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REVIEW ARTICLE

DIETARY SPICES IN HEALTH AND DISEASES : I

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Abstract : Spices are heterogeneous collections of a wide variety of volatile and non-volatile staple dietary additives. India with its wide climatic conditions and topographical features naturally possesses wide variety of medicinal flora. Spices have a diverse array of natural phytochemicals that have complementary and overlapping actions, including antioxidant effects, modulation of detoxification enzymes, stimulation of immune system, reduction of inflammation, modulation of steroid metabolism and antibacterial and antiviral effects. In the present essay, various studies on effects of different well characterized spices on molecular, cellular, autocrine, paracrine and endocrine mechanisms and their role in neuromodulation, immunomodulation, anti inflammatory, antioxidant, anti-carcinogenic, antimutagenic and psychoactive phenomena have been reviewed.

Key words : spices, condiments, herbs, nutraceuticals, chemoprevention, antioxidant, phytochemicals

Aristotle had stated in ‘Metaphysics’ that *“the search for truth is in one way hard and in another easy for no one can master it fully nor miss it totally but each one of us adds a little to the knowledge of nature and from the facts assembled there arises a certain grandeur”*. Study of spices is as good an example as any to illustrate the complementarity of science and tradition. Spices are a diverse group of a wide variety of staple dietary additives consumed all over the world, significantly more so in tropical, oriental, Hispanic and Mediterranean cuisines (1).

For centuries the inherent value as well as potential toxicity of phytochemicals to human health has been recognized (2–4). Plants are natural and traditional sources of medication in large parts of world; herbs, condiments and spices have been used since ancient times by physicians and laymen to treat a great variety of human diseases, yet many of them need to pass tests of modern, controlled, clinical experimentation (5, 6). A wide variety of herbs and spices singly and in mixtures have been extensively investigated in basic biological sciences to evaluate their chief as well as supplementary,

complementary and synergistic actions in health and diseases (7–11). Albeit spices are consumed in relatively small amounts, they are nevertheless consumed by large sections of population globally (12–14).

In the present review, an attempt has been made to collate current physiological and nutraceutical perspectives of chemicals from spices that we ingest regularly without much knowledge about them. In the process, we shall highlight scientific evidence, experimental trials and contemporary technological developments in this area of scientific investigation. We anticipate that this shall provide a basis for a full-scale investigation of the therapeutic potential of these staple dietary additives (15, 16).

General effects of flavour and aroma

In the production of gastronomic delight, great importance is attached to the organoleptic quantity of food. The human sensory apparatus is extraordinarily discriminating in ability, and the food industry has evolved a highly elaborate language to describe the most suitable yet critical differences in flavour (17). Several empirical and experimental observations do suggest that the effects of spices extend beyond taste and flavour (18–20). Taste is actually a mixture of taste and smell, and also in case of substances such as chilli pungency and pain (17). The human nose can distinguish more than 10,000 odours with the help of olfactory chemorecpors belonging to the large family of G-protein linked receptors (21, 22). Slight variations in structure may make for marked difference in olfactory response (Fig. 1) (17).

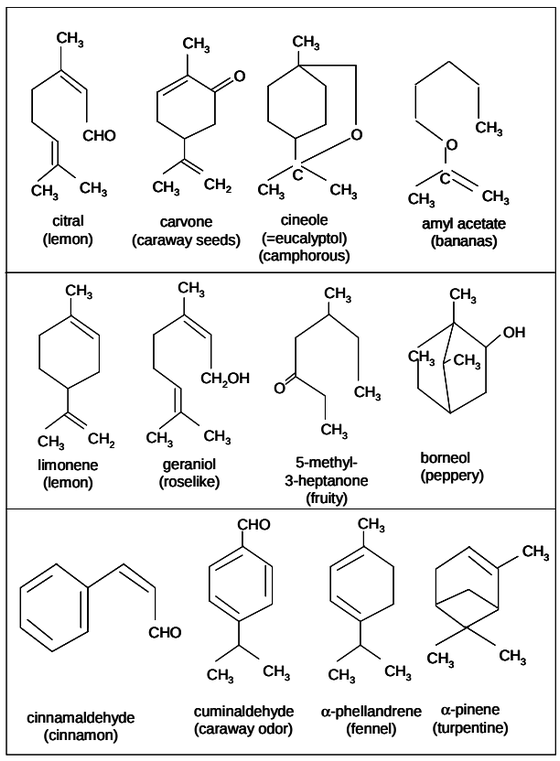

Fig. 1: Constituents of essential oils. For details see Max (17).

