in many cancers including breast, esophagus, head and neck, and prostate [60–64]. Curcumin has been shown to inhibit progression of the cell cycle by down-regulating the expression of cyclin D1 at the transcriptional and posttranscriptional level [54,65]. Cyclin D1 expression is regulated by NF-κB, and suppression of NF-κB activity by curcumin in multiple myeloma cells led to a down regulation of cyclin D1 [65]. This resulted in a decrease in the formation of cyclin D1/Cdk4 holoenzyme complex, resulting in suppression of proliferation and induction of apoptosis. In another study, curcumin induced G0/G1 and/or G2/M phase cell cycle arrest, up-regulated Cdk inhibitors such as p21/Cip1/waf1, and p27Kip1, and down-regulated cyclin B1 and Cdc2 [66]. Chaudhary and Hruska recently reported that curcumin reversibly inhibits normal mammary epithelial cell cycle progression by down-regulating cyclin D1 expression and blocking its association with Cdk4/Cdk6 as well as by inhibiting phosphorylation and inactivation of retinoblastoma protein [67].

Numerous reports indicate that resveratrol inhibits proliferation of cells by inhibiting cell-cycle progression at different stages of the cell cycle [55,68–70]. Wolter et al. showed the down-regulation of the cyclin D1/Cdk4 complex by resveratrol in colon cancer cell lines [71]. However, resveratrol-induced G2 arrest through the inhibition of Cdk7 and Cdc2 kinases in colon carcinoma HT-29 cells [70]. Similarly, the green tea component EGCG causes cell cycle arrest and promotes apoptosis via a dose- and time-dependent up-regulation of p21/Cip1/Waf1, p27Kip1, and p16/INK4A, and down-regulation of proteins such as cyclin D1, cyclin E, Cdk2, and Cdk4 [72].

Genistein induced apoptosis and G2 arrest and inhibited proliferation in a variety of human cancer cell lines, regardless of p53 status [56]. Six dietary isothiocyanates (ITCs) from cruciferous vegetables, allyl-ITC, benzyl-ITC, phenethyl-ITC, sulforaphane, erucin, and iberin, were examined for their effects on cell cycle progression in multidrug-resistant HL60/ADR (MRP-1-positive) and HL60/VCR (Pgp-1-positive) cells. All the ITCs induced time- and dose-dependent G2/M arrest, with the allyl-ITC being most effective [57]. The dietary flavonoid apigenin induces G2/M phase arrest in two p53-mutant cancer cell lines, HT-29 and MG63, in parallel with a marked increase in the production of p21/WAF1 [58].

Dietary agents also synergize with chemotherapeutic drugs, thereby reducing the toxicity of chemotherapeutic drugs. Silibinin strongly synergized the growth-inhibitory effect of doxorubicin in prostate carcinoma DU145 cells that was associated with a strong G2/M arrest in cell cycle progression. The underlying mechanism of G2/M arrest showed a strong inhibitory effect of the combination on Cdc25c, Cdc2/p34, and cyclin B1 protein expression and Cdc2/p34 kinase activity [59].

2.4. *Apoptosis*

Apoptosis helps to establish a natural balance between cell death and cell renewal in mature animals by destroying excess, damaged, or abnormal cells. However, the balance between survival and apoptosis often tips towards the former in cancer cells. Several reports published within the last decade showed that activation of NF-κB promotes cell survival and proliferation and down-regulation of NF-κB sensitizes the cells to apoptosis induction [14]. Expression of several NF-κB-regulated genes including Bcl-2, Bcl-XL, cIAP, survivin, TRAF1, and TRAF2 have been reported to function primarily by blocking the apoptosis pathway [14]. Several phytochemicals that are known to inhibit NF-κB or AP-1 activation can significantly suppress cell proliferation and sensitize cells to apoptosis induction [73,74].

Most notably, phytochemicals such as curcumin, resveratrol, guggulsterone, flavopiridol, betulinic acid, ursolic acid, indole-3-carbinol, zerumbone, evodiamine, and green tea polyphenols are also known to down-regulate the expression of apoptosis suppressor proteins, such as Bcl-2 and Bcl-X_L, in several cancer cell lines. We have found that curcumin induces apoptosis through mitochondrial pathway involving caspase-8, BID cleavage, cytochrome *c* release, and caspase-3 activation. Our results also suggest that Bcl-2 and Bcl-X_L are critical negative regulators of curcumin-induced apoptosis [75]. Curcumin suppresses the constitutive expression of Bcl-2 and Bcl-X_L in mantle cell lymphoma [76] and multiple myeloma [65] cell lines. Curcumin also activates caspase-7 and caspase-9 and induced polyadenosine-5′-diphosphate-ribose polymerase (PARP) cleavage in both cell lines.

Numerous studies continue to report that resveratrol exerts its anti-cancer effects by causing cell cycle arrest and inducing apoptosis in many different human cancers (for references see [77]). These include colon adenocarcinoma cells (Caco-2), esophageal carcinoma cells, medulloblastoma cells, the highly invasive and metastatic breast cancer cell line MDA-MB-231, melanoma cells, pancreatic carcinoma cells, esophageal adenocarcinoma cells (Seg-1 and Bic-1), human esophageal squamous carcinoma cells (HCE7), human colon carcinoma cells (SW480), human breast carcinoma cells, numerous human leukemia cell lines, and lung cancer cells. Resveratrol induction of apoptosis has repeatedly been reported to be accompanied by increased caspase activity, cell cycle arrest in the G1 phase, or inhibition of cell cycle progression from S to G2 phase, decreased protein levels of cyclin D1 and cyclin-dependent kinase (Cdk)-4, decreased Bcl-2 and Bcl-XL levels, and increased Bax levels and induction of the Cdk inhibitor p21WAF1/CIP.

