Systematic Reviews in Pharmacy., 2016;7(1):46-56
A Multifaceted Review Journal in the field of Pharmacy and Allied Sciences
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Review Article

Spices as an Alternative Therapy for Cancer Treatment

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ABSTRACT

Cancer is among the leading causes of morbidity and mortality worldwide. Current therapy available for cancer treatment is associated with number of side effects. However, plants offer an alternative route for the treatment of cancer. In fact Traditional Knowledge of using herbs and spices for medicinal purposes provide promising new leads that could be utilized for developing new therapies for cancer treatment. The therapeutic properties of spices is due to bioactive components such as alkaloids, terpenes, flavonoids, phenylpropanoids and anthocyanins present in them. Many of these spice derived secondary metabolites have the ability to trigger free radical scavenging pathway at cellular level and thus protect from various metabolic syndromes. Some of the spice based active constituents which are widely known for their chemopreventive action against various malignancies are curcumin and curcuminoids (turmeric), limonene (cardamom), allicin, allyl isothiocyanate (garlic), cinnamic aldehyde, 2-hydroxycinnamaldehyde and eugenol (cinnamon), gingerol, zingiberone, zingiberene (ginger), dipropyle disulfides and quercetin (onion), piperidine piperine, (black pepper), crocetin, crocin and safranal (saffron). These therapeutic agents arrest the activity of cytochrome P450 and isozymes CYP 1A1, cyclooxygenase-2, reducing the activator of transcription-3 (STAT-3) and signal transducer. In addition to this they also down regulate expression of cell cycle protein which in activate caspases killer and suppress Kappa-B activation. Spices also act serve as immunomodulators and regulate inflammatory disorders. The present review highlights the role of common spices in combating cancer.

Keywords: Cancer, Spices, Allium, Curcumin, Basil, Pepper.

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DOI : 10.5530/srp.2016.7.7

INTRODUCTION

Herbs and spices are intimately linked with food. There are number of evidences available which highlight the role of foods in providing particular heath benefits. Hippocrates has rightly said "Let food be thy medicine and medicine be thy food". Continuous efforts are being made by various laboratories to find out the role food and its ingredients such as spices against various deadly diseases. Spices are generally described as aromatic plants whose main role is in the seasoning of food besides providing nutrition.[1,2] From the time immemorial spices have been used in Traditional Medicine for the treatment of different diseases. For example their role in fighting indigestion, skin diseases, viral and bacterial infections, inflammation and neurodegenerative disorders is well documented. Research carried out in different laboratories have demonstrated the role of phytochemicals derived from spices against various cancer cell lines including pancreatic, colon, breast and lung.[3] The phytochemicals present in spices inhibit carcinogenesis through their bioactive components which block the activity of cytchrome P450, cyclooxygenase -2, and downregulate signal tranducers. The bioactive components also influence the expression of proteins involved in cell cycle, activate caspases killers and supress kappa beta–activation.[4] Some of the spice based biologically active components that are responsible for the anticancer effects are curcumin, diallyl sulfide, S-allyl cysteine, allicin, lycopene capsaicin, catechin, euginol, isoeuginol, isoflavones, saponins, D-limonene. They carry out their function by altering cell proliferation pathways , transformation, inflammation and metastasis.[5] Spice have also been categorized as immune boosters. This certainly has increased their demand many folds globally.[6] There are studies showing that 6 out of every 10 people with cancer use herbal medicine and some of them overlap with food.

Cancer is an uncontrollable and to a large extent incurable disease. It may occur at any time at any age and in any part of the body. It is caused by a complex, poorly understood interplay of genetic and environmental factors. It is a major public health burden in both developed and developing countries. It kills annually about 3500 per million populations around the world. One of the reasons for the development of cancer is, metabolically generated free radicals in the body. They may bring about various changes in the body which include cell injury, gene mutation, and consequently lead to development of cancer. Natural products are the most important anticancer agents. Literature survey reveals that out of 140 anticancer agents approved since 1940 and available for use approximately 60% have originated from natural origin.[7,8] The vinca alkaloid isolated from the plant *Vinca rosea* and the taxanes from the bark of Western yew *Taxus brevifolia* are some of the cytotoxic compound which are commonly used in cancer treatment.[9] Other important compounds which fall in this category include paclitaxel and docitaxel. These compounds have been semi synthetically derived from camptothecin.[10]

Drugs which have been conventionally used and are available in the market are based on one disease–one drug–one strategy. But drugs belonging to this category will be of limited use for cancer treatment since pathogenesis of cancer is multifactorial in nature. Nevertheless, plant drugs whose therapeutic efficacy is due to synergistic action of biologically active components offer a new approach of treatment.[11] Under the present circumstances it becomes essential to discusses chemopreventive role of some of the widely used spices against various malignancies. The present study highlights anticancer properties of dietary spices which could be utilized for developing new strategies for cancer treatment.

A large number of synthetic chemo preventive agents are also available for the treatment of various types of cancers, but because of the side effects associated with them their use is limited. Also the treatment available today is at times beyond the reach of common men. There is an urgent need to explore alternative sources for effective and less toxic drugs. This alternative source could be microbes, marine flora and fauna and of course medicinal plants particularly spices. A number of laboratories and pharmaceutical industries are engaged in new drug development from natural sources. More than 50% of all modern drugs in clinical use have been derived from natural resources. At present there are more than 1500 anticancer drugs in the process of development and over 500 of the drugs under clinical trials. It needs to be emphasized here that synthetic drugs derived from the natural sources are mostly based on single constituent showing biological activity. But the medici-

nal activity of a medicinal plant is because of synergistic and antagonistic interaction of various constituents present in it. Therefore while developing a new drug one needs to understand the synergistic and antagonistic interaction of different constituents of the plant.[11] Drugs developed using this approach are cheap, less toxic and compatible to the human body. But it requires knowledge on traditional uses of plants for cancer treatment. Literature survey reveals number of plants particularly spices showing anticancer properties. Some plants work as anticancer agent by enhancing the detoxification function of the body whereas there are certain plants which function by reducing the side effects of chemotherapy and radiotherapy. The health benefits associated with spices arise from their antioxidant and immunomodulatory properties. Numbers of researchers have contributed evidences on the possible action of natural antioxidants in suppressing and eradicating oxidative stress and in the treatment of cancer. In fact many of them have the ability to induce apoptosis in various cancer cells of human origin and are being marketed as anticancer drugs. The present study discusses some ethnomedicinally important spices which have been shown to have anticancer activities.

