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Back to basics: how natural products can provide the basis for new therapeutics

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Phytochemicals have potent antitumor properties and have provided multiple active compounds in the past. Although there is an increasing focus on 'designer' targeted therapeutic anticancer agents, the broad spectrum of activity of natural products across multiple signaling pathways remains inadequately explored. The chemical diversity, structural complexity, affordability, lack of substantial toxic effects and inherent biologic activity of natural products makes them ideal candidates for new therapeutics. Natural products not only disrupt aberrant signaling pathways leading to cancer (i.e., proliferation, deregulation of apoptosis, angiogenesis, invasion and metastasis) but also synergize with chemotherapy and radiotherapy. This review focuses on the mechanism of action of key natural products and promising preclinical data on their efficacy as anticancer agents, as single agents and in combination with standard therapies.

Keywords: Akt, angiogenesis, AP-1, apoptosis, chemosensitization, growth factor receptors, invasion, MAPK, metastasis, NF-κB, phytochemicals, proliferation, radiosensitization, STATs

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1. Introduction

Cancer is a major public health problem in the US and other developed countries. At present, one in four deaths in the US is attributable to cancer [1]. After 25 years of rapid advances, cancer research has generated a rich and complex body of knowledge, revealing cancer to be a multifactorial disease involving stepwise accumulation of dynamic changes in the genome. Although carcinogenesis involves a complex interplay between genes and environment and multiple cumulative mutational events are required for the progression from normal to fully malignant phenotype, the quintessential traits of the cancer cell are six fundamental alterations in cell physiology that collectively dictate malignant growth [2]. Essentially, self-sufficiency in growth signals, insensitivity to growth inhibitory (anti-growth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis are the key features of tumorigenesis. Perturbation of the complex circuits hardwired within cells often involves growth factor signaling pathways (e.g., platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and the SOS-Ras-Raf-MAPK cascade), transcription factors (e.g., NF-κB and AP-1), apoptotic signaling proteins (e.g.,caspases, polyadenosine-5′-diphosphate-ribose polymerase, Bcl-2 and Bcl-X_L), protein kinases (e.g., IKK, JNK, PI3K, Akt and MAPK), cell-cycle proteins (e.g., cyclins, cyclin-dependent kinases [CDKs] and retinoblastoma protein) and cell adhesion molecules (e.g., integrins, selectins, cadherins, intercellular adhesion molecule and vascular adhesion molecule). However, despite a better understanding of the mechanisms of carcinogenesis and the development of tailored targeted therapies,

the incidence of cancer remains high and the cure rate has not greatly improved.

In the continuing search for agents that may treat or ameliorate the affliction of cancer, natural products have provided an endless supply of active compounds that are increasingly being exploited. Indeed, natural products have been the mainstay of cancer chemotherapy over the last three decades [3,4] and plant extracts have been used to treat cancers for even longer [5]. For instance, the chemotherapeutic drugs etoposide and teniposide are derivatives of podophyllotoxin, the chief constituent of the extracts from the roots of mayapple, *Podophyllum peltatum*. These root extracts have been used by generations of American Indians for the treatment of skin cancers. Similarly, the vinca alkaloids, vinblastine and vincristine, are derived from the Madagascar periwinkle plant (*Catharanthus roseus*, formerly known as *Vinca rosea*), which was used as a hypoglycemic agent in Asia. Ayurveda, one of the major traditional forms of medical practice in India dating back thousands of years, has used plant-based medicines for cancer prevention [6]. The efficacy of these agents in the treatment of a wide spectrum of cancers [7] persuaded the National Cancer Institute to begin a large-scale screening program for antitumor agents from natural sources in the 1960s [8]. The most prominent antitumor agent that emerged from this screening was paclitaxel obtained from the bark of the Pacific yew tree, *Taxus brevifolia*. Although the plant kingdom has provided an unparalleled pool of bioactive compounds useful in treating cancer, there are other valuable natural sources for anticancer drugs. Microorganisms have provided some key antitumor antibiotics, most notably the bleomycins, dactinomycin, mitomycin C and the anthracyclinones (doxorubicin and daunorubicin). The marine world also possesses a wealth of biologically potent chemicals with interesting pharmacodynamic properties [9-11]. For instance, goniodomin-A, an antifungal macrolide from the dinoflagellate *Goniodoma pseudogoniaulax*, has been shown to have anti-angiogenic activity [12] and trabectedin (yondelis), aplidin and kahalalide F are some of the new anticancer drugs that are undergoing clinical trials [13]. However, the purpose of this review is not to encompass the gigantic pool of anticancer natural products from every possible source but to focus on plant-derived natural dietary products that have potent antitumor properties. This article reviews the present data regarding several natural products from dietary sources, the cellular signaling pathways that they target and strategies to integrate these compounds with present cancer therapeutic modalities.

2. Background of selected plant-derived natural products

Plants are excellent sources of macronutrients (carbohydrates, proteins, fats and fiber) and micronutrients (antioxidants, vitamins and trace minerals). In addition, they are sources of an amazing diversity of secondary metabolites (phytochemicals), which are not essential for normal bodily function but are still biologically active and of medicinal value. Phytochemicals can be classified into various families, such as alkaloids, flavonoids, isoflavones, isothiocyanates organosulfur compounds, capsaicinoids and phytosterols, which are chiefly found in dark, leafy vegetables, yellow/orange fruits and some pungent vegetables such as onion and garlic. Many of these compounds have proven chemopreventive properties [14,15] and their active ingredients are being studied extensively for their antitumor activity. The active components of dietary phytochemicals with chemopreventive properties include curcumin, genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, [6]-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, isothiocyanates, indole-3-carbinol, isoflavones, phytosterols, folic acid, β-carotene and flavonoids [16]. **Figure 1** illustrates the chemical structures of some of the phytochemicals discussed in this review. In this section, the authors present an overview of some promising active phytochemicals.

2.1 Curcumin

Curcumin (diferuloylmethane), a polyphenol derived from the rhizomes of *Curcuma longa*, is the major constituent of the yellow spice turmeric, a spice or dietary flavoring agent commonly used in Asian cooking. Although the broad medicinal properties of curcumin have been known for centuries, its promising antitumor and chemopreventive activities have only recently become the focus of renewed interest [17,18]. Curcumin has been shown to suppress proliferation and induce apoptosis in a wide variety of tumor cells in culture and in animal models. The characterized mechanisms of action of curcumin include downregulation of various transcription factors such as NF-κB and activator protein-1; downregulation of the expression of COX-2, matrix metalloprotease-9 (MMP-9), urokinase plasminogen activator, TNF, chemokines, cell surface adhesion molecules and cyclin D1; inhibition of the activity of growth factor receptors such as EGFR and human epidermal receptor 2 (HER2); inhibition of the activity of intermediate signaling cascade kinases such as JNK, PI3K, Akt, MAPK and IKK; and immunomodulation via activation of host macrophages, lymphocytes and natural killer cells [19]. Apart from its anticancer activity, curcumin has been also been shown to possess potent antioxidant and anti-inflammatory properties.

