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Phytochemicals: cancer chemoprevention and suppression of tumor onset and metastasis

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Abstract Carcinogenesis is a multi-step process which could be prevented by phytochemicals. Phytochemicals from dietary plants and other plant sources such as herbs are becoming increasingly important sources of anticancer drugs or compounds for cancer chemoprevention or adjuvant chemotherapy. Phytochemicals can prevent cancer initiation, promotion, and progression by exerting anti-inflammatory and anti-oxidative stress effects which are mediated by integrated Nrf2, NF-κB, and AP-1 signaling pathways. In addition, phytochemicals from herbal medicinal plants and/or some dietary plants developed in recent years have been shown to induce apoptosis in cancer cells and inhibition of tumor growth *in vivo*. In advanced tumors, a series of changes involving critical signaling molecules that would drive tumor cells undergoing epithelial–mesenchymal transition and becoming invasive. In this review, we will discuss the potential molecular targets and signaling pathways that mediate tumor onset and metastasis. In addition, we will shed light on some of the phytochemicals that are capable of targeting these signaling pathways which would make them potentially applicable to cancer chemoprevention, treatment and control of cancer progression.

Keywords Phytochemicals · Herbs · Cancer chemoprevention · Metastasis · Molecular targets

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1 Introduction

Carcinogenesis is a multi-step process which begins with initiation followed by promotion and progression. Cancer initiation, promotion, and progression involve a series of epigenetic and genetic alterations affecting oncogenes and tumor suppressor genes [1–4]. Inhibition of each stage of carcinogenesis has been shown to be achievable by administering chemical agents. The initiation stage could be inhibited by chemical agents that can inactivate carcinogens, function as antioxidant, or induce antioxidant enzymes, while later stages could be inhibited by agents that suppress tumor growth or stimulate apoptosis [5]. Cancer chemoprevention is thus described as a strategy to reverse or suppress the process of carcinogenesis using chemical compounds [6] and has been described in as early as the 1960s [7]. Currently, the concept of chemoprevention has been expanded to target all stages of cancer development: apart from prevention of cancer initiation through DNA repair, detoxification, free-radical scavenging, and carcinogen metabolism, prevention of tumor promotion and progression through inhibition of proliferation and angiogenesis, induction of apoptosis, and differentiation and reduction of inflammation and increase immunity [8, 9].

Cancer chemopreventive effects could be induced by phytochemicals, which includes a wide variety of compounds produced from plants [10]. Phytochemicals from dietary

plants, such as selenium in garlic, phenethyl isothiocyanate (PEITC) in crucifers, and genistein in soy products [11–13], have been shown to protect against different types of tumor development. On the other hand, based on their traditional usage as therapeutic medicines, phytochemicals from non-dietary plants such as herbs have emerged as a new and promising source of anticancer remedies or as adjuvant of chemotherapeutic drugs to enhance their efficacy and to ameliorate their side effects. In some cases, some of the phytochemicals from herbs have already been introduced as single chemical entities in modern medicine [14, 15]. In the USA, it is estimated that one third of adults use dietary herbal supplements on a regular basis [15]. The scientific foundation of this kind of practice has not been soundly established since, besides the claimed health benefit, many herbal supplements and botanicals also possess potent pharmacological activity that may contribute to adverse effects and drug–botanical interactions [16, 17]. Therefore, detailed chemical analysis of those botanical medicines and mechanistic investigation on the related molecular events are required to define their health benefit and to establish safe and effective clinical practice.

According to the current knowledge on carcinogenesis, anti-inflammatory and antioxidant effects and genomic stability remain to be important primary targets in chemoprevention [18, 19]. They are tightly related to induction of apoptosis and growth inhibition of cancer cells. In this review, we will summarize some chemopreventive compounds developed in recent years, especially those extracted from herbs and dietary plants. We will also discuss some of the common pathways that are mediated by the chemopreventive compounds, including nuclear factor-E2-related factor 2 (Nrf2) and Kelch-like erythroid cap'n' Collar (CNC) homologue-associated protein 1 (Keap1), and their roles in the regulation of antioxidant system and redox signaling. We will also discuss NF-κB pathway that could be regulated by chemopreventive compounds and their effects on inflammation and cell proliferation, followed by a description of intrinsic and extrinsic apoptotic pathways. We will further explore some of the common pathways regulated by chemopreventive compounds that are associated with the inhibition of cancer development and metastasis. In particular, the inhibition of angiogenesis pathway and the different molecular targets involved will be discussed in great detail.

2 Phytochemicals and discovery of anticancer drugs

Natural products occupy a large proportion of all available anticancer drugs. For example, among the drugs developed between 1981 and 2002, the natural compounds or natural product-derived drugs comprised 28% and 24%, respectively [14]. Dietary and medicinal plants are major sources of phytochemicals, and they have played an important role in the treatment of cancers [20]. Current clinically used phytochemcials can be categorized into four main classes of compounds: vinca (or *Catharanthus*) alkaloids, epipodophyllotoxins, taxanes, and camptothecins [21].

Some phytochemicals have already been shown to be effective in cancer treatment. For example, Vinblastine and vincristine, isolated from *Catharanthus roseus* (L.) G. Don (Apocynaceae) [21], have already years of clinical application; Camptothecin, which was isolated from *Camptotheca acuminata* Decne. (Nyssaceae), and it was found to act by selective inhibition of topoisomerase I, involved in cleavage and reassembly of DNA [22]; in addition, paclitaxel was originally isolated from *Taxus brevifolia* Nutt. (Taxaceae) and was introduced to the US market for clinical use in the early 1990s [23].

There are also a large number of phytochemicals subject to various phases of clinical trial, such as curcumin (extract from *Curcuma longa* Linn; colon and pancreatic cancer); epigallocatechin gallate (EGCG, extract from green tea; breast and prostate cancer); soy isoflavones (breast and prostate cancer) etc. (see the website www.clinicaltrials.gov). These compounds have shown anticancer effects both *in vitro* and *in vivo* (Table 1) [24–26].

