

Potential Health Benefits of Indian Spices in the Symptoms of the Metabolic Syndrome: A Review

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Spices used in Indian cooking have a long history of use as medicines to prevent and treat diseases. Many studies have confirmed that spices can be useful medicines, but the major challenge is now to provide scientific evidence and plausible mechanisms for their therapeutic responses. This review focuses on the therapeutic potential of Indian spices to treat multiple symptoms of the metabolic syndrome such as insulin resistance, diabetes, obesity, altered lipid profile and hypertension. The metabolic syndrome is prevalent and has become an important financial burden to the healthcare system in both developed and developing countries. Inflammation and oxidative stress have been proposed as initiators of the metabolic syndrome, especially of insulin resistance. Natural products with anti-inflammatory and anti-oxidant properties are found in spices. Adequate doses of these compounds may be effective in treating the metabolic syndrome. Testing these potential treatments requires adequate animal models, usually rodents, so the limitations of these models are important. Furthermore, this review highlights the need for adequate legislation and regulation to ensure the safety and success of evidence-based functional foods and nutraceuticals.

Keywords: Spices, Diabetes, Cardiovascular disease, Metabolic syndrome, Inflammation, Oxidative stress, Nutraceuticals, Food safety

Introduction

Dietary choice remains the basis for maintaining a healthy lifestyle and well-being, especially relating to cardiovascular disease (CVD), despite remarkable advances in medicine and pharmaceutical drug development^{1,2}. Besides food being a lifestyle choice, age-old anecdotal reports from many cultures strongly suggest a role for diet as well as Indian spices in both preventive and therapeutic medicine^{3,4}. However, the major challenge in the use of spices as preventive and therapeutic medicines is in demonstrating their health benefits by scientific means, comparable with the standards applied for pharmaceutical agents³. Further, unlike pharmaceutical agents which are administered in predetermined doses as pure and concentrated preparations, spices are consumed in combinations and in unmeasured and variable quantities in different cultural settings. Therefore, the major challenge is to provide scientific evidence to define these benefits as well as plausible mechanisms by which these products are effective in a disease setting.

Around 60% of the world's population depends on herbal medicine, a broad term including spices, for primary healthcare⁵. Spices are pungent or aromatic substances from dried seeds, fruits, roots, bark or leaves used as additives to flavour, colour or preserve food; the differences with dried herbs used for flavouring is somewhat arbitrary. In India, many of these spices are part of everyday cooking and significant quantities may be consumed in a single meal. It is estimated that an adult in India can consume 80-200 mg/day of curcumin, the bioactive component of turmeric³. Some Indians have been reported to consume up to 50 g of garlic in a week^{3,6}. These data suggest a realistic possibility to achieve therapeutic doses of the active ingredients in spices by dietary consumption alone. However, for many patients, treatment with functional foods or nutraceuticals with enhanced concentrations of the active ingredients of the spices may be necessary. There is a widespread research effort in India to define the potential health benefits of herbal medicines, including spices, and identify the active ingredients, especially compounds with anti-oxidant and anti-inflammatory properties^{4,5}.

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This review investigates the potential of commonly used spices in India for treatment for the symptoms of metabolic syndrome in humans. To do this, we will define the metabolic syndrome and the likely mechanisms for the symptoms, discuss the choice of an appropriate rodent model for preclinical studies and present the available evidence for individual products. Two other important issues will then be presented: evaluation of the quality of the evidence as well as testing the safety and efficacy of these products.

Metabolic syndrome and its significance

The spices used in Indian cooking have potential for use in the treatment of the metabolic syndrome, a central preliminary pathological indication in the development of cardiovascular diseases, causing

major public health challenges worldwide⁷⁻⁹ and especially in the Indian sub-continent¹⁰. Metabolic syndrome refers to the clustering of several cardiovascular and metabolic risk factors, including dyslipidaemia, hyperglycaemia and increased blood pressure, where abdominal obesity and insulin resistance represent core parameters of this cluster^{7,8,11}. There are several definitions of the metabolic syndrome (Table 1), of which the first functioning definition was provided by the World Health Organization (WHO), emphasising insulin resistance and hyperglycaemia as key symptoms with additional associated metabolic symptoms. More recently, the US National Cholesterol Education Program Adult Treatment Panel III, International Diabetes Federation and the American Heart Association and National Heart, Lung, and Blood

Table 1—Diagnostic criteria and definitions for the metabolic syndrome provided by major agencies around the world