2.2 Resveratrol

Resveratrol, *trans*-3,5,4′-trihydroxystibene, was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum O. Loes*) but has since been found in various other plants, including grapes, berries and peanuts. Apart from its cardioprotective effects, resveratrol exhibits anticancer properties, as suggested by its ability to suppress

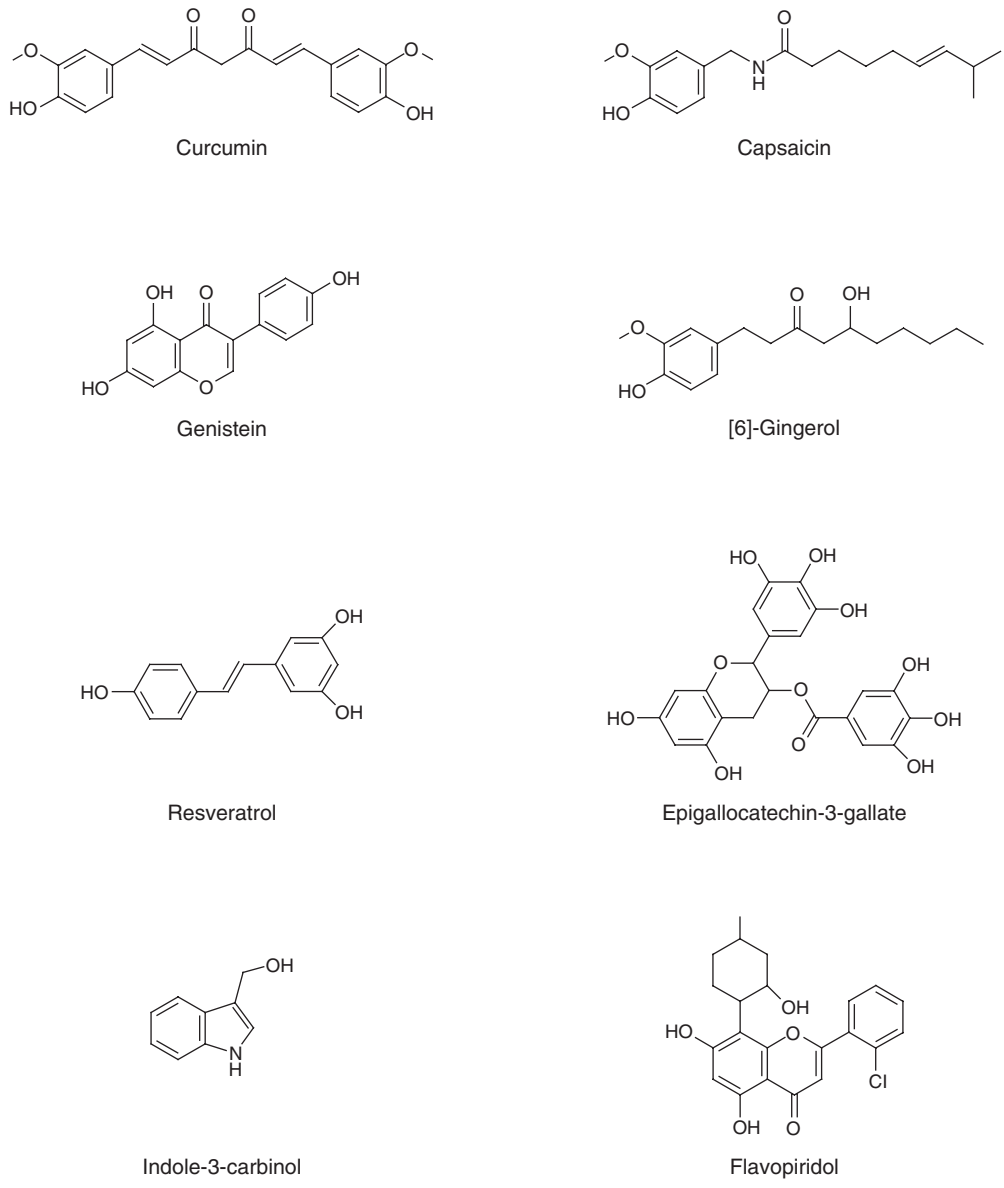

Figure 1. Chemical structures of selected phytochemicals with anticancer properties.

proliferation of a wide variety of tumors, including lymphoid and myeloid cancers, multiple myeloma and cancers of the breast, prostate, stomach, colon and pancreas [20]. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; induction of apoptosis via the Fas/CD95, p53, ceramide activation, tubulin polymerization, mitochondrial and adenylyl cyclase pathways; upregulation of $p21^{Cip1/WAF1}$, p53 and Bax; downregulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-X_L and cellular inhibitor of apoptosis proteins; activation of caspases; suppression of NO synthase; suppression of transcription factors such as NF-κB, AP-1 and early growth response-1 (Egr-1); inhibition of COX-2 and lipo-oxygenase; suppression of adhesion molecules; and inhibition of angiogenesis, invasion and metastasis [21].

2.3 [6]-Gingerol

Gingerol, or [6]-gingerol, the phenolic substance responsible for the spicy taste of fresh ginger (*Zingiber officinale* Roscoe), has diverse pharmacologic (antioxidant, anti-apoptotic and anti-inflammatory) effects. Ginger has a long history of medicinal use dating back 2500 years and has been traditionally used for varied human ailments in different parts of the globe, to aid digestion and treat dyspepsia, diarrhea and nausea. More recently, it has been shown to have anticancer and chemopreventive properties [22]. Inhibition of COX-2 expression by blocking the p38 MAPK-NF-κB signaling pathway has been proposed as the molecular basis for its antitumor effects [23].

2.4 Capsaicin

The chemical compound capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the active component of chilli peppers (*Capsicum annuum* L.) and is responsible for added spice or 'heat' (piquancy). It has been suspected to act as a carcinogen or a co-carcinogen in experimental animals because of its irritant properties, but other studies have indicated that the compound has chemopreventive and chemoprotective effects. Apart from inhibition of transcription factors such as NF-κB [24] and STAT3 [25], capsaicin is also reported to inhibit angiogenesis *in vitro* and *in vivo* [26].

2.5 Epigallocatechin gallate

Epigallocatechin gallate (EGCG), or (-)-EGCG, is the major catechin antioxidant and chemopreventive polyphenol that is found in green tea, one of the most consumed beverages in the world. EGCG, derived from *Camellia sinensis*, has been shown to inhibit a variety of processes involved in cancer cell growth, survival and metastasis [27]. These include blocking the nuclear translocation of the transcription factor NF-κB, cell-cycle arrest in G1 phase and activation of caspases [27].

2.6 Genistein

Genistein (4,5,7-trihydroxyisoflavone) is a naturally occurring isoflavone and a major soy metabolite. Soy isoflavones have been identified as dietary components having an important role in reducing the incidence of breast and prostate cancers. Genistein was originally identified as possessing weak estrogenic activity and has a chemical structure that resembles estradiol. The biochemical mechanisms of genistein and its anticancer activities have been extensively reported in the literature. Genistein can induce cell-cycle arrest and apoptosis in cancer cell lines, as well as inhibit the action of transcription factors such as NF-κB [28] and known growth-stimulating pathways such as Akt and MAPK [29].

2.7 Flavopiridol

Flavopiridol is a semisynthetic flavonoid that is closely related to a compound originally isolated from the stem bark of *Dysoxylum binectariferum*, a plant indigenous to India. Flavopiridol has been shown to be a potent inhibitor of CDK-1, CDK-2, CDK-4 and CDK-7. Through inhibition of CDKs, flavopiridol induces arrest of cell growth at the G1 and G2 phases of the cell cycle [30]. Flavopiridol also induces apoptosis, suppresses inflammation and modulates the immune response. Flavopiridol suppresses TNF-induced activation of NF-κB in a dose- and time-dependent manner in several cell types [31].

2.8 Silymarin

Silymarin consists of a family of flavonoids (silybin, isosilybin, silychristin, silydianin and taxifoline) commonly found in the dried fruit of the milk thistle plant *Silybum marianum*. Milk thistle was used in classical Greece to treat liver and gallbladder diseases and to protect the liver against toxins. Recently, a role for silymarin as an anticancer agent has begun to emerge [32]. Silybin, the chemically active component of silymarin, has been shown to modulate various cell-signaling pathways including inhibition of NF-κB activity, inhibition of EGFR-MAPK/ERK1/2 signaling, modulation of the activity of retinoblastoma protein and elongation factor-2 proteins and inhibition of IGF-receptor signaling. Pro-apoptotic and anti-angiogenic activities of silybin have contributed to the promise of silymarin as an anticancer agent (reviewed in [33]).

3. Natural products and the cancer cell

Despite the marked molecular heterogeneity and complex pathophysiologic manifestations of cancers, discrete molecular pathways have been observed to be consistently and repetitively deregulated across a wide spectrum of cancers. This suggests a critical role for these pathways in the establishment and/or maintenance of the neoplastic phenotype and indicates that specifically targeting these pathways may confer significant antitumor effects in a wide range of neoplastic diseases. Concurrent with the development of novel, highly specific antitumor therapies targeting these complex networks of signaling circuits, natural dietary products are also increasingly being identified as potent inhibitors of several of these pathways [34,35]. **Figure 2** illustrates the multiple steps of the cancer progression continuum at which natural products may exert their anticancer properties. **Table 1** outlines the specific molecular pathways targeted by these agents.