Anise (*Pimpinella anisum L.*)

Pimpinella anisum L. is an annual herb and a grassy plant with white flowers and small green to yellow seeds, which grows in the Mediterranean region, India and many other warm regions in the world. *Pimpinella anisum L.* is primarily grown for its fruits (seeds) that are currently used for flavouring and for different purposes. The essential oil from *Pimpinella anisum L.* seeds is used in food preparation, traditional medicine and perfumery industry. Anise seeds have several therapeutic effects[12] on several conditions such as digestive, neurologic, cough[13] and respiratory disorders. Ethanolic extract of anise seeds has significant anticancer effect on prostate cancer (PC-3 cell line) compared to normal cell line (L6)[14,15] and promyloleukemic cell by activation of nuclear factor κB[16] (Dirsch *et al*., 1998).

Chemical studies demonstrated that anise contains estrarole, anethol, eugenol, anisaldehyde, methylchanicol, coumarins and terpenes among others as the major compounds[17] (Table 1). Anise and its compounds have been identified as free radicals or active oxygen scavengers.[18] These ingredients seem to be an important first-line defense against harmful stimuli.[19]

BayLeaf (*Cinnamomum tamala)*

Cinnamomum tamala commonly known as Tejpata belongs to family Lauraceae. It is a moderate sized evergreen tree attaining a height of 8 m, and a girth of 150 cm. Its bark produces mucilage and leaves are lanceolate, glabrous, alternately placed, opposite and short stalked. 3-nerved from the base. *Cinnamomum tamala* is found in tropical and sub-tropical Himalayas, Khasi and Jaintia hills and in eastern Bengal, India. The essential oil from the tejpatta leaves, mostly contain monoterpenoides. Linalool (50%) is the major compound, whereas a-pinene, p-cymene, ß-pinene and limonene range around 5 to 10% each cinnamic aldehyde 1% and phenylpropanoids is present only in traces.

The leaves are used extensively in northern India as a spice-Tejpat (Table 1). Leaves of *C. tamala* are used in colic and diarrhoeal preparations. The plant is useful in the treatment of circulation, muscles and joints complications and relieves arthritis, inflamed joints, muscular pains, rheumatism and sprains.[20] Ethanolic extract of tejpatta has shown the cytotoxic and antitumor properties Ehrlich ascites carcinoma (EAC) in mice.[21] CT is found to be selectively cytotoxic to human cancer cells, thus emphasizing its potential antitumor activity.[22]

Basil (*Ocimum sanctum)*

Ocimum sanctum (also tulsi, tulasī, or Holy Basil) is an aromatic plant in the family Lamiaceae which is native throughout the old world tropics and widespread as a cultivated plant and an escaped weed. The leaf of *Ocimum sanctum* (OS) contains 0.7% volatile oil comprising about 71% eugenol and 20% methyl eugenol. The oil also contains carvacrol and sesquiterpine hydrocarbon caryophyllene.[23]

Fresh leaves and stem of OS extract yielded some phenolic compounds (antioxidants) such as

cirsilineol, circimaritin, isothymusin, apigenin and rosameric acid and appreciable quantities of eugenol.[24] Two flavonoids, viz., orientin and vicenin from aqueous leaf extract of OS have been isolated ursolic acid, apigenin, luteolin, apigenin-7-O-glucuronide, luteolin-7-Oglucuronide, orientin and molludistin have also been isolated from the leaf extract2 (Table 1) . OS also contains a number of sesquiterpenes and monoterpenes viz., bornyl acetate, α-elemene, neral, α-and β-pinenes, camphene, campesterol, cholesterol, stigmasterol and β-sitosterol[25] The alcoholic extract of leaves of OS has a modulatory influence on carcinogen metabolizing enzymes such as cytochrome P-450, cytochrome-b5, aryl hydrocarbon hydroxylase and glutathione-S-transferase (GST), which are important in detoxification of carcinogens and mutagens have been reported to be modulated by OS.[26,27] The anticancer activity of OS has been reported against human fibrosarcoma cells culture.[28] OS significantly decreased the incidence of benzo (a) pyrine induced neoplasia of stomach of mice and 3'-methyl-4-dimethylaminoazobenzene induced hepatomas in rats.[29] 7, 12- dimethylbenz (a) anthracene (DMBA) induced papillomagenesis significantly reduced the tumour incidence, average number of papillomas mouse and cumulative number of papillomas in mice. Oral treatment of fresh leaves paste of Tulsi may have the ability to prevent the early events of DMBA induced buccal pouch carcinogenesis.[30] Leaf extract of OS blocks or suppresses the events associated with chemical carcinogenesis by inhibiting metabolic activation of the carcinogen.[31]

Black Cumin Seed (Nigella sativa)

Nigella sativa is a flowering plant whose seeds have been used for medicinal purposes for centuries. It originated from Southeastern Asia and also used in ancient Egypt, Greece, Middle East and Africa. The seed is called black cumin in English, 'Panacea' meaning 'cure all' in Latin; in Arabic it is termed as 'Habbah Sawda' or 'Habbat el Baraka' translated as 'Seeds of blessing'. It is also known as 'Kalo jeera' (in Bangladesh), 'Kalonji' (in India) and 'Hak Jung Chou' in (China).[32] The crude oil and thymoquinone (TQ) extracted from its seeds and oil are effective against many diseases like cancer, cardiovascular complications, diabetes, asthma, kidney disease etc. It is effective against cancer in blood system, lung, kidney, liver, prostate, breast, cervix, skin with no toxicological effect.[33,34] Studies showed that TQ has antioxidant role and improves body's defense system, induces apoptosis and controls Akt pathway.[35] The cumin seeds contain both fixed and essential oils, proteins, alkaloids and saponin.[37] Thymoquinone is responsible for the most of the biological activities of the seeds[36] Four pharmacologically important components present in cumin seed oil are: thymoquinone (TQ), dithymoquinone (DTQ), thymohydroquinone (THQ), and thymol (THY),.[37] TQ has been shown as potent anti-oxidant,[38,39] anti-carcinogenic and anti-mutagenic agent.[40,41] Alpha (α)-hederin, a pentacyclic triterpene saponin isolated from the seeds of *N. sativa*, was also reported to have potent *in vivo* antitumor activity.[42] TQ exhibits anti-proliferative effect in human myeloblastic leukemia HL-60 cells.[43] Aqueous and alcohol extracts of *N. sativa* were found to be effective *in vitro* in inactivating MCF-7 breast cancer cells.[44] *N. sativa*, in combination with melatonin and retinoic acid reduced the carcinogenic effects of DMBA (7, 12-di-methylbenz(a) anthracene) in mammary carcinoma of rats.[45] Gali-Muhtasib *et al*., (2004)[46] suggested