Clinical measure	WHO* (1998)	EGIR [^] (1999)	AACE [%] (2003)	ATP III [#] (2004)	IDF ^{**} (2005)	AHA/NHLBI ^{^^} (2005)
Insulin resistance	Impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or insulin resistance (IR) plus any 2 of the following:	Plasma insulin > 75th percentile plus any 2 of the following:	Impaired glucose tolerance, impaired fasting glucose plus any of the following:	NONE	Any 3 of the following 5 features:	
Dyslipidaemia	Triglycerides (TG): ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)	TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidaemia	TG ≥ 1.69 mmol/L and HDL-C < 1.03 mmol/L	TG ≥ 1.695 mmol/L HDL-C < 40 mg/dL (male), < 50 mg/dL (female)	TG ≥ 1.7 mmol/L or on TG Rx, HDL-C < 1.03 mmol/L or on HDL-C Rx	TG ≥ 1.69 mmol/L or on TG Rx, HDL-C < 1.03 mmol/L or on HDL-C Rx
Blood pressure	$\geq 140/90$ mm Hg	$\geq 140/90$ mm Hg	$\geq 130/85$ mm Hg	$\geq 130/85$ mm Hg	$\geq 130/85$ mm Hg	$\geq 130/85$ mm Hg
Plasma glucose	≥ 7.0 mmol/l (Fasting)	≥ 6.1 mmol/l (Fasting)	IGT or IFG (but not diabetes)	> 5.6 mmol/L	≥ 5.6 mmol/L (includes diabetes)	≥ 5.6 mmol/L or on hypoglycemic
Central obesity	Waist: hip ratio > 0.90 (male); > 0.85 (female), and/or body mass index > 30 kg/m ²	Waist circumference ≥ 94 cm (male), ≥ 80 cm (female)	BMI ≥ 25 kg/m ²	Waist circumference ≥ 102 cm (male), ≥ 88 cm (female)	Waist circumference > 94 cm	Waist circumference ≥ 102 cm
Other	Urinary albumin excretion ratio ≥ 20 mg/min or albumin:creatinine ratio ≥ 30 mg/g					

*World Health Organization²², [^]The European Group for the Study of Insulin Resistance²³, [%]American Association of Clinical Endocrinologists²⁴, [#]The US National Cholesterol Education Program Adult Treatment Panel III²⁵, ^{**}International Diabetes Federation²⁶, ^{^^}American Heart Association and National Heart, Lung, and Blood Institute¹²; Rx, medication; BMI, body mass index.

Institute have suggested that at least three of the following conditions must be met for a diagnosis of metabolic syndrome, although threshold values may differ: abdominal obesity, elevated triglyceride concentrations, reduced HDL-cholesterol concentrations, elevated blood pressure or fasting glucose concentrations¹² (Table 1).

The metabolic syndrome is common in adult populations throughout the world. In Australian adults, its prevalence ranges between 13.4 and 30.7%, depending on the definition used^{13,14}. In the USA, its overall percentage in adults was 22.8% for men and 22.6% for women¹⁵. In the Japanese population, 51% of male and 53% of female subjects met the WHO criteria for the metabolic syndrome, whereas 45% of male and 38% of female subjects met the US National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome¹⁶. In Finland, metabolic syndrome was present in 38.8% of men and 22.2% of women¹⁷.

This situation appears to be similar in the Indian sub-continent with recent data suggesting about one-fourth to one-third of the adult Indian population suffer from the metabolic syndrome^{18,19}. Some communities such as the Punjabi Bhatia community in north India are more prone to be obese with type II diabetes and the symptoms of metabolic syndrome^{18,19}. The prevalence of metabolic syndrome in the Sri Lankan population is high with 35% and 51% in males and females, respectively^{18,19}. In adults aged 25 years and older from an urban population in Karachi (Pakistan), the prevalence of metabolic syndrome was 34.8 and 49%, according to the International Diabetes Federation and US National Cholesterol Education Program Adult Treatment Panel III definitions, respectively²⁰. The overall prevalence in Pakistan has been reported as 18-46%, comparable to other South Asian countries^{19,21}. Comparable data from Bangladesh and Nepal are not available, but the prevalence would be expected to be similar. Intrauterine and early postnatal under-nutrition has been suggested as an important cause of the relatively high incidence of cardiovascular disease and metabolic syndrome in Indian populations¹⁰. Thus, the metabolic syndrome provides many challenges to governments and healthcare providers from birth to death.