3.1 Agents targeting signaling cascades regulating cell growth and proliferation

Within normal tissues, multiple antiproliferative signals operate to maintain cellular quiescence and tissue homeostasis. Many of the molecular alterations that are associated with carcinogenesis occur in cell-signaling pathways that regulate cell proliferation and differentiation. One of the central components of this intracellular signaling network is the family of proline-directed serine/threonine kinases: the MAPKs. Abnormal or improper activation or silencing of the MAPK pathway or its downstream transcription factors can result in uncontrolled cell growth, leading to malignant transformation. Cell-signaling pathways other than MAPKs, such as protein kinase C (PKC) and PI3K/Akt pathways, are also important targets of certain phytochemicals [16]. These upstream kinases activate a distinct set of transcription factors, including NF-κB and AP-1. Numerous intracellular signal transduction pathways converge at the activation of transcription factors such as NF-κB, AP-1 and the STATs, which act independently or coordinately as final effectors to regulate target-gene expression.

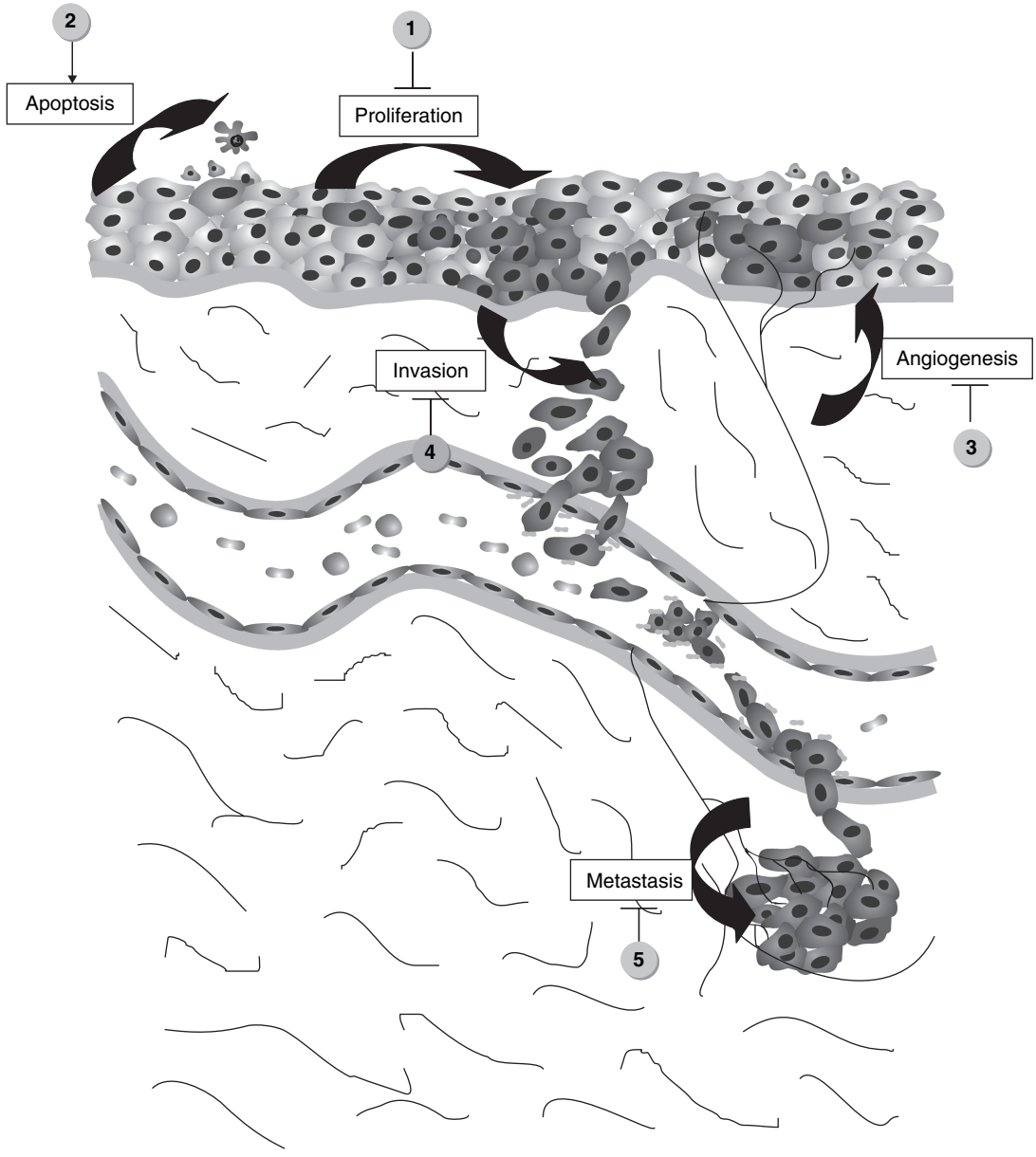

Figure 2. Depicts the various mechanisms by which natural products modulate cancer progression. The mechanisms involved in the evolution of the malignant phenotype are denoted by curved arrows and the various targets of natural products in the entire process are shown in gray circled numbers. Normal cells are depicted in lighter gray scale and transformed cells are depicted in darker gray scale. Natural products can (**1**) block the proliferation signaling pathways that provide tumor cells a competitive survival advantage over normal cells, (**2**) induce apoptosis in tumor cells that are known to evade programmed cell death, (**3**) deregulate angiogenic pathways critical for tumor cell survival, (**4**) inhibit pathways leading to tumor cell motility and invasion of the basement membrane and (**5**) inhibit the development of metastases.

3.1.1 Mitogen-activated protein kinases

The MAPKs are a family of kinases that transduce signals from the cell membrane to the nucleus in response to a wide range of stimuli, including stress [36]. Conventional MAPKs consist of three family members: the ERK, the JNK and the p38-MAPK, with each family member having its own subfamilies. The MAPK pathway consists of a cascade in which a MAP3K activates a MAP2K that activates a MAPK (ERK, JNK and p38), resulting in the activation of NF-κB, cell growth and cell survival. MAPK signaling pathways have long been viewed as attractive targets for anticancer therapies, based on their central role in regulating the growth and survival of cells from a broad spectrum of human tumors. Dietary phytochemicals such as curcumin, resveratrol, indole-3-carbinol and green tea polyphenols have been shown to modulate

Table 1. Molecular targets phytochemicals in the cancer cell.

Phytochemical	Molecular mechanisms of anticancer action	Ref.
Curcumin	Inhibition of JNK activation	[37]
	Inhibition of EGFR tyrosine phosphorylation	[47,48,50]
	Inhibition of Akt activity	[61,62]
	Suppression of NF-κB and NF-κB-regulated gene products	[70,83,84]
	Suppression of AP-1	[89,90]
	Inhibition of STAT3 phosphorylation and nuclear translocation	[95]
	Induction of apoptosis through Fas receptor/caspase-8 pathway	[115,121]
	Activation of caspases	[70,116,121]
	Downregulation of p53	[131]
	Inhibition of hypoxia-stimulated angiogenesis and downregulation of VEGF expression	[143]
	Inhibition of expression of ICAM-1, VCAM-1 and E-selectin	[153]
	Inhibition of matrix metalloproteinases	[156]
Resveratrol	Suppression of EGFR-dependent Erk1/2 activation	[39]
	Downregulation of EGF	[45]
	Inhibition of Akt phosphorylation	[66,67]
	Suppression of NF-κB	[67,72]
	Suppression of AP-1	[72]
	Apoptosis induction by caspase activation	[124-126]
	Apoptosis induction through p53 activation	[133]
	Suppression of VEGF and FGF receptor-mediated angiogenesis	[140]
	Inhibition of invasion	[158]
	Decrease in the expression of MMP-2	[160]
[6]-Gingerol	Suppression of NF-κB	[23]
	Inhibition of PMA-induced COX-2 expression	[23]
Capsaicin	Suppression of NF-κB	[24,71]
	Inhibition of STAT3	[25]
	Inhibition of Akt activation	[26]
	Apoptosis induction by caspase activation	[127]
	Inhibition of VEGF-induced angiogenesis	[26]
Epigallocatechin gallate	Inhibition of JNK and p38 phosphorylation	[38]
	Inhibition of ERK1/2 phosphorylation	[54]
	Inhibition of EGFR and HER2 activation	[53]
	Inhibition of Akt activation	[54,64,65]
	Inhibition of AP-1 activation	[88]
	Downregulation of STAT3 phosphorylation	[94]
	Induction of apoptosis	[105,108-112]
	Activation of caspases	[110,111]
	Inhibition of angiogenesis	[145]

EGFR: Epidermal growth factor receptor; FGF: Fibroblast growth factor; MMP: Matrix metalloprotease; PMA: Phorbol 12-myristate 13-acetate.