that TQ is anti-neoplastic and pro-apoptotic against colon cancer cell line HCT116. Salim and Fukushima (2003)[47] demonstrated that the volatile oil of *N. sativa* has the ability to inhibit colon carcinogenesis of rats. TQ, the major constituent of *N. sativa* oil extract, also induced apoptosis and inhibited proliferation in PDA (pancreatic ductal adenocarcinoma) cells.[48] Swamy and Huat (2003)[49] mentioned the antitumor activity of α-hederin from *N. sativa* against LL/2 (Lewis Lung carcinoma) in BDF1 mice. Also, supplementation of diet with honey and *N. sativa* has a protective effect against MNU(methylnitrosourea)-induced oxidative stress, inflammatory response and carcinogenesis in lung, skin and colon.[50] Topical application of *N. sativa* extract inhibited two-stage initiation/promotion [dimethylbenz[a]anthracene (DMBA)/croton oil] skin carcinogenesis in mice. Khan and Sultana (2015)[51] reported the chemopreventive effect of *N. sativa* against ferric nitrilotriacetate (Fe-NTA)-induced renal oxidative stress, hyper-proliferative response and renal carcinogenesis. TQ, from *N. sativa*, inhibited DNA synthesis, proliferation, and viability of cancerous (LNCaP, C4-B, DU145, and PC-3) but not non-cancerous (BPH-1) prostate epithelial cells by down-regulating AR (androgen receptor) and E2F-1 (a transcription factor.[52] Shafi *et al*., (2009)[53] reported that methanol, n-Hexane and chloroform extracts of *N. sativa* effectively killed HeLa (human epithelial cervical cancer) cells by inducing apoptosis. Terpene-terminated 6-alkyl residues of TQ on multidrug-resistant KB-V1/Vb1 cervical carcinoma and found the derivatives inducing cell death by apoptosis[54] (Effenberger *et al*., 2010). The toxicity of other anticancer drugs (for example, cyclophosphamide) is decreased when administered with *N. sativa* an up-regulation of antioxidant mechanisms, indicating a potential clinical application for these agents to minimize the toxic effects of treatment with anticancer drugs[55] (Alenzi *et al*., 2010). Cemek *et al*., (2006)[56] showed that *N. sativa* and glutathione treatment significantly antagonize the effects of radiation. Assayed (2010)[57] investigated the radio-protective potential of *N. sativa* crude oil against hemopoietic adverse effects of gamma irradiation. Thus it has radioprotective potential.

Cardamom (*Elettaria cardamomum*)

Cardamom (*Elettaria cardamomum*) known as "Queen of Spices" is one of *Zingiberaceae* family with evergreen erected thick stem 2 to 4 m tall perennial plant. Cardamom is ranked third most expensive spices after vanilla and saffron. It produces segmented aromatic pods or capsules with15 to 20 seed. One of the cardamom types *Amomum subulatum* is generally recognized as black, Indian, Nepal or winged cardamom.[58,59] Cardamom has been demonstrated to have antioxidant properties for their ability to scavenge radicals. The ethyl acetate-soluble fraction, containing several phenolic compounds (protocatechualdehyde, protocatechuic acid, 1,7-bis (3,4-dihydroxyphenyl) hepta- 4E, 6E-dien-3-one, and 2,3,7-trihydroxy-5-(3,4-dihydroxy-E-styryl)-6,7,8,9-tetrahydro-5H-benzocycloheptene), scavenged about 90% of DPPH radicals.[60] Cardamom phytochemicals i.e. cineole and limonene have shown protective role against cancer progression. Cardamom has also been demonstrated to decrease azoxymethane-induced colon carcinogenesis due to its anti-inflammatory, antiproliferative, and proapoptotic activities. Aqueous cardamom suspension can enhance detoxifying enzyme (GST activity) and decrease lipid peroxidation.[61] The ability of cardamom to inhibit chemical carcinogenesis was shown by Banerjee *et al.* (1994)[62] He demonstrated that feeding of cardamom oil to Swiss albino mice at a dose of 10 µL/day for two weeks caused a significant decrease in liver CYP.

Aqueous extract of cardamom (1, 10, 50, and 100 mg/mL) reported to significantly enhance splenocyte proliferation in a dose-dependent manner, especially when combined with black pepper.[63] Another study showed that when cardamom and black pepper when given together significantly enhanced the cytotoxic activity of natural killer cells against YAC-1 lymphoma cells. These findings provide evidence that cardamom may have anticancer benefits by modifying immunocompetence.[62] The azoxymethane (AOM) induced colonic aberrant crypt foci (ACF) behavior of cardamom was assessed in Swiss Albino mice. Moreover, cardamom modulates cell proliferation, modification of cyclooxygenase- 2 (COX-2) and expression of inducible nitric oxide synthase (iNOS) which induces apoptosis development. The concluding results suggested cardamom protective effects on experimentally induced colon carcinogenesis.[64] The essential oils from spices like ginger, nutmeg, celery, cardamom, black pepper and cumin were found to inhibit adduct formation momentously in a dose dependent manner. The adduct formation appeared to be modulated through action on microsomal enzymes due to formation of activated metabolite of different oil. The resultant enzymatic modulation of chemical constituents of oils showed anticarcinogenic activity (Table 1).[65] Cardamom in can inhibit the viability and proliferation of MM (Multiple Myeloma) cells and cardamom in is the anti-myeloma drug with strong viability.[66]

Clove (*Eugenia caryophyllata*)