Spices and flavoring agents contain volatile essential oils and hydrocarbons which stimulate glandular secretion and may have a weak action on the nervous system. The high value that most societies place on warm food as a catalyst of social intercourse possibly evolved from intractable relationship between olfaction and the neurochemistry of mood. While humans like other mammals are capable of surviving on raw meat and uncooked plants, so much effort is put into the biologically almost valueless activity of cooking is that odour is maximized in hot food and hedonic aspects of odour enhance the social values of eating. Olfaction is the oldest phylogenetic sense keeping in view

that the brain can be conceived of as being a functionally specialized piece of gut tissue evolved at the consuming end of the gut as a tool for recognizing food (22). Odor is more important than taste because it is more sensitive, operates over a greater distance and there is high susceptibility to odorant conditioning. The excitatory amino acid receptor agonists like glutamate, trichoclomate and ibotenate are all potent flavour enhancers, especially in traditional oriental cooking (23, 24). All receptors physiologically are chemorecepors, responding to either exogenous or endogenous chemicals (25). Many spicy compounds indeed exhibit desensitization which has important neurochemical implications (26, 27).

Physiological chemistry of spices and spice metabolites

Many spice components are terpenes and other constituents of essential oils (Fig. 1) Terpenes are associated with secretory structures in plants such as oil cells, resin ducts, hair-like trichomes or glandular epidermis. They inhibit bacterial and fungal growth (28–30) and germination of competitors (7, 31, 32). A critical prediction of the antimicrobial hypothesis is that spice use yields a health benefit; cleansing food of parasites and pathogens before it is eaten. In support most spices have antimicrobial properties and their use is greatest in tropics where the diversity and growth rates of microorganisms are highest (33). The fragrant, aromatic and pungent character is caused by essential oils including terpenes, sesquiterpenes, pinenes, alcohols, esters, ketones and aldehydes. Certain spices have components other than volatiles, alkaloids like capsaicin, piperine, chavicene, saponins like trignollenine imparting pungent and bitter taste respectively to peppers and fenugreek (1, 13, 14, 34). Occassionally a strong coloring matter like curcumin, carotene, saffrole, crocin and picrocin is present as in turmeric, chillies and saffron. Condiments used as souring agents carry various acids. Tamarind has tartaric acid, and kokam hydroxyl citric acid, mangopowder malic acid, pomegranate seeds oxalic acid and caper buds rutic acid (1, 13, 14, 34). Table I shows some common spices with their chief constituents that confer on them a distinctive flavour, taste and resulting physiological actions.

Nutritive value of spices

Since spices, condiments and herbs are consumed in very small quantities every day, their contribution by way of macroelements of nutrition namely carbohydrates, proteins and fats cannot obviously be of significance. Occassionally however exceptionally high levels of a mineral or a vitamin could have micronutritive value. The core of classical nutrition research has been witnessing a paradigm shift in the last two decades where seemingly biologically inert substances have apparently demonstrated rather profound effects in health and diseases. These new nutrients, including in large measure, dietary spices are being identified which maintain human health by their antioxidative, chemopreventive, antimutagenic, antiinflammatory, immune modulatory effects on cells and a wide ranging array of putative beneficial effects on human health via action on gastrointestinal, cardiovascular, respiratory, metabolic, reproductive, neural and other

TABLE I: Chief constituents of common spices.

Name	*Chief Constituents*
Pimento	Eugenol
Aniseed	Anethole
Arecanut	Catechin, Arecolin
Asafoetida	Mixed Allyl sulphides
Bay Leaf	Linalool, Methyl cinnamate
Betel	Eugenol
Bishop's weed	Thymol
Caper	Rutic acid
Caraway	Carvone
Cardamom	Cineol, Borneol, Camphor
Celery	Limonene
Chillies and capsicum	Capsaicin
Chillies paprika or Spanish pimento	Capsaicin
Cinnamon bark	Cinnamaldehyde
Cinnamon leaves	Eugenol
Clove	Eugenol
Coriander leaf	Decyladehyde
Coriander seeds	Decyladehyde
Cumin, white	Cinnamaldehyde
Cumin, black	Carvone, Limonenene
Curry leaf	Pinene; dipentene
Dill	Dillephole, Carvone, Phellandrene
Fennel	Anethole, bitter alkaloid, Trigonelline, Niacin
Garlic	Dilalkyl and trisulphides, Allicin
Ginger	Camphene, Zingiberene,
Kokam	Hydroxycitric acid
Mace	Pinene, camphene
Mango, green	Malic acid
Mango ginger	Ocimene, Mycrene, Limonene
Marjorum	Menthol, Menthyl acetate, Menthone
Mustard	Thioglucosides, Isothicoyanates
Nutmeg	Myristicin, Geraniol, Pinene, Camphene
Onion	Alkyl Disulphide
Oreganum	Thymol, Carvacrol, Terpenes
Parsley	Apiole, Alpha-pinene
Pepper, black	Menthol, Limonene, Menthone
Pomegrenate	Oxalic acid
Poppy	Opioids
Saffron	Picrocrocin
Sage	Thujone, Linelyl Acetate, Camphol, Tannin, Picrosalvin
Spearmint	Carvone, Terpenes
Tamarind	Tartaric Acid, Glucose, Fructose, Pectin
Tarragon or Estregon	Chavicol, Phellandrene, Ocimene
Thyme	Thymiol
Turmeric	Curcumin, Zingiberene, Sesqueterpenes, Borneol
Vanilla	Methyl vanillin

