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Natural products as potential cancer therapy enhancers: A preclinical update

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Abstract

Cancer is a multifactorial disease that arises as a consequence of alterations in many physiological processes. Recently, hallmarks of cancer were suggested that include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis, along with two emerging hallmarks including reprogramming energy metabolism and escaping immune destruction. Treating multifactorial diseases, such as cancer with agents targeting a single target, might provide partial treatment and, in many cases, disappointing cure rates. Epidemiological studies have consistently shown that the regular consumption of fruits and vegetables is strongly associated with a reduced risk of developing chronic diseases, such as cardiovascular diseases and cancer. Since ancient times, plants, herbs, and other natural products have been used as healing agents. Moreover, the majority of the medicinal substances available today have their origin in natural compounds. Traditionally, pharmaceuticals are used to cure diseases, and nutrition and herbs are used to prevent disease and to provide an optimal balance of macro- and micro-nutrients needed for good health. We explored the combination of natural products, dietary nutrition, and cancer chemotherapeutics for improving the efficacy of cancer chemotherapeutics and negating side effects.

Keywords

Cancer, cancer therapy, natural products, herbs, nutrition

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Introduction

A long history exists of natural products originating from plants, fungi, and microorganisms that have been used for the treatment and prevention of human diseases. In recent years, there has been an emerging focus on the exploration of natural products, including dietary phytoconstituents, in cancer prevention and treatment. An analysis of the origin of drugs developed between 1981 and 2002 showed that natural products or natural-product-derived drugs comprise 28% of all novel chemical entities (NCEs) launched into the market.[1] Examples of anti-cancer agents originating from natural sources include vinblastine from *Vinca rosea*, one of the earliest examples, and paclitaxel, the most recent example, which originates from a Chinese pacific yew plant.[2] Other plant-derived anti-cancer agents include etoposide, teniposide, homoharringtonine, and camptothecin derivatives.

Natural products as inhibitors of cancer cell proliferation and as inducers of cancer cell cycle arrests and apoptosis

Proliferation is the multiplication or reproduction of cells resulting in the rapid expansion of a cell population. Mammalian cell growth and proliferation are mediated via cell cycle progression. In each cell division cycle, chromosomes are replicated once (DNA synthesis or S-phase) and segregated to create two genetically identical daughter cells (mitosis or M-phase). These events are spaced by intervals of growth and reorganization (gap phases G1 and G2). Progression through the G1 phase of the cell division cycle is

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Table 1. Major anti-cancer natural products and their principal target genes.

Major natural products	Principal target genes
Curcumin	*Wnt/β-catenin* pathway;[65]*MMP2*;[40,63]*MMP14*;[40]*TIMP-1*;[63]*Gelatinase*;[40]*EGF*;[51–54]*MMP9*;[41,39,43]*VEGF*;[39,43,63]*bFGF*;[63]*NF-κB*;[5]*STAT3*;[5]*PI3K/AKT*;[5]*mTOR*;[6,7]*JNK*;[51]*ERK1/2*;[51]*uPA*;[51]*VEGF*;[42] *KDR*;[42]*Angiopoietin1/2*[42]
Sulforaphane (SFN)	*Wnt/β-catenin* pathway;[72]*IL-6*;[60] *IL-1β*;[60]*TNFα*;[60]*PDGF*;[60]*VEGF*;[60] *NF-κB*;[74] *GATA6*[74]
Resveratrol	*β-catenin*;[71]VEGF;[46]*Src*;[15,46]*NF-κB*;[14,15]*AP1*;[14,15]*Egr1*;[14,15]*MAPKs*;[14,15]*AR*;[16]*AKT*;[14,16]*Caspase-9*;[14]*COX*;[15]*NOS*;[15]*IL-1β*;[75]*PI3K*[75]
Caffeic acid phenethyl ester (CAPE)	*Wnt/β-catenin* signaling;[65]*NF-κB*; [30]*HER2*;[31]*AKT*;[32]*ERK*;[32]*ER-α*;[32]*MMP2*[66]
Quercetin	*Wnt/β-catenin* signaling;[65]*EGF*;[51,53]*VEGF*;[54]*HER2/neu*;[51,53]*HER3*;[51,53]*VEGF-R2*;[36]*COX-2*;[52]*iNOS*;[52]*TGF-α*;[53] c-*Raf*;[53]*MEK1/2*;[53]*Elk-1*;[53]*AKT*;[36,53]*mTOR*[36]
EGCG	*Wnt/β-catenin* signaling;[65]*NF-κB*;[17]*DNMT*[76–78]
Lycopene	*NF-κB*;[64]*MMP9*;[64]*IGF-1*;[25]*AKT*;[23–25]*β-catenin*;[25]*cyclin D1*;[24]*Bad*;[24]*AR*;[25]*PSA*;[26]*pRb*;[23]*ICAM-1*;[22]*TNFα*;[22]*SP-1*;[64]*IGF-1R*[64]
Genistein	*EGF*;[18,51]*FOXO3*;[18]*NF-κB*;[18]*Notch-1*;[18]*uPA*;[51]*JNK*;[51]*ERK1/2*[51]
13-cis-retinoic acid	*IL-2*;[44]*TIMP-1*;[44]*NF-κB*;[44]*ATF-2*;[44]*c-fos*[44]
Indol-3-carbinol (I3C)	*IGF1R*;[8]*IRS-1*;[8]*ERα*[8]
Urolithin, ellagitannins and punicalagin	*PSA*;[20]*Aromatase*;[21]*NF-κB*[20]
Amentoflavone	*COX-2*;[52] *iNOS*[52]
Indirubin	*VEGF-R2*;[38]*JAK/STAT3*[38]
Salvianolic Acid B (Sal B)	*TGF-β1*;[62]*Smad2/3*;[62]*Smad7*;[62]*MMP2*[62]