The pregnadienedione steroid, guggulsterone induced apoptosis in acute myeloid leukemia cell lines and primary leukemic blast cells in culture [78]. Guggulsterone induced externalization of phosphatidylserine and loss of mitochondrial membrane potential in AML cells. EGCG treatment of human colorectal carcinoma HT-29 cells resulted in classic signs of apoptosis including nuclear condensation, DNA fragmentation, caspase activation, disruption of mitochondrial membrane potential and cytochrome *c* release, which all appeared to be mediated by the JNKs pathway [79]. In human prostate carcinoma LNCaP cells, treatment with EGCG induced

apoptosis and was associated with stabilization of p53 and also with a down-regulation of NF-κB activity, resulting in a decreased expression of the anti-apoptotic protein Bcl-2 [80]. In liver cancer cells (HepG2), EGCG has been shown to induce apoptosis and block cell cycle progression at G1 [81]. These effects were accompanied by increased expression of p53 and p21/WAF1 proteins and proapoptotic Fas and Bax proteins [82].

Evidence suggests that ginger and other related compounds may act as chemopreventive agents by inducing apoptosis. Two structurally related compounds of the ginger family, 6-gingerol and 6-paradol, block EGF-induced cell transformation and both can induce apoptosis [83]. Another recent study showed that 6-paradol and other structurally related derivatives inhibit proliferation of oral squamous carcinoma cells and induce apoptosis through a caspase-3-dependent mechanism [84]. Exposure of Jurkat human T cell leukemia cells to various ginger constituents resulted in apoptosis mediated through the mitochondrial pathway [85]. Apoptosis was accompanied by a down-regulation of anti-apoptotic Bcl-2 protein and an enhancement of proapoptotic Bax expression, further supporting the idea that ginger compounds are potential anti-cancer agents.

2.5. *Cell survival kinase Akt*

The serine/threonine protein kinase Akt/PKB is the cellular homologue of the viral oncogene v-Akt and is activated by various growth and survival factors. In mammals, there are three known isoforms of the Akt kinase, Akt1, Akt2, and Akt3. Akt is activated by phospholipid binding and phosphorylation at Thr308 by PDK1 or at Ser473 by PDK2 [86]. Akt plays critical roles in mammalian cell survival signaling and has been shown to be activated in various cancers [87,88]. Activated Akt promotes cell survival by activating the NF-κB signaling pathway [89,90] and by inhibiting apoptosis through inactivation of several proapoptotic factors including Bad, Forkhead transcription factors, and caspase-9 [91–93]. This kinase has also been considered an attractive target for cancer prevention and treatment. Several phytochemicals including genistein [94], indole-3-carbinol [95], diosgenin [30], curcuminoids [96], EGCG [97] and black raspberries [98] are known to suppress the activation of Akt.

Li and Sarkar found that genistein inhibited both Akt and NF-κB pathways in prostate cancer cell lines [94]. Genistein pretreatment also abrogated the activation of Akt by EGF, thus inhibiting the NF-κB pathway. Down-regulation of NF-κB and Akt signaling pathways by genistein may be one of the molecular mechanisms by which genistein inhibits cancer cell growth and induces apoptosis. Chinni and Sarkar showed that indole-3-carbinol pretreatment also abrogated EGF-induced Akt activation [95]. Our laboratory has shown that diosgenin, a steroidal saponin present in fenugreek, suppresses TNF-induced activation of Akt [30].

We have found that curcuminoids down-regulate expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IκBα kinase and Akt activation [96]. Several reports by other investigators also suggest that curcumin has molecular targets within the Akt signaling pathways, and the inhibition of Akt activity may facilitate inhibition of proliferation and induction of apoptosis in cancer cells [99,100]. Curcumin completely inhibited Akt activation in the human prostate cancer cell lines LNCaP and PC-3, but not Du-145, suggesting that one way curcumin inhibits prostate cancer is via inhibition of Akt [67].

A recent report has shown that EGCG from green tea inhibits VEGF-induced angiogenesis in vitro through suppression of VE-cadherin phosphorylation and inactivation of Akt [97]. Masuda et al. also found that treatment with EGCG inhibited the constitutive activation of the Akt, EGFR, and Stat3 in both YCU-H891 head and neck squamous cell carcinoma and MDA-MB-231 breast carcinoma cell lines [101]. Black raspberries have also been shown to exert their chemopreventive activity through the inhibition of the PI-3K/Akt/AP-1/VEGF pathway [98]. Thus, these studies provide evidence to suggest targeting of the Akt pathway with specific dietary agents in order to suppress the development of cancers.

2.6. *Tumor-suppressor gene p53*

p53 is a tumor-suppressor and transcription factor. It is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA-damage, genomic stability, cell cycle control, and apoptosis. The protein activates the transcription of downstream genes such as p21WAF1 and Bax to induce the apoptotic process, inhibiting the growth of cells with damaged DNA or cancer cells [102,103]. Mutant p53 loses its ability to bind DNA effectively, and as a consequence the p21 protein is not made available to regulate cell division. Thus cells divide uncontrollably and form tumors. Subjects with only one functional copy of the p53 gene are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. Beyond its effects in these early cancer syndromes, p53 mutants are found in most tumor types, where they contribute to the complex network of molecular events leading to tumor formation. Some of the dietary agents that are known to modulate p53 activity are curcumin [104], resveratrol [105], EGCG [72], indole-3-carbinol [106], and silibinin [107].

Curcumin is a powerful inhibitor of tumor cell proliferation. In B cells, it down-regulates the expression of the tumor-suppressor gene p53 as well as the survival genes egr-1, c-myc, and Bcl-X_L [104]. The dietary spice is known to induce apoptosis in eight melanoma cell lines, four with wild-type and four with mutant p53 without inducing additional expression of p53 [108]; however, in human breast cancer cells curcumin induces apoptosis through p53-dependent Bax induction [109,110]. Curcumin also inhibits cell cycle progression of immortalized human umbilical vein endothelial cells by up-regulating the cyclin-dependent kinase inhibitors, $p21^{WAF1/CIP1}$, $p27^{KIP1}$, and p53 [66]. In neuroblastoma, both curcumin and resveratrol up-regulate p53 expression and induce nuclear translocation of p53, followed by induction of $p21^{WAF1/CIP1}$ and Bax expression [111].