Beyond dietary phytochemicals, a number of extracts from herbs have been tested for their antioxidant effects and inhibition of cancer cell proliferation in *in vitro* and animal experiments. Traditional Chinese medicine, Japanese Chinese medicine (kampo), Korean Chinese medicine, jamu (Indonesia), ayurvedic medicine (India), and phytotherapy in Europe and America have been extensively accepted as "alternative medicine." Combined with the application of conventional medicine, they are termed as "integrative medicine" [27]. Synergistic analysis of anticancer agents is an important approach to determine the ratio and/or dose of drugs for clinical combination therapy [28]. The phytochemicals extracted from herbal and dietary plants in recent years are summarized for their anticancer effect and the molecular mechanism examined (Table 1). For example, Evodiamine, a major constituent of the Chinese herb *Evodiae fructus*, possesses anticancer activities both *in vitro* and *in vivo* by inhibiting proliferation, invasion, and metastasis, inducing apoptosis of a variety of tumor cell lines [15]; Triptolide, a diterpene triepoxide, was isolated from *Tripterygium wilfordii*, and its semisynthetic analog, PG490–88 (12, 14-succinyl triptolide sodium salt), exerts antiproliferative and pro-apoptotic activities on primary human prostatic epithelial cells as well as tumor regression of colon and lung xenografts [29]. In a National Cooperative Drug Discovery Group Project, Dr. Kinghorn and his group have taken an extensive investigation on thousands of plants to determine the effect of extracts of plants,

Table 1 Anticancer effect and mechanisms of phytochemicals (including some dietary compounds)

Compound(s)	Plant	Cancer cell lines	Effects/molecular targets (references)	*In vivo* test
Acutiaporberine	*Thalictrum acutifolium* Boivin	NSCLC; PLA-801	Induced apoptosis; down-regulated bcl-2; activated bax and c-myc [162]	Not specified
Andrographolide	*Andrographis paniculata*	PC-3; K-562	Up-regulated bax; down-regulated bcl-2; inhibited expression of VEGF [163]	Enhanced natural killer cell activity in normal and tumor-bearing animals [164]
Artesunate (ART)	*Artemisia annua*	RAW 264.7 SP2/0 HepG2	Inhibited proliferation and induced apoptosis and necrosis; induced DNA breakage; increased γ-H2AX; inhibited NO [165–167]; decreased the expression level of NF-κB p65 protein in the nucleus [168]	Inhibited tumor growth In HepG2 xenograft mice [169]
Ascaridol	*Chenopodium anthelminticum L.*	CCRF-CEM; HL60; MDA-MB-231	Antineoplastic effects [170]	Modest inhibition in sarcoma 180 tumor model [171]
Bisacurone	*Curcuma longa* Linne (Zingiberaceae)	U937; Hep-2; QLL-I; SCC-15	Inhibited TNF-α-mediated expression of VCAM-1; inhibited the induction of ROS generation by TNF-α; blocked NF-κB p65 nuclear translocation; inhibited phosphorylation of Akt and PKC [172]	Not specified
Boswellic acid acetate (BC-4)	*Boswellia carterii*	HL-60; U937; ML-1	Induced monocytic differentiation, inhibited growth of multiple cell lines [173]	Not specified
BITC	Cruciferous vegetables	BxPC-3; Capan-2; MDA-MB-231	Decreased the expression and activity of histone deacetylase (HDAC) 1 and HDAC3 in BxPC-3 and HDAC3 in Capan-2 cells, inhibit NF-κB [174], Cell cycle inhibitor, Sensitize TRAIL for cytotoxicity [175]; down-regulation of vascular endothelial growth factor (VEGF) receptor 2 [176]	Retarded growth of MDA-MB-231 cells subcutaneously implanted in female nude mice [176]
Curcumin	*Curcuma longa*	HCT116; prostate cancer; gastrointestinal cancers etc.	Induced apoptosis; exerted anti-inflammatory effect; inhibited NF-κB by blocking IκB degradation; inhibited phosphorylation of Akt, ERK [177, 178]; inhibited activity of AP-1; down-regulated the cytokines tumor necrosis factor-α; down-regulated endogenous bcl-2 and Bcl-xL; enhanced cell death in LNCaP cells in combination with TNF-related apoptosis-inducing ligand (TRAIL) [179, 180]	Decreased incidence of prostate tumor formation in PC3 implanted nude mice [181]
(−)-Epigallocatechin gallate (EGCG)	green tea	HT29; DU145; PC3 etc.	Induced G0/G1 cell cycle arrest; inhibited NF-κB activity; inhibited COX-2; NF-κB activity, inhibited DNA methyl transferase 1 (DNMT1) [182], acted as inhibitor of matrix metalloproteinase-2; blocked induction of VEGF; inhibition of angiogenesis via blocking of ERK-1/2; modulated NF-κB, AP-1; induced cytochrome C release; regulated VCAM-1; inhibited the expression of p38 MAPK [183, 184]	Reduced tumor size and completely and abrogated tumors in both androgen-repressed LNCaP 104-R and the androgen-refractory PC3 tumor xenograft in athymic nude mice [185]
Evodiamine	*Evodiae fructus*	A375-S2; COLO-205; KBM-5; Jurkat; H1299; U266; NCI/ADR-RES	Inhibited cell proliferation, induce G2/M cell cycle arrest and apoptosis [186]; Inhibited PI3K; inhibit phosphorylation of IκBα [187]; inhibited tumor necrosis factor (TNF)-induced Akt activation; inhibited Bcl-2, Bcl-xL, Cyclin D1, c-Myc, COX-2, MMP-9, ICAM-1 [188]	Inhibited tumor growth in xenografted nude mice [189]

Table 1 (continued)

Compound(s)	Plant	Cancer cell lines	Effects/molecular targets (references)	*In vivo* test
Parthenolide	feverfew (*Tanacetum parthenium*)	K562; Kasumi-1; MV4-11; MCF7; CWR22Rv1	Inhibited activity of STAT and MAP kinase; induced sustained JNK activity; induced cell death mainly in cancer cells; inhibited NF-κB activation [190], inhibited DNMT2 activity, reduced HDAC1; induced p53 [191]	Augmented efficacy of docetaxel and restored sensitivity to anti-androgen therapy in xenograft mice [192]
Ganoderic acid T (GA-T)	*Ganoderma lucidum*	95-D	Inhibited the proliferation; induced apoptosis of metastatic lung tumor cells through intrinsic pathway related to mitochondrial dysfunction and p53 expression [193]	Suppressed the growth of human solid tumor in athymic mice [193]
6-Gingerol	Ginger	JB-6	Enhanced TRAIL-induced apoptosis; inhibited TPA-induced phosphorylation of p65 and p38 [194, 195]	Topical application onto shaven backs of female ICR mice inhibited 7,12-dimethylbenz[a]anthr acene-induced skin papillomagenesis [196]
Ginsenosides	*Panax ginseng*	LNCaP	Suppressed prostate specific antigen (PSA), androgen receptor (AR) and 5alpha-reductase (5alphaR) and proliferating cell nuclear antigen (PCNA); ginsenoside Rg3 induced G1 cell cycle arrest, increased expression of p21 and p27 [197, 198]	Rh2 alone do not inhibit tumor growth in xenografted mice used alone [199]; Rg3 suppress the invasion induced by LPA [200]
Honokiol	*Magnolia officinalis*	PC-3; LNCaP; C4-2; COLO-205; Hep-G2	Induced Bax, Bak, and Bad; decreased Bcl-xL and mcl-1 protein levels; regressed formed solid tumor with COLO-205 implanted subcutaneously in nude mice [201]; induced G1 cell cycle arrest; inhibited phosphorylation of Akt and Rb, up-regulated PTEN [202–204]	Retard growth of PC-3 xenografts in nude mice [205]
Hydroxyisovaleryls hikonin (beta-HIVS)	*Lithospermum radix*	Ishikawa; HHUA; HEC-1B; SK-OV-3; OMC-3	Inhibitor of protein-tyrosine kinases induce G0/G1 cell cycle arrest and apoptosis, with higher sensitivity to cancer cells than normal healthy cells [206]; inhibit phosphorylation and expression of VEGFR2 and Tie2 but not VEGFR1 [207]	Not specified
Indiosides	*Solanum indicum L*	Bel-7402	Inhibited proliferation; induced mitochondria-dependent apoptosis [208]	Not specified
Jaceosidin (4′, 5, 7-trihydroxy-3′, 6-dimethoxyflavone)	*Artemisia vestita* Wall	CAOV-3; SKOV-3; HeLa; PC3	Increased apoptosis [209]	Not specified
Licochalcone (LA) Isoliquiritigenin	Licorice	MGC-803; LNCaP; CT-26	Weakly induced apoptosis; induce G2/M arrest; inhibited cyclin B1 and cdc2; inhibit phosphorylation of Rb (at S780); reduced expression of cycline D1, CDK4 and 6, but increased of cyclin E [210–212]	Inhibited the size of the tumors in CT-26 cell-inoculated Balb/c mice [213]
Matrine	*Sophora flavescens* Ait (Kushen)	H22; K562	Inhibited proliferation; induced cell cycle arrest at G1 phase; induced Bax [214, 215]	Inhibit tumor growth by I.P. in BALB/c mice [216]
3-Methyl-1,6,8-trihydroxy anthraquinone (emodin)	*Rheum palmatum*	HSC5; MDA-MB-231; K562	Induced cell cycle arrest at G0/G1; decreased the expression of Bcl2; inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced *in vitro* invasion, inhibited TPA-induced MMP-9; reduce transcriptional activity of AP-1 and NF-κB [217]	Decreased of tumor volume and tumor weight in comparison to the control