13C: indol-3-carbinol; SAL B: salvianolic acid B; *MMP*: matrix metalloproteinase; *TIMP-1*: tissue inhibitor of metalloproteinase-1; *NF-κB*: nuclear factor kappa-light-chain-enhancer of activated B cells; *EGF*: epidermal growth factor; *FOXO3*: forkhead box O3; *VEGF*: vascular endothelial growth factor; *HER2*: human epidermal growth factor receptor 2; *bFGF*: basic fibroblast growth factor; *STAT3*: signal transducer and activator of transcription 3; *mTOR*: mammalian target of rapamycin; *JNK*: c-Jun N-terminal kinases; *ERK*: extracellular-signal-regulated kinase; *uPA*: urokinase-type plasminogen activator; *KDR*: kinase insert domain receptor; *IL*: interleukin; *TNF*: tumor necrosis factor; *PGDF*: platelet-derived growth factor receptor; *MAPK*: mitogen-activated protein kinase; *AR*: androgen receptor; *COX*: cyclooxygenase; NOS: nitric oxide synthase; *ER-α*: estrogen receptor-alpha; *iNOS*: inducible nitric oxide synthase; *DNMT*: DNA cytosine methyltransferase; *IGF*: insulin-like growth factor; *PSA*: prostate specific antigen; ICAM: intercellular adhesion molecule; *SP-1*: specificity protein 1; *ATF-2*: activating transcription factor 2; *GATA6*: GATA-binding factor 6 .

a rate-limiting step in mammalian cell proliferation and is governed by numerous mitogenic pathways until the restriction point is passed. Cyclin-dependent kinases (CDK), *CDK4* and *CDK6*, complexed with cyclin D1 are responsible for cell cycle progression through the G1 phase, and the *CDK2*/*cyclin E* complex functions in the progression of the cell from the late G1 to the early S-phase.

Apoptosis is the predominant mechanism by which cancer cells die when subjected to chemotherapy or irradiation. However, cancer cells develop resistance to these therapies that may be due, at least in part, to the development of effective anti-apoptotic mechanisms.[3]

More than 600 natural products are reported to possess pharmaceutical activity and many of them exhibit anti-cancer activity. Among the 600 natural products, curcumin (diferuloylmethane), a yellow spice and phenolic compound derived from the plant *Curcuma longa*, is one of the most powerful and promising chemo-preventive and anti-cancer agents.[4] Curcumin has been found to exert preventive and therapeutic effects in various cancers, in part, due to its ability to influence a diverse range of molecular targets and signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*), signal transducer and activator of transcription 3 (*STAT3*), *PI3K* and *AKT* pathways. Moreover, the number of its proposed cellular targets grows as research continues. Recently, curcumin was implicated in modulating cancer cell proliferation by targeting the mammalian target of rapamycin (*mTOR*) signaling pathways[6,7] (Table 1).

Another natural product which exhibited anti-cancer activity is indol-3-carbinol (I3C), a natural hydrolysis product of glucobrassicin in cruciferous vegetables. 13C was reported to block proliferation of cancer cells by modulating the expression of insulin-like growth factor receptor-1 (*IGF1R*) and insulin receptor substrate-1 (*IRS1*), and to induce protein degradation of estrogen receptor-alpha (*ER-α)*.[8] Moreover, cruciferous vegetables contain sulforaphane (SFN), a naturally occurring organosulfur compound formed by the hydrolysis of glucosinolates that possess anti-cancer and anti-oxidant activities. Epidemiologic studies suggest that cruciferous vegetable intake may lower overall cancer risk, including colon and prostate cancers.[9] SFN was shown to block proliferation and induce cell survival and cell cycle arrest in both in vitro and in vivo systems. SFN also exhibited anti-cancer activity in cancer animal models, as evident from the significant reduction in tumor volume in treated animals.[10] Another indole compound derived from cruciferous vegetables is brassinin, which was reported to exhibit anti-proliferative effects against cancer in both in vitro and in vivo models[11] (Table 1).