There are numerous reports about the effects of resveratrol on p53. Huang et al. found that resveratrol-induced apoptosis occurred only in cells expressing wild-type p53, not in p53-deficient cells [105]. These results demonstrated for the first time that resveratrol induces apoptosis through activation of p53 activity. Hsieh et al. showed that resveratrol inhibited

proliferation of pulmonary artery endothelial cells, which correlated with suppression of cell progression through the S- and G2-phases of the cell cycle and was accompanied by increased expression of p53 and elevation of the level of the Cdk inhibitor p21Cip1/WAF1 [69]. She et al. elucidated the potential signaling components underlying resveratrol-induced p53 activation and induction of apoptosis [112]. They found that, in the JB6 mouse epidermal cell line, resveratrol activated ERK1/2, JNK, and p38 MAPK and induced serine-15 phosphorylation of p53. Shih et al. also showed that resveratrol acted via a Ras-MAPK kinase-MAPK signal transduction pathway to increase p53 expression, serine phosphorylation of p53, and p53-dependent apoptosis in thyroid carcinoma cell lines [113]. Apoptosis and the expression of the non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1), a member of the TGFβ superfamily that has been associated with proapoptotic and antitumorigenic activities, is induced by resveratrol-induced NAG-1 expression through an increase in the expression of p53 [114].

EGCG treatment resulted in a dose-dependent increase of p53 in LNCaP cells (carrying wild-type p53), but not in DU145 cells (carrying mutant p53) [72]. EGCG induced stabilization of p53, which caused an up-regulation in its transcriptional activity, thereby resulting in the activation of its downstream targets such as p21WAF1 and Bax and the induction of apoptosis. In a human liver cancer cell line, EGCG also significantly increased the expression of p53 and p21WAF1 protein, and this contributed to cell cycle arrest [81]. Several studies examined the potential effects of I3C and DIM on the proliferation and induction of apoptosis in human prostate cancer cell lines with different p53 status. They found that induction of apoptosis by I3C was p53-independent [115], and induction of p21WAF1 expression by DIM was independent of estrogen-receptor signaling and p53 [106].

2.7. *Growth factors signaling pathways*

Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Some of the growth factors implicated in carcinogenesis are epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors (TGF)-α and -β, erythropoietin (Epo), insulin-like growth factor (IGF), interleukin (IL)-1, 2, 6, 8, tumor necrosis factor (TNF), interferon-γ (INF-γ) and colony-stimulating factors (CSFs). The potent cell proliferation signals generated by various growth factor receptors such as the EGF receptor, IGF-1 receptor, and VEGF-receptor networks constitute the basis for receptor-driven tumorigenicity in the progression of several cancers [116]. Abnormal growth factor signaling pathways lead to increased cell proliferation, suppression of apoptotic signals, and invasion contributing to metastasis.

Several chemopreventive phytochemicals including curcumin, genistein, resveratrol, and catechins have been shown to be potent inhibitors of several growth factor signaling pathways. Curcumin inhibits the ligand-stimulated activation of EGFR, indicating that it has the potential to break the autocrine loops that are established in several advanced cancers [117]. A blockade of EGFR may lead the cancer cells to enter apoptosis. Moreover, inhibition of EGFR abrogates the invasive potential of the cancer cells. Most of these chemopreventive chemicals function by inhibiting other tyrosine kinases such as c-Src that are involved in the coupling of activation of the G-protein-coupled receptor to the transactivation of EGFR, which occurs extensively in established cancers. The HER2/neu receptor is overexpressed in breast, prostate, ovarian and lung cancers. Curcumin has been shown to not only inhibit the tyrosine kinase activity of this receptor but also to deplete the protein itself, by interfering with the function of the ATP-dependent GRP94 chaperone protein, which is involved in the maintenance of the properly folded state of the receptor [118].

Resveratrol inhibited IL-6 production in cortical mixed glial cells under hypoxic/hypoglycemic conditions [119] and stimulated peritoneal macrophages of mice [120]. Shen et al. found that resveratrol suppressed IL-8 gene transcription in phorbol ester-treated human monocytic cells [121]. Resveratrol has also been shown to suppress proliferation of Ishikawa cells through down-regulation of EGF [122].

EGCG, the major component of green tea, suppresses the expression of IL-6 [123] and IL-8 [124] in vitro. VEGF has been implicated in angiogenesis, and EGCG has been shown to suppress the production of VEGF in swine granulosa cells [125] and breast carcinoma cells [126]. Tang et al. found out that green tea catechins inhibited VEGF-induced angiogenesis in vitro through suppression of VE-cadherin phosphorylation and inactivation of Akt [97]. EGCG blocks PDGF-induced proliferation and migration of rat pancreatic stellate cells [127]. Weber et al. found out that the plasma membrane incorporated EGCG or soluble EGCG directly interacts with PDGF-BB, thereby preventing specific receptor binding leading to the inhibitory effects of EGCG on platelet-derived growth factor-induced cell signaling and mitogenesis [128]. EGCG inhibits growth and activation of EGFR and human EGFR-2 signaling pathways in human colon cancer cells [129]. Sah et al. found that EGCG inhibits EGFR signaling pathway, most likely through the direct inhibition of ERK1/2 and Akt kinases [130]. Green tea also inhibits the expression of FGF [131], VCAM-1 [132], and HER-2/neu [133].

2.8. *Chemokines and metastasis*

Chemokines are small, chemotactic cytokines that direct migration of leukocytes, activate inflammatory responses, and participate in regulation of tumor growth. Thus agents that modulate chemokines could become important in the development of new anti-cancer therapies. Most chemokines are expressed in response to a stimulus, but some are constitutively expressed in a tissue-specific manner. Chemokines exert their migration-inducing properties on leukocytes through binding to chemokine receptors. Interleukin 8 (IL-8/CXCL8) was the first chemokine discovered to stimulate endothelial cell chemotaxis, proliferation, and in vivo angiogenesis [134]. Elevated levels of the angiogenic CXC chemokine IL-8 have been detected in a variety of tumors. The dietary agents curcumin [135], resveratrol [121], quercetin [136], green tea polyphenols [137], theaflavin [138], genistein [139], and capsaicin [140] have been shown to target the chemokines.

