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NON-THEMATIC REVIEW

Dietary phytochemicals alter epigenetic events and signaling pathways for inhibition of metastasis cascade

Phytoblockers of metastasis cascade

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Abstract Cancer metastasis is a multistep process in which a cancer cell spreads from the site of the primary lesion, passes through the circulatory system, and establishes a secondary tumor at a new nonadjacent organ or part. Inhibition of cancer progression by dietary phytochemicals (DPs) offers significant promise for reducing the incidence and mortality of cancer. Consumption of DPs in the diet has been linked to a decrease in the rate of metastatic cancer in a number of preclinical animal models and human epidemiological studies. DPs have been reported to modulate the numerous biological events including epigenetic events (noncoding micro-RNAs, histone modification, and DNA methylation) and multiple signaling transduction pathways (Wnt/β-catenin, Notch, Sonic hedgehog, COX-2, EGFR, MAPK-ERK, JAK-STAT, Akt/PI3K/mTOR, NF-κB, AP-1, etc.), which can play a key role in regulation of metastasis cascade. Extensive studies have also been performed to determine the molecular mechanisms underlying antimetastatic activity of DPs, with results indicating that these DPs have significant inhibitory activity at nearly every step of the metastatic cascade. DPs have anticancer effects by inducing apoptosis and by inhibiting cell growth, migration, invasion, and angiogenesis. Growing evidence has also shown that these natural agents potentiate the efficacy of chemotherapy and radiotherapy through the regulation of multiple signaling pathways. In this review, we discuss the variety of molecular mechanisms by which DPs regulate metastatic cascade and highlight the potentials of these DPs as promising therapeutic inhibitors of cancer.

Keywords Dietary phytochemicals · Micro-RNAs · Epigenetic modifications · Signaling pathways · Cancer · Metastasis · Combine therapy · Nanochemoprevention

Abbreviations

ABCG2	ATP-binding cassette sub-family G member 2
ACSL1	Acyl-CoA synthetase long-chain family member 1
AKBA	Acetyl-11-keto-β-boswellic acid
ALDH	Aldehyde dehydrogenase
AP-1	Activator protein-1
APC	Adenomatous polyposis coli
BAFF	B cell activating factor of the TNF family
Bcl-2	B cell lymphoma-2
BTG3	B cell translocation gene 3
CCND2	Cyclin D2
Cdk	Cyclin-dependent kinase
COX-2	Cyclooxygenase-2
CSCs	Cancer stem cells
DNMT	DNA methyltransferase
DRs	Death receptors
EGCG	Epigallocatechin-3-gallate
EMT	Epithelial–mesenchymal transition
ERK	Extracellular signal-regulated kinase
FOXO	Forkhead box O
GSK3β	Glycogen synthase kinase 3 beta
GSTP1	Glutathione *S*-transferase pi 1
GTPs	Green tea polyphenols
HAT	Histone acetyltransferase
HDAC	Histone deacetyltransferase

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HER2	Human epidermal growth factor receptor 2
Hh	Sonic hedgehog
hMLH1	Human mutL homologue 1
hTERT	Human telomerase reverse transcriptase
I3C	Indole-3-carbinol
ICAM-1	Intercellular adhesion molecule-1
IkBα	Inhibitory kappa B alpha
IKK	IkBα kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IRAK-1	IL-1 receptor-associated kinase 1
JAK/STAT	Janus kinase/signal transducers and activators of transcription
JNK	c Jun N-terminal kinase
LDH	Lactate dehydrogenase
LOX	Lipoxygenase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinases
MBD2	Methyl-CpG binding domain protein 2
MGMT	Methyl guanine methyl transferase
miRs	Micro-RNAs
MMP	Matrix metalloproteinase
MTA-2	Metastasis-associated protein 2
mTOR	Mammalian target of rapamycin
NF-AT	Nuclear factor of activated T cells
NF-κB	Nuclear factor-kappa B
NIK	NF-κB-inducing kinase
PARP	Polyadenosine-5′-diphosphate-ribose polymerase
PDGF	Platelet-derived growth factor
PDK	Pyruvate dehydrogenase kinase
PGE_2	Prostaglandin E2
PI3K	Phosphoinositide 3-kinase
PITCH	Phenyl isothiocyanate
PTEN	Phosphatase and tensin homolog
RARβ	Retinoic acid receptor β
SFN	Sulforaphane
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TPA	Phorbol 12-*O*-tetradecanoate-13-acetate
TRAMP	Transgenic adenocarcinoma of mouse prostate
TSGs	Tumor suppressor genes
UVB	Ultraviolet B
VEGF	Vascular endothelial growth factor
ZEB1	Zinc finger E-box binding homeobox 1

1 Introduction

Metastasis is a multistep process in which a cancer cell spreads from one organ or part to another nonadjacent organ or part. The new occurrences of cancer thus generated are referred to as metastasis. Metastasis is the most deadly aspect of cancer and results from several interconnected processes including cell multiplication, angiogenesis, cell adhesion, migration, and invasion into the surrounding tissue. There is now increasing evidence that diet plays a key role in tumorigenesis. Regular intake of dietary phytochemicals (DPs) has been linked to a decrease in the rate of metastatic cancer in a number of population-based studies and offers significant promise for reducing the incidence and mortality of cancer [1]. DPs are known to modulate the transcription factors (e.g., zinc finger transcription factors (GLI), Wnt, nuclear factor-kappa B (NF-κB), activator protein-1 (AP-1), signal transducer and activator of transcription 3 (STAT3)), antiapoptotic proteins (e.g., Akt, mammalian target of rapamycin (mTOR), B cell lymphoma-2 (Bcl-2), Bcl-xL), proapoptotic proteins (e.g., caspases, DRs, polyadenosine-5′-diphosphate-ribose polymerase (PARP), and Bax), protein kinases (e.g., inhibitory kappa B alpha (IkBα) kinase (IKK), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), c Jun N-terminal kinase (JNK), and mitogen-activated protein kinase (MAPK)), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), cell adhesion molecules, cyclooxygenase-2 (COX-2), growth factor, and multiple signaling transduction pathways [2–8]. In this regard, it has been estimated that more than 40 % of cancer death in worldwide may be related to malnutrition and deficiency of dietary factors [9]. For more than a decade, there has been considerable interest in the use of DPs for their health benefits including antimetastatic activity [2, 8, 10–18].

Cancer prevention and therapy through dietary intervention recently have arisen as a potential strategy. Cancer prevention is defined as active measures to decrease the risk of cancer, while therapy is a treatment that is intended to cure medical condition from occurring [3, 19]. Chemoprevention is defined as the inhibition or reversal of carcinogenesis by the use of natural or synthetic pharmacological compounds. Chemoprevention of cancer is an important aspect of biomedical research which in addition to offering a practical approach to identify potential useful inhibitors of cancer development also offers an opportunity to study the mechanism of tumorigenesis [8]. DPs have become not only important potential chemopreventive agents, but also therapeutic natural agents [3, 4]. DPs from fruits, vegetables, medicinal plants, and spices have drawn a great deal of attention from both the scientific community and the general public due to their outstanding demonstrated ability to inhibit the mechanism of cancer development. The questions that remain to be answered are which substance of these dietary sources is responsible for the anticancer effects and what is the actual molecular mechanism by which they suppress cancer? Fruits, vegetable, spices, herbs, and medicinal plants consist of a wide variety of bioactive constituents that are being used for management of

metastatic cancer. As early as 2,500 years ago, Hippocrates recognized and professed the importance of various foods.

Antimetastatic natural agents derived from plants have shown great potential in preventing and treating a wide variety of human cancers. Dietary plants consist of many groups of phytochemicals that are ubiquitous in plants, many of which have been used as ancient traditional medicines. These plants are not only an excellent source of fiber and minerals, but also contain pharmacologically bioactive molecules such as polyphenols, terpenoids, alkaloids, vitamins, and pigments that may serve more than a basic nutrition function. Many of these phytochemicals including curcumin (turmeric), epigallocatechin-3-gallate (EGCG) (green tea), resveratrol (red grapes, peanuts, and berries), sulforaphane (cruciferous vegetables), 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), dietary fiber, polyphenols, rosmarinic acid, naringenin, nobiletin, naringin, apigenin, hesperidin, morin, flavonoids, tocopherols, and ascorbates (Figs. 1 and 2) have been reported to effectively suppress metastasis cascade [7, 8, 10, 20].

Several clinical studies indicated an inverse relationship between consumption of green tea, vegetables, fruits, and herbs and risk for cancers: pancreatic, prostate, stomach, esophagus, neck, lung, oral cavity and pharynx, endometrium, head, and colon [8, 21]. This is highly related, as solid organ cancer has an extremely poor prognosis once it has progressed to the metastatic stage. DPs have therefore become one of the most widely studied inhibitors of both cancer cell growth and metastasis and have the potential to be of substantial clinical benefit to patients with various types of cancers. The recent discovery that microRNA (miR) expression is frequently dysregulated in cancer has uncovered an entirely new horizon of molecular targets upstream of gene expression, which warrants extensive investigation to further elucidate their precise role in malignancy. *In vitro* and *in vivo* studies indicate that the phytochemicals prevent human cancer by controlling micro-RNA (miR) expression. Epidemiological studies have proved that many of the

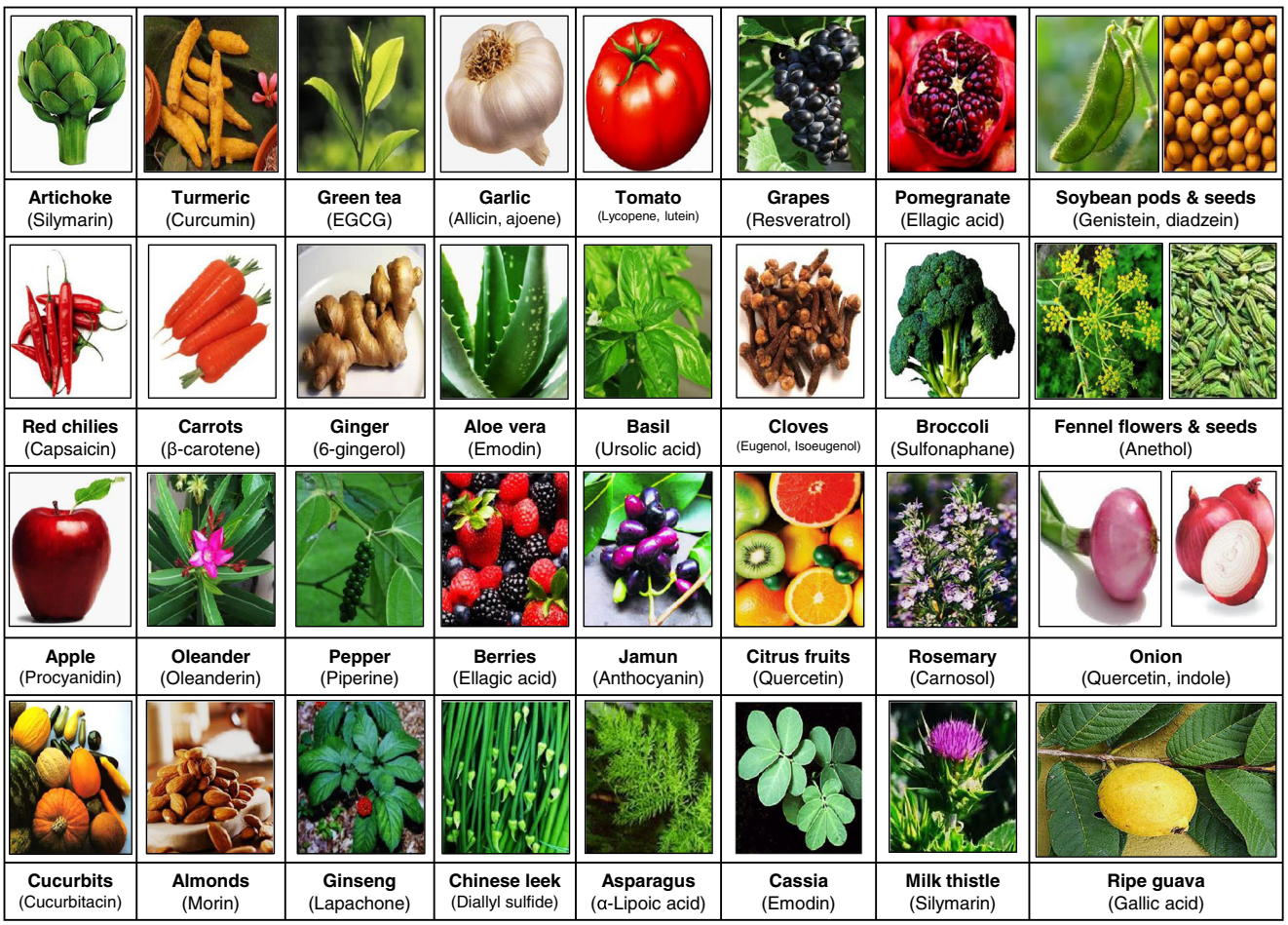


Fig. 1 Dietary source of antimetastatic bioactive phytochemical(s) (source: https://www.google.com)

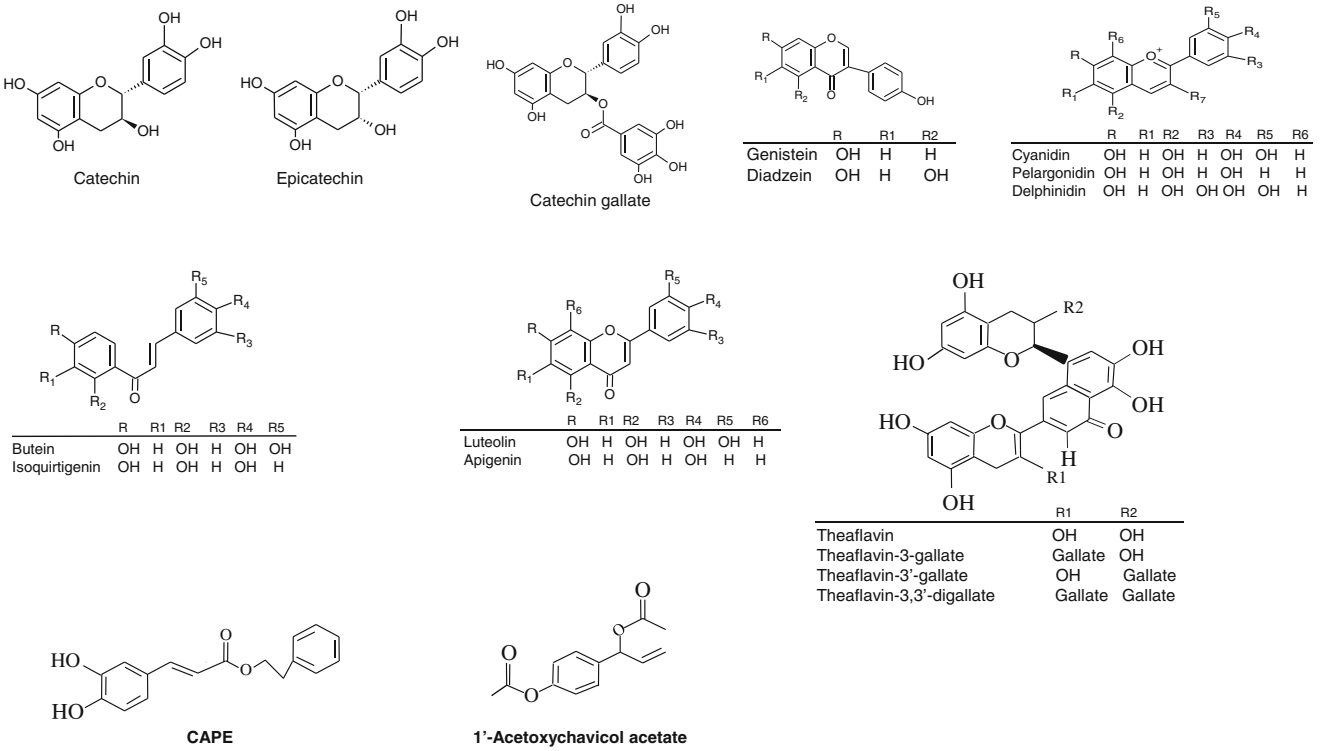


Fig. 2 Chemical structure of antimetastatic phytochemicals

DPs also modulate multiple intracellular signaling pathways such as Wnt/β-catenin, Notch, Sonic hedgehog, Janus kinase/signal transducers and activators of transcription (JAK/STAT), MAPK-extracellular signal-regulated kinase (ERK), Akt/phosphoinositide 3-kinase (PI3K)/mTOR, EGFR, tumor necrosis factor (TNF)-α, NF-κB, AP-1, and COX-2 (Table 1) [17, 22]. In this review, we discuss the variety of molecular mechanisms by which DPs regulate metastatic cascade, including molecular targets, cell proliferation, and cell apoptosis, and highlight the potentials of these natural agents as promising therapeutic inhibitors of cancer metastasis.

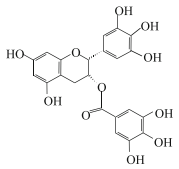
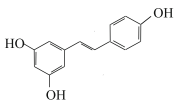
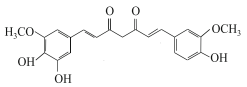
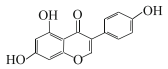
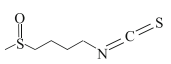
2 DPs affect metastasis cascade by targeting DNA integrity and epigenetic profile

The emerging interest in cancer as epigenetics stems from the fact that epigenetic events are associated in virtually every step of tumorigenesis has markedly accelerated over the past decade. DPs are recognized to affect DNA integrity and this in turn can impact on chromatin integrity and epigenetic profile [23]. Dr. S.M. Hadi and his group was first to investigate the transition metal-mediated oxidative DNA damage-dependent anticancer mechanism of DPs in human cancer cells and also concluded that this property of DPs could be further explored for the development of anticancer agents with higher therapeutic indices [23–29]. Copper, a key metal found in chromatin, was observed to be elevated in a number of malignancies [30]. A large body of evidence indicates that DPs including quercetin, resveratrol, and others can elicit oxidative DNA damage in the presence of copper ions [23, 27, 31]. This revolutionary strategy showed one of the major antitumor mechanisms of DP mobilization of endogenous copper, possibly chromatin-bound copper, and the consequent pro-oxidant action [32]. More interestingly, epigenetic modifications are reversible and somatically inheritable DNA sequence-independent traits, but have the potential to alter metastasis cascades [22]. Epigenetics refers to partially reversible, somatically inheritable, but DNA sequence-independent traits that modulate gene expression, chromatin structure, and cell functions such as cell cycle and apoptosis. Noncoding miR expression, DNA methylation, and histone modifications are examples of crucial epigenetic events. DNA hypermethylation and changes in the levels of key histone configurations important to activation and repression of gene transcription have also been frequently found in metastatic tumors and the blood of patients with cancer [33].

