

MINIREVIEW

Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis

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Despite the fact cancer is primarily a preventable disease, recent statistics indicate cancer will become the number one killer worldwide in 2010. Since certain cancers are more prevalent in the people of some countries than others, suggests the role of lifestyle. For instance cancer incidence among people from the Indian subcontinent, where most spices are consumed, is much lower than that in the Western World. Spices have been consumed for centuries for a variety of purposes—as flavoring agents, colorants, and preservatives. However, there is increasing evidence for the importance of plant-based foods in regular diet to lowering the risk of most chronic diseases, so spices are now emerging as more than just flavor aids, but as agents that can not only prevent but may even treat disease. In this article, we discuss the role of 41 common dietary spices with over 182 spice-derived nutraceuticals for their effects against different stages of tumorigenesis. Besides suppressing inflammatory pathways, spice-derived nutraceuticals can suppress survival, proliferation, invasion, and angiogenesis of tumor cells. We discuss how spice-derived nutraceuticals mediate such diverse effects and what their molecular targets are. Overall our review suggests “adding spice to your life” may serve as a healthy and delicious way to ward off cancer and other chronic diseases. *Exp Biol Med* 234:825–849, 2009

Key words: nutraceuticals; spices; inflammation; cancer; apoptosis; invasion; angiogenesis

Introduction

Spices have shaped a large part of the world’s history; for example, they led such legendary explorers as Christopher Columbus and Vasco de Gama to search the world for its most precious commodities—spices. Throughout the ancient and medieval world, spices carried a high value and were considered so special they often came with a very high price tag. Spices have been used for centuries, serving a variety of purposes in a wide variety of cultures. They have been used as flavor agents, as colorants to add special taste to dishes, and also as a preservative to prevent the growth of bacteria. But today, the importance of spices has become even more evident than they were throughout history. Due to their high antioxidant and anti-inflammatory properties, the common spices in today’s diet have been demonstrated to also have medicinal value, and much of this potential has only been realized over the last 50 years.

The major focus of this review is on the role that spices play in the various phases of tumorigenesis, serving as agents both for prevention and treatment. Examinations of dietary patterns of people around the world have demonstrated that populations that consume more spices have been shown to have a lower incidence of cancer. For example, in a comparison of the incidence of the various types of cancer between the United States and India, the US was found to have much higher rates of colorectal cancer. In 2000, the US had 356 colon cancer cases reported and 139 deaths per 1 million people. In contrast, India only had 40 reported cases

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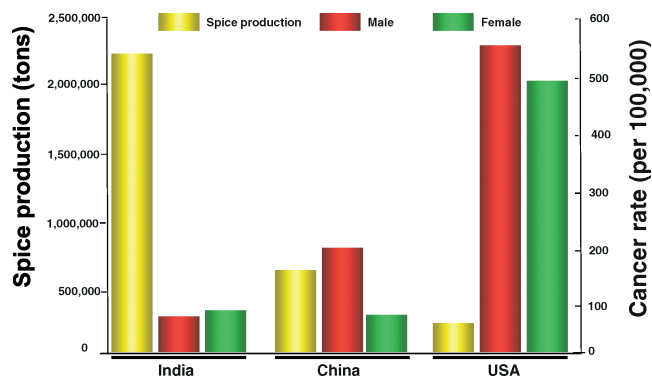


Figure 1. Relationship between production of spices and cancer incidence. Data is modified from 2000 faostat.fao.org (http://www.foodmarketexchange.com/datacenter/product/herb/herb/detail/dc_pi_hs_herb0406.htm) and cancer data from the World Health Organization GLOBOCAN 2002. A color version of the figure is available in the online journal.

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 factor (Fig. 1) (1).

Despite continued cancer research and positive breakthroughs, the overall rates of cancer over the past 50 years have not changed substantially. The percentage of people who develop cancer and the percentage of people who die from cancer have shown virtually no improvement over the past few decades. Among the chronic diseases, cancer is expected to become the number one killer in 2010, accounting for more deaths than even heart attack. Yet it is now believed that 90–95% of all cancers are attributable to lifestyle, while the remaining 5–10% can be attributed to faulty genes (2) (see Fig. 2). The implications of the above statements indicate that as of today, the best and only true “cure” for cancer is through prevention.

Cancer is a complicated disease that develops over a number of years (see Fig. 3). The basic theory of tumorigenesis starts with a normal cell that is transformed through the activation of proto-oncogenes and the suppression of tumor suppressor genes such as p53. After the cell has been transformed, it no longer behaves like a normal cell, but begins to exhibit the properties of a cancer cell. These transformed cells acquire the capability to proliferate uncontrollably through self-sufficiency in growth signals and insensitivity to anti-growth signals. In addition, these cells are able to evade apoptosis, resulting in tumor growth. The transformation of a normal cell to a cancer cell along with uncontrolled proliferation and evasion of apoptosis is a process that can take between ten to twenty years. As the tumor continues to develop, this growth is aided through the development of new blood vessels that provide nutrients to the tumor, allowing it to sustain itself and even begin to invade other tissues, resulting in metastasis that is ultimately lethal.

Nutraceutical is a term first coined by Stephen DeFelice

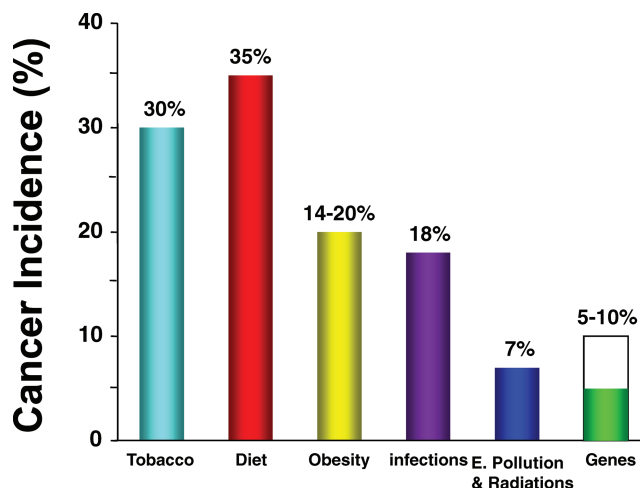
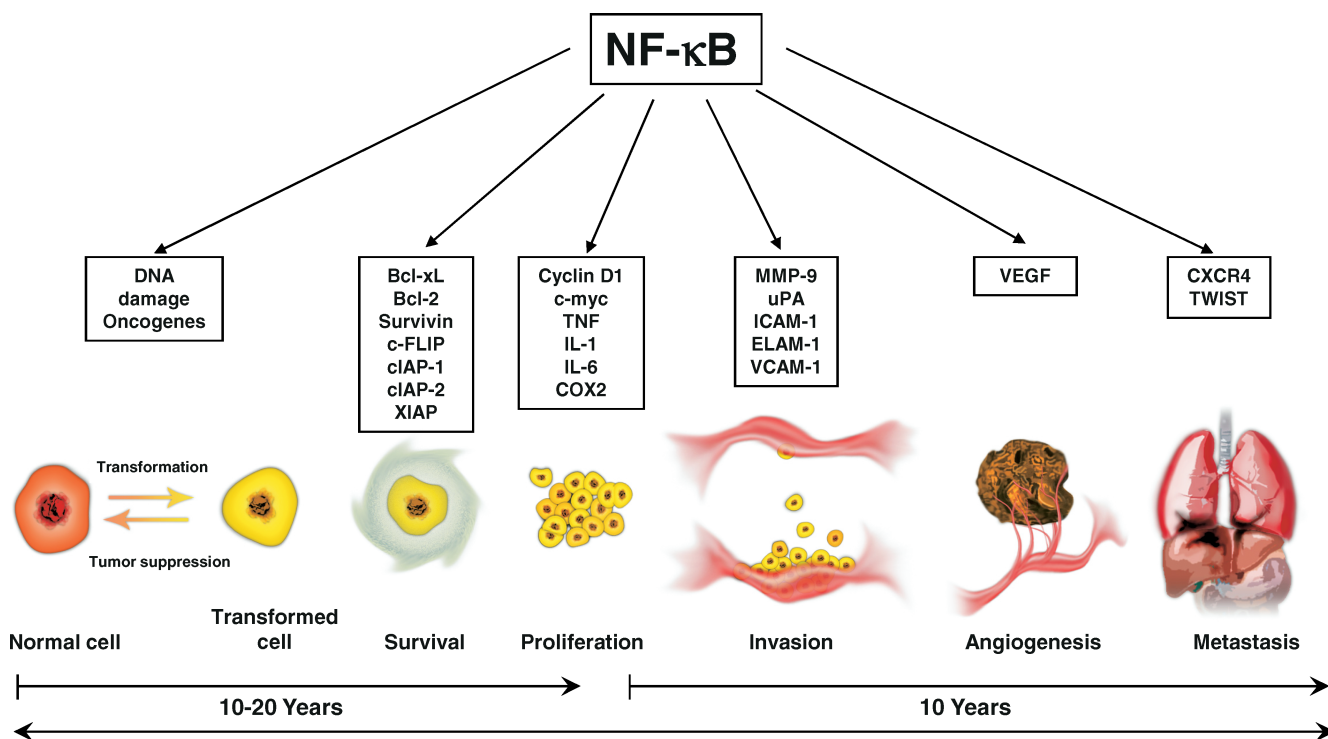


Figure 2. Cancer is a preventable disease that requires major changes in lifestyle. A color version of the figure is available in the online journal.

in 1989 from “nutrition” and “pharmaceutical”. According to DeFelice, nutraceutical can be defined as, “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease” (3, 4). This review will focus on the specific nutraceuticals derived from 41 common herbs and spices (see Fig. 4) (Table 1) (5–50) that target one or more of the various phases of tumorigenesis. The five focuses are on targets for inflammation, proliferation, apoptosis, invasion, and angiogenesis. Over 182 spice-derived nutraceuticals have been identified and the major well-studied compounds are listed in Figure 5. A large portion of these nutraceuticals do indeed show great potential for targeting cancer at various phases, showing down-regulation of transcription factor (e.g. nuclear factor- κ B), anti-apoptotic proteins (e.g. Bcl-2 and Bcl-xL), promoters of cell proliferation (e.g. cyclooxygenase-2, cyclin D1 and c-Myc), and invasive and metastatic genes (e.g. matrix metalloproteinases, intracellular adhesion molecule-1, and angiogenic protein vascular endothelial growth factor) (Table 2) (51–130). This article shows that “adding spice to your life” has the potential to not only improve the flavor of your favorite dishes, but to help fight the various stages of tumorigenesis.

Molecular Targets of Nutraceuticals. As we now know, cancer is not a simple disease, but a complex interaction between multiple genes, within the cell itself, and with its neighboring tissues. In order for a tumor to develop, somewhere between 300–500 genes have gone wrong. These “bad genes” can lead to up-regulation of undesired products such as anti-apoptotic proteins or down-regulation of tumor suppressor proteins such as p53. This section will focus on some of the most commonly known targets that are shown to cause undesired effects in tumor development.