Table 1 (continued)

Compound(s)	Plant	Cancer cell lines	Effects/molecular targets (references)	*In vivo* test
Diterpenoid compounds (including oridonin, ponicidin, xindongnin A, and xindongnin B)	*Rabdosia rubescens*	SPC-A-1; MCF-7; MDA-MB-231; K562; HL-60	Inhibited proliferation and induce apoptosis; inhibited NF-κB transcription activity and downstream COX-2, NO [218]; Oridonin and ponicidin inhibited translocation of NF-κB from the cytoplasm to nuclei without affecting IκBα phosphorylation and degradation [219]; induced S/G2M arrest and G1/S block in MCF-7 cells; decreased in p65 or p50 forms of NF-κB [220, 221]	Low toxicity to mice [222]
PG490 (triptolide)	*Tripterygium wilfordii*	RPMI8226; U251MG; U87MG; MDA-435; TSU; MGC80-3	Inhibited proliferation and colony formation more potent than Taxol at low concentrations [223]; induced G0/G1 cell cycle arrest and apoptosis; decreased histone H3K9 and H3K27 methylation; inhibit PI3k/Akt/NF-κB; attenuated Ras/ERK and Ras/Akt pathways [224–226]	Inhibited the growth of xenografts, inhibited metastasis of B16F10 to lung and spleen [223]
Phenethyl isothiocyanate (PEITC)	Cruciferous vegetables	HT-29; PC-3; LNCaP; HeLa; SKOV3	Induced apoptosis through caspase-3 [227]; up-regulated p53, bax; down-regulated expression of XIAP, Bcl-2, Bcl-xL and Mcl-1 [228]; increased ROS generation, sensitize cells to PEITC [229]; up-regulated CYP1A1 and CYP1A2 and phase II genes; decreased iNOS and COX-2; inhibited NF-κB transcriptional activity [230]; inhibited MAPK [231]; decreased DNA and hemoglobin adduct formation induced by NNK [232]	Inhibited intestinal carcinogenesis in Apc (Min/+) mice [233]. retarded the growth of PC-3 xenografts [234]; inhibited NNK-induced lung carcinogenesis [235]
Plumbagin	*Plumbago zeylanica* L.	PC-3; LNCaP; C4-2	Decreased in cell viability correlated with apoptosis induction; increased ROS generation and depletion of intracellular GSH levels [236]	Inhibited cell growth in nude mice [237]
Quercetin	Vegetable and fruits	MDA-MB-231; Hela; K562; COLO320 DM; PC-3; DU145 etc.	Induced cell arrest; decrease Bcl 2, Bcl-xL protein levels; up-regulated NQO-1, CYP1A1; sensitized TRAIL-induced apoptosis through ERK-MSK1-mediated deacetylation of H3; increase Bax; increased DR5; down-regulated c-Myc and K-ras oncogenes, [238–241]	Suppressed development of preneoplastic lesions and proliferation azoxymethane (AOM) induced aberrant crypt foci (ACF) [242]
Rhein	*Rheum palmatum*	SCC-4; JB6	Induced S-phase arrest and apoptosis through ER stress by reactive oxygen species (ROS), Ca2+ release and mitochondrial dysfunction; inhibited phosphorylation of c-Jun, JNK, but not ERK and p38 kinase, decrease Bcl-2 levels; inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced cell transformation and activator protein-1 (AP-1) activation [243, 244]	Inhibited tumor growth on MCF-7 xenografts in athymic mice [245]
Solamargine (SM)	*Solanum incanum*	A549; Hep3B; NSCLC	Increased expression of TNF-R1 and -R2 overcame the resistance of A549 cells to TNF-α and -β; down-regulated Bcl-2 and Bcl-xL; increased Bax expression and downstream caspases; down-regulated HER2, promoted chemotherapy-induced apoptosis. [246–249]	Not specified
Sulforaphane (SFN)	Cruciferous vegetables	HeLa; HepG2; T24; LNCaP; C4-2; HT29	Induced cell cycle arrest and apoptosis; induce phase II enzymes; promote the mitochondrial formation of ROS and induce DNA breakage [250]; suppressed phosphorylation	Retarded prostate tumor growth in TRAMP mouse [256]; suppress the growth of PC-3 in nude mice. [257]

Table 1 (continued)

