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Cancer Cell Signaling Pathways Targeted by Spice-Derived Nutraceuticals

Bokyoung Sung, Sahdeo Prasad, Vivek R. Yadav, and Bharat B. Aggarwal

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Extensive research within the last half a century has revealed that cancer is caused by dysregulation of as many as 500 different gene products. Most natural products target multiple gene products and thus are ideally suited for prevention and treatment of various chronic diseases, including cancer. Dietary agents such as spices have been used extensively in the Eastern world for a variety of ailments for millennia, and five centuries ago they took a golden journey to the Western world. Various spice-derived nutraceuticals, including 1'-acetoxychavicol acetate, anethole, capsaicin, car-damonin, curcumin, dibenzoylmethane, diosgenin, eugenol, gambogic acid, gingerol, thymoquinone, ursolic acid, xanthohumol, and zerumbone derived from galangal, anise, red chili, black cardamom, turmeric, licorice, fenugreek, clove, kokum, ginger, black cumin, rosemary, hop, and pinecone ginger, respectively, are the focus of this review. The modulation of various transcription factors, growth factors, protein kinases, and inflammatory mediators by these spice-derived nutraceuticals are described. The anticancer potential through the modulation of various targets is also the subject of this review. Although they have always been used to improve taste and color and as a preservative, they are now also used for prevention and treatment of a wide variety of chronic inflammatory diseases, including cancer.

INTRODUCTION

Four decades after U.S. President Nixon officially declared the “War on Cancer,” the overall rates of cancer have not substantially changed. Despite significant progress in the treatment of certain forms of cancer (such as childhood leukemia), cancer in general remains a major cause of death. Why are we losing the war against cancer? Is cancer a more complex and challenging disease than expected (1)? In any case, what is the future of cancer research? We argue that the primary cause is a too narrow focus in the effort to develop cancer drugs for a single target, usually a single gene, gene product, or signaling pathway that has been identified on the basis of genetic analysis or biological observations (2). Theoretically, targeting therapy should be sufficient to achieve a significant therapeutic effect; in reality, however, such therapies have had very little therapeutic impact (3–5). In fact, they have generally been highly ineffective against complex diseases (e.g., cancer) or diseases affecting multiple tissues or cell types (e.g., diabetes and immunoinflammatory disorders).

Only 5% to 10% of all cancers are caused by inheritance of mutated genes and somatic mutations, whereas the remaining 90–95% has been linked to lifestyle factors and the environment (6). Almost 30% of all cancers have been attributed to tobacco smoke, 35% to

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Address correspondence to Bharat B. Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: 713-794-1817. Fax: 713-745-6339. aggarwal@mdanderson.org.

diet, 14–20% to obesity, 18% to infections, and 7% to radiation and environmental pollutants. The underlying mechanisms by which these risk factors induce cancer are becoming increasingly evident. One process that seems to be common to all these risk factors is inflammation (6–9). Therefore, most risk factors for cancer, including tobacco, obesity, alcohol, infections, stress, food carcinogens (e.g., grilled meat), and environmental pollutants, have been shown to be components of a proinflammatory lifestyle, one leading to tumorigenesis (Fig. 1A).

The World Cancer Research Foundation 2007 report (10) estimates that 35% of the cancer incidence worldwide could be attributable to lifestyle factors such as food, nutrition, and physical activity. Increasing evidence has indicated that a diet protective against cancer would include fruits, vegetables, spices, cereals, pulses, and nuts (Fig. 1B). The specific substances in these dietary foods that are responsible for preventing cancer and the mechanisms by which they achieve this have also been examined extensively.

According to the U.S. Food and Drug Administration, spice is an “aromatic vegetable substance in the whole, broken, or ground form, the significant function of which in food is seasoning rather than nutrition” and from which “no portion of any volatile oil or other flavoring principle has been removed.” Although spices have been used for thousands of years and are known for their flavor, taste, and color in the food, they are not usually recognized for their medicinal value. The results from Italy with gastric cancer patients and healthy people indicate that individuals who consume more fresh fruit, raw vegetables, and spices were associated with lower incidence of cancer (11). In addition, in a comparison of the incidence of the various types of cancer between the United States and India, the United States was found to have much higher rates of colorectal cancer. In 2000, the United States had 356 colon cancer cases reported and 139 deaths per 1 million people. In contrast, India only had 40 reported cases of colon cancer and 26 deaths per 1 million people. Why cancer incidence is so much lower in India than in most Western countries is not fully understood, but the high spice consumption could be one of the contributing factors (12).

In this review, we will focus on the selected nutraceuticals derived from spices (Fig. 2) that target multiple cellular signaling pathways in tumorigenesis. The spicy nutraceuticals, described here, do indeed show great potential for modulating multiple targets such as transcription factors (e.g., NF- κ B, STAT3, activator protein (AP-1), NRF-2, peroxisome proliferator-activated receptor (PPAR γ), and HIF-1 α), growth factor receptors [e.g., vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), HER2 (EGFR2), and insulin-like growth factor-1 receptor (IGF-1R)], kinases (e.g., phosphoinositide 3-kinase (PI3K), AMP-activated protein kinase (AMPK), Bcr-abl, and Raf/Ras), inflammatory mediators, and other targets involved in tumor progression.

MOLECULAR TARGETS OF SPICE-DERIVED NUTRACEUTICALS

As described earlier, cancer is not a simple disease but a complex interaction between multiple signaling pathways with various target molecules. In this review, we will focus on some selected spice-derived nutraceuticals (see Fig. 2 and Table 1). This first section will focus on some of the most commonly known targets that cause undesired effects in tumor development (Fig. 3). How spice-derived nutraceuticals modulate these particular targets will then be discussed.

Transcription Factors

Transcription factors regulate the expression of genes within a cell and ultimately control cell behavior. Thousands of these factors have been identified. They are frequently locked in an “on” position in cancer cells; while the transcription factors are shut off, a cancer cell will

generally stop growing or begin to die. A number of oncogenic transcription factors such as AP-1, NF- κ B, STAT3, and others are overactivated in human cancer and thus may present promising targets for treatment and prevention of cancer (13–16). Although the effect of various nutraceuticals on the transcription factors is discussed below individually, there is extensive cross-talk between these factors as recently described from our laboratory (13). Although the modulation of some these targets in some cases by spice-derived nutraceuticals may occur directly, in other cases the effects may be indirect.

Nuclear Factor-Kappa B (NF- κ B)—We know that a number of genes involved in regulation and control of cancer growth and its' metastasis are controlled by certain transcription factors. Among these, NF- κ B plays a major role in development and progression of cancer because it regulates more than 500 genes, ones involved in inflammation, cell survival, cell proliferation, invasion, angiogenesis, and metastasis. In 1986, Sen and Baltimore discovered NF- κ B as a nuclear factor that binds to the enhancer region of the κ B chain of immunoglobulin in B cells (17). Upon activation, it is translocated to the nucleus, where it induces the expression of target genes. Many of the target genes are critical to the establishment of the early and late stages of aggressive cancers, including expression of cyclin D1, apoptosis suppressor proteins such as Bcl-2 and Bcl-xL, and those required for metastasis and angiogenesis, such as matrix metalloproteases (MMP) and VEGF. NF- κ B is constitutively expressed in almost all cancer types and suppresses apoptosis in a wide variety of tumors. Its constitutive expression has been reported in human cancer cell lines in culture, carcinogen-induced mouse mammary tumors, and biopsies from cancer patients (13, 18).

A number of studies from our laboratory have shown that spice-derived nutraceuticals exert their anticancer effects through the suppression of NF- κ B. Curcumin as well as various other curcuminoids from turmeric mediate their therapeutic effects by regulating NF- κ B and the NF- κ B-regulated gene products cyclooxygenase-2 (COX-2), cyclin D1, adhesion molecules, MMPs, inducible nitric oxide synthase, Bcl-2, Bcl-xL, and tumor necrosis factor (TNF) (19,20). The fennel-derived nutraceutical anethole blocks both early and late cellular responses transduced by tumor necrosis factor through suppression of NF- κ B activation. Thus, its analogues eugenol and isoeugenol also inhibit TNF-induced NF- κ B activation (21). Numerous spice-derived phytochemicals, such as cap-saicin (22), cardamonin (23), dibenzoylmethane (DBM) (24), diosgenin (25), gambogic acid (26), [6]-gingerol (27), thymoquinone (28), xanthohumol (29), ursolic acid (30), and zerum-bone (31) may also suppress NF- κ B activation and antiapoptotic gene products and induce apoptosis in cancer cells.

Signal Transducer and Activator of Transcription 3—STAT3 is a transcription factor, first identified in 1994 as a DNA-binding factor that selectively binds to the interleukin (IL)-6-responsive element in the promoter of acute-phase genes from IL-6-stimulated hepatocytes (32). STAT3 was also independently identified as a DNA-binding protein in response to epidermal growth factor (EGF) (33). It is normally present in the cytoplasm of most cells. In response to certain inflammatory stimuli (e.g., IL-6) and growth factors (e.g., EGF), STAT3 undergoes sequential tyrosine phosphorylation, homodimerization, nuclear translocation, DNA binding, and gene transcription. Several protein kinases that cause specific phosphorylation of STAT3 have been identified, including Janus-activated kinase 1, 2, and 3. Protein phosphatases that dephosphorylate STAT3 also have been identified. The molecule is associated with inflammation, cellular transformation, survival, proliferation, invasion, angiogenesis, and metastasis of cancer. Gene products linked with survival (e.g., Bcl-xL), proliferation (e.g., cyclin D1), and angiogenesis (e.g., VEGF) are regulated by STAT3 activation (16). STAT3 is constitutively

active in most tumor cells but not in normal cells. Its activation has also been associated with chemoresistance and radioresistance (34).

One nutraceutical with potential to target STAT3 pathways is curcumin, a potent anticancer agent that induces apoptosis by inhibiting the STAT3 pathway. As first reported by Bharti et al. (35), curcumin has the potential to suppress STAT3 activation in human multiple myeloma (MM) cells. The same research group also reported that STAT3 is constitutively active in CD138+ cells derived from MM patients, and curcumin can inhibit STAT3 activation (36). The suppression of STAT3 by curcumin also occurs in a variety of other human cancer cells including glioma (37), cutaneous T-cell lymphoma (38), Hodgkin's lymphoma (39), T-cell leukemia (40), ovarian cancer (41), endometrial cancer (41), and head and neck cancer (42). Bhutani et al. (43) found that capsaicin suppressed the STAT3 signaling pathway in human MM cells and inhibited the growth of human MM xenograft tumors in male athymic nu/nu mice. They showed that capsaicin inhibited the activation of janus-activated kinase-1 and c-Src, which are both implicated in STAT3 activation. In glial tumors, capsaicin was reported to downregulate the IL-6/STAT3 pathway by depleting intracellular gp130 pools through the endoplasmic reticulum (44). Li et al. (45) found that the spice-derived steroidal saponin, diosgenin, inhibited the STAT3 signaling pathway, leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma cells. Thymoquinone is also known to inhibit the activation of STAT3 and potentiate the apoptotic effects of thalidomide and bortezomib in MM cells (46). Pathak et al. (47) found that ursolic acid in basil inhibited both inducible and constitutive activation of STAT3. Ursolic acid downregulated STAT3-regulated antiapoptotic genes such as Bcl-2, Bcl-xL, survivin, and Mcl-1 and inhibited proliferation in human MM cells.