2.1 miR expression

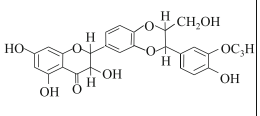
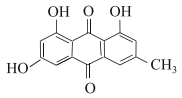
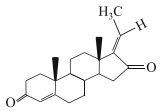
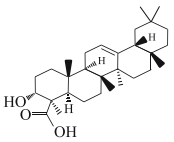
miRs are a family of small, noncoding RNAs 18 to 24 nucleotides in length that regulate gene expression in a sequence-specific manner. Sequence-specific base pairing of miRs with 3′ untranslated regions of the target miR results in degradation or translational inhibition. Besides, miRs have been linked

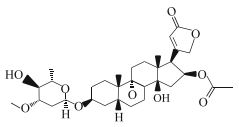
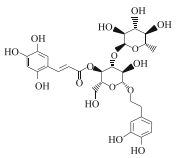
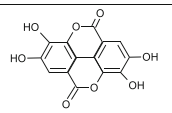
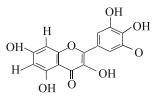
Table 1 Major DPs and their molecular targets to inhibit metastasis cascade

Bioactive dietary phytochemicals	Chemical structure	Source	Molecular target
EGCG		Green tea (*Camellia sinensis*)	↓Notch; ↓STAT1; ↓STAT3; ↓STAT5; ↓SIRT1; ↑DR4; ↑DR5; ↓PTCH; ↓cyclin D; ↓cyclin E; ↓CDK1; ↓CDK2; ↓CDK4; ↓CDK6; ↓PCNA; ↑16; ↑p18; ↑p21; ↑p27; ↑pRb; ↓GLI; ↑Fas; ↑p53; ↑mdm2; ↑ROS; ↑caspase-3; ↑caspase-8; ↑caspase-9; ↑cytochrome c; ↑Smac/DIABLO; ↓↑Bax; ↑Bak; ↑cleaved PARP; ↓Bcl-2; ↓Bcl-xL; ↓Bid; ↓c-myc; ↓pAKT; ↓pmTOR; ↓c-IAP1; ↓c-IAP2; ↓Mcl-1; ↓survivin; ↓XIAP; ↓CYP1A1 ↓CYP2E; ↓PI3K; ↓AKT; ↓↑ERK; ↓p90RSK; ↓FKHR; ↓PDGFRα; ↓EGFR; ↓↑c-fos; ↓EGR-1; ↓AP-1; ↓NF-κB; ↓IKK; ↓COX-2; ↑JNK; ↑Ras; ↑MEKK1; ↑MEK3; ↓↑p38; ↑IjB; ↑AMPK; ↑PGE2; ↑TNF-α; ↓HIF-1α; ↓VEGF; ↓VEGFR1; ↓VEGFR2 ↓ErbB2; ↓ErbB3; ↑FOXO; ↓MMP-2; ↓MMP-9; ↓FAK; ↓proMMP-2; ↓MRLC; ↓Vimentin; ↓Laminin; ↓Integrina2b1; ↓uPA; ↓HuR; ↑proMMP-7; ↑TIMP-2; ↑MT1-MMP; ↓DNMTs; ↑HAT; ↓HDCA; ↓acetylation of H3/H4; ↑RARb; ↑MGMT; ↑MLH1; ↑CDKN2A; ↑RECK; ↑TERT; ↑RXRa; ↑CDX2; ↑GSTP1; ↑WIF1; ↓20S/26S proteasome complex; ↑acetylation of histones
Resveratrol		Grapes (*Vitis vinifera*)	↓TLR4; ↓STAT; ↓Notch; ↓Mcl1; ↓PGC-1α; ↓p-AKT, ↓HER-2/neu; ↓Bcl-2, ↓Bcl-xL, ↑Bax; ↑Bak1; ↓PKB; ↓p-mTOR, ↓AMP-activated protein kinase; ↑caspases, ↑p21 Cip1/WAF1↑HO-1, ↓$p27^{Kip1}$; ↓VEGF, ↓IKK; ↑Bik/Nbk; ↑Bnip3; ↑Hrk/Dp5; ↑Bid; ↑PmaiP1/Noxa; ↑Bbc3/Puma; ↑PARP; ↑Bmf; ↓IFN-γ; ↓5-LOX, ↓COX-2; ↓COX-1; ↓iNOS, ↓AR, ↓PSA, ↓kallikarin-2; ↓ ARA70; ↓MEK, ↓QR2; ↓NF-κB, ↓SIRT1, ↓endothelin-1; ↑cytochorome c; ↓c-IAP1; ↓c-IAP2; ↓Mcl-1; ↓XIAP; ↑p53, ↓survivin, ↓cyclin D1, ↓cyclin A1, B1, D1 and E; ↓ROS; ↓CIAP, ↓Egr-1, ↓PKC, ↓PKA; ↓JNK, ↓PKD, ↓casein kinase II, ↓IL-1, ↓IL-2; ↓IL-6, ↓IL-8, ↓IL-12; ↑Nrf2, ↓AP-1, ↓CYP1A1, ↓TypeII-Ptdlns-4kinase, ↓Cdc2 (Tyr15); ↓estrogen receptor α; ↓nuclear factor-E2-related factor-2;
			↑acetylation of histones; ↓CYP1B1; ↓E-Selectin; ↑TGF-β2; ↑TGF-α; ↓IGF-1R; ↑ nSMase; ↑ceramide; ↓Cdk4; ↓PPARγ
Curcumin and curcuminoids		Turmeric (*Curcuma longa*)	↓Notch-1; ↓ELAM; ↓SHP-2; ↑Nrf2, ↑MDR, ↑caspases; ↑PARP; ↓p-mTOR; ↓HER2; ↓NF-κB; ↓COX-2; ↓AP-1; ↓TF; ↓Egr-1; ↓STAT1; ↓STAT3; ↓STAT4; ↓STAT5; ↑GSH-px; ↓PPARγ; ↓EpRE; ↓CBP; ↓β-catenin; ↑IKK; ↓EGFR; ↓pAKT; ↓Src; ↓JAK2; ↓TYK2; ↓JNK; ↓PKA; ↓PKC; ↓VCAM-1; ↓Bcl-2; ↓Bcl-xL; ↓ICAM-1; ↓AR/ARP; ↑p14ARF; ↑p16; ↑p21; ↑p53, ↓ELAM-1; ↓FTPase; ↑GST; ↓uPA; ↑HO; ↓XOD; ↓cyclin D1; ↓5-LOX; ↓iNOS; ↓MMP-9; ↓MPP-10; ↓TNF; ↓IL-1; 2, 6, 8, 12, 18; ↑Bax; ↑Bad; ↑Bim; ↑Cdk inhibitors; ↓VEGF; ↓MIF; ↓MIP; ↓ MCP; ↓PLD; ↓PKB; ↓CDPK; ↓cAK; ↓ERK; ↓pp60c-src; ↓FAK; ↓IRAK; ↓MAPK; ↓VCAM; ↓ICAM-1; ↓WT1; ↓Hsp70; ↓NAT-1; ↓CTGF; ↓MDR-1; ↓TIMP-3; ↓IAP; ↑DR-5; ↑Fas
Genistein		Soyabean (*Glycine max*)	↓HDAC; ↓DNMT1; ↓GLI-1; ↓Wnt-1, 5, 7; ↓c-myc; ↓cyclin D1; ↓Notch; ↓NF-κB1; ↑caspase-3; 12; ↑p21/WAF1; ↑glutathione peroxidase; ↑PARP; ↓pAKT; ↓pmTOR; ↓β-catenin; ↓PPARγ; ↓BCL11A; ↓Bcl-2; ↓Bcl-xL; ↓BCLAF-1; ↓FAIM2; ↓MAP2K5; ↑Fas; ↑TNFSF9; ↑BIRC3; ↑Bam; ↓KIF-2C; 4A 14, 15, 20, 23; ↓BUB1; ↓PLK-1; 4, ↓CENPO; ↓CENPF ESPL1; ↓DLG7; ↓TTK; ↓NEK2; ↓SPC25; ↓E2F2; ↓E2F8; ↑NEU1 (sialidase1); ↑CD68; ↑Insig1; ↑GPNMB; ↑Nrf2; ↓EGF-R; ↓v-src; ↓5-LOX; ↓iNOS; ↓JNK; ↓JAK; ↓CD44; ↓MAPK; ↓TGF-β; ↑FOXO; ↓HOX; ↓ER; ↓EGFR-TK; ↓PDGFRα; ↓TNF-α; ↓IL-1β; ↓IL-6; ↓HDAC; ↓DNMT1; ↑HAT
Sulforaphane (SNF)		Cruciferous vegetables (*Brassica* sp.)	↓p34(cdc2); ↓E2F-1; ↑GSK3β; ↓CYP3A4; ↑DR4; ↑DR5; ↑Fas; ↓DNMT1; ↓HADC; ↓cIAP1; ↓cIAP2; ↓XIAP; ↓AP-1; ↓NF-κB; ↓survivin; ↓cyclin D1; ↓Bcl-2; ↓Bcl-xL; ↑Bak; ↑Nrf2; ↑caspase-3; 8, 9; ↑PARP; ↓Wnt-9a; ↓β-catenin; ↓ERK/MAPK; ↓MPP-9; ↓Hsp90; ↑ROS; ↑acetylation of histones; ↓TLR4; ↑QR; ↑GSTA1; ↑HO-1; ↑JNK1/2; ↓CDK4, 6

with tumorigenesis by functioning as tumor metastasis suppressors or oncogenes. Acting in these properties, miRs have been revealed to be expressed in a tissue-specific manner and modulate the hallmarks of cancer progression, including stress response, differentiation, sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Fig. 3) [34]. Several well-orchestered

Table 1 (continued)

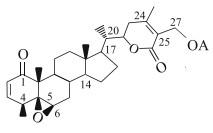
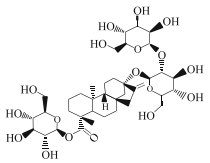
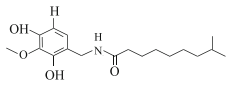
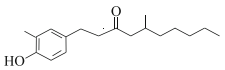
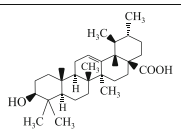
Silymarin, silibinin		Milk thistle (*Silybum marianum* L.)	↓COX-2; ↓cyclin D1; ↓NF-kB; ↓AP-1; ↓MMP-9; ↓JNK, ↑IFN-γ; ↑IL-4; ↑IL-10; ↑Bcl-2/Bax; ↑PARP, ↑p53; ↑p21CIP1; ↑caspases; ↑cytochrome C; ↑Apaf-1; ↓EGFR; ↓MAPK; ↓ERK1/2; ↓IGF-receptor; ↓MMP-2; ↓TNF-α; ↓COX-2; ↑Kip1/p27; ↓cyclin D1; ↓cyclin D3; ↓cyclin E; ↓Cdk2; ↓Cdk4; ↓CDC2 kinase; ↓IKKβ; ↓TGF-β; ↓c-myc; ↑IkappaBα; ↓erbB1-Shc
Emodin		Aloe (*Aloe vera*)	↓mTOR complex2; ↓AKT; ↓ERCC1; ↓PKCδ; ↓Rad51; ↓AR; ↑caspase-3; ↑caspase-6; ↑caspase-9; ↓HER-2/neu; ↓ABCG2; ↓NF-κB; ↓CYP1A1; ↓CYP1B1; ↓MMP-2; ↓MMP-9; ↓PRL-3; ↓VEGF; ↓eNOS; ↓Bcl-2; ↑Bax; ↓CXCR4; ↓RhoB; ↑ROS; ↓calpain-2; ↓E3A; ↓Her2/neu; ↓surviving; ↑Cytochrome C; ↓IL-6; ↓JAK2/STAT3; ↓Mcl-1; ↓PI3K-Cdc42/Rac1; ↓MDR1; ↓HIF-1α
Guggulsterone		Guggulu (*Commiphora mukul*)	↓NF-kB p65; ↓IAP1; ↓XIAP; ↓Bfl-1/A1; ↓Bcl-2; ↓cFLIP, ↓survivin; ↓cyclin D1; ↓c-Myc; ↓MMP-2; ↓MMP-9; ↓COX-2; ↓VEGF; ↓BAR; ↓CYP7A1; ↓FXR; ↑CYP3A; ↓Cyp2b10; ↑Bax; ↑Bad; ↑cytochrome C; ↑PARP; ↑caspase-3; ↓VEGF-C; ↑STAT3; ↑EGFR; ↓PI3K/AKT; ↓CdX2; ↓HIF-1α; ↓cIAP-1; ↓cIAP-2; ↑Bid; ↑Fas; ↑pJNK; ↑p-c-Jun; ↓IKKα/β; ↓p38 MAPK; ↓ERK1/2
Boswellic acid		Boswellia (*Boswellia serrata*)	↓5-LOX, ↓IAP ↓NF-κB, ↓cyclin D1, ↓Bcl-2, ↓Bcl-xL, ↑p38 MAPK, ↑p42 MAPK, ↓survivin, ↓STAT3; ↓SHP-1; ↓iCAM-1, ↓TNF; ↓Fxr; ↓ER; ↓cFLIP; ↑BSEP; ↑SOCS-3; ↑p21↓XIAP; ↓AP-1; ↓c-myc; ↓C/EBPα, β; ↓Bfl-1; ↓GM-CSF; ↓Cyclin D1; ↓Mcl-1; ↓MRP; ↑caspase-3, 7, 8, 9; ↑cytochrome C; ↓Src; ↓CYP7A1; ↓PXR; ↓CDC2; ↓AR; ↓GR; ↓AKT; ↓PR; ↓VEGFR; ↓VEGF; ↓PPAR-γ; ↓JAK; ↓PXR; ↓COX-2; ↑VDR; ↑JNK; ↑PARP; ↑p27

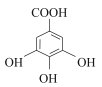
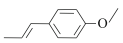
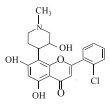
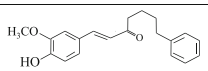
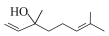
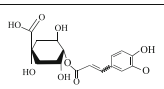
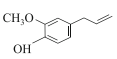
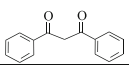
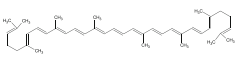
Oleandrin		Oleander (*Nerium oleander*)	↑Caspase-3; ↑Fas; ↓NF-κB; ↑ROS; ↑FGF-2; ↓AP-1; ↑DR4; ↑DR5; ↓JNK; ↓COX-2; ↑PARP; ↓cyclin D1; ↓MMP-9; ↓pERK;
Verbascoside		*Verbascum* sp *Pithecoctenium* sp *Tynanthus panurensis* *Leucosceptrum* sp	↑PARP-1; ↑p53; ↑caspase-3; ↓ROS; ↓COX-2; ↓iNOS; ↓NF-κB;
Ellagic acid		Pomegranate (*Punica granatum*)	↑Nrf2; ↓NF-κB; ↑Bax; ↑caspase-3, 9; ↓COX-2; ↓cyclin A, B1; D1; ↑cyclin E; ↓MMP-1, 8, 9, 13; ↓PDGFR; ↓VEGFR-2; ↑p21/WAF1; ↑p53; ↓CDK2; ↑cytochrome C; ↑CDl lb; ↑MRP-14; ↓ATP; ↑ROS; ↓Bcl-2; ↓Bcl-xL; ↑TGFβ;
Quercetin		Onion (*Allium cepa*) Citrus fruits (*Citrus* spp.) Apple (*Malus domestica*)	↑anti-CD95; ↓XIAP; ↑caspase-2, 3, 7, 9; ↓Bid; ↑PARP; ↑Gadd 45; ↓NF-κB, ↑Bax; ↓Bcl-2; ↓cyclin D1; ↑p53; ↓survivin; ↑ROS; ↓Hsp70; ↑p38/MAPK; ↓AKT; ↓ERK; ↓TNF-α; ↓Bcl-xL:Bcl-xS; ↓Bcl-2; ↓c-Jun; ↑phospho-p53; ↑p21; ↓Bcl-2/Bax; ↑DR4; ↑DR5; ↓Mcl-1; cytochrome C; ↑AIF; ı
Zerumbone		Pinecone ginger (*Zingiber zerumbet*)	↓IL-2, 6, 12; ↑Bax; ↓Bcl-2; ↑p21; ↑DR4; ↑DR5; ↑p38/MAPK; ↓NF-κB; ↓cIAP1; ↓XIAP; ↓Bfl-1/A1; ↓Bcl-2; ↓cFLIP; ↓survivin; ↓cyclin D1; ↓c-Myc; ↓MMP-9; ↓COX-2; ↓TRAF1; ↑p53; ↑caspase-3; ↓IKKα; ↓AKT; ↓FOXO1; ↓cyclin B1; ↓cdk-1; ↑↓Cdc25C; ↓Cdc25B; ↑Nrf2; ↑NQO1; ↑HO-1; ↑Cdc2

regulatory mechanisms involving miRs have been identified, with the potential to target multiple signaling pathways dysregulated in a wide variety of human cancers [34, 35]. Various miRs including let-7, miR-221, miR-146a, miR-519, and miR-222 act as tumor suppressors in human cancer cells and tissues. Since miRs frequently target hundreds of miRs and expression of multiple genes and thereby tune multiple points in cancer metastasis, miRs and their regulated genes represent interesting drug targets (Fig. 3).

In addition to epigenetic modifications, miRs can regulate the expression of numerous functional proteins by regulating miR stability and translation in cancer progression. Fabbri and coworkers reported that miR-29 family can increase expression of DNMT3a and DNMT3b, thereby causing a global

Table 1 (continued)

Withonalide		Ashwagandha (*Withania somnifera*)	↓survivin; ↓cyclin D1; ↓cIAP; ↓NF-κB; ↓COX-2; ↓MMP-9; ↓cyclin E; ↓Bcl-2; ↓Bcl-xL
Stevioside		Bertoni (*Stevia rebaudiana*)	↑Bax; ↑cytochrome c; ↑ROS; ↑NF-E2-related factor-2; ↑caspase-9;
Capsaicin		Red chilli (*Capsicum annum*)	↑GSK3β; ↑ATF3; ↑C/EBPβ; ↓NF-κB; ↑GADD153; ↑GRP78; ↓Smac/DIABLO; ↓XIAP; ↑Bad/Bax; ↓cyclin B1, D1; ↓cdk-1, 2, 4; ↑ROS; ↑PARP; ↑ACC; ↑NAG-1; ↓survivin; ↓cyclin D1; ↓Cdc2; ↓Bcl-2; ↓Bcl-xL; ↓cIAP1; ↓Cdc25; ↓Cdk1; ↑Fas, ↑DR4; ↑caspase-3; ↑p53; ↑Bax; ↑cytochrome c; ↓JNK; ↓ERK; ↓AKT
Gingerol, paradol		Ginger (*Zingiber officinale*)	↑caspase-3, 9; ↑Bax; ↑p53; ↓Bcl-2; ↓survivin; ↓NF-κB; ↓AP-1; ↓COX-2; ↓p38MAPK; ↓cyclin A, D2, E; ↓cdk; ↓Rb; ↓ODC; ↓iNOS; ↓HIF; ↓VEGF; ↓TNF; ↑$p21^{cip1}$; ↓AKT; ↓cdc25A; ↑CDKI; ↑p15; ↑p27; ↓MMP-2, 9; ↓Apaf-1; ↑cytochrome c
Ursolic acid		Prunes and plums	↑DR4; ↑DR5; ↓STAT3; ↓NF-κBp65; ↓NF-κBp50; ↓NF-κBc-Rel; ↓c-FOS; ↓ATF-2; ↓CREB-1; ↑caspase3, 8, 9; ↓EGFR; ↓ERK1/2; ↓p38 MAPK; ↓JNK; ↓Bcl-2; ↓Bcl-xL; ↓miR-21; PDCD4; ↓COX-2; ↓cyclin D1; ↓MMP-9; ↓VEGF; ↓PTEN; ↓PI3K/AKT; ↑TNF-α; ↓IL-1β; ↓IL-6; ↓GM-CSF; ↑Fas; ↑PARP; ↓c-scr; ↓Mcl-1; ↓survivin

Gallic acid		Guava (*Psidium guajava*) (*Toona sinensis*)	↑TNF-α; ↑TP53BP2; ↑GADD45A; ↓survivin; ↓cIAP1; ↑cdc25A/C-cdc2; ↑caspase-3, 9; ↑PARP; ↓I-κB; ↑p53; ↑NF-κB; ↑ROS; ↓Bcl-2, ↑Bax, ↓pAkt; ↓IL-1β; ↓IL-6; ↓CCL-2/MCP-1; ↓CCL-7/MCP-3; ↓COX-2; ↓MMP-9
Anethole		Sweet Fennel (*Foeniculum vulgare*)	↓IκBα; ↓NF-κB, ↓AP-1, ↓p38; IL-1β; IL-17; ↓JNK, ↓MAPK; ↓TNF-α; ↓MMP-2, 9; ↑TIMP-1; ↓AKT; ↓ERK
Flavopiridol		Rohitukine (*Dysoxylum binectrariferum*)	↑E2F1; ↓Mcl-1; ↓NF-kB; ↓MDM2; ↓COX-2; ↑caspase-3, 8; ↑Bid; ↓cyclin D1, ↓MMP-9, ↓Bcl-2; ↑Bax; ↑cytochrome c; ↓Bcl-xL; ↓Mcl-1; ↓c-Jun; ↑Smac/DIABLO; Bcr/Abl; Lyn, Hck, CrkL; AKT; ↑SEK1/MKK4; ↓↑p38/MAPK; ↓p44/p42 MAPK; ↓IAP-1; ↓IAP-2; ↓XIAP; ↓TRAF-1; ↓adhesion molecule-1; ↓c-Myc; ↓c-Fos; ↑PARP; ↓ERK
Yakuchinone A&B		Galanga (*Alpinia officinarum*)	↓AP-1; ↓COX-2; ↓iNOS; ↓NF-kB; ↓adhesion molecules; ↓TNF; ↓5-HETE
Linalool		Coriander (*Coriandrum sativum*)	↓NF-kB; ↓Bcl-xL; ↓AP-1; ↓JNK; ↓MAPK
Caffeoylquinic acid		Quince (*Cydonia oblonga*)	↑PGAM1; ↑G3PDH; ↓NF-κB; ↓JNK; ↓PI3K; ↓AKT; ↓COX-2; ↓cyclin D1; ↓MMP-9; ↓Bcl-2; ↑ATP
Eugenol		Cloves (*Eugenia caryophyllus*)	↑PARP; ↑p53; ↑caspase-3; ↓NF-κB; ↑ROS; ↓MMP-2, 9; ↓VEGF; ↓VEGFR1; ↓TIMP-2; ↓RECK; ↓Bcl-2; ↓Bcl-xL; ↑cytochrome c; ↑Bax; ↑Bid; ↑Bad; ↑Apaf-1
Dibenzoylmethane		Licorice (*Glycyrrhiza echinata*)	↓ cyclin A, D1; ↓c-Myc; ↓pRb; ↑ROS; ↓COX-2; ↑caspase-3; ↓LOX; ↑cytochrome c; ↓HIF; ↓VEGF; ↑$p21^{CIP1}$; ↓PDK-1; ↓pAKT; ↓pS6
Lycopene		Tomato (*Lycopersicon lycopersicum*) Gac (*Momordica cochinchinensis*)	↓cyclins D1, E; ↓cdk 4; ↓pRb; ↓pAKT; ↑IGF-BP; ↓PPARγ; ↑RARβ; Nrf2; ↓IGF-1; ↓JNK

genomic hypermethylation and silencing of methylation-sensitive tumor suppressor genes (TSGs) such as FHIT and WWOX [36]. Several studies have indicated that tumor suppressor miRs repress tumor formation, thus reinstating that these miRs could be therapeutically beneficial [37]. Recent evidence further suggests that DPs can restore tumor suppressor activity of miRs, with successful suppression of metastasis cascade which include induction of cell death and inhibition of cell proliferation