Compound(s)	Plant	Cancer cell lines	Effects/molecular targets (references)	*In vivo* test
			of Akt (Ser-473) and then inhibited hTERT phosphorylation [251]; acted as an HDAC inhibitor, enhanced histone acetylation [252]; decreased the expression and phosphorylation of [253]; increased expression and phosphorylation of p38 [254]; up-regulated TRAIL-R1/DR4, TRAIL-R2/DR5 [255]	
Tanshinones	*Radix Salvia miltiorrhiza* (Danshen)	MCF-7; MDA-MB-231; HepG2	Tanshinone I inhibited cell proliferation and induced apoptosis; tanshinone IIA caused HepG2 cytotoxicity through apoptosis without influencing oxidative stress [258, 259]	Not specified
Thymoquinone (TQ)	*Nigella sativa Linn* (black seed)	HL-60; HCT-116; MG63; COS31; COS31/rCDDP etc.	Inhibited proliferation and induced apoptosis, which is modulated by Bcl-2 and dependent on p53; exert antineoplastic and anti-inflammatory effects when used alone or in combination [260–266]	Prevented tumor angiogenesis in a pc3 xenograft mouse [267]
Wogonin	*Scutellaria baicalensis*	NB4; HL-60; MGC-803; HeLa; T47D; MDA-MB-231	Inhibited proliferation and induced cell differentiation; increased expression of Cdk4 and cyclin D1; up-regulated phospholipids scramblase 1 (PLSCR1) and phosphorylated PKC delta (Ser643); scavenge oxidative radicals and attenuated NF-κB activity; suppressed COX-2; acted as an inhibitor of P-glycoprotein [268–271]	Inhibited tumor growth of xenograft in athymic nude mice [271].
Polyphyllin D (PD) (diosgenyl alpha-L-rhamnopyranosyl-(1–>2)-(alpha-L-arabinofuranosyl)-(1–>4)-beta-D-glucopyranoside)	*Paris polyphylla*	MCF-7; MDA-MB-231 R-HepG2 (HepG2 cell with drug resistance) Lewis lung cancer cells	Induced apoptosis via mitochondrial dysfunction; reduced tumor growth [216, 272, 273]	Reduced tumor growth for I.V. injection of MCF7 cell in nude mice [273]

including anticancer activity. Several selected compounds are currently undergoing further investigation including betulinic acid, pervilleine A, and silvestrol [29]. From higher plants, some compounds including Vinca alkaloid, Taus diterpenes, camptotheca alkaloids, and podophyllum lignans and their analogs have also been shown to be clinically useful anticancer drugs [27].

3 Keap1–Nrf2 axis in redox signaling for the phytochemical effect as antioxidant

Phytochemicals are promising cancer blocking agents that could prevent the occurrence of DNA mutation caused by carcinogens. While some of them directly react with carcinogens, many of them elicit their chemopreventive effects indirectly through the modulation of phase I and phase II metabolizing enzymes existing in the tissues where carcinogens/procarcinogens are metabolized [30]. Phase I metabolism includes oxidation, reduction, and hydrolysis of xenobiotics. Phase I reactions, especially those mediated by cytochrome P450 enzymes, are responsible for the bioactivation of many procarcinogens. During phase II metabolism, carcinogens and their activated phase I metabolites are conjugated with amino acids, glucuronic acid, or glutathione to yield water-soluble derivatives that are excreted in urine or bile, which is recognized as phase II detoxifying metabolism. In the promoters of these drug-metabolizing enzyme genes, there exists xenobiotic response element (in both phase I and phase II/detoxifying genes) and antioxidant response element (ARE, in phase II/detoxifying genes) [31–33]. Under stress conditions, some detoxifying genes with ARE enhancer identified such as glutathione *S*-transferases, γ-glutamylcysteine synthetase, NADP(H):quinone oxidoreductase 1, UDP: glucuronosyl transferases and heme oxygenase 1 are transactivated by a basic leucine zipper transcription factor NF-E2-related factor 2 (Nrf2, or NFE2L2), which plays a central role in the mediation of detoxifying and antioxidant enzymes [33–36].

Through sequence comparisons of Nrf2 protein structure in different species, six Neh domains were identified in Nrf2 protein [37]. The Neh1 domain contains the conserved CNC and bZip motifs, which are required for DNA binding and dimerization with small Maf proteins (MafG and MafK), while the Neh4 and Neh5 domains are involved in the recruitment of transcriptional coactivators [38]. Two conserved motifs within the Neh2 domains of Nrf2, ^{29}DLG^{31}, and ^{79}ETGE^{82} bind to a single overlapping site in the double glycine repeat domain of cytoskeleton anchoring protein Kelch-like ECH-associated protein 1; the binding between Keap1 and Nrf2 via the high-affinity ^{79}ETGE^{82} motif of Nrf2 provides the "hinge"; here Nrf2 still has a relatively free space to move, while the concomitant binding via the lower affinity ^{29}DLG^{3} provides the "hatch" which allows Keap1 to bind Nrf2 tightly and enables optimal positioning of target lysine for conjugation with ubiquitin; deletion of this ETGE motif attenuates the interaction between Nrf2 and Keap1 and stabilizes Nrf2 expression [39].

Under homeostatic conditions, Nrf2 remains in an inactive cytoplasmic form and is sequestered in the cytoplasm by Keap1. Keap1 could also work as an adaptor that bridges Nrf2 to Cul 3 for protein ubiquitination as well [40]. Under the oxidative condition, Nrf2 is released from Keap1 repression, translocates to the nucleus, and forms heterodimer with small Mafs, and this protein complex binds to the ARE motif, activating the ARE gene battery. Meanwhile, the translation of Nrf2 is increased by an internal ribosomal entry site (IRES)-mediated translation initiation upon oxidant exposure [36, 41]. This redox-sensitive regulation makes Nrf2 an important mediator of detoxifying responses during chemical challenges and oxidative stress.

In the Keap1–Nrf2 antioxidant axis, Keap1 was proposed to be a primary redox sensor, since the cysteine-rich structure of Keap1 is sensitive to the presence of electrophiles and reactive oxygen species (ROS) [42, 43]. Recently, it was proposed that Nrf2 itself can be a redox sensor because of its NES_{TA} motif, which also plays a role in the subcellular localization of Nrf2 [44].

The transactivation activity of Nrf2 can be regulated directly through several kinase pathways, including mitogen-activated protein kinase (MAPK), PI3K, or protein kinase C (PKC) [45–48], or indirectly by changing the ability of activating the transcription of its target genes [49] with its coactivators, such as cAMP-response element-binding protein (CREB)-binding protein (CBP). Extracellular regulated kinase (ERK) and Jun *N*-terminal kinase (JNK) increase Nrf2 transactivation domain activity, while p38 does not, suggesting various MAPKs may have different regulation on Nrf2 signaling cascade [50].

Some dietary phytochemicals such as phenethyl isothiocyanate and sulforaphane (SFN) are potent inducers of phase II/detoxifying genes, and this activation is Nrf2-dependent [51]. PEITC may induce the phosphorylation of ERK and JNK and consequently phosphorylate Nrf2 and induce its nucleus translocation. Attenuated PEITC-induced ARE activity was observed when ERK and JNK signaling were inhibited [52]. Curcumin and (−)-epigallocatechin-3-gallate have been reported to regulate Nrf2 activity via similar pathway [53, 54], while SFN may stabilize Nrf2 through the modification of Keap1 and Nrf2 interaction and translocation of Nrf2. Evidence showed that SFN was able to react with thiols of Keap1 by forming thionoacyl adducts [55].