Signal Transducer and Activator of Transcription 5—Stat5A was discovered as a transcription factor regulating milk protein expression. It was originally identified as a mammary gland factor (48) but renamed Stat5 according to homology within the Stat family (49). Further studies demonstrated that Stat5 has 2 different isoforms A and B. Stat5B is a crucial signaling protein mediating the biological effects of growth hormone, whereas the key function of Stat5A is to transduce the signals initiated by prolactin receptors (50). In addition, Stat5A/B can be activated by several other ligands including IL-2, IL-3, IL-5, IL-7, granulocyte-macrophage colony-stimulating factor, insulin, erythropoietin, and thrombopoietin (51).

Stat5 is persistently activated in certain human cancer cell lines and tumor tissues (52,53). The activation of Stat5 signaling has been shown to promote tumorigenesis in a number of cases, such as chronic myelogenous leukemia (CML) and myeloproliferative disease that is induced by TEL-JAK2 (50). In CML, the oncogenic BCR-ABL chromosomal translocation also known to cause persistent activation of Stat5 (54). Stat5 is also constitutively activated by the FMS-like tyrosine kinase 3 receptor tyrosine kinase (FLT3) in AML and thus an inhibitor for FLT3 blocks Stat5 signaling in these cells (55). In solid tumors instance prostate and breast, have also been shown that activation of Stat5A/B is significantly (56,57). Above information indicate that Stat5 inhibitors might be potent as anticancer therapies.

Among spice-derived compounds, curcumin is known to inhibit Stat5 signaling pathway. Rajasingh et al. (40) showed that curcumin induced a dose-dependent decrease in Stat5 phosphorylation resulting in the induction of growth-arrest and apoptosis in T-cell leukemia lines, MT-2, HuT-102, and SLB-1. Results from other group indicated that curcumin inhibited INF γ -induced nuclear translocation of Stat5 without affecting its phosphorylation of Stat5 in human CML cells (58).

AP-1—AP-1 acts as a dimer consisting mainly of the Jun (c-Jun, JunB, JunD) and Fos (c-Fos, FosB, Fra-1, Fra-2) subfamilies that harbor a basic leucine zipper (bZIP) domain and can form duplexes between themselves and with other bZIP proteins. Bernstein and Colburn (59) elucidated the role of AP-1 in tumorigenesis. They reported a lack of responsiveness to AP-1 activation in transformation-resistant JB6 cells, whereas AP-1 was functional in transformation-sensitive JB6 cells. Later the requirement for AP-1 activity during tumor promotion in JB6 cells was demonstrated by expression of a transactivation-minus mutant of c-Jun (TAM67) (60,61). Numerous data suggest that the activation of AP-1 plays a major role in proliferation and metastasis of tumor cells (62,63). AP-1 regulates the expression of genes that mediate proliferation and angiogenesis such as c-myc and fos, and genes for COX-2, urokinase-type plasminogen activator, MMP-9, cyclin D1, and VEGF (62,64). This transcription factor also represses tumor-suppressor genes such as p53, p21cip1/waf-1, and p16 (65). Curcumin has been shown to suppress the activation of 12-*O*-tetradecanoylphorbol-13 acetate (TPA)-induced AP-1 in HL-60 and Raji cells (66,67). Curcumin treatment also suppresses constitutive AP-1 activity in prostate cancer cell lines (68). Inhibition of AP-1 transcriptional activity by curcumin correlates with inhibition of Lewis lung carcinoma invasion in an orthotopic implantation model (69). In HT1080 human fibrosarcoma cells, ursolic acid represses the expression of MMP-9 by stimulating the nuclear translocation of glucocorticoid receptor and the translocated glucocorticoid receptor, probably by downmodulating the transactivating function of AP-1 to MMP-9 promoter region (70).

3.1.5. Nuclear Factor-Erythroid 2-Related Factor 2 (Nrf2)—Nrf2 is a transcription factor that plays a crucial role in protecting cells against inflammation, as well as oxidative and electrophilic stresses. Under stress conditions such as oxidative or electrophilic stress, Nrf2 translocates into the nucleus, binds to antioxidant response elements (ARE), and transactivates phase II detoxifying and antioxidant genes. Among the antioxidant genes that are regulated by Nrf2 are NAD(P)H:quinone oxidoreductase (NQO1), heme oxygenase-1 (HO-1), thioredoxin reductase 1, glutamate-cysteine ligase modifier subunit, and glutamate-cysteine ligase catalytic (GCLC) subunit (71). Several lines of evidence have indicated the roles of Nrf2 in susceptibility to carcinogenesis. The colorectal tumor incidence, multiplicity, size, and stage of progression are higher in Nrf2-deficient mice exposed to azoxymethane-dextran sodium sulfate (AOM/DSS) (72). Beside colorectal carcinogenesis, Nrf2-deficient mice are also more susceptible to skin tumorigenesis (73), lung cancer (74), gastric neoplasia (75), urinary bladder carcinoma (76), and hepatocarcinogenesis (77) compared to their wild-type counterparts. A recent review by Hayes and McMahon (78) indicated frequent mutation of KEAP1, an inhibitor of Nrf2, and NRF2 in human cancers. KEAP1 mutation (C23Y) found in tumors from breast cancer patients has been associated with impaired ubiquitination of Nrf2 (79), and recurrent KEAP1 gene alterations were observed in gallbladder cancer with a frequency of 30% (80). Furthermore, it has been noted that patients with lung tumors containing mutant KEAP1 or NRF2 showed a poorer prognosis than patients with nonmutant tumors (81).

Administration of curcumin induced the expression and nuclear translocation of Nrf2 in the liver and lung of mice treated with benzo[a]pyrene (B[a]P) (82). Moreover, curcumin increased ARE-binding of Nrf2 and induced the activity as well as expression of GST and NQO1 and their mRNA transcripts, and the liver and lung of mice treated with dietary curcumin had reduced oxidative stress and inflammation (83). Dibenzoylmethane (DBM), a constituent of licorice, induced the ARE-luciferase reporter activity and attenuated B[a]P-induced DNA adduct formation in the lung of A/J mice. These findings were in agreement with increased mRNA expression of NQO1, GSTA2, and GCLC in mouse hepatoma cells, which was negated by dominant-negative mutation of Nrf2 (84). Recently, a study conducted with DBM on AOM/DSS-induced colon cancer model showed that DBM

increased induction of Nrf2 transcription factor and phase II detoxifying enzymes (85). Lee et al. (86) demonstrated that a chalcone, xanthohumol, exerts antiinflammatory activity through Nrf2-ARE signaling and upregulation of downstream HO-1 in mouse microglial BV2 cells. Interestingly, this chalcone alkylated 27 cysteine sulfhydryl groups of Keap1, which led to Nrf2 nuclear accumulation, upregulation of cytoprotective gene expression by the binding of Nrf2 to ARE, and prevention of degenerative diseases, such as cancer (87). Capsaicin, a major pungent ingredient of red pepper, is also reported to have chemoprotective effects through activation of Nrf2 and upregulate the expression of HO-1 (88).

PPAR- γ —PPAR- α , - β (or δ), and - γ are 3 of 100 nuclear receptors in the orphan receptor class. PPAR γ (PPAR γ) is the most extensively studied subtype of the PPARs. It is mainly expressed in adipose tissue and in colonic epithelium. Lower levels are expressed in beta cells of the pancreas, vascular endothelium, macrophages, and many other tissues. Over the last decade, research on PPAR γ unveiled its role in important biological processes, including lipid biosynthesis, glucose metabolism, anti-inflammatory response, and atherosclerosis (89), and in regulating tumor suppression and promotion (90–92). Earlier research suggested a relationship between PPAR γ activation and cellular differentiation accompanied by cell cycle arrest (93). Later research demonstrated PPAR γ expression in multiple tumor types, leading to further insights into the role of PPAR γ in cell cycle arrest and growth inhibition of human and rodent tumor cells (94–96). The role of PPARs in carcinogenesis is not fully understood and remains controversial. However, numerous lines of evidences indicate the dysregulation of PPAR γ correlates with carcinogenesis in head and neck cancer (97), thyroid follicular carcinomas (98), colon cancer (99), and bladder cancer (96).

PPAR γ agonists in the drug development pipeline are undergoing clinical trials in patients with advanced metastatic cancer, anaplastic thyroid cancer, or leukoplakia (100,101). Curcumin has been reported to significantly induce the expression of PPAR and inhibit cell proliferation, induce apoptosis, and suppress extracellular matrix gene expression. Blocking the transactivity by PPAR γ antagonist significantly decreased the effects of curcumin on the inhibition of cell proliferation. Recent studies reported that the activation of PPAR γ by curcumin in Moser cells inhibited the growth and mediated the suppression of gene expression of cyclin D1 and EGFR (102). Kim et al. (103) reported that capsaicin had a role as PPAR γ agonist and induced apoptosis in HT-29 human colon cancer cells. This capsaicin-induced cell death was completely blocked by bisphenol A diglycidyl ether, a specific PPAR γ antagonist.

β -catenin/Wnt—Two genes, one from wingless fruit flies (*Drosophila melanogaster*) and one for a protooncogene causing mammary tumors (wingless and int-1, respectively) were found to encode identical proteins, and so the new name Wnt was generated (104). Wnt family proteins are secreted lipid-modified glyco-proteins with highly conserved cysteine residues (105). The extracellular Wnt glycoproteins bind to cell surface receptors to stimulate intracellular events. The best characterized Wnt signaling pathway is the canonical Wnt/ β -catenin signaling pathway. There are also one or more “non-canonical” or β -catenin-independent Wnt signaling pathways that are less well understood, and that act in a β -catenin-independent manner, leading to changes to cytoskeletal dynamics, adhesion, and motility (106). The highly conserved canonical Wnt/ β -catenin signaling pathway is activated by the binding of Wnt ligand to the receptors frizzled (FZD) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), triggering a series of downstream events that culminate in the cytosolic accumulation and nuclear translocation of the multifunctional protein β -catenin. In the absence of active Wnt ligands, β -catenin is bound to the scaffold proteins axis inhibition protein and adenomatosis polyposis coli (APC) and is constitutively

phosphorylated at 4 N-terminal residues via interaction with glycogen synthase kinase (GSK)-3 β . Accumulated β -catenin then translocates to the nucleus, where it interacts with transcription factor T-cell factor (TCF) and/or lymphoid enhancer factor (LEF) and regulates the expression of target genes that mediate the ultimate effects of this pathway on cellular processes including cell fate, proliferation, and migration. Wnt pathways have been intimately linked to cancer.