Curcumin is a potent anti-cancer agent that inhibits the production of proinflammatory chemokines, including IL-8, by tumor cells. Curcumin inhibited both IL-8 production and signal transduction through IL-8 receptors. It suppressed constitutive production of IL-8 in human pancreatic carcinoma cell lines and enhanced the expression of two IL-8 receptors, CXCR1 and CXCR2 [135]. Curcumin down-regulates the expression of MCP-1 [141] and interferon-inducible protein-10 kDa (IP-10) in mouse bone marrow stromal cell line by down-regulating the levels of MCP-1 and IP-10 mRNA expression by TNF, IL-1, and LPS. The suppressive effect of curcumin on both the chemokine mRNAs are reversible with complete recovery from suppression occurring within 24 h after removal of curcumin [142].

Resveratrol inhibits PMA-induced IL-8 production in U937 cells at both protein and mRNA levels. The suppression of IL-8 gene transcription by resveratrol is, at least partly, due to inhibition of AP-1 activation [121]. The bioflavonoid quercetin inhibits IL-1-induced transcriptional expression of MCP-1 in glomerular cells via suppression of NF-κB [136]. Soybean saponins also inhibit the release of PGE2, NO, TNF and MCP-1 in a dose-dependent manner in LPS-treated peritoneal macrophages. These anti-inflammatory properties of soybean saponins may be useful for suppressing tumor progression [143].

EGCG has been shown to suppress the production of chemokines and PGE_2 in colon epithelial cells. Treatment of TNF-stimulated HT29 cells with EGCG dose-dependently inhibited the synthesis of IL-8, MIP-3α, and PGE2 [137]. EGCG causes concentration-dependent suppression of the transient increase in cytokine-induced neutrophil chemoattractant (CINC)-1-induced intracellular free calcium level in both rat neutrophils and rat CXC chemokine receptor 2 (CXCR2)-transfected HEK 293 cells. EGCG also inhibits CINC-1 production by IL-1beta-stimulated rat fibroblasts (NRK-49F cells) and lipopolysaccharide-stimulated rat macrophages [144]. The black tea polyphenol, theaflavin, inhibits TNF-mediated interleukin-8 gene expression, most likely through the suppression of interleukin-8 transcription and, in part, by inhibition of IKK and AP-1 pathways [138].

Genistein, the major isoflavone inhibits collagen-induced platelet aggregation, NO production by macrophages, and secretion of MCP-1, ICAM-1 and VCAM-1 [139]. Another polyphenol, capsaicin has been shown to inhibit constitutive as well as IL-1β-induced and TNF-induced IL-8 expression in melanoma cells through the suppression of NF-κB [140]. Thus, the tumor-promoting chemokines are another very important target of dietary agents.

2.9. *Tumor necrosis factor (TNF)*

Tumor necrosis factor (TNF), initially discovered as a result of its antitumor activity, has now been shown to mediate tumor initiation, promotion, and metastasis (for references see [145]). In agreement with these observations, mice deficient in TNF have been shown to be resistant to skin carcinogenesis [146]. The induction of proinflammatory genes by TNF has been linked to most diseases. The proinflammatory effects of TNF are primarily due to its ability to activate NF-κB. Almost all cell types, when exposed to TNF, activate NF-κB, leading to the expression of inflammatory genes. These include cyclooxygenase-2 (COX-2), lipoxygenase-2 (LOX-2), cell-adhesion molecules, inflammatory cytokines, chemokines, and inducible nitric oxide synthase (iNOS). TNF has been found to be a growth factor for most tumor cells [147]. These include ovarian cancer cells, cutaneous T cell lymphoma [148], glioblastoma [149], acute myelogenous leukemia [150], B cell lymphoma [151], breast carcinoma [152], renal cell carcinoma [153], multiple myeloma [154], and Hodgkin's lymphoma [155]. Various fibroblasts, including normal human fibroblasts, scleroderma fibroblasts, synovial fibroblasts, and periodontal fibroblasts, proliferate in response to TNF.

Because of the critical role of TNF in mediating tumorigenesis, agents that can suppress TNF activity have potential for therapy of TNF-linked diseases. Phytochemicals such as curcumin [76], green tea polyphenols [156], gingerol [157], resveratrol, kaempferol and apigenin [158] have been shown to suppress TNF production.

The constitutive activation of NF-κB in mantle cell lymphoma (MCL) cells is due to autocrine expression of TNF [76]. TNF mRNA is constitutively expressed in the MCL cell lines; curcumin inhibits the expression of both TNF mRNA and TNF protein in mantle cell lymphoma cell lines. Suppression of TNF by curcumin led to inhibition of NF-κB and cell proliferation, as was the case when TNF secretion was neutralized using anti-TNF antibody [76].

Green tea polyphenols are potent antioxidants that demonstrate both anti-cancer and anti-inflammatory effects. EGCG, the major green tea polyphenol, have been shown to down-regulate LPS-induced TNF production in a dose-dependent fashion [156]. Pungent vanillyl ketones, including [6]-gingerol and [6]-paradol from the rhizome of ginger, have been reported to possess a strong anti-inflammatory activity and suppress TNFα production in TPA-treated female ICR mice [157]. The dried rhizome of *Ligusticum chuanxiong* Hort. is a traditional Chinese medicine herb for the prevention and treatment of inflammatory and cardiovascular diseases. Two phthalide lactones from the herb, Z-ligustilide and senkyunolide A, have been identified as inhibitors of LPS-induced TNF mRNA production in monocytes [159]. Similarly, an aqueous acetone extract obtained from the pericarps of *Mallotus japonicus*, was observed to inhibit TNFα and interleukin-6 production by LPS-activated RAW 264.7 murine macrophage-like cell line [160].

Flavonoids have been reported to bring benefits in lowering inflammation and oxidative stress and exert positive effects in cancer and cardiovascular and chronic inflammatory diseases. Apigenin, kaempferol, and resveratrol, which are present in fruits, vegetables, and grains, exert inhibitory effects on the expression of TNF [158]. Thus, a diet rich in fruits and vegetables exerts a protective role against inflammatory diseases through the suppression of TNF.