4 Nuclear factor-κB signaling pathways for the anti-inflammatory effect of phytochemicals

Inflammation may be associated with the alteration of genetic instability and expression of some oncogenes and tumor suppressor genes [56]. Persistent inflammation in the tumor microenvironment promotes proliferation and survival of malignant cells, angiogenesis, and metastasis [57, 58]. NF-κB may be involved in tumor initiation and progression. The direct evidence is the deletion of IKKb, which is tightly related to NF-κB transcription factor, leads to a dramatic decrease of tumor incidence in a colitis-associated cancer model [59].

NF-κB is a key orchestrator of innate immunity/inflammation responses [60]. Over 150 target genes are activated by NF-κB, including different inflammatory cytokines and chemokines, immunoreceptors, adhesion molecules, enzymes in the prostaglandin synthase pathway, such as cyclooxygenase 2 (COX-2) and nitric oxide (NO) synthase, angiogenic factors, as well as various stress response genes [61].

The Rel/NF-κB family of eukaryotic transcription factors are homodimers or heterodimers of several structurally related proteins, including six family members NF-κB1 (p50/p105, p50 and its precursor p105), NF-κB2 (p52/p100, p52 and its precursor p100), RelA (p65), RelB(p68), c-Rel (p75), and v-Rel. A conserved Rel homology domain in the N-termini of all these proteins is responsible for dimerization, DNA binding, nuclear localization, and interaction with inhibitory IκB proteins. A transactivation domain is located at the C-termini of RelA, RelB, and c-Rel. These different homo- and hetero-dimers bind to distinct kB sites, a 10-bp DNA element GGGRNNYYCC (R, purine; Y, pyrimidine; N, any base), to regulate the transcriptions of different genes. In unstimulated cells, NF-κB is retained in the cytoplasm as an inactive complex with the inhibitor IκBs (IκBα, IκBβ, IκBγ, and IκBε and Bcl-3). Bound IκB masks the NF-κB nuclear localization signal and thereby inhibits its nuclear transport [62]. IκB protein phosphorylation is a common activation pathway; under various kinds of stimulation, such as TNF-α, IL-1 or lipopolysaccharide (LPS), IκB proteins will be phosphorylated at serine and threonine by the upstream IKK complex containing IκB kinase IKKα, IKKβ, and regulatory protein IKKγ (NF-κB essential essential modulator, NEMO) [63] or IKK-associated protein 1 [64], followed by ubiquitinylation/proteasome-mediated degradation. The degradation of IκBs leads to translocation of NF-κB into the nucleus [62, 65].

NF-κB pathway is important in driving cancer-related inflammation, such as in gastrointestinal and liver cancer [59, 66]. Aberrant activation of NF-κB is frequently observed in many cancers, and suppression of NF-κB limits the proliferation of cancer cells [67, 68]. It has also been shown that NF-κB is an important pathway in tumor-associated macrophages for the integration of signals from the tumor microenvironment that promote carcinogenesis. There are two particular macrophage phenotypes: the "classical" M1 macrophages are pro-inflammatory and increase the production of pro-inflammatory cytokines, reactive nitrogen, and oxygen intermediates, while the "alternative" M2 macrophages are immunosuppressive and produce anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGFβ) [69, 70]. Tumor-associated macrophages represent a phenotype of M-2 type and are associated with increased angiogenesis and metastasis and with high level expression of IL-10 and TGF, as well as vascular endothelial growth factor (VEGF), COX-2, epidermal growth factor receptor (EGFR), and matrix metalloproteinases (MMP) [71–73].

Potential crosstalk between the NRF2 and NF-κB pathways has been examined. After pretreatment with an inducer of Nrf2 pathway sulforaphane, the anti-inflammation effect of Nrf2 (−/−) primary peritoneal macrophages was attenuated compared with the Nrf2 (+/+) macrophages upon LPS stimulation. Compared with Nrf2 (−/−) peritoneal macrophages, inflammation-related signals such as tumor necrosis factor (TNF), IL-1, COX-2 and iNOS have much less expression in Nrf2 (+/+) peritoneal macrophages, suggesting a potential cross talk between Nrf2 and inflammation regulation [74]. In addition, Nrf2-deficient mice are more sensitive to dextran sulfate sodium-induced colitis and colorectal carcinogenesis, and the decreased expression of downstream phase II detoxifying enzymes is highly associated with the increased expression of pro-inflammatory cytokines/biomarkers. However, the involved mechanisms are subjected to further investigation [36].

As listed in Table 1, a wide variety of phytochemicals from dietary plants target NF-κB pathway: PEITC has been shown to target NF-κB signaling by stabilizing IκBα; both of them have been shown to inhibit transcriptional activity and p65 nuclear translocation and therefore down-regulate the expression of NF-κB target genes such as iNOS and COX-2 [51]; Curcumin also inhibits NF-κB activity by blocking IκB degradation [75, 76]. Phytochemicals from the herbal plants such as bisacurone block NF-κB p65 nuclear translocations [77]; and evodiamine inhibits the phosphorylation of IκBα etc. [78].

5 Intrinsic and extrinsic apoptosis pathways

Deficiency in apoptosis is one of the key hallmarks of cancer [79]. Apoptosis is induced by both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. The intrinsic pathway involves mitochondrial outer-

membrane permeabilization and release of pro-apoptotic factors, including cytochrome c, apoptosis inducing factor (AIF), and smac-DIABLO and endonuclease G (endoG) from the mitochondria into cytoplasm [79–81], and subsequently promotes caspase activation through the cytochrome c/Apaf-1/caspase-9 cascade [82]. The BCL-2 superfamily constitutes a critical intracellular checkpoint. This intrinsic pathway involves complex interactions among pro- and anti-apoptotic members of the Bcl-2 family of proteins. BH3-only proteins, including Bid, Bad, Bim, Bmf, PUMA, and NOXA, act as upstream sentinels of cellular damage and derangement. These proteins activate the pro-apoptotic multi-BH domain proteins Bax and Bak by operating in both the endoplasmic reticulum (ER) and mitochondria [83]. In non-apoptotic cell, Bax and Bak exist in the cytosol or attach loosely to the membrane as monomers. When the death signals are received, these two proteins together form a requisite gateway by inserting into the mitochondria outer membrane as homo-oligomerized multimers [84, 85]. For the extrinsic pathway, the cell death is activated through the binding of extracellular ligands of tumor necrosis factor family of proteins to pro-apoptotic death receptors (DRs) by forming a death-inducing signaling complex to activate caspases 8 and 10, followed by the activation of caspases 3, 6, and/or 7, the same caspase machinery of intrinsic pathway [86, 87]. The well-known death receptors are CD95/Fas and DR4/DR5 (TNFRSF10A/TNFRSF10B) with their ligands as CD95L/FasL and Apo2L/TRAIL (Apoptosis ligand 2 TNF-related apoptosis-inducing ligand). Other DRs identified include TNFR1 (TNFRSF1A), DR3 (TNFRSF12) and DR6 (TNFRSF21) [88, 89]. Some other ligands of the TNF superfamily include TNFα and lymphotin and have been tested in clinical research. The FAS receptor–ligand complex allows the adaptor molecule Fas-associated death domain (FADD) to bind the death domain of Fas so that FADD can recruit pro-caspases 8 and 10 into the complex. c-FLICE inhibitory protein has been reported to be able to block the caspase activation by interacting with death effector domain of FADD and finally abrogate pro-apoptotic receptor stimulation [90, 91]. Different cell types may have different response to stimulation of ligands. In type 1 cells, such as H9 SKW6.4 and SW480, extrinsic Fas pathway without help from mitochondria is sufficient to induce complete apoptosis, while in type 2 cells, apoptosis relies on the cleavage of the BH3-only protein Bid and stimulation of Bak and Bax mitochondrial translocation induced by caspase 8 activation. This type 2 program affords a crosstalk between the extrinsic and BCL2 family of protein-controlled intrinsic pathways [92].