Resveratrol (3,4′,5-trihydroxy-trans-stilbene), another widely recognized natural product, is a polyphenolic found in grapes, showing chemo-preventive properties against

several cancers, heart diseases, inflammation, and viral infections. Resveratrol was reported to block proliferation, promote cell cycle arrest, and induce apoptosis in cancer cells, mediated by the suppression of extracellular-signal-regulated kinase (*ERK*)1/2 signaling pathway, *p53, Rb/E2F*, cyclins, and *CDKs*. Furthermore, resveratrol affects the activity of transcriptional factors involved in proliferation and stress responses, such as *NF-κB*, activator protein 1 (*AP1*) and *Egr1*, mitogen-activated protein kinases (*MAPK*s) and tyrosine kinases (e.g. *Src*), leading to apoptosis induction.[12–15] In addition, resveratrol also inhibits cellular proliferation of prostate cancer cells in both androgen receptor (*AR*)-dependent and independent mechanisms.Resveratrol inhibits *AR* transcriptional activity and stimulates phosphatase and tensin homolog (*PTEN*) expression and decreased *AKT* phosphorylation[16] (Table 1).

Drinking green tea is also associated with a decreased frequency of cancer development, mainly due to the presence of epigallocatechin gallate (EGCG) and other polyphenols. EGCG suppresses androgen receptor expression and signaling via several growth factor receptors. Moreover, EGCG blocks nuclear translocation of the transcription factor *NF-κB*.[17]

Genistein is an isoflavone found in soy. Soy consumption is associated with a lower incidence of a number of cancers, including colon cancer which is believed to be mediated by genistein. Genistein was reported to inhibit cancer progression and block proliferation, in part by attenuating the negative effect of epidermal growth factor (*EGF*) on forkheadbox O3 (*FOXO3*) activity.[18] However, its therapeutic actions in vivo has been questioned due to contradictory reports from animal studies. Recent in vivo data argue that genistein exhibited a cancer promoting effect[19] (Table 1).

Ellagitannins are bioactive polyphenols found in berries and pomegranate fruit which have attracted recent attention due to their anti-cancer and anti-atherosclerotic, anti-oxidant, and anti-inflammatory bioactivities. Ellagitannins are not absorbed intact into the bloodstream but are hydrolyzed to ellagic acid. They are also metabolized by gut flora into urolithins which are conjugated in the liver and excreted in the urine. These urolithins are also bioactive and inhibit cancer cell proliferation, mediated in part by interfering with the activity of the *NF-κB* pathway. In clinical studies, pomegranate juice administration led to a decreased rate of prostate specific antigen *(PSA*) rise after primary treatment with surgery or radiation.[20] Moreover, urolithin, an ellagitannins derivative, significantly inhibited testosterone-induced MCF-7aro (MCF-7 that over-expresses aromatase protein) cell proliferation, probably by exhibiting anti-aromatase activity[21] (Table 1).

Epidemiological studies have shown that the consumption of lycopene is inversely related to human prostate cancer. Moreover, experimental studies have shown that lycopene inhibits the growth of breast, prostate, and endometrial cancer cells with regulation of cell-cycle-related genes, mediated by interfering with *NF-κB* activity.[22] In colon cancer cells, lycopene was reported to inhibit the activity of *AKT* signaling[23] and consequently induced apoptosis.[24] In addition, it has been reported that lycopene inhibited insulin-like growth factor-1 (*IGF-1*) mediated *AKT* and *AR* signaling in rat prostate cancer.[25] Clinical trials have revealed that lycopene supplements could reduce tumor size and *PSA* level in localized prostate cancers,[26] consistent with the down-regulation of *AR* nuclear translocation found during in vitro studies (Table 1).

Moreover, a widely recognized nutritional dietary supplement called Propolis made by honeybees and containing flavonoids, phenolic acids and esters, and caffeic acid phenethyl ester (CAPE) exerted a variety of anti-cancer activities by modulating cell proliferation; induction of cell cycle arrest and apoptosis[27] mediated by inhibition of *NF-κB, PI3K*, and *p53* signaling pathways;[28–30] and reduction in phosphorylated human epidermal growth factor receptor 2 *(HER2*) protein in breast cancer cell lines.[31] Furthermore, the presence of CAPE augmented activity of docetaxel and paclitaxel in prostate cancer cells that was mediated by interfering with *AKT, ERK*, and *ER-α* activity[32] (Table 1).