Cloves are flowers buds of the evergreen tree *Eugenia caryophyllata*, which are picked before they bloom completely. The buds contain an aromatic l bioactive components, including tannins, terpenoids, eugenol, and acetyleugenol (Table 1).[67] A dose-dependent response was observed for several detoxifying enzymes by feeding cloves to mice. Changes in phase I and II enzymes by clove may account for the ability of eugenol to serve as an antimutagen.[68] Clove also inhibit carcinogen-induced genotoxicity.[69] Kluth *et al*., (2007)[67] examined the influence of several spice extracts on phase I and II enzymes in cultured human liver carcinoma and human colon adenocarcinoma cells. Result showed a shift in the nuclear transcription factor Nrf2 was responsible for the induction. Evidence also exists that clove extracts might interfere with β-catenin activity and thereby decrease colon carcinogenesis, but further studies are needed on this.[70] Eugenol present in clove oil extract is an effective cytotoxic agent for different type of cancer cells like HeLa (cervical cancer), MCF-7(ER +) and MDAMB-231 (ER-) (breast cancer), DU-145(prostate cancer) and TE-13 (Esophageal cancer). It also showed apoptotic inducing capability suggesting that eugenol may constitute a potential antitumor compound against different kind of cancer cells.[71,72,73]

Cinnamon (*Cinnamomum cassia)*

Cinnamomum cassia is an evergreen tall tree belonging to the family Lauraceae. It's bark contains several active components such as essential oils (cinnamic aldehyde and cinnamyl aldehyde), tannin,eugenol, terpinene, carvacrol, linalool, safrole, benzyl benzoate, and coumarin, mucus and carbohydrate.[74] These compounds show various biological functions like anti-oxidant, anti-microbial, anti-inflammatory, anti-diabetic and anti-tumor activity.[75,76,77] Further, cinnamon bark oil has been found by researchers to be one of the most effective inhibitors of bacteria, such as Helicobacter pylori**,** that facilitate the invasion and progression of cancer.[78]

The cinnamon essential oil (CEO) isolated from Cinnamomum was studied as cochemoterapeutic agent of cisplatin on HeLa cells covering cytotoxic effect, cell cycle modulation and induction of apoptosis. CEO showed cytotoxic effect on HeLa cells with IC50 value of 250 µg/mL, while cisplatin showed cytotoxic effect with IC50 value of 18 µM. Combination of CEO and cisplatin reduced cells viability compared to cisplatin solely. Analysis on the cell cycle progression showed that CEO induced S-phase arrest on HeLa cells, cisplatin induced G1 arrest, while combination of CEO and cisplatin induced G2/M arrest. Thus, the inhibition of HeLa cells growth at 24 hours is likely through cell cycle modulation rather than apoptosis.[79]

Cinnamon has antioxidant activity and decrease lipid peroxidation that lead to cancer. Studies showed that anticancer activity of cinnamon extracts is associated with modulation of angiogenesis and AP-1 of CD8+T cells.[80] Cinnamon extract also showed proapoptotic activity by inhibiting the activities NFκB and AP1target genes such as Bcl-2 and Bcl-xLin mouse melanoma model.[75] Yet another study showed that cinnamon suppresses the toll like receptor 4 activation mediated through the inhibition of receptor oligomerization.[77] These studies strongly suggest that potent anti-tumoral effects of cinnamon extract are mediated by multiple action mechanisms.

Coriander (*Coriandrum sativum)*

Coriandrum sativum, commonly known as coriander, is a culinary and medicinal herb of the family Apiaceae and is native to southern Europe and northern Africa to southwestern Asia. Although all parts of the plant are edible, its fresh leaves and dried seeds are most frequently used in cooking. Previous studies on this herb show their various medicinal properties, including antidiabetic, antioxidant, hypocholesterolemic, antihelmintic, antibacterial, hepatoprotective, anticancer and anxiolytic activities.[81,82] The phenolic compounds, apigenin, catechin and *p*-coumaric acid, and aliphatic alkenals and alkanals have been reported in aerial parts of *C. sativum*[83] while linalool, geranyl acetate and petroselinic acid were found in the fruit.[84] Several animal studies provide evidence that coriander seeds can promote the hepatic antioxidant system.[85,86] Although relatively few studies focus on coriander for its anticancer properties, those that are available suggest coriander may be important.[87] Antioxidant and anticancer effects of *C. sativum* root extract on the breast cancer cell line, MCF-7.[88]

Fennel (*Foeniculum vulgare*)

Fennel (*Foeniculum vulgare*) is a flowering plant species belonging to family of Apeacea or Umbelliferae. It is a hardy, perennial herb with yellow flowers and feathery leaves. Fennel phytonutrients—including the flavonoids rutin, quercitin, and various kaempferol glycosides—that give it strong antioxidant activity. Anethole, major constituent of fennel oil, is known to possess anti-inflammatory and anti-tumor activities.[89] Researchers evaluated anti-metastatic and toxic effects of anethole on highly-metastatic human tumor cells (1080 HT-1080 human fibro sarcoma tumor cells.[90] The study showed that despite weak cytotoxicity against the cells, anethole inhibited adhesive and invasive activities of cancer cells in a dose-dependent manner. Mechanism of Fennel; involves the shutting down of tumor necrosis factor (or TNF)-mediated signalling pathway.[91]

By shutting down this signaling process, the anethole in fennel prevents activation of a potentially strong gene-altering and inflammation-triggering molecule called NF-kappaB. In addition, anethole suppressed the enzyme-regulated activities necessary for cancer cell multiplication . Findings indicate that anethole is a potent anti-metastatic drug that functions through inhibiting MMP-2/9 and AKT/mitogen-activated protein kinase (MAPK)/NF-κB signal transducers.[92]

Mohammad *et al*., (2011)[93] evaluated the efficacy of fennel seed methanolic extract (FSME) for its antioxidant, cytotoxic, and antitumor activities and for its capacity to serve as a nontoxic radioprotector in Swiss albino mice. The study showed FSME contained different ompounds such as flavonoids, terpenoids, alkaloids, phenols, and sterols; estragole (71.099%) was found to be the most predominant alcohol, gallic acid was the phenolic compound (18.895%), and L-limonene was the most prevalent monoterpene hydrocarbon (11.967%) showing inhibitory concentrations of 50 ± 0.03 µg/mL for the MCF7 breast cancer cell line and 48 ± 0.22 µg/mL for the HEPG-2 liver cancer cell line.