Table 1. Molecular targets phytochemicals in the cancer cell (continued).

Phytochemical	Molecular mechanisms of anticancer action	Ref.
Genistein	Inhibition of NF-κB	[63,81,163]
	Inhibition of Akt	[163]
	Inhibition of endothelial cell proliferation	[144]
	Inhibition of metastasis *in vivo*	[157]
Flavopiridol	Suppression of NF-κB	[31]
	Cell-cycle arrest by inhibition of cyclin-dependent kinases	[30]
Silymarin	Apoptosis induction through caspase activation	[117,118]
	Inhibition of Akt activation	[118]

EGFR: Epidermal growth factor receptor; FGF: Fibroblast growth factor; MMP: Matrix metalloprotease; PMA: Phorbol 12-myristate 13-acetate.

MAP kinases. Chen and Tan [37] found that curcumin inhibits JNK activation induced by various agonists, including phorbol 12-myristate 13-acetate (PMA) plus ionomycin, anisomycin, ultraviolet-C, γ-radiation, TNF and sodium orthovanadate. EGCG was reported to inhibit oxidative stress-mediated phosphorylation of MAPK signaling pathways [38]. Resveratrol can modulate all three MAPKs, leading to modulation of gene expression (readers are referred to [21]). Resveratrol antagonized EGFR-dependent ERK1/2 activation in human androgen-independent prostate cancer cells with associated isozyme selective PKC-α inhibition [39]. However, resveratrol has also been shown to activate ERKs. In human osteosarcoma cells, the antiproliferative effects of resveratrol were preceded by enhanced phosphorylation of ERK1/2 at Thr202/Tyr204 [40]. Resveratrol-induced ERK and p38 kinase activation was also observed in mouse epidermal cell lines [41]. Resveratrol-mediated activation of MAPK in some cells and inhibition in others may be dependent on the cell type and dose of resveratrol. Although it is difficult to explain the anticancer effects of resveratrol on the basis of its MAPK-modulating activities, resveratrol-induced ERK activation leads to apoptosis via p53 phosphorylation [41], which could contribute to its anticancer effects.

3.1.2 Growth factors signaling pathways

Promiscuous proliferation is a hallmark of malignant cells. Consequently, metazoan somatic cells are obligatorily dependent for their survival on the continuous availability of external, mostly locally produced, growth factors, which are often in limited supply and spatially restricted [42] and which exert their proliferative action after binding to appropriate receptors to induce a cascade of responses (signal transduction). One mechanism to enable constant activation of these proliferative signals is for cancer cells to manufacture growth factors, thus creating an autocrine loop and obviating their dependence on stimulation from their microenvironment. Some of the growth factors implicated in carcinogenesis are EGF, PDGF, fibroblast growth factors (FGFs), TGF-α and -β, IGF, IL-1, -2, -6 and -8, TNF, IFN-γ and colony-stimulating factors. The potent cell proliferation signals generated by various growth factor receptors such as the EGF receptor, IGF-1 receptor and VEGF-receptor networks constitute the basis for receptor-driven tumor progression in several cancers [43].

Several phytochemicals, including resveratrol, curcumin, genistein and catechins, have been shown to be potent inhibitors of several growth factor signaling pathways. Resveratrol suppressed IL-8 gene transcription in phorbol ester-treated human monocytic cells [44]. It has also been shown to suppress proliferation of Ishikawa cells through downregulation of EGF [45]. EGFR (erbB1/HER1) is a member of the family of four erbB receptors. Activation of EGFR is initiated by binding of ligands, including EGF and TGF-α. This results in receptor dimerization, activation of the intracellular tyrosine kinase of both components of the dimer by transautophosphorylation, which, in turn, leads to signaling cascades via PI3K/Akt, MAPK and PKC pathways that regulate the expression of target genes. Aberrant activation of the EGFR pathway is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis and angiogenesis [46]. Curcumin has been shown to inhibit ligand-induced EGFR phosphorylation [47,48].

PPARs belong to the superfamily of nuclear receptors. PPAR-γ, the most widely studied subtype, controls the expression of genes involved in cellular differentiation and the cell cycle and has been implicated as a target for cancer prevention [49]. Curcumin activated PPAR-γ in Moser cells, a human colon cancer-derived cell line, leading to inhibition of cell growth by inhibiting tyrosine phosphorylation of EGFR and suppressing gene expression of EGFR and cyclin D1 [50]. Curcumin inhibited human colon cancer cell growth by suppressing gene expression of EGFR by reducing the *trans*-activation of the transcription factor, Egr-1 [51]. EGCG, the major component of green tea, is known to modulate many signaling events that are important in cancer therapy (reviewed in [27]). EGCG not only suppresses

the expression of IL-6 [52] *in vitro* but also inhibits the activation of EGFR, HER-2 and multiple downstream signaling pathways in colon cancer cell lines [53]. EGCG most likely inhibits the EGFR signaling pathway through the direct inhibition of ERK1/2 and Akt kinases [54]. Green tea also inhibits the expression of FGF in human breast cancer and endothelial cells [55] and HER-2/neu and downstream signaling pathways in human head and neck and breast carcinoma cells [56]. EGCG also blocks PDGF-induced proliferation and migration of rat pancreatic stellate cells [57].

3.1.3 *Akt*

The serine/threonine protein kinase Akt/protein kinase B plays a critical role in mammalian cell survival signaling and is constitutively activated in various cancers [58]. Activated Akt promotes cell survival by activating the NF-κB signaling pathway [59] and by inhibiting apoptosis through inactivation of proapoptotic factors such as caspase-9 [60]. Not surprisingly, many natural products with antitumor properties exert their effects via targeting of this kinase. Several reports suggest that curcumin has molecular targets within the Akt signaling pathway and the inhibition of Akt activity may facilitate inhibition of proliferation and induction of apoptosis [61,62]. Genistein inhibits NF-κB activation via the Akt signaling pathway in PC3 cells [63]. Several recent reports have shown that EGCG modulates the Akt pathway. In T24 human bladder cancer cells, EGCG promotes apoptosis via modulation of the PI3K/Akt pathway and Bcl-2 family proteins [64]. Sen *et al.* [65] showed that EGCG impedes the activation of both Akt and NF-κB by repetitive stress and as a result preserves the normal apoptotic response during subsequent acute stress. Recent reports indicate the resveratrol induces apoptosis by interfering with the Akt pathway. In prostate cancer cell line LNCaP, resveratrol treatment resulted in significant dose-dependent inhibition of the constitutive expression of PI3K and phosphorylated (active) Akt [66], which, in turn, resulted in the modulation of Bcl-2 family proteins, thereby promoting apoptosis. In another study, resveratrol has been shown to induce apoptosis in multiple myeloma cells through suppression of constitutively active NF-κB and Akt [67].

3.1.4 *NF-κB*

The transcription factor NF-κB is a family of closely related protein dimers that bind to a common sequence motif in DNA called the κB site (readers are referred to [68]). NF-κB is a key regulator of genes involved in cell activation and proliferation. Under resting conditions, the NF-κB dimers are sequestered in the cytoplasm by inhibitors of κB (IκBs). They can be activated by a plethora of factors ranging from free radicals and cytokines to γ-radiation and ultraviolet light. On activation, NF-κB released from the IκB complex translocates to the nucleus, where it induces the expression of > 200 genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance and inflammation. These target genes are critical to the establishment of the early and late stages of aggressive cancers and include genes for cell-cycle regulatory proteins such as cyclin D1, those for apoptosis-suppressor proteins such as Bcl-2 and Bcl-X_L and genes required for metastasis and angiogenesis such as MMPs and VEGF [69]. Aberrant activation of NF-κB has been associated with protection against apoptosis and stimulation of proliferation in malignant cells and overexpression of NF-κB is causally linked to the phenotypic changes that are characteristic of neoplastic transformation. Many dietary phytochemicals have been shown to suppress NF-κB. These include curcumin [70], capsaicin [71], resveratrol [72], guggulsterone [73], ursolic acid [74], betulinic acid [75], [6]-gingerol [23], flavopiridol [31], indole-3-carbinol [76], anethole [77], green tea catechins [78], S-allyl cysteine [79], lycopene [80], genistein [81] and diosgenin [82].