Natural products interfering with cancer angiogenesis

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels. It is a normal process in growth and development as well as in wound healing. However, this is also a fundamental step in the transition of tumors from a dormant state to a malignant state. Tumors induce angiogenesis by secreting various growth factors, such as vascular endothelial growth factor (*VEGF*) and basic fibroblast growth factor (*bFGF*), which induce capillary growth into the tumor and allow it to grow by supplying nutrients and oxygen and removing waste products. In addition, the new vessels allow tumor cells to escape into the circulation and lodge in other organs (i.e. tumor metastases). A vast array of products of natural origin have been shown to have anti-angiogenic potential in preclinical models,[33] including *Artemisia annua* (Chinese wormwood), *Viscum album* (European mistletoe), *Curcuma longa* (curcumin), *Scutellariabaicalensis* (Chinese skullcap), resveratrol and proanthocyanidin (grape seed extract), *Magnolia officinalis* (Chinese magnolia tree), *Camellia sinensis* (green tea), *Ginkgo biloba*, quercetin, *Poriacocos, Zingiberofficinalis* (ginger), *Panax ginseng, Rabdosiarubescenshora*(Rabdo sia), and Chinese destagnation herbs[34,35] (Table 1).

Quercetin, at non-toxic concentrations, was reported to significantly inhibit micro-vessel sprouting, endothelial cell proliferation, migration, invasion, and tube formation, which are key events in the process of angiogenesis. Furthermore, quercetin exhibited anti-angiogenic activity in ex vivo angiogenesis assays, using the chicken egg chorioallantoic membrane (CAM) assay. Moreover, quercetin also exhibited in

vivo anti-tumor activity manifested by significant reduction of tumor size in a xenograft mouse model by targeting angiogenesis[36] (Table 1).

Green tea polyphenols down-regulated the activity of a number of key enzymes, including *MAPK* and vascular endothelial growth factor receptor (*VEGFR*) signaling, leading to blocking the proliferation of endothelial cells.[17] Also, ellagitannin-rich pomegranate extract was demonstrated to inhibit the proliferation of endothelial cells and to block tumor-associated angiogenesis in animal models.[37]

Indirubin, the active component of a traditional Chinese herbal medicine, Banlangen, exhibited anti-angiogenic activity when tested in the CAM assay and mouse corneal model. Moreover, indirubin inhibited endothelial cell migration, tube formation, and in vitro cell survival[38] (Table 1).

Curcumin was reported to down-regulate the expression of the *VEGF* and *MMP9* genes that are associated with angiogenesis.[39] Additionally, curcumin interfered with the activity of both *MMP2* and *MMP9* and, consequently, reduced degradation of the extracellular matrix (ECM),[40] leading to a reduction in the levels of released angiogenic factors stored in the ECM. Furthermore, curcumin also inhibits growth factor receptors, such as *EGFR* and *VEGFR*, and the other intracellular signaling tyrosine kinases implicated in angiogenesis. Recent reports implicated curcumin in decreasing the gelatinolytic activities of *MMP9*. In addition, treatment with curcumin inhibited glioma-induced angiogenesis.[41]The membrane-bound enzyme *CD13* (aminopeptidase N) is found in blood vessels undergoing active angiogenesis. Curcumin binds to *CD13* and blocks its activity, thereby inhibiting angiogenesis and invasion of tumor cells[42,43] (Table 1).

13-cis-retinoic acid significantly inhibited in vitro angiogenesis, as well as micro-vessel sprouting, vascular endothelial (VE) cell proliferation, migration, and tube formation.[44]

Resveratrol inhibits *VEGF*-induced angiogenesis by disruption of reactive oxygen species–dependent *Src* kinase activation and subsequent VE-cadherin tyrosine phosphorylation.[45,46] Edible berries contain high concentrations of proanthocyanidin which inhibits tumor necrosis factor (*TNF*)α-induced *VEGF* expression. Feeding proanthocyanidins to mice with tumor xenografts resulted in reduced intratumoral microvasculature[47–49] (Table 1).