Aetiology of metabolic syndrome

The aetiology of metabolic syndrome involves many complex biochemical pathways. Different

mechanisms linking the symptoms of metabolic syndrome have been postulated, all possibly hampering normal cardiovascular function. Increased levels of reactive oxygen species (ROS), non-esterified fatty acids, oxidized LDL and lipotoxicity may be related to insulin resistance²⁷. Adipose tissue releases numerous bioactive mediators, including pro-inflammatory cytokines that not only influence body weight homeostasis, but also induce changes in cardiovascular structure and function, glucose metabolism, blood pressure, lipid metabolism, coagulation and inflammation, leading to endothelial dysfunction and atherosclerosis^{27,28}.

Inflammation has been proposed as the critical process initiating the symptoms of metabolic syndrome²⁹. The pro-inflammatory state of obesity and metabolic syndrome is probably initiated by an excessive caloric intake in a high carbohydrate/high fat diet^{29,30}. Increased oxidative stress in the adipose tissues of obese subjects is closely linked to enhanced inflammatory signals, adipokine dysregulation and insulin resistance³¹⁻³³. Redox regulation of inflammatory signalling occurs at several levels, including direct effects of oxidants, modulation by antioxidants, alterations in the redox equilibrium (for example, ratio of reduced: oxidized glutathione and thioredoxin) and activation of oxidant- and redox-sensitive transcription cofactors such as NF- κ B and AP-1^{34,35}.

Activation of the NF- κ B pathway has been linked to a range of inflammatory disorders, including atherosclerosis, myocardial infarction and diabetes; this pathway can be interrupted by phytochemicals derived from the spices³⁶. The pro-inflammatory/pro-oxidant state induces insulin resistance, leading to the clinical and biochemical symptoms of metabolic syndrome^{27,32}. This resistance to insulin action promotes inflammation through an increase in free fatty acid concentrations and hinders the anti-inflammatory effects of insulin^{29,30}. Both human and animal studies have shown that diets rich in carbohydrates and saturated fats contribute to insulin resistance, metabolic defects, excess body weight, lipid abnormalities, increased reactive oxygen/nitrogen species, decreased anti-oxidant defences and the development of pre-diabetic or diabetic state²⁷. The contributions towards this metabolic dysfunction from insulin signalling, oxidative stress and inflammation (Figure 1) have been difficult to separate²⁷.

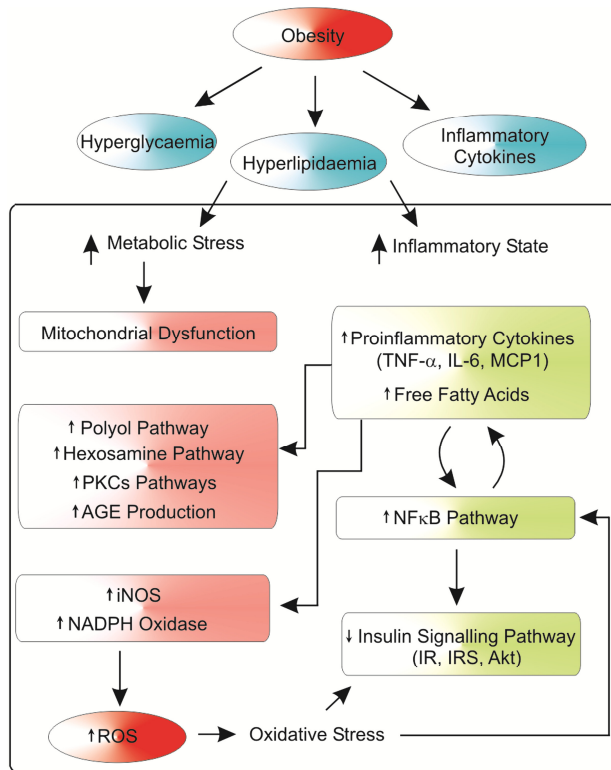


Fig. 1—Metabolic changes in obesity. Hyperglycaemia, hyperlipidaemia and elevated inflammatory cytokines are found in obese and diabetic conditions, which elevate both metabolic and inflammatory stress. Mitochondrial dysfunction, polyol pathway, hexosamine pathway, AGE pathway, and pro-oxidative genes such as iNOS and NADPH oxidases are associated with ROS generation and result in oxidative stress. Such stresses combine to activate PKCs and NF- κ B signalling pathways, which cause insulin resistance by attenuating the insulin signalling pathway. *Abbreviations used:* TNF- α , tumour necrosis factor- α ; IL6, interleukin 6; MCP, Monocyte chemoattractant protein; NF κ B, nuclear factor kappa B; IR, insulin receptor; IRS, insulin receptor substrate; PKC, protein kinase C; AGE, advanced glycation end-products; iNOS, inducible nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; Akt, thymoma viral proto-oncogene designated as protein kinase B (PKB). Figure adapted from³³