Among the 33 phytochemicals listed in Table 1, most of them have shown effects on induction of apoptosis except lichchalcone, which has been reported to induce apoptosis weakly [93]. A large number of them are through modulation of the expression level of Bc2 family proteins, activating the extrinsic apoptosis pathway, while some of them, such as ganoderic acid T and polyphyllin D (PD), induce apoptosis via mitochondrial dysfunction and/or activation of tumor suppressor gene p53 [94–97].

Apol2/TRAIL induces apoptosis of many malignant cells but not normal cells, and its anti-tumor capability has been tested in many tumor types, tumor xenografts mouse models, and clinical investigations [98, 99]. More importantly, TRAIL in combination with conventional therapy, such as 5-fluorouracil (5-FU) or CPT-11 (irinotecan hydrochloride), [100] was able to cause synergistic activation of apoptosis and reduce drug resistance in cancer cells, therefore sensitizing cancer cells to immune system-mediated cytotoxicity [101]. Retinoids have been used successfully in treatment of acute myeloid leukemia alone or in combination with chemotherapeutic agents, through induction of TRAIL [102]. The combination of TRAIL and all-trans-retinyl acetate induces apoptosis of antigen-presenting cell (APC)-deficient premalignant cells, dramatically reduce tumor growth in APC^{min} mice and promote cell death in human polyps [103]. Benzyl isothiocyanate (BITC), a component of cruciferous vegetables, has also been reported to be able to sensitize pancreatic adenocarcinoma cells to TRAIL and activate both extrinsic and intrinsic apoptotic pathways [104]. Wogonin, a component from *Scutellaria baicalensis*, also enhances TRAIL-induced cytotoxicity in LNcaP cells [105].

6 Phytochemicals on suppression of metastasis

Invasion and metastasis have been described as the sixth hallmark of cancer, besides immortality, abnormal growth regulation, self-sufficient growth, evasion of apoptosis, and sustained angiogenesis [79]. Tumor cells could disseminate into blood, lymphatics, or even across body cavities, giving rise to secondary tumors. However, not all tumors are metastatic, and even in a metastatic tumor, not all cells within it are capable of metastasizing [106]. Therefore, how a subpopulation of tumor cells acquires metastatic potential has always been a hot topic of research.

Metastatic tumor cells possess several distinctive characteristics: they undergo epithelial–mesenchymal transition (EMT) and become invasive, become resistant to apoptosis and anoikis, and acquire the ability to disseminate and colonize secondary sites [107]. The “seed and soil” concept that was first proposed by Stephen Paget in 1889 still holds true today since metastasis depends on cross talk between the selected cancer cells (seeds) and the microenvironment (soil) [108]. This concept could exemplify itself in different steps of metastasis: acquisition of invasive phenotype depends on the tumor cellular context as well as signals

from the stromal cells [109], and finally dormancy or growth of the tumors cells on secondary sites also depends on the microenvironment [110, 111]. With the advancement of technology, different genes and signaling pathways have been shown to be involved in the regulation of these processes. Some of the processes and the possible use of phytochemicals for intervention targets are discussed below.

7 Epithelial–mesenchymal transition

A recent review paper has described the classification of three different EMT subtypes, each with very different functional consequences [112]. Type 1 EMT is encountered during normal physiological processes such as implantation, embryogenesis, and organ development. Type 2 EMT is associated with tissue regeneration and organ fibrosis. Type 3 EMT is related to cancer progression and metastasis. Though it has been questioned whether EMT really happens in human cancers [113], the role of EMT as a critical mechanism for acquisition of malignant phenotype by epithelial cancer cells has been proposed and confirmed in some studies [114].

Carcinoma cells can acquire mesenchymal phenotype and express mesenchymal markers such as α-SMA, FSP1, vimentin, and desmin [115]. These cells are usually found in the invasive fronts of cells in tumor and are capable of subsequent intravasation, circulation in blood, extravasation, and eventually colonization. One interesting observation is that EMT-transited cells form tumors at secondary sites which resemble the primary tumor, with the disappearance of mesenchymal phenotype. The shedding of mesenchymal phenotype during the course of secondary tumor formation is termed as mesenchymal–epithelial transition (MET). This EMT-MET mechanistic model could be important in explaining metastasis of cancer cells: EMT induces change in cell phenotype which allows the escape of epithelial cancer cells from their structural constraints imposed by tissue architecture, while MET reverses these changes and facilitates colonization in secondary sites [116].

There is increasing evidence supporting the notion that tumor–microenvironment interactions are important in the development of metastasis. For instance, fully malignant breast cancer cells could be reverted to a normal phenotype by exposing them to non-permissive stroma [117]. Therefore, apart from the cellular context, the microenvironment (tumor-associated stroma) could provide signals that induce EMT. These signals include hepatocyte growth factor (HGF), epidermal growth factor, platelet-derived growth factor, and TGFβ and have been shown to be responsible for the induction or activation of EMT-inducing transcription factors such as Snail, Slug, zinc-finger E-box binding homeobox 1 (ZEB1), Twist, Goosecoid, and FOXC2. Intracellular signaling molecules such as MAPK, PI3K-Akt, Smads, RhoB, β-catenin, lymphoid enhancer binding factor, Ras, c-Fos, and cell surface proteins such as β4 integrins, α5β1 integrins, and αVβ6 integrin are also shown to be mediating the EMT program [118].