Fenugreek (*Trigonella foenum-graecum*)

Fenugreek [*Trigonella foenum-graecum* Linn. (Fabaceae)], a seed spice used to enhance flavor, color and texture of food, is employed for medicinal purposes in many traditional systems. A number of epidemiological studies and laboratory research have unraveled the biological actions of fenugreek.[94] Crude extracts of fenugreek (FCE) contain the saponins and sapogenins, diosgenin as active agents. Diosgenin inhibits azoxymethane-induced aberrant crypt foci formation in F344 rats and induce apoptosis in HT-29 human colon cancer cells.[95] Diosgenin also inhibits osteoclastogenesis, invasion, and proliferation through the down regulation of Akt, I kappa B kinase activation and NF-kappa B-regulated gene expression in tumor cells.[96] It is also an active component responsible for the anti-diabetic and hypocholesterolemic activity of fenugreek.[97] Protodioscin is another active agent which induces cell death and morphological changes indicative of apoptosis in the leukemic cell line H-60, but not in gastric cancer cell line KATO III.[98] In an *Ehrlich ascites* carcinoma model in BALB/c mice, fenugreek seed extract produced a 70% inhibition of tumor cell growth when compared to controls.[99] Fenugreek may be able to selectively kill developing PCa cells in this mouse while leaving the normal cells unharmed.[100] The induction of apoptosis by FCE is effected by its ability to increase the expression of pro-apoptotic genes caspase -3, caspase-8, caspase-9, p53, Fas, FADD, Bax and Bak in a time-and dose-dependent manner in MCF cell lines.[101] Significant chemotherapeutic effects of Fenugreek seeds were observed against leukemic KG-1 (a myeloblastic cell line) cell line.[102] Mahmoud *et al*., (2015)[103] introduced FCE as a promising nontoxic herbal with therapeutic potential to induce apoptosis is in HepG2 cells through p53, Bax, and PCNA upregulation in caspase-3 dependent manner. This spice holds promise for consideration in complementary therapy for breast cancer patients.

Garlic *(Allium Sativa)*

Allium sativum belongs to Amaryllidaceae family,commonly known as Garlic, Stinking Rose, Poor Man's Treacle. Garlic bulb contains approximately 65% water, 28% carbohydrates (mainly fructans), 2.3% organosulfur compounds, 2% protein (mainly allinase), 1.2% amino acids (mainly Arginine), and 1.5% fiber. Garlic bulb contains more than 200 chemical compounds like volatile oil with sulphur-containing compounds: allicin, alliin, and ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide), citral, a-phellandrene, geraniol, β-phellandrene and linalool. Also it is rich in enzymes likeallinase, peroxidase and myrosinase.

Allicin, alliin, cycroalliin, and diallyl disulphide (DADS) are active sulphur containing ingredients of garlic. It also contains flavonoids, Vitamin A, vitamin B1 and vitamin C, potassium, phosphorous, selenium, sulphur, magnesium, calcium, sodium, germanium, and manganese, iron, and trace amount of iodine. Garlic also contains 17 amino acids including eight essential amino acids.[104]

Garlic and related allyl sulfur compounds block tumors in the colon, lung, breast, liver and tumor proliferation/apoptosis.[105,106,107,108,109] Alterations in glutathione: oxidized glutathione ratios, shift in sulfhydryl groups and resultant changes in cellular redox status may be involved in some of the phenotypic changes caused by allyl sulfur compounds and it may also cause hyper phosphorylation of specific cell cycle proteins and histone hyperacetylation that has correlation with suppression tumor cell proliferation.[110,111]

The anticancer effect of diallyltrisulfide in human colon cancer cells HCT-15 and DLD-1 was due to disrupted microtubule network formation of the cells[112] (Milner *et al*., 2009). Organo sulphur compounds of garlic inhibit carcinogen activation, enhance phase 2 detoxifying processes, cause arrest at G2/M phase of cell cycle, induce mitochondrial apoptotic pathway and increase acetylation of histones, like modulation of cellular redox state, influence gap-junctional intercellular communi-

Table 1: Spices that have Anti-Cancer activity

Spice Name	Scientific Name	Family	Important Bioactive compound
Anise	*Pimpinella anisum* L	Apiaceae	Anethole, phytoestrogen
Bay Leaf	*Cinnamomum tamala*	Lauraceae	Linalool ,a-pinene, p-cymene, ß-pinene and limonene, cinnamzic aldehyde 1%and phenylpropanoids
Basil	*Ocimum basilicum*	Lamiaceae	Eugenol, apigenin, limonene, ursolicacid, methylcinnamate, 1,8-cineole, α-terpinene, anthocyanins, β-sitosterol, carvacrol, cintronellol, farnesol, geraniol, kaempherol, menthol, p-coumaric acid, quercetin, rosmarinic acid, rutin, safrole, tannin, catechin
Cardamom	*Elettaria cardamomum*)	Zingiberaceae	Limonene, caffeic acid, cineole
Cinnamon	*Cinnamomum cassia*	Lauraceae	(cinnamic aldehyde and cinnamyl aldehyde),tannin, mucus and carbohydrates
Cumin Seed Black (jeera)	*Nigella sativa*	Ranunculaceae	conjugated linoleic (18:2) acid, thymoquinone, nigellone (dithymoquinone),melanthin, nigilline, damascenine, and tannins
Cloves	*Syzygium aromaticum*	Myrtaceae	Eugenol, isoeugenol, gallic acid tannins, terpenoids ,acetyleugenol , beta-caryophyllene and vanillin, crategolic acid, tannins such as bicornin, gallotannic acid, methyl salicylate, the flavonoidseugenin, kaempferol, rhamnetin, and eugenitin, triterpenoids such as oleanolic acid, stigmasterol, and campesterol, and several sesquiterpenes
Coriander	*Coriandrum sativum*	Apiaceae	Quercetin, caffeic acid, cineole, geraniol,borneol, 1,8-cineole, α-terpinene, β-carotene,β-pinene, β-sitosterol, cinnamic acid, ferrulic acid, γ-terpinene, kaempferol, limonene,myrcene, p-coumaric acid, p-cymene, quercetin, rutin, vanillic acid
Cumin	*Cuminum cyminum*		α-Pinene, β-pinene, γ-terpinene, p-cymene, cuminaldehyde, carvone, 1,8-cineole,β-carotene, β-sitosterol, caffeic acid, carvacrol, carvaol, geranial, kaempferol, limonene, p-coumaric acid, quercetin, tannin, thymol
Fennel	*Foeniculum vulgare*	Apeacea or Umbelliferae.	α-Pinene, β-carotene, limonene, quercetin, benzoic acid, β-sitosterol, caffeicacid, cinnamic acid, ferulic acid, fumaric acid, kaempferol, myristicin, 1,8-cineole,p-coumaric acid, quercetin, rutin, vanillic acid, vanillin
Garlic	*Allium sativum*	Liliaceae	Allicin, diallyl disulfide, allyl isothiocyanateAlliin, allicinalliin, alliinase, S-allylcysteine (SAC), diallyldisulphide(DADS), diallyltrisulphide (DATS) andmethylallyltrisuphide
Ginger	*Zingiber officinale*	Zingiberaceae	Zingerone, zingiberene, ingerol, paradol, curcumin, shagoal, gingerenone A, Gingeols
Turmeric	Curcuma longa	Zinziberaceae	Tumerone, curcumine
Poppy seeds	Papaver somniferum	Papaveraceae	tocopherols other than vitamin E (alpha-tocopherol). alpha and gamma tocotrienolscampesterol, stigmasterol, sitosterol and delta 5-avenasterol, linoleic acid.
Saffron	Crocus sativus	Iridaceae.	carotenoids. Safranal (2, 6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde, C10H14O), crocin , crocetin