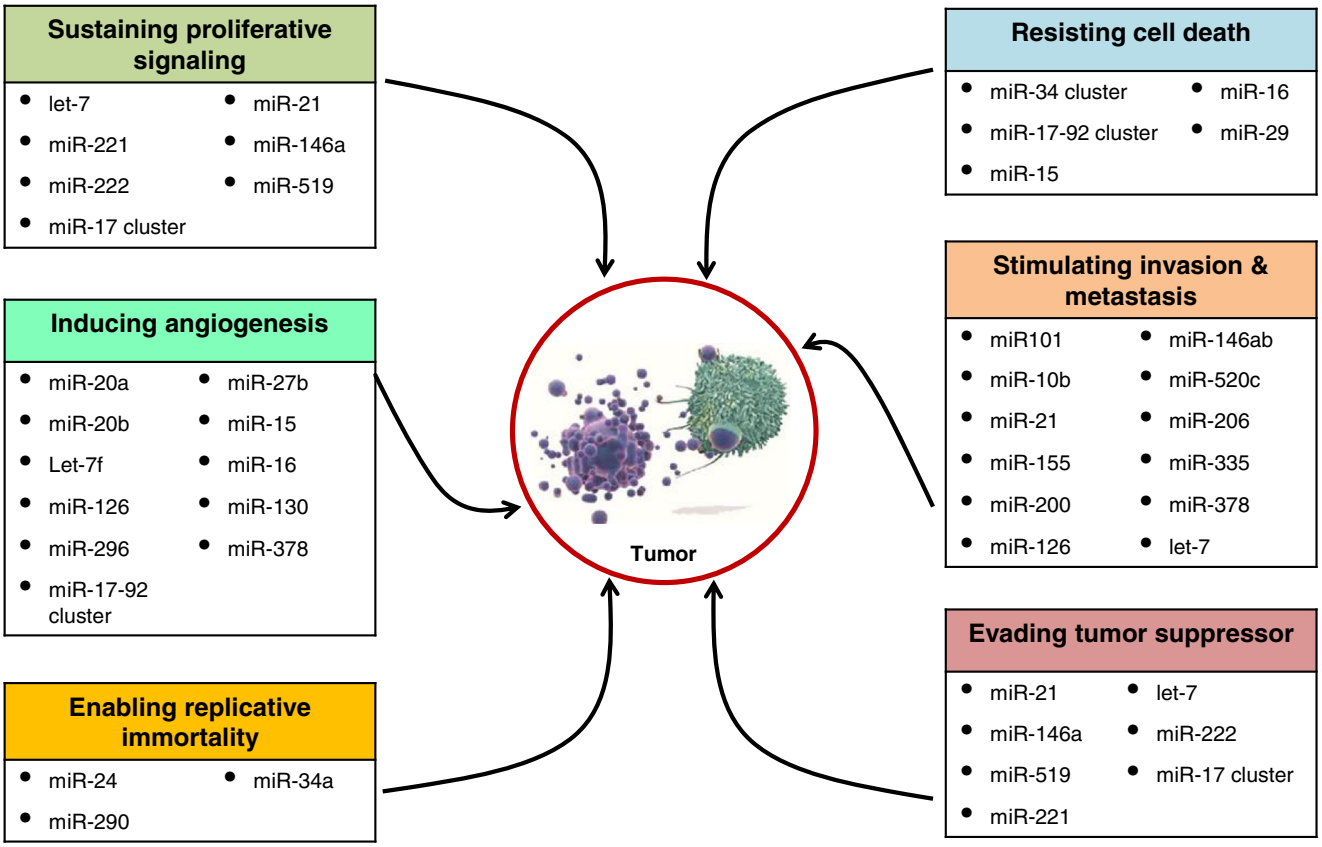


Fig. 3 Aberrant micro-RNA (miR) expression affects signaling pathways to enhance tumorigenesis. Representative miRs are depicted that have been shown to act as oncogenes or tumor suppressor genes to affect the six common hallmarks of cancer

(Fig. 4) [37]. So far, these "miR mimics" have been evaluated *in vitro* and experimental validation *in vivo* is awaited.

Recently, it has been shown that curcumin induces apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells, associated with upregulation of miR-186 (>2.5-fold) [38]. Moreover, curcumin suppressed the expression of miR-196 (an oncogenic miR) and induced miR-22 expression (a tumor suppressor miR) in gastric cancers [38]. The expression of miR-200 was downregulated upon difluorinated curcumin (CDF), alone or in combination with curcumin, leading to the induction of tumor suppressor phosphatase and tensin homolog (PTEN) in pancreatic cancers. Besides, CDF also suppressed sphere-forming ability by modulating miR-21 and miR-200 expressions and cancer stem cell (CSC) markers [39]. Very recently, CDF (a novel analog of the dietary ingredient curcumin) has been shown to inhibit the growth of 5-flurouracil + oxaliplatin-resistant colon cancer cells, downregulated miR-21 in chemoresistant colon cancer HCT116, HT-29, and metastatic SW620 cells but also restored PTEN levels with subsequent reduction in Akt phosphorylation [40]. Recently, Tili and colleagues observed that resveratrol downregulated the expression of oncogenic miRs, miR-21, miR-196a, miR-25, miR-17, and miR-92a-2, and simultaneously induced miR-663-dependent regulation of Dicer, PDCD4, PTEN, and transforming growth factor (TGF)β signaling by regulating the SMAD promoter in colon cancer cells [41]. Resveratrol treatment to monocytic cells inhibited AP-1 expression by upregulating miR-663 and also reduced expression of oncogenic miR-155 [42]. 1,3-di-*O*-galloyl-4,6-(*s*)-HHDP-b-D-glucopyranose, an ellagitannin, was found to be upregulated in 17 miRs and downregulated in 8 miRs, including let-7 family members, miR-370, miR-373, and miR-526b, thereby inhibiting metastasis events such as proliferation and differentiation in HepG2 cells [43].

Exposure of pancreatic cancer cells to soy genistein suppressed their invasive potential due to induction of miR-146a and downregulation of EGFR, NF-κB, IRAK-1, and MTA-2 [44]. Soy isoflavones, including genistein, daidzein, and glycitein, were recorded to downregulate the expression of miR-200, miR-223, and let-7 families in gemcitabine-resistant versus gemcitabine-sensitive pancreatic cancer cells [45, 46]. Nevertheless, these isoflavones upregulated miR-200 and let-7 family miRs, which are associated with suppression of EMT transcription factors, such as vimentin, slug, and ZEB1. Treatment of genistein downregulated the expression of MCM2 in prostate cancer cells by inducing miR-1296 expression (5-fold) thereby resulting in inhibition of growth and metastasis [47]. Genistein inhibited proliferation of human

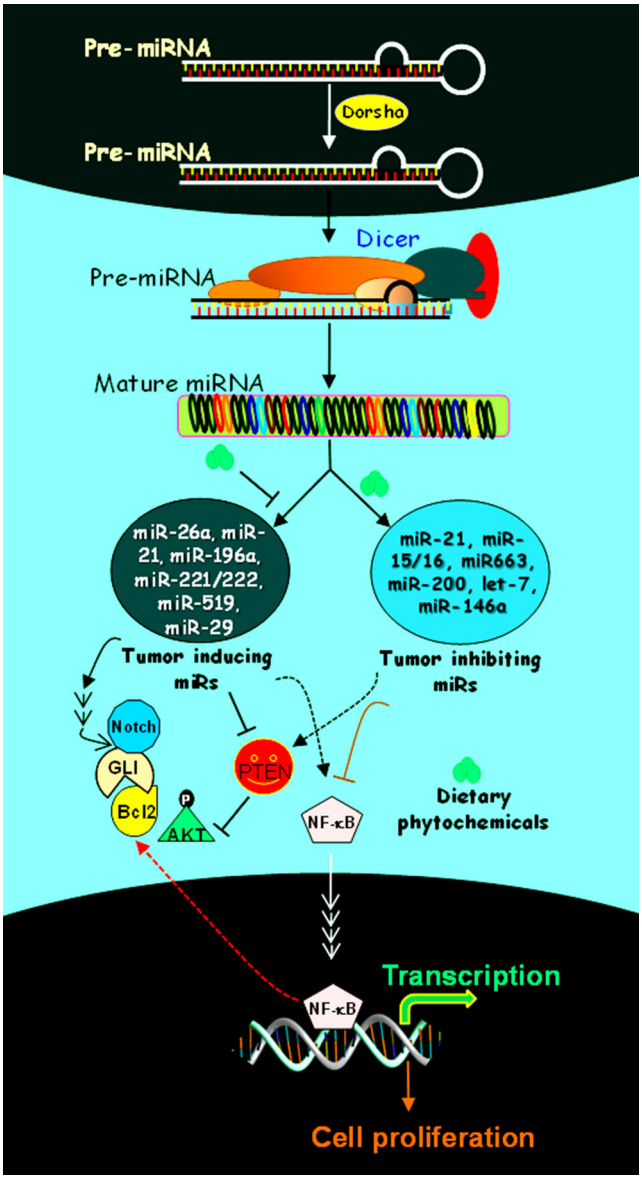


Fig. 4 Regulation of micro-RNA (miR) expression by DPs. Pri-miR (primary miR) are transcribed in the nucleus into which is further cleaved by Drosha into precursor miR (pre-miR). Pre-miR is exported from nucleus to the cytoplasm and further processed by Dicer into miR duplex. Single strand of miR duplex (also called mature miR) leads this complex to miR cleavage or translation repression, which is dependent on miR: mRNA complementarity. Dependent on various factors, miR can have either an oncogenic role, called as onco miRs) if the target mRNA is a tumor suppressor gene or a tumor suppressive role, called as tumor suppressor miRs if the target molecule is an oncogene. DPs can alter the expression level of miRs and participate in gene expression regulation

uveal melanoma cells by downregulating miR-27a, while on the other hand, its target gene, ZBTB10, was found to be upregulated [48]. Izzotti et al. found that PITCH alone or in combination with indole-3-carbinol (I3C) restores tumor inhibitor miRs such as miR-192 (Ras activation); let-7a, let-7c (cell proliferation, angiogenesis, Ras activation); miR-146 (NF-κB activation); and miR-123, miR-222, (angiogenesis, cell proliferation), and miR-99b (apoptosis) [49]. Reactivation of miRs by targeting ERBB2 activation (miR-125a), p53 functions (miR-34b), TGF-β expression (miR-26a), and angiogenesis (miR-10a) was recorded with the treatment of five dietary agents, including I3C in rats exposed to environmental cigarette smoke [50]. EGCG has been recently found to suppress the expression of oncogenic miRs and induce tumor inhibitor miR-16 in HepG2 cells [51]. Induction of miR-16 was associated with apoptosis induction by downregulating Bcl-2. Overall, these investigations support a growing interest in the chemopreventive DPs as regulators of miR cancer metastasis and invasion (Fig. 4).

2.2 DNA hypermethylation

DNA methylation refers to the covalent addition of a methyl group to the fifth carbon position in the pyrimidine ring of cytosine in eukaryotic DNA. DNA methylation typically occurs at the context of CpG dinucleotides, whereas non-CpG methylation is often found in embryonic stem cells. DNA methylation is regulated by a group of proteins known as the DNA methyltransferases (DNMTs) (for references see [22]). Several studies have shown that hypermethylation of CpG islands in gene promoter and abnormal gene silencing may be one key cellular modification which can allow cancer cells and CSCs to survive the toxic surroundings of cancer risk states and take advantage of key gene mutations (Fig. 5) [52]. Various genes involved in angiogenesis, metastasis, invasion, cell cycle regulation, apoptosis, drug resistance, detoxification, and genes associated with DNA have been found to undergo hypermethylation in cancer (for more references see [53]).

Epigenetic regulation, specifically DNA hypermethylation, has attracted considerable interest as a molecular target of chemopreventive phytochemicals for prevention and therapy of cancer. Many nutraceutically important phytochemicals have shown promising results in suppression of DNMT activity and reactivation of TSGs [4]. For example, green tea EGCG [54], genistein [55], apigenin [56], curcumin [57], sulforaphane (SFN) [57, 58], and resveratrol [59] have been demonstrated to inhibit DNA hypermethylation (Fig. 5) (for more reference see [17]). Recently, green tea polyphenol has shown to play a role in the reactivation of glutathione *S*-transferase pi 1 (GSTP1) by inhibiting DNMT1 activity in LNCaP cells [60]. A major green tea polyphenol (GTP), EGCG, was found to inhibit DNMT1 activity and reactivate several genes including $p16^{INK4a}$, retinoic acid receptor β (RARβ), MGMT, and hMLH1 of human esophageal KYSE 510 and 150 cells [54]. It also induced promoter demethylation of WIF-1 in lung cancer cells [61]. Authors also reported that EGCG can block the entry of the key nucleotide cytosine into the active site of DNMT by hydrogen bonds and, thus,

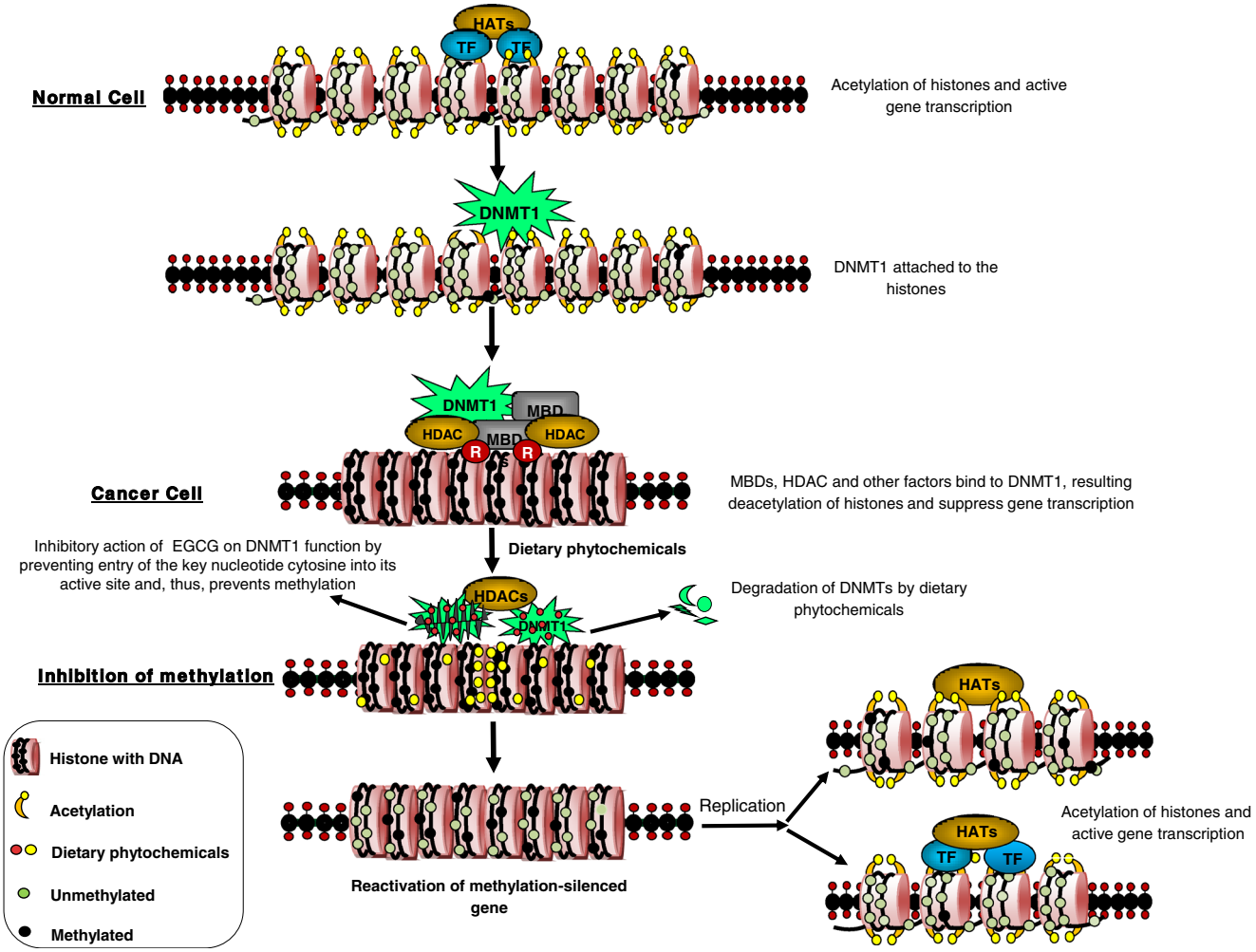


Fig. 5 DPs affect DNA methylation pattern. In normal cells, genes are generally unmethylated and packaged with acetylated histone proteins associated with histone acetyltransferases (*HATs*) as well as basal transcription factors. These epigenetic elements establish an "open" chromatin structure which favors active transcription. In cancer cells, the same genes may become hypermethylated. The methylated CpG sites are recognized by the methyl-binding proteins (*MBDs*), which are coupled with repressor (*R*) and histone deacetyltransferase (*HDAC*) proteins to remove the acetyl group from the histones, generating a tightly closed chromatin structure to switch off gene expression. DNA methyltransferase (*DNMT*) activity is inhibited by DPs. Newly synthesized DNA strands are hemi-methylated after the first round of DNA replication and become progressively more demethylated after several rounds of replication due to the dilution effect. Using DPs as DNMT inhibitors, the methylation-silenced genes could be reactivated to an active status

prevent DNA methylation, which was further confirmed by molecular modeling analysis. Berletch et al. found that EGCG suppressed tumor promoter genes such as human telomerase reverse transcriptase (*hTERT*), a catalytic subunit of telomerase [62]. Lee and coworkers observed that tea polyphenols such as catechin, epicatechin, EGCG, quercetin, fisetin, and myricetin suppressed significantly SssI DNMT/DNMT1-dependent DNA methylation [63]. Treatment of oral squamous carcinoma cells with EGCG has been shown to induce epigenetic reactivation of *RECK* leading to suppression of matrix metalloproteinases (MMPs) and inhibition of tumor invasion, angiogenesis, and metastasis [64]. Hypomethylation has also been observed in a wide variety of cancers including pancreatic, prostate, liver, colon, breast, cervical, and hematological cancers (for references see [17]). EGCG has been reported to inhibit ultraviolet B (UVB)-induced DNA hypomethylation pattern in a photocarcinogenesis model [65]. Indirect inhibition of DNA methylation pattern was also measured with the treatment of chlorogenic acid and caffeic acid [66]. This was associated with the decrease in available *S*-adenosyl-L-methionine and an increase in *S*-adenosyl-L-homocysteine and homocysteine levels. Later on, Fang and coworkers confirmed this conjecture by using EGCG as drinking water for experimental animals [56].