systems (7, 35–41). In following sections, some of these actions shall be discussed.

Chemopreventive effect

Chemoprevention is defined as nutritional or pharmaceutical interventions designed to prevent or delay cellular transformation. Based on published preclinical studies on a number of new compounds derived from citrus products and Asian foods and spices, it appears that certain dietary flavines and flavones target cell surface signal transduction enzymes, such as protein tyrosine and focal adhesion kinases, and the processes of angiogenesis and thus appear to be promising candidates as anticancer agents (7, 35–44). Cancer chemoprevention by phytochemicals obtained from vegetables, fruits, spices, teas, herbs and medicinal plants such as carotenoids, phenolic compounds and terpenoids have been proven to suppress experimental carcinogenesis in various organs (45–48). Phytochemicals may also be useful to develop "designer foods" or "functional foods" for cancer prevention. In prototype experiments, expression of genes for synthesis of phytochemicals, such as phytoene and limonene, has been successful in cultured animal cells (49).

Natural anti-inflammatory compounds are plentifuly present in herbs, and are found in green tea, the spices like turmeric and rosemary. Because the use of nonsteroidal anti-inflammatory drugs (NSAID) is associated with a reduced risk for several cancers, it is at least plausible that natural NSAID should be explored for possible use as cancer preventives (44, 45). A recent study conducted to determine salicylate content of a variety of commanly used spices

demonstrated good bioavailability of salicylic acid levels in them (50, 51).

The results of epidemiological data and some laboratory animal studies indicate that certain naturally occurring and synthetic spice components are able to block the carcinogenic process and inhibit the development of certain cancers (also see Fig. 2). Dibenzoylmethane (DBM), a curcumin-related beta ketone analogue has been reported to exhibit a remarkable inhibitory effect on 7,12-dimethylbenzanthracene (DMBA) induced mammary tumorigengenesis in Sencar mice (52). DBM inhibited DMBA metabolism and the formation of DMBA-DNA adducts in a dose-dependent manner. In vitro DBM showed weak estrogen receptor binding affinity and in vivo feeding of 1% DBM in the diet of immature Sencar mice for 4–5 weeks decreased the uterine and parametrial fat pad weights, and lowered the serum estrogen and triglyceride levels (53).

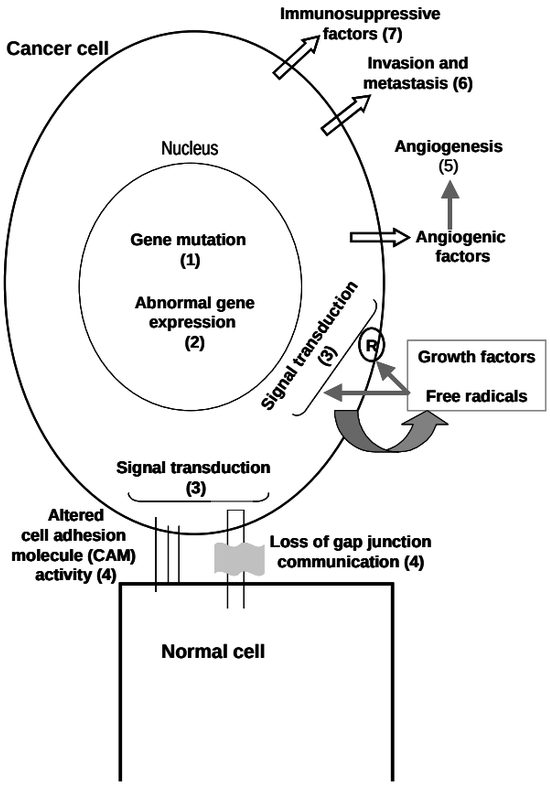

Fig. 2: Schematic illustration of seven critical gate ways to carcinogenesis. Seven processes include genetic mutation (1), abnormal genetic expression (2), abnormal signal transduction, abnormal cell-to-cell communication (4), angiogenesis (5), invasion and metastasis (6) and deficit in immuno-surveillance (7). Spices and spice principles may putatively act on any or more of these events and may exert additive, synergistic, combinatorial and antagonistic effects depending on their combination in diet.