2.10. *Signal transducer and activator of transcription (STAT)*

STAT proteins are signaling molecules with dual functions that were discovered during studies on interferon (IFN)-γ-dependent gene expression [161]. Seven mammalian STAT family members have been molecularly cloned and share

common structural elements [162]. They can be activated by phosphorylation through Janus kinase (JAK) or cytokine receptors, G-protein-coupled receptors, or growth factor receptors (such as EGFR); by platelet-derived growth factor receptors that have intrinsic tyrosine kinase activity; or by intracellular non-receptor tyrosine kinase recruitment [163,164]. Of the seven STAT proteins identified so far, constitutive activation of STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukemias, and several solid tumors, making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-X_L. Recently, STAT3 was shown to be a direct activator of the VEGF gene, which is responsible for increased angiogenesis. Elevated STAT3 activity has been detected in head and neck squamous cell carcinoma [165], leukemias [166], lymphomas [167], and multiple myeloma [168].

Several dietary agents like parthenolide [169], green tea [170], resveratrol [171], and curcumin [168] have been shown to suppress STAT activation in tumor cells. The sesquiterpene lactone parthenolide from the anti-inflammatory medicinal herb feverfew (*Tanacetum parthenium*) inhibited the STAT6 DNA-binding activity in IL-4-stimulated endothelial cells [169]. Green tea has been reported to show anti-inflammatory properties because of its inhibitory effects on the expression of several proinflammatory genes. Green tea mediates the down-regulation of the DNA binding activity of the transcription factor STAT1α but not of NF-κB. This down-regulation of the STAT1α–DNA binding was shown to result from reduced tyrosine phosphorylation of the STAT1α protein and not from antioxidative effects of the green tea extract [172]. EGCG has also been shown to down-regulate the phosphorylation of STAT3 [170]. Wung et al. have demonstrated that resveratrol inhibits IL-6-induced ICAM-1 gene expression, in part by interfering with Rac-mediated pathways via the attenuation of STAT3 phosphorylation [171].

Numerous reports suggest that IL-6 promotes survival and proliferation of multiple myeloma cells through the phosphorylation of STAT3. Our laboratory has demonstrated that curcumin inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. Curcumin had no effect on STAT5 phosphorylation but inhibited IFN-α-induced STAT1 phosphorylation [168]. We also demonstrated that suppression of NF-κB and STAT3 activation in multiple myeloma cells from patients by ex vivo treatment with curcumin decreased adhesion to bone marrow stromal cells, cytokine secretion, and the viability of cells [173]. Curcumin also suppressed JAK-STAT signaling via activation of Src homology two domain-containing protein tyrosine phosphatases (SHP-2), thus attenuating inflammatory response of brain microglial cells [174]. These studies suggest that several phytochemicals target the STAT-signaling pathway.

2.11. *Cyclooxygenase-2 (COX-2)*

Cyclooxygenases are prostaglandin H synthase, which convert arachidonic acid released by membrane phospholipids into prostaglandins. Two isoforms of prostaglandin H synthase, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in many tissues, but the expression of COX-2 is regulated by mitogens, tumor promoters, cytokines, and growth factors. COX-2 is overexpressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck, and esophagus [175]. Depending upon the stimulus and the cell type, several transcription factors including AP-1, NF-IL-6, NF-κB can stimulate COX-2 transcription [175]. Thus, all the dietary agents that can suppress these transcription factors have the potential of inhibiting COX-2 expression. Several dietary components including galangin, luteolin [176], apigenin [177], 6-hydroxykaempferol, quercetagenin [178], sasanquol [179], genistein [180], wogonin [181], green tea catechins [182], curcumin [183], and resveratrol [184] have been shown to suppress COX-2.

In 1980, Baumann et al. assessed rat medullar COX activity and reported that some dietary polyphenols, such as galangin and luteolin, inhibit arachidonic acid peroxidation [176]. Since then, several researchers have reported that many dietary polyphenols inhibit COX activity at the transcriptional level as well as at the enzyme level. Landolfi et al. found that flavone, chrysin, apigenin, and phloretin suppressed COX activity and inhibited platelet aggregation [177]. The flavonoids 6-hydroxykaempferol and quercetagenin, isolated from *T. parthenium* (feverfew), and 6-hydroxyluteolin and scutellarein, isolated from *Tanacetum vulgaris* (tansy), were shown to inhibit COX activity in leukocytes [178]. The triterpene sasanquol, isolated from *Camellia sasanqua* (Theaceae) and 3β-*p*-hydroxybenzoyl-dehydro-tumulosic acid from the fungus *Poria cocos* (Polyporaceae) inhibited both TPA- and AA-induced ear inflammation in mice [179], most likely through the suppression of COX-2. Genistein down-regulates COX-2 promoter activity in colon cancer cells transfected with a COX-2 reporter gene [180]. Wogonin and sophoraflavanone-G down-regulate COX-2 expression from TNF-treated NIH/3T3 cells and LPS-treated RAW cells, respectively [181].

Pretreatment with green tea extract enriched with catechin and EGCG inhibited COX-2 expression induced by TPA in mouse skin. Similarly, EGCG down-regulated COX-2 in TPA-stimulated human mammary cells (MCF-10A) in culture [185]. Both green tea catechin and EGCG displayed COX inhibition in LPS-induced macrophages [182]. Green tea polyphenols EGCG and EGC, as well as ECG and theaflavins from black tea, also inhibited COX-dependent arachidonic acid metabolism in microsomes from tumors and normal colon mucosa, indicating that tea polyphenols can affect arachidonic acid metabolism in human colon mucosa and colon tumors, perhaps altering the risk for colon cancer in humans [186].