Effect of Nutraceuticals on Inflammation. Inflammation comes from the Latin word *inflammatio*, which



Inflammation

Figure 3. Roles of NF-κB-mediated inflammatory pathway in cellular transformation, cancer survival, proliferation, invasion, angiogenesis and metastasis. A color version of the figure is available in the online journal.

means, “to set on fire.” The four classic hallmarks of inflammation are redness, heat, swelling, and pain. Inflammation is the body’s natural response to harmful stimuli and is achieved by the movement of plasma and leukocytes from the blood into injured tissues. This particular type of immune response is important for the body to ward off harmful pathogens and is classified as acute inflammation. Chronic inflammation, on the other hand, occurs when there is a progressive change in the type of cells that are present at the sight of inflammation where the body is attempting to heal, but tissue damage is occurring at the same time. Recently, more and more attention has been focused on chronic inflammation and its link to cancer. Research has shown that inflammation is a critical component of tumor progression and that many cancers arise from sites of infection, chronic irritation, and inflammation. The micro-environment provided by inflammatory cells is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration (131). The inflammatory microenvironment containing various inflammatory cells and a network of signaling molecules is necessary for the malignant progression of transformed cells, which is attributed to the mutagenic predisposition of persistent infection-fighting agents at sites of chronic inflammation. The inflammatory cells and regulators may facilitate angiogenesis and promote the growth, invasion, and metastasis of tumor cells (132).

One of the most important links between inflammation and cancer is the transcription factor nuclear factor-κB (NF-κB). This transcription factor can be activated in response to various types of stress, such as pro-inflammatory cytokines (TNF), viruses, γ-radiation, bacterial cell wall components (lipopolysaccharide, LPS), or chemotherapeutic agents (133). This DNA binding of NF-κB signals transcription of various cancer-promoting genes such as anti-apoptotic genes, pro-angiogenic genes, and pro-invasion genes (134). It is believed that NF-κB DNA binding leads to the activation of over 400 genes, many of which lead to a variety of diseases besides cancer such as Alzheimer’s disease and arthritis (135).

Other factors such as tumor necrosis factor (TNF), interleukins (IL-1β and IL-6), and chemokines (IL-8 or CXCL8) play an important role in the link between inflammation and cancer as well. TNF is part of a family of cytokines, mainly secreted from macrophages, that is responsible for the regulation of immune cells. However, its dysregulation and overproduction can lead to diseases, including cancer, and is known to be responsible for the activation of NF-κB. It does this by binding to a TNF-receptor on the cell’s surface that triggers a pathway that leads to the activation of IκBα kinase (IKK) (136). Interleukins are a group of cytokines that are released from a wide variety of bodily cells. However, the two interleukins this article discusses, IL-1β and IL-6, are mainly released

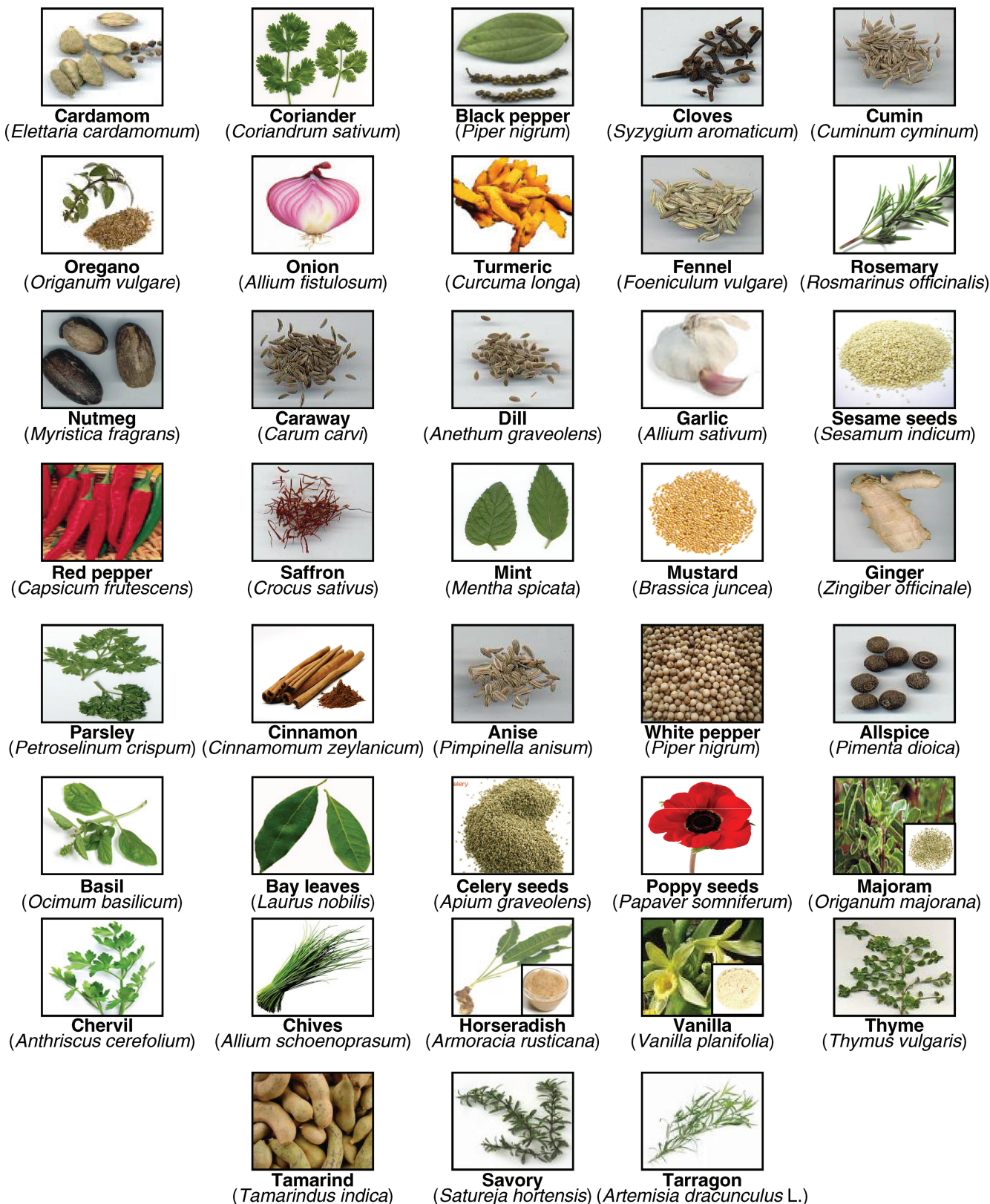


Figure 4. Common dietary spices. A color version of the figure is available in the online journal.

Table 1. A List of Common Spices and Nutraceuticals from Spices

Spice	Nutraceuticals
Allspice	Eugenol, methyl eugenol, myrcene, 1,8-cineol, α -phellandrene, quercetin, myricetin (5)
Anise	Anethole, bergapten, estragole, anisaldehyde, α -himalchalone (6)
Asafoetida	α -Pinene, phellandrenes, Farnesiferoles, hendecylsulphonyl acetic acid (7)
Basil	Ursolic acid, eugenol, caffeic acid, β -sitosterol, limonene, estragole, methyl eugenol, geraniol, 1,8-cineol, linalool, citral, methyl cinnamate (8)
Bay leaves	Linalool, α -terpinol, α -terpinyl acetate, thymol, caryophyllene, aromadendrene, β -selinene, farnesene, cadinene, methyl eugenol, myrcene, eugenol (9)
Black pepper	Piperine, β -caryophyllene, limonene, δ -3-carene, α -pinene, β -pinene, α -phellandrene, myrcene, terpinolene (10)
Caraway	S-Carvone, germacrene D, limonene, dihydrocarveol, α -pinene, β -pinene, sabinene, perillyl alcohol, carveol (11, 12)
Cardamom	α -Terpinyl acetate, 1,8-cineol, limonene, linalool, linalyl acetate, terpinolene, myrcene (13)
Celery seed	Apigenin, limonene, β -selinene, humulene, 3-butylphthalide, senkyunolide, α -pinene, β -pinene, myrcene, (Z)- β -ocimene, γ -terpinene, cis-allo-ocimene, (E)- β -farnesene, apiole, senkyunolide, neocnidilide (14)
Chervil	Estragole, apiin, hendecane (undecane) (15, 16)
Chives	Dipropyl disulfide, methyl pentyl disulfide, pentyl hydrodisulfide ^a , cis/trans 3,5-diethyl-1,2,4-trithiolane ^a , pentanethiol, diallyl sulfide (17)
Cinnamon	Cinnamaldehyde, cinnamyl acetate, cineol, eugenol, coumarin, ethyl cinnamate, linalool, humulene, β -caryophyllene, τ -cadinol (18)
Cloves	Carvacrol, thymol, eugenol, cinnamaldehyde, eugenyl acetate (19)
Coriander	Linalool, geraniol, geranyl acetate, camphor (20)
Cumin	Cuminaldehyde, γ -terpinene, β -pinene, <i>p</i> -cymene, <i>p</i> -mentha-1,3-diene-7-al, <i>p</i> -mentha-1,4-dien-7-al ^a (11, 21)
Dill	Carvones, limonene, dillapiol, trans-dihydrocarvone, cis-dihydrocarvone, myristicin (22)
Fennel	(E)-Anethole, limonene, fenchone, estragole, anisaldehyde, bergapten, β -sitosterol (23, 24)
Garlic	Ajoene, allacin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, S-allylcysteine, methiin, isoalliin, cycloalliin, S-allylmercaptocysteine (25)
Ginger	[6]-Gingerol, [6]-paradol, shogol, 6-gingerdiol, gingerdione, zingiberene, citral (neral and geranial), bisabolene, α -farnesene, β -phellandrene, cineol, zingerone (26, 27)
Horseradish	Sinigrin, allyl isothiocyanate, gluconasturtin, phenylethyl isothiocyanate, quercetin, kaempferol (28)
Marjoram	4-Terpinenol, (E)-sabinene hydrate, γ -terpinene, sabinene, β -pinene, limonene, β -phellandrene, (Z)-sabinene hydrate, terpinolene (12)
Mint (spearmint)	Menthol, R-carvone, limonene, β -pinene, β -myrcene, trans-thujan-4-ol, dihydrocarvone, β -bourbonene, β -caryophyllene, epi-bicyclosesquiphellandrene (29)
Mustard	Allyl isothiocyanate, sulforaphane (30)
Nutmeg	Eugenol, myristicin, elemicin, sabinene, safrole, methyl eugenol, α -pinene, β -pinene, myristic acid, 4-terpineol (31, 32)
Onion	Quercetin, allicepin ^a , allyl propyl disulphide, protocatechuic acid, quercetin dimer ^a , quercetin trimer ^a (33, 34)
Oregano	Carvacrol, cis-sabinene hydrate, thymol, linalyl acetate, β -caryophyllene, 4-terpineol, α -terpineol, caffeic acid (35)
Paprika	β -Carotene, α -, β -, and γ -tocopherols, canthaxanthin, capsaicin, dihydrocapsaicin (36)
Parsley	<i>p</i> -1,3,8-Menthatriene, β -phellandrene, apiole, myrcene, myristicin, rutin, apigenin (37)
Poppy seed	1-Pentanol, 1-hexanal, pentylfuran, caproic acid, linoleic acid, oleic acid, palmitic acid (38)
Red pepper	Capsaicin, β -carotene, zeaxanthin, lutein, caffeic acid, capsanthin (39)
Rosemary	Carnosol, rosmarinic acid, carnosic acid, α -pinene, camphor, limonene, camphene, borneol, cineole, (Z)-linalool oxide, bornyl acetate (40)
Saffron	Crocin, safranal, picrocrocin, crocetin, α - and β -carotene, lycopene, zeaxanthin (41)
Sage	1,8-Cineol, camphor, α -thujone, β -thujone, borneol, viridiflorol, manool, humulene, β -caryophyllene (11, 42)
Savory	Carvacrol, α -pinene, γ -terpinene, 4-terpineol, α -terpineol, cadinene, τ -cadinol, caryophyllene (43)
Sesame seed	Sesamin, sesamol, phytic acid, linoleic acid, oleic acid, β -sitosterol, campesterol, stigmasterol, γ -tocopherol, Δ 5-avenasterol, palmitic acid (44)
Tamarind	Tartaric acid, limonene, geraniol, safrole, cinnamic acid, ethyl cinnamate, methyl salicylate, pyrazine, phenylacetaldehyde, 2-furfural, palmitic acid (45)
Tarragon	(Z)-Anethole, (Z)- β -ocimene, (E)- β -ocimene, limonene, methyl eugenol, camphor, cineol (46)
Thyme	Thymol, carvacrol, <i>p</i> -cymene, γ -terpinene, linalool, borneol, β -caryophyllene, caffeic acid, β -pinene, thymodihydroquinone (12, 47)
Turmeric	Curcumin, zingiberene, turmerone, γ -atlantone, β -sesquiphellandrene, turmerol, bisabolone (48)
Vanilla	Vanillin, ethyl vanillin, 4-hydroxybenzyl alcohol, vanillyl alcohol, piperonal, ferulic acid, vanillic acid, 3,4-dihydroxybenzaldehyde, 4-hydroxybenzoic acid, 4-hydroxybenzaldehyde, <i>p</i> -coumaric acid (49)
White pepper	Piperine, β -caryophyllene, limonene, δ -3-carene, α -pinene, β -pinene, α -phellandrene, myrcene, terpinolene (50)