8 Invasion, migration, and angiogenesis—VEGF and MMPs

Angiogenesis is essential for both tumor growth and metastasis. The expression of VEGF in carcinoma is highly correlative to angiogenesis. VEGF is generally highly expressed in carcinoma cells. Immunohistochemistry and *in situ* hybridization on specimens from hepatocellular carcinoma (HCC) patients revealed that VEGF was highly expressed in HCC and played an important part in angiogenesis and metastasis [119]. In head and neck cancers, COX-2 was shown to have higher expression in primary tumor sample and lymph node metastasis samples. VEGF expression was correlated with COX-2 expression and tumor angiogenesis and metastasis [120]. Samples from esophageal squamous cell carcinoma patients also showed overexpression of VEGF and was correlated with de-differentiation of tumors and lymph node metastasis [121]. Down-regulation of VEGF expression by adenoviral-mediated p16 overexpression in breast cancer cells inhibited tumor angiogenesis and metastasis in a spontaneous metastasis model [122]. The administration of antihuman VEGF antibody also inhibited tumor angiogenesis and metastasis in xenograft model of human fibrosacoma HT1080 cells [123], providing direct evidence of VEGF-induced tumor angiogenesis in metastasis and that VEGF could be a good target for intervention.

Apart from VEGF, MMPs such as MMP-2 and MMP-9 play a critical role in invasion and metastasis of gastric carcinoma. Expression of these markers correlates with depth of invasion of carcinoma, lymphatic and venous invasion, and lymph node metastasis [124]. The ability of MMPs to degrade the extracellular matrix may be important for the metastasis of primary oral squamous cell carcinoma patients [125]. In different types of cancers, different signaling pathways have been found to increase expression of MMPs. α3β1 integrin signaling is necessary for MMP-9 expression and mammary carcinoma migration and invasion [126]. MMP-2 and MMP-9 have been associated with intrahepatic metastasis and vascular invasion in HCC patients. In particular, PI3K/PTEN/AKT/mTOR pathway is probably involved in the up-regulation of MMP-9 in this type of tumor [127]. MMP13 signaling has also been shown to be important in mediating metastasis. Complete

inactivation of MMP13 in stromal cell of mice significantly suppressed melanoma tumor growth and metastasis to various organs [128]. In laryngeal and hypopharyngeal squamous cell carcinomas, up-regulation of MMP13 could be mediated through CXCL12/CXCR4 activation and subsequent ERK/c-Jun pathway [129]. Different MMPs inhibitors have been shown to suppress tumor metastasis. For example, BMS-275291 is a potent inhibitor (nM) of the activities of MMP-1, MMP-2, MMP-7, MMP-9, and MMP-14 and inhibits tumor angiogenesis and metastasis in experimental models [130]. Another MMP-2 and MMP-9 inhibitor, FYK-1388, has also shown the same anti-metastatic effect [131]. Inhibition of MMP-1 using RNAi approach also reduces melanoma angiogenesis and metastasis [132]. Taking these results together, inhibitors of MMPs have generally been shown to be effective to reduce angiogenesis and metastasis in experimental model. Prevention of metastasis by phytochemicals that target MMPs is therefore highly feasible.

9 Carotenoids

Lycopene and β-carotene both have been shown to inhibit metastasis in experimental setting. The inhibition of lung metastasis by β-carotene has been shown with B16F-10 melanoma cells in C57BL/6 mice. After tumor induction, administration of β-carotene reduced formation of tumor nodule, collagen hydroxyproline in the metastasized lung, lung hexosamine content, uronic acid, serum sialic acid, and gamma glutamyl transpeptidase. These end points correlated with the improved histopathology of lung tissue with administration of β-carotene [133]. Another study highlights the efficacy of lycopene in the inhibition of lung metastasis. Human hepatoma SK-Hep1-1 cells were injected into athymic nude mice via the tail vein, and it was found that lycopene decreased the tumor number and cross-sectional area in the lung. Lycopene also decreases the level of vascular endothelial growth factor and metalloproteinase [134]. It has been commented that β-carotene appears to have a higher efficacy than lycopene in the inhibition of lung metastasis, taking into consideration the net increase of the two phytochemicals in the lungs and the factors associated with tumor invasion, proliferation, and angiogenesis [134, 135].

10 Alkaloids

Caffeine is a major phytochemical which belongs to the alkaloid class. Using the B16F-10 melanoma cell-induced experimental metastasis model, caffeine administered orally and intraperitoneally (i.p.) significantly reduced the tumor volume [136]. Further investigation using a spontaneous transgene-induced mammary tumor model has yielded more definite evidence in determining the inhibition of metastasis by caffeine. It has been shown that caffeine reduced primary tumor burden. More importantly, when caffeine was exposed after tumor appearance, metastasis is specifically suppressed possibly through an up-regulation of mRNA expression of multiple extracellular matrix genes, including Fbln1, Bgn, Sparc, Fbn1, Loxl1, Colla1, Col3a1, Col5a1, ColS5a2, ColSa3, Col6a1, Col6a2, and Col6a3. This indicates that caffeine could suppress metastatic activity through inhibition of malignant transformation of mammary epithelial cells, inhibition of conversion of dormant tumor cells to micrometastases, micrometastases to macrometastases, or inhibition of tumor cell adhesion and motility [137].

11 Polyphenols

EGCG and resveratrol belong to the flavonoids. The effect of EGCG in inhibition of metastasis was demonstrated recently. It has been shown that EGCG blocked HGF-induced invasion and metastasis of hypopharyngeal carcinoma cells. In hypopharyngeal carcinoma cells, HGF was shown to promote the autophosphorylation of c-Met and HGF receptor, activate Akt and Erk pathway, and enhance the activity of matrix metalloproteinase (MMP)-9 and urokinase-type plasminogen activator. These combined effects eventually lead to cancer cell proliferation, colony dispersion, migration, and invasion of tumors. It is noteworthy that EGCG at physiologically relevant concentration (1 μM) suppressed the molecular tumor motility and the molecular changes induced by HGF described. These results suggest that EGCG may serve as a therapeutic agent to inhibit HGF-induced invasion in hypopharyngeal carcinoma patients [138]. Another study has demonstrated EGCG inhibited cell proliferation (Ki-67 and PCNA staining), angiogenesis (vWF, VEGF, and CD31, circulating endothelial growth factor receptor 2 (VEGF-R2) positive endothelial cells), and metastasis (MMP-2, MMP-7, MMP-9 and MMP-12, reduced ERK activity) in AsPC-1 xenografted tumors, suggesting the use of EGCG in the prevention and treatment of pancreatic cancer growth, invasion, metastasis, and angiogenesis [139].