Curcumin was one of the first chemopreventive phytochemicals shown to possess significant COX-2 inhibiting activity through the suppression of NF-κB. Since COX-2-derived prostaglandins stimulate aromatase activity in an organ-specific manner, an independent source of estradiol generation in breast cancer patients undergoing anti-estrogen therapies can be blocked by curcumin and other chemopreventives that have significant COX-2 inhibitory activity. COX-2 inhibitors will be particularly useful in the treatment of advanced breast cancers through inhibition not only of HER-2/neu activity but also of aromatase activity [175].

Preclinical studies have shown that curcumin suppresses COX-2 activity through the suppression of NF-κB-inducing kinase (NIK) and IκBα kinase (IKK) enzymes [183]. Other chemopreventive agents, such as genistein and catechins may work through down-regulation of EGFR and HER-2/neu activity, resulting in reduced expression of COX-2. Resveratrol has also been shown to down-regulate COX-2 expression. Subbaramaiah et al. showed that resveratrol inhibits COX-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. Transient transfections utilizing COX-2 promoter deletion constructs and COX-2 promoter constructs, in which specific enhancer elements were mutagenized, indicated that the effects of PMA and resveratrol were mediated via a cAMP response element. Resveratrol blocked PMA-dependent activation of AP-1-mediated gene expression. In addition to these effects on gene expression, resveratrol also directly inhibited the activity of COX-2 [184]. Chung et al. showed that α-viniferin, and resveratrol inhibited COX-2 activity and COX-2 transcription in LPS-activated murine macrophage line RAW 264.7 [187]. Our laboratory recently showed the suppression of 7,12-dimethyl-benz(*a*)anthracene (DMBA)-induced mammary carcinogenesis in rats by resveratrol, and this correlated with inhibition of NF-κB, COX-2, and MMP-9 [188].

2.12. *Lipoxygenase (LOX)*

LOXs are the enzymes responsible for generating leukotrienes (LT) from arachidonic acid. There are three types of LOX isozymes depending upon the different cells and tissues they affect. 15-LOX synthesizes anti-inflammatory 15-HETE; 12-LOX is involved in provoking inflammatory/allergic disorders; and 5-LOX produces 5-HETE and LTs, which are potent chemoattractants and lead to the development of asthma. Aberrant arachidonic acid metabolism is involved in the inflammatory and carcinogenic processes. Several dietary agents known to suppress LOX are green and black tea polyphenols [186], resveratrol [189], curcumin [190], flavonols [191], artonin E [192] and baicalein [193].

The effect of plant polyphenols on 5- and 12-LOX has been studied extensively to elucidate their anti-cancer properties. Green and black tea polyphenols are potent inhibitors of LOX. At a concentration of 30 μg/mL, EGCG (−)-epigallocatechin (EGC) and (−)-epicatechin-3-gallate (ECG) from green tea and theaflavins from black tea inhibited LOX-dependent activity by 30–75% in colon tumors [186]. MacCarrone et al. demonstrated that resveratrol acted as a competitive inhibitor of purified 5-LOX and 15-LOX and prostaglandin H synthase, with inhibition constants of 4.5 IM (5-LOX), 40 IM (15-LOX), 35 IM (COX activity of prostaglandin H synthase), and 30 IM (peroxidase activity of prostaglandin H synthase) [189].

At 10 μM, tetrahydrocurcumin (THC) and curcumin effectively inhibited the release of arachidonic acid and its metabolites in LPS-stimulated RAW cells and A23187-stimulated HT-29 colon cancer cells. They potently inhibited the formation of prostaglandin E_2 in LPS-stimulated RAW cells. Curcumin and THC also inhibited the activity of human recombinant 5-LOX, with an IC_{50} value of 0.7 and 3 μM, respectively. Curcumin affects arachidonic acid metabolism by blocking the phosphorylation of $cPLA_2$, decreasing the expression of COX-2, and inhibiting the catalytic activities of 5-LOX. These activities may contribute to the anti-inflammatory and anticarcinogenic actions of curcumin and its analogs [190].

Flavonols, including kaempferol, quercetin, morin, and myricetin, were found to be potent inhibitors of 5-LOX [191]. Hamamelitannin and galloylated proanthocyanidins have been shown to inhibit 5-LOX with an IC50 ranging from 1.0 to 18.7 μM [194]. Some prenylated flavonoids, such as artonin E, are the most effective inhibitors of porcine leukocyte 5-LOX [192]. Baicalein was reported to selectively inhibit platelet 5-LOX [193].

2.13. *Inducible nitric oxide synthase (iNOS)*

Nitric oxide synthase is responsible for the release of the gaseous free radical nitric oxide during the formation of L-citrulline from L-arginine. Excessive and prolonged iNOS-mediated NO generation has been linked with inflammation and tumorigenesis. Several phytochemicals and dietary agents have been investigated for their effects on NOS. Kim et al. investigated 48 species of plants commonly eaten in Japan for in vitro NO generation inhibitory activities in a murine macrophage cell line, RAW 264.7, stimulated with LPS and IFNγ. Seventeen of the 48 extracts strongly inhibited NO generation. The extracts from avocado, taro, red turnip, sereves, komatsuna, basil, mitsuba and Chinese mustard markedly inhibited iNOS activity [195]. Flavonoid derivatives, including apigenin, quercetin, and morin, inhibit NO production in LPS/IFNγ-activated C6 astrocytes [196].

Several polyphenols, including 6-gingerol [197], EGCG [198], resveratrol [199], indole-3-carbinol [200], and oroxylin A [201], inhibit NOS expression in LPS-treated RAW 264.7 cell lines, most likely through the suppression of NF-κB. Lin et al. investigated the effect of various tea polyphenols and caffeine on the induction of NOS in LPS-activated peritoneal macrophages. Gallic acid, EGC, and EGCG, the major tea catechin, were found to inhibit iNOS mRNA and protein in activated macrophages through suppression of the binding of NF-κB to the iNOS promoter, thereby inhibiting the induction of iNOS [198].