Numerous reports indicate that curcumin downregulates the Wnt/ β -catenin signaling pathway. Jaiswal et al. (107) observed that curcumin induced caspase-3-mediated cleavage of β -catenin, E-cadherin, and APC; decreased transactivation of β -catenin/TCF/LEF; decreased promoter DNA-binding activity of the β -catenin/TCF/LEF complex; and decreased levels of c-myc protein in human colon cancer cells. Ryu et al. (108) reported that curcumin derivatives inhibit the Wnt/ β -catenin pathway by decreasing the amount of the transcriptional coactivator p300. The inhibition of Wnt/ β -catenin by curcumin was also found in estrogen receptor (ER)-positive (MCF-7) and ER-negative (MDA-MB-231) breast cancer cells (109). Interestingly, it was found that curcumin could inhibit mammosphere formation and could also decrease the amount of aldehyde dehydrogenase-positive cells in normal and malignant breast cells through the inhibition of Wnt signaling, suggesting the inhibitory effects of curcumin on breast cancer stem cells (110). Other than curcumin, the spice-derived nutraceuticals ursolic acid (111) and xanthohumol (112) also inhibit β -catenin and thus have anti-cancer properties.

Sonic Hedgehog—Hedgehog (Hh) was first discovered by Christiane Nusslein-Volhard and Eric Wieschaus nearly in 1980 as a “segment-polarity” gene that controls *Drosophila* embryonic cuticle pattern (113). Hh signaling is important not only in fruit flies, where it serves to pattern their embryonic cuticles and adult appendages, but also in humans, where it helps to determine cell fate and numbers in brains and spinal cords, to pattern limbs and internal organs, and even to regulate body height (114). However, in the past few years, it has become clear that aberrant activation of the Hh signaling pathway can lead to cancer (115,116). Emerging evidence implicates the activation of Hh signaling in the development of a variety of cancers including basal cell carcinomas, medulloblastomas, leukemia, glioma, and cancers of the gastrointestinal, lung, ovary, breast, prostate, and colon (117). The activation of Hh signaling is driven by endogenous expression of Hh ligands such as Sonic and Indian Hh. Key regulatory components of the Hh pathway signaling include Smoothed (SMO), a 7-transmembrane domain cell surface protein essential to pathway activation, and Patched homologue 1 (PTCH1), a cell surface receptor protein that serves as a primary repressor of SMO. Binding of any of 3 Hh ligands to PTCH1 relieves PTCH1 repression of SMO, leading to downstream pathway activation including modification of the 3 GLI family transcription factors (GLI1–GLI3), which in turn promote transcription of genes regulating cell growth and differentiation (117). Activation of the Hh pathway is also associated with poorly differentiated and more aggressive tumors (118, 119). These observations have sparked vigorous interest in the development of novel inhibitors of the Hh pathway.

Recently, Elamin and colleagues (120) reported that curcumin inhibited the Shh-GLI1 signaling pathway by downregulating the Sonic hedgehog (Shh) protein and its most important downstream targets GLI1 and PTCH1 in human medulloblastomas cells. Zerumbone was shown to exert cytotoxic activity in pancreatic cancer cells. This sesquiterpene suppressed GLI-mediated transactivation and led to downmodulation of Hh-related gene expression in PANC1 pancreatic cancer cells, which express Hh/GLI components (121). These results indicate that a spice nutraceutical may represent great promise as Shh-targeted therapy for cancer treatment.

Growth Factors

Most growth factors work through their specific receptors to mediate signals. Receptor tyrosine kinases (RTKs) are the high-affinity cell surface receptors for many polypeptide growth factors. Of the 90 unique tyrosine kinase genes identified in the human genome, 58 encode RTK proteins. Some protein tyrosine kinases are considered attractive targets for the therapy of malignant disease. In selected cancers, activating mutations in a tyrosine kinase appear to be etiologic, initiating the transformation from a benign to a malignant state. However, the drugs targeting RTK produced adverse effects and development of secondary resistance so new inhibitors of these factors are required.

EGFR—Aberrant EGFR signaling is a major characteristic of many human malignancies including breast cancer. Since the discovery of EGF in the 1960's and its receptor in the 1980s (122,123), our understanding of the EGF/EGFR pathway has been significantly advanced. EGFR is now considered a major oncogenic factor and an attractive therapeutic target (124). A transmembrane RTK, it plays a central role in regulating cell division and death. EGFR belongs to the HER family of receptors, which is composed of 4 related proteins (EGFR [HER1/ErbB1], ERBB2 [HER2], ERBB3 [HER3], and ERBB4 [HER4]). The HER receptors are known to be activated by binding to different ligands, including EGF, transforming growth factor- α , heparin-binding EGF-like growth factor, amphiregulin, betacellulin, and epiregulin. It plays a role in protein phosphorylation and in malignant transformation (125).

So far, 3 anti-EGFR agents have been approved for clinical use: gefitinib (Iressa) for non-small-cell lung cancer, the monoclonal EGFR antibody cetuximab (Erbix) for metastatic colorectal cancer, and most recently, erlotinib (Tarceva) for metastatic non-small cell lung cancer. These remain in clinical trial and their efficacy is uncertain. In any case, additional drugs that inhibit EGFR are urgently needed, and nutraceuticals are among the candidates. Curcumin, for example, inhibits the ligand-stimulated activation of EGFR, indicating that it has the potential to break the autocrine loops that are established in several advanced cancers (126). Curcumin inhibits EGFR in numerous cancer cells including breast (127), colon (102), prostate (128), lung (129), and head and neck (130) cancer. Ursolic acid suppresses the phosphorylation of EGFR, in direct relation to its cell growth inhibitory effect and also suppresses EGF-stimulated cell proliferation in human colorectal cancer cells (131). Thoenissen et al. (132) demonstrated that capsaicin causes cell-cycle arrest and apoptosis in ER-positive and -negative breast cancer cells in vitro by modulating the EGFR/HER-2 pathway. Capsiate, a capsaicin analog with an ester bond instead of the amide bond between the vanillyl moiety and the fatty acid chain, inhibits UVB-induced EGFR activation, which reduces the expression of inflammatory mediators, such as cytokines and COX-2 and angiogenic factors in vitro and decreases UVB-induced skin damage in vivo (133).

HER2—Growth of human breast cells is closely regulated by steroid hormone as well as peptide hormone receptors. Members of both receptor classes are important prognostic factors in human breast cancer. Clinical data indicate that overexpression of the HER-2 gene is associated with an ER-negative phenotype. Different ligand binding to HER-2 receptors results in dimerization and activation of their intrinsic kinase activity followed by phosphorylation of specific tyrosine residues in the receptor cytoplasmic tails. These phosphorylated tyrosines, in turn, provide recognition sites for intracellular signaling intermediates, which link RTKs to downstream transduction cascades (134). The selection and combination of pathways activated ultimately result in changes in gene expression, thereby triggering the appropriate biological response to the extracellular cues received. Driven by the binding specificities of the bivalent, EGF-related peptide ligands and the

complement of receptors available on the cell, HER-2 receptors form different homodimeric and heterodimeric complexes (135). Herceptin, an antibody against the HER-2 for breast cancer patients, binds to the extracellular domain of receptors in the same way, but because its target c-erbB2 has no known directing ligand, it presumably acts by other mechanisms (136). Although these approaches look very promising, confounding issues remain, the most important being side effects and drug resistance.

A nutraceutical alternative, curcumin, has been shown to not only inhibit the tyrosine kinase activity of this receptor but also to deplete the protein itself by interfering with the function of the ATP-dependent GRP94 chaperone protein, which is involved in the maintenance of the properly folded state of the receptor (137). Jung et al. (138) found that curcumin increased the association between CHIP, a chaperone-dependent ubiquitin ligase, and erbB2 (also called HER2), and thus induced ubiquitination and degradation of this receptor. Moreover, they found that curcumin's Michael reaction acceptor functionality appeared to be the pharmacophore responsible for its ability to promote erbB2 degradation. Curcumin also inhibits cell proliferation and invasion through modulation of HER2 in gastric cancer cells (139).

VEGFR—VEGF is a signal protein produced by cells that stimulates the growth of new blood vessels. Its receptor VEGFR is an important signaling protein involved in both vasculogenesis (the formation of the circulatory system) and angiogenesis (the growth of blood vessels from preexisting vasculature). Endothelial cells express 3 different VEGFR: VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). These all belong to the family of RTKs (140). Structurally, all VEGF receptors contain 7 immunoglobulin-like extracellular domains, 1 transmembrane region, and an intracellular split tyrosine kinase domain (141). VEGF signaling is activated by binding of the growth factor to the receptor, which leads to dimerization. Dimerization, in turn, triggers kinase activation (142). The angiogenic response of VEGF varies between different organs and is dependent on the genetic background of the animal. However, mitogenic activity in endothelial cells is mainly mediated by VEGFR-2, leading to their survival, proliferation, migration, and differentiation.

Several spice-derived nutraceuticals have been shown to downregulate VEGF signaling in vitro and others have been shown to prevent new blood vessel formation in vivo. [6]-Gingerol blocks capillary-like tube formation in endothelial cells, and inhibited sprouting of endothelial cells in rat aorta secretion in human endothelial cells in response to VEGF in vitro (143). Gambogic acid inhibits VEGFR2 signaling, thus inhibiting angiogenesis and prostate tumor growth (144).

Insulin-Like Growth Factor (IGF) 1-Receptor—IGFs exert multiple effects on glucose, fat, and protein metabolism. IGFs also play important roles in regulating cell proliferation, differentiation, apoptosis, and transformation (145). The IGF family consists of 2 ligands (IGF-I and IGF-II), 2 receptors (IGF-IR and IGF-IIR), 6 high-affinity IGF-binding proteins (IGFBP1–6), and other low-affinity IGFBP-related proteins. The interaction between ligand-receptor induces a conformational change in receptor subunits, resulting in activation of the tyrosine kinase of the cytoplasmic domain of IGF-IR. Phosphorylation of adaptor proteins, such as insulin receptor substrate-1 or -2, Src- and collagen-homology, and growth factor receptor-binding protein 2, leads to binding of additional proteins, allowing for signal transduction along several specific pathways. Some of the key pathways and their endpoints include phosphorylation of mitogen-activated protein kinase (MAPK) and a subsequent increase in proliferation, activation of PI3K, leading to decreased apoptosis, and modulation of mammalian target of rapamycin (mTOR), resulting in translational adaptation (146). The IGF system has been implicated in several

human malignancies, including various epithelial cancers, sarcomas, multiple myeloma, melanoma, and childhood cancers (147). More recent studies have suggested that high circulating IGF-I levels and/or low IGFBP3 levels are associated with increased risk of several cancers including breast (148), prostate (149), lung (150), colorectal (151), and bladder (152). The negative correlation between IGFBP3 levels and cancer risk is consistent with a protective role of IGFBP3.