Table 2—Rodent models of the metabolic syndrome

Spontaneously diabetic rodents

Otsuka Long-Evans Tokushima fatty rats (OLETF)^{43,44}

Goto-Kakizaki rats⁴⁵

Zucker diabetic fatty rats^{46,47}

The JCR: LA-Cp rat^{48,49}

Spontaneously hypertensive rat⁵⁰

ob/ob mouse⁵¹

db/db mouse⁵²

Genetically engineered diabetic mice

Insulin receptor-deficient mouse (IR^{-/-})⁵³

GLUT4 deficient mouse (GLUT4^{-/-})⁵⁴

IRS-1 deficient mice (IRS-1^{-/-})⁵⁵

Artificially-induced diabetic rodents

Fructose-fed rats^{56,57}

Sucrose-fed rats⁵⁸

High fat-diet model^{59,60}

Mild obesity, postprandial hyperglycaemia, insulin resistance, hyperinsulinaemia, hyperplasia with fibrosis followed by atrophy of the pancreatic islet, diabetic nephropathy, left ventricular fibrosis, endothelial dysfunction, hyperlipidemia

Non-obese, hyperglycaemia, hyperinsulinaemia, insulin resistance, endothelial dysfunction

Non-functional leptin receptors, obese, dyslipidaemia, hyperinsulinaemia, insulin resistance, hyperleptinaemia, moderately elevated blood pressure

Obese, insulin resistance, hyperinsulinaemia, impairment of endothelium-dependent vascular relaxation

Insulin resistance, hypertension, cardiac hypertrophy, endothelial dysfunction

Obesity, hyperglycaemia, impaired glucose tolerance, dyslipidaemia

Hyperinsulinaemia, insulin resistance, hyperglycaemia, polyuria, glycosuria

Fatty acid infiltration in the liver, increased ketone bodies production, hyperglycaemia, hyperinsulinaemia, increased serum triglycerides, death within a week

Retarded growth, decreased longevity, cardiac hypertrophy, post-prandial hyperinsulinaemia, insulin resistance

Highly reduced intrauterine growth, impaired glucose tolerance, decreased insulin/IGF-1-stimulated glucose uptake

Hyperinsulinaemia, impaired glucose tolerance, insulin resistance, hypertension, hypertriglyceridaemia, cardiac fibrosis, endothelial dysfunction

Insulin resistance, dyslipidaemia, obesity

Obesity, dyslipidaemia, insulin resistance, hyperinsulinaemia, hyperglycaemia, impaired glucose tolerance, endothelial dysfunction, hypertension, hyperleptinaemia

Rodent models of metabolic syndrome

Rat and mouse models of human diseases such as obesity, diabetes and cardiovascular diseases have been widely used to investigate the progression of disease symptoms (Table 2)³⁷⁻³⁹. Understanding the influence of diet as a cause of the symptoms of metabolic syndrome requires adequate animal models with the symptoms relevant to human pathology, such as diet-induced obesity, diabetic and cardiovascular symptoms, to test proposed treatment options and dietary interventions. The most-used rat models of the complications of diabetes are induced by either streptozotocin⁴⁰ or a high fructose diet^{41,42}. However, streptozotocin induces type I diabetes and a high fructose diet does not induce abdominal obesity⁴². Thus, results from these models may be relevant only to a small proportion of diabetic patients.

Diets including a significant component of animal-derived fats, such as lard or beef tallow, or plant oils such as corn or safflower oil may cause diabetes and obesity as well as cardiovascular changes³⁹. Obesity and diabetes increase the risk of cardiovascular disease and its associated metabolic risk factors, probably by the releasing bioactive mediators from adipose tissue initiated by an excessive caloric intake in a high carbohydrate/high fat diet^{27,29,30}. Thus, administering a high carbohydrate/high fat diet should induce the range of symptoms of metabolic syndrome rather than streptozotocin- or fructose-induced diabetes. These dietary interventions should serve as a more relevant model to investigate possible therapeutic interventions for the complications of metabolic syndrome.

Health benefits of Indian spices: what is the evidence?

The contribution of oxidative stress and inflammation in initiating the symptoms of metabolic syndrome is now well-known. Suitable therapeutic interventions targeting these oxidative and inflammatory processes may be effective in preventing and treating the metabolic syndrome. Several reviews have discussed the use of herbal medicines, including spices, in the treatment of the symptoms of metabolic syndrome such as diabetes^{4,61}, insulin resistance⁶², hypertension and other cardiovascular diseases⁶³, and inflammation⁶⁴. This section deals with the possible therapeutic benefits of the spices in the treatment of the symptoms of metabolic syndrome, in particular because of their anti-oxidant or anti-inflammatory effects.

