

Spices; a mechanistic anticancer treatise

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Abstract

Spices are the promising and cost effective choice due to their high antioxidant activity, ability to triggers the free radicals scavenging ability at cellular level thereby alleviating various metabolic syndromes. They are good and enrich source of bioactive moieties such as curcuminoids, curcumin limonene, allicin, cinnamic aldehyde, 2-hydroxycinnamaldehyde, allyl isothiocyanate, eugenol, zingiberone, gingerol, dipropyle disulfides, and zingiberene, have been identified as chemo-preventing agents against various malignancies. Chemo-preventive properties of spices are mediated by functional bioactive ingredients that arrest the activity of cytochrome P450 and isozymes CYP

1A1, cyclooxygenase-2, reducing activator of transcription-3 (STAT-3) and signal transducer. They are closely associated with tumorigenesis activated by interleukin-6 (IL-6) receptors and epidermal growth factors (EGF) relate to an array of tumors. They altered the expression of protein involved in cell cycle, activating caspases killer and suppressing Kappa-B activation. The current review article explains the health endorsing perspectives of all spices and their daily use in life.

Keywords: Spices, composition, chemo-preventive agent, anticancer potential, anti-diabetic role

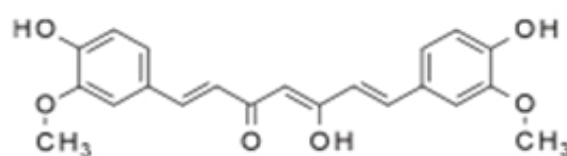
Introduction

There are approximately 180 spice-derived bio-active components have been reported as effective against various degenerative human diseases.¹ Herbs and spices are widely utilized as preventive and curative agents in degenerative diseases in Middle East since approximately 5000 BC.² These spices showed an impressive biological responses and curing role against wide arrange of ailments such as cancer, diabetes, cardiovascular and etc. These are potential source of chemical substances such as polyphenols, flavonoids, quinines, polypeptides, terpenoids, alkaloids and behaved like as antioxidant. They are valuable mixtures of mainly terpenoids like geraniol, linalool, menthol, α -terpineol, borneol, citronnillol, thujanol, and phenols including carvacrol, thymol, gaiacol, and eugenol and aromatic aldehydes i.e. cuminal, cinnamaldehyde, and phellandral. These are isolated from different parts of the plant such as buds, seeds, flowers, twigs, leaves, wood, bark, and roots.³ Spices and herbs suppress the oxidative rancidity, slow down the development of off-flavor and retardation of microbial growth in food containing products such as snack foods and meat products.⁴

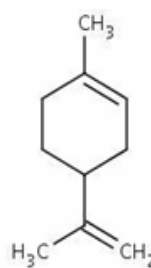
Turmeric

Turmeric (*Curcuma longa*) belongs to *Zingiberaceae* and comprises phenolic compounds and terpenoids such as diarylpentanoids, diarylheptanoids, sesquiterpenes, monoterpenes, triterpenoids, diterpenes, sterols, and alkaloid etc. Curcumin (diferuloyl methane) as the principal compound is comprises of 3-15% of turmeric and was isolated in 1815, while its chemical structure was determined in 1910 (Figure 1). It is a mixture of three curcuminoids 71.5% curcumin (curcumin I) (1), 19.4% demethoxycurcumin (curcumin II) (2), and 9.1% bisdemethoxycurcumin (curcumin III).⁵ Singh and Aggarwal⁶ determined that turmeric suppressed the activation of NF- κ B induced by PMA, TNF- α , or H₂O₂ through blocking the phosphorylation of IKK α . It abrogates LPS induced mitogen activated protein kinase (MAPK) activation and the translocation of NF- κ B p65 in DCs.

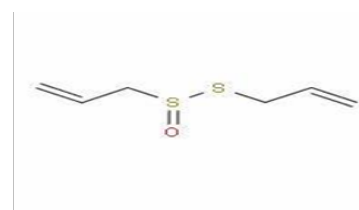
Curcumin down regulates TNF- α induced NF- κ B activation. In addition to, curcumin also blocks I κ B α degradation, cytokine-induced NF- κ B DNA binding activity, IKK activity in HT-29, RelA nuclear translocation, I κ B serine 32 phosphorylation, Caco-2, and EC-6 cells. The previous explorations of Kato et al.⁷ determined that high administration of curcumin high-dose of curcumin inhibited the BCG-induced IL-8 production and LPS-mediated TLR2 mRNA induction on mouse splenic macrophages in human monocytes and gingival fibroblasts through suppressing NF- κ B activation. Likewise, it also inhibits the activity of NF- κ B in primary ATL cells and HTLV-1 infected T-cell lines by abolished constitutive phosphorylation of Tax-induced NF- κ B transcriptional activity and I κ B α .⁸