Resveratrol inhibited tumor-induced neovascularization in lung metastasis model (mice bearing highly metastatic Lewis lung carcinoma (LLC) tumor). At concentrations of 10–100 μmol/L, resveratrol significantly inhibited the binding of vascular endothelial growth factor to human umbilical vein endothelial cells (HUVEC) and inhibited the formation of capillary-like tube from HUVEC, suggesting that the anti-metastatic activities of resveratrol might be due

to the inhibition of LLC-induced neovascularization and tube formation (angiogenesis) of HUVEC by resveratrol [140]. In a more physiologically relevant model, colorectal adenocarcinoma CT26 cells were injected into BALB/c mice via tail vein, and pulmonary metastasis was observed. Resveratrol was shown to reduce metastasis incidence and increase percentage of survival of the mice. The surviving mice have no tumor lumps or nodules detected in the lungs, indicating resveratrol possibly increases survival rate through prevention of metastasis [141]. Restriction of HIF-1 alpha protein expression and stabilization through inhibition of VEGF and MMP-9 mRNA expression could be one possible molecular mechanism for resveratrol's anti-metastatic action. It has been shown that Lovo cells (colon carcinoma cell) cultured under normoxia and hypoxia treated with resveratrol showed restricted migration, adhesion, invasion, and MMP-9 and MMP-2 secretion [142].

12 Isoflavones from soy

Soy and its active compound genistein have long been studied for their anti-metastatic effect. Increasing intake of dietary soy has been shown to increase the size of the mammary fat pad tumors after MDA-MB-435 human breast cancer cell was transplanted in nude mice to form solid tumors but interestingly reduced the severity of macroscopic lung metastasis [143]. Later studies also showed that dietary supplementation with isolated soy protein decreased metastasis measured by various end points (incidence, number, cross-sectional area, volume of mice with macroscopically visible tumors, and number of microscopically detectable tumors) [144] and had an even greater inhibitory effect when combined with high-selenium [145]. In one study of bladder tumor growth and metastasis, isoflavone-rich soy phytochemical concentrate (SPC) was shown to have superior anti-metastatic effect compared to genistein. Specifically, SPC but not genistein significantly inhibited lung metastases by 95% ($P<0.01$). This observation was associated with significant down-regulation of NF-κB expression in tumor tissues and reduction of circulating insulin-like growth factor-I levels [146].

Interestingly, genistein but not daidzein was shown to be effective in inhibition of lung metastasis induced by B16 F-10 melanoma cells in C57BL/6 mice, indicating not all dietary soybean isoflavones are anti-metastatic [147]. Besides reducing the metastasis of breast cancer cell to lung [148], studies have also suggested that genistein may be a useful chemotherapeutic agent to inhibit the growth and metastasis of accessory sex gland cancers such as those derived from the prostate [149], and to decrease the incidence of metastasis of intestinal tumor to the peritoneum by inhibiting cancer cell invasion into lymphatic vessels [150]. Genistein may also be a promising agent for prevention of prostate cancer to bone metastasis. Growth of PC3-cells on bone was inhibited with the inhibition of expression of various metalloproteinases (MMPs) such as MMP-9 [151]. Other genes targeted by genistein in early-stage breast cancer cells include TFPI-2, ATF3, DNMT1, and MTCBP-1, which inhibit invasion and metastasis, and MMP-2, MMP-7, and CXCL12, which promote invasion and metastasis [152]. A study by El Touny *et al*. revealed a novel gene targeted by genistein. Loss of a metastasis gene kangai-1 (KAI1) has been shown before to directly correlate with poor prognosis in human prostate and other cancer. The study demonstrated that genistein-enriched diet could reverse the age-dependent down-regulation of KAI1 in the TRAMP model. The induction of KAI1 by genistein is a critical mechanism in decreasing the invasiveness of prostate cancer cells (TRAMP-C2) since the knockdown of KAI1 abrogated the observed decrease of invasiveness of TRAMP-C2 treated with genistein [153].

Genistein also inhibited the activation of focal adhesion kinase [154, 155] and p38 mitogen-activated protein kinase–heat shock protein 27 (HSP27) pathway [155], which were shown to regulate cancer cell detachment and invasion, respectively.

13 Vitamin D3

Vitamin D has been recently shown mechanistically to boost immune system. In fact, the anti-metastatic effect of Vitamin D has been discussed in many articles. Vitamin D3 treatment has been shown in the metastatic Lewis lung carcinoma (LLC-LN7) tumor model to reduce granulocyte/macrophage-colony-stimulating factor (GM-CSF) secreted by the tumor and interrupt the myelopoiesis-associated immunosuppressor cascade stimulated by GM-CSF, leading to a prominent reduction in tumor metastasis [156]. 1,25-Dihydroxycholecalciferol (1,25-D3) has also been shown to reduce the number and size of lung metastases in highly metastatic Mat-lylu prostate cancer rat model [157]. Another possible mechanism for the suppression of metastasis could be through the inhibition of Stat3. Phosphorylation of Stat3 has been associated with TGFβ-mediated metastasis in pancreatic cancer cells. In fact, tyrosine phosphorylation of Stat3 induced by interleukin 12 (IL-12) has been shown to be inhibited by vitamin D3, suggesting blocking Stat3 by vitamin D3 possibly reduces metastasis [158]. Therefore, vitamin D3 is generally considered as anti-metastatic. A deficiency of vitamin D3 in the diet could promote metastasis. The effect of vitamin D deficiency was studied on the intraskeletal growth of the human breast cancer cell line MDA-MB-231-TxSA in a murine model. Osteolytic lesions appeared earlier and were significantly larger in vitamin D-deficient mice. These effects

could be due to the change of bone microenvironment mediated by vitamin D3 [159]. Although VitD3 has potent anti-invasive properties, its calcemic effect *in vivo* has limited its therapeutic application. Its analog EB1089 has low calcemic effect and still retains potent anti-metastatic activity in a breast cancer cell–bone metastasis model [160].

14 Concluding remarks

With increasing molecular mechanistic evidences coupled with considerations of quality, safety, and efficacy, phytochemicals from dietary and medicinal plants have emerged as very promising sources of potential anticancer agents and new chemotherapy adjuvants [161].

Current strategy for the evaluation of anticancer phytochemicals are based in part on: (1) cell cycle and apoptosis regulation; (2) anti-oxidative stress and anti-inflammatory activities; (3) drug resistance of cancer cells; and (4) specific molecular targets targeting carcinogenesis and metastasis. Some phytochemicals listed in this review were developed in recent years, and they have already been shown to possess potent anticancer capability. With more detailed investigations of their potential molecular targets in different tissues and tumor types, *in vitro* cellular signaling mechanisms coupled with *in vivo* animal models, the final clinical applications of these phytochemicals in cancer chemoprevention and suppression of tumor onset and metastasis will be forthcoming.

In summary, it is highly plausible that in "asymptomatic" individuals having extremely microscopic tumors undetectable by today's imaging or other diagnostic tools, relatively non-toxic phytochemicals found abundantly in vegetables, fruits and herbs could block cancer initiation through the Nrf2-antioxidative stress/anti-inflammatory pathways, induce apoptosis/cell cycle arrest/autophagy in pre-initiated/initiated tumor cells, while in more advanced tumors, these compounds could block tumor progression and metastasis. The major questions will be what type of phytochemicals, how much to give and what will be the appropriate combinations, will require further studies.

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