6-methylsulfinylhexylisothiocyanate (MS-ITC) isolated from Japanese domestic horseradish wasabi (*Wasabia japonica*) is a potential inhibitor of human platelet aggregation, and it induces glutathione-S transferase in-vitro and in-vivo in mice and rats. Probably the isothoicyanate moiety of MS-ITC plays an important role for antiplatelet and anticancer activities because of its high reactivity with sulfhydryl groups in biomolecules (54). In a separate study, antioxidant potential of curry leaves in rats treated with a known chemical carcinogen, dimethylhydrazine hydrochloride (DMH) was investigated. A 50% reduction was seen in the micronuclei induced by DMH and a 30% reduction in the activity of gamma-glutamyl transpeptidase when the rats were fed a curry leaf-supplemented diet. These results indicate that curry leaves have high potential as reducer of the toxicity of DMH (55).

Curcumin has been reported to possess chemopreventive effects against skin cancer, colon cancer and oral cancer in mice (56). Curcumin effectively inhibits N- diethyl nitrosamine (DEN)-induced hepatocarcinogenesis in mice. While hepatic

tissues obtained from the DEN-treated mice showed a remarkable increase in the levels of p21, PCNA and CDC2 proteins, eating a curcumin–containing diet reversed the levels of normal values (56) Curcuminoids also protected normal human keratinocytes from hypoxanthine oxidase injury (57). Capsaicin (trans-8-methyl-N-vanillyl-6-noneamide), the pungent ingredient of hot chilli pepper, protects against experimentally–induced mutagenesis and tumorigenesis, and induces apoptosis in various immortalized and malignant cell lines (58, 59). Diarylpeptanoids from curcumin and ginger suppress phorbol ester-induced activation of ornithine decadecarboxylase and production of tumor necrosis factor-alpha or interleukin-1alpha and their mRNA expression; they nullify the phorbol ester-estimated induction of activator protein 1 (AP-1) in cultured human promylelocytic leukemia (HL-60) cells (60). In addition, both yakuchinone A and B induced apoptotic death in HL-60 cells. (60).

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) contains such pungent ingredients as gingerol and 6-paradol, which also have anti-tumor promotional and antiproliferative effects as well as diverse inhibitory effects on cellular events associated with multi-stage carcinogenesis, such as cell growth and kinase activity inhibition, apoptosis induction, suppression of the secretion of matrix metalloproteinases, and tumor invasive behavior (58, 60). *In-vitro* studies have demonstrated that the water as well as organic solvent extract of ginger possesses antioxidative anti-inflammatory properties, inhibit epidermal ornithine decarboxylase (ODC), cyclooxygenase, and lipoxygenase activities, and edema and hyperplasia, lower the tumor burden and the mechanism of such effects may involve inhibition of tumor promoter-caused cellular, biochemical, and molecular changes in mouse skin (61).

The components in rosemary like carnosol and urosolic acid exhibit anti-tumorigenic activity. Carnosol can prevent DMBA-induced DNA damage and tumor formation in the rat mammary gland and thus has potential for use as a breast cancer chemopreventive agent (62, 63). Natural polyphenols found in rosemary have not only potent antioxidant activies but also anticarcinogenic properties. At least two mechanisms are involved in their chemopreventive action as appeared from in vitro human liver and bronchial cell studies: firstly, inhibition of metabolic activation of procarcinogens catalysed by the phase I cytochrome P 450 enzymes, and secondly, induction of the detoxification pathway catalysed by the phase II enzymes such as glutathione S-transferase (64). Activation of some inducible enzymes, including NADPH oxidase (NOX), inducible nitric oxide synthetase (iNOS) and cyclooxygenase (COX)-2 have been shown to play pivotal roles in the development of certain inflammatory diseases and oncogenesis. In an elegant mini-review, the molecular mechanisms of activation or induction of NOX, iNOS and COXs, as well as some food phytochemicals with marked potential to regulate those key inflammatory molecules have been highlighted (42).

Western blotting analysis revealed that clove infusion up regulates the expression of pro-apoptotic proteins like Bax, and down regulates the expression of anti-apoptotic protein like Bcl2 in precancerous stages (65).

Expression of caspase 3 and its activation by clove infusion were evident from a very early stage of carcinogenesis (65). Clove infusion was also found to down-regulate the expression of some growth-promoting proteins, viz, XOX-2, c Myc, Hras. The observations signify the chemopreventive potential of clove in view of its apoptogenic and anti-proliferative properties (65).

