

essential oils of spices are variations on a common theme yet given the wide range of botanical species and plant parts from which spices are derived, they can contribute significant variety and complexity to the human diet and diversity in their therapeutic usage (Table I) (15–21). Spices affect many body functions leading to diverse physiological effects on gastrointestinal, metabolic, cardiovascular, reproductive as well as peripheral, autonomic and central nervous systems (2, 11, 22–25). A few decades back it was considered that though dry, powdered spices contain significant

concentration of some vitamins and minerals, the normal levels of their use in daily food make their nutritional contribution negligible (26–29) (Table II). However, recently encouraging data have come up to include spices as the ‘new nutrients’ and ‘nutraceuticals’ because of manifold bioactive effects (29–41).

This review in continuation (Part-II) with the previous (Part-I) (1) cites salient relevant facts regarding the beneficial systemic physiologic and metabolic effects of dietary spices.

TABLE I: Representative volatile oils and spices.

Name	Part used	Botanical origin	Production areas	Important constituents	Use
Anise (aniseed)	the dried, ripe fruit	the annual herb, <i>Pimpinella anisum</i> (Apiaceae)	Spain, France, Egypt	1-3% volatile oil containing 80-90% (E) anethole, 10-15% chavicol	flavor
Caraway	the dried, ripe fruit	the biennial herb, <i>Carum carvi</i> (Apiaceae)	Netherlands, Roland, Russia Northern Africa	3-6% volatile oil containing 50-58% (+)- carvone, 40-50% (+) limonene	flavor
Citronella oil	volatile oil distilled with steam from freshly cut or partially dried leaves	the grass, <i>Cymbopogon winterianus</i> and <i>C. nardus</i> (Poaceae)	Sri Lanka, Indonesia, China Taiwan, Argentina, Brazil, India	5-55% (+) citronellol, 25-40% geraniol, (+)- citronellol	perfume, insect repellent
Eucalyptus oil	the dried, scythe-shaped leaf	the tree <i>Eucalyptus globules</i> and other species of <i>Eucalyptus</i>	Australia, Brazil, Spain, Portugal Angola, South Africa, China, India	70-85% cineole, 5-15% α -pinene	antiseptic, mild anesthetic, stimulating expectorant
Fennel	the dried, ripe fruit	the perennial herb <i>Foeniculum vulgare</i> (Apiaceae)	Spain, Russia Bulgaria, Italy	volatile oil containing 65-70% (E)-anethole, 10-15% limonene, 6-7% fenchone, 4% Methyl chavicol	flavor, carminative
Lavender oil	volatile oil distilled with steam from the fresh flowering	the dwarf shrub, <i>Lavandula angustifolia</i>	France, Bulgaria, Russia, Australia	30-60% (-)-linalyl acetate, (-), linalool cineole, terpinen-4-ol	perfume
Lemon oil	volatile oil obtained by expression without the aid of heat, from the fresh peel	the small evergreen tree <i>Citrus limon</i> (Rutaceae)	Spain, Italy, California, Florida, Argentina, Cyprus, Brazil, Israel, Australia, Ivory Coast, Greece]	70-80% (+) limonene, 8-10% β -pinene, 8-10% γ -terpinene, 2-4% citral	flavor perfume

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Orange oil	volatile oil obtained by expression from the fresh peel of the ripe fruit	the tree, Citrus sinensis (Rutaceae)	California, Florida, Brazil, Italy, Israel	1-2% decanal, more than 90% limonene	flavor
Pine oil	volatile oil obtained by extraction and fractionation or by steam distillation of the wood	the three, Pinus palustris and other species of Pinus (Pinaceae)	Southeastern United States	65% α -terpineol, 10% methyl chavicol and related phenol ethers, 9% borneol, 8% fenchol 4% methols	disinfectant deodorant
Rose oil (otto) of rose	volatile oil distilled with steam from the fresh flowers	perennial herbs of shrubs, Rosa gallica R. demascena, R. alba, R. centifolia, and varieties of these species (Rosaceae)	Bulgaria Southern France, Turkey, Morocco, Rusia	geranio, (-) citronellol, (-) citronellol, nerol, 2-phenylethanol	perfume
Spearmint oil	volatile oil distilled with steam from the fresh, overground parts of the flowering plant	the perennial herb Mentha spicata or of M. cardiac (Lamiaceae)	Washington Idaho, Wisconsin, Michigan Indiana, China	45-60% (-) carvone, (-) limonene, cineole	flavor, carminative
Thyme	the dried leaves and flowering tops	an evergreen herbaceous Shrub, Thymus Vulgaris, T. zygis, and its variety gracilis (Lamiaceae)	Spain, Italy, France, Greece	volatile oil containing thymol, carvacrol ρ -cymene α -terpinene γ -terpinene	flavor
Turpentine oil	volatile oil distilled from the oleoresin	the tree Pinus Palustris and other species of Pinus (Pinaceae)	Southeastern United States	65% α -pinene, 30% β -pinene	counterirritant
Wintergreen oil (gautheria oil, betula oil, sweet birch oil)	volatile oil distilled with steam from the dried plant material	the leaves of the shrublike perennial Gautheria procumbens (Ericaceae) or the bark of the Betula lenta (Betulaceae)	Eastern United States and Canada	98% methyl salicylates	flavor, counterirritant antiinflammatory

TABLE II: Micronutrients in some common Indian spices (mg/100 gm food).