cation and participate in the development of multidrug resistance, involvement in signal transduction and post-translational modification[113] (Iciek *et al*., 2009). Natural organosulfur compounds (OSCs) suppress the proliferation of tumor cells *in vitro* through the induction of apoptosis[111] (Melino *et al*., 2011). Ajoene as one of the important compounds in garlic has shown to inhibit proliferation and induce apoptosis of human leukaemic cells and act as an antileukaemic agent for acute myeloid leukaemia therapy. The apoptosis activity of ajoene is via the mitochondria-dependent caspase cascade through a significant reduction of the anti-apoptotic Bcl-2 that results in release of cytochrome C and the activation of caspase-3.[114] Aged garlic extract (AGE), increases natural killer (NK) cell activity. In addition, animal studies have shown that AGE induces the release of cytokines such as IL-2, TNF-α and INF-α.[115] It also enhances phagocytosis, an early immune stimulatory action, and killer cell activity and immune proliferation of lymphocytes in response to mitogen stimulation. These effects suggest that AGE, stimulates a Th1 cellular immune

response that is characteristic of effective antitumor immunotherapies. Sundaram and Milner (1996)[116] have reported that DADS was as effective as 5-fluorouracil (a potent anti-cancer drug) in inhibiting growth of tumors in transplanted human colon carcinoma cells.[117]

Ginger (*Zingiber officinalis)*

Ginger, the rhizome of *Zingiber officinalis,* is one of the most widely used species of the ginger family. History of medicinal use of ginger dates back to 2500 years. Major constituents of ginger are vallinoids, viz.[6]-gingerol and [6]-paradol, shogaols, zinerone (). Ginger contains active phenolic compounds such as gingerol, paradol and shogoal that have antioxidant,[118] anti-cancer[119] anti-inflammatory,[120] anti-angiogenesis[121] and anti-artherosclerotic properties.[122] It down-regulates NF-κB-regulated gene products involved in cellular proliferation and angiogenesis, including IL-8,[123] VEGF[124] and ovarian cancer cells.[125]

A number of mechanisms that may be involved in the chemopreventive effects of ginger and its components have been reported from the laboratory studies in a wide range of experimental models. 6-gingerol can reduce viability of gastric cancer cells and limit the spread of cancer.[126,127] Studies showed that pretreatment with [6]-gingerol resulted in a decrease in both TPA-induced DNA binding and transcriptional activities of NF-kappaB through suppression of Ikappa B alpha degradation and p65 nuclear translocation. Phosphorylation of both Ikappa B alpha and p65 was substantially blocked by [6]-gingerol. In addition, [6]-gingerol inhibited TPA-stimulated interaction of phospho-p65-(Ser-536) with cAMP response element binding protein, a transcriptional co-activator of NF-kappaB.[128] Also, [6]-gingerol prevented TPA-induced phosphorylation and catalytic activity of p38 mitogen-activated protein (MAP) kinase that regulates COX-2 expression in mouse skin. The p38 MAP kinase inhibitor SB203580 attenuated NF-kappaB activation and subsequent COX-2 induction in TPA-treated mouse skin.[124] [6]-gingerol inhibits angiogenesis and may be useful in the treatment of tumors and other angiogenesis-dependent diseases[124] 6-gingerol induced cell death in promyelocytic leukemia HL-60 cells, caused DNA fragmentation and inhibited Bcl-2 expression in HL-60 cells.[129] In liver cancer cells, NF-κB is constitutively activated and that blocking NFκB activation with ginger resulted in suppressed production of NF-κB and TNF-α.[130]

Poppy seeds (*Papaver somniferum)*

Poppy plant is a biennial herb of East Mediterranean, and Asia Minor origin belonging to the *Papaveraceae* family of the genus: Papaver. It's scientific name is ***Papaver somniferum.*** Individual fruit head measures about 4–6 cm in length and 3–4 cm in diameter, contains numerous tiny, bean (kidney) shaped seeds, which rattle when shaken inside dried capsules. Seeds poppy can be light gray to dark gray, black, or bluish depending on cultivar type. Its seeds, which are used as condiment spice and to press oil, indeed are very safe to use as food and contain negligible quantities of toxic alkaloids of the opium poppy. Poppy seeds yield 45–50% oil. Poppy seed oil is high in vitamin E, and has no narcotic properties and had long been used as a carrier for embolizing agents to treat tumors. Iodized poppy-seed oil has an especially high rate of uptake into the cells of hepatocellular carcinoma (HCC). Lipiodol is under investigation as an adjuvant and carrier for use in chemotherapy to treat hepatocellular carcinoma (HCC). It increases the uptake and hence the cytotoxicity of doxorubicin in HCC cells (and also in hepatoblastoma cells). As a carrier, it is under investigation in conjunction with a lipophilic compound of platinum, and in conjunction with a complex derivative of neocarzinostatin. It also is being investigated as a radiation therapy against hepatocellular carcinoma, by being loaded with an isotope of iodine, iodine-131. Miriplatin is a lipophilic platinum complex containing myristates as leaving groups, and can be easily suspended in ethyl esters of iodized fatty acids obtained from poppy seed oil. Miriplatin suspension was active and was retained selectively in rat hepatic tumors after intra-hepatic arterial administration with reduced toxicities in normal livers and the whole body. Similarly, lipiodol has been used with the chemotherapy agent epirubicin, but with less success than with doxorubicin."Water/oil/water" microemulsion, in which epirubicin was dissolved in droplets of water, and the droplets were suspended in lipiodol, significantly increased uptake of epirubicin by HCC cells.[131]