Cardamon or Elaichi (*Elettaria cardamomum*)

Cardamon, a perennial herb indigenous to the Indian subcontinent, contains a wide variety of compounds, including α -terpineol, myrcene, subinene, limonene, cineol, α -phellandrene, menthone, α and β -pinene⁶⁵, *cis/trans*-linalol oxides, *trans*-nerolidol⁶⁶, β -sitostenone, γ -sitosterol, phytol, eugenyl acetate⁶⁷, bisabolene, borneol, citronellol, p-cymene, geraniol, geranyl acetate, stigmasterol and terpinene⁶⁸. *In vitro* studies showed that cardamon inhibited platelet aggregation, when induced with agents such as ADP, epinephrine, collagen and calcium ionophore A 23187⁶⁹. Cardamon reduced blood pressure in rats, probably by acting through cholinergic and calcium antagonist mechanisms⁷⁰.

Cinnamon or Dalchini (*Cinnamomum verum*)

Cinnamon is a small evergreen tree, approximately 10-15 m tall, native to Sri Lanka and Southern India⁷¹. Its bark has been widely used as a spice and flavouring agent for centuries. Cinnamon has been suggested to have many pharmacological properties, including antioxidant activity and antimicrobial effects^{72,73}. The major active components of aqueous cinnamon extract appear to be doubly-linked procyanidin type-A polymers⁷⁴, cinnamaldehyde and esters such as ethyl cinnamate (Figure 2).

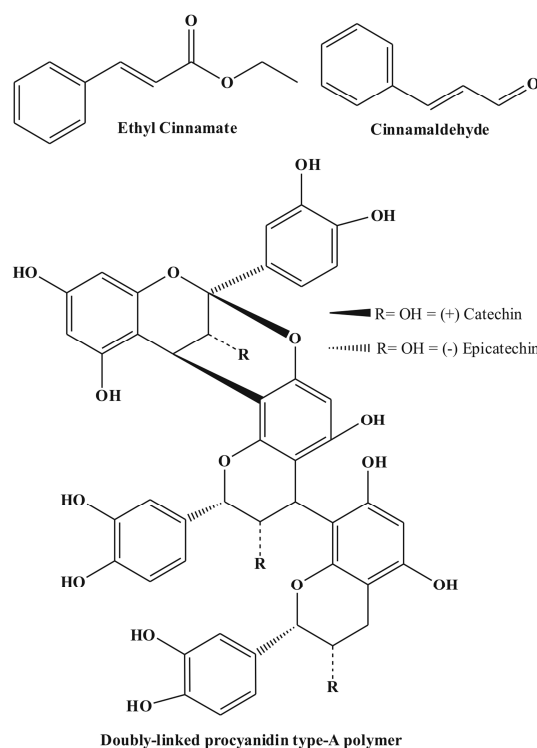


Fig. 2—Bioactive constituents in cinnamon

Pre-clinical and clinical data show that cinnamon attenuated the progression of type II diabetes^{75,76}. Cinnamon (8% w/w in diet) prevented sucrose-induced increases in blood pressure in spontaneously hypertensive rats⁷⁷ and a cinnamon extract (300 mg/kg/day) decreased insulin resistance in fructose-fed diabetic rats, partly by enhancing insulin signalling and partly by activating the NO pathway in skeletal muscle⁷⁸. An aqueous extract of cinnamon bark improved insulin resistance and prevented lipid abnormalities in fructose-fed rats⁷⁹. In cholesterol-fed rats, cinnamate (0.1 g/100 g diet) inhibited hepatic HMGCoA reductase activity and suppressed lipid peroxidation in the liver⁸⁰. Cinnamaldehyde (5-20 mg/kg/day) decreased plasma glucose, glycosylated haemoglobin, cholesterol and triglyceride concentrations, while increasing plasma insulin and HDL-cholesterol concentrations as well as hepatic glycogen in streptozotocin-induced diabetic rats⁸¹. Similar decreases were reported when poorly-controlled type 2 diabetic patients were given 1-6 g/day cinnamon for 40 days⁷⁵.

A related species, cassia cinnamon (*C. aromaticum*) also known as Chinese cinnamon, reduced fasting blood glucose concentrations, improved plasma lipid profiles in diabetic humans and reduced glucose and insulin responses in oral glucose tolerance testing^{75,82,83}. In subjects diagnosed with the metabolic syndrome, an aqueous extract of Chinese cinnamon standardised to doubly-linked polyphenol type-A polymers as the bioactive component (500 mg/day) reduced systolic blood pressure, fasting blood glucose concentrations and also attenuated whole body fat deposition to body weight ratio⁸⁴. The pre-clinical and clinical evidence for therapeutic usefulness of both common and cassia cinnamon has been reviewed⁷¹.