In addition to its effect on cell proliferation, *EGFR* is also implicated in cancer angiogenesis.[50]*EGF* stimulates urokinase-type plasminogen activator (*uPA*) expression, which is involved in angiogenesis promotion. Genistein, curcumin, resveratrol, and quercetin were reported to inhibit the effects of *EGF*.[45,51–54] In in vitro systems, genistein and curcumin inhibit *EGF*-stimulated *uPA* production. Another family member of *EGFR*, the *HER2/neu* gene, is amplified in more than 30% of patients with breast cancer and is correlated with higher levels of angiogenesis.[55] The activity of herceptin, a drug that inhibits *HER2/neu* expressing breast cancer cells, can be further enhanced by oleic acid.[56] Interestingly, emodin, a natural constituent of *Polygonummultiflorum* and aloe, inhibits *HER2/neu* expression and exhibits selective cellular toxicity to cancer cells[57] (Table 1).

Natural products interfering with cancer invasion and metastasis

Metastasis, the spread of cancer cells from the primary tumor to distant organs, is a multi-step process in which cancer cells must invade through the extracellular matrix, intravasate into the bloodstream, survive transport through the circulatory system and, finally, extravasate to distant organs.[58] Aberrant activation of a developmental program, termed the epithelial-to-mesenchymal transition (EMT), has recently been recognized as an important driver of the metastatic process. EMT is a conserved developmental process in which epithelial cells lose E-cadherin-mediated cell–cell contacts and apical–basal polarity and become motile and invasive. This program is accompanied by expression changes in a variety of genes.

SFN was reported to synergize with the multi-kinase inhibitor, sorafenib, in reducing tumor size of pancreatic cancer in an animal model, due to the blockage of proliferation and angiogenesis, and down-regulation of EMT modulators[59,60] (Table 1).

In addition, the bioactive component, grape seed proanthocyanidins (GSPs), interfered with the invasion potential of head and neck squamous cell carcinoma (HNSCC). The inhibition of cell invasion by GSPs was associated with the reversal of the EMT process.[61]

Salvianolic acid B (Sal B) is a water-soluble component from Danshen (Salvia miltiorrhiza Bunge), a traditional Chinese herb reported to prevent tubular EMT in the fibrotic kidney[62] (Table 1).

Curcumin is reported to possess anti-invasive activity which is partly mediated by down-regulation of *MMP2* and up-regulation of tissue inhibitor of metalloproteinase-1 *(TIMP1)*,[63] enzymes that are involved in the regulation of tumor cell invasion.

Experimental studies have shown that lycopene exhibited anti-cancer activity,[22] that mediated, in part, by inhibiting *NF-κB*-mediated expression of *MMP9*, leading to the inhibition of invasion of cancer cells.[64] In addition, EGCG reduced cancer cell invasiveness through the inhibition of *Wnt* signaling[65] (Table 1).

Moreover, CAPE found in the nutritional dietary supplement Propolis is reported to interfere with cancer metastasis and invasion by modulating activities of *MMP2*[66] (Table 1).

Natural products targeting cancer stem cells

The present understanding of cancer biology argues for the existence of a small portion of cells that show stem cell–like characters. These cells constitute a limited subpopulation of

primitive undifferentiated cancer cells that have the ability to self-renew, are tumorigenic and invasive, undergo asymmetrical divisions, and generate all aspects of cancers. Like non-malignant stem cells, putative cancer stem cells (CSC) show remarkable resistance to radiation and chemotherapy.[67] A number of reports implicate stem-like cells as a potential cause of chemo resistance.[68] The EMT process that regulates cancer metastasis is also implicated in the generation of CSC and has been associated with resistance to chemotherapy.[69] In order to cure cancer, it is necessary to eliminate CSC in addition to differentiated cancer cells, to decrease metastasis, reduce recurrence, and improve patient survival.

Diverse dietary constituents, such as vitamins A and D, genistein, EGCG, SFN, piperine, theanine, choline, and curcumin, have been shown to modify self-renewal properties of CSC and influence proliferation, as well as other functions in CSC,[70] suggesting the potential of using these dietary components in preventing resistance and cancer recurrence. *Wnt* signaling and modulation of β-*catenin* expression is essential for CSC. A number of phenolic compounds, such as CAPE, curcumin, resveratrol, quercetin, isoflavone, fisetin, EGCG, and isoflavone, were able to inhibit *Wnt* and *β-catenin* signaling[65] (Table 1).

Resveratrol has been shown to significantly decrease the level of *β-catenin* in the nucleus of cancer cells[71] (Table 1). Recent studies in breast cancer cells demonstrated that curcumin inhibited aldehyde dehydrogenases (*ALDH*)-expressing breast CSC self-renewal but did not cause toxicity to differentiated cells by suppressing *Wnt* signaling. Likewise, curcumin has been shown to inhibit *CD133* positive medulloblastoma, glioblastoma, pancreatic, and colon CSC proliferation.[72,73] Moreover, a recent report demonstrated that SFN suppresses the activity of *NF-κB*/*GATA6* and thus affects proliferation and migration of vascular smooth muscle cell (VSMC) as well as CSC.[74]Others have reported activity of SFN against stem cells that is mediated by blocking the *Wnt/β-catenin* self-renewal pathway[72] (Table 1).