Saffron (*Stigmata Croci*)

Saffron (*Stigmata Croci*) is the red dried stigmas of Crocus sativus L. flowers and used both as a spice and as a drug in traditional medicine. It is a perennial plant belonging to Iridaceae. *Crocus sativus,* is rich in carotenoids. Safranal (2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde, $C_{10}H_{14}O$) is an active ingredient in the saffron, which is used in traditional medicine. Two main natural carotenoids of saffron, crocin and crocetin, are responsible for its color. Saffron and crocus also have significant antitumorigenic properties. Crocin induce decrease in cell viability in a concentration- and time-dependent manner in human pancreatic cancer cell line.[132] The mechanisms underlying cancer chemopreventive activities of carotenoids include modulation of carcinogen metabolism, regulation of cell growth and cell cycle progression, inhibition of cell proliferation, anti-oxidant activity, immune modulation, enhancement of cell differentiation, stimulation of cell-to-cell gap junction communication, apoptosis and retinoid-dependent signaling.[133] The antitumor actions of saffron and its components have been proposed due to mechanism such as the inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis, the inhibitory effect on free radical chain reactions, the metabolic conversion of naturally occurring carotenoids to retinoid, the interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction.[134] Saffron and its derivatives can affect carcinogenesis in a variety of *in vivo* and *in vitro* models particularly crocin and crocetin have significant anticancer activity in breast, lung, pancreatic and leukemic cells.[135] It was reported that saffron and crocetin induced apoptosis on human breast cancer cell (MCF-7) *via* p53-mediated stimulation of apoptosis. Results indicated that caspase-dependent pathway was induced by saffron in MCF-7 cells and Bax protein expression was also increased in saffron-treated cells.[136] Synthesis of cellular nucleic acid was inhibited by the saffron extract in HeLa cells (derived from a cervical epitheloid carcinoma.[137]

Safranal (0.01-3 mM) or liposomal safranal (0.04-0.32 mM) showed dose dependent cytotoxic effect on HeLa, MCF7 and L929 cell lines in dose dependent manner. It has also shown to induce apoptosis. Liposome encapsulation improved anti-tumor effect of safranal. Liposome encapsulation of saffron effectively enhanced its antitumor activity towards Sarcoma-180 (S-180) and Ehrlich ascites carcinoma solid tumors in mice.[138] Safranal and its liposomal form could be promising chemotherapeutic agents in cancer treatment. Crocetin administration has shown inhibition of gastric adenocarcinoma (AGS) cells proliferation and induce apoptosis. It also shows suppression of Bcl_2 and upregualtion of Bax expression in AGS cells. Studies conducted demonstrates the antioxidant, anti-proliferative, and apoptotic activities of crocetin against gastric cancer that may benefit human stomach cancer treatment. Aqueous saffron preparations have been reported to inhibit chemically induced skin carcinogenesis.[139]

Crocetin significantly induced cell cycle arrest through p53-dependent and -independent mechanisms accompanied with p21 (WAF1/Cip1) induction. Therefore, crocetin caused anticancer effect in the 3 types of cancer cells i.e. (HeLa), non-small cell lung cancer cell line (A549) and ovarian cancer cell line (SKOV3) by enhancing apoptosis in a time-

dependent manner.[140] Crocus sativus extract and its major constituent, crocin, significantly inhibited the growth of colorectal cancer cells while not affecting normal cells[141] (Aung *et al*., 2007).

Saffron exerts a significant chemopreventive effect against diethylnitrosamine (DEN)-induced liver cancer (HepG2) through inhibition of cell proliferation *via* induction apoptosis, modulating oxidative damage and suppressing inflammatory response. Saffron treatment results in inhibition of nuclear factor-kappa B activation, increased cleavage of caspase-3, as well as DNA damage and cell cycle arrest.[142] Crocetin has been reported to have a significant antitumorigenic effect on both the *in vitro* pancreatic cancer cells and *in vivo* nude mice tumor *via* induction apoptosis. At the *in vitro* studies, pancreatic cancer cells (MIA-PaCa-2), crocetin significantly altered cell cycle proteins (Cdc-2, Cdc-25C, Cyclin-B1) and epidermal growth factor receptor (EGFR) and the *in vivo* results showed significant regression in tumor growth with inhibition of proliferation.[143]

Turmeric (*Curcumin Longa)*

Turmeric is a member of the *Zingiberaceae* (ginger) family, which is native to Southeast Asia.[144] Curcumin is a polyphenolic compound derived from the spice turmeric plant. *Curcumin* is lipophilic in nature which shows low solubility and stability in aqueous solution. It is extensively used in Ayurveda, Unani, Siddha, and Chinese medicine for the management of various diseases such as wound, inflammation, and cancer and used for culinary purposes.[145]

Numerous *in vivo* and *in vitro* studies showed that turmeric and its constituents have a significant role in cancer prevention or inhibition by various mechanisms. Curcumin enhances the activity of Phase II enzyme GST at protein as well as mRNA level. It also regulates mRNA expression of NQO1 in mouse tissues, suggesting a role of curcumin in transcriptional regulation of phase II enzymes,[146-151] Valentine *et al*.,(2006). Curcumin also induces GST expression by signalling through the nuclear erythroid-derived 2-related factor 2 (NRF-2) and NF-κB via an antioxidant response element.[152,153]

Studies showed that curcumin down-regulates the expression of p53, as well as the survival genes EGR-1, c-myc and bcl-XL in B cells.[154] Another report has also indicated that curcumin inhibits cell cycle progression of immortalized human umbilical vein endothelial cells via upregulating the CDK inhibitors p21WAF1/CIP1, p27KIP1, and p53.[155] Further studies reported that curcumin mainly acts in p53-dependent manner.[156]

Curcumin induces apoptosis in a range of tumor cell lines through activation of caspase-3, cytochrome c release, and downregulation of bcl-2.[157-159] *Curcumin* has also shown to inhibit various genes such as protein tyrosine kinase, protein kinase C, mRNA expression of c-myc and bcl-2 and also mitochondrial pathway.[160,161] Earlier studies have shown that curcumin possesses an apoptotic activity in different types of cancer cell such as human colon cancer cells, stomach, skin tumors, breast cancer cells, and prostate cancer cells.[162-165] Study of colon cancer cell line showed that apoptosis was increased in response to curcumin.[166,167] Curcumin also showed a vital role in decreasing cell proliferation in a dose dependent manner.[166] Curcumin may lower the incidence of various cancers, including urothelial malignancies.[168,169] It may also induce apoptosis in MBT-2 cells[170] and in breast cancer cell lines, and the activation of apoptosis was confirmed by PARP-1 cleavage and by the increased ratio between the pro-apoptotic Bax and the anti-apoptotic Bcl-2 proteins.[171] Curcumin treatment also down regulates of the expression of antiapoptotic protein.[172]