^a The structure is not available.



Figure 5. Chemical structures of nutraceuticals derived from different spices.



Figure 5. Continued.

Table 2. Molecular Targets of Nutraceuticals Derived from Spices

Pathways ^a	Inhibitors
Inflammation	
NF-κB	Anethole, carnosol, caryophyllene, cinnamaldehyde, curcumin, humulene, perillyl alcohol, quercetin, sulforaphane, ursolic acid (51–59)
TNF	Ajoene, allicin, allyl isothiocyanate, apigenin, curcumin, diallyl sulfide, eugenol, gingerol, humulene, kaempferol, paradol, piperine, zingerone (53, 60–68)
IL-1β	Allicin, apigenin, diallyl sulfide, eugenol, gingerol, humulene, kaempferol, phytic acid, piperine (53, 61, 63–66, 68, 69)
IL-8	Allicin, phytic acid (61, 69)
IL-6	Diallyl sulfide, phytic acid, piperine (64, 68, 69)
STAT3	Capsaicin (70)
Survival	
Bcl-2	Ajoene, allyl isothiocyanate, β-carotene, β-sitosterol, capsaicin, carnosol, cinnamaldehyde, curcumin, diallyl sulfide, gingerol, limonene, lutein, rosmarinic acid, S-allylcysteine, sulforaphane, ursolic acid (70–85)
Bcl-xL	Allyl isothiocyanate, β-carotene, capsaicin, sulforaphane (70, 72, 73, 84)
Bax	Cinnamaldehyde, curcumin, diallyl sulfide, limonene, lutein (76–78, 80)
Survivin	Capsaicin, curcumin (70, 77)
Caspases	Allicin, β-sitosterol, cinnamaldehyde, citral, diallyl disulfide, diallyl trisulfide, kaempferol, limonene, myristicin, paradol, shogaol, sulforaphane, terpinen-4-ol, ursolic acid (74, 76, 84–95)
p53	Diallyl sulfide, limonene, lutein, shogaol (78, 80, 95, 96)
Proliferation	
c-Myc	Apigenin, perillyl alcohol (97, 98)
Cyclin D1	Apigenin, capsaicin, curcumin, lutein, sesamin, sulforaphane, ursolic acid (59, 70, 97, 99–102)
COX-2	Eugenol, curcumin (55, 97)
Other cyclins	Bergapten, β-carotene, carnosol, diallyl trisulfide, geraniol, perillyl alcohol, rosmarinic acid (73, 82, 89, 103–105)
p53	Phytic acid, quercetin (106, 107)
Invasion	
MMP-9	Allyl isothiocyanate, caffeic acid, carnosol, curcumin, diallyl disulfide, quercetin, ursolic acid, vanillin (64, 108–113)
MMP-2	Allyl isothiocyanate, curcumin, diallyl disulfide, myricetin, quercetin (64, 108, 111, 114–116)
MMPs (non-specific)	Crocetin, piperine, sulforaphane (68, 117, 118)
ICAM-1	Allicin, apigenin, crocetin, kaempferol (117, 119, 120)
Angiogenesis	
VEGF	Alliin, caffeic acid, capsaicin, curcumin, diallyl disulfide, diallyl sulfide, gingerol, perillyl alcohol, phytic acid, rosmarinic acid, sulforaphane (58, 64, 121–130)

^a COX-2, cyclooxygenase-2; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; STAT3, signal transducers and activator of transcription 3; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

from macrophages. IL-1β is an important part of the inflammatory response against infection that increases the expression of adhesion factors on endothelial cells to allow movement of leukocytes to the sight of infection. IL-6 is a pro-inflammatory cytokine that is released in response to trauma or tissue damage. IL-8, also known as CXCL8, is a member of the CXC chemokine family. It has been shown to contribute to human cancer progression through its potential functions as a mitogenic, angiogenic, and mutagenic factor (137).

Many spice-derived nutraceuticals have been found to play a role in reducing inflammation. These include ajoene, allicin, allyl isothiocyanate, anethole, apigenin, capsaicin, carnosol, caryophyllene, cinnamaldehyde, curcumin, diallyl sulfide, eugenol, [6]-gingerol, humulene, kaempferol, limonene, myrcene, [6]-paradol, perillyl alcohol, phytic acid,

piperine, quercetin, sulforaphane, ursolic acid, and zingerone (Tables 2 and 3) (51–70, 138, 139). Many of these nutraceuticals target the transcription factor NF-κB, leading to its down-regulation.

The compound 2,8-Biapigenin blocks the action of NF-κB by preventing nuclear translocation of p65; this blocks the transactivation of inducible nitric oxide synthase (iNOS) and COX-2 genes, thus playing an anti-inflammatory role and causing cell cycle arrest (140). Anethole inhibits NF-κB activation, IκBα phosphorylation and degradation, and NF-κB-reporter gene expression induced by TNF, TNF receptor-associated factor 2 (TRAF2), and NF-κB-inducing kinase (NIK) *in vitro* (51). Capsaicin has an antioxidant potential and helps decrease oxidative stress induced cancer during exposure to benzopyrene in the lungs of mice (141). Carnosol limits the translocation of NF-κB subunits to the

Table 3. Inhibition of Inflammation by Spice-Derived Nutraceuticals

Nutraceutical	Responses ^a
Ajoene	Inhibits tumor-endothelial cell adhesion, as well as the <i>in vivo</i> TNF- α response to LPS in mouse melanoma cells (60).
Allicin	Inhibits the spontaneous and TNF- α -induced secretion of IL-1 β , IL-8, IP-10 and MIG in a dose-dependent manner from intestinal epithelial cells <i>in vitro</i> , suppresses the expression of IL-8 and IL-1 β mRNA levels and the degradation of I κ B (61).
Allyl isothiocyanate	Significantly inhibits the cellular production of proinflammatory mediators such as TNF- α and NO and inhibits the release of MCP-1 from 3T3-L1 adipocytes <i>in vitro</i> (62).
Anethole	Inhibits NF- κ B activation, I κ B α phosphorylation and degradation, and NF- κ B-reporter gene expression by induced by TNF, TRAF2, and NIK <i>in vitro</i> , suppresses TNF-induced activation of the transcription factor AP-1, JNK and MAPK <i>in vitro</i> (51).
Apigenin	Inhibits TNF- α in LPS stimulated macrophages resulting in diminished MCP-1 and inhibition of IL-1 β <i>in vitro</i> (63).
Capsaicin	Blocks the STAT3 activation pathway in multiple myeloma cells <i>in vitro</i> leading to down-regulation of cyclin D1, Bcl-2, Bcl-xL, survivin, and VEGF (70).
Carnosol	Decreases LPS-induced iNOS mRNA and protein expression, reduces NF- κ B subunits translocation and NF- κ B DNA binding activity in activated macrophages due to inhibition of IKK, inhibits iNOS and NF- κ B promoter activity (52).
Caryophyllene	Inhibits the LPS-induced NF- κ B activation and neutrophil migration in rat paw edema <i>in vivo</i> (53).
Cinnamaldehyde	Inhibits age-related NF- κ B activation and targets inflammatory iNOS and COX-2, inhibits the activation of NF- κ B via three signal transduction pathways, NIK/IKK, ERK, and p38 MAPK (54).
Curcumin	Down-regulates the constitutive activity of NF- κ B, decreases levels of phospho-I κ B α , decreases expression of NF- κ B-target genes COX-2 and cyclin D1, and induces apoptosis in mouse melanoma cells <i>in vitro</i> (55). Significantly inhibits the cellular production of proinflammatory mediators such as TNF- α and NO and inhibits the release of MCP-1 from 3T3-L1 adipocytes (62).
Diallyl sulfide	Significantly reduces the production of and serum levels of IL-1 β , IL-6, TNF- α and GM-CSF in mice with melanoma (64).
Eugenol	Blocks the release of IL-1 β , TNF- α , and prostaglandin E2 and suppresses the mRNA expression of IL-1 β , TNF- α , and COX-2 in LPS-stimulated human macrophages <i>in vitro</i> (65).
[6]-Gingerol	Inhibits the production of TNF- α , IL-1 β , and IL-12 in murine peritoneal macrophages exposed to several doses of 6-gingerol in the presence of LPS stimulation (66).
Humulene	Inhibits the LPS-induced NF- κ B activation and neutrophil migration in rat paw edema, prevents the production of TNF- α and IL-1 β and the <i>in vivo</i> up-regulation of kinin B(1) receptors (53).
Kaempferol	Inhibits TNF- α in LPS stimulated macrophages resulting in diminished MCP-1 and inhibition of IL-1 β <i>in vitro</i> (63), inhibits IL-4-induced STAT6 activation by specifically targeting JAK3 in hemopoietic cells from human and mouse origin <i>in vitro</i> (138).
Limonene	Inhibits the LPS-induced inflammation including cell migration and production of NO along with significant inhibition of γ -interferon and IL-4 production in mouse model of pleurisy (139).
Myrcene	Inhibits the LPS-induced inflammation including cell migration and production of NO along with significant inhibition of γ -interferon and IL-4 production in mouse model of pleurisy (139).
Paradol	Significantly inhibits the tumor-promoter-stimulated inflammation, TNF- α production, and activation of epidermal ornithine decarboxylase in mice (67).
Perillyl alcohol	Reduces NF- κ B DNA-binding activity and targets gene induction, which is associated with an increase in apoptosis in B-lymphoma cells and in estrogen receptor-negative breast cancer cells (56).
Phytic acid	Modulates IL-8 and IL-6 release from colonic epithelial cells stimulated with LPS and IL-1 β , suppresses IL-8 basal release, and it dose-dependently reduces IL-8 secretion by colonocytes and down-regulates IL-6 (69).
Piperine	Significantly reduces the expression of IL-1 β , IL-6, TNF- α , GM-CSF and IL-12p40 genes in melanoma cells (68).
Quercetin	Attenuates PMACI-induced activation of NF- κ B and p38 MAPK in human mast cell line HMC-1 (57).
Sulforaphane	Inhibits NF- κ B transcriptional activity, nuclear translocation of p65, and gene expression of NF- κ B-regulated VEGF, cyclin D1, and Bcl-xL in human prostate cancer cell (58).
Ursolic acid	Inhibits IKK and p65 phosphorylation leading to the suppression of NF- κ B activation induced by various carcinogens; this correlates with the down-regulation of COX-2, MMP- 9, and cyclin D1 <i>in vitro</i> (59).
Zingerone	Significantly inhibits the cellular production of proinflammatory mediators such as TNF- α and NO and inhibits the release of MCP-1 from 3T3-L1 adipocytes (62).