Natural products modulate epigenetic modifications

Epigenetics is defined as a heritable modification to the DNA that regulates chromosome architecture and modulates gene expression without changes to the underlying nucleotide sequence, ultimately determining phenotype from genotype. DNA methylation and post-translational histone modifications are classical levels of epigenetic regulation. Epigenetic changes in DNA methylation patterns at CpG sites or deregulated chromatin states of tumor promoting genes and non-coding RNAs emerge as major governing factors in tumor progression and cancer drug sensitivity. DNA methylation in mammals is an enzymatic process primarily mediated by active DNA cytosine methyltransferase (*DNMT*).[75] During cell division, methylation patterns in the parental strand of DNA are maintained in the daughter strand by the action of *DNMT1*, which catalyses the transfer of a methyl group from S-adenosylmethionine (SAM), the methyl donor, to the cytosine residues, restoring the symmetrically methylated CpG dinucleotide pair. Aberrant patterns and dysregulation of DNA methylation cause stable, heritable transcriptional silencing of the associated gene during tumorigenesis.[76,77] Epigenetic variability at specific transcription regulation sites appear to be susceptible to modulation by nutritional changes.[78] Therefore, dietary components which can affect the process of DNA methylation may influence tumorigenesis by regulation of the expression of certain key genes. Currently, the best evidence to show that nutritional components can modulate epigenetic status of mammal cells comes from studies with mice carrying the agouti viable yellow gene.[79,80] Various environmental factors, such as nutrition, remodel our epigenomes lifelong in a beneficial or detrimental way. Since epigenetic marks are reversible in contrast to genetic defects, chemo-preventive nutritional polyphenols are currently evaluated for their ability to reverse adverse epigenetic marks in cancer cells to attenuate tumorigenesis progression, prevent metastasis, or sensitize for drug sensitivity.[81,82]

Nutrients involved in one-carbon metabolism, namely folate, vitamin B12, vitamin B6, riboflavin, methionine, choline, and betaine, are involved in DNA methylation by regulating the levels of the universal methyl donor SAM and S-adenosylhomocysteine (SAH). Other nutrients and bioactive food components, such as retinoic acid, resveratrol, curcumin, SFN, and tea polyphenols, can modulate epigenetic patterns by altering the levels of SAM and SAH or affecting the catalytic activity of enzymes involved in DNA methylation and histone modifications.[83,84] Cancer and other age-related diseases are associated with profound changes in epigenetic patterns, although it is not yet known whether these changes are programmatic or stochastic in nature[85] (Table 2).

The green tea polyphenol, EGCG, is believed to be a key active ingredient for cancer inhibition through epigenetic control. It has been found that EGCG can reverse CpG island hypermethylation of various methylation-silenced genes and reactivate these gene expressions.[86] It was also reported that consumption of polyphenols could lead to a decrease in the availability of SAM and an increase in SAH and homocysteine levels. Currently, green tea extracts have been applied in clinical trials, including oral cancer prevention, indicating that tea polyphenols could be used in multiple human cancer preventive and therapeutic purposes due to their bioactivities, such as regulating epigenetic factors[87] (Table 2).

A methyl donor diet that is used for the synthesis of SAM, including folate and vitamin B12, is expected to affect DNA methylation. Studies on feeding in rats with diets deficient in folate showed a significant genome-wide DNA hypomethylation, as well as gene-specific DNA hypermethylation[88,89] (Table 2).

Table 2. Natural products as epigenetics modifiers.

Natural product	Epigenetic activity
EGCG	*DNMT* inhibitor[105,106]
	HAT[107]
	HDAC3[107]
Parthenolide	*DNMT* inhibitor[106]
Folate	Methyl group donor[89,90,108]
Genistein	*DNMT* inhibitor[91,92,94–96,109]
	HAT inhibitor[94–96,109]
	HDAC6[110]
Caffeic acid phenethyl ester (CAPE)	*HDAC* inhibitor[31]
Curcumin	*HDAC* inhibitor[111]
	HAT inhibitor[111]
	DNMT inhibitor[106,112,113]
Selenium	Decrease *DNMT1* expression[114]
	Affect homocysteine availability[114]
Methionine	Methyl group donor[108,115]
Choline	Methyl group donor[108,115]
Betaine	Methyl group donor[108,115]
Folate	Methyl group donor[115,108]
Vitamin B12	Methyl group donor[115,108]
Resveratrol	Activating *SIRT-1*[116]
Sulforaphane	*HDAC* inhibitor[117]

EGCG: epigallocatechin gallate; DNMT: DNA cytosine methyltransferase; HAT: histone acetyltransferases; HDAC: histone deacetylases.