Material	Calcium	Phosphorous	Iron	Thiamine	Riboflavin	Niacin	Vit. A	Vit C
Onion	0.3	0.29	Trace	0.42	0.06	0.6	14.7	0.5
Garlic	0.1	0.42	0.01	0.68	0.08	0.7	12.0	0.05
Ginger	0.1	0.15	0.01	0.05	0.13	1.9	12.0	0.05
Turmeric	0.2	0.26	0.05	0.09	0.19	4.8	49.8	0.05
Dhilly Powder	0.1	0.32	0.01	0.59	1.66	14.2	63.7	1.25
Green Chilli	0.03	0.08	1.2	0.19	1.18	0.5	111.0	Trace
Red (dried) Chilly	0.16	0.37	2.3	0.93	0.43	9.5	50.1	0.18
Mustard seeds	0.3	0.79	0.01	0.65	0.45	8.5	22.1	0.06
Tamarind	0.2	0.11	0.01	nil	0.07	0.7	3.0	0.03
Curry leaf	0.8	0.6	0.01	0.08	0.21	2.3	4.0	0.03
Dhaniya (coriander Seed)	0.8	0.44	0.01	0.26	0.23	3.2	4.0	3.78
Jeera (Cumin seed)	0.9	0.45	0.05	0.73	0.38	2.5	17.0	0.05
Adult daily requirement	0.5	0.5	0.024	1.4	1.7	19.0	40.0	0.75

Gastrointestinal effects

Using the tools and techniques of contemporary physiology, researchers are now elucidating mechanisms justifying the traditional use of dietary spices as appetite enhancers, digestives, carminatives, antifatulents, secretagogues, as well as beneficial in both diarrhoea and constipation (9–10, 12–15). Dietary spices may influence gastric emptying, gastrointestinal motility, secretion of gastric acid as well as intestinal bicarbonate, bilopancreatic secretions, absorptive processes and bacterial microflora (44–55). Local effects on gut mucosa, gastrointestinal reflexes and enteric nervous as well as systemic autonomic responses influence carbohydrate, protein and fat absorption in diverse ways (56–61). Changes in mucus barrier, gastroprotective effects, enterocyte and villous height change and cytoprotective adaptations all are now known to occur with intake of spices or spice principles (62–73). The following section highlights some of the salient and proven gastrointestinal actions of dietary spices.

Local actions on gastrointestinal tract

Spice intake has been known to be associated with many local actions on gut influencing secretion, motility, absorption and change in microflora (44–55, 73–80). Capsaicin the pungent active principle of red chilli or paprika has been shown to cause gastric mucosal oedema and hyperemia and decrease in the gastric acid output (64–66, 81). An analogue of capsaicin as well as dry capsaicin powder have been found to be responsible for gustatory sweating and increased salivation (42–43). An increase in the gastric clearance of aminopyrine and 14

C alanine has also been observed in response to capsaicin (43, 44).

The stimulation of afferent neurons by topical capsaicin protects the gastric mucosa against damage induced by pyloric ligation, ethanol and acidified asprine (67–68). Intra-gastric capsaicin promotes the release of vasodilator substances like nitric oxide (NO) (69, 70). Capsaicin-induced stimulation of afferent neurons within the gastric mucosa is associated with release of calcitonin gene related peptide (CGRP) which via formation of NO may cause both a prevention of mucosal injury and modulation of gastrointestinal motility (73, 81).

Effect on gastric acid secretion and ulcerogenesis

Chilli causes dyspepsia in patients with or without ulcer, and patients with ulcer are often advised to avoid its use (64, 66). Nevertheless, epidemiological and clinical data suggest that chilli ingestion may have a beneficial effect on human peptic ulcer disease (63–69). For instance chilli has a gastroprotective effect on aspirin-induced gastric mucosal injury in humans (67–69). Chilli ingestion has no detrimental effect on the healing rates of patients with duodenal ulcer and it does not cause macroscopic damage in humans (82–85). Serial gastroscopy had reported no deleterious effects of oral intake of 3 g chilli powder per day on ulcer healing in duodenal ulcer patients (63–66, 83, 86). Long-term chilli intake (360 mg daily for 4 weeks) protected against hemorrhagic shock-induced gastric mucosal injury, an effect that may be mediated by capsaicin-sensitive afferent neurons (67, 69). The protective effect of

capsicum could involve vanilloid receptors because resiniferatoxin an ultrapotent analogue of capsaicin, also displays antiulcer activity and both capsaicin and resiniferatoxin act on vanilloid (capsaicin) receptors (7).

Paprika, pepper and cinnamon increased gastric acid secretion in men and promoted histamine induced ulcer formation in dogs, whereas mustard decreased acid output (63, 66, 82). Video-endoscopy did not demonstrate visible gastro duodenal damage on intake of spicy foods (82–85). To study the effect of spices on gastric acid secretion the stomach of pentobarbitone-anesthetized rats was perfused at 0.15 ml/min with aqueous extracts (10% w/v) of red pepper (*Capsicum annuum*), fennel (*Foeniculum vulgare*), omum/ajwan (*Carum copticum*), cardamom (*Elettaria cardamomum*), black pepper (*Piper nigrum*), cumin (*Cuminum cyminum*) and coriander (*Coriandrum sativum*) or acetylcholine. All the spices tested increased acid secretion. Atropine abolished the acid secretion induced by acetylcholine and significantly reduced acid induction by red pepper, omum and coriander, but not that by fennel (85). The spices tested increased gastric acid secretion, in some by a cholinergic mechanism but by other mechanism(s) as well (85–87). Licorice, the root and rhizome of different varieties of *Glycyrrhiza glabra*, has been extensively used in medicine for its antiulcer activity (88). Carbenoxolone derives from the hydrolysis of glycyrrhizinic acid after its extraction from licorice root (7). Several mechanisms of action have been proposed to explain the pharmacological activity of carbenoxolone and many spices may conceivably act similarly (Table III).

TABLE III: Anti ulcer activity of Licorice: Proposed Mechanisms of Action.

1.	Stimulates gastric mucus production
2.	Enhances the rate of incorporation of various sugars into gastric mucosal glycoproteins
3.	Promotes mucosal cell proliferation
4.	Inhibits mucosal cell exfoliation
5.	Inhibits prostaglandin degradation
6.	Increases the release of PGE ₂ and reduces the formation of thromboxane B ₂
7.	Regulates DNA and protein synthesis in gastric mucosa

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) also has been suggested for potential utility in treating peptic ulceration due to its action as a thromboxane synthetic inhibitor (90). Synergy is implicated in the antiulcer effect as a result of an experiment where the extract was fractionated and assayed, and particularly high activity (97.7% inhibition at 125 ppm) found to occur in a fraction containing α -zingiberene, p sesquiphellandrene, bisabolene and curcumene (91).