Curcumin mediates its therapeutic effects through suppression of NF-κB and NF-κB-regulated gene products such as cyclin D1, adhesion molecules, MMPs, inducible NO synthase, Bcl-2, Bcl-X_L and TNF (reviewed in [18]). Curcumin has been shown to suppress tumor promotion in a mouse model of skin carcinogenesis. Furthermore, pretreatment of human colonic epithelial cells with curcumin inhibited TNF-α-induced COX-2 gene transcription and NF-κB activation [83]. In this study, curcumin inhibited IκB degradation by downregulation of NF-κB-inducing kinase (NIK) and IKKα/β. In another study by Siwak *et al.* [84], curcumin was shown to induce antiproliferative and pro-apoptotic effects that are associated with suppression of IKK and NF-κB in melanoma cells. [6]-Gingerol was reported to inhibit PMA-induced COX-2 expression. One of the essential transcription factors responsible for COX-2 induction is NF-κB. [6]-Gingerol suppressed NF-κB DNA binding activity in mouse skin [23]. Topical application of capsaicin inhibited PMA-induced mouse-skin tumor formation [85] and activation of NF-κB [71]. Guggulsterone (4,17[20]-pregnadiene-3,16-dione), the plant sterol derived from the gum resin (*guggulu*) of the tree *Commiphora mukul*, suppresses NF-κB activation by directly interacting with and suppressing the activation of IKK [73]. Resveratrol suppressed TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-κB and NF-κB-dependent reporter gene transcription. It also blocked NF-κB activation induced by various carcinogens and tumor promoters, including PMA, lipopolysaccharide, H_2O_2, okadaic acid and ceramide [72].

3.1.5 *AP-1*

AP-1 is another transcription factor that regulates expression of genes involved in cellular adaptation, differentiation and proliferation [86]. Functional activation of AP-1 is associated with malignant transformation as well as tumor promotion.

AP-1 consists of either homodimers or heterodimers of members of the JUN and FOS families, which interact via a leucine zipper domain. This transcription factor is also regulated by the MAPK-signaling cascade [87]. As with NF-κB, AP-1 is also a target for many of the aforementioned phytochemicals, including green tea catechins [88], resveratrol [72], curcumin [89] and capsaicin [71]. EGCG and theaflavins suppressed malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line by blocking activation of AP-1 [88]. Resveratrol inhibited TNF-dependent AP-1 activation in U-937 cells and pretreatment with resveratrol strongly attenuated TNF-activated JNK and MAP2K kinases [72]. Curcumin has been shown to suppress the activation of tissue plasminogen activator-induced AP-1 in HL-60 cells [89]. Curcumin treatment also suppressed constitutive AP-1 activity in the LNCaP and DU145 prostate cancer cell lines [90]. These results suggest that plant phytochemicals specifically targeting AP-1 or its activating kinases could be promising agents for the treatment of several cancers.

3.1.6 *STATs*

The JAK–STAT signaling pathway is an evolutionarily conserved pathway essential for cytokine receptor signaling [91]. The STAT proteins are a family of latent cytoplasmic transcription factors involved in cytokine, hormone and growth factor signal transduction. On activation by tyrosine phosphorylation, STATs alter their conformation to allow specific binding to DNA. Tyrosine phosphorylation can be induced through JAK tyrosine kinases or cytokine receptors, G-protein-coupled receptors or growth factor receptors (such as EGFR). Biologic effects of STATs include promotion of cell survival through increased expression of anti-apoptotic proteins such as Bcl-2 and Bcl-X_L. Amongs the seven STAT proteins identified as yet, constitutive activation of STAT3 and STAT5 has been implicated in several solid human tumors, lymphomas and leukemias, making these proteins rational targets for cancer therapy [92]. Green tea mediates the downregulation of the DNA binding activity of the transcription factor STAT1α. This downregulation of the STAT1α–DNA binding was shown to result from reduced tyrosine phosphorylation of the STAT1α protein and not from the antioxidative effects of the green tea extract [93]. EGCG has also been shown to downregulate the phosphorylation of STAT3 [94]. Numerous reports suggest that IL-6 promotes survival and proliferation of multiple myeloma cells through the phosphorylation of STAT3. Curcumin has been reported to inhibit IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation [95].

3.2 Agents targeting apoptotic pathways

Discovered and rediscovered several times by various developmental biologists and cytologists, programmed cell death has acquired a number of names over the past two centuries [96]. The term finally adopted is apoptosis, coined in 1972 to describe a common type of programmed cell death that was repeatedly observed in various tissues and cell types [97]. Apoptosis is a distinct conserved genetic and biochemical pathway, essential to metazoans, that enables the selective removal of cells from tissues, thus serving as a key regulator of tissue homeostasis and proper function of multicellular organisms [42,98,99] as well as chemotherapy-induced cell killing [100,101]. Evasion of apoptosis is one of the 'six capabilities' of cancer cells and a cornerstone of tumorigenesis [2]. Elucidation of the core machinery of apoptosis has provided new insights into cancer biology, revealing novel strategies for cancer therapy [102].

Phytochemicals such as curcumin, resveratrol, guggulsterone, flavopiridol, betulinic acid, ursolic acid, indole-3-carbinol, evodiamine and green tea polyphenols are known to downregulate the expression of apoptosis-suppressor proteins, such as Bcl-2 and Bcl-X_L, in several cancer cell lines. Resveratrol exerts its anticancer effects by causing cell-cycle arrest and inducing apoptosis in many different human cancers. It may interfere with apoptosis pathways both by directly triggering apoptosis-promoting signaling cascades and by blocking anti-apoptotic mechanisms (reviewed in [21,103]). Induction of apoptosis by resveratrol is accompanied by cell-cycle arrest in the G1 phase or inhibition of cell-cycle progression from S to G2 phase, decreased protein levels of cyclin D1 and CDK-4 and decreased Bcl-2 and Bcl-X_L levels. Recently, resveratrol has been shown to trigger p53-independent induction of p21 and p21-mediated cell-cycle arrest associated with survivin (a member of the inhibitor of apoptosis gene family) depletion [104]. EGCG has been shown to induce a pronounced and specific growth-inhibitory effect on cancer cells but not on their normal counterparts [105-107]. EGCG induces apoptosis in a variety of cancers such as leukemia [108,109], prostate cancer [105], gastric cancer [110], colon cancer [111] and lung cancer [112]. Emodin, the active component of Chinese herbs including *Rheum officinale* and *Polygonum cuspidatum*, inhibits the IL-6-induced JAK2/STAT3 pathway selectively and induces apoptosis in myeloma cells via downregulation of myeloid cell leukemia-1 (Mcl-1) [113].

Curcumin is known to induce apoptosis in numerous animal and human cell lines established from malignancies such as leukemia, melanoma and breast, lung, prostate, colon, renal, hepatocellular and ovarian carcinomas (readers are referred to [114]). Curcumin seems to induce apoptosis in human melanoma cells through the Fas receptor pathway and the expression of dominant-negative FADD (Fas-associated death domain) significantly inhibits curcumin-induced apoptosis [115]. Curcumin suppresses the constitutive expression of Bcl-2 and Bcl-X_L in mantle cell lymphoma [116] and multiple myeloma [70] cell lines.

Katiyar *et al.* showed that silymarin induces apoptosis involving Bcl-2/Bax, cytochrome C release and caspase

activation in preneoplastic epidermal keratinocytes [117], whereas in K562 leukemia cells, it causes caspase activation and apoptosis through inactivation of the Akt pathway [118].