The soybean product, genistein, has been shown to be associated with a lower incidence and mortality rate of breast cancer in Asian women who consume soybean products as their daily diet.[90,91] Genistein is believed to be a chemo-preventive agent against various types of cancer cells.[92] It is becoming clear that genistein exerts multiple effects on cancer cell growth, including regulation of gene expression, by modulating epigenetic events such as DNA methylation and/or chromatin modification[93–95] (Table 2). However, the anti-cancer properties of genistein in breast cancer have raised concerns because of its estrogen-like effect that may be contraindicated for women at high risk of breast cancer. Studies, both in epidemiology and animals, have confirmed that exposure to a soy diet in women in early life greatly impacts breast cancer risk, suggesting exposure time is essential for genistein to exert its effects on breast cancer prevention.

Selenium is an essential trace element with both anti-oxidant and pro-apoptotic properties.[96,97] Davis et al.[98] have demonstrated that in the colon and liver, selenium deficiency causes global hypomethylation and in addition promotes methylation of *p53* and *p16* genes, suggesting that impacting DNA methylation may be a crucial mechanism of selenium for cancer prevention. Selenium has been shown to inhibit *DNMT* through direct interaction and indirect action by influencing plasma homocysteine concentrations and the SAM:SAH ratio.[99,100]

Some of the dietary agents, such as butyrate, flavonoids, and curcumin, are capable of altering the epigenetic landscape which can modulate gene/microRNA (miRNA) transcription and subsequently trigger changes in cell proliferation, differentiation, and cell survival[101,102] (Table 2). Interestingly, several investigators have recently begun to explore how bioactive dietary agents alter the inter-regulatory patterns between promoter regions of miRNAs and several genes.[103]

Natural products' activity mediated by modulation of miRNA expression

miRNAs are small non-coding RNAs (~22 nucleotides long) that play a critical role in basic biological processes, including carcinogenesis. miRNAs are found in both plants and animals and regulate protein expression by acting through complementarity to 3′ un-translated regions (UTRs) of their "target" mRNAs, which results in the repression of target gene expression post-transcriptionally.[104] Currently, more than 800 human and mouse miRNAs have been identified that are involved in almost all human malignancies.[105] Furthermore, miRNAs have been correlated to tumor location, mutation status of several tumor suppressor genes/oncogenes, and cancer disease stages. Dietary intake of natural products contributes to disease prevention and therapy, partly due to their capacity to alter the expression of miRNAs and consequently regulate cellular signaling and biological behavior. Curcumin, isoflavone, 3,3′-diindolylmethane (DIM), I3C, and EGCG are typical examples of natural agents that have been demonstrated to regulate miRNA expression.[106]

A growing body of evidence demonstrates that a high intake of n-3 polyunsaturated fatty acids (PUFAs) is protective against tumorigenesis.[107] In contrast, diets rich in n-6 PUFAs (linoleic acid (LA) and arachidonic acid (AA)) enhance both the initiation and promotion of cancer.[108] Recently, miRNA expression of let-7d, miR-15b, miR-107, miR-191, and miR-324-5p were modulated by a n-3 PUFA-enriched diet,[109] arguing that miRNAs may be involved in mediating some of the anti-oncogenic and chemo-protective properties of PUFAs (Table 3).

Butyrate, a short-chain fatty acid produced via fermentation of dietary fiber, exhibited cancer protective effects which are believed to be mediated in part by modulating miRNA expression,[110] such as miR-17~92, miR~18b-106a, and miR-106b~25 clusters. The same applies to all-trans-retinoic acid, the most biologically active metabolites of vitamin A; up-regulated miR-186, miR-215, and miR-223;[111] and down-regulated miR-17, miR-25, miR-93, miR-193, and miR-181b[112] (Table 3).

Polyphenols are ubiquitous secondary metabolites found in dietary nutrition that exhibit chemo-prevention activity against a number of chronic diseases.[113] Some studies have demonstrated that curcumin has protective properties against several

Table 3. Natural products modulate miRNA expression.