It is worth mentioning a chemoprevention approach to therapeutics, given that many agents have the potential of upregulating the IGFBPs. A study conducted by Xia et al. (153) demonstrated that curcumin decreased the secretion of IGF-1 with a concomitant increase of IGFBP-3 in a dose-dependent manner. Thus, the IGF-1-stimulated IGF-1R tyrosine kinase activation was also abrogated by curcumin in human breast cancer cells. Thus, in colorectal cancer cell lines, curcumin enhanced the effect of FOLFOX (5-fluorouracil [5-FU] or 5-FU plus ox-aliplatin) on cell proliferation suppression and apoptosis. These changes were associated with decreased expression and activation (tyrosine phosphorylation) of several receptors, including IGF-1R, and upregulation of IGFBP-3.

Platelet-Derived Growth Factor (PDGF) Receptor—PDGF is the principal mitogen in serum for mesenchymal cells and consists of a family of A, B, C, and D polypeptides that promote cell migration, proliferation, and survival by binding to their cognate homo- or heterodimeric tyrosine kinase receptors, PDGFR α and PDGFR β (154,155). Enhanced signaling of PDGF has been implicated in the pathogenesis of atherosclerosis, balloon injury induced restenosis, pulmonary fibrosis, angiogenesis, and tumorigenesis (156). In malignant cells, autocrine function of PDGF plays a role on tumor growth by overexpression or hyperactivation of PDGFRs, or by PDGF stimulation of angiogenesis within the tumor. We see only constitutive activation of PDGFR α or PDGFR β in myeloid cells, and activating mutations of PDGFR α are seen in gastrointestinal tumors. Active PDGFR α was also found in non-small-cell lung cancer (157).

Two main approaches have been taken toward the inhibition of cancer growth when PDGF-PDGFR signaling is activated: 1) direct targeting of tumor cells in which PDGF signaling is activated and 2) indirect inhibition of tumors by targeting pericytes to block tumor angiogenesis independently of PDGF activity. Some natural compounds, such as curcumin and gambogic acid, have been identified as inhibitors of the activation of PDGFR and as blockades of the PDGF-mediated pathway. Yang et al. (158) showed that curcumin-inhibited cell migration, proliferation, and collagen synthesis by attenuating PDGF signal transduction, and inhibited the binding of PDGF to its receptors in vitro and neointima formation after carotid artery injury in rats. Another study, conducted by Lin and Chen (159), showed that the interruption of the PDGF and EGF signaling pathways by curcumin stimulates expression of PPAR γ in activated rat hepatic stellate cells in vitro. Recently, Zhao and Huang (160) demonstrated that curcumin blocks the expression of PDGF-BB, PDGFR β , and ERK1, which might explain curcumin's antifibrosis activity. Beside curcumin, dehydrozingerone, derived from ginger, and its structural analog isoeugenol also elicited a concentration-dependent inhibition of PDGF-stimulated VSMC migration, proliferation, collagen synthesis, and PDGF/H₂O₂-stimulated phosphorylation of PDGFR β and downstream Akt in VSMC cells (161). A study conducted by Liu et al. (162) showed that gambogic acid-induced G0/G1 cell cycle arrest and cell migration inhibition by suppressing PDGFR β tyrosine phosphorylation and Rac1 activity in rat aortic smooth muscle cells.

Protein Kinases

Of the 25,000 genes in the human genome, there are more than 500 protein kinases that might make targets for drug discovery in cancer. A large number of inhibitors of these protein kinases have been designed and have undergone clinical trials; however, the efficacies are not proved.

PI3K—PI3K signaling plays a pivotal role in translating the detection of extracellular cues into alterations in a variety of cellular functions. It belongs to a large family of PI3K-related kinases. A key downstream effector of PI3K is the serine-threonine kinase Akt, which in response to PI3K activation, phosphorylates and regulates the activity of a number of targets including kinases, transcription factors, and other regulatory molecules (163). The PI3K/Akt signal transduction cascade has been investigated extensively for its roles in oncogenic transformation through its involvement in cell cycle progression, apoptosis, and neoplastic transformation. The amplification of the genomic region containing PIK3CA, the gene coding for the p110 alpha subunit of PI3K, has been identified in 40% of cases of ovarian cancer (164). Activating mutations may occur in as many as 35% of the cases of breast cancer and is associated with a poor prognosis (165). Modifications of PIK3CA have also been identified in colon, brain, and lung cancers (166). PI3K also has a role in the metastatic phenotype (167).

A few nutraceuticals have demonstrated the capability to inhibit PI3K. Ursolic acid treatment moderately decreased PI3K levels in 2 endometrial cancer cell lines, SNG-II and the poorly differentiated HEC108 cell line, and thus induced apoptosis (168). Recently, Tang and colleagues (169) showed that the proapoptotic effects of ursolic acid were mediated by activation of caspase-3 and downregulation of survivin and were highly correlated with inactivation of PI3K/Akt/survivin pathway in human HepG2 cells. Lee et al. (170) reported that diosgenin inhibits melanogenesis by activating the PI3K pathway and also suggested that diosgenin may be an effective inhibitor of hyper-pigmentation. Curcumin-mediated apoptotic effects were observed in T-cell acute lymphoblastic leukemia malignant cells: curcumin suppressed constitutively activated targets of PI3K-kinase (AKT, FOXO, and GSK3), leading to the inhibition of proliferation and induction of caspase-dependent apoptosis (171). A recent study conducted by Chen et al. (172) showed that the level of PI3K in melanoma tumor tissue was lower in a curcumin-treated group (once a day at a dose of 100 mg/kg for 18 days) than the untreated control group.

AMPK—The AMPK is a Ser/Thr protein kinase that was first identified by its activation by AMP and its ability to phosphorylate and inactivate enzymes involved in lipid and cholesterol synthesis (173). At the cellular level, AMPK is activated by metabolic stressors that deplete ATP and increase AMP (e.g., exercise, hypoxia, glucose deprivation) (174). AMPK activation enhances insulin sensitivity, inhibits hepatic glucose production, stimulates glucose uptake in muscle, inhibits fatty acid synthesis and esterification, and diminishes proinflammatory changes (175). It has been shown that AMPK phosphorylates tuberous sclerosis complex-2 (a bona fide tumor suppressor) to inhibit mTOR signals (176). This observation reveals a direct connection of AMPK with cancer. Recently, great attention has been given to linkage between AMPK and cancer. AMPK, by regulating several downstream targets, such as mTORC1, p53, FOXO, and fatty acid synthase, and associated metabolic processes, controls intracellular energy levels in order to maintain the cell growth rate at an appropriate level. Likewise, AMPK activation under metabolic stress or by pharmacological activators can regulate various processes, including cell cycle checkpoint, cell polarity, senescence, autophagy, and apoptosis (177,178).

As has been the case for many other targets in the cancer cell signaling pathways, curcumin strongly activates AMPK, in this case in a p38-dependent manner in CaOV3 ovarian cancer cells, thus inducing cell death (179). Stimulation of AMPK by curcumin downregulates PPAR γ in 3T3-L1 adipocytes and decreases COX-2 expression in MCF-7 cells, which in turn affects the proliferation rate (180). Another study, conducted by Lee et al. (181), showed that curcumin exerted antitumorigenic effects through modulation of the AMPK-COX-2 cascade. Curcumin exhibited a potent apoptotic effect on HT-29 colon cancer cells at concentrations of 50 micromol/L and above. These apoptotic effects were correlated with the decrease in phospho-Akt and COX-2, as well as the increase in phospho-AMPK. Another nutraceutical, capsaicin, has been reported to activate AMPK and increase apoptosis in HT-29 colon cancer cells (182).

Bcr-abl—The Bcr-abl oncoproteins are translocation-specific gene products of the Philadelphia chromosome that are detectable in most CML. Bcr-abl regulates proliferation, survival, differentiation, and trafficking of hematopoietic cells by transcriptional and posttranscriptional mechanisms that require tyrosine kinase activity and formation of multiprotein complexes whereby signaling molecules are assembled and activated in the cytoplasm and in the nucleus (183). The expression of Bcr-abl induces resistance of CML to apoptosis induced by chemotherapeutic drugs (184). Overexpression of Bcr-abl also prevent apoptotic cell death by inducing a Bcl-2 expression pathway in leukemia cells (185). Additionally, Bcr-abl has been shown to regulate c-jun gene expression, activation of c-Jun N-terminal kinase, and the ras pathway, which may also contribute to suppression of apoptosis, transformation, and tumorigenesis (186). Downstream mediators of Bcr-abl are known to regulate by the proteasome degradation.

Several proteasome inhibitors such as bortezomib could suppress Bcr-abl signaling (187). Curcumin inhibits the proliferation of K562 cells and the effect is correlated with down-regulation of p210bcr/abl (188). The underlying mechanism of curcumin in downregulating p210bcr/abl was identified later: It dissociates the binding of p210bcr/abl with Hsp90/p23 complex (189). A study conducted by William (190) showed that cur-cumin inhibits proliferation and induces apoptosis of leukemic cells expressing wild-type or T315I-BCR-ABL and prolongs survival of mice with acute lymphoblastic leukemia. Xantho-humol was also reported to suppress Bcr-abl signaling. Mon-teghirofo et al. (191) showed that xanthohumol strongly inhibited Bcr-abl expression at both mRNA and protein levels. Thus, xanthohumol could induce apoptosis in all of Bcr-abl+ cells, CML cells, and clinical samples and retain its cytotoxicity in imatinib mesylate-resistant K562 cells (191).

Raf/Ras—Raf is a member of a serine/threonine specific protein kinase family and is an immediate downstream target of Ras, which is implicated in the transduction of signals from the cell surface to the nucleus (192). In the resting cell, Ras is tightly bound to GDP. It is activated by binding of extracellular stimuli such as growth factors, RTKs, T-cell receptors, and phorbol-12 myristate-13 acetate (PMA) to cell membrane receptors. Activated Ras interacts specifically with effector proteins, thereby initiating cascades of protein-protein interactions that may finally lead to regulation of cell proliferation, apoptosis, migration, fate specification, and differentiation (193). Ras also can activate a number of signaling pathways, such as Raf/MEK/ERK (extracellular signal-regulated kinases) pathway, the MEKK/SEK/JNK pathway, a PI3K/Akt/NF- κ B pathway, a p120-GAP/p190-B/Rac/NF- κ B pathway, and a Raf/MEKK1/inhibitor- κ B kinase (IKK)/NF- κ B pathway (194).

Among the spicy nutraceuticals, curcumin showed strong inhibition on Ras and Ras-related pathways. Curcumin modulates the Ras signal transduction pathway and inhibits the proliferation of K562 cells (188). Limtrakul et al. (195) showed that orally consumed

curcumin (0.2% or 1% in diet) significantly inhibited 7,12-dimethylbenz(a)anthracene- and TPA-induced skin tumor formation and ras and fos gene expression in mouse skin.

mTOR—mTOR is a key regulator of various cellular processes needed for growth, cell-cycle progression, and cell metabolism. It belongs to the family of PI3K-related kinases, along with ATM, ATR, DNA-PK, and hSMG1, and it is considered one of the most commonly activated signaling pathways in human cancer (196). Rapamycin, first isolated from the soil of Rapa Nui (Easter Island), was the first identified potent inhibitor of the PI3K/AKT/mTOR pathway. Rapamycin specifically inhibits the function of mTOR, a protein thus named when its rapamycin-inhibiting properties were discovered. The mTOR pathway plays a critical role in cell growth, proliferation, motility, survival, apoptosis, autophagy, and angiogenesis (197). This pathway is activated by a variety of signals, including nutrients such as amino acids, glucose, and oxygen and/or mitogens.