Coriander or Dhania (*Coriandrum sativum*)

Coriandrum sativum is a well-known herb, native to Europe and Western Asia, used as fresh and dried fruit and leaves to flavour meals and as an ingredient in curry powder (<http://www.botanical.com/botanical/mgmh/c/corian99.html>). It is generally used in gastrointestinal complaints such as anorexia, dyspepsia, flatulence, diarrhoea, griping pain and vomiting⁸⁵. The stems and leaves contain caffeic, chlorogenic, ferulic and gallic acids⁸⁶. The seeds were effective as an antidiabetic agent administered as 6.25% in food in streptozotocin-diabetic mice⁸⁷, and as a hypolipidaemic agent as 10% in food in rats fed

15% coconut oil and 2% cholesterol⁸⁸. Continuous intravenous infusion of the crude aqueous extract of coriander (40 and 100 mg/kg) induced dose-dependent diuresis, natriuresis, kaliuresis, increased chloride excretion and increased glomerular filtration rate in anaesthetized Wistar rats⁸⁹. Alcoholic extract of coriander (200 mg/kg) decreased fasting serum glucose concentration and increased insulin release from pancreatic β -cells in streptozotocin-induced diabetic rats⁹⁰. Oral intake of fruit powder (8% w/w of food) in cholesterol-fed rats decreased plasma total cholesterol, LDL-cholesterol and total lipid concentrations, while increasing the HDL-cholesterol⁹¹.

Cumin seeds or Jeera (*Cuminum cyminum*)

Cumin seeds are a common dietary spice consumed in fairly large quantities in India. They are widely used in Ayurvedic medicine for treatment of dyspepsia, diarrhoea and jaundice⁸⁰. Cuminaldehyde is suggested as the active ingredient in cumin seeds (Figure 3)⁹². An aqueous extract of cumin seeds prevented the accumulation of advanced glycation end-products due to fructose-mediated *in vitro* glycation of eye lens soluble proteins⁹². Hypoglycaemic effects of cumin seeds were also observed in normal rabbits⁹³. Dietary cumin showed marked hypoglycaemic responses in streptozotocin-diabetic rats by reducing blood and urinary glucose concentrations⁹⁴. An aqueous extract of seeds lowered blood glucose and plasma and tissue lipid concentrations in alloxan-induced diabetic rats⁸⁰.

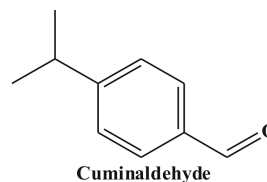


Fig. 3—Cuminaldehyde, an active ingredient of cumin

Curry plant/leaves or Kadipatta (*Murraya koenigii*)

Curry leaves are used as a culinary spice and also as a traditional medicine. Several carbazole alkaloids were reported in the plant⁹⁵. Recently, a 35 kDa antioxidant protein PII, purified from leaf powder, inhibited lipid peroxidation and lipoxygenase activity *in vitro* in human erythrocyte ghosts and also effectively scavenged ROS⁹⁶. The leaf extract supplementation (80 mg/kg) decreased blood cholesterol and glucose concentrations in diabetic *ob/ob* mice with

reduction in body weight⁹⁷. Extracts of leaves showed hypoglycaemic effect in both normal and alloxan-induced diabetic dogs and rabbits⁹⁸. In alloxan-induced mild and streptozotocin-induced moderately diabetic rats, feeding of 15% curry leaf powder diet reduced blood glucose concentrations by 21.4% and 8.2% respectively⁹⁹. In normal rats, 10% leaf administration in food increased hepatic glycogen concentration and glycogenesis by increased activity of glycogen synthetase, and decreased glycogenolysis and gluconeogenesis by decreased activity of glycogen phosphorylase and gluconeogenic enzymes¹⁰⁰. Curry leaf supplementation lowered lipid peroxidation and also modulated the hepatic function to near normal level in rats fed with a high-fat diet¹⁰¹. Supplementation with 10% curry leaves in high fat-fed young male albino rats reduced total serum cholesterol, LDL and VLDL concentrations, increased HDL concentration, lowered release of lipoproteins into the circulation and increased the lecithin cholesterol acyltransferase (LCAT) activity¹⁰².