Curcumin



Limonene



Allicin

Figure 1 Chemical compounds in spices

Curcumin also showed the anti-carcinogenic and chemopreventive role against numerous targets such as, apoptotic genes, growth regulators, adhesion molecules, cellular signaling molecules, transcription factors, and angiogenesis regulators. Curcumin also inhibits the activation of activator protein-1 (AP-1) by blocking phosphorylation of I- κ B through inactivation of I- κ B kinase complex.⁹ The findings

of Leu and Maa¹⁰ assessed that curcumin reduced the activity of a number of different enzymes including cytochrome P450 and COX-2. Similarly, it also induced apoptosis in a number of different cells including prostate cancer cells, inhibited the AP-1 and down regulates endogenous bcl-2 and baxxL proteins in DU145 cells.¹¹

Table 1 Chemical composition of spices

Spices	Constituents	References
Turmeric	sesquiterpenes, monoterpenes, triterpenoids, diterpenes, sterols	5
Clove	eugenol, alpha-terpinyl acetate, alpha-humulene	12
Basil	carvacrol, borneol, methyl eugenol, iedol	15
Cumin	Thymoquinone, cuminaldehyde	22
Ginger	beta-bisabolene, curcumene, betaphellandrene, camphene	25
Garlic	alliin, cycroalliin, diallyl disulphide (DADS), and ajoene, β -phellandrene	29

Table 2 Anticancer role of spices

Spices	Mechanisms	References
Turmeric	Suppressed the activation of NF- κ B	6
	Blocked the phosphorylation of IKK α . It abrogates LPS	
	Inhibited the BCG-induced IL-8 production and LPS-mediated TLR2 mRNA induction	7
	Suppressed the activity of NF- κ B in primary ATL cells and HTLV-I infected T-cell lines	8
Clove	Inhibited the activation of activator protein-1 (AP-1) by blocking phosphorylation of I- κ B through inactivation of I- κ B kinase complex.	9
	Down-regulated the H-ras, c-Myc, and Bcl2 expression	13
	Up regulated the Bax, p53, and active caspase-3 expression	
Basil	Suppressed the growth of orthotopically transplanted cancer cells	16
	Up regulated the genes that suppress the induce apoptosis (BAD), and metastasis (E-cadherin) Down regulated such genes that promote chemo/ radiation resistance, and survival (Bcl-2 and Bcl-xL).	
Cumin	Induced apoptosis on p53-deficient lymphoblastic leukemia Jurkit cells mediated by p73-dependent pathway	23
	Inhibited the activation of I-kappa B alpha-kinase, I-kappa B alpha degradation, I-kappa B alpha phosphorylation, p65 nuclear translocation, the NF-kappa B-dependent gene expression	24
	Down regulated the expression of proliferative (cyclooxygenase-2, c-Myc, and cyclin D1), NF-kappa-B-regulated antiapoptotic (IAP1, IAP2, Bcl-xL, XIAP Bcl-2, and survivin)	26
Activated caspase and up regulated p21 level		
Ginger	Down regulated cyclin A, cyclin B1, Cdc25C, Cdc2	31
Garlic	Caused arrest at G2/M phase of cell cycle	
	Enhanced phase 2 detoxifying processes	

Clove

The herbs and spices stimulates the pancreas to interfere with dietary glucose absorption, produce and recreate insulin, and insulin sparing action of the bioactive ingredients. Clove is prominent source of essential oils such as caryophyllene, eugenol, alpha-terpinyl acetate, alpha-humulene, methyl eugenol, eugenyl, naphthalene, actyl eugenol, heptanone, sesquiterpenes, chavicol, vanillian, and methyl salicylate pinene and used in many food based products.¹² Skin tumors were induced by application of DMBA croton oil and eugenol was orally administered for 15 days to subjects to curtain the cancer effects. Eugenol treated mice were developed the 42% skin anti-tumor effect as compared to control rats. The mean height (0.519 cm) of skin tumors of eugenol treated group was significantly higher than control group (1.789 cm). The orally administrated eugenol is restricted the proliferation of carcinogenesis at the premalignant stage. It also down-regulates the H-ras, c-Myc, and Bcl2 expression along with up regulates the Bax, p53, and active caspase-3 expression in the skin lesions of the rats. Furthermore, eugenol protects the depletion of GSH and antioxidant enzymes caused by TPA.¹³ Prakash and Gupta¹⁴ determined that orally administrated clove protect the living organism from damage caused by free radicals, lipid per-oxidation, DNA strand breaking, and protein damage.¹⁴