Various studies have shown that plant polyphenols can effectively inhibit carcinogenesis in various *in vitro* and *in vivo* systems. Inhibition of DNMTs was achieved by the treatment of SFN in breast cancer and colon cancer cells [58,

67]. In breast cancer cells, SFN inhibited expression of *hTERT*, but it had negligible effect on breast normal cells [58]. Reactivation of TSGs such as *GSTP1*, $p21^{WAF1/CIP1}$, and $p16^{INK4a}$ by genistein was found in prostate cancer cells, associated with the regulation of promoter methylation and histone modification [68]. Moreover, genistein induced reactivation of *BTG3* by inhibiting DNMT activity in renal carcinoma cells and *hTERT* expression in breast cancer cells [55]. In contrast to DNA methylation inhibitory effect of genistein, methylation of *RARβ2* and *CCND2* was also observed after genistein administration in premenopausal women, assessed in intraductal specimens [69]. Liu et al. reported that curcumin covalently blocks the catalytic thiolate of C1226 of DNMT1, which was confirmed by molecular docking analysis [70]. Authors also found hypomethylation in curcumin-treated leukemia cells's DNA. Resveratrol was found to partially prevent silencing of BRCA-1 in MCF-7 cells, which was related with the inhibition of DNMT1 activity, MBD2, and enrichment of mono-methylated H3K9 [59]. These effects of DPs on DNA methylation suggest their role in decreasing cancer metastasis and as potential therapeutic target.

2.3 Histone modifications

The alteration of posttranscriptional events, particularly histone acetylation and deacetylation by DPs through regulation of histone acetyltransferase (HAT) and histone deacetyltransferase (HDAC) activities, has received considerable attention in management of various cancers. In brain cancer cells, curcumin has been found to decrease acetylation of H3 and H4 by inhibiting HAT activity, associated with caspases-dependent cellular apoptosis [71]. Curcumin was also found to be associated with restoration of UV-hyperacetylated inflammatory-related genes: COX2, ATF3, and MKP1, in human keratinocytes [72]. Recently, Yun and coworkers have shown that curcumin inhibits high glucose-induced proinflammatory cytokines in THP-1 cells through inhibition of HAT activity, p300, acetylating CBP/p300 gene expression, and induction of HDAC2 expression [73]. In male Sprague–Dawley rats, curcumin administration was also found to downregulate H3 hyperacetylation, NF-κB binding, and p300 and H3S10 phosphorylation [74].

Exposure of human colorectal cancer HCT116 cells to SFN increased acetylation at the $p21^{WAF1/CIP1}$ promoter through downregulation of HDAC activity [75]. Additionally, pretreatment of SFN suppressed HDAC activity and enhanced expression of TOPflash (β-catenin-responsive reporter) in human embryonic kidney 293 cells [75]. SFN treatment also inhibited HDAC activity and increased histone acetylation-dependent expression of $p21^{WAF1/CIP1}$, thereby inducing growth arrest, apoptosis, and antimetastatic events in prostate cancer cells [76]. An animal study demonstrated that 7.5 μM SFN/animal for 21 days significantly suppressed prostate cancer PC-3 tumor xenografts via downregulation of HDAC activity [77]. Single oral administration of 10 μM SFN suppressed tumorigenesis in Apc/+ mice due to its HDAC inhibitory activity in colonic mucosa with increased acetylation of $p21^{WAF1/CIP1}$ and Bax expression [76]. Notably, a human study conducted by Myzak and colleagues found that a single dose of 68 g of SFN-rich broccoli sprouts downregulated HDAC activity significantly in peripheral blood mononuclear cells [77]. Taken together, SFN derived from cruciferous vegetables has been found to be a potent HDAC inhibitor both *in vitro* and *in vivo* models, which has can be formed as the basis for development of biopharmaceuticals.

In a study, EGCG strongly abrogated p300-induced p65 acetylation *in vitro* and *in vivo* which associated with the inhibition of HAT activity [78]. In addition, EGCG did not show any significant changes in HDACs, HMTs, and SIRT1 activities. However, recently, Pandey and coworkers demonstrated that GTPs at 1–10 μg/ml showed inhibitory potential on HDAC1-3 expression and increased the levels of acetylated histone H3 (LysH9/18) and H4 levels, thereby reactivating GSTP1 gene, which is an important hallmark in prostate tumorigenesis. These studies have also been initiated using combinations of EGCG and GTPs with known HDAC inhibitors such as vorinostat (SAHA) to de-repress TSGs regulating key cell functions such as metastasis, cell growth, and apoptosis in human cancer cells [79]. Administration of 0.05 % (*w*/*w*) polyphenon E induced a significant decrease in HDAC1 expression in dimethylaminoazobenzene-induced hepatocarcinogenesis in male Sprague–Dawley rats [80]. Further, soy genistein has also been reported to increase acetylation of histones at the $p21^{WAF1/CIP1}$ and $p16^{INK4a}$ transcription start sites by inducing HAT activity followed by cell cycle arrest and cyclin and caspase-dependent apoptosis [68]. Another polyphenol, resveratrol, induced activation of SIRT1 and p300 (type III HDAC inhibitors) in multiple *in vitro* and *in vivo* models, thereby regulating cell proliferation through inhibition of survivin expression, because of SIRT1 deacetylase activity (for references see [81]). In addition to the aforementioned phytochemicals, many other plant-derived bioactive molecules including apigenin, baicalein, cyanidins, isothiocyanate, rosmarinic acid, and silymarin have been reported to have antimetastasis activity either through inhibition of DNMT activity or histone modifications [56].

3 DPs potentially control metastasis by modulating signaling pathways

3.1 Wnt/β-catenin pathway

Wnt/β-catenin pathway was demonstrated to regulate the process of cell proliferation, migration, apoptosis, differentiation, epithelial–mesenchymal interactions, and stem cell self-

renewal [82]. It has been shown that the aberrant activation of the canonical Wnt/β-catenin signaling is one of the most frequent signaling abnormalities known in human cancers including gastric [83], leukemia [84, 85], endometrial [86], thyroid [87] melanoma [88], ovarian [89] breast [82, 90, 91], colon [92–94], liver [95], lung [96], and head and neck [97]. Activated Wnt signal promotes β-catenin accumulation in the nucleus, resulting in the consequent transcriptional activation of specific target genes (Fig. 6) such as c-myc, cyclin D, c-jun, gastrin, CD44, survivin, vascular endothelial growth factor (VEGF), endothelin-1, interleukin-8, nanog, snail, Jagged1, Sox17, PITX2, APCDD1, Wnt3a, P16ink4A, RANK ligand, and Met [99–101]. Excess accumulation of β-catenin in mouse mammary stem/progenitor cells was shown to promote resistance to radiation [100, 102]. To enhance the oncogenic potential, nuclear β-catenin induces the expression of antiapoptotic protein survivin that promotes cellular metastasis cascades such as invasion, migration, cell proliferation, and cell survival by increasing resistance against apoptosis which has been observed in human colorectal CSCs as well as cancer cells [88, 101, 103]. Hyperactivation of the Wnt/β-catenin signaling has been found in osteosarcoma tumorigenesis and metastasis. Wnt activity could define colon CSCs which could be regulated by the microenvironment as recently reported by Kanwar and coworkers [104]. However, the activation of the Wnt signaling may occur in a different manner in prostate or breast cancers because the mutations in adenomatous polyposis coli (APC) are rare. Beta-catenin, the essential mediator of canonical Wnt signaling, participates in cell to cell adhesion after its sequestration by the epithelial E-cadherin adhesion protein [105] and cooperation with the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF) as a transcription activator which eventually leads to activation of Wnt target genes such as c-Jun, c-myc, fibronectin, and cyclin D1 [101, 106]. β-catenin phosphorylation at Ser33/Ser37/Thr41 by glycogen synthase kinase 3 beta (GSK3β) leads to ubiquitin-proteasome degradation [107]. Activated phospho-Akt Ser473-phosphorylated Ser9 on GSK3β has been observed, which may be responsible for decreasing the activity of GSK3β, thereby stabilizing β-catenin [108].

Several natural products, such as genistein [109, 110], SFN [111], curcumin [112, 113], fisetin [114], green tea EGCG [111], resveratrol [115, 116], silibinin [117], lupeol [118], vitamin D3 [119], and lycopene [120], have been shown to suppress Wnt/β-catenin signaling in human cancers which could potentially be excellent candidates for targeting metastasis cascades in cancer cells and CSCs. Li and coworkers have reported that isoflavone inhibited Wnt signaling to induce apoptosis and inhibit prostate cancer cell growth [110]. This finding correlated with the induction of GSK3β binding to β-catenin, modulation of the GSK3β expression, and increase in β-catenin phosphorylation. Genistein inhibited basal and Wnt-1-induced growth and also inhibited the expression of downstream targets of Wnt/β-catenin signaling such as Wnt-1 targets, c-myc, and cyclin D1 [121]. Genistein also downregulated the expression of Wnt-5a [122] and Wnt-7a [123]. Downregulation of Wnt signaling by genistein was confirmed using microarray gene expression analysis and animal experiments [122]. Moreover, treatment of genistein showed decreased expression of Wnt-targeted genes such as cyclin D1 (inhibitor of apoptosis), in mammary ductal epithelium [122]. More importantly, exposure of HEK293 cells with genistein could decrease the migration effect of Dkk-1 and significantly increase the membrane localization of β-catenin and E-cadherin, suggesting the inhibitory effects of genistein on Wnt signaling and metastasis [124].

Beta-catenin/TCF transcription activity was significantly inhibited by curcumin treatment in all tested cancer cell lines, including gastric, colon, and intestinal cancer cells, which was attributed to the reduced accumulation of nuclear β-catenin and TCF-4 proteins examined by Park and coworkers. [125]. Very recently, it was observed that the suppression of mammosphere formation along serial passage and reduction in the percent of ALDH-positive cells in breast stem/progenitor cells is related with the treatment of curcumin. On the contrary, curcumin had little impact on differentiated cells [126]. This study confirmed that the therapeutic effect of curcumin on breast cancer stem/progenitor cells was mediated through its potent inhibitory effect on Wnt/β-catenin signaling confirmed by using the TCF/LEF reporter assay [126]. In HCT116 intestinal cancer cells, curcumin-induced caspase-3-mediated cleavage of β-catenin leads to inhibition of Wnt/β-catenin signaling [127]. Furthermore, the expression of Wnt receptor Frizzled-1 was potently suppressed by curcumin confirmed by gene transcription profile analysis [128]. Inhibitory effect of β-catenin to Wnt-3a was observed by curcumin in colon cancer cells through the downregulation of p300, a positive regulator of Wnt/β-catenin signaling and metastasis [129].

Green tea catechin EGCG along with fish oil suppressed tumor formation in APCmin/+ mice [130]. EGCG treatment resulted in a significant reduction in nuclear β-catenin levels, further implicating the Wnt/β-catenin signaling pathway. Similarly, in breast cancer cells, EGCG was found to inhibit Wnt/β-catenin signaling [131]. Additionally, administration of EGCG decreased expression of Wnt-induced genes such as TCF/LEF binding and suppressed c-myc expression. This suppression of Wnt/β-catenin signaling was mediated through the stabilization of HBP-1 (a potential transcriptional suppressor of Wnt/β-catenin signaling and metastasis) [132]. Downregulation of Wnt-9a expression by SFN has also been examined in ApcMin/+ mouse adenomas [133]. The expression of β-catenin was shown to be significantly downregulated in human cervical carcinoma HeLa and hepatocarcinoma HepG2 cells treated with SFN [134]. This positive effect of

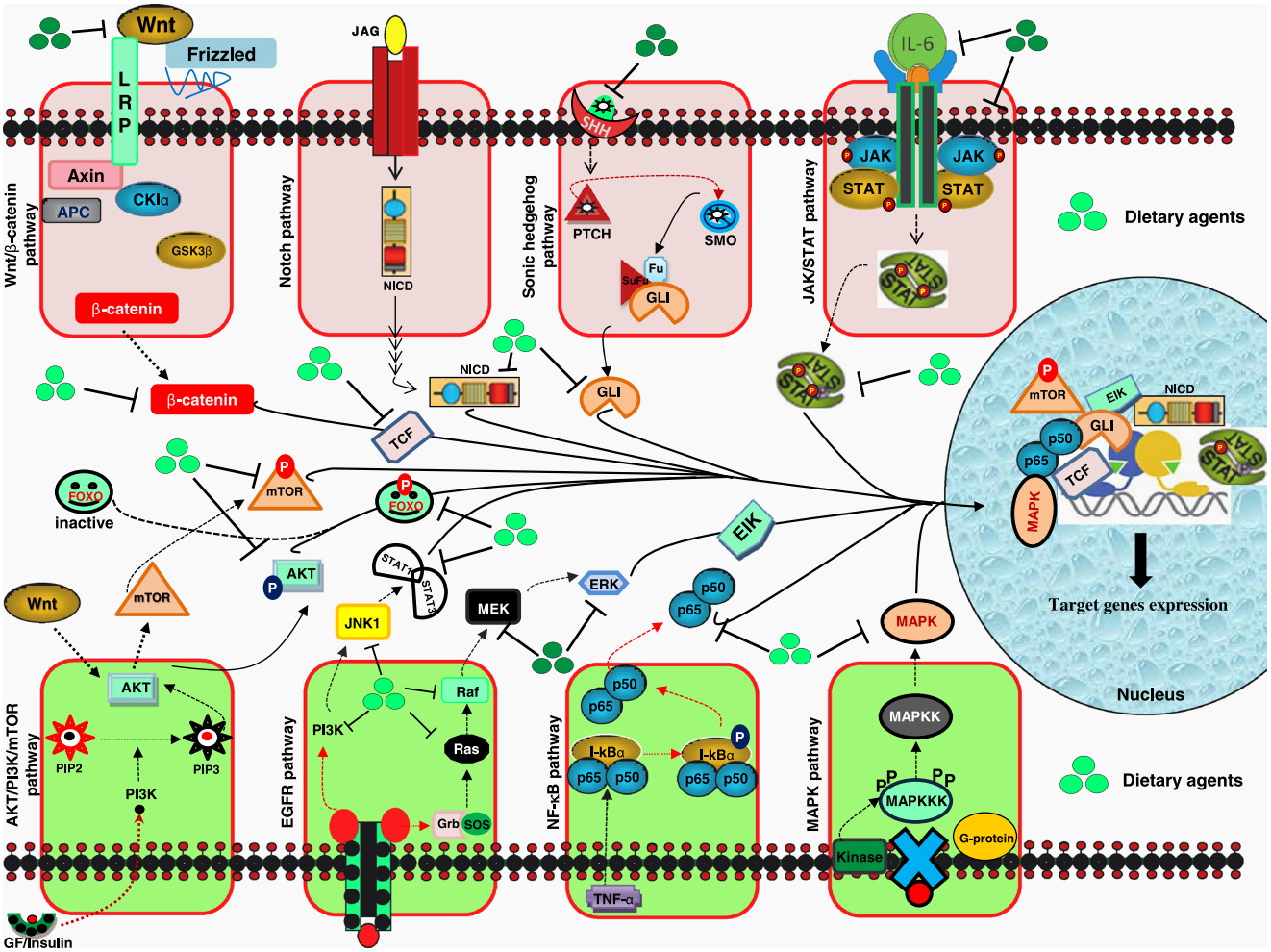


Fig. 6 Regulation of cancer-related signaling pathways by DPs. Wnt signaling: when Wnt binds to its receptor, signaling via Frizzled activates β-catenin expression. Import of β-catenin and its binding to TCF transcription factors induces expression of Wnt target genes. Notch signaling: binding of JAK to its receptor activates translocation of NICD in the nucleus where it binds to the CSL transcription factor family members and acts as a transcription co-activator of recombination signal sequence-binding protein Jκ (RBP-J) to activate downstream target genes. Hedgehog signaling: binding of Hh to Patched (*PTCH*) relieves suppression of Smo, disrupts the cytoplasmic complex, and stabilizes GLI1GLI2. Hh signaling also antagonizes a suppressor of the Fused kinase (*SuFu*), facilitating GLI1/GLI2 activation. Loss of PTCH constitutively activates the pathway. JAK/STAT signaling: STAT family members can be activated by phosphorylation through 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. Constitutive activation of STAT is related with malignant transformation induced by various tyrosine kinases (oncoproteins), such as Src, Bcr-Abl, or EGFR. The STATs target some genes such as cyclins D1/D2, Myc, Bcl-xL, and Mcl-1. AKT/PI3K/mTOR signaling: PI3K, which is activated via many growth factor receptors, catalyzes the conversion of phosphatidylinositol (4,5) bis-phosphate (*PIP2*) to PIP3. PIP3 recruits the AKT kinase to the plasma membrane where it undergoes phosphorylation by PDK1 (not shown) and targets mTOR. AKT and mTOR phosphorylates are substrates that foster cell cycle progression, cancel apoptosis, and facilitate translation of capped mRNAs. EGFR signaling: EGFR, a cell surface receptor family, has been implicated in a multiplicity of cancer-related signal transduction pathways like cellular proliferation, apoptosis, inactivation, adhesion, and migration. NF-κB signaling: Under normal condition, the NF-κB dimers reside in the cytoplasm. In mammalian cells, five members of NF-κB family have been identified: RELA (p65), c-BEL, RELB, NF-κB1 (p50/p105), and NF-κB2 (p52/p100). The range of stimuli include free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, γ-radiation, UV light, and X-rays that activate the REL-mediated expression of targeted genes including cell proliferation and inflammation. MAPK signaling: MAPK pathway is initiated by downstream kinase cascades which include extracellular signal-regulated protein kinases (*ERKs*), c-Jun N-terminal kinases/stress-activated protein kinases (*JNKs/SAPKs*), and p38 kinases [98]. The extracellular mitogen binds to the membrane ligand and allows Ras (a GTPase) to swap its GDP for a GTP and activates a MAP3K (e.g., Raf), which in turn activates ERK, JNK, and p38. Several *in vitro*, *in vivo*, and epidemiological studies have reported that the consumption of fruits, vegetables, herbs, grains, pulses, and medicinal plants may decrease cancer risk. DPs have been shown to regulate signaling pathways for inhibiting tumor invasion and angiogenesis which are essential for tumor growth and metastasis

SFN on human cancer cell lines was based on the activation of caspase-3 [134]. It was also observed that SFN reduced aldehyde dehydrogenase-positive cell population in human breast cancer cells and decreased the size and number of

primary mammospheres by inhibiting Wnt/β-catenin pathway, suggesting the effect of SFN against breast CSCs [135], which indeed could become useful for the prevention and cancer invasion and metastasis. Vitamin D_3, a group of fat-soluble cholecalciferol has been shown to induce apoptosis and cell cycle arrest of various cancer cells thereby reducing the incidence of human breast, prostate, and colon [136]. Vitamin D_3 was also found to promote the differentiation of colon carcinoma cells through the induction of E-cadherin expression and the inhibition of β-catenin signaling [119]. In a study, treatment of colon carcinoma cells with ligand-activated vitamin D receptor competes with TCF-4 for β-catenin binding, thereby decreasing the levels of c-Myc, peroxisome proliferator-activated receptor, TCF-1, and CD44 [119]. These findings would tailor our knowledge for further investigations of vitamin D_3 in terms of chemoprevention of human cancers. In another report, piperine was found to target breast CSCs and inhibit Wnt/β-catenin signaling pathway [126]. Similarly, in colon cancer cells, resveratrol significantly decreased nuclear localization of β-catenin which could be due to decreased expression of lgs and pygoI (regulators of β-catenin localization) [137]. In another report, Waldenstrom's macroglobulinemia cells treated with resveratrol inhibited proliferation and cell survival by inducing apoptotic cell death through downregulation of Wnt signaling pathway [138]. Cruciferous indole diindolylmethane (DIM) has been shown to participate in the regulation of Wnt/β-catenin signaling and cancer metastasis. Multiple lines of evidence indicate that there is a crosstalk between Akt and Wnt signaling pathways through the signal communication between GSK-3β and β-catenin. Since DIM inhibits the activation of Akt, it could also prevent Wnt activation [139]. Indeed, Li and their colleagues found that DIM significantly enhanced the phosphorylation of β-catenin and suppressed β-catenin nuclear translocation, suggesting that DIM could downregulate the activation of Wnt signaling.