Fenugreek or Methi (*Trigonella foenum*)

Fenugreek, a strongly scented annual herb, is recommended for the treatment of rheumatism in traditional medicine. Saponins, glycoside-D and trigofenoside-A are major components in the seeds¹⁰³, while alkaloids, cardiac glycosides and phenols are found in the leaf extract¹⁰⁴. The steroidal saponins present in the seeds as parent compounds for physiological steroid production could influence the local inflammatory response^{105,106}. Galactomannan, a guar gum comprising approx. 50% of the seed weight is postulated as another active ingredient in fenugreek seeds¹⁰⁷. In high sucrose-fed rats, galactomannan feeding reduced appetite, body weight gain, glycemic response, plasma insulin concentrations and plasma triglycerides and total cholesterol concentrations¹⁰⁸. In human studies, galactomannan reduced post-prandial blood glucose concentrations^{109,110} and improved

insulin sensitivity in both non-diabetic¹¹¹ and diabetic subjects¹¹². Feeding guar-galactomannan fibre reduced both total and LDL cholesterol concentrations in healthy and type 2 diabetic subjects¹¹³.

Garlic or Lahsun (*Allium sativum*)

Garlic has been used as both an important dietary constituent and a medicine in different cultures around the world. A broad range of therapeutic responses to garlic has been reported, including decreases in blood pressure, blood lipid and glucose concentrations and the risk of atherosclerosis as well as antimicrobial, anticancer and hepatoprotective effects¹¹⁴⁻¹¹⁶. The responses with garlic have been attributed to its sulphur-containing antioxidants (Figure 4). Allicin (diallyl thiosulphinates) is the major bioactive thiosulphinates compound found in garlic homogenate and is liberated from alliin by the enzyme alliinase when garlic is crushed or bruised¹¹⁷. Other important sulphur-containing compounds include allyl methyl thiosulphonate, 1-propenyl allyl methyl thiosulphonate and γ -L-glutamyl-S-allyl-L-cysteine¹¹⁷.

In vitro animal and human tissue studies showed that garlic inhibited angiotensin II responses, possibly by inhibition of angiotensin converting enzyme to promote vasodilation¹¹⁸⁻¹²⁰. In animal studies, dose-dependent antioxidant and organ-protective effects of raw garlic homogenate (125, 250 and 500 mg/kg doses) have been observed in various organs such as heart, liver and kidneys^{121,122}. An aqueous extract of garlic neutralised free radicals and reduced oxidative damage in rabbit liver homogenates¹²³. Furthermore, an aged garlic extract inhibited the development of thickened, lipid-filled lesions by approximately 50% in preformed neointimas produced following injury of the right carotid artery in cholesterol-fed rabbits, in addition to reducing the surface area of the thoracic aorta covered by fatty streaks (64% decrease)¹¹⁴. Two meta-analyses have demonstrated that garlic preparations reduced blood pressure in hypertensive

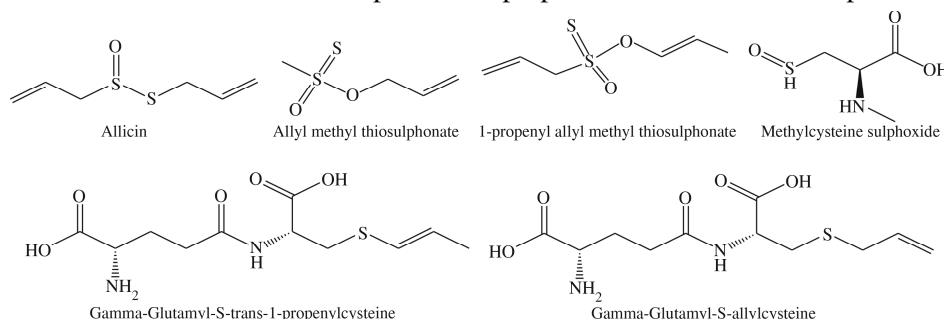


Fig. 4—Bioactive constituents in garlic

patients^{124,125}, although an earlier review concluded that the reported effects were too small to be clinically meaningful¹²⁶.

Ginger or Sonth (*Zingiber officinale*)

The therapeutic potential of ginger is recognised in a wide range of unrelated disease states including stomach aches, diarrhoea, nausea, asthma, respiratory disorders, toothache, gingivitis and arthritis^{127,128}. Recent research has focussed on elucidating the anti-inflammatory properties of ginger. As with most herbal preparations, ginger extracts are complex with more than 400 chemical compounds already isolated and identified¹²⁹. A subfraction containing the structurally related compounds gingerols, shogaols and paradols is likely to account for the anti-inflammatory properties of ginger (Figure 5)¹²⁹. The anti-inflammatory effect of ginger was attributed to its ability to inhibit cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), the enzymes critical in prostaglandin and leukotriene synthesis, respectively¹²⁹. Ginger lowered blood pressure through both stimulation of muscarinic receptors and blockade of calcium channels^{128,130}.