Aqueous extracts of columbo weed, long pepper, parsley, tarragon, nutmeg, yellow-berried nightshade, threadstem carpetweed, sage and cinnamon had bactericidal activities against *Helicobacter pylori* and those of turmeric, borage and parsley were able to inhibit the adhesion of *H. pylori* strains to the stomach section (92). In another study the *in vitro* susceptibility of extracts of spice and food plants from Thai traditional medicine inhibited the growth of *H. pylori* (93). These data indicate that these plants may have chemopreventive activities and thus may partly explain the reduced incidence of gastric cancer in Asian countries (93).

Action on enzymes and secretions of gastrointestinal tract

Dietary curcumin, capsaicin, piperine and ginger prominently enhanced intestinal lipase activity and also the disaccharidases sucrase and maltase in rats (74). Dietary cumin, fenugreek, mustard and asafoetida brought about decreases in the levels of phosphatases and sucrase in intestinal mucosa (74). Platel et al reported that spice mixes containing coriander, turmeric, red chilli, black pepper, cumin, ginger and onion enhanced the activities of pancreatic lipase, chymotrypsin and amylase (75). The spice mixes customized so as to include spices that are traditionally considered as digestive stimulants had the highest stimulatory influence particularly on bile secretion, bile acid output and the activities of pancreatic enzymes (75). The higher secretion of bile especially with an elevated level of bile acids and a beneficial stimulation of pancreatic digestive enzymes, particularly of lipase could probably be the two mechanisms by which these combinations of spices aid in digestion (74–75).

Action on gastrointestinal motility

Chilli ingestion was associated with gastro esophageal reflux and the magnitude of the induced reflux seems to be related to the kind of chilli (94). *Cuminum cyminum* is widely used in Ayurvedic medicine for the treatment of dyspepsia, diarrhea and jaundice (99). Several controlled clinical trials suggest that ginger root (*Zingiber officinale*) can relieve symptoms of motion sickness by a mechanism of action that differs from that of antihistamines. The responsible constituents are believed to be gingerols and

shagaols (100–104). Ginger could be an effective and cheap antimemetic adjunct to cancer chemotherapy but one double blind randomized control trial proved its ineffectiveness in low doses (100–101). The mechanism of action of ginger in reducing nausea and vomiting is unknown but it is speculated that it probably works regionally on the gastro intestinal tract rather than on the central nervous system (102–103). It may increase gastric motility and absorb neutralizing toxins and acids and affectively block gastrointestinal reflexes and subsequent nausea feedback with no reported side effect (102–104). Peppermint and cardamom oil exert their antispasmodic action through muscarinic receptor blockage. (97, 98). Nine commercial essential oils produced four different effects on the rat isolated phrenic nerve-diaphragm preparation whilst only a contracture in guinea-pig ileum preparations (105). The intestinal transit time of Indians is shorter and their stool weight larger than that of the Europeans on a comparable fibre intake (106). One factor which may be responsible for this phenomenon is the presence of several spices in the Indian diet (2, 106–108). Ingestion of dietary spices is associated with a slower gastric emptying but a faster whole gut transit (108). A high chilli diet increases the motility in normal subjects but has no effect on symptoms in patients with irritable bowel syndrome (109).

Actions on membrane permeability and transport properties

Hot spices may interact with epithelial cells of the gastrointestinal tract to modulate their transport properties (110). Permeability for fluorescein isothiocyanate (FITC)-labeled

dextrans with graded molecular weight, and morphological alterations of tight junctions by immunofluorescence were studied using an anti-ZO-1 antibody, a marker for tight junction integrity (110). Extracts from black or green pepper, bay leaf or nutmeg increased the transepithelial electrical resistance and macromolecular permeability remained low (110). Capsaicin transiently reduced resistance and piperine increased resistance, making them candidates for causing the effects seen with crude spice extract (111).

Both black and red pepper may induce epigastric pain by removing the stomach's hydrophobic lining and activating intramucosal pain receptors (112). Histopathological studies showed lesser infiltration into the submucosa, fewer papillae and lesser changes in the cytoplasm of the cells in the colon in cumin and black pepper groups when compared to the Dimethyl hydrazine (DMH) and chilli treated animals (112). The mechanism by which dietary pepper causes dyspepsia and epigastric pain is poorly understood. Cumin and black pepper may protect the colon by decreasing the activity of beta-glucuronidase and mucinase (113). Both black and red pepper rapidly induced a decrease in gastric surface hydrophobicity in a dose dependent fashion (114).

Action of absorption across gastrointestinal tract

Capsaicin decreased glucose absorption from everted sacs of hamster and rat intestine (44, 70, 71, 115). Perfusion studies carried out using jejunal segment demonstrated reversible reduction in the

absorption of water, glucose and alanine in the presence of capsaicin (70–71, 116). When spice active principles were associated with mixed micelles their *in vitro* intestinal absorption was relatively higher (117). Chilli and turmeric being rich in phenolic compounds would be expected to bind iron in the intestine and inhibit its absorption in humans. Despite the much higher amount of phenolics in the turmeric meal, it did not affect iron absorption (118). Capsaicin affected carbohydrate absorptive ability of duodenal epithelial cells but lipid absorption was not affected (79, 80, 119, 120).

Piperine the pungent alkaloid present in *Piper nigrum* Linn, and *P. longum* Linn enhanced the bioavailability of various structurally and therapeutically diverse drugs (111). It may act as an apolar molecule forming an apolar complex with drugs and solutes and may modulate membrane dynamics due to its easy partitioning thus helping in efficient permeability across the barriers (111, 121). It was observed that the less weight gain in rats fed with North Indian traditional spice mixture garam masala as compared to the control group although the animals were consuming similar quantities of diet could be due to changes in absorption (122). Garam masala when consumed for a period of four weeks decreased the length and weight of the intestine in weanling rats but mucosal enzymes were not studied (122–123).

Possible mechanisms of action

Release of serotonin from mucosal enterochromaffin cells triggered by luminal substances is one of the key events in the regulation of gut motility and secretion.