Low concentrations of curcumin inhibited NO production by suppression of iNOS mRNA and protein induction in macrophages [202]. Inducible NOS is overexpressed in colonic tumors of humans and also in rats treated with a colon carcinogen. Curcumin inhibited the formation of aberrant colonic crypt foci, suggesting that developing iNOS-specific inhibitors may provide a selective and safe chemopreventive strategy for colon cancer [203]. Onoda and Inano investigated the inhibitory activity of curcumin for the production of NO in rat mammary glands by using an organ culture system to validate the effectiveness and usefulness of curcumin in the pathophysiology of the mammary gland. They found that curcumin inhibited iNOS induction by LPS in the mammary gland [204]. Thus, NO serves as an important target of dietary phytochemicals.

2.14. *Mitogen-activated protein (MAP) kinases*

In addition to NF-κB and Akt pathways, MAPK pathway has received increasing attention as a target molecule for cancer

prevention and therapy. The MAPK cascades include extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs), and p38 kinases. ERKs are believed to be strongly activated and to play a critical role in transmitting signals initiated by growth-inducing tumor promoters, including 12-O-tetradecanoyl-phorbol-13-acetate (TPA), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) [205,206]. On the other hand, stress-related tumor promoters, such as ultraviolet (UV) irradiation and arsenic, potently activate JNKs/SAPKs and p38 kinases [207–209]. The MAPK pathway consists of a cascade in which a MAP3K activates a MAP2K that activates a MAPK (ERK, JNK, and p38), resulting in the activation of NF-κB, cell growth, and cell survival [210]. The dietary phytochemicals curcumin [211], indole-3-carbinol [212], resveratrol [113], and green tea polyphenols [213] have been shown to modulate the MAP kinases.

The ability of curcumin to modulate the MAPK signaling pathway might contribute to the inhibition of inflammation by curcumin. Salh et al. reported that curcumin is able to attenuate experimental colitis through a reduction in the activity of p38 MAPK [214]. Chen and Tan found that curcumin inhibits JNK activation induced by various agonists including PMA plus ionomycin, anisomycin, UV-C, gamma radiation, TNF, and sodium orthovanadate [215]. Although both JNK and ERK activation by PMA plus ionomycin were suppressed by curcumin, the JNK pathway was more sensitive. Indole-3-carbinol from cruciferous vegetables is a potent inhibitor of the MAP kinase pathway. Microarray data from a high-throughput gene chip that contained 22,215 known genes revealed that 1–3-C and DIM down-regulated the expression of MAP2K3, MAP2K4, MAP4K3, and MAPK3 in PC3 prostate cancer cells [212].

Resveratrol can modulate all three MAPKs, which leads to modulation of gene expression (for references see [77]). Resveratrol appears to activate MAPK in some cells and inhibit it in others. This variability may depend on the cell type and the dose of resveratrol used. Resveratrol-induced activation and nuclear translocation of ERK1/2 in papillary and follicular thyroid carcinoma cell lines [113]. Thus, resveratrol appears to act via a Ras-MAPK kinase-MAPK signal transduction pathway in thyroid carcinoma cell lines. She et al. found that resveratrol activated JNKs at the same dosage that inhibited tumor promoter-induced cell transformation [112]. Thus, JNK acts as a mediator of resveratrol-induced activation of p53 and apoptosis, which may occur partially through p53 phosphorylation. Woo et al. showed that resveratrol inhibited PMA-induced matrix metalloproteinase (MMP)-9 expression by inhibiting JNK [216]. Stewart and O'Brian showed that resveratrol antagonized EGFR-dependent ERK1/2 activation in human androgen-independent prostate cancer cells with associated isozyme selective PKC-α inhibition [217].

EGCG showed strong inhibition of tyrosine kinase and MAPK activities in transformed NIH-pATM ras fibroblasts without affecting the kinases in the normal cells [218]. When human epidermal keratinocyte cells were pretreated with EGCG, H_2O_2-induced phosphorylation of ERK1/2, JNK, and p38 was significantly inhibited [213]. Thus EGCG has the potential to inhibit oxidative stress-mediated phosphorylation of MAPK signaling pathways. Maeda-Yamamoto et al. also reported that EGCG inhibited the phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and suppressed p38 MAPK activity in human fibrosarcoma HT1080 cells [219]. However, EGCG has also been found to activate all three MAPKs (ERK, JNK and p38) in a dose- and time-dependent manner in human hepatoma HepG2-C8 cells [220]. In the breast cancer cell line T47D, catechin (containing approximately 53% of EGCG) phosphorylated JNK/SAPK and p38. The phosphorylated JNK/SAPK and p38 inhibited the phosphorylation of Cdc2 and regulated the expression of cyclin A, cyclin B1, and Cdk proteins, thereby causing G2 arrest [221]. It is possible that activation of MAPK by low concentration of EGCG results in induction of ARE-mediated gene expression, whereas higher concentration of EGCG causes activation of such MAPKs as JNKl leading to apoptosis [220].

2.15. *DNA methylation*

DNA methylation is a covalent modification resulting in the addition of a methyl group to the cytosine ring. Hypermethylation leads to gene silencing through the suppression of transcription. DNA methylation is brought about by a group of enzymes known as the DNA methyltransferases (DNMT). Numerous genes have been found to undergo hypermethylation in cancer (for references see [222]). Genes involved in cell cycle regulation ($p16^{INK4a}$, $p15I^{NK4a}$, Rb, p^{14ARF}), genes associated with DNA repair (BRCA1, MGMT), apoptosis, drug resistance, detoxification, angiogenesis, and metastasis are susceptible to hypermethylation. Green tea polyphenols and bioflavonoids have been demonstrated to reverse the effects of DNA hypermethylation.

EGCG inhibits DNMT activity and reactivates methylation-silenced genes in cancer cells [223]. Treatment of human esophageal cancer cells with 5–50 μM of EGCG for 12–144 h caused a concentration- and time-dependent reversal of hypermethylation of $p16^{INK4a}$, retinoic acid receptor beta (RARβ), O(6)-methylguanine methyltransferase (MGMT), and human mutL homologue 1 (hMLH1) genes. Reactivation of some methylation-silenced genes by EGCG was also demonstrated in human colon cancer HT-29 cells, esophageal cancer KYSE 150 cells, and prostate cancer PC3 cells. In addition to tea polyphenols (catechin, epicatechin, and EGCG), bioflavonoids (quercetin, fisetin, and myricetin) inhibited DNMT-mediated DNA methylation in a concentration-dependent manner [224].