The effects of curcumin on mTOR pathway have been demonstrated in a variety of cancer cell lines. Curcumin exhibits anticancer activity by inhibition of mTOR pathway in adenoid cystic carcinoma (198) intestinal microvascular endothelial cells (199), head and neck squamous cell carcinoma (200), glioblastoma (201), glioma (202,203), colorectal carcinoma (204), and prostate cancer (205,206). Interestingly, curcumin can disrupt the mTOR-raptor complex (207). Curcumin inhibited mTORC1 signaling not by inhibition of the upstream kinases, such as IGF-IR and PDK1, and altered the TSC1/2 interaction. Curcumin was able to inhibit phosphorylation of S6K1 and 4E-BP1 and to dissociate raptor from mTOR, leading to inhibition of mTORC1 activity. These data suggest that curcumin may represent a new class of mTOR inhibitor (207). A study conducted by Deeb et al. (208) showed that the apoptosis induced by xanthohumol was associated with the inhibition of prosurvival Akt, NF- κ B, and mTOR signaling proteins and NF- κ B-regulated antiapoptotic Bcl-2 and survivin in hormone-sensitive and hormone-refractory human prostate cancer cells line. Diosgenin was reported to suppress fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR, and JNK phosphorylation (209). De Angel et al. (210) showed that ursolic acid had potential to disrupt cell cycle progression and induce necrosis in a clonal MMTV-Wnt-1 mammary tumor cell by modulating Akt/mTOR signaling.

Proinflammatory Mediators

The mixture of cytokines and proinflammatory mediators that is produced in the tumor microenvironment has an important role in tumor development and progression. In other words, cancer cells can respond to proinflammatory mediators that promote growth, attenuate apoptosis, and facilitate invasion and metastasis. Therapeutic manipulations that are aimed at inhibiting or attenuating the production of proinflammatory mediators might prevent and treatment cancer.

Proinflammatory Cytokines

Tumor necrosis factor (TNF): α . Although TNF- α was first isolated as an anticancer cytokine, the major role of this cytokine has been as the key player to an onset of a wide variety of chronic diseases, including cancer (211). TNF- α has itself been shown to be one of the key molecules of inflammation due to its ability to activate NF- κ B (212). Almost all cell types, when exposed to TNF, activate NF- κ B, leading to the expression of inflammatory genes. These include COX-2, lipoxygenase (LOX)-2, cell-adhesion molecules, inflammatory cytokines, chemokines, and inducible nitric oxide synthase. TNF- α has been found to be a growth factor for most tumor cells (213). TNF- α is produced by cancer cells and can act as an endogenous tumor promoter. The role of TNF- α has been linked to all steps involved in tumorigenesis, including cellular transformation, promotion, survival,

proliferation, invasion, angiogenesis, and metastasis. Curcumin has been known to inhibit the expression of both TNF- α mRNA and TNF- α protein in mantle cell lymphoma cell lines. Suppression of TNF- α by curcumin led to inhibition of NF- κ B and cell proliferation, as was the case when TNF- α secretion was neutralized using anti-TNF- α antibody (214). [6]-Gingerol, vanillyl ketone from ginger, has been reported to exhibit a strong antiinflammatory activity and suppress TNF- α production in TPA-treated female ICR mice (215). The chalcone, cardamonin, has been identified as inhibitors of lipopolysaccharide (LPS)-and interferon-gamma-induced TNF- α production in monocytes (216). Similarly, eugenol (217,218), gambogic acid (219), thymoquinone (220,221), zerumbone (222), and xanthohumol (223) also exert inhibitory effects on the expression of TNF- α .

Interleukins: Several inflammatory interleukins including IL-1 β and IL-6 have been linked with tumorigenesis, which suggests that inflammation is associated with cancer development. Interleukins are involved in different steps in tumorigenesis. IL-1 β promotes growth and confers chemoresistance in pancreatic carcinoma cell lines (224). High levels of IL-1 β have a key role in chemoresistant in pancreatic cell lines. IL-1 β also affects the production of several angiogenic factors from tumor and stromal cells that promotes tumor growth through hyperneovascularization in lung carcinoma growth in vivo (225). Lewis et al. (226) reported that the elevation of IL-1 was found in human breast, colon, lung, head and neck cancers, and melanomas and correlated to bad prognoses in patients with cancer.

IL-6 has a direct growth stimulatory effect on many tumor cells through the activation of several signaling pathways. By activating Ras/Raf pathway, IL-6 induces proliferation of tumor cells (227,228). IL-6 upregulates the expression of cyclins D1, D2, and B1, and myc by activating STAT3 and thus promotes the cell cycle arrest (229–231). IL-6 also increases the expression of antiapoptotic gene products, including Bcl-2, Bcl-xL, Mcl-1, survivin, and XIAP, and contributes chemoresistance and constitutive activation of STAT-3 that are resistant to chemotherapeutic agents (34). IL-6 also plays an important role in promoting metastasis to organs other than the bone. By activating STAT3, IL-6 promotes the growth of metastatic tumors in the brain by upregulating basic fibroblast growth factor, MMP-2, and VEGF, which contribute to invasion and angiogenesis (16).

A number of studies have shown that the spices-derived nutraceuticals possess anticancer potential through the inhibition of interleukins. Curcumin has been found to suppress the expression of several inflammatory cytokines including IL-1 (232,233). Chan et al. (233) showed that curcumin, at 5 μ M, inhibited LPS-induced production of TNF- α and IL-1 in human macrophage cell line Mono Mac 6. Although the effect of cap-saicin on cytokine production is controversial, Kang et al. (234) showed that capsaicin suppressed the mRNA and protein expression of IL-6 from the adipose tissues and adipocytes of obese mice, whereas it enhanced the expression of the adiponectin gene and protein. This inhibitory effect of capsaicin is associated with suppression of NF- κ B and/or activation of PPAR γ . These results suggest that capsaicin may be a useful phytochemical for attenuating obesity-induced inflammatory responses. Recently, Jung et al. (235) examined the effects of diosgenin on the production of inflammatory mediators in macrophage stimulated by LPS/IFN- γ . The pretreatment with diosgenin resulted in the inhibition of the production of IL-1 and IL-6 but not that of TNF- α . Indeed, the inhibition of these inflammatory mediators appears to be at the transcriptional level, since diosgenin decreased LPS/IFN- γ -induced NF- κ B and AP-1 activity. These results indicate that diosgenin may exert its immunosuppressive effects by inhibiting proinflammatory cytokine expression. Murakami et al. (222) found that oral feeding of zerumbone significantly lowered the levels of IL-1 β [inhibitory rate (IR) = 34%], TNF- α (IR = 29%), and prostaglandin (PG) E2 (IR = 73%) and suppressed DSS-induced colitis mice model. Overall, the intervention of proinflammatory

cytokines, including TNF- α , IL-1 β , and IL-6, by using spicy nutraceuticals may be an attractive therapeutic strategy to prevent tumor progression and treat cancer.

Proinflammatory Enzymes

Cyclooxygenase (COX)-2: COX-2 is one of the key enzymes implicated in the modulation of inflammation and acts by catalyzing the rate-limiting step that leads to the formation of prostaglandins from arachidonic acid. It is also known to be regulated by NF- κ B, which mediates tumorigenesis. COX-2 has been implicated in the growth and progression of a variety of human cancers. Indeed, overexpression of COX-2 has been found in a number of cancers (236). Results from clinical studies have shown that dysregulation of COX-2 is correlated with a poor prognosis (236,237). Enhanced COX-2 expression has been found in colon cancer tissues from subjects with clinically diagnosed colorectal cancer (238). Cyclooxygenase regulates colon carcinoma-induced angiogenesis by modulating the production of angiogenic factors by colon cancer cells (239,240). Indeed, the dysregulation of COX-2 is found in invasive breast cancers, lung adenocarcinoma, and head and neck cancer cells (241–244). So far, the clinical strategy to target COX-2 has been via inhibition of its activity. Non-steroidal inflammatory drugs (NSAIDs) are the first class of inhibitors of COXs available on the market for a variety of diseases. However, intake of NSAIDs for a long period caused severe side effects, such as induced gastrointestinal problems or increased incidence of cardiovascular disease (245,246).

Among the spice-derived nutraceuticals, curcumin has been reported to suppress PG production; it has become clear that this compound plays multiple roles toward COX-2 regulation and directly prevents COX-2 gene expression (247). Ammon et al. (248) showed that curcumin exerts antiinflammatory properties in vivo animal models through inhibition of 5-LOX and 12-LOX activity in rat peritoneal neutrophils and COX activity in human platelets. Curcumin also revealed that this phenolic compound could inhibit chenodeoxycholate- or PMA-induced expression of COX-2 in several gastrointestinal cell lines (249). Treatment with chenodeoxycholate or PMA increased binding of AP-1 to DNA. This effect was also blocked by curcumin, leading to downregulation of COX-2. In addition to the above effects on gene expression, Zhang et al. found that curcumin directly inhibits the activity of COX-2 (249). Capsaicin suppresses the expression of both COX-1 and COX-2 by redox status-dependent regulation, leading to apoptosis in human SK-N-SH human neuroblastoma cells (250). [6]-Gingerol and structurally related pungent principles of ginger exert inhibitory effects on biosynthesis of PGs and leukotrienes through suppression of prostaglandin synthase or 5-LOX (251,252). It has been reported that eugenol is able to modulate COX-2 expression by inhibiting NF- κ B pathway in human osteoblast (253). Indeed, eugenol exhibited a significant inhibition of PGE₂ production (IC₅₀ = 0.37 μ M) and suppression of COX-2 expression in LPS-stimulated mouse macrophage cells (254). Eugenol inhibited the proliferation of HT-29 cells and the mRNA expression of COX-2 but not COX-1. This result suggests that eugenol might be a plausible lead candidate for further developing the COX-2 inhibitor as an antiinflammatory or cancer chemopreventive agent. Other than above compounds, cardamonin (216), DBM (255), gambogic acid (26), thymoquinone (256,257), and zerumbone (222) are known to suppress COX-2 expression or activity, thus have the potential to perturb tumorigenesis.