Serotonin release was measured in culture supernatants by a serotonin enzyme immunoassay and amperometry (124). Calcium imaging studies revealed that odorant ligands of the identified olfactory receptors cause calcium influx, elevation of intracellular free calcium levels, and, consequently, serotonin release (124). Spices and odorants present in the luminal environment of the gut may stimulate serotonin release via olfactory receptors present in human enterochromaffin cells.

The capsaicin sensitive primary neurons have been implicated in local regulation of inflammation, visceral tract motility, trophic effects and immune function via their various peptides (125). An attractive speculation arises that just like capsaicin and its multipotent action via effects on primary sensory neurons leads to a host of autonomic responses, there is a strong possibility of occurrence of endogenous receptors and ligands homologous to capsaicin (125). Similarly the various other spice principles could have yet undiscovered homologues or like-structured stereo chemical ligands which may modulate activity (2, 11, 21, 41). Capsaicin has been used extensively as a probe to elucidate the function of sensory neurons in various organs and systems (including the stomach), because of its ability to excite and later defunctionalize a subset of primary afferent neurons (131, 134). The diverse effects of spices on these networks thus indicate the wide ranging potential therapeutic use of spices (2). The gastroprotective (69, 70, 73) as well as gastropropulsive (71, 76, 77, 78) effect of capsaicin as well as the cholinomimetic effect of certain spices is well known (126, 127). Both central autonomic as well as local

effector systems seem to mediate this effect (Fig. 1). Noncholinergic noradrenergic nerves may also play a part to modulate the final outcome (128). The exact site of action of spices still remains to be elucidated though hypotheses including action via nitric oxide release abound (129, 130).

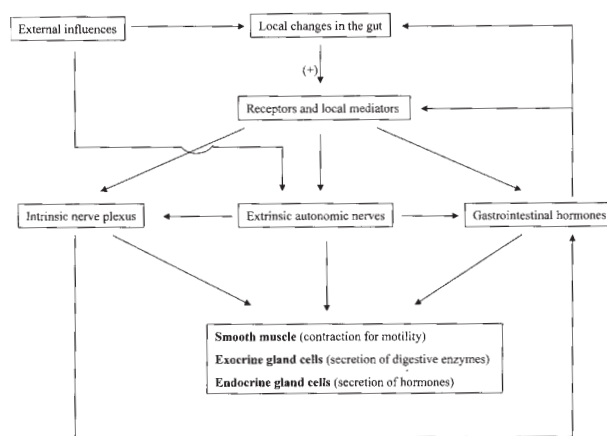


Fig. 1: Summary of pathways controlling gastrointestinal function and influenced by dietary spices.

Effect on carbohydrate metabolism

Spices are known to exert several beneficial physiological effects including the antidiabetic influence via short term hypoglycemia and long term improved glucose tolerance (Fig. 2) (135–139). A number of condiments and spices including pepper, asafetida, aloes, ocimum and eugenol from Jamun have been ascribed a hypoglycaemic action in normal as well as experimentally induced diabetic animal models and also in humans (140–150). A recent comprehensive review has cited evidence from animal experimentation as well as clinical trials where spices, their extracts or their active principles were examined for treatment of diabetes (139).

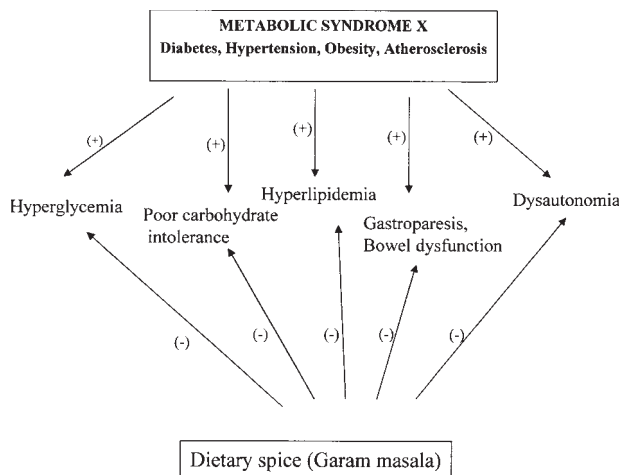


Fig. 2 : Dietary spices may act as putative antimetabolic syndrome X prescriptions [for details, see Kochhar (2)].

Fenugreek seeds (*Trigonella foenumgraecum*), garlic (*Allium sativum*), onion (*Allium cepa*), and turmeric (*Curcuma longd*) have been experimentally documented to possess potential to function as antidiabetic agents (139). Cumin seeds (*Cuminum cyminum*), ginger (*Zingiber officinale*), mustard (*Brassica nigrd*), curry leaves (*Murraya koenigii*) and coriander (*Coriandrum sativum*) have also been reported to have hypoglycaemic effects (139).

Oral administration of Cumin for 6 weeks to diabetic rats resulted in significant reduction in blood glucose and body weight and an increase in total hemoglobin and glycosylated hemoglobin. It also prevented a decrease in body weight. (99). Cumin supplementation was found to be more effective than glibenclamide in the treatment of diabetes mellitus (99). Fructose feeding has been shown to induce insulin resistance in rats, associated with hyperinsulinemia, hyperglycemia, and hypertriglyceridemia (167). Rajamani et al. investigated the effect

of administering food seasoning spices mixture on glucose, insulin, and lipids in circulation and carbohydrate enzymes in the erythrocytes of high fructose-fed rats (167). High homeostatic model assessment (HOMA) value indicated that administration of food seasoning spice mixture improved glucose metabolism and plasma lipid profile in fructose-fed rats and corrected insulin resistance possibly through improved insulin-sensitizing actions of the active spice constituents (167). Various spices display insulin-potentiating activity in vitro, and in particular, cinnamon spice and its phenolic extracts (168–170). Cinnamon ingestion reduced total plasma glucose responses as measured by area under the curve (AUC) to oral glucose ingestion as well as improved insulin sensitivity (169). Cinnamon supplementation may thus be important to *in vivo* glycaemic control and insulin sensitivity in humans, and not only are its effects immediate, they also appear to be sustained for 12 hour (169). Cinnamon also significantly delayed gastric emptying and profoundly lowered post prandial glycaemic response without any significant effect on satiety (170). The hypoglycaemic mechanism of efficacy of sumac (*Rhus coriaria* L.) and black cumin (*Bunium persicum* Boiss) was investigated and the inhibition of a glycoside hydrolase-alpha amylase may have interest in the treatment and prevention of hyperglycemia and diabetes as well as dyslipidemia and obesity (171).