3.2 Notch pathway

Notch signaling and its components are actively involved in a wide variety of developmental processes including organogenesis, vasculature system development, central nervous system development, and adult-type hematopoietic stem cell generation [6, 140]. Notch signaling is activated by direct cell to cell contact. The pathway is believed to be aberrantly activated in cancer cells and CSCs, ultimately leading to uncontrolled proliferation and CSC self-renewal [6, 141]. Notch pathway was also found to be an important signaling pathway for the self-renewal and metastasis functions of malignant breast CSCs [142].

Binding of Notch ligands such as JAG1, JAG2, Dll-1, Dll-3, and Dll-4 to Notch family receptors (Notch 1–4) induces transcriptional activation of target genes. Activated Notch leads to proteolytic cleavage of the intracellular domain of Notch (NICD) (Fig. 6). NICD translocates in the nucleus where it binds to the CSL transcription factor family members and acts as a transcription co-activator of recombination signal sequence-binding protein Jκ (RBP-J) to activate downstream target genes, e.g., c-Myc, cyclin D1, p21, and NF-κB [143]. Notch1 has been examined and found to crosstalk with NF-κB pathway in diverse cellular situations [144, 145]. Therefore, Notch-1 is an essential receptor for expression of several NF-κB subunits [146] and stimulates NF-κB promoter activity. Based on the conservation of double TCF/LEF-binding sites within the 5′ promoter region of mammalian JAG1 orthologues, JAG1 is expected to be an evolutionarily conserved target of the canonical Wnt signaling pathway [147]. Recently, Chen and coworkers examined that the Notch3 and Wnt/β-catenin signaling pathways regulate JAG1 expression in ovarian cancer [148] necessary for the proliferation of cancer cells [149] and self-renewal of hematopoietic stem cells [150].

Several phytomolecules form dietary source like resveratrol [151], curcumin [6, 152, 153], honokiol [154], genistein [155], EGCG [156], and SFN [157] and are well-known natural chemopreventive molecules that have been found to be potent inhibitors of Notch signaling pathway. Curcumin, a common flavoring agent and bioactive polyphenolic compound of the Indian spice turmeric, inhibits Notch signaling pathway in esophageal, pancreatic, osteosarcoma, and oral carcinoma CAL-12 cancer cells [6, 153, 158]. The work of Wang and coworkers strengthened the point that curcumin downregulated Notch-1 mRNA level in pancreatic cancer cells, suggesting an inhibitory potential of curcumin on transcriptional inactivation of Notch-1 [158]. Moreover, inactivation of NF-κB DNA-binding activity by curcumin was potentially mediated by Notch-1 signaling pathway [158].

Resveratrol, a polyphenol derived from a wide variety of plants such as grapes, berries, plums, and peanuts [159, 160], has been shown to possess chemopreventive and chemotherapeutic potentials by affecting the Notch pathway against human cancers and CSCs [151, 161, 162]. It has been found to induce Notch2-mediated apoptosis and suppression of neuroendocrine markers in medullary thyroid cancer [163]. Administration of resveratrol induces apoptosis in MOLT-4 acute lymphoblastic leukemia cells through inhibition of blocking Notch signaling and their downstream effectors [151]. Resveratrol appeared to affect Notch at the posttranslational level because Notch mRNA levels were not affected. Moreover, in the presence of resveratrol, mRNA levels of downstream effectors of Notch were decreased [151]. A recent study conducted by Pinchot et al. showed that resveratrol induces Notch signaling pathway and growth inhibition associated with S-phase cell cycle arrest in human pancreatic carcinoid cell and NCI-H727 bronchopulmonary cells [164]. Silencing of Notch by using Notch anti-sense RNAs into GI

carcinoid cells results in the inhibitory effect of resveratrol on ACSL1 suppression, Notch expression, and the NE markers CgA and 5-HT [164]. Genistein exhibited potent antiproliferative effect on various cancers [165]. According to Wang et al., genistein inhibited Notch signaling, which led to the downregulation of NF-κB activity, resulting in the inhibition of cell proliferation and metastasis in pancreatic cancer cells [166]. Several studies have also reported that isoflavone, genistein, could inhibit the expression of Notch-1 and Notch-2 [122, 167]. The pathway array assessment of 107 proteins indicated that Notch signaling pathways were activated in squamous carcinoma cells CAL-27, SCC-25, and KB, suggesting heterogeneity at the signaling network level. After treatment with EGCG, Notch pathway was significantly affected, which, in turn, affected cell cycle and metastasis-related networks [156]. Therefore, targeting Notch signaling pathway through DPs could be a potential therapeutic approach for the prevention of tumor progression and/or treatment of metastatic cancer cells as well as CSCs [168].

3.3 Sonic hedgehog pathway

It is another crucial pathway that plays a key role in metastasis cascades including self-renewal, cell fate, proliferation, survival, and differentiation of cancer cells and stem cells is Sonic hedgehog (Hh) signaling pathway [168–171]. Aberrant activation of this pathway has been shown to be the core mechanism of human cancers including pancreatic [168], colon [172, 173], breast [174], brain [175], medulloblastoma [176], esophagus [177], liver [178], squamous cell carcinoma [177], and ovary [179, 180]. Clement et al. reported the essential role of hedgehog-GLI signaling in controlling the self-renewal behavior of human glioma CSCs and tumorigenicity [181]. In the absence of hedgehog short-acting polypeptide ligands, namely Sonic hedgehog, Desert hedgehog, and Indian hedgehog, their transmembrane receptor Patched (PTCH1 or PTCH2) associates with Smoothened (Smo) and diminishes Smo reactivity. This complex translocates to nuclease and triggers dissociation of transcription factors (GLI1, GLI2, and GLI3), leading to transcriptional activation of targeted genes including cyclin D, cyclin E, Myc, Bcl-2, platelet-derived growth factor (PDGF)Rα, and elements of EGF pathway (Fig. 6) [168, 182]. GLI transcriptional factors have dual functions such as activator and repressor that are defined only partially and can respond to combinatorial and cooperative GLI activity. The GLI factors play key roles in the mediation and interpretation of Hh signals. Hh-driven cancers arise from a variety of mutations that modulate different components, including the key transcriptional effector GLI proteins [168]. Hh was also shown to increase the level of angiopoietins I and II and the VEGF family signaling proteins, indicating the role of tumor-associated fibroblasts in combination with Hh signaling to mediate blood vessel formation [183]. Blockage of Hh signaling has been shown to inhibit tumor development and metastasis in both cancer cells and CSCs prostate and pancreatic adenocarinomas [184]. Recently, pancreatic, breast, brain, prostate, ovarian, and colon CSCs were shown to express high levels of Hh [174, 179], which is interesting given the implications for Hh in self-renewal and proliferation. Hh signals are also known to induce stem cell markers BMI1, LGR5, CD44, and CD133 based on crosstalk with other signaling pathways.

Most outstanding phytochemicals such as cyclopamine [185, 186], EGCG [187], curcumin [188], resveratrol [189, 190], isoflavones [191], vitamin D [191], apigenin, baicalein, and quercetin [192] dietary agents are also known to inhibit Hh signaling pathway. Cyclopamine, a phytomolecule found in corn lily (*Veratrum californicum*), was the first Hh inhibitor that was observed to inhibit the activation of Smo in CSCs of pancreatic cancer, breast cancer, and multiple myeloma [187, 193]. Cyclopamine decreased mammosphere formation and proliferation in breast cancer and multiple myeloma CSCs, respectively [185]. In a study, cyclopamine treatment of murine medulloblastoma induced cell death and neuronal differentiation, effectively reducing the cancer stem cell population [194]. The study also demonstrated that the tumor burden in a mouse tumor allograft was reduced after administration of cyclopamine along with induction of cytotoxicity in human medulloblastoma cells. According to Feldmann and coworkers, cyclopamine synergizes with gemcitabine and inhibits metastatic spread thereby reducing primary tumor burden in pancreatic orthotopic xenografts [195]. Combination therapy of cyclopamine and gefitinib showed a synergistic effect against L3.6pl cells, but an additive effect against MIA PaCa-2 cells was not examined. Caspase 3/7 activity was also increased when this combination therapy was used, indicating apoptotic cell death [196]. Wang et al. showed that EGCG increases the number of BrdU-labeled cells in adult hippocampal neural progenitor cell (NPC) cultures and markedly improves spatial cognition in mice [197]. These events are associated with the Hh signaling pathway. Moreover, EGCG triggered a robust upregulation of PTCH mRNA and protein expression in cultured NPCs [197]. EGCG was also found to inhibit the components of Hh pathway such as Smoothened, PTCH, GLI1, and GLI2 as well as GLI transcriptional activity [187]. Furthermore, combination of EGCG with quercetin had synergistic inhibitory effects on self-renewal and metastatic functions of pancreatic CSCs through attenuation of GLI activities [187]. Recently, Elamin et al. have reported that curcumin attenuates the Hh signaling pathway and induces apoptotic cell death in medulloblastoma cells by downregulating the Shh protein and its most important downstream targets GLI1 and PTCH1 [188].

Very recently, Zhang and coworkers examined that genistein treatment not only led to the downregulation of prostate cancer, CSC markers CD44, but also inhibited Hh-GLI1

pathway, which may contribute to the anti-CSC effect of genistein in prostate cancer tumor cells [198]. Resveratrol induced apoptosis and G0/G1 phase cell cycle arrest, decreased the expression of Hh pathway components (GLI1, PTCH1, and Smo), and suppressed the expression of downstream target genes of this pathway (CCND1 and Bcl-2). However, resveratrol did not act on the GLI1 promoter directly confirmed by reporter luciferase assay. The seven DPs such as apigenin, baicalein, curcumin, EGCG, genistein, quercetin, and resveratrol can act similarly to the Hh antagonist cyclopamine in transgenic adenocarcinoma of mouse prostate (TRAMP) mice as well as prostate cancer cells, recently reported by Slusarz et al. [192]. This study further demonstrated that among these compounds, genistein, curcumin, EGCG, and resveratrol inhibited Hh signaling as monitored by real-time reverse transcription-PCR analysis of Gli1 mRNA concentration or by GLI reporter activity. However, apigenin, baicalein, and quercetin decreased GLI1 mRNA concentration, but not GLI reporter activity [192]. Thus, it could be said that one of the probable mechanisms by which chemopreventive DPs exercise their antitumor properties is through the suppression of the Hh signaling pathway.

3.4 JAK-STAT pathway

The JAK/STAT is the principal signaling mechanism for a wide array of cytokines and growth factors affecting various cellular functions, such as metastasis, proliferation, growth, and immune response [199]. Constitutive activation of STAT is related with malignant transformation induced by various tyrosine kinases (oncoproteins), such as Src, Bcr-Abl, or EGFR [200]. STAT family members can be activated by phosphorylation through 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 (Fig. 6). The target genes of STATs, such as cyclins D1/D2, Myc, Bcl-xL, and Mcl-1 among others, appear to contribute to cancer metastasis by activating cell cycle and inhibiting apoptosis [200]. Activation of this pathway stimulates differentiation, cell migration, cell proliferation, and apoptosis. These cellular events are crucial to regulate hematopoiesis, immune development, mammary gland development, lactation, adipogenesis, sexually dimorphic growth, and other processes [201]. JAK/STAT pathway has been implicated in various cancers including prostate [202], gastric [203], breast [204], pancreatic [205], colon [206], brain [207], rectal [206], etc. Moreover, JAK/STAT pathway plays an important role in self-renewal and continual maintenance of germline stem cell population [208]. Once in the nucleus, dimerized STATs bind specific regulatory sequences which induce or repress the expression of many genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, and metastasis [208].

Several chemopreventive natural dietary agents including resveratrol [209], curcumin [210, 211], cryptotanshinone [212], ursolic acid [213, 214], acetyl-11-keto-β-boswellic acid (AKBA) [215], cucurbitacin Q [216], thymoquinone [217], EGCG [218, 219], static [220], β-escin [221], capsaicin [222], quercetin [203], flavopiridol [223], delphinidin [224], celastrol [225], butein [226], γ-tocotrienol [227], and diosgenin [228] have been shown to be potent inhibitors of JAK-STAT signaling pathway and cancer metastasis. Resveratrol suppresses interleukin (IL)-6-induced ICAM-1 expression by interfering with Rac-mediated pathways via the attenuation of STAT3 phosphorylation [229]. A number of studies have shown that the cryptotanshinone, a natural compound found in *Salvia miltiorrhiza* Bunge, inhibits the rapid phosphorylation of tyrosine 705 in STAT3, thereby resulting in the suppression of prostate cancer cell's growth [212]. The inhibition of STAT3 phosphorylation leads to a decrease in the expression of STAT3 targets, including cyclin D1, survivin, and Bcl-xL, which are accountable for survival of cancerous and CSCs. In a study, cryptotanshinone is reported to be a potent candidate for inhibiting formation of STAT dimers by binding directly to STAT3 at the SH2 domain level [212]. The sesquiterpene lactone parthenolide isolated from feverfew (*Tanacetum parthenium*) decreases the STAT6 DNA-binding activity in IL-4-stimulated endothelial cells [230]. Thymoquinone (TQ) isolated from the medicinal plant *Nigella sativa* has been reported to inhibit both constitutive and IL-6-induced STAT3 phosphorylation, c-Src, and JAK2 activation [217]. Furthermore, TQ potentiated the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells. Similar mechanisms were detected in multiple myeloma cells with the natural chalcone butein, which inhibited tyrosine phosphatase Src homology region 2 domain-containing phosphatase 1 (SHP-1)-dependent STAT3 activation [231]. Green tea has also been reported to decrease the DNA binding activity of the transcription factor STAT1a, but not of NF-κB by decreasing tyrosine phosphorylation of the STAT1a protein and not from antioxidative effects [232]. Downregulation of STAT3 by EGCG treatment was also examined in human head and neck squamous cell carcinoma cell lines [233]. EGCG suppressed the constitutive activation of the STAT3 in both YCU-H891 head and neck squamous cell carcinoma and breast carcinoma cell line MDA-MB-231 [234]. According to Bhutani et al., capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide) blocks the constitutive and inducible activation of STAT3 due to downregulation of the gene expression involved in cell survival, proliferation, metastasis, and angiogenesis [222]. The authors also reported that capsaicin inhibits STAT3-DNA binding activity and the constitutive activation of several kinases, such as JAK1, c-Src, and ERK.

There are numerous reports about the effects of curcumin on STAT signaling. Bharti and colleagues found that curcumin acts as a reversible inhibitor of constitutive STAT3 due to inhibition of STAT3 nuclear translocation, but not of STAT5 phosphorylation in human multiple myeloma cells [235]. JAK/STAT signaling has also been found to be suppressed with the treatment of curcumin in various cell lines including brain microglial [236] and U266 [237]. Zhang et al. also showed that curcumin at the concentration of 5–20 μM induced apoptosis in a in MJ-, Hut78-, and HH CTCL-derived cell lines associated with the downregulation of STAT-3 protein, mRNA expression levels, survivin and bcl-2, and activation of caspase-3 and induced PARP cleavage. Curcumin was also observed to inhibit the transcription factor STAT3, resulting in reduction in expression of STAT3 target genes, such as JAK2, v-src, and cyclin D1 [238]. Other natural compounds such as diosgenin [228], β-escin [221], butein [226], and γ-tocotrienol [227] have also been shown to inhibit proliferation and to induce apoptosis of HCC cells concomitantly by inhibiting both constitutive and inducible activation of STAT3 through the inhibition of cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1 and VEGF, c-Src, JAK1, and JAK2 activation. Flavopiridol, an alkaloid isolated from rohitukine (*Dysoxylum binectariferum*), was also found to induce cell cycle arrest and apoptosis in acute myeloid leukemia in correlation with STAT3 repression [223].

Natural triterenoid AKBA isolated from the Indian frankincense *Boswellia serrata* inhibited both constitutive and inducible STAT3 activation through the induction of the SHP-1 [220]. This effect correlated with an inhibitory activity on JAK and c-Src, resulting in the suppression of proliferation and induction of apoptosis in multiple myeloma cells. In addition, AKBA also suppressed the growth of glioma, colon cancer, prostate, and leukemic cells [239]. The triterpene celastrol (a Chinese herbal product), a potent anticancer agent, has been found to inhibit the growth of multiple myeloma cells in correlation with the inhibition of constitutive and induced activation of STAT3 [225]. Additionally, it enhanced bortezomib- and thalidomide-mediated apoptosis in multiple myeloma cells via downregulation of STAT3 target genes, including cyclin D1, Bcl-2, Bcl-xL, survivin, XIAP, and Mcl-1. A natural compound, the pentacyclic triterpenoid ursolicacid (3-β-hydroxy-urs-12-en-28-oic-acid), has also been further reported to be a potent inhibitor of constitutive and inducible STAT3 activation in prostate cancer cells through the upstream inhibition of JAK2 and Src activation [214]. Cucurbitacin Q, a triterpenoid found in Cucurbitacea family plants, has antimetastasis property in lung cancer cells through inhibition of cancer cell growth and induction of apoptosis through downregulation of phosphorylated STAT3 [216]. Taken together, dietary agents target the JAK/STAT signaling pathway, highlighting a potential and novel paradigm for prevention and therapy of cancer.

3.5 PI3K/Akt/mTOR pathway

Tumorigenesis is the outcome from synergistic interactions of a complex of signal transduction processes, including multiple tumor suppressors such as Akt/PI3K/mTOR, PTEN, oncoproteins, etc. [240]. The Akt/PI3K/mTOR pathway plays a crucial role in the initiation and progression of malignancies, enhancing cell survival through activation of cell proliferation and inhibition of cell metastasis [241]. This pathway is a prototypic survival pathway that is constitutively activated in variety of human cancer cells [242]. Mechanisms for signaling include engagement of receptor tyrosine kinases (RTKs) and activation of PI3K (Fig. 6). RTKs engage and activate PI3K upon activation by a ligand, which in turn converts membrane-bound phosphatidylinositol (4,5)-bisphosphonate to phosphatidylinositol (3,4,5)-triphosphonate [243]. Three known isoforms of the Akt kinase, Akt1, Akt2, and Akt3 are identified in mammals. Akt is activated by phospholipid binding and phosphorylation at Thr308 by pyruvate dehydrogenase kinase (PDK)1 or at Ser473 by PDK2 [244]. Further activation of Akt phosphorylation is initiated by phosphatidylinositol (3,4,5)-triphosphonate that leads to the promotion of cell proliferation, which regulates multiple signaling pathways that maintain cell cycle, proliferation, metastasis, and resistance to apoptosis, such as Bcl-2, caspases, inhibitor of kappa light chain polypeptide gene enhancer B cells kinase, GSK3, Forkhead-related transcription factor 1, endothelial nitric oxide synthase, and mTOR [243, 245]. The mTOR, a serine/threonine protein kinase known to exist in two distinct functional complexes, mTORC1 and mTORC2, regulates metastasis cascades including cell growth, cell proliferation, cell motility, cell survival, invasion, and migration [246]. Activation of mTORC1 (rapamycin sensitive) promotes phosphorylation of p70S6 and 4E-BP1. mTORC2 consists of mTOR and the rapamycin insensitive companion of mTOR (rictor), which regulates Akt phosphorylation [247]. PTEN acts as a vital negative regulator of Akt/PI3K/mTOR pathways [98]. Moreover, recent data from *in vitro* and *in vivo* studies suggests that mTOR plays an important role in Akt/PI3K-mediated signaling for self-renewal and resistance of CSCs during chemotherapy or radiotherapy [6]. This is believed to be the root cause of treatment failure, cancer recurrence, and activation of metastatic activity. Therefore, it is important to examine therapeutic agents that explicitly target this pathway, specifically in tumors that harbor activation of the Akt/PI3K/mTOR pathway. Several phytochemicals including EGCG [248], delphinidin [224], resveratrol [249], genistein [250], indole-3-carbinol [251], diosgenin [252], fisetin [253], silibinin [254], curcuminoids [255], curcumin [256], and black raspberries [257] are known to suppress the activation of Akt/PI3K/mTOR pathway.