5-LOX: 5-LOX is a key enzyme in the metabolism of arachidonic acid to leukotrienes. Several studies suggest that there is a link between 5-LOX and carcinogenesis in humans and animals. In addition to the important role of leukotrienes as mediators in allergy and inflammation, these intermediates are also linked to pathophysiological events in the brain, including cerebral ischemia, brain edema, and increased permeability of the blood-brain barrier in brain tumors (258). The dysregulation of 5-LOX are also found in process of

colonic adenoma formation promoted by cigarette smoke (259). The expression of 5-LOX is also regulated by NF- κ B, and it has been linked with the progression and development of cancer of the kidney, breast, and pancreas (260–262). Several phytochemicals known to suppress 5-LOX are curcumin (255) and diosgenin (263). Hong and colleagues (255) showed that curcumin potently inhibited the activity of human recombinant 5-LOX, showing estimated IC₅₀ values of 0.7 μ M, respectively. The results suggest that curcumin affects arachidonic acid metabolism, inhibiting the catalytic activities of 5-LOX, and this activity may contribute to the antiinflammatory and anticarcinogenic actions of curcumin and its analogs.

Other Important Targets

Proteasome—The synthesis and degradation of protein is a tightly regulated process that is essential for cellular homeostasis. The degradation of as much as 80% of cellular proteins is regulated by the proteasomes. The latter compose a multicatalytic enzyme complex containing 1 catalytic core, the 20S proteasome, and 2 19S regulatory complexes. The proteolytic activity of the proteasome resides in the 20S proteasomal subunits, β 1, β 2, and β 5, which are responsible for caspase-, trypsin-, and chymotrypsin-like activities, respectively (264). Numerous proteins such as cyclins (265), p53 (266), Bax (267), p27 (268), and the inhibitor of NF- κ B (I κ B α) (269), which are, involved in carcinogenesis and cancer survival, are known as targets for proteasome. Thus, the inhibition of proteasome leads to accumulation of proapoptotic proteins and induces cell death in cancer cells (270,271).

Cancer cells are also known to be more sensitive to proteasome inhibition than normal cells, indicating the potential role of proteasome inhibitors as anticancer drugs (272). Indeed, a proteasome inhibitor, bortezomib (PS-341, Velcade) was approved by the Food and Drug Administration for the treatment of MM (272). Likewise, curcumin possesses inhibitory effects against proteasome, with its greatest potency being chymotrypsin-like activity (273). Inhibition of the proteasome activity by curcumin was associated with colorectal cancer cell apoptosis in vitro and regression of tumor growth in nude mice (273). Mori et al. (274) reported that capsaicin inhibited TNF- α -stimulated NF- κ B activation through suppression of degradation of I κ B α by inhibition of proteasome activity in human prostate cancer PC-3 cells. Recently, capsaicin was also reported to cause increased accumulation of ubiquitinated proteins as well as various target substrates, such as p53, Bax, and p27, thereby inducing cell death in mouse neuro 2a cells (275). Thymoquinone has been shown to possess 20S and 26S proteasome inhibition activity and induce the accumulation of p53 and bax, leading to apoptosis in cancer cells (276). The spice-derived chalcone, xantho-humol, also induced a proapoptotic pathway by its proteasome inhibitory properties and was able to induce endoplasmic reticulum stress in human chronic lymphocytic leukemia cell lines (277).

Epigenetic Changes—The term *epigenetic* (literally “over” or “upon” genetics) was coined by Conrad Waddington in 1942 and was used to explain why genetic variations sometimes did not lead to phenotypic variations and how genes might interact with their environment to yield a phenotype (278). But the word currently refers specifically to the study of mitotically and/or meiotically heritable changes in gene expression that are not attributable to a change in the DNA sequence. Epigenetic regulation includes DNA methylation, posttranslational histone modifications, and noncoding RNA-mediated silencing pathways. The disruption of such changes underlies a wide variety of pathologies, including cancer (279). Therefore, cancer is a multistep process derived from combinational crosstalk between genetic alterations and epigenetic influences through various environmental factors (280). Epigenetic mechanisms controlling gene transcription are often involved in cell proliferation, differentiation, and survival and are casually linked with

tumor development. Alterations in epigenetic processes, including chromatin modifications such as DNA methylation and histone acetylation, are common targets studied in cancer epigenomics (281). DNA methylation usually takes place at the 5' position of the cytosine ring within CpG dinucleotides, and its consequence is the silencing of genes and noncoding genomic regions. DNA methylation is mediated by a family of DNA methyltransferases (DNMT1–3) and can inhibit gene expression either by promoting the recruitment of methyl-binding domains, which in turn recruit histone-modifying and chromatin-remodeling proteins to the methylation sites, or by directly disrupting the recruitment of DNA-binding transcription factors. The methylation of DNA is generally associated with gene silencing (282). In contrast to DNA methylation, histone modifications are highly complex in terms of both the number of sites that can be modified and in the variety of possible modifications. The enzymes that add and remove such modifications are, respectively, histone acetyltransferases (HATs) and deacetylases (HDACs and sirtuins), methyltransferases and demethylases, kinases and phosphatases, ubiquitin ligases and deubiquitinases, SUMO ligases and proteases, and so on. Finally, these modifications recruit additional transcriptional regulators (283).

Among all the spice-derived nutraceuticals, curcumin has been examined maximally for epigenetic changes (284). Recent evidence has shown that curcumin inhibits DNMT activities and histone modification such as HDAC inhibition in tumorigenesis. Molecular docking of the interaction between curcumin and DNMT1 suggested that curcumin covalently blocks the catalytic thiolate of C1226 of DNMT1 to exert its inhibitory effect. Further, curcumin treatment with extracted genomic DNA from a leukemia cell line induced global hypomethylation (285).

Curcumin has been identified as a strong inhibitor for HATs in both in vitro and in vivo cancer models. Balasubramanyam et al. (286) showed that curcumin is a specific inhibitor of p300/CREB-binding protein (CBP) HAT activity, but not of p300/CBP-associated factor, in vitro and in vivo. Filter binding and gel HAT assays showed that acetylation of histones H3 and H4 by p300/CBP was strongly inhibited covalently by curcumin. Another study demonstrated that curcumin restored ultraviolet radiation-induced hyperacetylation in the promoter region of inflammatory-related genes ATF3, COX2, and MKP1 that are involved in inflammation (287).

Besides curcumin, Chen et al. (288) showed that ursolic acid increased histone H3 acetylation in HL60 cells. These results demonstrated that ursolic acid induces cell death partially through increasing acetylation of histone H3 and inhibition of HDAC activity.

CLINICAL TRIALS

Several clinical trials have been conducted with spice-derived nutraceuticals for prevention and treatment for cancer in human (Table 2).

Clinical Trials With Curcumin

Clinical trials with curcumin have been reported in a several cancers such as oral, vulva, breast, skin, liver, colorectal, pancreas, bladder, and cervical cancer (308).

Colorectal Cancer—Sharma and colleagues (289) studied the pharmacodynamic and pharmacokinetic effect of oral Curcuma extract in patients with advanced colorectal cancer. Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies received Curcuma extract daily for up to 4 mo. The extract was well tolerated, and dose-limiting toxicity was not observed. Neither curcumin nor its metabolites were detected in blood or urine, but curcumin was recovered from feces. Ingestion of 440 mg of Cur-cuma

extract for 29 days was accompanied by a 59% decrease in lymphocytic glutathione-*S*-transferase activity. At higher dose levels, this effect was not observed. Leukocytic M(1)G levels were constant within each patient and unaffected by treatment. Radiologically, stable disease was demonstrated in 5 patients for 2 to 4 mo of treatment. Another Phase I study conducted by the same group (290) showed that a daily dose of 3.6 g curcumin engendered 62% and 57% decreases in inducible PGE₂ production in blood samples taken 1 h after dose on days 1 and 29, respectively, in advanced colorectal cancer patients. Garcea et al. (309) conducted a pilot trial with 12 patients having hepatic metastasis from colorectal cancer who received 450–3,600 mg of curcumin daily, for 1 wk prior to surgery, to investigate whether oral administration of curcumin results in concentrations of the agent in normal and malignant human liver tissue sufficient to elicit pharmacological activity. They concluded that doses of curcumin required to furnish hepatic levels sufficient to exert pharmacological activity are probably not feasible in humans. Another dose-escalation pilot study, this one conducted by Plummer et al. (310), showed that a standardized formulation of Curcuma extract in 15 patients with advanced colorectal cancer revealed a dose-dependent inhibition of COX-2 activity, measured as basal and LPS-mediated PGE₂ production, in blood revealing the efficacy of curcumin in colorectal cancer.

Familial Adenomatous Polyposis—The clinical trial conducted by Cruz-Correa et al. (293) in patients with familial adenomatous polyposis (FAP) showed that curcumin could reduce adenomas in patient with FAP. Five FAP patients received curcumin (480 mg) and quercetin (20 mg) orally 3 times a day for 6 mo prior to colectomy. The number and size of polyps were assessed at baseline and after therapy. All 5 patients had a decreased polyp number (60.4%) and size (50.9%) from baseline with minimal adverse side effects and no laboratory abnormalities after a mean of 6 mo of treatment with curcumin and quercetin.

Various External and Internal Cancerous Lesions in Different Cancers—An early clinical trial with 62 cancer patients having external cancerous lesions of various sites (breast–37, vulva–4, oral–7, skin–7, and others–11) reported reduction in smell (in 90% patients), reduction in itching (in almost all patients), reduction in lesion size and pain (in 10% patients), and reduction in exudates (in 70% patients) after topical application of an ointment containing curcumin. In this study, an adverse reaction in terms of increased local itching was noticed in only 1 scalp melanoma patient out of the 62 patients evaluated (292).

In a Phase I clinical trial, a daily curcumin dose of 8,000 mg taken orally for 3 mo resulted in histological improvement of precancerous lesions in patients having uterine cervical intraepithelial neoplasm (in 1 out of 4 patients), intestinal metaplasia (in 1 out of 9 patients), bladder cancer (in 1 out of 2 patients), and oral leucoplakia (in 2 out of 7 patients) (299).

Metastatic Breast Cancer—An open-label phase I trial with metastatic breast cancer was conducted to investigate the feasibility and tolerability of the combination of docetaxel and curcumin (294). Fourteen patients were accrued in this open-label phase I trial. Curcumin was well tolerated at maximal tolerated dose, 8 g by mouth daily. Eight patients out of 14 had measurable lesions according to RECIST criteria, with 5 partial responses and 3 stable diseases. Some improvements as biological (decrease in carcinoembryonic antigen tumor marker across the treatment) and clinical responses (regression of nonmeasurable lesions) were observed in most patients. Further investigation is ongoing in a Phase II randomized clinical trial to confirm the efficacy of such a combination in advanced and metastatic breast cancer patients.

Multiple Myeloma—Studies conducted by our group showed that curcumin suppressed constitutive activation of NF- κ B, STAT3, and expression of COX-2 in the peripheral blood

mononuclear cell (PBMC) from multiple myeloma patients. Curcumin was given at 2, 4, 8, and 12 g/day orally, daily, which was well tolerated with no adverse events. Out of 29 patients, 12 patients continued treatment for 12 wk and 5 completed 1 full yr of treatment with stable disease (295).