Administration of turmeric or curcumin to Alloxan diabetic rats reduced the blood sugar, hemoglobin and glycosylated hemoglobin levels (172). Turmeric and curcumin supplementation also reduced the oxidative stress encountered by these

diabetic rats as demonstrated by the lower levels of TBARS (thiobarbituric acid reactive substances) which may have been due to the decreased influx of glucose into the polyol pathway leading to an increased NADPH/NADP ratio and elevated activity of the potent antioxidant enzyme GPx (172). Moreover, the activity of sorbitol dehydrogenase which catalyses the conversion of sorbitol to fructose, was lowered significantly on treatment with turmeric or curcumin (172).

Both *Murraya koenigii* and *Brassica juncea* showed significant hypoglycemic action in experimental rats (144, 173). There was increase in the concentration of hepatic glycogen and glycogenesis, as evident from the decreased activity of glycogen phosphorylase and gluconeogenic enzymes (173, 174). The stimulatory effect of capsaicin on serum insulin may be via capsaicin induced beta adrenergic activity on B cell receptors in pancreatic islets (175–177). Many enzymes of the liver including gluconeogenic, enzymes have been reported to be affected by spices both in vitro cell culture systems as well as in vivo in experimental animals (174, 175–183). The increased levels of glucose 6 phosphate dehydrogenase, the ability of insulin to activate lipoprotein lipase activity and also the effect of long term spice ingestion on these lipotropic effects could be responsible for the net hypoglycaemic effects indicating a more efficient optimal utilization of dietary carbohydrate on intake of spices (2) (164, 184–190).

Effect on lipid metabolism

Several active ingredients of spices including capsaicin (red pepper) piperine

(black pepper), curcumin (turmeric), eugenol (clove), ferulic acid (turmeric) and myristic acid (mace, amla) have been reported to influence lipid metabolism predominantly by mobilization of fatty acids (120, 190–195). Curcumin and capsaicin altered bile salt secretion to make it less lithogenic and also lowered cholesterol levels, without any significant effect on fat absorption (193–194). Capsaicin acted as a lipotrope, preventing triglyceride accumulation and increasing preferential utilization of fats (190–198). It also stimulated lipid mobilization and lowered perirenal adipose tissue weight and serum triglycerides in fat fed rats (197). Curcumin, eugenol and ferulic acid reduced fatty acid biosynthesis in rat liver and increased skeletal muscle lipoprotein lipase activity (120). Salimnath and Satyanarayana have reported that capsaicin inhibits calcium and calmodulin dependent phosphodiesterase activity in rat adipose tissue via an adrenaline releasing action of capsaicin reported earlier (189).

Embelic acid and turmeric are potential hypolipidemic and hypocholesterolemic agents (194–195). In rats rendered hypercholesterolemic by maintaining them on a cholesterol-enriched diet (0.5%) for 8 weeks, inclusion of curcumin (0.2%) capsaicin (0.015%) or garlic powder (2.0%) in the diet, produced the expected hypolipidemic effect (199). Dietary curcumin, capsaicin and garlic were observed to cause a 10–14% decrease in erythrocyte membrane cholesterol content and correct the increased fragility of erythrocytes (199). Cloves, mace and cardamom demonstrated significant ability to inhibit initiation as well as propagation of lipid peroxidation due to their polyphenol

content, strong reducing power and superoxide radical scavenging activity (199).

Modulation of inflammatory responses in obesity may be useful for preventing or ameliorating obesity-related pathologies (200). Woo et al in an elegant study treated raw 264.7 macrophages with an adipose tissue conditioned medium with or without active spice-derived components (i.e. diallyl disulfide, allyl isothiocyanate, piperine, zingerone and curcumin and measured macrophage migration and activation (200). Allyl isothiocyanate, zingerone, and curcumin significantly inhibited the cellular production of proinflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha) and nitric oxide, and significantly inhibited the release of monocyte chemo attractant protein MCP-1 from adipocytes (200).

Laboratory studies have shown that the resistance of isolated LDL-cholesterol or linoleic acid to oxidation is increased in incubations with chilli extracts or capsaicin (201). It is unknown if these in vitro antioxidative effects also occur in the serum of individuals eating chilli regularly. In a randomized cross-over study, twenty-seven participants ate 'freshly chopped chilli' blend and 'no chilli' diets for 4 weeks each (201). Regular consumption of chilli for 4 weeks increased the resistance of serum lipoproteins to oxidation (201). Capsaicin and curcumin have also been shown to reduce the susceptibility of LDL to oxidation in a concentration-dependent manner (202). Ahuja et al investigated the effects of (202). A 50% increase in lag time copper-induced oxidation

of serum lipoproteins (from control) was observed at different concentrations of capsaicin, dihydrocapsaicin, and curcumin (202).

Cumin treatment improved glucose tolerance and also resulted in a significant reduction in U-associated hyperlipidemia assessed by plasma and tissue cholesterol, phospholipids, free fatty acids and triglycerides and significantly reduced the fatty changes and inflammatory cell infiltrates in pancreas (99). The ethanolic extract of nutmeg (*myristica fragrans*) showed platelet anti-aggregatory ability and significantly lowered total cholesterol: HDL ratio and LDL: HDL ratio in experimentally induced hyperlipidaemia in albino rabbits (203). Rats fed *M. Koenigii* (curry leaf) and *B. juncea* (mustard) showed decreased concentration of malondialdehyde while hydroperoxides and conjugated dienes as well as superoxide dismutase and catalase activity were found to be increased in liver and heart (204). Glutathione levels in liver, heart and kidney were lowered and glutathione reductase, glutathione peroxidase and glutathione-S-transferase activity showed a sharp increase in the experimental groups (173, 204). Curry leaf or mustard seeds resulted in a reduction in total serum cholesterol and LDL+VLDL, an increase in the HDL, lower release of lipoproteins into the circulation and an increase in the LCAT activity (203–205). Dried flowers of *A. alliaceum* when fed at 2% level in diet for 6 weeks to experimental rats rendered hypercholesterolemic by cholesterol-feeding, exhibited blood cholesterol lowering effect by limitation in intestinal cholesterol absorption (205).