^a AP-1, activator protein-1; COX-2, cyclooxygenase-2; ERK, extracellular signal regulated kinase; GM-CSF, granulocyte-macrophage colony-stimulating factor; IKK, I κ B kinase; IL-1 β , interleukin-1 β ; iNOS, inducible nitric oxide synthase; IP-10, inducible protein-10; Jak 3; janus kinase 3; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MIG, monokine induced by interferon gamma; NF- κ B, nuclear factor- κ B; NIK, NF- κ B-inducing kinase; NO, nitric oxide; PMACI, phorbol-12-myristate 13-acetate plus calcium ionophore A23187; TRAF2, TNF receptor associated factor-2; VEGF, vascular endothelial growth factor.

nucleus and reduces NF- κ B DNA binding activity in activated macrophages due to the inactivation of IKK (52). Caryophyllene and humulene inhibit LPS-induced NF- κ B activation and neutrophil migration in rat paw edema *in vivo* (53). Cinnamaldehyde inhibits age-related NF- κ B activation and targets inflammatory iNOS and COX-2 (54). In addition, cinnamaldehyde can inhibit the activation of NF- κ B through three different signal transduction pathways—NIK/IKK, extracellular signal-regulated kinase (ERK), and p38 mitogen activated protein kinase (MAPK) (54). Perillyl alcohol reduces NF- κ B DNA-binding activity and target gene induction in estrogen receptor-negative breast cancer cells *in vitro* (56). Quercetin attenuates the expression of phorbol-12-acetate-13-myristate (PMA)-induced activation of NF- κ B and p38 MAPK in human mast cells *in vitro* (57). Sulforaphane inhibits NF- κ B transcriptional activity, nuclear translocation of p65, and gene expression of NF- κ B-regulated gene products such as VEGF, cyclin D1, and Bcl-xL in human prostate cancer cells *in vitro* (58). Ursolic acid inhibits IKK and p65 phosphorylation leading to the suppression of NF- κ B activation induced by various carcinogens *in vitro*. This NF- κ B suppression leads to the down-regulation of its regulated gene products COX-2, MMP-9, and cyclin D1 (59).

Many of the spice-derived nutraceuticals target TNF- α , either by blocking its production or its function. Ajoene inhibits TNF- α production in response to LPS stimulation in mouse melanoma cells *in vivo* (59). Allyl isothiocyanate (AITC), curcumin, and zingerone significantly inhibit the cellular production of TNF- α and nitric oxide and inhibit the release of monocyte chemoattractant protein-1 (MCP-1) from adipocytes *in vitro* (62). [6]-Paradol inhibits TNF- α production in mouse skin papillomagenesis initiated by 7,12-dimethylbenz[a]anthracene in female ICR mice (67). Many of the spice-derived nutraceuticals target both TNF- α and IL-1 β . Apigenin and kaempferol inhibit TNF- α in LPS stimulated macrophages resulting in diminished MCP-1 and inhibition of IL-1 β *in vitro* (63). Apigenin inhibits the production of nitric oxide, prostaglandin E(2), p38 MAPK and c-Jun N-terminal kinase (JNK) phosphorylation. This apigenin also has an inhibitory effect on the expression of TNF- α and IL-1 β genes in macrophages, thus playing a protective role against inflammation. Apigenin also plays an important role in decreasing oxidative stress causing a decrease in macromolecular damage to hepatocellular cells, thus preventing hepatocellular carcinogenesis (142). Diallyl sulfide significantly reduces the production of and serum levels of TNF- α and IL-1 β in mice with melanoma (64). Eugenol is the essential active substance in clove; it possesses antimicrobial, antioxidant, anti-inflammatory and cytotoxic properties (19). Eugenol blocks the release of TNF- α and IL-1 β and suppresses their mRNA expression in LPS-stimulated human macrophages *in vitro* (143). [6]-Gingerol inhibits the production of TNF- α and IL-1 β in LPS-stimulated murine peritoneal macrophages *in vitro*

(66). Humulene prevents the production of pro-inflammatory cytokines TNF- α and IL-1 β in rat paw edema *in vivo* (53). Piperine significantly reduces the expression of TNF- α and IL-1 β in human melanoma cells *in vitro* (68).

AITC also down-regulates proinflammatory cytokines such as IL-1 β , IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eugenol causes initiation of membrane oxidative damage and intracellular reactive oxygen species (ROS) generation in combination with gamma-radiation, which plays an important role in radio-sensitization of various tumors (144). Also it increases sensitivity of cisplatin-induced cytotoxicity by decreasing the expression of multidrug resistance protein 2 (MRP2) (145). Eugenol decreases the incidence of radiation-induced thymic lymphoma in mice (146). Eugenol contained in clove oil was found to have modulating effects on murine skin papillomagenesis; it was found to exert its effect by increasing levels of glutathione S-transferase (GST) and cytochrome B5 (147). It also inhibited CCl₄-induced hepatotoxicity in rat (148). *In vivo* treatment of rats with eugenol resulted in decrease in mutagenicity of B[a]P in *Salmonella typhimurium* mutagenicity assay in hepatoma cell line HepG2 (149). Eugenol inhibited tobacco induced mutagenicity and nitrosation of methylurea in a dose-dependent manner (150). Jeng *et al.* found that frequent exposure of oral mucosa to low concentrations of eugenol at a concentration less than 1 mmol/L might protect cells from the genetic attack of ROS *via* inhibition of xanthine oxidase activity and lipid peroxidation, thus preventing oral submucosal fibrosis; however, higher concentrations may predispose to carcinogenesis (151). In rat liver cells, dietary administration of eugenol was found to enhance UDP-glucuronyltransferase, UDP-glucose dehydrogenase, and GST activities, which would reduce intermediates of various carcinogens, and active intermediates of drugs (152).

The remaining nutraceuticals target IL-6 and IL-8. Allicin inhibits the spontaneous and TNF- α induced secretion of IL-1 β and IL-8 from intestinal epithelial cells *in vitro*. It also suppresses the mRNA levels of IL-1 β and IL-8 and the degradation of I κ B α (61). Diallyl sulfide significantly reduces the production and serum levels of IL-6 in mice with melanoma (64). Phytic acid modulates IL-6 and IL-8 release from colonic epithelial cells stimulated with LPS and IL-1 β . It suppresses IL-8 basal release and reduces the secretion of IL-8 by colonocytes, as well as down-regulates IL-6 (69). Piperine reduces the expression of IL-6 in human melanoma cells *in vitro* (68).

Effect of Nutraceuticals in Tumor Cell Survival and Apoptosis. Apoptosis is a process of programmed cell death that in Greek literally means “falling away.” Apoptosis is a natural, organized process that cells go through in the human body on a daily basis. The human body is made up of 6 trillion cells, with approximately 3 billion cells replaced every minute. This equates to 1% of the human body being turned over every day, and a “new

body” being generated every three months. Cells are also triggered to go through apoptosis when intracellular sensors detect abnormalities such as DNA damage, oncogene activation, nutrient deficiency, or hypoxia. However, cancer cells are able to acquire the capability to evade apoptosis, allowing tumors to grow rapidly and uncontrollably. One of the most common ways this can occur is through mutation of the p53 tumor suppressor gene, resulting in functional inactivation of the p53 protein. Without the p53 protein, the cell lacks important DNA damage sensor capability that would normally induce the apoptotic cascade. For this reason, many pharmaceutical companies are trying to develop new drugs that target steps in the apoptotic pathway. Many are still in clinical trials, and it is unclear at this time which targeted therapies will be most effective. Current cancer treatments, such as radiation and chemotherapy, are believed to shrink tumors through triggering apoptosis, but this is still uncertain, and cells often become resistant to such therapies.

There are two different types of apoptosis: mitochondria dependent and mitochondria independent. In mitochondria dependent form, apoptotic signals cause the release of cytochrome C from the mitochondria, a potent catalyst of apoptosis that activates caspases. Caspases are proteases that cleave other proteins and therefore are essential for apoptotic cell death. Apoptotic signals may come in the form of members of the Bcl-2 family of proteins, such as pro-apoptotic Bax that can be up-regulated by tumor suppressor protein p53 in response to sensing DNA damage. Apoptosis can also be triggered through extracellular signals (or “death signals”) that bind to receptors on the cell’s surface and trigger caspase activation inside the cell. This receptor-mediated apoptosis is often triggered by cytokines such as TNF or TNF-related apoptosis-inducing ligand (TRAIL), or by the binding of the Fas receptor and Fas ligand.

Some other important players in apoptosis are the members of the Bcl-2 family of proteins including Bcl-2 and Bcl-xL. Both of these proteins are anti-apoptotic proteins that are found to be overexpressed in a wide variety of cancers. They are also playing a role in resistance to traditional cancer treatments. Survivin is another anti-apoptotic protein found to be overexpressed in cancer cells. If ways to down-regulate Bcl-2, Bcl-xL, and survivin, and ways to up-regulate p53, Bax, and caspases, can be found, these could help to trigger apoptosis in cancer cells.