An important study demonstrated that curcumin showed as an anticancer, antioxidant, and anti-inflammatory effect via downregulation of the transcription factors NF-κB, AP-1, Egr-1[173] and repression of the genes for cell adhesion molecules (chemokines, TNF, Cox-2, and MMP-9).[174,175] Another study showed that curcumin is a pharmacologically safe agent and has been involved in the suppression of NF-κB activation and NF-κB gene products.[175] Curcumin suppresses the expression of a variety of NF-κB regulated gene products involved in cancer development and progression such as cyclin D1, VEGF, COX-2, c-myc, Bcl-2, ICAM-1, and MMP-9[176-178] Curcumin down regulated N-myc[179] in various cancer types and decreased the expression of proto-oncogenes such as *ras* and *fos* in tumorous skin.[180] Curcumin in hepatocellular carcinoma is reported to block transactivation of the c-Met promoter through AP-1.[181] Another finding on curcumin effect in the downregulation of oncogene showed that curcumin induced the antiproliferative, antimigratory and apoptotic effects via the downregulation of various genes, including c-Myc, N-Myc, cyclin D1, and antiapoptotic factors Bcl-2 and Bcl-xL.[182] Several other studies showed the effect of curcumin in the inhibition or downregulation of various oncogenes such as EGFR, HER-2, PI3 K/Akt, and MAPK pathway.[183-185] Curcumin is involved in the induction of apoptosis through downregulating the expression of c-myc, Bcl-2, and mutant-type p53, and upregulating the expression of Fas.[186]

A study showed curcumin effects on colon cancer cells confirmed growth inhibition and stimulation of the transactivating activity of peroxisome proliferator-activated receptor c (PPAR-c), which appears to mediate the suppression of gene expression of cyclin D1 and the epidermal growth factor receptor (EGFR).[187] Curcumin shows a vital role in the inhibition of MMP-9 activities and finally plays a role in the management of cancer. A study showed that curcumin inhibits TPA-induced MMP-9 expression and cell invasion through suppressing NF-κB and AP-1 activation.[188] Curcumin showed inhibition of phorbol ester-induced upregulation of cyclooxygenase-2 and matrix metalloproteinase-9 in MCF10A human breast epithelial cells study.[189]

CONCLUSION

Spices taken with everyday food have several health benefits on human body. There are number of spices and their phytochemicals which have the ability to regulate multiple cancer related processes in experimentally induced tumors when they are present in physiologically relevant concentrations. With this view in mind they can be considered as one of the important sources for new drug development programme. It requires further research in this area with a focus on identification of drug targets involved in cell signalling pathway as these pathways severely affected in cancer patients. It also calls for the development of stringent norms considered by international organizations in terms of their manufacturing practices, quality control, safety, efficacy, and of course regulatory norms. Research in this field can certainly provide safe and effective drugs for cancer treatment.

ACKNOWLEDGEMENT

Authors express their gratitude to Amity University Authorities for constant motivation and encouragement and for providing infrastructure for writing this manuscript.

CONFLICT OF INTEREST

No conflict of interest to declare.

ABBREVIATION USED

PC-3: Prostate cancer cell line; **κB:** Nuclear factor; **EAC:** Ehrlich ascites carcinoma; **CT:** Cinamomumtamala; **OS:** Oscimum sanctum; **GST:** Glutathione-s-tansferase; **DMBA:** 12-dimethyl benz(a)anthracene; **TQ:** Thymoquinone; **DTQ:** Dithymoquinone; **THQ:** Thymohydroquinone; **THY:** Thymol; **LL/2:** Lewis lung carcinoma; **MNV:** Methylnitrosourea; **Fe-NTA:** Ferric nitrilotriacetate; **AR:** Androgen receptor; **E2F:** A transcription factor; **HeLa:** Human epithelial cervical cancer cells;

AOM: Azoxymethane; **ACF:** Colonic abberentcryptfoci; **COX-2:** Cyclo-oxygente-2; **iNOS:** inducible nitric oxide synthase; **MM:** Multiple myeloma; **CEO:** Cinnamon essential oil; **IC-50:** Half maximal inhibitory conc.; **NFκB:** Nuclear factor kappa-light-chain-enhancer of activated B cell; **API:** Active pharmaceutical ingredients; **BCL-2:** B cell lymphoma -2; **BCL-xl:** B-cell lymphoma extra large; **TNF:** Tumor nuclear factor; **MAPK:** Mitogen activated protein kinase; **FSME:** Fennel seeds methanolic extract; **FCE:** Fenngreek crude extract; **DAD:** Diallyldisulphide; **AGE:** Aged garlic extract; **NK:** Natural killer; **TPA:** Tissue plasminogen activator; **HCC:** Hepatocellular carcinoma; **DEN:** Diethylnitrosamine; **EFG:** Epidermal growth factor receptor; **Cdc-2:** Cell cycle protein; **NRF:** Nuclear erythroid derived related factor-2.

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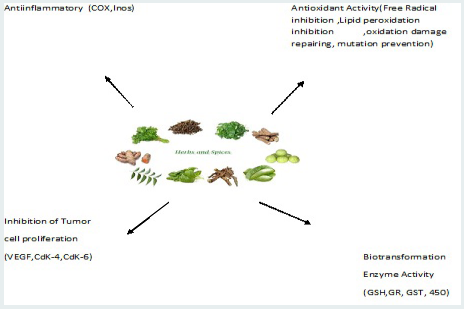
PICTORIAL ABSTRACT



SUMMARY

• Cancer is uncontrollable and incurable disease caused by complex multiple factors. It kills annually 3500 per million populations both indeveloped and developing countries. Due to high cost and toxic side effects of the anticancer drugs alternative therapies are need of the hour. Spices taken everyday contain many phytochemicals and active ingredients which have ability to regulate multiple cancer related processes. Such spices can offer a promising alternative strategy for treatment and prevention of cancer.

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