Chilli supplementation promotes colon carcinogenesis, whereas cumin or black pepper suppresses colon carcinogensis in the presence of the procarcinogen 1,2-dimethylhydrazin(DMH) (66). Cumin and black pepper may protect the colon by decreasing the activity of beta-glucuronidase and mucinase (67). Histopathological studies also showed lesser infiltration into the submucosa, fewer papillae and lesser change in the cytoplasm of the cells in the colon in cumin and black pepper groups when compared to the DMH and chilli treated animals (66, 67). In view of the increasing interest in the association between dietary flavonoids and cancer initiation and progression, this important field is likely to witness expanded effort and to attract and stimulate further vigorous investigations in order to develop flavonoid-based anticancer strategies.

Antioxidant effect

Endogenous antioxidants in plants play an important role in antioxidative defense systems against oxidative stress. Intensive search for novel natural antioxidants has been carried out on numerous plant materials, including those used as foods, and have been isolated and identified (68–72).

Antioxidant activities of volatile extracts isolated from thyme, basil, rosemary, chamomile, lavender, and cinnamon were evaluated by two independent assays: the aldehyde/carboxylic acid assay and the conjugated diene assay. The antioxidant activites of the extracts decreased in the following order in both of the lipophilic assay systems: thyme>rosemary>chamomile> lavender and cinnamon. (73). Dietary lipid plays a key role in determing cellular susceptibility to oxidative stess, and that could be modulated by cereals, pulses and spices in diet (74). Modulatory effect of a formulated diet based on cereals, pulses and spices on oxidative stress and antioxidant enzymes was studied in rat, liver and kidney. Significant increase in hepatic antioxidant enzymes, catalase and glutathione peroxidase was observed. Kidney antioxidant enzymes did not show much change compared those in liver indicating the dietary spice induced anti-oxidiative effect (74).

Water extracts of several herbs that are constituents of curry and curry powder were screened for superoxide anion radical (0_2.-) scavenging activity. Among the screened samples, only clove, allspice, and basil are shown to decrease DMPO-(0_2.-) adduct yields by more than 50%. Clove and basil directly eliminated (0_2.-) like superoxide dismutase (SOD), whereas allspice reduced the amount of (0_2.-) by inhibition of formation of (0_2.-) (75).

A proprietory formulation containing extract of turmeric (*Curcuma longa*), obtained by supercritical carbon dioxide gas extraction and post-supercritical

hydroethanolic extraction, (together with extracts of green tea and other spices whose presence synergistically increases the activity of turmeric) was found to scavenge superoxide radicals generated by photoreduction of riboflavin and hydroxyl radicals generated by Fenton reaction and reduced lipid peroxidation (76). Administration of this spice-herb preparation, to mice was found to elevate antioxidant enzymes such as catalase and superoxide dismutase in blood as well as in liver and kidney. Glutathione-S tranferase activity was found to be significantly elevated in liver and kidney thus indicating that turmeric extract has potent antioxidant activity, could inhibit phase I enzymes and increase detoxifying enzymes, which makes it an effective chemoprotective herbal formulation (76). Indian minor spice, Nagkesar (buds of *Mammea longifolia*) is extensively used in culinary preparations especially in spice blend in India. It was identified that the polar fraction of buds containing procyanidin oligomers exhibited strong antioxidant and radical scavenging activities (77).

Water and ethanol crude extracts from black pepper (*Piper nigrum*) were investigated for their antioxidant and radical scavenging activities in six different assay, namely, total antioxidant activity, reducing power, 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical savenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating activities. Both water extract and ethanol extract of black pepper exhibited strong total antioxidant activity (78).

In the central nervous system, hydrogen peroxide radical (HO^{-1}) has been reported to operate as a fundamental defensive mechanism for neurons exposed to an oxidant challenge. A significant expression of quinine reductase and glutathione S transferase, two members of phase II detoxification enzymes, was found in astrocytes exposed to 5–15 µM curcumin (79). Moreover, the effects of curcumin on HO^{-1} activity were explored in cultured hippocampal neurons (79). Elevated expressions of HO^{-1} mRNA and protein were detected after 6 h incubation with 5–25 µM curcumin, while higher concentration of curcumin (50–100 µM) caused a substantial cytotoxic effect with no change in HO^{-1} protein expression (79).