For example, many spice-derived nutraceuticals have been shown to induce apoptosis in different types of cancer cells through a wide variety of mechanisms. Major ones are ajoene, allicin, allyl isothiocyanate, bergapten, β -carotene, α -sitosterol, canthaxanthin, capsaicin, carnosol, cineole, cinnamaldehyde, citral, crocin, curcumin, diallyl disulfide, diallyl sulfide, diallyl trisulfide, [6]-gingerol, kaempferol, limonene, lutein, myristicin, [6]-paradol, rosmarinic acid, S-allylcysteine, S-allylmercaptocysteine, sesamin, sesamol, shogaol, sulfuraphane, terpinen-4-ol, turmerone, and ursolic

acid (Table 4) (70, 73–75, 78–93, 95, 96, 153–157). One of the most common targets of these nutraceuticals is Bcl-2, an anti-apoptotic protein. Research has shown that by down-regulating Bcl-2, apoptosis can be induced in cancer cells.

AITC, a major component of garlic, induces apoptosis by a variety of mechanisms. Apoptosis with AITC was associated with cleavage of p22 BID protein to p15, p13, and p11 fragments and activation of JNK. In isothiocyanate-induced apoptosis, the caspase pathway has an essential role along caspase-8 and caspase-3; the JNK pathway a supporting role (72). Cells treated with AITC also show a significant reduction in the expression (31–68%) of anti-apoptotic protein Bcl-2 and approximately 58% reduction in Bcl-xL protein expression. Also there is significant reduction in expression of several proteins that regulate G2/M progression including cyclin B1, cell division cycle (cdc) 25B (44–48% reduction) and cdc25C (> 90% reduction), and cyclin dependent kinase 1 (CDK1) (32–50% reduction) (72). AITC in high doses can increase activity of phase II detoxification enzymes such as quinone reductase (QR) and GST in many rat tissues, while in moderate doses an increase in enzyme activity is mainly found in the bladder of rats (158). Induction of Phase II enzymes may contribute to lower incidences of bladder cancer. AITC causes induction of activities of ethoxyresorufin O-deethylase (EROD) and GST at dose levels which were protective towards benzo(a)pyrene-induced DNA damage (159). AITC can also cause increased acetylation of histones. AITC administration inhibits growth of PC-3 xenografts *in vivo* by inducing apoptosis and reducing mitotic activity (160).

Apigenin is a flavone mainly present in parsley and celery and possesses hydroxylized B ring, which makes it a natural and potent proteasome inhibitor and a tumor cell apoptosis inducer (161). The presence of C2-C3 double bond is associated with its growth inhibitory potential (162). Apigenin is implicated in inhibition of human cytochrome CYP1B1; this isoform metabolizes both polycyclic aromatic hydrocarbons and estrogenic compounds into carcinogenic by-products (163). The different ways through which apigenin induces apoptosis are listed below.

In human breast cancer cells, it inhibits proteasome function and through estrogen receptor (ER)-dependent and ER-independent pathways; it induces apoptosis in MCF-7 cells (164). In HER2/neu-overexpressing breast cancer cells, this phytoestrogen induces apoptosis by decreasing levels of HER2 protein, which in turn decreases levels of phosphorylated HER3, thus suppressing the signaling of HER2/HER3-phosphatidylinositol 3-kinase (PI3K)/Akt pathway (165).

In Jurkat T cells, apigenin activates caspase-3 and induces cleavage of poly (ADP-ribose) polymerase (PARP) (166). In human prostate cancer 22Rv1 cells, this flavonoid inhibits NF- κ B/p65 transcriptional activity and induces p21/WAF-1 in a dose- and time-dependent manner. Besides this it was also found to increase expression of KIP1/p27, INK4a/p 16 and INK 4c/p18; it caused down modulation in

Table 4. Induction of Apoptosis by Spice-Derived Nutraceuticals

Nutraceuticals	Response ^{a,b}
Ajoene	↑ caspase-3, Bcl-2 cleavage (153)
Allicin	↑ caspases-3, -8 and -9, cleaves PARP (86)
Allyl isothiocyanate	↓ Bcl-2, ↓ Bcl-xL (154)
β-Carotene	↓ Bcl-2, ↓ Bcl-xL (73)
β-Sitosterol	↓ Bcl-2, ↓ PARP, ↓ phospholipase C-γ1, ↑ caspase-3 (74)
Capsaicin	↓ STAT3, ↓ Bcl-2, ↓ Bcl-xL, ↓ survivin, ↑ caspase (70, 155)
Carnosol	↓ Bcl-2 (75)
Citral	↑ DNA fragmentation, ↑ caspase-3 (87)
Diallyl disulfide	↑ caspase-3 (88, 89)
Diallyl sulfide	↑ p53, ↑ Bax, ↓ survivin, ↓ Bcl-2 (78)
Diallyl trisulfide	↑ caspase-3 (89)
[6]-Gingerol	↓ Bcl-2 (79)
Kaempferol	↑ caspase-3, ↑ AIF (90)
Limonene	↓ Bcl-2, ↓ p53, ↑ Bax, ↑ caspase-9, ↑ caspase-3 (80, 91, 156)
Lutein	↓ Bcl-2, ↑ Bax, ↑ p53, ↓ Bcl-2, ↑ Bax:Bcl-2 ratio (81, 96)
Myristicin	↑ cytochrome C, ↑ caspase-3 (92)
[6]-Paradol	↑ caspase-3 (93)
Rosmarinic acid	↓ Bcl-2 (82)
S-Allylcysteine	↓ Bcl-2 (83)
S-Allylmercaptocysteine	↓ MT assembly, ⊥ mitosis, ↑ JNK, ↑ caspase-3 (157)
6-Shogaol	↑ DNA fragmentation, ↑ caspase-3 (95)
Sulforaphane	↑ Fas ligand, ↑ caspase-3, ↑ caspase-8, ↑ caspase-9, ↓ Bcl-2, ↑ cytochrome C, ↑ PARP cleavage (84)
Ursolic acid	↑ caspase-9, ↓ Bcl-2 (85)

^a AIF, apoptosis inducing factor; JNK, c-Jun NH2-terminal kinase; MT, microtubule; PARP, poly (ADP-ribose) polymerase; STAT3, signal transducer and activator of transcription 3.

^b ↑, up-regulate; ↓, down-regulate; ⊥, block/arrest.

the protein expression of cyclins D1, D2 and cyclin E along with cyclin dependent kinases such as cdk2, cdk4, and cdk6. It was found to cause a decrease in retinoblastoma phosphorylation at serine 780 (167). Apigenin also elevated the levels of insulin-like growth factor-1 (IGF-1) and inhibited the growth of human prostate xenograft in nude mice. ROS were generated with Apigenin by the action of NADPH oxidase, which resulted in rapid glutathione depletion, disruption of mitochondrial membrane potential and cytosolic release of cytochrome C and apoptosis. Apigenin led to a decrease in the levels of Bcl-xL and Bcl-2 and increase in Bax, which in turn triggered caspase-3, -7, -8, and -9 activation. It also concomitantly cleaved the inhibitor of the apoptosis protein, c-IAP2 (168). Apigenin also was found to induce sensitivity of SQ-5 spheroids (cells growing in three-dimensional structure, simulating the growth and microenvironment of *in vivo* tumors) to radiation. This action of apigenin along with induction of p21/WAF-1 and decreased expression of Bcl-2 also serves to increase radiosensitivity of certain tumors (169). In human esophageal adenocarcinoma cells this flavonoid was found to cause G2/M arrest through the up-regulation of GADD45β and 14-3-3 sigma, down-regulation of p53 at the mRNA and protein levels and up-regulation of PI3K and cleavage of caspase-3 and -9 causing p53-independent mitochondrial-mediated apoptosis (170). It also induced apoptosis via an increase in intracellular free calcium with calpain activation (171). Induction of apoptosis in certain

types of cancer (e.g. prostate and breast) cells by apigenin is associated with its potential to inhibit fatty acid synthesis (172). Apigenin also exhibits prooxidant effect causing oxidation of various thiols through the formation of various phenoxyl radicals, thus leading to abortive pathways leading to necrotic cell death (173). In solid tumors, apigenin inhibits hypoxia-activated pathways that lead to cancer progression especially the PI3K/Akt/glycogen synthase kinase-3 (GSK-3) pathways (174). Vitexin, natural derivative of apigenin, decreases mRNA levels of hypoxia inducible genes such as aldolase A, smad 3, enolase1, and collagen type III (175). In neuroblastomas this phytoestrogen acts by inducing caspase-dependent, p53-mediated apoptosis (162). It also induces glutathione depletion in human prostate tumor cells (176). It was observed that the combination of apigenin and gemcitabine enhanced anti-tumor activity through NF-κB and Akt activity suppression and apoptosis induction (177). Treatment with this flavonoid results in significant dose-related reduction in genotoxic activity of chemotherapeutic agents such as induced by mitomycin C and cyclophosphamide (178). Apigenin is also implicated in aromatase inhibition and could act as a chemopreventive agent in hormone-dependent cancers (179). Apigenin induces the expression of death receptor-5 and synergizes with exogenous soluble recombinant human TRAIL to selectively induce apoptosis in tumor cells but not in normal cells (180). Apigenin has been shown to decrease the differentiation of normal human keratinocyte cells by

suppressing normal MAPK signal transduction and activator protein-1 (AP-1) transcription factor level (181).

Curcumin, the major polyphenol present in turmeric is a potent inducer of apoptosis in cancer cells. Curcumin induces up-regulation of pro-apoptotic proteins such as Bax, Bim, Bak, Puma and Noxa and down-regulates the expression of anti-apoptotic Bcl-2 and Bcl-xL (182, 183).

Both β -sitosterol and carnosol increase apoptosis through down-regulating Bcl-2 in human leukemia cells *in vitro* (74, 75). Curcumin down-regulates the expression of survivin and Bcl-2, while it up-regulates the expression of pro-apoptotic Bax leading to apoptosis in human multiple myeloma cells *in vitro* (77). Diallyl sulfide down-regulates the expression of both survivin and Bcl-2, but up-regulates the expression of Bax and p53 in mouse skin tumors (78). Eugenol prevents radiation-induced oxidative cell membrane damage resulting in formation of reactive oxygen species and induction of apoptosis in cells (184). [6]-Gingerol induces cell death with DNA fragmentation by inhibiting expression of Bcl-2 in promyelocytic leukemia cells *in vitro* (79). Lutein decreases the expression of Bcl-2 and increases the expression of Bax, stimulating apoptosis in esophageal carcinoma cells *in vitro* (81). In addition, mice fed lutein were found to have higher apoptotic activity in mammary tumors than control animals with an increase in expression of Bax and p53 and decrease in expression of Bcl-2 (96).

Rosmarinic acid induces apoptosis with corresponding suppression of Bcl-2 in human T-cell leukemia *in vitro* (82). S-allylcysteine inhibits Bcl-2 expression from hamster buccal pouch carcinogenesis, leading to apoptosis (83).