Basil

The basil (*Ocimum sanctum*) belongs to family *Labiatae*. It is promising source of essential oil such as octane, α -Thujene, ethyl 2-methyl butyrate, α -pinene, (Z)-3-hexanol, myrecene, β -pinene, limonene (Figure 1), ethyl benzene, allo-oc-imene, terpinolene, α -cubebene, butyl-benzene, eugenol, linalool, carvacrol, borneol, methyl eugenol, iedol, humulene oxide, germacrene-D, τ -cadinol, α -guaiol, (EZ)-famesol, α - bisbolol, elemol, cissesquisainene hydrate, selin-11-en-4- α -ol, tetradecanal, and 14-hydroxy-f-humulene. These bioactive ingredients depends on the processing & storage conditions, type of soil, and harvesting time.¹⁵ Basil bioactive compounds suppress the different stages of cancer such as invasion, migration, proliferation, and induce apoptosis of cancer cells. They also down regulate the FAK, activated ERK-1/2, and p65 (subunit of NF- κ B). The aqueous extract of basil considerably suppresses the growth of orthotopically transplanted cancer cells. It up regulated the genes that suppress the induce apoptosis (BAD), and metastasis (E-cadherin) and down regulated such genes that promote chemo/radiation resistance, and survival (Bcl-2 and Bcl-xL).¹⁶ Basil possesses the anticancer mechanisms through the following (1) lowering nitric oxide amount, decreasing the incidence of 3-methyl di-methyl amino azobenzene, and benzo (a) pyrine-induced neoplasia and inducing hematomas in rats.¹⁷ The utilization of ethanolic extract of basil leaves significantly lower the values of papillomas tumor incidence in the skin of albino mice.¹⁸ Another group of researchers, they noted that basil reduced the size of tumor cells and enhanced the life expectancy of mice having Sarcoma-180 solid tumors. The promising components of basil plant such as urosolic acid and oleanic acid exhibit anticancer activity in Lewis- lung carcinoma rats.¹⁹ The alcoholic extract of basil plant enhances the activities of cytochrome b5, glutathione S-transferase, cytochrome p450, and aryl hydrocarbon hydroxylase that detoxify the carcinogens and mutagens.²⁰

Cumin

Cumin (*Nigella sativa*. L) belongs to family *Ranunculaceae* and is promising source of thymoquinone, thymol and dithymoquinone compounds. These compounds are effective against cardiovascular,

different types of human cancers, diabetes complications, kidney disease, asthma etc.²¹ Thymoquinone (TQ) shows anti-cancer effect against human myeloblastic leukemia HL-60 cells. It also induces apoptosis linked with DNA laddering and a decrease in mitochondrial membrane potential in 518A2 melanoma and HL-60 cells. Thymoquinone inhibits the MCF-7 breast cancer cells lines in mice.²²

*It also induces apoptosis in HepG2 cell line. It also induces apoptosis on p53-deficient lymphoblastic leukemia Jurkat cells mediated by p73-dependent pathway that targets the epigenetic integrator UHRF1 and HDAC1, and DNMT1.*²³ Thymoquinone suppresses the NF-kappa B activation through inhibition of the activation of I-kappa B alpha-kinase, I-kappa B alpha degradation, I-kappa B alpha phosphorylation, p65 nuclear translocation, the NF-kappa B-dependent gene expression, and p65 phosphorylation. It inhibits the direct binding of recombinant p65 and nuclear p65 to the DNA, and this binding was reversed by DTT. It did not suppress p65 binding to DNA when cells were transfected with the p65 plasmid containing cysteine residue 38 mutated to serine. It also down regulates the expression of proliferative (cyclooxygenase-2, c-Myc, and cyclin D1), NF-kappa-B-regulated antiapoptotic (IAP1, IAP2, Bcl-xL, XIAP Bcl-2, and survivin), and angiogenic (vascular endothelial growth factor and matrix metalloproteinase-9) gene products.²⁴