3.2.1 *Caspases*

The family of cysteine proteases, the caspases, has now been proved to be the pivotal executioners of apoptotic cell death. Caspases are synthesized as relatively inactive zymogens that become activated by scaffold-mediated transactivation or by cleavage via upstream proteases in an intracellular cascade [119]. Caspases can be classified as initiators and effectors [120]. Although the initiator or regulatory caspases of the death receptor (caspase-8 and -10) or of the mitochondria and apoptosome (caspase-9) participate in initiation and signal transmission, the effector caspases (caspase-3, -6 and -7) execute the apoptotic process. Several phytochemicals are known to induce tumor cell apoptosis via caspase activation.

The apoptosis-inducing effects of curcumin involve activation of caspase-7 and -9 in mantle cell lymphoma [116] and multiple myeloma [70]. In gastric (KATO-III) and colon (HCT-116) cancer cells, curcumin triggers the Fas signaling pathway of apoptosis, activating caspase-8 and caspase-3 and thereby leading to cleavage of polyadenosine-5′-diphosphate-ribose polymerase (a substrate of caspase-3) [121]. Anto *et al*. showed that curcumin induces apoptosis through the mitochondrial pathway involving caspase-8, BID cleavage, cytochrome C release and caspase-3 activation [122]. In Jurkat cells, curcumin induces caspase-3-dependent apoptotic pathway but inhibits DNA fragmentation factor 40/caspase-activated DNase endonuclease [123].

Resveratrol has been shown to induce extensive apoptosis in human acute lymphoblastic leukemia cells via induction of the mitochondrial/caspase-9-specific pathway independently of CD95 signaling [124]. In human malignant B cells, resveratrol induces apoptosis by activating caspase-3 and p38 MAP kinase pathways [125]. Recently, Mohan *et al*. have dissected the mechanism of resveratrol-induced apoptosis upstream of mitochondria and shown that resveratrol induces apoptosis through activation of caspase-2 [126]. The activated caspase-2 triggers conformational changes in Bax/Bak with subsequent release of mitochondrial cytochrome C, apoptosis-inducing factor and endonuclease G. Capsaicin has been shown to induce apoptosis in human leukemic HL-60 cells via release of cytochrome C and activation of caspase-3 [127]. ECGC-induced apoptosis is also known to involve caspase activation. ECGC treatment elevates levels of caspase-3, -8 and -9 in human gastric carcinoma [110] and caspase-3 and -9 in human colorectal carcinoma [111].

3.2.2 *Tumor-suppressor gene p53*

The tumor-suppressor p53 is a critical regulator in many cellular processes including cellular response to DNA-damage, genomic stability, cell-cycle control and apoptosis [128,129]. Activated by various stresses such as DNA damage, ultraviolet light and oncogenes, p53 initiates various cascades that eventually stop the growth of pre-cancerous cells by triggering cell-cycle arrest, senescence or apoptosis. The fact that p53 is defective in > 50% of human tumors has generated substantial interest in generating p53-targeted cancer therapies including attempts to both activate and inhibit p53 [130].

Many dietary phytochemicals such as curcumin, resveratrol, EGCG, indole-3-carbinol and silibinin are known to modulate p53 activity. Curcumin causes growth arrest and apoptosis of B cell lymphoma by downregulation of egr-1, c-myc, Bcl-X_L and p53 [131]. It induces apoptosis in human melanoma cell lines, both wild-type and mutant p53, without inducing additional expression of p53 [115]. However, curcumin inhibits cell-cycle progression of immortalized human umbilical vein endothelial cells by up-regulating the cyclin-dependent kinase inhibitors, $p21^{WAF1/CIP1}$, $p27^{KIP1}$ and p53 [132].

Several reports document effects of resveratrol on p53. By showing that resveratrol-induced apoptosis occurred only in cells expressing wild-type p53, not in p53-deficient cells, Huang *et al*. demonstrated for the first time that resveratrol induces apoptosis through activation of p53 activity [133]. The expression of NAG-1 (NSAID) drug-activated gene-1, a member of the TGF-β superfamily, has been shown to be associated with pro-apoptotic and antitumorigenic activities. Resveratrol enhances NAG-1 expression by increasing the expression of p53 in human colorectal cancer cell lines [134]. In another study, resveratrol was shown to exert its anti-proliferative effects on osteosarcoma cells through the activation of the ERKs/p53 signaling pathway [40]. Genistein induced apoptosis and G2 arrest and inhibited proliferation in a variety of human cancer cell lines, regardless of p53 status [135]. In human liver cancer cell line HepG2, EGCG significantly increased the expression of p53 and p21/WAF1 protein and this contributed to cell-cycle arrest [136]. This study suggested that the induction of p53 and the activity of the Fas/FasL apoptotic system play major roles in the antiproliferative activity of EGCG.

3.3 Agents targeting angiogenesis

The vasculature is a flexible conduit for the delivery and exchange of nutrients, wastes, hormones and immune cells and hence is crucial for organ growth in the embryo and repair of wounded tissue in the adult. Angiogenesis, the growth of new capillary blood vessels, is also central to the growth of cancer [137]. The tumor angiogenic process consists of the degradation of the basement membrane surrounding capillaries, invasion of the stroma by endothelial cells, proliferation of endothelial cells and finally their three-dimensional organization into a network of new blood vessels. Tumor cells, in response to hypoxia and other environmental and cellular stimuli, produce angiogenic factors such as VEGF, which bind to the

receptors on the resident endothelial cells and stimulate them to proliferate and migrate to form new vascular networks for tumors. Many proteins, including VEGF, FGF, EGF, PDGF, TGF-α, TNF and angiopoietins, have been identified as angiogenic factors released by tumors [138]. Inhibiting angiogenesis is a promising strategy for the treatment of cancer and a wide range of natural products have angiogenesis-modulating properties (readers are referred to [139]). These include resveratrol [140,141], curcumin [142,143], genistein [144], luteolin [145], capsaicin [26] and catechins [146,147]. Cao and Cao [148] reported that both green tea and EGCG significantly inhibit angiogenesis. Further work showed that EGCG suppresses the oxidant-induced production of the pro-angiogenic cytokine IL-8 and inhibits VEGF-induced Akt activation and E-cadherin phosphorylation at physiologic doses [146,147]. Resveratrol inhibited tumor-induced neovascularization *in vivo* without causing severe side effects when administrated orally [149]. Curcumin, genistein and green tea components also interfere with endothelial cell function by inhibiting specific integrin engagement and signaling [150].

3.4 Agents targeting invasion and metastasis

The spread of tumor cells from the initial site to distant settlements (metastasis) is the major cause of treatment failure, morbidity and mortality. Invasion and metastasis are exceedingly complex processes, involving changes in the physical coupling of cells to their microenvironment and activation of extracellular proteases [151]. The tethering of cells to their surroundings is facilitated by a variety of proteins that are altered in cells possessing invasive or metastatic capabilities. Curcumin causes degradation of cell–cell adhesion proteins such as β-catenin, E-cadherin and adenomatous polyposis coli protein; inhibits the production of cytokines relevant to tumor growth (e.g., TNF-α and IL-1); and reduces the expression of membrane surface molecules that play a role in cellular adhesion [152-154]. It can interfere with the activity of MMP-2 and -9, reducing the degradation of the extracellular matrix [155]. Both curcumin and catechin inhibit the invasion of B16F-10 melanoma cells by inhibition of MMPs [156]. Genistein has been reported to reduce the metastatic burden by decreasing tumor cell proliferation and increasing tumor cell death in the lung in post-surgical orthotopic breast cancer models [157]. The anti-invasive effects of resveratrol have been well documented. Resveratrol suppressed the invasion of hepatoma cells independently of its antiproliferative action [158]. In another study, resveratrol has been shown to induce the expression of tensin, a cell-matrix adhesion protein, in the human erythroleukemic K562 cell line [159]. Tensin is a member of the tumor suppressor family of the actin cytoskeleton-associated proteins. Through tensin induction, resveratrol mediates restoration of the cell-matrix adhesion and inhibition of the invasive potential in tensin-deficient tumor cells. In human cultured glioblastoma cells, resveratrol decreased the expression of MMP-2 and secreted protein acidic and rich in cysteine (a glycoprotein that modulates cell-matrix interactions), both of which are major factors in ECM remodeling associated with tumor invasion [160].