Actions on vascular endothelium

Protection of endothelial integrity by elimination of certain risk factors has proven to be effective in maintaining hemostasis and in slowing the progress of the cardiovascular disease (206–208). Rings of rat aorta with or without an intact endothelium, were mounted in tissue baths, contracted with phenylephrine, and then exposed to diluted extracts of herbs and spices (206). Many but not all extracts exhibited endothelium-dependent relaxations that were reversed by NG-monomethyl-L-arginine and also increased tissue levels of cyclic GMP, the mediator of nitric oxide-induced vascular smooth muscle relaxation (206).

Foeniculum vulgare, *Murraya koenigii*, *Curcuma aromatica*, *Mentha arvensis* and *Curcuma longa* demonstrated potent dose dependent scavenging of nitric oxide (NO) (207). Spices might be potent and novel therapeutic agents for scavenging of NO and the regulation of pathological conditions caused by excessive generation NO and its oxidation product, peroxynitrite as indicated by inhibition of lipopolysaccharide and interferon gamma induced nitrite production in mouse peritoneal cells by epigallocatechin gallate, carnosol, and curcumin (Fig. 3) (208).

Garlic and turmeric are potent vasorelaxants as well as reduce the atherogenic properties of cholesterol (209–213). Garlic has long been widely used not only as a flavoring agent but also as a folk medication (8–9). Its consumption has been reported shown to have antiatherosclerotic activity to increase high-density lipoprotein (HDL) levels, which may help to remove excess cholesterol from arterial tissue in

animal models and human cell cultures (7). It has been reported to have lipid-and blood pressure-lowering action, as well as antiplatelet, antioxidant, and fibrinolytic effects (7). The sulfur-containing component, allicin, is often considered to be the principal active ingredient of garlic, but several other bioactive ingredients, have also been isolated (186).

Some of the beneficial effects of garlic have been attributed to its consistent hypolipidemic and antioxidant properties (7–9). Long-term exposure to garlic, water-soluble garlic extracts, or garlic oil resulted in dose dependent decreased serum levels of cholesterol and triglycerides in rats and rabbits fed with high lipid diet (213). Perhaps the hypolipidemic action is primarily due to the decrease in hepatic cholesterolgenesis in garlic-treated rats probably by the inhibition of 3-OH-3-methyl glutaryl CoA reductase (HMG-CoA), the rate-limiting enzyme, early in cholesterol synthesis; whereas the triacylglycerol-lowering effect of garlic appears to be due to inhibition of fatty acid synthesis (213). A notable restoration of arterial blood pressure was seen in animals on garlic and turmeric supplemented diet (213). The vasorelaxant response to adenosine, acetylcholine, isoproterenol was enhanced and contractile effect of 5-hydroxytryptamine was significantly attenuated (213).

Onion oil has been shown to inhibit cyclooxygenase and 12-lipoxygenase in platelets as well as platelet aggregation induced by epinephrine, ADP, or arachidonic acid (AA) (214). More specifically, “cepaenes” found in onions have been found to be potent inhibitors of sheep seminal microsomal

cyclooxygenase and porcine leukocyte 5-lipoxygenase (7, 191, 214). Both aqueous and organic garlic extracts have been found to inhibit several steps of the incorporation of AA into platelet phospholipids, directly and also by inhibiting deacylation of platelet phospho-lipids upon stimulation with the calcium ionophore A23187, resulting in less eicosanoid synthesis (214). More recently, Ali et al. observed noncompetitive and irreversible inhibition of cyclooxygenase by aqueous extracts of raw garlic (215).

Wei and Lau (216) determined the effects of aged garlic extracts (AGE) on the generation of hydrogen peroxide and superoxide anion (O_2^-) and the activity of three antioxidant enzymes on bovine pulmonary artery endothelial cells (PAEC) (216). Confluent monolayers of PAEC were incubated with AGE, and oxidative stress was triggered by hypoxanthine and xanthine oxidase or H_2O_2 (216). AGE exhibited both concentration- and time-dependent suppression of H_2O_2 and O_2^- generation, and it also significantly increased the activities of SOD, CAT and GPX. The results suggest that AGE may be an effective antioxidant in preventing or treating disorders related to endothelial cell injury associated with free radicals (216). It has been suggested that due to their eicosanoid-modulating property, spices may serve to provide clues to drugs directed at arachidonic acid (AA) pathway enzymes as pharmacological targets (216-218). Curcumin, inhibited platelet aggregation induced by arachidonate, adrenaline and collagen and thromboxane B₂ production from exogenous arachidonate with a concomitant increase in the formation of 12-lipoxygenase products (219). Moreover, it inhibited the incorporation of amino acids

into platelet phospholipids as well as the deacylation of amino acid labeled phospholipids on stimulation with calcium ionophore A23187 (220). Curcumin's anti-inflammatory property may, in part, be explained by its effects on eicosanoid biosynthesis (219-220).

Excess nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS) is implicated in the development of a number of diseases including cardiovascular diseases. Due to absence of any natural specific enzymatic defense system in vivo, the consumption of certain foods which exhibit selective suppress NO overproduction might boost the host's protective effects against NO-mediated toxicity (222-223). Spices, rich in phenolics, are speculated conceivably to act as potential NO-scavengers or iNOS suppressors (219). Several mediterranean culinary spices including rosemary, tarragon, cinnamon, oregano, basil, marjoram and allspice with the exception of clove, displayed a rather linear dose-dependent NO-suppressing effect without any effect upon cell viability (219). Polyphenolic test extracts resulted in considerable endothelium-dependent relaxation in rings of rat aorta and mesenteric vascular beds in rats that appears to be mediated via NO-independent and non-prostanoid mechanisms (222).