Advanced Pancreatic Cancer—The results of phase II clinical trial from our group (296) showed that curcumin inhibited pancreatic cancer in patients. Twenty-five patients were enrolled in this study. Patients received 8 g of curcumin orally daily until disease progression, with restaging every 2 mo. Serum cytokine levels for IL-6, IL-8, IL-10, and IL-1 receptor antagonists and PBMC expression of NF- κ B and COX-2 were monitored. Out of 25 patients, 21 were evaluable for response. Two patients showed clinical biologic activity. One had ongoing stable disease for more than 18 mo; interestingly, 1 additional patient had a brief, but marked, tumor regression of 73%, accompanied by significant increases (4- to 35-fold) in serum cytokine levels. No toxicities were observed. Curcumin suppressed expression of NF- κ B, COX-2, and phosphorylated STAT3 in PBMC from patients (most of whom had baseline levels considerably higher than those found in healthy volunteers). This result suggested oral curcumin was well tolerated and, despite its limited absorption, has biological activity in some patients with pancreatic cancer.

Recently, another clinical trial was conducted to evaluate the safety and feasibility of combination therapy using curcumin with gemcitabine-based chemotherapy (297). Gemcitabine-resistant patients ($n = 21$) with pancreatic cancer received 8 g oral curcumin daily in combination with gemcitabine-based chemotherapy. No dose-limiting toxicities were observed in the phase I study, and oral curcumin 8 g/day was selected as the recommended dose for the phase II study. Median survival time after initiation of curcumin was 161 days (95% confidence interval 109–223 days) and 1-yr survival rate was 19% (4.4–41.4%). This result indicated that combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with pancreatic cancer and its efficacy warranted further investigation.

Prostatic Intraepithelial Neoplasia—Rafailov et al. (311) conducted phase I trial to investigate the effect of Zyflamend, a herbal preparation containing curcumin, against prostatic intraepithelial neoplasia (PIN). After 6 mo the biopsy revealed benign prostatic hyperplasia alone, and at the end of 18 mo biopsy was negative for cancer and PIN, indicating that the patient was free of cancer and PIN.

Clinical Trials With Ginger

Ginger (*Zingiber officinale*), an age-old spice, is best known for its role as a flavor for Asian and Indian kitchens. For the last 4 centuries, the powdered rhizome of ginger has been used in Indian (Ayurvedic) and traditional Chinese medicine to treat gastrointestinal complaints such as nausea and excessive flatulence. Recently, it has been shown to be effective in reducing experimental induced motion sickness, seasickness, postoperative nausea, and vomiting, and nausea-vomiting of pregnancy (312). Pillai et al. (302) conducted a clinical trial to investigate the effect of ginger against acute chemotherapy-induced nausea and vomiting (CINV) in cancer patients. Acute CINV was defined as nausea and vomiting occurring within 24 h of start of chemotherapy (days 1–4) and delayed CINV as that occurring after 24 h of completion of chemotherapy (days 5–10). They found that ginger root powder was effective in reducing the severity of acute and delayed CINV as additional therapy to ondansetron and dexamethasone in patients receiving high emetogenic chemotherapy. Another study conducted by Livine et al. (304) demonstrated that ginger with high-protein meals reduced the delayed nausea of chemotherapy and reduced the need for antiemetic medications. However, in a phase II, randomized, placebo-controlled clinical

trial, the efficacy of ginger for chemotherapy-associated nausea in patients with cancer was evaluated: The addition of ginger to currently recommended antiemetic regimens did not improve the CINV (303,312,313). These results suggest that the use of ginger for reduced acute CINV require additional study before further clinical trials are conducted.

Clinical Trials With Capsaicin

Capsaicin (trans-8-N-vanillyl-6-nonenamide) is the primary irritant in *Capsicum* fruits, both green and red peppers, that are widely used as spices. Recently, the structural analogues of capsaicin, such as capsiate and dihydrocapsiate, the nonirritating capsinoids from CH-19 sweet pepper, possess the anticancer as well as chemopreventive activity to capsaicin but without the pungent property (314). These analogues might be considered replacements for capsaicin with potential in the prevention of cancer.

There has been a turning point on the question of using capsaicin as a pain relief. One pilot study examined the ability of oral capsaicin to provide temporary relief of oral mucositis pain in patients with cancer. Oral capsaicin in a candy (taffy) vehicle that produced substantial pain reduction in 11 patients with oral mucositis pain from cancer therapy. However, this pain relief was not complete for most patients and was only temporary. Results from this study suggested that an additional research would be required to fully utilize the properties of capsaicin desensitization and thus optimize analgesia (306).

Ellison and colleagues (305) performed a clinical trial to examine the efficacy of capsaicin cream (0.075%) for management of surgical neuropathic pain in cancer patients. Ninety-nine assessable cancer patients participated in this placebo-controlled trial. After stratification, patients received treatment with 0.075% capsaicin cream for 8 wk followed by 8 wk of an identical-appearing placebo cream or vice versa. A capsaicin/placebo cream was to be applied to the site with pain, 4 times daily. The results showed that the capsaicin cream arm had substantially more pain relief ($P = 0.01$) after the first 8 wk, with an average pain reduction of 53% vs. 17%. After completion of the 16-wk study, patients were asked which treatment period was most beneficial. The 60% of the responding patients chose the capsaicin arm, 18% chose the placebo arm, and the rest chose neither. The results indicated that topical capsaicin cream reduced postsurgical neuropathic pain and, despite some toxicity, was preferred by patients over a placebo. Taken together the proof of a practically safe dose of capsaicin should be established before further clinical trials.

Clinical Trials With Anethole

A trial reported by Lam et al. (307) investigated the effects of anethole dithiolethione (ADT) in smokers with bronchial dysplasia. ADT belongs to the dithiolethione class of organosulfur compounds, which have antioxidant, chemotherapeutic, radioprotective, and chemopreventive properties. In the lesion-specific analysis, the progression rate of preexisting dysplastic lesions by 2 or more grades and/or the appearance of new lesions was statistically significantly lower in the ADT group (8%) than in the placebo group (17%) ($P < 0.001$). This study suggests that ADT may exhibit chemopreventive potential for lung cancer control.

LIMITATIONS AND ADVERSE EFFECTS OF SPICE

The majority of the literature from *in vitro* and *in vivo* studies suggest that spice possesses potent chemopreventive activities. However, there are reports that some spices or their components exhibit harmful effects in some people. For instance, turmeric-induced skin allergies have been reported among workers in turmeric factories. Cases of allergic contact dermatitis and contact urticaria from curcumin mediated by 2 different mechanisms have been reported (315). There are also similar reports with ginger, nutmeg, and oregano (316).

Although the anticancer potential of capsaicin was well accepted, its beneficial effect in cancer patients is controversial. An early Italian case-control study revealed that chili consumption was protective against stomach cancer (11), whereas epidemiologic study from Mexico City showed that chili consumers were at greater risk of developing stomach cancer than nonconsumers (317). Indeed, there is evidence that capsaicin or chili extracts may also act as cocarcinogen or tumor promoter (318). There is not enough evidence documenting whether or not smaller amounts of a greater variety of spices, known to have similar health effects, would result in comparable health benefits. However, it is an area requiring further study.

CONCLUSIONS

Although the earliest evidence of the use of spice by humans was around 5,000 B.C., their biological activities have been investigated last several decades. Today, considerable data regarding the beneficial effect of spice nutraceuticals on prevention and treatment of cancer in preclinical settings are available. However, the translation of the *in vitro* efficacy of nutraceuticals in the prevention of cancer to clinical use requires attention to establishing physiologically relevant concentrations and chronic exposures to imitate *in vivo* conditions. For optimizing the desired physiological response, further consideration should be given to the significant intake of nutraceuticals, their duration, and their validation in suitable animal models. A huge amount of data from *in vivo* settings using experimental rodents supports the anticancer potential of spice-derived nutraceuticals. However, clinical trials or further studies with these nutraceuticals must be done in order to elucidate and understand their efficacy in the treatment and prevention of human cancer. There is also a potential that these spices, when consumed in combination, exhibit synergistic potential. This is clearly the case when turmeric is combined with black pepper. This needs to be further explored. Spices should be viewed as a part of an everyday lifestyle rather than as pharmaceuticals. In addition, although over 100 pilot clinical trials have been done with spices and their components in human subjects, more evidence is still needed to demonstrate their potential in prevention and treatment of chronic inflammatory disease, including cancer. The possibility for spice-derived nutraceuticals to exhibit multiple effects and for ability to counteract treatment regimens exists, just as the potential of a once-unknown world was first shown by the explorers Christopher Columbus and Vasco da Gama in their search for valuable spices several centuries before.

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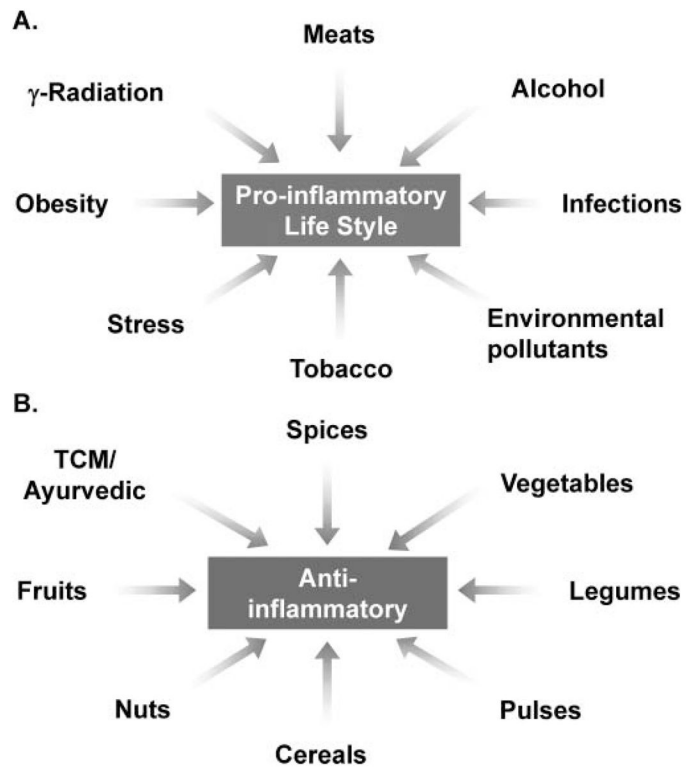


FIG. 1. Various life factors induced proinflammatory lifestyle related to tumorigenesis and chemopreventive agents, including spices, suppress cancer.