4. Better together: blending natural products with conventional therapeutic modalities

Cancer therapy often involves a multi-pronged approach that incorporates surgical, chemotherapeutic and radiotherapeutic strategies. It is increasingly evident that the success of these interventions is hampered by development of resistance to these therapies and the inability to continue these therapies indefinitely due to their cumulative toxicities. One strategy that merits consideration in this battle against cancer is that of combining these traditional therapies with nontoxic agents that augment their effectiveness by selectively sensitizing cancer cells to the cytotoxic effects of chemotherapy and/or radiotherapy [161].

4.1 Natural products as chemosensitizers

Most cytotoxic drugs, including fluoropyrimidines and nucleoside analogues, dactinomycin, platinum compounds, cyclophosphamide and taxanes, act primarily by inducing apoptosis in cancer cells (reviewed in [100]). Natural products that potentiate tumor cell death by these agents could be used as chemosensitizers. Several reports have highlighted the enhanced efficacy of chemotherapy when combined with plant phytochemicals. Three potential mechanisms of interaction between cytotoxic chemotherapy and natural products could be proposed. First, the resistance of many tumors to EGFR blockade may be mediated by activation of signaling molecules downstream of EGFR via redundant pathways that remain unaffected by EGFR blockade. Therefore, EGFR-independent activation of Akt, PI3K, MAPK and NF-κB may circumvent the potential benefit of upstream EGFR blockade. Consequently, combining anti-EGFR agents with natural products with a broad spectrum of activities, as noted above, could be additive and/or synergistic. In EGFR-expressing lung cancer cells, genistein combined with cisplatin, doxorubicin or etoposide enhanced the antiproliferative effects of these drugs and induced apoptosis [162]. Genistein potentiated apoptosis induced by erlotinib and gemcitabine in pancreatic cancer cells, possibly via inhibition of Akt and NF-κB [163]. Curcumin downregulated NF-κB and sensitized multiple myeloma cells to vincristine and melphalan. Furthermore, the NF-κB target genes *Bcl-2, Bcl-X_L, cyclin D1* and *IL-6* were downregulated by curcumin, leading to the suppression of proliferation and arrest of cells at the G1/S phase of the cell cycle [70].

Second, natural products could potentiate the cytotoxic effects of traditional chemotherapy via induction of mutually exclusive and alternate apoptotic pathways. Pretreatment of

lung cancer cells with resveratrol significantly enhanced the subsequent antiproliferative effect of paclitaxel by inducing apoptosis [164]. Flavopiridol potentiated the cytotoxic effects of mitomycin C by promoting drug-induced apoptosis in breast and gastric cancer cells: this effect was dependent on the order of treatment [165]. Flavopiridol is also reported to sensitize retinoblastoma protein-deficient sarcoma cells to doxorubicin-induced cell killing [166].

Third, cancer cells that escape the cytotoxic effects of chemotherapy may do so by activating specific pro-survival signaling pathways. By abrogating signaling via these pathways, natural products could exert synergistic effects with standard chemotherapeutic agents. In one study, curcumin potentiated the cytotoxic effects of doxorubicin, 5-fluorouracil and paclitaxel in prostate cancer cells and it suppressed both the constitutive and TNF-induced activation of NF-κB [167]. Similarly, emodin sensitized HeLa cells to arsenic trioxide via generation of reactive oxygen intermediates and reactive oxygen intermediate-mediated inhibition of two major pro-survival transcription factors, NF-κB and AP-1 [168]. Aloe-emodin has been shown to potentiate the inhibitory effects of several chemotherapeutic agents including cisplatin, doxorubicin and 5-fluorouracil on Merkel cell carcinoma cells [169]. It is clear from these reports that natural products can serve as good chemo-sensitizers via a variety of mechanisms and could possibly do so without any of the known cumulative toxicities observed with combination chemotherapy regimens in widespread clinical use.

4.2 Natural products as radiosensitizers

Most patients with cancer receive radiotherapy at some point during the course of their treatment. The efficacy of treatment depends on the total dose of radiation, the fractionation scheme, the degree of oxygenation of tumors and the normal tissue response to radiation. Given the heterogeneity of tumors and their response to treatment, early experimental and theoretical studies in radiobiology focusing on differences in the relative radiosensitivity of different tumors identified four classical mechanisms of radioresistance: DNA strand-break repair, repopulation of cancer cells between radiation fractions, reoxygenation of tumors after a radiation fraction and redistribution of cells into a radioresistant phase of the cell cycle. Although enhancement of tumor radiosensitivity can be achieved by targeting any or all of these processes, understanding the molecular basis of these processes can permit selective targeting of the molecules and pathways that regulate cellular radioresponse. In broad terms, it may be possible to target the pro-survival signaling pathways activated by radiation, to target normal tissue responses such as angiogenesis and/or to exploit radiation-induced gene expression to induce targets for other therapeutic modalities.

The initial experience with radiosensitization was limited to the combination of radiation therapy with traditional cytotoxic agents such as hydroxyurea, 5-fluorouracil and cisplatin. However, it is increasingly recognized that, although the primary target of ionizing radiation is DNA, radiation also affects cellular macromolecules, such as PKC, JNK, ceramide and MAPK, which stimulate various signal transduction pathways [170]. Consequently, radiation therapy has now been combined with molecular targeted agents that block specific pro-survival signaling pathways (for example, using monoclonal antibodies such as cetuximab or small-molecule tyrosine kinase inhibitors such as erlotinib, both of which target EGFR signaling) [171]. However, toxicity and expense remain major challenges in the clinical implementation of many of these strategies. In contrast, radiosensitization strategies using natural products could potentially improve the efficacy of radiotherapy without increasing toxicity or expense.

Radiation therapy combined with genistein in treating prostate cancer cell lines *in vitro* significantly inhibited cell growth and colony formation [172]. Combination therapy also demonstrated greater inhibition of the primary tumor growth and lymph node metastasis in an orthotopic prostate carcinoma model [173]. Synergy between genistein and radiation has been attributed to inhibition of NF-κB activity, leading to altered expression of regulatory cell-cycle proteins such as cyclin B and/or $p21^{WAF1/CIP1}$, thus promoting G2/M arrest and increased radiosensitivity [174]. An alternative explanation proposed by the same group is that genistein downregulates apurinic/apyrimidinic endo-nuclease-1/redox factor-1 to exert its radiosensitizing effects [175]. However, when given alone, genistein was noted to increase lymph node metastases, possibly due to an increase in hypoxia [176]. In contrast to this, a soy isoflavone mixture consisting of genistein, daidzein and glycitein, that is commonly used clinically, failed to increase nodal metastases but maintained the radiosensitizing effects noted with genistein alone [176]. Curcumin has been also shown to sensitize prostate cancer cells to radiation [177] via inhibition of TNF-α-mediated NF-κB activity, resulting in Bcl-2 protein downregulation. Li *et al.* [178] recently reported that curcumin exerts its radiosensitizing effect by downregulating the *MDM2* oncogene in cells with either wild-type or nonfunctional p53 and that this effect was mediated by inhibition of the PI3K/mTOR/erythroblastosis virus transcription factor 2 pathway that governs *MDM2* transcription. The Ras, PI3K and mTOR signaling pathways are some of the most frequently targeted pathways in human cancers [179]. Flavopiridol significantly enhanced the induction of apoptosis by radiation in colon and gastric cancer cells; this effect was optimal when flavopiridol followed the radiation treatment [180]. In contrast to this, Raju *et al.* noted no increase in apoptosis in cells treated with radiation and flavopiridol over that induced by flavopiridol alone [181]. The mechanistic explanations for enhancement of radiation response have been variably attributed to inhibition of DNA damage repair [181,182],