Recently, it has shown that EGCG (40, 80 mg/kg) decreases the level of B cell activating factor of the TNF family

(BAFF), anti-CII antibody, IgA, IgG, IgM, and the expressions of BAFF receptor, P110δ, p-Akt, mTORC1, Bcl-xL in collagen-induced arthritis rats, and Bim expression [258]. In TRAMP, mice green tea phytochemicals modulated IGF/IGFBP-3 [23]. Further studies also showed that EGCG could reduce the expression of P110δ and mTORC1 *in vitro*. Treatment of EGCG to YCU-H891 head and neck squamous cell carcinoma and MDA-MB-231 breast carcinoma cell lines induced the inactivation of Akt [234]. Peairs and coworkers found that EGCG effectively inhibits the immune-stimulated PI3K/Akt/mTOR pathway independently of AMPK, by decreasing phosphorylation of Akt, suggesting an alternate mechanism for EGCG-mediated anti-inflammatory action in mesangial cells [259]. Adhami et al. reported that green tea polyphenols reduce PI3K levels by 67–79 % and phosphorylation of Akt by 65 % in the TRAMP mouse model [260]. It was found to be associated with an inhibition of protein expression of PI3K, phospho-Akt, and ERK 1/2 with concomitant inhibition of markers of angiogenesis and metastasis such as VEGF, uPA, and MMP-2 and MMP-9 EGCG pretreatment inhibited cigarette smoke condensate-induced phosphorylation of ERK1/2, JNK, and p38 MAPKs and resulted in a decreased level of Akt/PI3K/mTOR signaling molecules [261]. EGCG was found to decrease PI3K and phospho-Akt levels in both DU145 and LNCaP cells [262]. A study done by Tang et al. has shown that green tea catechin EGCG inhibits VEGF-induced angiogenesis *in vitro* through inactivation of Akt [248]. Moreover, EGCG inhibits the activation of AP-1 via blocking EGFR transactivation and its downstream events ERKs/Akt/PI3K/mTOR/p70(S6K) [263]. It was observed that EGCG attenuated this migration/invasion by suppressing the HRG-stimulated activation of EGFR-related protein B2 (ErbB2)/ErbB3/Akt, while the disruption of the HRG-stimulated activation of ErbB2/ErbB3 but not Akt which was associated with the inhibition of migration/invasion by EGC [18].

Several studies suggest that curcumin has potential to inhibit Akt activity which might facilitate inhibition of cell proliferation and metastasis in human cancer cells [264]. Curcuminoids have also been reported to downregulate the expression of antiapoptotic and metastatic genes through inhibition of Akt activation [255]. Chaudhary and coworkers reported that curcumin completely inhibits Akt activation in the human prostate cancer cell lines LNCaP and PC-3, but not Du-145 [265]. Curcumin has also been shown to chemosensitize and radiosensitize nude mice bearing pancreatic PC3 xenografts by downregulating PI3K/mTOR pathway [266]. Another phytochemical, resveratrol, decreased both the expression and phosphorylation of Akt. In a study, inhibitors of PI3K (LY294002) and Akt (SH-6) were found to increase resveratrol-induced LDH release and caspase-3 activation [249] in human U251 glioma cells. Moreover, resveratrol decreased phosphorylation of ribosomal protein S6 and the mTOR inhibitor rapamycin which further enhanced resveratrol-induced cell death [249]. The activation of mTOR signaling by the proatherogenic oxidized LDL (oxLDL) requires the upstream activation of PI3K and Akt. Resveratrol reportedly blocked the oxLDL-induced phosphorylation and activation of the Akt/PI3K/mTOR/p70S6K pathway and strongly inhibited both the DNA synthesis and proliferation of smooth muscle cell [267].

Delphinidin synthesized in pigmented fruits and vegetables possesses potent antioxidant, anti-inflammatory, and anti-angiogenic properties. Treatment of cells with delphinidin prior to exposure to MCF-10A breast cells resulted in significant inhibition of PI3K/Akt/mTOR/p70S6K pathway [224]. Black raspberry extracts have also been shown to exert their anticancer activity through the inhibition of PI3K/Akt pathway [257]. Fisetin (3,7,3′,4′-tetrahydroxyflavone), a member of the flavonoid (a flavonol) that also includes quercetin, myricetin, and kaempferol, is commonly found in apples, persimmons, grapes, kiwis, strawberries, onions, and cucumbers. Adhami et al. demonstrated that fisetin acts as a dual inhibitor of the PI3K/Akt and the mTOR pathways in prostate and lung adenocarcinoma cells [253]. In a study, soy genistein inhibited both Akt and NF-κB pathways in PC3 cells and MDA-MB-231 prostate cancer cell lines [250]. Chinni and Sarkar showed that indole-3-carbinol pretreatment also abrogated EGF-induced Akt activation [251]. This group also showed that diosgenin, a steroidal saponin present in fenugreek, suppresses TNF-induced activation of Akt [252]. García-Maceira and Mateo found that suppression of HIF-1alpha accumulation by silibinin correlated with strong dephosphorylation of mTOR and its effectors ribosomal protein p70S6K and 4E-BP1 at the translational level in human cervical (HeLa) and hepatoma (Hep3B) cells [268]. Silibinin also exerted an inhibitory effect on the phosphorylation of Akt examined by Chen and their colleagues in A549 cells [254]. Thymoquinone found in *N. sativa* has been shown to inhibit tumor growth and angiogenesis through downregulation of Akt/PI3K pathway [269]. Thus, these studies provide evidence suggesting targets of the Akt/PI3K/mTOR pathway with specific dietary phytomolecules in order to suppress the development of cancers.

3.6 FOXO pathway

The Forkhead box O (FOXO) pathway has received increasing attention as a therapeutic target for prevention and therapy of cancer. FOXO family of forkhead transcription factors is characterized by a distinct forkhead DNA binding domain [270]. FOXO plays a direct role in fundamental cellular processes, including cell differentiation, cell cycle arrest, metabolism, and DNA repair [271]. In mammals, four FOXO species, encoded by four distinct genes, have been identified: FOXO1/or FKHR, FOXO3/or FKHRL1, FOXO4/or Afx,

and FOXO6. Posttranslational modification of FOXO proteins may be done by phosphorylation and/or acetylation at differentially conserved serine/threonine and lysine residues, respectively.

Deregulation of FOXO proteins is involved in tumorigenesis (Fig. 6). For example, translocation of FOXO3 gene with the MLL gene is associated with secondary acute leukemia [272]. Downregulation of FOXO activity is often seen in cancer (e.g., by an increase in Akt activity resulting from loss of PTEN). FOXO transcriptional factors are known as a tumor suppressor by inducing apoptosis through upregulation of cell death-associated genes, such as Bim and PUMA [273], or by downregulating antiapoptotic proteins [274]. Phosphorylation of FOXO proteins via Akt facilitates activation of PI3K pathway, disturbing the DNA binding ability, and increases in its affinity for 14-3-3 protein. This complex is transferred from the nucleus which leads to the inactivation of the multiple signaling transduction pathways. PI3K follows similar mechanism to translocate some other downstream effectors such as active FKHRL1, FKHR, and AFX that regulates cell cycle arrest and apoptosis. Recently, Chen et al. demonstrated the involvement of FOXO-mediated antiproliferative effect of resveratrol in LNCaP prostate cancer cells [275]. Downregulation of PI3K/Akt/mTOR signaling pathway by resveratrol may be one of the molecular mechanisms by which this polyphenol inhibits proliferation of cells. In addition, resveratrol suppresses phosphorylation of FOXO, thereby indirectly assisting its nuclear translocation, FOXO-DNA binding, and transcriptional activities [275]. It further induced expression of Bim, TRAIL, p27/KIP1, DR4, and DR5 and inhibited cyclin D1 expression [275]. Benzyl isothiocyanate (BITC), a constituent of edible cruciferous vegetables, accelerated FoxO1-mediated autophagic death in cultured human breast cancer cells [276]. These include MDA-MB-231, MCF-7, MDA-MB-468, BT-474, and BRI-JM04 and MDA-MB-231 xenograft mice. Autophagy induction by BITC was associated with increased expression and acetylation of FOXO1. Recently, Ross and their colleagues investigated the effects of genistein on the molecular program of male urethral development [277]. Female mice were fed diets supplemented with genistein (500 mg/kg diet) which resulted in modulation of MAPK and TGF-β signaling pathways and those controlled by FOXO, HOX, and ER transcription factors, contributing to tissue morphogenesis, cell proliferation, and cell survival [277].

A number of studies have demonstrated the effect of green tea EGCG on FOXO. Very recently, *in vivo* study has shown that EGCG significantly inhibited the tumor growth by decreasing reduced phosphorylation of FKHRL1/FOXO3a, regulated FOXO-targeted genes Bim, and activated caspase-3 [278]. Moreover, EGCG modulated markers of cell cycle (p27/KIP1), angiogenesis (CD31, VEGF, IL-6, IL-8, SEMA3F, and HIF1α), and metastasis (MMP2 and MMP7). In a report, at 1 μM, EGCG stimulated FoxO transcription factor, nuclear accumulation, and DNA binding activity in human skin fibroblasts in culture [279].

Resveratrol treatment to pancreatic cancer cell lines (PANC-1, MIA PaCa-2, Hs766T, and AsPC-1) inhibited phosphorylation of FOXOs and enhanced their nuclear translocation, FOXO-DNA binding, and transcriptional activities [280]. Furthermore, knockdown of FOXO genes abolished resveratrol-induced cell cycle arrest and apoptosis. Finally, resveratrol-treated mice showed significant inhibition in tumor growth which was associated with reduced phosphorylation of FOXO1 and FOXO3a [280]. Ganapathy et al. reported that resveratrol enhanced the apoptosis-inducing potential of TRAIL by activating FKHRL1 and its targeted genes such as TRAIL-R1/DR4, TRAIL-R2/DR5, Bax, and p27(/KIP1) and inhibited the expression of Bcl-2 and cyclin D1 [281]. Among the multifarious effects, phosphorylation-deficient mutants of FOXOs induced FOXO transcriptional activity and enhanced antiangiogenic effects of resveratrol by inhibiting human umbilical vein endothelial cell (HUVEC) cell migration and capillary tube formation [282]. Another group of phytochemicals, soy isoflavones, was found to inhibit the phosphorylation of FOXO3a, thereby enhancing the cell death of prostate cancer cells [110]. Therefore, regulation of FOXO transcription factors by resveratrol may play an important role in angiogenesis which is important for cancer metastasis.

3.7 MAPK-ERK pathway

The MAPK pathway has received increasing attention as a target molecule for cancer prevention and therapy. MAPK pathway is initiated by a downstream kinase cascades which include ERKs, c-Jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs), and p38 kinases (Fig. 6) [283]. The extracellular mitogen binds to the membrane ligand allowing Ras (a GTPase) to swap its GDP for a GTP and activates a MAP3K (e.g., Raf), which in turn activates ERK, JNK, and p38. MAPK further activated a transcription factor, such as myc, resulting in the transduction of a wide variety of signals, leading to a variety of cellular responses including inflammation, NF-κB, growth, differentiation, and cell death [283, 284]. On the other hand, stress-related tumor promoters, such as ultraviolet (UV) irradiation and arsenic, potently activate JNKs/SAPKs and p38 kinases [285]. It has also been stated that MAPK is hyperactivated in various types of cancer and that the activation of MAPK is also linked to cancer angiogenesis, invasion, and metastasis [286].

The DPs curcumin [287, 288], EGCG [289], lovastatin I3C [290], DIM [290], SFN [291], gingerol [292], genistein [27], lovastatin [293], resveratrol [294], isothiocyanates [295], and green tea polyphenols [294] have been reported to alter the MAPKs (Fig. 6). Among the mentioned DPs, the potential of curcumin to regulate the MAPK/ERK signaling pathway thus

might contribute to the inhibition of inflammation. Curcumin downregulates TLR2 expression and inhibits the MAPK-JNK while it activates p38 and ERK, confirmed using human disc cells [288]. It was also reported to inhibit experimental colitis through suppression of p38 MAPK activity [296]. Curcumin significantly increased the phosphorylation of ERK, JNK, and their downstream molecules (c-Jun and Jun B), thereby resulting in induction of apoptosis in human monocytic leukemia THP-1 cells [297]. Phytochemicals such as curcumin, EGCG, and lovastatin as well as their combination suppressed esophageal cancer cell growth and reduced the expression of Ki67, phosphorylated ERK1/2, c-Jun, and COX-2, but activated caspase 3 in esophageal cancer cells and nude mouse xenograft model [293]. Curcumin also attenuated the activation of JNK induced by various agonists including phorbol 12-myristate 13-acetate (PMA) plus ionomycin, anisomycin, UV-C, γ-radiation, and TNF [298].

Similarly, green tea EGCG has been shown to attenuate the activation of MAPK/ERK pathway in various cancer cell lines. EGCG potently activates JNK1, p38, and ERK2 activities in HepG2 cells, HeLa cells [299], and HT-29 cells [289]. EGCG (53 %) has been reported to phosphorylate JNK/SAPK and p38 in the breast cancer cell line T47D, resulting in the suppression of phosphorylation of Cdc2 and thus regulated the expression of cyclin A, cyclin B1, and Cdk proteins, thereby causing G2 growth arrest [300]. Exposure of HepG2 cells to green tea polyphenols potently enhanced JNK1 and ERK2 activities [301]. EGCG was also found to inhibit viability, capillary tube formation, and migration of HUVEC. Moreover, in AsPC-1-xenografted tumors, EGCG treatment exhibited significant reduction in proliferation (Ki-67 and PCNA staining), angiogenesis (vWF, VEGF, and CD31), metastasis (MMP-2, MMP-7, MMP-9, and MMP-12), induction of apoptosis, caspase-3 activity, and growth arrest ($p^{21/WAF1}$) [25]. EGCG also inhibited circulating endothelial growth factor receptor 2 and positive endothelial cells derived from xenografted mice. The ERK/MAPK cascades are known to positively activate transcriptionally antioxidant responsive element (ARE)-mediated reporter gene induced by SFN [291], while JNK1 positively activated ARE-mediated reporter gene induced by isothiocyanates [295]. Exposure of human fibrosarcoma HT1080 cells to EGCG attenuated the phosphorylation of ERK1/2 and inhibited p38 MAPK activity [302]. Nevertheless, in human hepatoma HepG2-C8 cells, EGCG has also been associated with the activation of ERK, JNK, and p38 [299]. Green tea EGCG and black tea theaflavins (5–20 μM) also inhibited JB6 mouse epidermal cell transformation, AP-1-dependent transcriptional activity, and DNA binding activity through the inhibition of JNK-dependent mechanism [303]. Other investigators also reported that genistein blocked the activation of p38 MAPK by TGF-β while p38 MAPK was necessary for TGF-β-mediated induction of MMP-2 and cell invasion in prostate cancer [27]. A polyphenolic fraction of grape seeds caused growth inhibition of breast carcinoma MDA-MB468 cells by inhibiting MAPK activation and by inducing G1 growth arrest and metastasis [304]. Bioactive ingredient I3C found in cruciferous vegetables acts as a potential inhibitor of the MAPK/ERK signaling pathway. A gene chip analysis done by cDNA microarray revealed that 13C and DIM suppressed the expression of MAP2K3, MAP2K4, MAP4K3, and MAPK3 in PC3 prostate cancer cells [290]. Gingerol was also found to suppress PMA-induced IκBα degradation and translocation of p65 to nucleus in mouse skin by blocking of upstream kinase p38 MAPK [292].

3.8 NF-κB pathway

Among the transcriptional regulatory proteins described, NF-κB seems to possess a particular importance in modulating the expression of more than 200 genes which are related to inflammation and immune responses, cellular transformation, invasion, cell growth, apoptosis, metastasis, chemoresistance, radioresistance, and the expression of certain viral genes [305]. Numerous studies have found it to be one member of a ubiquitously expressed family of REL-related transcription factors that serve as critical regulators of cancer development. Under normal condition, the NF-κB dimers reside in the cytoplasm. The range of stimuli including free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, γ-radiation, UV light, and X-rays that activate members of the REL family is extensive and growing, which emphasizes their central role in transcriptional responses. Upon activation, NF-κB is translocated to the nucleus, where it induces REL-mediated expression of targeted genes including cell proliferation and inflammation [306]. Many of the target genes including cyclin D1, Bcl-2, Bcl-xL, MMP, and VEGF are activated to the establishment of the early and late stages of aggressive cancers (Fig. 6) [306]. In the mammalian cells, five members of NF-κB family have been identified: RELA (p65), c-BEL, RELB, NF-κB1 (p50/p105), and NF-κB2 (p52/p100). Among them, transcriptionally active proteins are RELA, c-REL, and RELB, whereas NF-κB1 and NF-κB2 are synthesized as longer precursor molecules, which are further processed to smaller, transcriptionally active forms.

DPs from plants including polyphenols, alkaloids, and terpenes have a range of biological properties specifically anticancer. Typically, these phytochemicals show inhibitory effect on multiple signal pathways. NF-κB is one of the most frequent targets of compounds such as kaempferol [307], lycopene [308], SFN [309], curcumin [310], chalcones (see review [311], zerumbone [312], ursolic acid [313], apigenin [314], protocatechuic acid [315], EGCG [316, 317], betulinic acid [318], emodin [319], gingerol [320], elagic acid, piperine [321], anethole [322], S-allyl cysteine [323], flavopiridol

[252], diosgenin [252], genistein [324], luteolin, silibinin, deguelin, gallic acid, parthenolide, anthocyanin, quinoclamine, and dehydroxymethylepoxyquinomicin [325]. Several studies have shown that crude extracts from strawberry, deerberry, pomegranate fruit, and potato sprouts have inhibitory effect on NF-κB activation [326]. Kaempferol is a known antioxidant that possesses anti-inflammatory properties [11] which in a study was found to reduce age-related increase in NF-κB activity and NF-κB-dependent pro-inflammatory gene activity [307]. Lycopene treatment suppressed cystathionine γ-lyase (CSE)-induced NF-κB-DNA binding, NF-κB /p65 nuclear translocation, and phosphorylation of IKKα and IkBα by decreasing CSE-induced ROS production and NOX-4 expression [308]. Moreover, lycopene also inhibited CSE-induced phosphorylation of the redox-sensitive ERK1/2, JNK, and p38 MAPKs [308]. Author also stated that lycopene prevented CSE-induced IL-8 production through a mechanism involving an inactivation of NF-κB. Treatment of lycopene significantly inhibited the binding activity of NF-κB and the expression of NF-κB target gene MMP-9, leading to the attenuation of invasion of human hepatoma cells [327]. Recently, ursolic acid, a triterpenoid antioxidant, showed anti-inflammatory activity in lymphocytes. This was related with suppression of the activation of immunoregulatory transcription factors NF-κB, NF-AT, and AP-1 [313]. In a report, apigenin potentiated human T cells to induce cell death by inhibiting NF-κB activation and suppressing NF-κB-regulated antiapoptotic molecules such as cFLIP, Bcl-xL, Mcl-1, XIAP, and IAP, but not Bcl-2 [314]. In another study, Lin and coworkers reported that protocatechuic acid inhibits AGS cancer cell metastasis and invasion involving the downregulation of NF-κB pathway and MMP-2 production by targeting RhoB activation [315].

Several *in vitro* and *in vivo* studies conducted by Dr. B.B. Aggarwal's group have shown that the Indian spices exhibit their anticancer properties through the suppression of NF-κB. Recently, Guimaraes and coworkers observed that the curcumin significantly inhibits cytokine gene expression and activation of NF-κB in the gingival tissues, but did not suppress p38 MAPK activation [310]. Recently, it has been observed that curcumin disrupts pro-metastatic feedback loop between NF-κB and CXCL1/-2 feedback loop by the inhibition of NF-κB signalling leading to reduced metastasis formation *in vivo* [328]. Further, curcumin alone and in combination with chemotherapy and radiotherapy has been shown to potentially inhibit the NF-κB activation, thereby suppressing the initiation, progression, invasion, and metastasis of different cancers in various orthotopic or xenotransplant models [329–331]. Also, Aggarwal and colleagues observed that curcumin inhibited the paclitaxel-induced NF-κB pathway and inhibited lung metastasis of human breast cancer cells and in nude mice, respectively [332, 333]. In addition to the mentioned properties, treatment of curcumin induced HLJ1, through activation of the JNK/JunD pathway, and inhibited lung cancer cell invasion and metastasis by modulating E-cadherin expression [328].