Crocus sativus stigmas (saffron) are one of the widely known spices and consist of usually polar carotenoids. Among spices, saffron displayed the highest antioxidant capacity (80). The water-methanol (50:50, v/v) extract of *C. sativus* stigmas possesses good antioxidant properties, higher than those of tomatoes and carrots, and inhibited amyloid beta (Aβ) fibrillogenesis which is considered as a marker of Alzheimer's disease in a concentration and time-dependent manner (80). The main carotenoid constituent, trans-crocin-4 (digentibiosyl ester of crocetin), could inhibit Aβ fibrillogenesis at a lower concentration compared with dimethylcrocetin (81). Administration of 50 mg of saffron dissolved in 100 ml of milk twice a day to 20 human subjects resulted in marked decline of lipoprotein oxidation susceptibility after 3 and 6 weeks (82). In another related study in rats fed with high fat diet, *Murraya koenigi* and *Brassica juncea* demonstrated appreciable antioxidant activity. The peroxidation activity measured by thiobarbituric acid reactive substances

reduced to a benefical extent and hepatic functions recovered to near normal level (83). In a study attempted to generate a database on the antioxidant activity and phenolic content of commonly consumed plants including spices black pepper demonstrated highest antioxidant activity (84). A sighnificant correlation was observed between the antioxidant activity and phenolic content of the plant foods studied in general (r=0.465), but the coefficient of correlation and determination were very high in spices (r=0.86 and r2=74%, respectively) (84).

The potential antioxidant activities of selected spices extracts in water and alcohol (1:1) were investigated on enzymatic lipid peroxidation. Water and alcoholic extract (1:1) of commonly used spices (garlic ginger, onion, mint, cloves, cinnamon and pepper) dose dependently inhibted oxidation of fatty acid, linoleic acid in presence of soybean lipoxygenase (85). Cloves exhibited highest while onion showed least antioxidant activity (85). The relative antioxidant activities decreased in the order of cloves, cinnamon, pepper, ginger garlic, mint and onion. Spice mix namely ginger, onion and garlic showed cumulative and synergistic inhibition of lipid peroxidation. The antioxidant activity of spice extracts were retained even after boiling for 30 min, indicating that the spice constituents were resistant to thermal denaturation. (85). The antioxidative activity of the dried pericarp and seed of Japanese pepper *(Xanthoxylum piperitum DC*) was studied; both exhibited antioxidative activity and radical scavenging activity radical (86). Japanese pepper contained 3.9 and 2.9 mg/ 100 g of dry weight of tocopherols in the pericarp and seed, respectively, alpha-tocopherol in the former constituting 82% of total tocopherol and gamma-tocopherol in the latter constituting 96% (86).

Studies on spices and herbs have put forth us over a hundred compounds, known and new, having high antioxidant activity. *Labiatae* family, *Rosmarinus officinalis*, *Thymus vulgaris*, *Origanum vulgare* and *O. majorana* yielded 26 active compounds. Over 40 antioxdative compounds from *Zingiber officinale*, 26 compounds from *Curcuma domestica, C. longa, C. xanthorrhiza* and *Z. cassumunar* were determined belonging to the family *Zingiberacae*. From the family *Myrtaceae*, 25 compounds from the berries of *Pimenta dioica* were determined and 3 carbazoles were isolated from *Murraya koenigii* (87).

The alcohol extracts of rosemary and sage showed strong antitumorigenic activities; rosemary and sage extracts contain active antioxidative factors such as phenolic diterpenes, flavonoids and phenolic acid (75, 88). Cinnamon and cardamom significantly enhanced hepatic and cardiac antioxidant enzymes and restored glutathione content in fat fed rats (89). Rosemary and Provencal herbs extract inhibted peroxidation of phospholipids liposomes, and also inhibted human immunodeficiency virus (HIV) infection (90). Pimentol from allspice, and biflorin from clove markedly inhibted the formation of malondialdehyde (MDA) via inhibition of advanced glycation end products and pentosidine which are biomarkers of dibetes mellitus (91–92).

Mechanism of action

As discussed above, a wide variety of phenolic compounds and flavonoids present

in spices possess potent antioxidant, antimutagenic and anticarcinogenic activities. One of the underlying major mechanisms is their action on cellular enzymatic pathways. Effect of aqueous extracts of turmeric, cloves, pepper , chilli, cinnamon, onion and also their respective active principles, curcumin, eugenol, piperine, capsaicin, cinnamadehyde, quercetin, and allyl sulfide were tested on human polymorphonuclear leuckocyte 5-lipooxygenase (PMNL 5-LO) activity and observed that the formation of leukotrienes was significantly inhibited in a concentration-dependent manner (93). Quercetin, eugenol and curcumin with one or more phenolic ring and methoxy groups in their structure showed high inhibitory effect while the non-phenolic spice principle allyl sulfide showed least inhibitory effect on 5-LO. The inhibitory effect of quercetin, curcumin and eugenol was similar to that of synthetic 5-LO inhibitors-phenidone. The synergistic or antagonistic effect of mixtures of spice active principles and spice extracts were investigated and all the combinations of spice active principles/extracts exerted synergistic effect towards inhibiting 5-LO activity (93). These findings clearly suggest that phenolic compounds in spices might have physiological role in modulating 5-LO pathway (93).