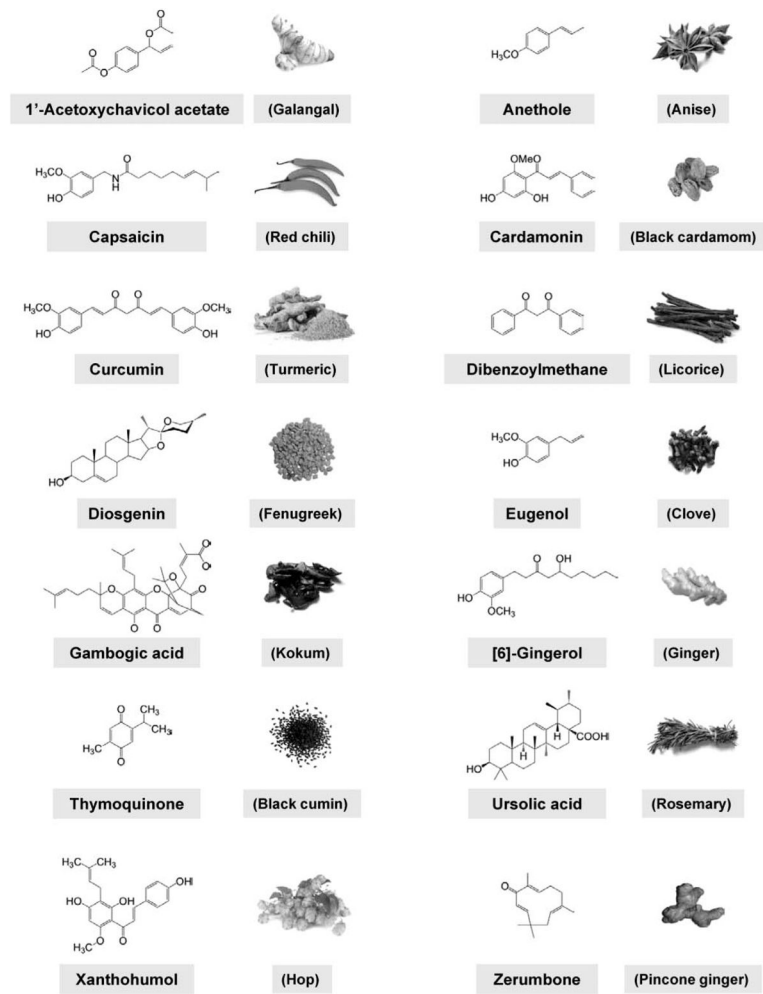
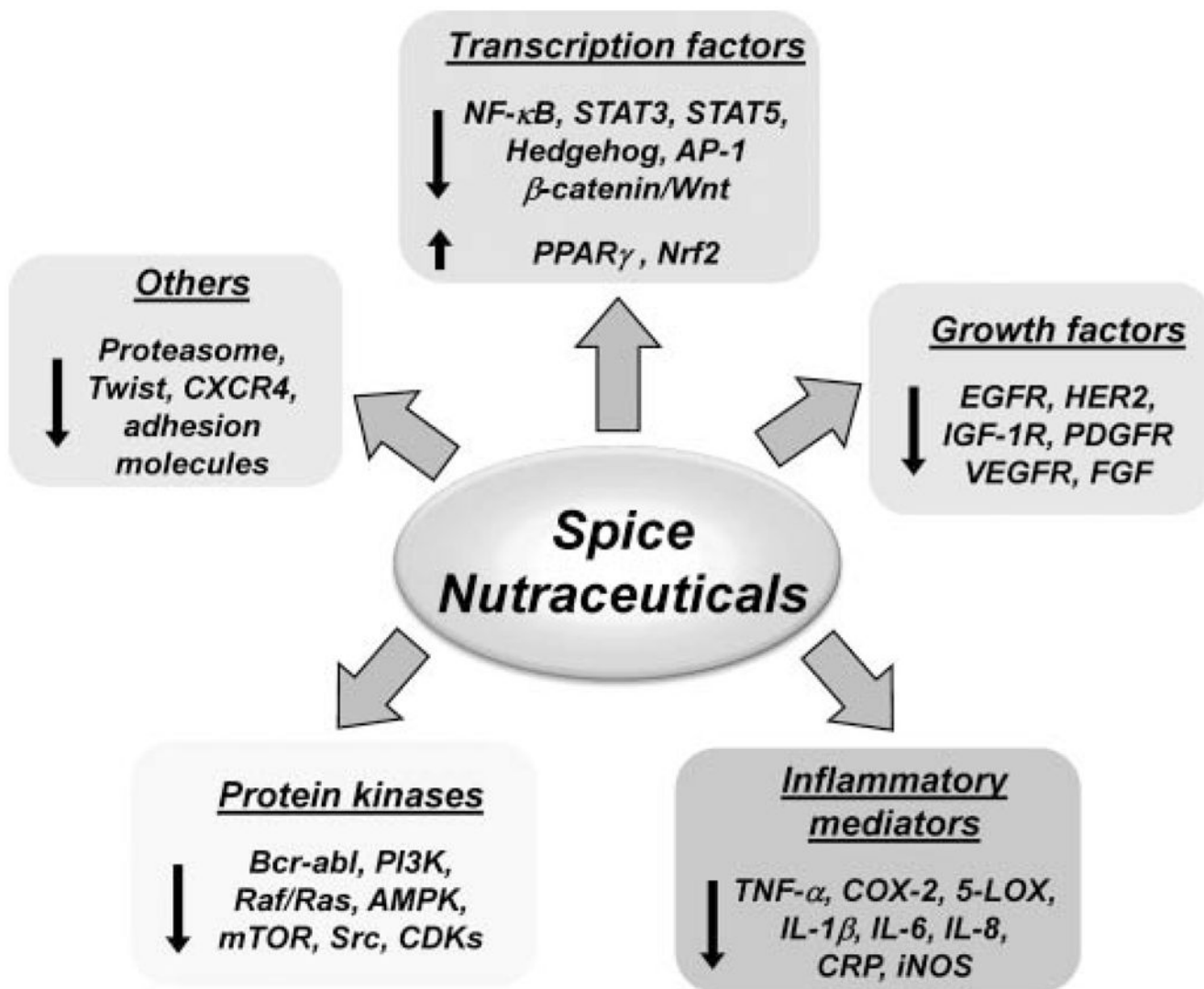


FIG. 2.
Chemical structures of selected spice-derived nutraceuticals.

**FIG. 3.**

Molecular targets of spice-derived nutraceuticals in cancer. The nutraceuticals from spices modulates multiple targets including transcription factors, growth factors, and kinases involved in cancer cell growth, proliferation, survival, and metastasis. The single-head arrow indicates activation or positive regulation, whereas the blunt-end arrow indicates inhibition or negative regulation. 5-LOX indicates 5-lipoxygenase; AMPK, 5' adenosine monophosphate (AMP)-activated protein kinase; AP-1, activator protein 1; CDK, cyclin-dependent kinase; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CXCR4, C-X-C chemokine receptor type 4; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; IGF-1R, insulin-like growth factor-1 receptor; IL-1 β , interleukin 1beta; iNOS, inducible nitric oxide synthase; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor-kappa B; NRF-2, NF-E2-related factor 2; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; PPAR γ , peroxisome proliferator-activated receptor gamma; STAT3, signal transducer activator of transcription 3; TNF- α , tumor necrosis factor alpha; VEGFR, vascular endothelial growth factor receptor.

TABLE 1

A list of spice-derived nutraceuticals and natural sources

Nutraceuticals	Sources	Botanical name
[6]-Gingerol	Ginger, marjoram	Zingiber officinale Roscoe; Origanum majorana
Anethol and analogues*	Anise, fennel, cloves, licorice, star anise, tarragon	Pimpinella anisum; Foeniculum vulgare; Syzygium anisatum; Glycyrrhiza glabra; Illicium verum; Artemisia dracunculus L.
Capsaicinoids	Pepper, red chili, paprika	Capsaicum spp.; Euphorbia spp.; C. annum; C. frutens
Curcumin	Turmeric	Curcuma longa
Dibenzoylmethane	Licorice	Glycyrrhiza sp.
Diosgenin	Fenugreek, crape ginger	Trigonella foenum graecum; Costus speciosus
Eugenol	Clove, nutmeg, cinnamon, basil, bay leaf, allspice, coriander	S. aromaticum; Myristica fragrans; genus Cinnamomum; Ocimum basilicum; Laurus nobilis; Pimenta dioica; Coriandrum sativum
Gambogic acid	Gamboge	Garcinia sp.
Thymoquinone	Blackseed	Nigella sativa
Ursolic acid	Basil, salvia, rosemary, berries	Rosmarinus officinalis; O. sanctum; Aronia melanocarpa; Oxycoccus quadripetalus; Origanum majorana; Diospyros melanoxylon; Salvia przewalskii Maxim
Xanthohumol	Hop	Humulus lupulus L.
Zerumbone	Pinecone ginger	Zingiber zerumbet; Curcuma ochrorhiza; C. heyneana

TABLE 2

A list of clinical trials with spice-derived nutraceuticals in patients with different cancer

Cancers	Dose/frequency	Patients	End point modulation	References
Curcumin				
Colorectal cancer	36–180 mg/day × 120 days	15	Decreased lymphocytic GST	(289)
Colorectal cancer	450–3,600 mg/day × 120 days	15	Lowered inducible serum PGE2 levels	(290)
Colorectal cancer	450–3,600 mg/day × 7 days	12	Decreased M1G DNA adducts	(291)
External cancer lesions		62	Reduction in lesion size and pain	(292)
FAP	480 mg × 3/day × 180 days	5	Decrease in the number of polyps was 60.4%	(293)
Metastatic breast cancer	500–8,000 mg/day × 7 days	14	Reached to RECIST criteria (57%) with 5 PR and 3 SD	(294)
Multiple myeloma	2–12 g/day	24	Inhibits NF- κ B, COX-2 and pSTAT3	(295)
Pancreatic cancer	8 g/day	25	73% reduction in tumor in one patient	(296)
Pancreatic cancer	8 g/day	21	8 g/day of curcumin is safe and feasible	(297)
Pancreatic cancer	8 g/day × 3 × 4 wk	17	One of 11 patients had PR, 4 had SD, and 6 had tumor progression	(298)
Precancerous lesions	8 g/day × 90 days	19	Well tolerated up to 3 mo	(299)
Precancerous lesions *	1 g/day × 7 days	25	Increased serum and salivary vitamins C and E	(300)
Prostate cancer or PIN **	100 mg/day × 180 days	100	Decreased PSA level	(301)
Ginger extracts				
Bone sarcoma		57	Moderate to severe vomiting	(302)
Various primary sites	1–2 g/day	162	No differences in the prevalence of nausea, vomiting, CINV, or severity	(303)
Various primary sites	250 mg × 2/day × 3 days	28	Reduced the delayed nausea of chemotherapy, reduced use of antiemetic medications	(304)
Capsaicin				
Pancreatic cancer	0.075% cream × 56 days	49	Reduced pain	(305)
Various primary sites	0.02–0.048 g × 2–4 days	11	Reduced pain temporary	(306)
Anethole				
Lung cancer ***	75 mg/day × 6 mo	112	Lowered progression rate	(307)

* Patients with oral leukoplakia, oral submucous fibrosis, or lichen planus.

** Combination of curcumin (100 mg) + isoflavone (40 mg).

*** Anethole dithiolethione.

FAP indicates familial adenomatous polyposis; CINV, chemotherapy-induced nausea and vomiting; PR, partial response; SD, stable disease; RECIST, response evaluation criteria in solid tumors.