In a report, resveratrol was found to suppress mammary carcinogenesis in a mouse model through suppression of 7,12-dimethylbenz(*a*)anthracene-induced NF-κB activation, downregulation of COX-2, and MMP-9 expression [334]. In the normal human epidermal keratinocytes, resveratrol blocked UVB-mediated activation of NF-κB by inhibiting UVB-mediated phosphorylation and degradation of IKBα and by activating IKKα [335]. In a study, authors found that the resveratrol treatment decreased the expression of p65 and IkappaB-alpha in treated rats [336]. Resveratrol was found to downregulate TNF-induced activation of NF-κB, TNF-induced phosphorylation, nuclear translocation of the p65 subunit of NF-κB and NF-κB-dependent reporter gene transcription in various cancer cell lines [337, 338]. Recently, resveratrol was associated with inhibition of lipopolysaccharide-induced NF-κB translocation into the nucleus [339]. Resveratrol treatment inhibited NF-κB activation and resulted in a reduction of TNF-α, IL-1β, IL-6, and COX-2 gene expression and a reduction of secreted IL-6 and prostaglandin E2 (PGE_2) [333]. Resveratrol supplementation (1 mg/kg/day) in MAC 16 tumor-bearing rats potentially suppressed NF-κB activity and protein degradation in skeletal muscle [340]. Exposure of LNCaP cells to resveratrol also downregulated the expression of NF-κB and p65 [341]. Similarly, curcumin and curcuminoids have also been reported to exert their anticancer effects by regulating the transcription factor NF-κB and its targeted genes [342].

Multiple lines of evidence indicate that EGCG can inhibit NF-κB pathway. EGCG has been found to negatively regulate NF-κB activity in various cancer cells [317]. Furthermore, Kim et al. reported that EGCG exhibits antitumor action due to suppression of NF-κB activation and phosphorylation of p38 MAPK and JNK in human astrocytoma U373MG cells [343]. Yang and coworkers found that EGCG inhibits NF-κB activation by blocking IKK activity [344]. In a report, drinking water of TRAMP mice supplemented with 0.1 % *w/v* GTP resulted in reduction in the expression of NF-κB, IKKα, IKKβ, RANK, and NIK compared with control mice [309]. Moreover, treatment of GTPs through spray application to mouse skin resulted in inhibition of UVB-induced activation of NF-κB, activation of IKKα, and phosphorylation and degradation of IκBα [316].

Chalcones are polyphenolic compounds that have a variety of pharmacological properties, including antioxidant [345], antimutagenic, antitumorigenic [346], and anti-inflammatory properties [347]. Chalcones such as broussochalcone A, 4-hydroxylonchocarpin, and 2,5-dihydroxy-4-chloro-dihydrochalcone prevents the degradation of IκBα and inducible nitric oxide synthase (iNOS) protein expression, which in turn would block NF-κB activation and iNOS protein

expression [348]. Another chalcone, butein, suppressed the NF-κB activation induced by various inflammatory agents and carcinogens and inhibited the NF-κB reporter activity due to suppression of phosphorylation and the nuclear translocation of p65 [349]. Hydroxysafflor yellow A isolated from *Carthamus tinctorius* L showed the inhibition of both IκB degradation and subsequent translocation of p50 and p65 NF-κB subunits from the cytoplasm to the nucleus as well as suppression of p65 expression and induction of the mRNA expression of anti-inflammatory cytokine IL-10 [350]. Another molecule, xanthohumol, isolated from the hop plant exhibits inhibitory potential on both constitutive and inducible NF-κB activation through inhibition of phosphorylation and degradation of IκBα, suppression of p65 nuclear translocation, and NF-κB-dependent reporter gene transcription [351]. Isoliquiritigenin 2′-methyl ether, obtained from *Caesalpinia sappan* L inhibited activation of NF-κB transcription factors, phosphorylated the MAPK, JNK, and ERK [352]. Similarly, licochalcone A isolated from the root of *Glycyrrhiza inflata* significantly inhibited the receptor activator of NF-κB ligand and formation of osteoclasts without any effect on cell viability [353].

Sanguinarine and emodin act as anticancer agents by blocking the degradation of IκBa. Moreover, both phytochemicals can attenuate phosphorylation and degradation of IκBa in response to TNFα stimulation [354]. SFN abrogated the resistance of pancreatic TICs to TRAIL by interfering with TRAIL-activated NF-κB signaling [355]. Moreover, SFN treatment has been reported to downregulate NF-κB function in prostate and colon cancer cells [356]. Piperine was shown to significantly inhibit the nuclear import and activation of NF-κB [321]. The inactivation of NF-κB by genistein has also been found, eventually leading to cell growth inhibition and apoptosis in several cancers [324, 357, 358]. In a study, guggulsterone was also found to inhibit NF-κB activation through suppression of IKK activation, resulting in induction of apoptosis [359]. Inhibition of binding of p50–p65 complex directly to the DNA was observed through treatment of caffeic acid phenethyl ester, which was correlated with the suppression of NF-κB activation [360]. Above findings indicate that NF-κB suppression by dietary phytomolecules may be essential for its antitumor activities.

3.9 EGFR pathway

EGFR, a cell surface receptor family, has been implicated in a multiplicity of cancer-related signal transduction pathways like cellular proliferation, apoptosis, invasion, adhesion, and migration. It has been confirmed that the several growth factors are required for carcinogenesis including EGF, PDGF, FGFs, TGF-α and TGF-β, erythropoietin, IGF, IL-1, IL-2, IL-6, IL-8, TNF, INF-γ, and CSFs. Cellular proliferation signals induced by numerous growth factor receptors, such as the EGF receptor, IGF-1 receptor, and VEGF receptor networks, constitute the basis for receptor-driven tumorigenicity and tumor progression in several cancers [361]. It is a member of the ErbB family of receptors, which is a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4) [362]. Assembling of these receptors causes conformational change leading to auto-phosphorylation of EGFR and eventually induces cell proliferation and angiogenesis and inhibits programmed cell death. Unregulated expression of growth factors can lead to abnormal growth and development, resulting in malignant transformation [363]. Aberrant activation of the EGFR and EGFR-driven pathways has been reported in a wide variety of human malignancies (Fig. 6) (see review [364]). This cancerous effect has been mediated in part through the activation of the EGFR-MEK-ERK-NF-κB signaling pathways. Phytochemicals derived from fruits, vegetables, herbs, and spices also referred as chemopreventive agents like curcumin [363], genistein [365], resveratrol [366], and EGCG [367] are reported to be potential suppressors the EGFR pathway that initiates cell proliferation, invasion, and metastasis.

The EGFR has been reported as a “hot spot” target of curcumin. The expression levels of pEGFR and pERK1/2 in the curcumin-treated triple-negative breast cancer MDA-MB-231 cells were significantly decreased compared with those of the control cells [363]. Chen et al. observed that curcumin inhibits EGFR signaling-dependent growth of Moser cells by downregulating EGFR tyrosine phosphorylation and blocking EGFR gene expression that is mediated by activation of PPAR-γ [368]. The growth of lung adenocarcinoma PC-14 and pancreatic adenocarcinoma p34 cells was suppressed due to curcumin treatment through inhibition of phosphorylation of ERK1/2 and reduction of COX-2 and the EGFR [369]. Several studies have indicated that the HER2/neu receptor is overexpressed in breast, prostate, ovarian, and lung cancers. Curcumin has been shown to inhibit the expression of HER2/neu and EGFR activity representing one of the mechanisms by which curcumin suppresses the growth of breast cancer cells [370]. In a study, curcumin inhibited HER2/neu receptor activity and its protein level, by interfering with the function of the ATP-dependent GRP94 chaperone protein, which is required for the maintenance of the properly folded state of the receptor [370]. The effects of three curcuminoid analogs such as curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin on prostate cancer cells were examined, and among them, DMC was found to be the most effective cytotoxic agent on PC3 cells [371]. This was associated via AMPK-induced downregulation of HSP70. Authors also stated that DMC sustains EGFR activation by suppressing the phosphatases PP2a and SHP-2. In addition, DMC enhanced the interaction between EGFR and Cbl and increased the tyrosine phosphorylation of Cbl. Strimpakos and

Sharma reported that the expression of various pro-angiogenic growth factors like VEGF, FGF, and EGF and angiogenesis can be inhibited by curcumin [372]. Curcumin inhibits the migratory and invasive ability of mouse hepatoma Hca-F cells by inactivating Cav-1 and EGFR signaling pathways [373]. Treatment of curcumin has shown potential to suppress the ligand-stimulated activation of EGFR, highlighting that curcumin can break the autocrine loops that are established in several advanced cancers [374]. Difluorinated curcumin, a novel curcumin analog, induced cell death, apoptosis, and disintegration of colonospheres by downregulating the membrane transporter ABCG2 and attenuating EGFR, IGF-1R, and NF-κB signaling consistent with inactivation of β-catenin, COX-2, c-Myc, and Bcl-xL and activation of the pro-apoptotic Bax [375].

Very recently, Chang and coworkers reported that individual or combined treatment with EGCG and gefitinib suppressed phosphorylation of EGFR in CAL-27 human oral squamous cell carcinoma cells [376]. Green tea catechin EGCG was also reported to downregulate the expression of both IL-6 [377] and IL-8 [378] in cultured keratinocytes and respiratory epithelium, respectively. Further, in rat pancreatic stellate cells, treatment of EGCG inhibited PDGF-induced proliferation and migration [379]. Also, EGCG treatment inhibited the growth of ARO cells by inhibiting phosphorylation of EGFR, ERK1/2, JNK, and p38. These changes were correlated with increased p21, activated caspase-3, and cleaved PARP and reduced cyclin B1/CDK1 expression [380]. In another study, EGCG downregulated EGFR, MMP-2, MMP-9, and EMMPRIN and inhibited the invasion of MCF-7 tamoxifen-resistant cells [381]. The inhibitory effects of plasma membrane incorporated EGCG or soluble EGCG on platelet-derived growth factor-induced cell signaling and mitogenesis were found out by Weber et al. [382]. The authors stated that EGCG directly interacted with PDGF-BB, thereby preventing specific receptor binding. Shimizu et al. concluded that green tea catechins exert anticancer and chemopreventive effects by inhibiting the activation of specific receptor tyrosine kinases, especially EGFR, IGF-1R, and VEGFR2 [367]. VEGF was involved in angiogenesis, and EGCG inhibited the production of VEGF in various cancer such as gastric cancer AGS cells [383], swine granulosa cells [384], colon cancer cells [383], stomach cancer cells [385], head and neck cancer cells [386], lung cancer cells [387], and breast carcinoma cells [388]. EGCG was also reported to suppress tumor cell migration and invasion by downregulating paracrine and autocrine hepatocyte growth factor/scatter factor [389]. EGCG has been reported to inhibit EGFR signaling pathway, most likely through the direct inhibition of VE cadherin phosphorylation, ERK1/2, and Akt kinases [390]. Down the line, EGCG also inhibited the expression of EGFR-2 [391], FGF [392], ErbB2 [393], VCAM-1 [390], EGF-induced MMP-9 expression [394], and HER-2/neu [395].

Resveratrol, another phytochemical, also inhibited arsenic-mediated ERK1/2 activation by shifting the balance of c-Src regulatory domain phosphorylation. These effects significantly altered the response of the EGFR pathway to growth factor-induced stimulation [396]. Resveratrol has also been shown to inhibit proliferation of Ishikawa cells by suppressing of EGF [366]. The production of IL-6 and stimulated peritoneal macrophages were downregulated by resveratrol in cortical mixed glial cells and mice, respectively. Resveratrol antagonizes EGFR-dependent Erk1/2 activation in human androgen-independent prostate cancer cells with associated isozyme-selective PKC alpha inhibition [397]. Pretreatment of resveratrol suppressed EGF-mediated migration and expression of MED28 and MMP-9 in MDA-MB-231 cells [398]. Combined treatment of curcumin and resveratrol caused a greater inhibition of constitutive activation of EGFR and its family members as well as IGF-1R leading to apoptotic cell death of colon cancer HCT-116 cells [399]. Suppression of IL-8 gene transcription was observed in phorbol ester-treated human monocytic cells exposed to resveratrol [400].

Soybean isoflavone genistein is a highly specific and non-competitive inhibitor of EGFR-TK. Genistein effectively reduced the IGF-I/EGF-mediated DNA synthesis, which was associated with an inhibition of GFR protein expression [401]. Genistein in combination with tyrosine receptor kinases reduced the expression of EGFR, pAkt, COX-2, and PGE(2,) consistent with inactivation of NF-κB [365]. In contrast, genistein increased proliferation and metastasis linked with activation of EGFR and its downstream Src under in advanced human prostate cancer [402]. Genistein together with gefitinib reduced p-EGFR, p-Akt, and p-mTOR expressions in human lung cancer H1975 cells, whereas caspase-3 and PARP activities were increased, thereby inducing apoptosis and cell death [403]. Functional analysis done by Yan et al. suggested that genistein regulates protein tyrosine phosphorylation particularly by inhibiting the activity of tyrosine kinase EGFR, PDGFR, insulin receptor, Abl, Fgr, Itk, Fyn, and Src [404]. Inhibition of p65 binding activity and the transcriptional level of TNF-α, IL-1β, and IL-6 and induction of the mRNA expression of anti-inflammatory cytokine IL-10 were found with the treatment of hydroxysafflor yellow A (chalcone), purified from *C. tinctorius* L [350].

3.10 AP-1 pathway

AP-1, a transcription factor that is a homodimer and heterodimer composed of basic region-leucine zipper proteins, belongs to the c-Fos, c-Jun, ATF, and JDP families [405]. Phosphorylation of AP-1 components by kinases such as the JNK and ERK MAP kinases is critical for functional activation of the AP-1 complex which can then regulate downstream

target genes involved in a variety of biological functions. Some of the target genes activated by the AP-1 transcriptional protein and by NF-κB include Blimp1, cyclin D1, Bcl-2, Bcl-X_L, VEGF, MMP, and uPA [406]. A variety of stimuli, including growth factors, stress, cytokines, and bacterial and viral infections regulate AP-1 activation, required for tumor promoter-induced transformation in mouse epidermal JB6 cells and for progression in mouse and human keratinocytes. AP-1 plays a key role in regulating a number of cellular processes including metastasis cascade, differentiation, proliferation, and apoptosis [407]. Most importantly, 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 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 posttranscriptional and translational modifications [406]. The expression and activity of AP-1 altered in many cancers, including breast, ovarian, endometrial, Hodgkin's lymphoma, colorectal, cervical, lung, bladder, and osteosarcoma, suggests that it may be fundamental to the process of oncogenesis (see review [406]). Several studies have shown that suppressing AP-1 function has a profound effect on the behavior of cancer cells and tumors, often interfering with the transformed phenotype. Taken together, this suggests that AP-1 is a promising target for cancer prevention and therapy.

In vitro and *in vivo* studies have shown that the several natural chemopreventive compounds such as phenethyl isothiocyanate, SFN [408], benzyl isothiocyanate [409], EGCG [410], quercetin [411], resveratrol [411], curcumin [412], delphinidin [413], capsaicin [414], oleandrin [415], anethole [322], and beta-lapachone [416] prevent from cancer by inhibiting the AP-1 activity. Jeong and their colleagues observed inhibitory effect of phenethyl isothiocyanate, SFN, curcumin, and resveratrol at higher concentration on AP-1-luciferase activity in the presence or absence of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) [408]. Benzyl isothiocyanate also blocked TNF-α-induced MMP-9 secretion via downregulation of NF-κB and AP-1 [409]. Pterostilbene, isolated from *Vaccinium* berries, has been shown to suppress TPA-induced activation of AP-1 in mouse epidermis [417]. Carnosol, an antioxidant in rosemary, also inhibited COX-2 gene transcription by blocking PKC signaling and the binding of AP-1 to the CRE of the COX-2 promoter in human mammary epithelial cells [418]. Also, quercetin and naringenin have been reported to effectively suppress NF-κB and AP-1 signaling in human endothelial cells and activated macrophages. Similarly, kaempferol, cyanidin, delphinidin, and menthone have also been found to inhibit the expression of COX-2 by inhibiting AP-1 activation, C/EBPδ nuclear translocation, STAT-1, MAPK, and NF-κB signaling [419, 420].

Inhibition of TPA- and EGF-dependent transformation of JB6 mouse epidermal cells was examined in the presence of EGCG and theaflavins [410]. Authors correlated this effect with the suppression of AP-1-DNA binding and transcriptional activity and inhibition of JNK activation. The activity of EGCG to regulate AP1 activity has been demonstrated by several studies. EGCG has been found to suppress malignant transformation by blocking activation of AP-1 in a PMA-stimulated mouse epidermal JB6 cell line [303]. Zhao et al. also observed that EGCG inhibits the survival of CNE1 and nasopharyngeal carcinoma (CNE)-LMP1 cells and the activity of AP-1 caused by LMP1 in CNE-LMP1 cells. In human keratinocyte HaCaT and Ha-ras-transformed human bronchial cells, EGCG was associated to suppress the UVB-induced c-Fos activation [421] and phosphorylation of c-Jun, ERK1/2, ELK1, and MEK1/2, respectively [422]. Moreover, EGCG has been shown to significantly increase MAPK-dependent AP-1 activity-associated responses in normal human keratinocytes, highlighting that the anticancer mechanism of EGCG could depend upon type of cells [423]. GTP treatment resulted in the attenuation of formation of signaling complexes, viz., uPA, uPA receptor, vitronectin, and integrin receptor, responsible for cell adhesion and migration by inhibiting the invasive behavior of breast cancer cells [2].

A multiple lines of evidence indicate that suppression of c-Jun/AP-1 binding to its corresponding site on DNA sequence by curcumin administration may be responsible for the inhibition of c-Jun/AP-1-mediated gene expression including c-fos, c-myc, endothelial tissue factor, chemokines, and metastasis (see review [424]). In a study, chenodeoxychlate or PMA is reported to increase AP-1 affinity to DNA, but treatment of curcumin decreased this effect [425]. Curcuminoids have also been found to the downregulated FGF-2-mediated DNA binding activity of AP-1 [426]. With respect to inflammation, curcumin has been associated with the inhibition of stimulation of free radical-activated NF-κB and AP-1 [427]. The TPA-induced AP-1-DNA binding was found to be inhibited by curcumin pretreatment in cultured human promyelocytic leukemia HL-60 cells [412]. Curcumin also strongly suppressed TNFα-induced NF-κB and TPA-induced AP-1 binding to the sequences of GSTP1-1 gene promoter [428]. In a mouse model of skin carcinogenesis, treatment curcumin was associated to inhibit tumor promotion, cell proliferation, and metastasis by preventing the PMA-induced activation of both NF-κB and AP-1 [429]. Curcumin also suppressed c-Fos transcription factor activation due to inhibition of ERK and JNK I in breast cancer cells [264]. Interestingly, Dickinson and coworkers observed that curcumin modifies AP-1 dimer composition [430]. Moving down the line in the list of chemopreventive phytochemicals, quercetin was found to suppress the transformation of overexpressing c-Fos rat liver epithelial cell line through the regulation of c-Fos/AP-1 complexes [431]. It was also found to inhibit lipopolysaccharide (LPS)-induced TNF transcription in RAW 264.7 macrophages through suppression of AP-1 DNA binding, TNF

transcription, phosphorylation, and activation of JNK/stress-activated protein kinase [432].

3.11 COX/LOX pathway

COX is a prostaglandin H synthase, which converts arachidonic acid (AA) released by membrane phospholipids into prostaglandins. Substantial evidence supports a functional role of lipoxygenase (LOX) in catalysis of AA and linoleic acid and thus implicated key role in cancer development [433]. Emerging reports now indicate alterations of COX and LOX-dependent metabolism of AA with carcinogenesis, and many COX and LOX inhibitors are being investigated as potential anticancer drugs. A considerable amount of evidence from several clinical studies in the world supports that COX/LOX is upregulated in many tumors such as colon, pancreatic, breast, prostate, lung, skin, urinary bladder, and liver cancers [433]. Three isoforms such as COX-1, COX-2, and COX-3 have been identified. Among these isoforms, the expression of COX-2 is regulated by mitogens, tumor promoters, cytokines, and growth factors and is overexpressed in practically every premalignant and malignant condition [434]. On the basis of regiospecificity, 5-LOX, 8-LOX, 12-LOX, and 15-LOX isoforms have been identified in different cells and tissues. In addition, the 5-LOX pathway has been reported to have profound influence on the development and progression of human cancers [435]. Accumulating evidences suggest that several transcription factors including AP-1, NFIL-6, and NF-κB can stimulate transcription of COX/LOX. Therefore, inhibitors blocking COX/LOX-catalyzed activities may be effective in preventing cancer.

Most important anti-inflammatory mechanisms of chemopreventive agents are the inhibition of eicosanoids generating enzymes COX/LOX thereby inhibiting the production of prostanoids and leukotrienes. Several chemopreventive dietary agents including galangin, luteolin [436], alpha-viniferin [437], apigenin [438], quercetin [439, 440], 6-hydroxykaempferol, quercetagenin [441], kaempferol, morin, myricetin [442], sasanquol [443], tyrosol [444], genistein [439], baicalin, baicalein, wogonin [445], green tea catechins [446, 447], curcumin [448], flavonols, artonin E, and resveratrol [449] have shown their effectiveness to suppress COX/LOX in order to reduce prostaglandins and leukotriene production, thus exerting an important anti-inflammatory action.