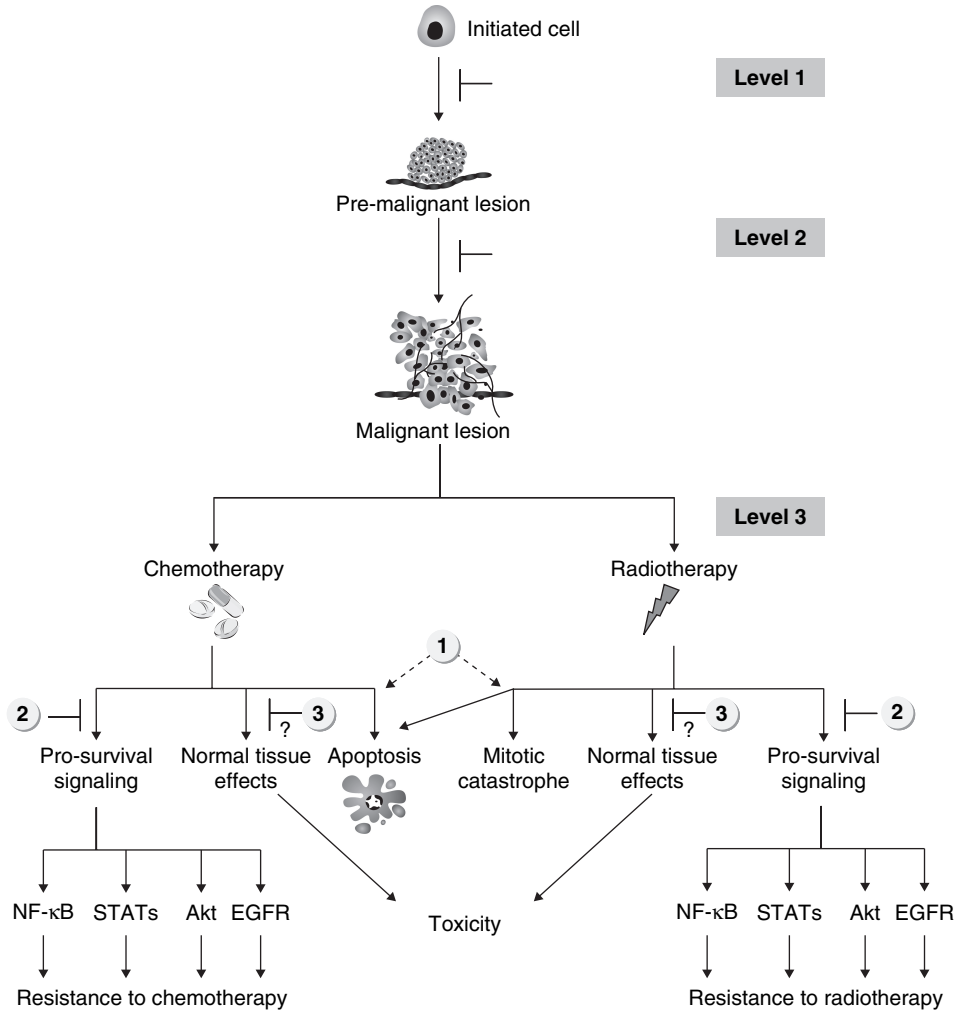

Figure 3. Synopsis of the different levels at which natural products exert their anticancer effects, thereby modulating both the process of tumorigenesis and the efficacy of anticancer therapies. The levels at which natural products influence the initiation, progression and therapy of cancer are depicted on the side in boxes. **Level 1.** Natural products inhibit the initial processes of tumorigenesis by inhibiting different steps that govern the transformation of an initiated cancer cell to a premalignant lesion. These are chiefly dietary phytochemicals and the role they play is chemopreventive. **Level 2.** Natural products exert their anticancer effects on multiple processes that result in the progression of premaligant lesions into overtly malignant tumors. This stage is detailed in **Figure 2. Level 3.** Natural products can be combined with conventional therapeutic modalities in order to achieve better tumor cell kill and to overcome the resistance of tumors to these therapies. The thickness of each arrow is roughly proportional to the relative predominance of each effect. (**1**) Natural products enhance the apoptotic cell death and/or clonogenic death induced by chemotherapy and/or radiotherapy. (**2**) Natural products abrogate various pro-survival signaling pathways upregulated by tumors in an effort to overcome the cell kill triggered by chemotherapy and radiotherapy. Representative pathways/molecules are shown here (readers are referred to Sections 4.1 and 4.2 for details). (**3**) Natural products could minimize the toxicity of conventional therapies by inhibiting the physiologic processes induced by these therapies within normal tissues. The inherent lack of toxicity of natural products and the potential reduction of toxicity of cytotoxic therapies could improve the therapeutic ratio of cancer treatment.

inhibition of angiogenesis [183] and cell-cycle redistribution [181]. Resveratrol has also been shown to augment radiation response via alteration of cell-cycle progression and enhanced cell death [184].

5. Conclusions

Despite the remarkable progress in understanding the biology of cancer at a molecular level, the lack of addiction of most tumors to a single 'druggable' target has resulted in relatively few instances of durable and effective tumor control using highly targeted agents. In contrast to these targeting agents, natural products often modulate multiple targets simultaneously, are relatively non-toxic and are emerging as promising chemopreventive and anticancer agents. In addition to having potent antitumor properties as single agents, these natural products have also demonstrated potential synergy with established cytotoxic therapeutic modalities in pre-clinical studies. **Figure 3** summarizes the various ways by which natural products can influence the process of carcinogenesis and modulate the response to traditional therapeutic modalities. These observations warrant further systematic and rigorous investigation in randomized clinical trials.

6. Expert opinion: food for thought

Recent advances in our knowledge of the complexity of the biology of cancer have unearthed a mesh of cell signaling pathways involved in the initiation and progression of cancer. Processes that were previously thought to operate independently of each other (e.g., inflammatory pathways and oncogenic signaling pathways) are now known to be intricately involved in the development of cancer and the response of cancer to treatment. Identification of these pathways has led to the development of highly specific 'designer' targeting agents that block aberrantly signaling receptors (monoclonal antibodies), overactive downstream kinases (small-molecule inhibitors) or mRNA expression (antisense oligonucleotides). Although these specific targeted therapies may prove to be effective by themselves or in combination with other established therapeutic modalities, the success of such therapies in clinical practice has been limited to a few cancers and a few molecules. This is exemplified by the success of agents such as imatinib, transtuzumab, bevacizumab and cetuximab. The relative scarcity of such success stories is probably best explained by the paucity of clinical scenarios in which a given tumor is addicted to merely one aberrant signaling pathway. Treatment resistance resulting from the prevalence of redundant signaling pathways in most cancers has led to an increasing use of combinations of these specific targeted therapies to simultaneously target several pathologic processes. However, until rational ways to combine these agents to overcome the redundancy of oncogenic pathways are developed, there is still a role for broad-spectrum agents such as natural products that simultaneously target multiple signaling pathways.

Natural products from plant sources have distinct advantages over synthetic products in some respects. First, they are likely to be better ligands for biologically active proteins than purely synthetic compounds as they are likely to have developed from similar parent molecules evolutionarily and some degree of structural and functional conservation may enhance their interaction with biologically active proteins. Second, the ability of these drugs to target multiple targets simultaneously has the potential to minimize the likelihood of treatment resistance. As an example, infectious diseases caused by more virulent bacteria and viruses (such as *Mycobacterium tuberculosis* and HIV) are notoriously resistant to single-agent therapies but tend to respond to multi-pronged and sustained treatment with a spectrum of biologically active agents. Similar multi-drug therapy with combinations of specific targeted therapies are slowly being explored in cancer clinical trials, particularly in cancers that do not have a clear clonal etiology. Third, these agents tend to exert their antitumor effects without causing undue toxicity and at considerably lower financial burden to society. Finally, the chemical diversity, structural complexity and inherent biologic activity of natural products could serve as templates for rationally designed libraries of synthetic compounds with varying chemical, structural and biologic properties.

Despite these inherent advantages of natural products as active agents in the treatment of cancer, their role in the clinical management of a cancer patient remains undefined. This is largely because of the persisting need to identify and characterize active ingredients in many natural products, manufacture standardized and reproducible batches of chemically uniform mixtures of active ingredients and/or metabolites, implement rigorous scientific methodologies to interrogate and validate multi-pathway pharmacologic activity in the clinic that serves as a surrogate for clinical efficacy and perform adequately statistically powered and scientifically sound clinical trials. With the adoption of comparable regulatory requirements for these products and synthetic compounds, there is an increasing need to systematically translate preclinical findings to the clinic with rationally designed placebo-controlled randomized clinical trials with relevant correlative studies.

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Declaration of interest

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