Hypomethylation is another methylation defect that is observed in a wide variety of cancers including hepatocellular cancers, cervical cancer, prostate tumors and hematologic malignancies (for references see [222]). Mittal et al. found that EGCG induced a significant inhibition of UVB-induced DNA hypomethylation pattern in a photocarcinogenesis model [225]. Thus, the green tea polyphenols modulate both DNA hypomethylation and hypermethylation. These observations suggest the potential use of EGCG for the prevention or reversal of related gene silencing in the prevention of carcinogenesis.

2.16. *Angiogenesis*

Tumor angiogenesis is the proliferation of a network of blood vessels that penetrates into cancerous growths, supplying

nutrients and oxygen and removing waste products. Tumor angiogenesis actually starts with cancerous tumor cells releasing molecules that send signals to surrounding normal host tissue. This signaling activates certain genes in the host tissue that, in turn, make proteins to encourage growth of new blood vessels. It is one of the best examples of how a tumor can take control of these processes and deregulate them to its own advantage. More than a dozen different proteins (e.g., FGF, EGF, GC-SF, IL-8, PDEGF, TGFα, TNF, VEGF), as well as several smaller molecules (e.g., adenosine, PGE), have been identified as angiogenic factors released by tumors as signals for angiogenesis. Among these molecules, VEGF and bFGF appear to be the most important for sustaining tumor growth. VEGF and bFGF are produced by many kinds of cancer cells and by certain types of normal cells, too.

Several chemopreventive phytochemicals have been found to target these pathways. These include curcumin [226,227], resveratrol [228], genistein [229], luteolin [230], and catechins [231]. Curcumin can interfere with the activity of MMP-2 and -9, reducing the degradation of ECM which forms the basis of angiogenic switch [227]. Thus, it can also interfere with the release of angiogenic and other growth factors that are stored in the ECM. By inhibiting several growth factor receptors such as EGFR and VEGFR, it can also significantly affect the mechanisms of angiogenic switch and vessel cooption that are necessary for the growth of new blood vessels in the tumor [232]. Dietary agents such as curcumin, genistein, and green tea can interfere with the non-receptor tyrosine kinases such as Src and FAK, thereby inhibiting the downstream PI-3 kinase signaling responsible for the induction of such angiogenic target genes as COX-2, VEGF, IL-8, and the MMPs [233].

Curcumin also inhibits MMP-2, which is implicated in the formation of loose and primitive looking meshwork formed by aggressive cancers such as melanoma and prostate cancers. This plasticity of the cancer cells mimicking the endothelial cells is mainly brought about by the capacity of the cancer cells to express endothelium associated genes such as VE-cadherin, Src, FAK and PI-3 Kinases, all of which are good targets for these chemopreventive agents. Recent findings showed that curcumin can also inhibit another member of the MMP family, aminopeptidase N (APN), which is implicated in the angiogenic switch [234]. Most notably, curcumin and to a lesser extent genistein [229] can also interfere with the expression of VEGF by processes other than hypoxia, such as transforming growth factor (TGF)-β release, COX-2 overexpression, hydrogen peroxide release from bone cells, constitutive and aberrant EGFR and Src signaling and most importantly, by aberrant NF-κB signaling in established cancers. Chemopreventive phytochemicals such as curcumin, genistein, and green tea components are also known to interfere with the endothelial cell function by inhibiting specific integrin engagement and usage [235].

Lin et al. investigated the mechanism by which resveratrol inhibited vascular endothelial growth factor (VEGF)-induced angiogenic effects in human umbilical vein endothelial cells [236] and showed that resveratrol abrogated VEGF-mediated tyrosine phosphorylation of vascular endothelial (VE)-cadherin and its complex partner, β-catenin. Used at concentrations present in human plasma following moderate wine consumption, resveratrol inhibited adhesion molecule expression by TNF-stimulated endothelial cells [237]. Resveratrol also significantly prevented cytokine-induced vascular leakage. Fulgenzi et al. showed that TNF-induced vascular permeability changes were inhibited by resveratrol, not only in vitro but also in vivo [238]. Woo et al. found that resveratrol significantly inhibited PMA-induced increases in MMP-9 expression and activity [216]. These effects of resveratrol were dose-dependent and correlated with suppression of MMP-9 mRNA expression. PMA caused about a 23-fold increase in MMP-9 promoter activity, which was suppressed by resveratrol. Brakenhielm et al. found that resveratrol suppressed angiogenesis, tumor growth and wound healing [228].

Bagli et al. found that the flavonoid luteolin inhibited tumor growth and angiogenesis in a murine xenograft model. Luteolin inhibited VEGF-induced in vivo angiogenesis in the rabbit corneal assay. In agreement, luteolin inhibited both VEGF-induced survival and proliferation of human umbilical vein endothelial cells. The antisurvival effects of luteolin were mediated via blockage of PI3K/Akt-dependent pathways, whereas the antimitotic effects were mediated through the inhibition of the PI3K/p70 S6K pathway [230].

3. Conclusion

From this discussion it is clear that numerous agents in fruits and vegetables can interfere with multiple cell-signaling pathways. These agents can be used either in their natural form for the prevention and perhaps in their pure form for the therapy, where large doses may be needed. While these agents are pharmacologically safe in most situations, one of the concerns commonly expressed is the lack of bioavailability. Experience again indicates that these agents exhibit bioresponse at serum concentrations that are insufficient to demonstrate in vitro response; thus suggesting that their bioavailability should not be evaluated in the same manner as synthetic compounds. Most modern medicines currently available for treating cancers are very expensive, toxic, and less effective in treating the disease. Thus, one must investigate further in detail the agents derived from natural sources, described traditionally, for the prevention and treatment of cancer and disease. More clinical trials are also needed to validate the usefulness of these agents either alone or in combination with existing therapy.

Acknowledgement

We would like to thank Walter Pagel for a careful review of the manuscript.

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