Many spices and herbal teas demonstrated significant inhibitory activity on in vitro metabolism of drug marker substrates by human cytochrome P-450 (CYP) isoforms. Spices and single-entity herbal teas showed spices–specific isoform inhibition with sage, thyme, cloves, St. John's Wort and goldenseal having the highest activity against several isoforms (94). Assessment of in vitro CYP inhibition potential for these natural products has important implications for predicting the likelihood of natural product-drug interactions if these products are taken concomitantly (94). Cinnamaldehyde is a natural product from spices that inhibits cell separation in Bacillus cereus (95). FtsZ, a prokaryotic homolog of tubulin assembles into the Z-ring at the site of cell division. Cinnamaldehyde decreases the in vitro assembly reaction and bundling of FtsZ. This suggests that cinnamaldehyde is a potential lead coumpound that can be developed as an anti-FtsZ agent towards drug design (95).

Among the spices, saffron (*Crocus sativus*, L) a member of the large family Iridaceae, has drawn attention because apart from its use as a flavouring agent, pharmacological studies have demonstrated many health promoting properties including radical scavenging, anti-mutagenic and immuno-modulating effects (96). The effects of an aqueous infusion of saffron on two stage skin papillogenesis/carcinogenesis in mice demonstrated significant reduction papilloma formation both pre– and post–initiation. The inhibition appeared to be at least partly due to modulatory effects of saffron on glutathione-S-transferase and glutathione peroxidase as well as catalase and superoxide dismutase (96). The extracts of saffron (*Crocus sativus*) and selenite have also been shown to inhibit the colony formation and nucleic acid synthesis by Hela cells in vitro. Treatment of tumor Hela cells with saffron extract in combination with selenite increased the level of inhibition of the colony formation and nucleic acid synthesis (97).

In a screening study of extracts of edible herbs for inhibitors of phagocytosis by peritoneal exudate macrophages, 1'-

acetoxychavicol acetate isolated from the ethyl acetate extract of *Languas galanga* strongly inhibited phagocytosis at an IC_{50} value of 1.2 μM with neglibible effects on pinocytosis and cell viability (98). One of the targets of 1-acetoxychavicol acetate was suggested to be down stream of the signal transduction pathway that is mediated by protein kinase (98).

Garlic extract was found to inhibit the mutagenicity produced by direct acting mutagens such as N-methyl-N-nitro-N-nitrosoguanidine and sodium azide. Asafoetida and turmeric extract as well curcumin and eugenol were found to inhibit microsomal activation dependent mutagenicity of 2-acetamidoflourene (99). These results indicate that some spices may ameliorate the effect of environmental mutagens especially present in the food (99).

Dietary polyphenolics with phenol rings also oxidized human erythrocyte oxyhemoglobin and caused erythrocyte hemolysis more readily than polyphenolics with catechol rings. It is concluded that polyphenolics containing a phenol ring are generally more proxidant than polyphenolics containing a catechol ring (100). Spice phenolic active principles like curcumin, quercetin and capsaicin strongly inhibited low density lipoprotein (LDL), while non-phenolic antioxidant allyl sulfide was less potent (101). These data suggest that the above spice active principles, (which constitute about 1–4% of above spices are effective antioxidants and offer protection against oxidation of human LDL (101). In another study to compare the antioxidant effect of capsaicin on lipid peroxidation in homogeneous solution micelle dispersions and liposomal membranes the antioxidant activity of capsaicin was found to be about 60 times less than that of alpha-tocopherol in homeneous solution. However, in micelle oxidation, the difference in antioxidant activity of the two antioxidants was much smaller. Furthermore, in the membrane, capsaicin inhibited the oxidation almost as effectively as alpha-tocopherol. These results suggest that capsaicin can act as an effective antioxidant in the biomembrane (102).