In different experimental models such as mice leukocyte infiltration, rat peritoneal leukocyte, and in guinea pig epidermis, quercetin was associated to suppress COX and LOX activities [440]. Green tea epicatechin inhibited LPO in LDL induced by myeloperoxidase in the presence of physiologically relevant concentrations of nitrite, a NO metabolite [450]. Inhibition of COX-2 expression by EGCG in mouse skin and TPA-stimulated human mammary cells (MCF-10A) has been observed by Kundu et al. [451]. Pro-delphinidin B-4 3′-O-gallate [452] and pro-delphinidin B2 3,3′-di-O-gallate [453], GPTs, inhibited mRNA and protein expression of COX-2 in LPS-activated murine macrophage RAW264 cells through the suppression of NF-κB and MAPK pathways. Moreover, green tea catechin and EGCG showed COX downregulation in LPS-induced macrophages [446]. Green tea EGC, GC, ECG, CG, EGCG, and black tea theaflavins have been shown to have arachidonic acid-dependent COX-1/COX-2 inhibitory activity in different cancer cell lines [446, 451, 454]. Catechins and theaflavins have been reported to inhibit 30–75 % LOX-dependent activity in colon tumors [447].

Curcumin, another chemopreventive natural agent found to significantly downregulate NF-κB pathway, resulted in inhibition of COX-2 activity. In addition, preclinical studies have also proven that curcumin downregulated the expression of NF-κB-inducing kinase and IκBa kinase enzymes, which is associated with the suppression of COX-2 activity in colon cells. It has been reported that COX-2-derived prostaglandins stimulate aromatase activity (an independent source of estradiol generation in breast cancer patients) undergoing anti-estrogen therapies can be inhibited by COX-2 inhibitor curcumin [455].

Likewise, oleuropein glycoside, caffeic acid, and tyrosol were associated with inhibition of 5-LOX pathway, thereby inhibiting LTB4 production in human-activated leukocytes [444]. Few more DPs, tyrosol, lycopene, and quercetin prevented gliadin-stimulated RAW 264.7 macrophage activation by downregulating COX-2 and iNOS gene expression through the inhibition of NF-κB [456]. Moreover, 5-LOX activity was inhibited through the administration of tannins such as hamamelitannin and galloylated proanthocyanidins with an IC_{50} ranging from 1.0 to 18.7 mM [457]. In LPS-stimulated J774 murine macrophages, hydroxytyrosol [458] and oleocanthal [459] were able to inhibit COX-2 and iNOS genes expression. Baicalein was found to selectively downregulate platelet 5-LOX [460]. In LPS-stimulated human whole blood cells, kaempferol has suppressed the production of PGE_2 [442]. Kaempferol, quercetin, morin, and myricetin were found to be powerful inhibitors of 5-LOX [461]. Secretion of AA and its metabolites was inhibited with the treatment of 10 mM tetrahydrocurcumin and curcumin in LPS-stimulated RAW cells and A23187-stimulated HT-29 colon cancer cells. This was associated with the inhibition of cPLA2 phosphorylation, COX-2 expression, and catalytic activities of 5-LOX [448].

Aggarwal and Shishodia confirmed that soy genistein and green tea catechins inhibit COX-2 expression by downregulating EGFR and HER-2/neu activities [8]. Similarly, in phorbol ester-treated human mammary epithelial cells, red grape resveratrol suppressed COX-2 transcription and activity [449]. Resveratrol has been found further to be acting as competitive inhibitor of purified COX-2, 5-LOX, and 15-LOX and prostaglandin H synthase, with inhibition constants

of 35 μM (COX-2 activity of prostaglandin H synthase), 4.5 μM (5-LOX), 40 μM (15-LOX), and 30 μM (peroxidase activity of prostaglandin H synthase) [462]. Moreover, resveratrol suppressed DMBA-induced mammary carcinogenesis via downregulation of NF-κB, COX-2, and MMP-9 in rats [334]. In LPS-activated murine macrophage line RAW 264.7, the oligomeric stilbene alpha-viniferin and resveratrol inhibited COX-2 activity and COX-2 transcription [437]. Also, a prenylflavone, artonin E, was examined as most effective inhibitor of porcine leukocyte 5-LOX [463].

Theaflavin, theaflavin digallate, and EGCG inhibited MMP-2 and MMP-9 from the culture medium of tumor cells, resulting in the attenuation of invasion of highly metastatic mouse Lewis lung carcinoma LL2-Lu3 cells, suggesting that these molecules inhibited tumor cell invasion by inhibiting type IV collagenases [31]. Also, in human colon cancer HCT116 and HT29 cells, EGCG occurred in the presence or absence of catalase-attenuated Met signaling and helped in inhibition of H_2O_2-dependent metastasis mechanisms [464].

4 Synergy between DPs to inhibit metastasis

Epidemiological studies have consistently shown that regular consumption of whole foods such as fruits, vegetables, and grains is strongly associated with good health and reduced risk of cancer. Therefore, it is reasonable for researchers to identify the bioactive compounds responsible and hope to find the magic bullet to inhibit metastasis and invasion. The key question here is whether a single phytochemical has the same health benefit as the compound when its source is a food or a combination of phytochemicals. It is now widely believed that the efficacy of the DPs alone does not explain the remarkable antimetastasis activities of diets rich in fruits and vegetables, taken as single [286, 465]. Numerous studies have shown that the combination of DPs exhibits strong antimetastatic activity [328, 466]. These studies proposed that the synergistic effects of phytochemicals in fruits and vegetables are responsible for anticancer activity.

A number of studies report enhanced anticancer effects of mixtures of polyphenols from dietary sources. Apple extracts are reported to contain bioactive phytochemicals in peel that potentially inhibit colon cancer cell proliferation by 43 %. However, this was reduced to 29 % when apple was used without peel [467]. In a study, ellagic acid, calcium D-glucarate, resveratrol, and grape seed extract were tested as components of diets. All combinations showed decreased cell proliferation, cell survival, metastasis, invasion, and Bcl2 expression; decreased p21, a regulator of cell cycle; and decreased marker of inflammation cyclooxygenase-2 [468]. In 2003, Temple and Gladwin studied >200 cohort and case–control studies that provided risk ratios concerning intake of whole foods and risk of cancer. They concluded that cancer prevention is best achieved by consumption of diet rich in fruits and vegetables, although one group of fruits and vegetables may dominate for a particular cancer [469]. Moreover, the combination of soy phytochemical concentrate and black tea synergistically inhibited prostate tumorigenicity, final tumor weight, and metastasis to lymph nodes *in vivo* [470]. In combination protocols with conventional chemotherapeutic drugs, tamoxifen plus EGCG showed a synergistic cytotoxic effect towards ER-negative breast cancer cells [471]. Similarly, genistein and tamoxifen combination synergistically delayed the growth of breast tumor via decreased estrogen level and activity and downregulated EGFR expression [472]. Vitamin C supplementation has also been shown not only to lower the incidence of cancer and heart disease, but also suppress metastasis [473].

Epicatechin, another important GTP, was found to enhance EGCG-induced apoptosis, growth inhibition of PC-9 lung tumor cells, and inhibition of tumor necrosis factor-α release [474]. These effects when induced by other tea polyphenols with a galloyl moiety were also increased in a dose-dependent way by EC. The results indicated that as a result of synergistic effects between green tea polyphenols, whole tea is a more efficient mixture for cancer prevention than supplementation with EGCG alone. Due to synergy between phytochemicals, the green tea extracts exhibited mixed agonist/antagonist activity on the Ah receptor, whereas EGCG acted as a strict AhR antagonist [475]. Co-treatment of human hepatocytes with tetrachlorodibenzo-*p*-dioxin (TCDD) and different mixtures of tea catechins synergistically inhibited TCDD-induced CYP1A promoter-driven luciferase reporter activity and CYP1A1 expression in primary hepatocytes. The optimal synergy was found for a combination of the four major tea catechins, EC, EGCG, EGC, and ECG [476]. The combination of I3C and crambene significantly protected against aflatoxin B1-induced toxicity in a rat model, showing synergistic effects [477]. An exceptionally strong 10-fold synergy was found between grape polyphenols and tea catechins in the inhibition of tNOX [478]. These findings suggest that the combination of DPs that have synergistic effects may help us to design novel food products or biopharmaceuticals for management of human cancer.

5 Nanotechnology enhances metastasis potential of DPs

Despite the considerable promise that natural phytochemicals are efficacious and safe phytocompounds for prevention and therapy of cancer, it has by no means been embraced by the cancer community as a "panacea for all ills." The single most important reason for this reticence has been the reduced bioavailability of orally administered EGCG and curcumin [479, 480]. Moreover, widespread *in vitro* and *in vivo* applications of these relatively efficacious agents in cancer and other diseases

have been failed to prove their worth at the last and most expensive step, i.e., in preclinical settings in a wide variety of animal models [481, 482]. The applicability of chemoprevention from "bench to bedside" for human use has met with very limited success. Many reasons have been attributed to this failure that range from lack of clearly defined mechanism of action to poor aqueous solubility and, consequently, minimal systemic bioavailability [481, 483]. Therefore, in order to achieve maximum comeback of these chemopreventive agents for human use, strategies that can bypass these limitations are mandatory. Strategies that could lead to sustained release of these agents could critically improve their bioavailability and in turn reduce the perceived toxicity associated with high doses that are typically required for optimum efficacy with an agent.

The advents of nanotechnological approaches have unleashed enormous prospects for drug delivery center on developing nanomaterials to improve drug bioavailability [481, 484]. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. Several different approaches have been employed in nanotechnology to optimize drug delivery in a tumor-specific manner. Nanotechnology currently is being evaluated in cancer as nanovectors which can be loaded with natural products to enhance delivery that are based on the solubility properties of drugs to be loaded. Application of nanotechnology is considered to have great potential due to the ability to engineer devices with unique therapeutic potentials that because of their tiny size can penetrate tumors extremely with a high level of specificity. This "nanochemoprevention" area of research is highly accepted, even by the National Cancer Institute, which considers that nanotechnology offers an extraordinary paradigm-shifting opportunity to make significant advances in cancer treatment. Nanochemoprevention has been successively evaluated by numerous groups of researchers worldwide and has now become an attractive and advancing field in cancer prevention research.

In recent years, nanotechnology has been evaluated and implemented in different areas of cancer therapeutics and cancer management and is offered considerable opportunities to researchers for the development of innovative drugs for cancer treatment, diagnosis, and detection. This technology has permitted the development of nanoscale devices such as nanoparticles (NPs) that can be conjugated with several functional dietary agents simultaneously. Since these NPs are 100- to 1,000-fold smaller than human malignant cells, they can be easily transferred through leaky blood vessels and interact with targeted tumor-specific proteins both on the surface of and inside cancer cells. The term nanochemoprevention coined by Mukhtar and coworkers for the first time used the multifunctionality of biodegradable polylactic acid (PLA)–polyethylene glycol (PEG) NPs to load the "EGCG" and showed effective antitumor efficacy in a prostate model [485]. Moreover, the nanovectors (i.e., PLA/PEG NPs) when injected systemically were rapidly cleared by the mononuclear phagocytic system by the process of endocytosis, thereby diminishing carrier-induced unwanted cytotoxicity. Meanwhile, in its advent in the field of cancer, nanotechnology has provided scientific groups with knowledge to explore new streets for management of various diseases. Utilization of nanotechnology has enabled the development of devices in nanometer sizes which could be designed to nanovector-mediated efficacious and safe drugs that have shown excellent results. As the knowledge of the dynamics of nanoencapsulation evolves, it is expected that researchers will bring forward newer and far more superior nanochemopreventive agents that may become standard drugs for treating cancer.

6 DPs improve antimetastatic activity of conventional cancer therapies

Conventional therapies (CTs) such as surgery, chemotherapy, and radiotherapy have limitations in the management of cancer. However, these play important role in the overall treatment of most solid tumors. Emerging evidence suggests that the combination of chemopreventive DPs and CTs can enhance anticancer potential and life span of patients due to their synergic action or compensation of inverse properties [286, 486]. In recent years, a number of DPs have been documented as cancer chemopreventive agents because of their strong anticancer activity [56]. Moreover, these agents also exhibit the antimetastasis activities through regulation of different cellular signaling pathways [18]. The combine therapy can also reduce the systemic toxicity caused by CT such as chemotherapies or radiotherapies as lower doses could be used.

Recent studies suggest that genistein and other DPs may enhance the efficacy of CT by modulating molecular targets. EGCG and tamoxifen synergistically induced apoptosis and growth cell death in MDA-MB-231 human breast cancer cells [487]. Administration of EGCG inhibited lung metastases in mice bearing B16-F3m melanomas, while a combination of EGCG and dacarbazine was found to be more effective in decreasing the number of pulmonary metastases and primary tumor growths and enhancing the survival rate of melanoma-bearing mice [23]. Additionally, EGCG was also found to chemosensitize resistant tumor cells to doxorubicin by increasing in the accumulation of doxorubicin in the tumors of human carcinoma xenograft model [488]. Soy isoflavone genistein enhanced growth inhibitory and apoptosis-inducing potentials of cisplatin, docetaxel, doxorubicin, and gemcitabine in prostate, breast, pancreas, and lung cancer cell lines [489–491]. It has also been reported that the genistein sensitizes chemoresistant HT-29 colon cancer cells to induce apoptosis and inhibit metastasis and invasion of cells treated with 5-fluorouracil by modulating AMPK and COX-2

signaling pathways. Under *in vitro* and *in vivo*, studies also found that genistein could sensitize diffuse large cell lymphoma to cyclophosphamide, doxorubicin, vincristine, prednisone, and chemotherapy [486]. Genistein was also found to potentiate necrotic-like cell death in HER-2-overexpressing breast cancer cells treated with adriamycin. In a study, curcumin and celecoxib synergistically reduced the cell survival of colorectal cancer cells [492]. Moreover, curcumin also potentiated the antimetastatic activities of cisplatin, doxorubicin, and Taxol in HA22T/VGH hepatic cancer cells, HeLa cells, or CAOV3 and SKOV3 ovarian cancer cells. Similarly, theanine caused enhancement of the suppressive efficacy of doxorubicin on hepatic metastasis of M5076 ovarian sarcoma cell line transplanted subcutaneously in mice [30]. These results suggest that DPs potentiate anticancer activity of CT (for more see review [286]).

7 Application of computational approaches to predict antimetastasis potential of DPs

Regular consumption of phytochemical-rich food has been used as treatments for human ailments for centuries. The mechanisms of action of DPs are now a major area of investigation. A large number of DPs have shown chemopreventive and antimetastasis activities. It is recognized that isolationist/reductionist approaches focusing on a single pathway will not allow for gaining full understanding of the myriad pathways modulated by most of these natural agents and their mixtures. Recently, more holistic approaches have been used in order to understand their mechanism of action. A number of computational strategies have been used on Ayurvedic medicine-derived agents and on Chinese herbal medicines as well [493]. Computational approaches for determining molecular protein targets of DPs have received a great deal of attention. Researchers have applied computational methods such as virtual screening, shape similarity screening, and molecular docking to determine potential molecular targets of phytochemicals. These computational-based approaches have provided effective and low-priced tools to gain further understanding of the anticancer activity exerted by DPs.

7.1 Virtual screening method

Virtual screening is a computational technique that involves the identification and compilation of relevant chemical structures from large chemical libraries. The recognized chemicals bind to a protein receptor selected using different computer programs or identified experimentally. Virtual screening by molecular docking is the key computational method used in drug discovery for “hit” identification [494]. Structure-based virtual screening was used in the primary methodology, which includes docking of thousands of candidate ligands into a protein target followed by scoring the protein–ligand binding interaction to estimate the binding energy of the ligand [495]. Structure-based virtual screening needs the 3D structure of the ligands. More than 13 million purchasable compounds in 3D docking format are available in the ZINC database; these are freely available for virtual screening [496]. For targeted virtual screening, smaller and more specific high-quality libraries can be developed by using this huge database. The National Institute of Health's PubChem online database (http://pubchem.ncbi.nlm.nih.gov/) is another available database containing 2D forms of molecules which comprised over 27 million unique structures. Quercetin and kaempferol bounded within the ATP banding site of p90 ribosomal S6 kinase 2 (RSK2), which indicated that both might also be a potential inhibitor of RSK2 confirmed by virtual screening [497].

7.2 Shape similarity screening method

The shape similarity screening relies on the intuitive principle that structurally similar molecules may have similar properties. The output is a ranked list based on the computed similarities and allows the selection of potential hits. The method includes consideration of the atomistic and spatial characteristics of the target molecule. The pharmacophore and physical features of the molecule are quantitatively compared with one or more reference active compounds in a database. When searching for potential target proteins, the compound database used is composed of crystallized ligands extracted from the most recent version of the protein databank (PDB) [498]. Since the atoms are oriented in a style optimized for binding to the protein, the ligand confirmation in crystal structure is applied. Any available library can be used when searching for similar molecules. The PHASE module of Schrödinger's molecular modeling software package is the most useful program that can perform this type of shape similarity search [499]. The atom type information is also considered align potential pharmacophore points between the queries and targets. Recently, the smaller compound (i.e., flavonoid) database has also been created by Chen and colleagues and the latest version of the PDB, which contains more than 500,000 protein structure complexes with ligands, was used for shape similarity screening [497]. The PDB for screening kinase that targets this group also created a specific kinase database of about 4,000 structure complexes with ligands separately. To find potential flavonoid inhibitors of PI3-K, myricetin [500] and isorhamnetin [501] were chosen to use as the query structure and shape similarity screening was performed using our flavonoid database and the PHASE module. Authors have validated myricetin and isorhamnetin as direct inhibitors of PI3-K.

7.3 Molecular docking method

In the field of molecular modeling, docking has become a standard tool for guessing the binding orientation of small molecule with their protein targets to form a stable complex. Knowledge of the preferred orientation in turn may be used to guess the strength of binding affinity between two molecules used for example scoring functions. Thus, molecular docking plays a key role in the rational design of drugs. A software, GLIDE from the Schrödinger Suite 2011, is being uses to perform docking [497]. The connections between biomolecules such as proteins, nucleic acids, carbohydrates, and lipids play an important role in signal transduction. Furthermore, the comparative orientation of the two interacting partners may affect the type of signal produced. Therefore, molecular docking is useful for predicting both the strength and type of signal produced. Two approaches are used within the molecular docking community. One approach uses a matching technique that defines the protein and the ligand as complementary surfaces [502]. The second approach simulates the actual docking process in which the ligand–protein pairwise interaction energies are considered [503]. The gallic acid moiety of EGCG inhibited interaction with the catalytic site of the human DNMT1, and its binding with the enzyme is stabilized by Mg^{2+} studied by computational modeling [63]. Another study also supported this conclusion and suggested that EGCG forms hydrogen bonds with Pro^{1223}, Glu^{1265}, Cys^{1225}, Ser^{1229}, and Arg^{1309} in the catalytic pocket of DNMT [54]. Very recently, it has also been found that isorhamnetin forms some favorable connections and docks nicely within the MEK1 ATP-noncompetitive binding site. Some important hydrogen bonds were also observed between isorhamnetin and the backbone of MEK1, like $Val1^{27}$ in the ATP-noncompetitive binding site and Ser^{212} in the activation loop [497]. Moreover, isorhamnetin was associated to form hydrophobic interactions with the side chain of MEK1 at Ile^{99}, Phe^{129}, Ile^{141}, Phe^{209}, and Leu^{118}.

8 Conclusion and future directions

The growing field of nutritional genomics targets nutrient-related cellular signaling pathways and epigenetic changes for prevention and therapy of various cancers. Current review clears that DPs hold great potential for prevention and therapy of cancers by modulating genetic and epigenetic targets. The anticancer effects of these natural agents make them strong candidates for chemoprevention and/or therapy against human malignancies. However, more clinical trials are required to evaluate the effects of these agents for the prevention of cancer development and also for the treatment of cancer either alone or in combination with conventional cancer therapeutics. At present, very few phytochemicals have entered clinical evaluation. It should be noted that clinical application of any of these agents can only happen after they have passed preclinical toxicity profiling, pharmacokinetic profiling, and other types of profiling in advanced animal model systems.

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