Rietz et al. investigated the susceptibility of rat Langendorff heart preparation to ventricular arrhythmias under the conditions of cardiac ischemia and reperfusion (223). The incidence of ventricular fibrillation (VF) during 20-minute occlusion of the descending branch of the left coronary artery (LAD) was significantly reduced in the rats fed pulverized wild garlic leaves (223).

Acetylsalicylic acid could not completely prevent the cardioprotective effects suggesting that the prostaglandin system does not play a decisive role in the cardioprotective action of wild garlic (223). Furthermore, a moderate angiotensin-converting enzyme (ACE) inhibiting action of wild garlic was found in vitro as well as in vivo that could contribute to its cardioprotective and blood pressure-lowering action (223).

Effect on energy balance, metabolic rate and respiratory quotient

Capsaicin and piperine have been reported to reduce thermogenesis and cause thermal analgesia (11, 226–230). On the other hand ginger has been reported to be thermogenic (134). Spicy food has been shown to lower metabolic rate (228–230). Spicy foods also have been estimated to be rich in salicylates (Table IV) (164, 231) and liberate acetyl choline in vivo (126, 127). Many reports, quite a few of them preliminary have emerged but the resultant effect of a spicy 'mixture' on long term effect on body temperature and sleep activity cycle are still nebulous (161, 162, 232–237). Possibly this could be due to mutual antagonism, cross-reactivity, cross sensitization or competitive inhibition of certain endogenous receptor sites for these functions in free living humans (238–239). There is a great difference in the effects of capsaicin on local ingestion and parenteral administration since the metabolites of capsaicinoids seem to have no extrahepatic metabolism and no active metabolites were observed after x first pass' in liver (240–241).

Ciapsaicin initially increased oxygen consumption and respiratory quotient

TABLE IV: Naturally occurring salicylates in dietary spices.

	Type	mg/100 g
Spices		
Allspice	Powder, dry	5.2
Aniseed	Powder, dry	22.8
Bay leaf	Leaves, dry	2.52
Basil	Powder, dry	3.4
Canella	Powder, dry	42.6
Cardamom	Powder, dry	7.7
Caraway	Powder, dry	2.82
Cayenne	Powder, dry	17.6
Celery	Powder, dry	10.1
Chilli	Flakes, dry	1.38
	Powder, dry	1.3
Cinnamon	Powder, dry	15.2
Cloves	Whole, dry	5.74
Coriander	Leaves, fresh	0.2
Cumin	Powder, dry	45.0
Curry	Powder, dry	218.0
Dill	Fresh	6.9
	Powder, dry	94.4
Fennel	Powder, dry	0.8
Fenugreek	Powder, dry	12.2
Five spice	Powder, dry	30.8
Garam masala	Powder, dry	66.8
Garlic	Bulbs, fresh	0.1
Ginger	Root, fresh	4.5
Mace	Powder, dry	32.2
Mint	Garden, fresh	9.4
Mixed herbs	Leaves, dry	55.6
Mustard	Powder, dry	26.0
Nutmeg	Powder, dry	2.4
Oregano	Powder, dry	66.0
Paprika	Hot powder, dry	203.0
	Sweet powder, dry	5.7
Parsley	Leaves, fresh	0.08
Pepper	Black powder, dry	6.2
	White Powder, dry	1.1
Pimento	Powder, dry	4.9
Rosemary	Powder, dry	68.0
Sage	Leaves, dry	21.7
Turmeric	Powder, dry	76.4
Thyme	Leaves, dry	183.0

followed by a decrease in both before the levels returned to normal, resulting in an overall enhancement of energy metabolism. The effect was direct as well as via adrenalin release from adrenal medulla (175–176). According to Eldershaw crude extracts of both fresh and dry ginger induce the perfused hind limb to consume more oxygen in association with increase in perfusion pressure and lactate production (163). Previous studies have shown that the rats

consuming a diet containing garam masala spent more time in locomotion, moved a greater distance and had more average speed as compared to control animals (122–123). A single bolus of spice may not change thermic effect of feeding acutely but spices may have a modulatory role after cumulative intake (190–193). Since liver is the chief organ of metabolism there may be a change in the metabolic status of animals (190–193).

Long term intake of spices leads to alterations in the levels of hepatic enzymes in response to intake of spices and also influences the basal metabolic rate (228). Liver microsomal cytochrome p-450 dependent aryl-hydroxylase has been shown to be generally stimulated by spices (247). Singh and Rao have assessed the chemopreventive role of garam masala through its impact on hepatic levels of detoxication enzymes like glutathione-S-transferase, cytochrome b-5 and cytochrome p-450. They have reported that dietary doses of garam masala modulate the hepatic levels of these enzymes (243–244).

Effects on autonomic functions

Green chillies cause gustatory sweating associated with lacrimation, salivation and flushing of the face and the distribution of sweating is the same as thermal sweating (42). On intake of spicy meal a trend towards slight lowering of blood pressure soon after the meal intake or even post prandial hypotension was observed (245–247). Post prandial meal responses to food have been shown to be altered by capsaicin analogues (248–249). Acute haemodynamic effects of pan masala powdered mixture of areca nut, slaked lime, catechu and condiments caused

acute increase in pulse and systolic as well as diastolic blood pressure (225). Capsaicin analogues mediate a number of gastro-cardiovascular and pancreatico-cardiovascular reflexes (240, 250–255). Conversely the autonomic nervous system itself influences dietary thermogenesis (256–258). The nutritional status of the subject also influences autonomic function as well as B adrenergic responsiveness (258–259).