Ginger

Ginger (*Zingiber officinale*) belongs to the *Zingiberaceae* and prominent source of gingerol (5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one. It comprises of carbohydrates 60-70%, water 9-12%, protein 9%, ash 8%, fatty oil 3-6%, crude fiber 3-8%, and volatile oil 2-3%. It is also promising source of essential volatile oils including 30-70% alpha-zingiberene, 15-20% beta-sesquiphellandrene, 10-15% beta-bisabolene, curcumene, betaphellandrene, camphene, and zingiberene. Gingerol suppresses the production of reactive oxygen species induced by ferric chloride FeCl3-ascorbatesystem and also inhibits the oxidation activity of xanthine. It also enhances the concentration of catalase and SOD in the tissues whilst the level of oxidized glutathione lowers. Likewise, it inhibits the colon carcinogenesis induced through aprocarcinogen, dimethylhydrazine (DMH).²⁵

The previous findings of Hsu et al.²⁶ demonstrated that 6-dehydrogingerdione (DGE) prevented from the breast cancer through activating caspase, up regulating p21 level and down regulating cyclin A, cyclin B1, Cdc25C, Cdc2, and hence arrested cells at G2/M phase and caused apoptosis. Similarly, 6-gingerol has anticancer effect on cell proliferation, NF- κ B activation, and angiogenesis and also arrests cell cycle at G1 phase through down regulating cyclin D1. In addition to, 6-paradol and 6-gingerol have exhibited a strong anti-cancer activity through inhibiting TNF- α production in TPA-treated female ICR-mice. Apparently, ginger work as an anti-cancer agent through blocking NF- κ B activation by the inhibition of TNF- α pro-inflammatory cytokine.²⁷

Garlic

Garlic (*Allium sativum* L) is the most widely researched and oldest cultivated plant and has been used in food based products for over 4000 years. The garlic word was derived from the Anglo-saxon 'gar-leac' or spear plant. It contains more than 200 chemical compounds and more important compounds are alliin (Figure 1), alliin, cycloalliin, diallyl disulphide (DADS), and ajoene, β -phellandrene, geraniol, citral, α -phellandrene, linalool and enzymes (allinase, myrosinase, and peroxidase).²⁸ Regarding pharmacological role, garlic has potential to

prevent the cells from the different cancer stages through neutralizing free radicals, enhancing glutathione contents, increasing the activities of antioxidant enzymes i.e. s-transferease, glutathione, catalase, suppression of cytochrome p4502E1, preventing of chromosomal damage1, and DNA repair mechanisms. As an anti-carcinogenic agent, garlic and its organosulfur compounds (OSCs) inhibit the cell proliferation through blocking cell cycle progression, inhibition of DNA adduct formation, inducing apoptosis, up regulation of antioxidant defenses, modulation of carcinogen metabolism, and DNA repair systems.²⁹ These dietary bioactive OSCs modulate the cancer cascades and acts as potential chemo preventive and chemotherapeutic agents.³⁰ The selenium-enriched garlic or garlic sulfur analogues and its extracts exhibit the higher rate of inhibition of progression of carcinogenesis and breast cancer cells in rats. The garlic and its oil soluble compounds such as diallyl disulfide (DADS) are more effective to synergize the effect of antagonize the effect of linoleic acid and eicosapentaenoic acid. These sulphur containing compounds suppress the carcinogen activation, cause arrest at G2/M phase of cell cycle, enhance phase 2 detoxifying processes, increase acetylation of histones, induce mitochondrial apoptotic pathway, influence gap-junctional intercellular communication, involvement in signal transduction, modulation of cellular redox state, and post-translational modification.³¹

Cinnamon

Cinnamon is primarily used in the food based products such as perfumes, and medicinal due to its fragrance. Cinnamon is prominent source of cinnamaldehyde and trans-cinnamaldehyde essential oils that exhibited various health endorsing properties.³² It is promising source of several bioactive components i.e. cinnamaldehyde, cinnamic acid, cinnamate, and several essential oils including cinnamyl acetate, trans-cinnamaldehyde, L-borneol, eugenol, b-caryophyllene. Cinnamon shows the anticancer activity in mouse melanoma that are mediated by modulation of angiogenesis and cytotoxic activity of CD8+ T cells. It also induced the apoptosis in a cancer cells lines. Similarly, it reduces the levels and activities of AP1 and NF- κ B and their target genes such as Bcl-2 and BclxL.³³ Moreover, cinnamon significantly decreases the growth rate of SiHa cells in a dose dependent manner and restricts the growth of cervical cancer cells in rats.³⁴ The photo-chemo-preventive activity through suppressing reactive oxygen species-induced photo-oxidative stress in cells of human skin were reported. Similarly, oral supplementation of cinnamon and cinnamaldehydes suppressed the thioredoxin reductase and activated the Nrf2 in a murine xenograft model of the disease.³⁵ Cinnamon and its polyphenols extract suppressed the proliferation of cancer cells lines and induced cell death of tumor cells through inhibiting AP1 and NFkappaB activity and their target genes i.e. Bcl-xL, Bcl-2, and up-regulating pro-apoptotic molecules.³³ It also lowers the levels of HIF-1 α and Cox-2 in melanoma cell lines and in the melanoma mouse model.³⁶ Cox-2 expression is associated with growth factors such as FGF, EGF, and VEGF and cytokines including IL1-b, and TNF-a. The increased level of Cox-2 enzyme is led to tumor progression through inducing angiogenic and metastatic progression and immune suppression. Hence, cinnamon treatment lowers the Cox-2 and HIF-1 α expression in the tumor tissues.³⁶