Natural product	Up-regulated miRNA	Down-regulated miRNA	Target genes and pathways
EGCG	miR-16, let-7c, miR-18, miR-25, miR-92,[137] miR-210[138]	miR-129, miR-196, miR-200, miR-342, and miR-526[137]	*HIF-1*α
Genistein	miR-200[130]		*ZEB1*, Slug, Vimentin, EMT regulators
Resveratrol	miR-663, miR-21, miR-25, miR-92a, and miR-520h[134]		EMT, *TGF-*β,*FOXC2*[134]
Curcumin	miR-15a, miR-15b,[132] miRNA-22,[129] miR-200[130]	miR-21,[131] miR-199a[129]	*Bcl2, Cdc25A*, EMT
Butyrate	miR-17~92, miR~18b-106a, and miR-106b~25[124]		
All-trans-retinoic acid	miR-186, miR-215, miR-223[125]	miR-17, miR-25, miR-93, miR-193, and miR-181b[126]	
n-3 PUFA	let-7d, miR-15b, miR-107, miR-191, and miR-324-5[123]		

miRNA: microRNA; PUFA: polyunsaturated fatty acids; EMT: epithelial-to-mesenchymal transition; *HIF*: hypoxia-inducible factor; *ZEB1*: zinc finger E-box-binding homeobox 1; *FOXC2*: forkhead box protein C2; *TGF*: transforming growth factor.

types of cancers by the modification of gene expression,[114] as well as up-regulation of a subset of miRNAs such as miRNA-22 and down-regulation of another subset of miRNAs such as miR-199a.[115] Moreover, DIM and curcumin have been shown to increase the level of the miR-200 family in pancreatic cancer cells, which is involved in the regulation of EMT and invasion behavior, and which was also mechanistically linked to stem cell signatures.[116] Curcumin and its synthetic analog, diflourinated curcumin (CDF), down-regulated miR-21 expression[117] and reduced the expression of *Bcl2* by up-regulating miR-15a and miR-15b.[118] DIM was reported to increase the expression of miR-21 and consequently reduced the expression of its target, *Cdc25A*.[119] In addition, resveratrol was also reported to affect the EMT process and transforming growth factor beta (*TGF-β)* and forkhead box protein C2 (*FOXC2*) expression by regulating miR-663, miR-21, miR-25, miR-92a, and miR-520h.[120] Furthermore, the anti-cancer activity of ellagitannins was shown to be mediated in part by regulating the expression of a number of miRNAs[121] (Table 3).

The EGCG compound exerts its anti-cancer activity by inducing apoptosis, suppressing *NF-κB*, up- or down-regulating tumor suppressor genes/oncogenes, and modulating epigenetic changes of the chromatin.[122] Interestingly, some EGCG activities are mediated by affecting the expression of miRNAs such as miR-16, let-7c, miR-18, miR-25, and miR-92 which were up-regulated and miR-129, miR-196, miR-200, miR-342, and miR-526 which were down-regulated.[123] Moreover, EGCG affects the expression of the hypoxia-inducible factor 1 alpha (*HIF-1α*) pathway, an effect which is mediated by regulation of miR-210[124] (Table 3).

Soy isoflavones, such as daidzein, genistein, and glycitein, have been reported to have anti-carcinogenic effects mediated by inhibition of cell growth, invasion, and metastasis.[125] Genistein regulates the expression of miRNAs implicated in controlling cancer cell proliferation,[126] and also up-regulating miR-200, which was associated with the down-regulation of validated targets zinc finger E-box-binding homeobox 1 (*ZEB1*), slug, and vimentin, known to play a role in the EMT process[116] (Table 3).

Concluding remarks

Many natural products or dietary substances exhibit anti-cancer activity in in vitro systems against a variety of cancer cell lines, including leukemia, lymphoma, breast, prostate, liver, lung, and myeloma cells. The anti-cancer activity of natural products includes the inhibition of proliferation, induction of apoptosis, induction of cell cycle arrest, inhibition of invasive behavior, and suppression of tumor angiogenesis in many experimental systems. We suggest a need for more in-depth studies that focus on the most promising herbal-derived substances, such as curcumin, genistein, and others. Preliminary clinical data have shown promising efficacies of natural products in cancer treatment as well as in other indications. Yet, few of these natural products have been subjected to randomized clinical trials (RCTs) under the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines to determine their efficacy and/or safety. The data summarized here show that many non-clinical in vitro and in vivo studies on herbal medicines have commonly supported the traditional therapeutic claims. However, systematic reviews of the study protocols or data interpretation and validation are lacking. We believe that there is a need to explore the full potential of the dietary supplements of natural products, and to assess their safety and efficacy in well-designed, double-blinded, randomized, placebo-controlled clinical trials as stand-alone treatments or in combination with other treatments. To achieve this goal, standardization of pure natural products or active extracts is an important element. Because the composition and amount of biologically active substances depend on sites of production, cultivation conditions, and extraction procedures, standardization will help the acceptance of natural products as suitable for cancer treatment. However, there is a need for the identification and prediction of potential herb–drug interactions.

Declaration of conflicting interests

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