On acute administration, both peripherally and centrally, capsaicin produced hypothermia and vasodilatation via stimulation of hypothalamic temperature sensitive neurons whereas chronic or intra cerebral injection led to a desensitization, impairment of heat dissipating mechanism and loss of behavioral thermoregulatory responses to high ambient temperature (254). Capsaicin has potent hypertensive effects on intravenous administration and a pressor response on intracarotid injection (240). It sensitizes aortic baroreceptors via vagus nerve (250). Similarities between cardiovascular responses to food ingestion and to gastric intra arterial capsaicin ingestion suggested that the compound stimulates gastric distension receptors (257). Splanchnic nerve itself contains capsaicin sensitive neurons which can mediate cardiovascular effects (248, 253, 256). Piperine (black pepper) and capsaicin showed positive inotropic and chronotropic effects in isolated rat atria and exhibited cross tachyphylaxis (253). Air way reactivity is initially increased by capsaicin followed by desensitization (254). The respiratory effects of capsaicin vary from apnoea to tachyapnoea depending on route of administration (254). Aloe, garlic, onion and ginger are also beneficial in improving the symptoms of asthma (260, 261).

Donnerrer et al suggested a possible mechanism for the self-limiting effects on general autonomic responsiveness because of the fact that a majority of capsaicinoids undergo complete metabolism in the first pass in the liver (241, 263). Therefore the effect of locally ingested and systemically ingested spice principles may be different (263, 266).

Several Indian spices have been screened for cholinomimetic activity (126–127). The freeze dried aqueous extracts from roasted seeds (analogous to the farm garam masala used in Indian cooking) confirmed the presence of acetylcholine and also choline in large amounts when subjected to gas chromatography and mass spectrometry (126, 127). Thus the extracts from these spices stimulated muscarinic cholinergic receptors in 'rat blood pressure' and 'rat jejunum' biological preparation and also stimulated nicotinic receptors in 'frog rectus' (126). These effects were blocked by specific antagonists. Roasting appears to bring out the presence of acetylcholine in the aqueous extracts. There does not appear to be any destroying enzyme like cholinesterase in the aqueous extracts of spices (126, 127, 131). This gives rise to the possibility of certain endogenous neuropeptide analogues which are similar or may even inhibit gastro intestinal and vasoactive actions due to structural similarity (41, 128, 130).

Effects on reproductive system

Spices are considered as sexual invigorators in the Unani System of medicine. Aniseed has been used as an estrogenic agent (7). It has been reported to increase milk secretion, promote

menstruation, facilitate birth, alleviate symptoms of the male climacteric, and increase libido (7). Ginger root is a putative agent for preventing ageing dependent penile vascular changes and impotence (267). The extracts of the nutmeg and clove were found to stimulate the mounting behaviour of male mice, and also to significantly increase their mating performance devoid of any conspicuous general short term toxicity (267). Pimentol from allspice, rosmarinic acid and luteolin 7-0 beta glucuronide from thyme, quercetin 3-0 beta glucuronide from thyme, coriander and rutin from tarragon inhibited ovalbumin permeation through Caco-3 cell monolayers were identified as the active principles (268). A structure-activity relationship study among these spices active and their active principles indicated that the presence of catechol structure played an important role in the inhibitory activity of each compound (268).

Daware et al studied the effect of piperine on estrous cycle, mating behaviour, toxicity to male germ cells, fertilization implantation and growth of pups (269). Piperine interfered with several crucial reproductive events in a mammalian model (269). It increased the period of the diestrus phase which seemed to result in decreased mating performance and fertility. Considerable anti-implantation activity was recorded after five days post-mating on oral treatment with piperine and intrauterine injection of piperine caused the total absence of implants in either of the uterine horns (16.66%) or one of the horns (33%) (269). Glycyrrhizin decreases plasma clearance and increases plasma concentrations of prednisolone (270). Oral contraceptive use may increase sensitivity of glycyrrhizin acid; women are reportedly

more sensitive than men to adverse effects of licorice (270). Many of the commonly consumed foods, herbs, and spices contain phytoestrogens and phytoprogestins that act as agonists and antagonists in vivo (271). Over 150 herbs traditionally used for treating a variety of health problems were extracted and tested for their relative capacity to compete with estradiol and progesterone binding to intracellular receptors for progesterone (PR) and estradiol (ER) in intact human breast cancer cells (271). The six highest ER-binding herbs that are commonly consumed were soy, licorice, red clover, thyme, turmeric, hops and verbena. The six highest PR-binding herbs and spices commonly consumed were oregano, verbena, turmeric, thyme, red clover and damiana (271). Acute and chronic oral toxicity studies on the ethanolic extracts of *Cinnamomum zeylanicum* and *Piper longum* in mice induced a significant increase in reproductive organ weights, sperm motility, sperm count and failed to illicit any spermatotoxic effect (271).

Conclusion

Reports from studies on animals models and in vitro system, leads us to direct future research perspectives in this area by targeting study of controlled systemic, planned, blinded, quality assured trials on normal subjects as well as in patients of lifestyle related diseases like diabetes mellitus, hyperlipidemia, obesity, atherosclerosis, hypertension, dysautonomia and metabolic syndrome X and gastro intestinal diseases like acid reflux, peptic ulcer and functional bowel disorders. The analgesic, antioxidant, antiinflammatory as well as immune modulating roles of spices need further

elaboration. The action of spices on reproductive functions as well as their potential role as regulators of fertility and/or conception also is an area holding great future promise.

It is obviously a large task to comprehensively capture and review at any one time the now extensive literature on spices and herbs. Over the last decade the great excitement and interest in the mechanism, epidemiology, and preclinical and clinical effects of dietary spices on various body systems continues and is reflected in the large number of publications on this topic from Asian countries and the United States. The potential clinical promise is tempered by disappointment in the lack of efficacy of epidemiologically predicted micronutrient additives. Most of the work on spices has been done on animal models for whom spice intake is novel and not "physiological". Even in humans the usual intake is in the form of groups or mixtures of spices (2). Synergy and polyvalent action are important concepts in spice physiology and have a pharmacokinetic basis. Components of whole spices which are not active themselves can act to improve the stability, solubility, bioavailability or half-life of the active components. Hence a particular chemical might in pure form have only a fraction of the pharmacological activity that it has in its plant matrix thus suggesting that measuring an individual's food intake and assessing individual variation in disposition, bioavailability, and metabolism of micronutrients might allow for more accurate and individualized nutritional approaches for dietary prescription. Dietary modifications will only work if they are in consonance with individual preferences, culture values, and philosophical orientations toward health and disease.

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