Rosemary

Rosemary (*Rosmarinus officinalis* L.) belongs to the family *Lamiaceae* and is being used as a food flavoring agent due to its powerful antimicrobial, anticancer, anti-diabetic activities and also as a chemo-preventive agent.³⁷ It constitutes a wide variety of

bioactive phytochemicals such as, carnosic acid, carnosol, 7-methyl-epirosmanol, rosmanol, rosmadial, isorosmanol, rosmaridiphenol, caffeic acid, and rosmariquinone, approximately 90% of the antioxidant activity of rosemary is owing to the presence of carnosol and carnosic acid.³⁸ Chemoprevention is a strategy to the administration of chemical agents, individual drugs and as naturally occurring compounds to curtail the effects of cancer proliferation. Rosemary extracts lowers the NF- κ B activation, TNF- α -induced ROS generation, and then enhanced the TNF- α -induced apoptosis.³⁹ Carnosol is induced the apoptotic cell death in lymphoblastic leukemia carnosol and lowered the tumor proliferation. It also reduces the cell death in the pre-B ALL lines REH, and SEM, RS4;11. Rosemary bioactive compounds show the anticancer activity through enhancing the serum level of CYT-C in colorectal cancer-induced rats. This anticancer activity is attributed due to carnosol, rosmarinic acid, carnosic acid, rosmanol and ursolic acid compounds.⁴⁰ In another study, Kim et al.⁴¹ determined that ursolic acid suppress the different stages of cancer such as tumorigenesis, tumor promotion, and angiogenesis. Ursolic acid induces apoptosis in human breast cancer cell line, MDA-MB-231 and lowers the cell proliferation rate. It also induces apoptotic molecules related to either extrinsic or intrinsic apoptosis signal pathway in MDA-MB-231 cells.⁴²

Oregano

The oregano (*origanum vulgare*) belongs to family *Lamiaceae* and comprises of oleanolic acid, flavonoids, ursolic acid, caffeic, terpinene, hydroquinones, p-cymene, carvacrol, lithospermic, thymol, and rosmarinic acids, and tannins. Phenolic compounds have 71% of the total oil.⁴³ The ethanol crude extract of oregano show anti-proliferative activity in MCF-7 human breast adenocarcinoma cell lines.⁴⁴ The earlier findings of Yin et al.⁴⁵ determined that carvacrol suppressed the growth of human hepatocellular carcinoma cell line HepG-2 through inducing apoptosis. The investigations of Sriharia et al.⁴⁶ determined that oregano exhibited the anticancer activity through the suppression of the development of induced colon cancer in rats in a dose and time dependent manner. It also has preventive role against radiation induced DNA damage and oxidative stress. Carvacrol and thymol protect the DNA from variety damaging agents and inhibit the proliferation of cancer cells.⁴⁷ Likewise, Stanojković et al.⁴⁸ observed that oregano extract exhibited the significant proliferative activity against human breast cancer cell lines (MDR-MB-453), and (MDA-MB-361).

Conclusion

The spices and bioactive molecules have been found for their promising phytochemical profiles. A summary of the chemical compositions of spices and their anticancer mechanisms can be seen in Tables 1 and 2. The chemical structures These phytochemicals include chlorogenic acid, caffeic acid and kaempferol which exert strong anticancer potential against different human cancer cells lines. These compounds also induce apoptosis, caused cell cycle arrest, and suppress the invasion and suppression of cancer cells lines. Researchers and investigators are trying to explore new phytochemicals which have been could be open the new horizons to treat other human disorders.

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