Many of the spice-derived nutraceuticals target caspases, which are essential for apoptotic cell death. Allicin activates caspases-3, -8, and -9 and increases PARP cleavage in cancer cells of both human and murine origin *in vitro* (86). Citral induces apoptosis in several hematopoietic cancer cell lines *in vitro* through activation of caspase-3 (87). Diallyl disulfide and diallyl trisulfide also induce apoptosis through the activation of caspase-3 (88, 89). Kaempferol induces apoptosis with significant DNA condensation with a marked increase in caspase-3 activity in human large-cell lung carcinoma cells *in vitro* (90). Myristicin triggers apoptosis through an accumulation of cytochrome C and caspase-3 activation in human neuroblastoma cells *in vitro* (92). [6]-Paradol causes proteolytic cleavage of caspase-3 to induce apoptosis in human squamous cell carcinoma *in vitro* (93). S-Allylmercaptocysteine activates caspase-3 by binding directly to tubulin and disrupting the microtubule assembly in human colon cancer cells *in vitro* (157). Shogaol induces apoptotic cell death in human hepatoma p53 mutant cells through a caspase-dependent mechanism (95). Terpinen-4-ol induces caspase-dependent apoptosis in human melanoma cells *in vitro* (94).

A few of the compounds have been shown to both activate caspase activity and down-regulate expression of

Bcl-2 or Bcl-xL. Ajoene activates caspase-3 and cleaves Bcl-2 in human myelocytic leukemia cells *in vitro* (153). Capsaicin down-regulates the expression of signal transducer and activator of transcription 3 (STAT3)-regulated gene products Bcl-2, Bcl-xL, and survivin, but activates caspases to induce apoptosis in multiple myeloma cells *in vitro* (70). Apoptosis in prostate PC-3 cells involves the mechanism of ceramide accumulation, and JNK and ERK activation in addition to ROS generation (155). Eugenol and related dimers induce cytotoxicity by way of interaction with the cell membranes of their phenoxyl and benzyl radicals (185). Limonene induces apoptosis by down-regulating expression of Bcl-2 and mutant p53 in human leukemia cells *in vitro* (80). In addition, limonene up-regulates Bax coupled with the release of cytochrome C from mitochondria leading to increased caspase-3 and caspase-9 (80, 91, 156). Gambogic acid (GA) is a derivative of the gamboge, a brownish residue from the *Garcinia hanburry* tree. It is a highly effective anticancer medication with low toxicity to normal tissue (186). According to studies seeking to explore the structure activity relation of GA, the 9, 10 carbon-carbon double bond of the alpha, beta-unsaturated ketone was responsible for biological activity (187). GA induces apoptosis by action with the transferrin receptor, thus increasing the action of TNF and inhibiting the NF- κ B signaling pathway (188); besides GA is also implicated in increasing the cellular expression of apoptosis-regulated gene Bax, and decreasing the expression of apoptosis-regulated factor Bcl-2 (189). GA is an inhibitor of survivin and reverses docetaxel resistance in stomach cancer cells (190). GA also represses telomerase activity, by repressing human telomerase reverse transcriptase (hTERT) transcriptional activity *via* c-Myc and posttranscriptional modification of hTERT *via* Akt (191). Studies have been conducted both *in vitro* and *in vivo* showing that GA can pass the blood-brain barrier and reduce glioma mass by triggering the intrinsic mitochondrial pathway of apoptosis and antiangiogenesis (192).

Sulforaphane activates apoptosis in breast cancer cells *in vitro* through the activation of the Fas ligand, which in turn activates caspase-3 and caspase-8. In other breast cancer cell lines, sulforaphane is also able to decrease Bcl-2 activity while activating caspase-3 and caspase-9, leading to PARP cleavage and apoptosis (84). Ursolic acid induces apoptosis in human colon cancer cells *in vitro* through down-regulation of Bcl-2 and increased expression of caspase-9 (85).

A few nutraceuticals have demonstrated the capability to induce apoptosis in tumor cells, but their specific mechanism or molecular targets are unclear. Canthaxanthin inhibits cell growth and induces apoptosis in human colon adenocarcinoma and melanoma cells *in vitro* (193). Cineole induces apoptosis in human leukemia cells *in vitro* with morphological changes with apoptotic bodies appearing (194). Crocin causes tumor cell shrinkage, vacuole-like areas, pyknotic nuclei, and reduced cytoplasm consistent

with apoptosis (195). Both sesamin and episesamin (an epimer of sesamin) induce apoptosis in human lymphoid leukemia cells *in vitro*, as demonstrated by such morphological changes as apoptotic bodies (196). Both sesamin and turmerone induce apoptosis in human leukemia cells seen by DNA fragmentation into oligonucleosomal-sized fragments (197).

Effect of Nutraceuticals on Tumor Cell Proliferation. One of the hallmarks of cancer is aggressive proliferation of cells. In normal cells, proliferation is finely regulated by a balance of growth signals and anti-growth signals. However, cancer cells often encounter uncontrolled growth from both ends—not only do they acquire the capability to generate their own growth signals, they also become insensitive to anti-growth signals (198). There are many important factors that regulate the cell through its natural progression; however, certain factors can be up-regulated causing the cell to replicate uncontrollably. Some of these major factors are the cyclins, a family of proteins that regulate cell cycle progression, plus COX-2, and c-Myc. The most commonly affected cyclin is cyclin D1, which is an important cell cycle regulator that transitions the cell from G1 phase to S phase. In cancers, cyclin D1 overexpression has been linked to the development and progression of the disease. Deregulation of cyclin D1 degradation appears to be responsible for the increased levels of cyclin D1 in several cancers. COX-2 is a protein that is normally absent from cells, but appears rapidly in large amounts in pathological and often inflammatory situations. COX-2 was first described as being induced by a viral oncogene or tumor promoter, but it has also been shown to be inducible by a variety of growth factors and mitogens, making it relevant to the processes of cell growth and carcinogenesis (199). c-Myc is an oncoprotein that functions as a positive regulator of G1-specific cdk and, in particular, cyclin E/cdk2 complexes, which is necessary for cell cycle transit from G1 into S phase. c-Myc prevents cell cycle arrest in response to growth-inhibitory signals, differentiation stimuli, and mitogen withdrawal, and activation of c-Myc induces entry into the cell cycle in the absence of growth factors (200). Uncontrolled proliferation can often also be attributed to the down-regulation or inactivation of tumor suppressor protein p53. The latter acts as a checkpoint in the cell cycle, either preventing or initiating programmed cell death. It is believed that 50–55% of all cancers can be attributed, at least partially to inactivation of p53.

Several spice-derived nutraceuticals have been shown to halt cell proliferation by affecting cell cycle factors, both *in vitro* and *in vivo*. These nutraceuticals are AITC, apigenin, bergapten, β -carotene, β -sitosterol, capsaicin, carnosol, cinnamaldehyde, cinnamic acid, crocin, curcumin, diallyl disulfide, diallyl trisulfide, eugenol, geraniol, limonene, lutein, perillyl alcohol, phytic acid, quercetin, rosmarinic acid, S-allylmercaptocysteine, sesamin, sulforaphane, and ursolic acid (Table 5) (55, 59, 70, 73, 76, 82, 89, 97–107, 143, 156, 195, 201–205). Apigenin causes a

decrease of c-Myc, cyclin D1, nuclear β -catenin and an increase of E-cadherin in the prostates of mice (97). In pancreatic cell lines, apigenin induced G2/M phase cell cycle arrest by reducing levels of cyclin A, cyclin B, phosphorylated forms of cdc2 and cdc25 which are proteins required for cell cycle transition (206). Eugenol suppresses COX-2 gene expression in mouse macrophages (143).

The majority of the nutraceuticals listed above affect cyclins and cyclin dependent kinases (cdk) causing cell cycle arrest. The most commonly affected cyclin is cyclin D1, which is an important cell cycle regulator that transitions the cell from G1 phase to S phase. Capsaicin down-regulates the expression of cyclin D1 causing multiple myeloma cells to arrest in G1 phase, thereby inhibiting proliferation (76). Lutein significantly down-regulates the expression of cyclin D1 and halts the cell cycle at G0/G1 phase in esophageal cancer *in vitro* (100). Sesamin was shown to down-regulate cyclin D1 expression in a wide variety of tumors including lung cancer, transformed renal cells, immortalized keratinocyte, melanoma, and osteosarcoma cells *in vitro*, as well induce growth arrest at G1 phase in human breast cancer cells *in vitro* (101). Sulforaphane down-regulates the expression of cyclin D1 and cell cycle transition regulators cdk4 and cdk6 in both mouse and human ovarian cancer cell lines *in vitro* (102). Ursolic acid down-regulates cyclin D1 expression in non-specific cell types *in vitro* (59).

Eugenol and curcumin target COX-2. Eugenol suppresses COX-2 gene expression in mouse macrophages *in vivo*. In addition, it inhibits the proliferation of human colon cancer cells *in vitro* by inhibiting COX-2 mRNA expression (143). Eugenol causes arrest of proliferating melanoma cells in the S phase of the cell cycle. Eugenol inhibits the E2F family of transcription factors; down-regulation of E2F1 is responsible for eugenol mediated growth inhibition of human melanoma cells (207). AITC, diallyl trisulfide, and S-allylmercaptocysteine (SA) all cause mitotic block by targeting tubulin. AITC disrupts α -tubulin in human adenocarcinoma cells *in vitro* resulting in mitotic block (201). Diallyl trisulfide directly modifies specific cysteine residues on β -tubulin molecules causing disruption of spindle formation and mitotic arrest in human colon cancer cells *in vitro* (89). SA binds directly to tubulin disrupting the MT assembly and thereby arresting cells in mitosis in human colon cancer cells *in vitro* (205). Apigenin has been shown to decrease both c-Myc and cyclin D1 in human colon cancer cells *in vitro* (97). It also inhibits geminin and Cdc6 at the mRNA and protein levels. Geminin and Cdc6 are proteins involved in replication of pancreatic cancer cell lines. It also decreased cell proliferation in Dunning rat prostate MAT Ly Lu model. Apigenin suppresses differentiation in normal human keratinocytes by decreasing AP-1 expression. It also inhibits increase in promoter activity associated with overexpression of protein kinase C-delta (PKC δ), constitutively active Ras, or MEKK1, which leads to a decrease in keratinocyte differentiation (208). Perillyl