Two well-defined eukaryotic transcription factors, nuclear factor-kappa B (NF-κB) and activator protein 1 (AP-1) have been implicated in pathogenesis of many human diseases including cancer (103). They are known to be activated by wide arrary of external stimuli, such as tumor promoter 12-0-tetradecanoylphorbol 13 acetate (TPA), tumor necrosis factor, reactive oxygen species, bacterial lipopolysaccharide, and ultraviolet radiation (103). Topical application of curcumin and capsaicin significantly attenuated TPA-induced activation of each transcription factor in mouse skin. Likewise, both compounds inhibited NF-κB and AP-1 activation in cultured human promyelocytic leukemia (HL-60) cells stimulated with TPA. Based on these findings, it appears that curcumin and capsaicin exert anti-tumor promotional effects through suppression of the tumor promoter-induced activation of transcription factors, NF-kappaB and AP-1 (60, 103–104). Activator protein 1(AP-1) has a critical role in tumor promotion, and blocking of tumor promoter-induced activation of AP-1 inhibits neoplastic transformation. Epidermal growth factor induces cell transformation and AP-a activity. Both 6-gingerol and 6-paradol block

EGF-induced cell transformation but act by different mechanisms (105).

Dietary use of curcumin has been linked to many beneficial effects on several body functions although the underlying molecular mechanisms are still not very clear (106). Traditionally, known for its an anti-inflammatory effects, curcumin has been shown in the last two decades to a be a potent immunomodulatory agent that can modulate the activation of T cells and B cells. Curcumin can also down-regulate the expression of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-kB (106). Correlations have been established between curcumin exposure and increases in enzymes for glutathione synthesis, particularly glutamate-cysteine ligase (GCL), metabolism as well as glutathione content, suggesting the eliciting of an adaptive response to stress (107). Mechanism of curcumin-induced GCL elevation occurred via transcription of the two Gcl genes. Curcumin caused modest but sustained increases in binding of proteins to DNA sequences. Curcumin exposure increased Jun-D and c-Jun content in AP-1 complexes and increased Jun D while decreasing Mafg/Mafk in EpRE complexes. Thus, the beneficial effects elicited by curcumin appear to be due to changes in the pool of transcription factors that compose EpRE and AP-1 complexes, affecting gene expression of GCL and other phase II enzymes. (107).

Somatic mutation and recombination test (SMART) in wings of *Drosophilla melanogaster* was used to study the modulating action of bell pepper (*Capsicum annuum*) and black pepper. *Drosophilla* larvae were fed genotoxins alone or in combination with each of the two spices. Both bell pepper and black pepper were effective in reducing the induced mutational events (108). Suppression of metabolic activation or interaction with the active groups of mutagens could be the mechanisms by which the spices exert their antimutagenic action (108).

Two new bisalkaloids, dipiperamides D and E, were isolated as inhibitors of a drug metabolizing enzyme cytochrome P450 (CYP) 3A4 from the white pepper (109). Two purified polysaccharides isolated from black pepper demonstrarted anti complementary action thereby suggesting usefulness of black pepper as a supplement for immune enhancement (110). Oral administration of capsaicin and curcumin lowered the levels of inflammatory serum glycoproteins with concomitant lowering of paw inflammation (111).

The effect of extracts of the commonly used spices like cinnamon and clove, and their main ingredients on the activity of various ATPases were investigated. Na+/ K+ATPase, Cu2+ATPase and F0F1ATPase are possible intracellular targets for the action of spices components that result in a decrease in ATP level (112). Spices induced protection against genotoxicity of heterocyclic aromatic amines in metabolically competent mammalian cells as well as under conditions of the *Salmonella* reversion assay (113). These results are suggestive for enzyme inhibition as a mechanism of protection by complex mixtures of plant origin including spices and herbs (113).

Conclusion

The capacity of spices to affect markers associated with cancer prevention mechanisms provides important leads that can guide chemoprevention strategies in the human. Data from in vitro and animal studies are promising, however, generally these studies used high doses of pure compounds or spice extracts, whose metabolism in humans has not been elucidated. Only a handful of spices and their constituents have been tested and not much is known about the interactions and contributions of spice mixtures. Given that spices are seldom consumed as single flavorings but rather as part of complex dishes, it appears reasonable to consider the potential synergistic effects of mixtures of spices within the context of the total diet. It should also be continually recognized and emphasized that as we acquire additional experience with known drugs, it often occurs that new uses for existing agents are identified. The original therapeutic utility of an agent may be expanded as new disease states are recognized and as experience with an agent affords more empirical observations upon with to base recommendations for such new therapeutic uses. Today when all over the world is experiencing an epidemiologic shift towards non-communicable diseases more and more, we do need to answer questions on whether prescription of certain select spices is beneficial in health and diseases. Controlled clinical trials including blinded trials and metanalyses of observed effects need to be done to clearly and unequivocally resolve this issue. Today when the world all over is going 'green' we need to channel our resources and research skills to formulate studies which clearly elucidate and elaborate the role of dietary spices in health and disease (20).

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