Table 5. Inhibition of Proliferation by Spice-Derived Nutraceuticals

Nutraceutical	Cell type/animal model	Responses ^a
Allyl isothiocyanate	Human colon adenocarcinoma	↓ α -tubulin-mitotic block (201)
Apigenin	Human prostate cancer cells	↑ E-cadherin, ↓ nuclear translocation of β -catenin, ↓ c-Myc and cyclin D1 levels (97)
	TRAMP mice	↑ E-cadherin ↓ nuclear β -catenin, c-Myc, and cyclin D1 (97)
Bergapten	Human hepatocellular carcinoma	↓ cyclin B, $\perp$ G2/M (103)
	Human colon adenocarcinoma	↓ cyclin A, $\perp$ G2/M (73)
β -Sitosterol	Human breast cancer	$\perp$ G2/M (202)
Capsaicin	Multiple myeloma cells	↓ cyclin D1, $\perp$ G1, ↓ proliferation (70)
Carnosol	Human colonic adenocarcinoma	$\perp$ G2/M phase, ↑ cyclin B1 (104)
Cinnamaldehyde	Human hepatoma cells	S-Phase arrest (76)
Cinnamic acid	Lung adenocarcinoma cells	$\perp$ G1/G0 phase (203)
Crocin	Breast cancer cells	↓ proliferation (195)
Curcumin	Human HNSCC, mouse melanoma cells	↓ cyclin D1 (55, 99)
		↓ NF- κ B, ↓ COX-2, ↓ cyclin D1 (99)
	Mouse skin tumors	↓ tumor growth (99)
Diallyl disulfide	Human gastric cancer cells	G2/M arrest, ↑ p38 MAPK (204)
Diallyl trisulfide	Human colon cancer cells	↓ spindle formation, ↑ cyclin B1, mitotic arrest (89)
Eugenol	Human colon cancer cells	↓ proliferation, ↓ mRNA expression of COX-2 (143)
	LPS-stimulated mouse macrophage	↓ COX-2 (143)
Geraniol	Pancreatic adenocarcinoma cells	$\perp$ G0/G1, ↑ p21 and p27, ↑ cyclin A, ↑ Cdk2
		↑ cyclin B1 (105)
Limonene	Human erythroleukemia cells	$\perp$ G1 phase (156)
Lutein	Esophageal cancer cell line	$\perp$ G0/G1, ↓ cyclin D1 (100)
Perillyl alcohol	Bcr/Abl-transformed leukemia cells	↑ p21 and p27, ↑ cyclin A, ↑ cyclin B1, ↑ Cdk2
	Pancreatic adenocarcinoma cells	G0/G1 arrest (98, 105)
Phytic acid	Human colon carcinoma cell lines	↓ cell growth, ↓ cell proliferation, ↑ 53 and p21 gene, $\perp$ G1 phase (106)
Quercetin	Human hepatoma cells	$\perp$ G1, ↑ p21, ↑ p27, ↑ p53 (107)
Rosmarinic acid	Leukemia cells	↓ cyclin D3, ↓ p21, ↑ p27 (82)
S-Allylmercapto-cysteine	Human colon cancer cell lines	↓ growth, $\perp$ G2-M, ↓ MT assembly (205)
Sesamin	Human breast cancer cells, lung cancer, renal cells, immortalized keratinocyte, melanoma and osteosarcoma	$\perp$ G1 phase, ↓ cyclin D1 (101)
Sulforaphane	Human ovarian cancer cells	↓ cyclin D1, cdk4, and cdk6 (102)
Ursolic acid	Non-specific cell types	↓ cyclin D1 (59)

^a ↑, up-regulate; ↓, down-regulate; $\perp$, block/arrest; COX-2, cyclooxygenase; HNSCC, head and neck squamous cell carcinoma; MAPK, mitogen-activated protein kinase; MT, microtubule; NF- κ B, nuclear factor- κ B; TRAMP, transgenic mouse prostate adenocarcinoma.

alcohol also targets c-Myc causing c-Myc-dependent apoptosis through a G0/G1 cell cycle arrest in transformed leukemia cells *in vitro* (98). Phytic acid inhibits cell growth and decreases proliferation through the up-regulation of p53 in human colon carcinoma cell lines, leading to arrest in G1 phase (106). Quercetin also induces cell cycle arrest at G1 by elevating p53 in human hepatoma cell line *in vitro* (107).

The remaining nutraceuticals cause cell cycle arrest at various stages of the cell cycle, many through effects exhibited on cyclins. Bergapten (5-methoxypsoralen) inhibits cyclin B1 in human hepatocellular carcinoma cells *in vitro* preventing cells from entering M phase (103). β -Carotene inhibits the growth of several human colon adenocarcinoma cell lines *in vitro* by reducing the expression of cyclin A causing cell cycle arrest at G2/M phase. β -Sitosterol induces cell cycle arrest at G2/M phase in human breast cancer cells *in vitro* (202). Carnosol causes accumulation of human colonic adenocarcinoma cells at G2/M phase along with an increase in cyclin B1 *in vitro* (104).

Cinnamic acid causes cell cycle arrest at G1/G0 phase, therefore inhibiting the proliferation of lung adenocarcinoma cells *in vitro* (203). Crocin shows inhibition of growth in breast cancer cells *in vitro* (195). Diallyl disulfide induces G2/M phase arrest in human gastric cancer cell lines *in vitro* (204). The antiproliferative effect of gambogic acid results from its inhibition of the catalytic activity of topoisomerase (Topo) II α ; it binds to the ATPase domain of the enzyme Topo II α (209). In human gastric carcinoma cells, GA causes a cell cycle arrest in the G2/M phase by decreasing the CDK7 mediated phosphorylation of CDC2/p34 (210). Geraniol induces a G0/G1 cell cycle arrest that coincides with a reduction in the levels of cyclin A, cyclin B1, and cyclin-dependent kinase 2 proteins in pancreatic adenocarcinoma cells *in vitro*. It also results in an increase in the expression of cyclin inhibitor proteins p21 and p27 (105). Limonene halts the cell cycle at G1 phase in human erythroleukemia cells *in vitro* (156). Rosmarinic acid inhibits proliferation of leukemia cells *in vitro* by suppress-

Table 6. Inhibition of Invasion by Spice-Derived Nutraceuticals

Nutraceuticals	Response ^a
Allicin	Inhibited TNF- α induced ICAM-1 expression in HUVECs (120).
Allyl isothiocyanate	Down-regulated mRNA level and activity of MMP-2/-9 in human hepatoma SK-Hep1 cells (108).
Apigenin	Inhibited TNF- α induced ICAM-1 expression (119).
Caffeic acid	Inhibited MMP-9 activity in human hepatocellular carcinoma cell line (109).
Carnosol	Suppressed expression and activation of MMP-9 in mouse melanoma B16/F10 cells (110).
Croctetin	Suppressed advanced glycation end product-induced ICAM-1 expression in bovine endothelial cells (117).
Curcumin	Down-regulated MMP-2 expression and activity and expression of integrin receptors, FAK, and MT1-MMP in HEp2 cells (115).
Diallyl disulfide	Inhibited activity of MMP-2 and MMP-9 in HUVECs (64).
[6]-Gingerol	Suppressed expression and enzymatic activity of MMP-2/MMP-9 in human breast cancer cells (213).
Kaempferol	Inhibited TNF- α induced ICAM-1 expression (119).
Myricetin	Inhibited expression and activity of MMP-2 in colorectal cancer cells (116).
Phytic acid	Modulated integrin dimerization, cell surface expression and integrin-associated signaling pathway and secretion of MMP-9 in human breast cancer MDA-MB-231 cells (214).
Piperine	Inhibited the matrix metalloproteinase production in B16F-10 melanoma cells (68).
Quercetin	Decreased the expressions of MMP-2 and MMP-9 in PC-3 cells (111).
Sulforaphane	Inhibited the activation of MMPs (118).
Ursolic acid	Down-regulated MMP-9 in HT1080 human fibrosarcoma cell line (112).
Vanillin	Inhibited invasion and migration of cancer cells and inhibited enzymatic activity of MMP-9 secreted by the cancer cells (113).

^a FAK, focal adhesion kinase; HBMECs, human brain microvascular endothelial cells; ICAM-1, intracellular adhesion molecule-1; MMP, matrix metalloproteinases; MT1-MMP, membrane type 1-matrix metalloproteinases; PMA, phorbol 12-myristate 13-acetate; TNF- α , tumor necrosis factor- α ; VCAM, vascular cell adhesion molecule.

ing the expression of cyclin D3 and p21 while up-regulating p27 (82).

Effect of Nutraceuticals in Tumor Cell Invasion.

Invasion, also known as metastasis, involves the migration of cancer cells from their original site of origin to other parts of the body either via the bloodstream or lymphatic system. Some of the major factors influencing invasion, whether or not a tumor will metastasize, include the presence of MMPs and ICAM-1. MMPs are members of a family of enzymes that are instrumental in freeing cells from surrounding tissue, enabling them to move and spread. MMPs (specifically MMP-2 and MMP-9) are endopeptidases that degrade a wide range of basement membrane components, a process important for tumor invasion (211). It has been shown that if MMP-9 is blocked, colorectal cancer cells are unable to metastasize. This illustrates the importance of targeting MMP-9 to block its production and release, not only in colon cancer cell lines, but also in a variety of tumor cell lines. ICAM-1 is a type of intercellular adhesion molecule that is constantly present in low concentrations on the surface of leukocytes and endothelial cells. The concentration of ICAM-1 can be greatly increased by cytokine stimulation, such as from TNF or IL-1 β . ICAM-1 protein expression on the cell surface has been positively correlated with metastatic potential of five human breast cancer cell lines. ICAM-1 mRNA levels have been shown to be elevated in breast tumor compared with adjacent normal tissue (212).

Several spice-derived nutraceuticals have been shown through a variety of mechanisms to inhibit MMP-2, MMP-

9, and ICAM-1, thereby limiting the metastatic potential of tumors. These spice-derived nutraceuticals are allicin, AITC, apigenin, caffeic acid, carnosol, croctetin, curcumin, diallyl disulfide, [6]-gingerol, kaempferol, myricetin, phytic acid, piperine, quercetin, sulforaphane, ursolic acid, and vanillin (see Table 6) (64, 68, 108–113, 115–120, 213, 214). Allicin has been shown to inhibit the TNF- α induced expression of ICAM-1 in human endothelial cells (120) and kaempferol and apigenin have been shown to follow a similar mechanism in respiratory epithelial cells (119). Croctetin suppresses both ICAM-1 and MMPs in bovine endothelial cells (117).

The remaining nutraceuticals inhibit the expression MMP-2, MMP-9, or both. AITC suppresses both MMP-2 and MMP-9 at both protein and mRNA levels in human hepatoma cells *in vitro* (108). It also results in elevated tissue levels of tissue inhibitor of metalloproteinases (TIMP). In the Dunning rat prostate MAT Ly Lu model, treatment with apigenin was found to increase the intensity of connexin 43-mediated gap junctional coupling and decrease cell motility. In breast cancer cells, the HER2-HER3-PI3K-Akt pathway inhibition by apigenin also plays an important role in inhibition of the multiplication, survival, adhesion, and motility of cancer (165). Apigenin also has a role to play in inhibiting metastasis of lung melanoma cells by inhibiting vascular cell adhesion molecule-1 (VCAM-1) expression in a dose-dependent manner (215). *In vitro* studies have shown that apigenin inhibited invasiveness of tumor cells; the possibility is that it

would prevent tumor penetration of healthy tissues *in vivo* (216). Caffeic acid shows a strong inhibitory effect on MMP-9 activity in non-specific cell types *in vitro* (109). Carnosol results in a reduction of MMP-9 levels in mouse melanoma cells *in vitro* through the down-regulation of NF- κ B and AP-1 (110). Diallyl disulfide was shown to have an inhibitory effect on the activation of MMP-2 and MMP-9 in human umbilical vein endothelial cells *in vitro* (64). [6]-Gingerol inhibits cell adhesion, invasion, motility and activities of MMP-2 and MMP-9 in human breast cancer cell lines *in vitro* (213). Myricetin inhibits MMP-2 protein expression and enzyme activity in colorectal carcinoma cells *in vitro* (116). Phytic acid inhibits cancer cell adhesion, migration, and invasion in human breast cancer cells *in vitro*. This inhibited invasion is mediated through the modulation of integrin dimerization, cell surface expression, and the integrin-associated signaling pathway (214). Piperine inhibits MMP production in melanoma cells *in vitro* preventing the collagen matrix invasion in a dose-dependent manner (68). Quercetin decreases the expressions of MMP-2 and MMP-9 in a dose-dependent manner in prostate cancer cells *in vitro* (111). Ursolic acid induces down-regulation of MMP-9 gene in human fibrosarcoma cells *in vitro* (112).

Both sulforaphane and vanillin have shown *in vivo* effects in mice. Sulforaphane inhibits the activation of MMPs, thereby inhibiting lung metastasis induced by melanoma cells in mice. This led to a 95.5% inhibition of lung tumor nodule formation and 94.06% increase in the life span of metastatic tumor-bearing animals (118). Vanillin reduces numbers of lung metastasized colonies in mice with mammary adenocarcinoma when administered orally (113). In addition, vanillin inhibits invasion and migration of cancer cells and inhibits enzymatic activity of MMP-9 secreted by the cancer cells *in vitro* (113).

Effect of Nutraceuticals in Tumor Cell Angiogenesis. Angiogenesis is a physiological process where new blood vessels grow from pre-existing ones. Angiogenesis is a normal, natural process that occurs during growth and wound healing; however, angiogenesis is also a marker that a tumor had changed from a dormant to malignant state. The growth of human tumors and development of metastases depends on the de novo formation of blood vessels (217). Angiogenesis enhances tumor growth by delivering oxygen and nutrients to its interior via new blood flow. Some pro-angiogenic factors include IL-8, TNF, fibroblast growth factor-2 (FGF-2), and platelet-derived growth factor (PDGF). However, one of the most important factors in angiogenesis is VEGF, which has been shown to be a potent stimulator of angiogenesis *in vitro* (217). By limiting VEGF in tumors, the blood supply to the tumor is reduced by potentially causing blood vessels to die as well as preventing the growth of new ones. Inhibition of the VEGF tyrosine kinase signaling pathway blocks new blood vessel formation in growing tumors, leading to stasis or regression of tumor growth. Due to this, finding agents that

can down-regulate or inhibit the expression of VEGF or its signaling pathway in tumor cells may be very helpful in preventing increased tumor growth and metastasis.

Currently, there is only one FDA-approved pharmaceutical on the market, Avastin (bevacizumab), a monoclonal antibody directed against VEGF for patients with metastatic colorectal cancer. However, some major side effects of Avastin include gastrointestinal perforation, fatal pulmonary hemorrhage, and complications in wound healing (www.avastin.com) and it costs around \$4,400 a month for treatment.

Many spice-derived nutraceuticals have been shown to down-regulate the expression of VEGF *in vitro* and others have been shown to prevent new blood vessel formation *in vivo*. These nutraceuticals are AITC, alliin, caffeic acid, capsaicin, curcumin, diallyl disulfide, diallyl sulfide, gingerol, lutein, perillyl alcohol, phytic acid, quercetin, rosmarinic acid, and sulforaphane (see Table 7) (58, 64, 96, 110, 121–123, 126, 127, 147, 218–221).

AITC is highly potent in the down-regulation of VEGF and IL-1 β , IL-6, and GM-CSF, which are proinflammatory cytokines; it also elevates levels of IL-2 and TIMP, which are potent antiangiogenic factors (218). Also AITC down-regulates nitric oxide and TNF- α production, and inhibits tumor specific angiogenesis (218). Apigenin prevents the activation of downstream target gene VEGF and angiogenesis in hypoxic solid tumors (189). It also inhibits expression of hypoxia inducible factor (HIF) (219). In ovarian tumor cells, apigenin inhibits VEGF and HIF-1 via the PI3K/AKT/p70S6K1 and HDM2/p53 pathways (222). It also inhibits tube formation by human umbilical vein endothelial cells. Apigenin has an inhibitory effect on HGF (hepatocyte growth factor)-promoted invasive growth and metastasis involving blocking PI3K/Akt pathway and integrin β 4 functions. Alliin had been shown to significantly reduce VEGF secretion in human fibrosarcoma cells (121). Diallyl disulfide reduces the expression and secretion of VEGF in human promyelocytic leukemia cells *in vitro* (125). [6]-Gingerol blocks capillary-like tube formation by endothelial cells in response to VEGF secretion in human endothelial cells *in vitro* (126). Phytic acid significantly reduces VEGF in both pancreatic cancer cell lines and melanoma cell lines *in vitro* (129, 130). Gambogic acid inhibits VEGFR2 signaling, thus inhibiting angiogenesis and prostate tumor growth (221). Rosmarinic acid reduces VEGF expression in human umbilical vein endothelial cells *in vitro* (128). Sulforaphane inhibits gene expression of NF- κ B-regulated VEGF in human prostate cancer cells *in vitro* (58).

A few of the spice-derived nutraceuticals have been shown to reduce VEGF *in vivo*. Alliin has been shown to reduce the secretion of VEGF in the chick chorioallantoic membrane (CAM) assay (121). Caffeic acid inhibits the expression of VEGF in mice renal carcinoma (122). Diallyl sulfide significantly reduces serum levels of VEGF in melanoma cells in mice (64). In addition, a few nutraceut-

Table 7. Inhibition of Angiogenesis by Spice-Derived Nutraceuticals^a

Nutraceuticals	Responses
Allyl isothiocyanate	Acted as angiogenesis inhibitors through the down-regulation of VEGF and proinflammatory cytokines such as IL-1 β , IL-6, GM-CSF, and TNF- α and up-regulation of IL-2 and TIMP (218).
Apigenin	Inhibited expression of HIF-1 and VEGF in different cancer cells under both normoxic and hypoxic conditions (219).
Alliin	Inhibited both FGF2 and VEGF secretion from human fibrosarcoma cells.
Caffeic acid	Inhibited FGF2-induced EC tube formation and angiogenesis in CAM model (121).
Capsaicin	Suppressed STAT3 phosphorylation, HIF-1 α expression, vascularization and STAT3-inducible VEGF gene expression in Caki-I bearing mice (122).
	Inhibited VEGF-induced chemotactic motility, and capillary-like tube formation of primary cultured human endothelial cells (123).
	Reduced both VEGF-induced vessel sprouting in rat aortic ring assay and VEGF-induced vessel formation in the mouse Matrigel plug assay (123).
Curcumin	Reduced the overexpression of COX-2 and serum VEGF in hepatocellular carcinoma cell-implanted nude mice (220).
Diallyl sulfide	Reduced serum level of VEGF in B16F-10 melanoma bearing C57BL/6 mice (64).
Gingerol	Blocked VEGF-induced capillary-like tube formation in endothelial cells and inhibited sprouting in endothelial cells in the rat aorta and formation of new blood vessel in the mouse cornea (126).
Gambogic acid	Inhibited VEGF-induced proliferation, migration, invasion, tube formation, and microvessel growth of HUVECs (221).
	Inhibited tumor angiogenesis in xenograft prostate tumor model (221).
Lutein	Lowered angiogenic activity in mouse mammary tumor model (96).
Perillyl alcohol	Decreased the release of VEGF from cancer cells but stimulated the expression of Ang2 by endothelial cells (127).
Phytic acid	Decreased tumor microvessel density and inhibited tumor-secreted VEGF levels in prostate cancer animal model (147).
Rosmarinic acid	Inhibited angiogenesis, VEGF expression and IL-8 release in HUVECs (110).
Sulforaphane	Inhibited NF- κ B-regulated VEGF expression in human prostate cancer PC-3 C4 cells (58).

^a Ang2, angiopoietin 2; CAM, chick chorioallantoic membrane; COX-2, cyclooxygenase-2; EC, endothelial cell; FGF2, fibroblast growth factor 2; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIF-1, hypoxia inducible factor-1; HUVECs, human umbilical vein endothelial cells; IL-1 β , interleukin-1 β ; NF- κ B, nuclear factor- κ B; STAT3, signal transducer and activator of transcription 3; TIMP, tissue inhibitor of metalloproteinase; TNF- α , tumor necrosis factor- α ; VEGF, vascular endothelial growth factor.

icals have been shown to prevent angiogenesis by diminishing the growth of new blood vessel formation *in vivo*. These nutraceuticals are capsaicin, curcumin, lutein, perillyl alcohol, and quercetin. Capsaicin has been shown to inhibit VEGF-induced vessel sprouting in the CAM assay and rat aortic ring assay *in vivo* (123). Curcumin treatment results in the decrease in neocapillary density in nude mice with hepatocellular carcinoma (220). Lutein-fed mice were found to have lower angiogenic activity in mammary tumors in comparison to mice that were not supplemented with lutein (96). Perillyl alcohol prevents new blood vessel growth in the *in vivo* CAM assay (127). Quercetin displays an antiangiogenic effect in the CAM assay *in vivo* (223).

Conclusion

This review has illustrated the effects of nutraceuticals in spices on the initiation and progression of cancer. By analogy, including spice or spice-derived nutraceutical in one's diet should help prevent cancer. In addition, these nutraceuticals show great potential in being used as agents to aid in cancer treatment, either alone or in combination with existing standard of care. However, it is important to note that the majority of these nutraceuticals have only been

tested under pre-clinical conditions, either *in vitro* or in animal models. 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. This does not mean that these nutraceuticals shouldn't be used as an option in cancer treatment, as the beauty of using plant-derived nutraceuticals is that there is generally little to no cytotoxicity that occurs resulting in minor to no side effects in patients. What are the doses required to exert these effects and whether they could be obtained by consuming spices or whether they could only be obtained by using supplements, are the questions unclear at present. Whether long-term consumption of the spices by people from certain countries is directly linked to lower incidence of cancer and other chronic diseases, is supportive but not proven.

In addition, the spices mentioned in this article and their respective nutraceuticals that play a role in halting the various phases of tumorigenesis, support the idea that a diet high in plant-based foods may help prevent and treat disease. Many of the spices mentioned in this article have been regarded in a variety of cultures as having health benefits for centuries, such as garlic and ginger. However,

some of the spices have begun to receive more and more attention due to their nutraceutical composition and their effectiveness in disease prevention and treatment. 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. The possibility for spices to exhibit multiple effects and for ability to counteract treatment regimens exists just like any other drug. Unlike conventional drugs, however, spices have been consumed by healthy people for centuries.

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