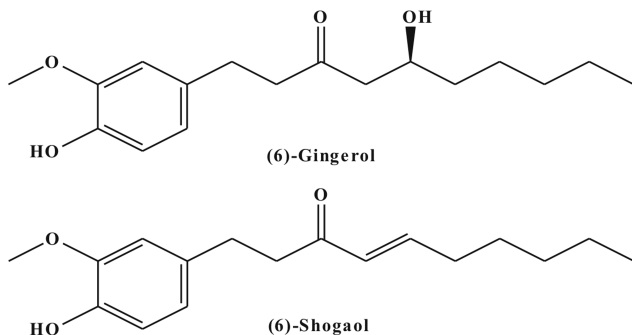


Fig. 5—Bioactive compounds in ginger; shogaols are formed upon drying.

Malabar tamarind or Imli (*Garcinia cambogia*)

Fruits of *G. cambogia* are commonly known as gambooge or brindleberries. The active ingredient is hydroxycitric acid (Figure 6), a potent inhibitor of adenosine triphosphate (ATP) citrate lyase¹³¹. ATP

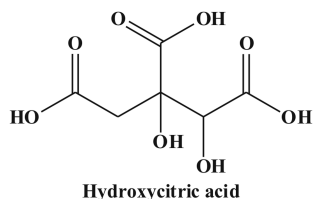


Fig. 6—Hydroxycitric acid, the active principle of Malabar tamarind

citrate lyase is critical in catalyzing the cleavage of citrate to oxaloacetate and acetyl-coenzyme A. Inhibition of ATP citrate lyase can reduce the availability of acetyl-coenzyme A units for fatty acid synthesis and lipogenesis, thus modulating fat metabolism¹³¹. In human studies, oral intake of hydroxycitrate increased fat oxidation, when supplemented with moderate intensity exercise¹³². In animal studies, oral intake of *G. cambogia* extract effectively attenuated body weight gain, visceral fat accumulation, blood and hepatic lipid concentrations and plasma insulin and leptin concentrations in obese mice fed a high fat diet¹³³. The extract ameliorated diet-induced obesity by modulating multiple genes associated with adipogenesis, such as aP2, SREBP1c, PPAR γ 2, and C/EBP α in the visceral fat tissue¹³³. The calcium-potassium salt known as HCA-SX or Super citrmax, a derivative of hydroxycitric acid, reduced food intake and body weight gain in obese Zucker rats and also attenuated the increased inflammation, oxidative stress and insulin resistance in untreated Zucker rats¹³⁴. In a human study, treatment with HCA-SX for 8 weeks decreased body weight and BMI by 5.4% and 5.2%, respectively¹³⁵.

Turmeric or Haldi (*Curcuma longa*)

Turmeric is a perennial herb, yielding a rhizome widely used as a culinary ingredient. Both Ayurvedic and traditional Chinese medicines have used turmeric for the treatment of inflammatory and digestive disorders. Research has focussed the antioxidant, hepatoprotective, anti-inflammatory, anticarcinogenic and anti-microbial properties of turmeric, in addition to its use in cardiovascular disease and gastrointestinal disorders¹³⁶. Curcuminoids constitute 5% of the turmeric rhizome and are suggested as the active ingredients, showing both antioxidant and anti-inflammatory effects. Both turmeric extract and curcumin (Figure 7), one of the major curcuminoids, have been widely examined for possible therapeutic effects in the symptoms of metabolic syndrome. In *in vitro* studies, turmeric prevented protein glycosylation and lipid peroxidation induced by high

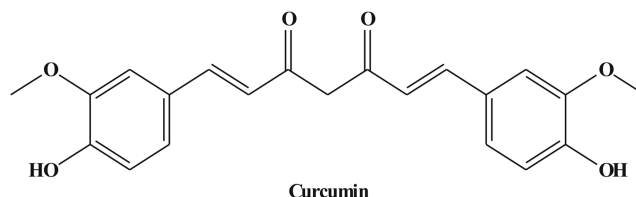


Fig. 7—Curcumin, the major bioactive ingredient of turmeric.

glucose concentrations¹³⁷. Curcumin showed anti-differentiation effects, possibly through AMPK α -PPAR- γ in 3T3-L1 adipocytes¹³⁸. It also inhibited NF κ B-mediated cytokine expression in adipocytes¹³⁹. In this study, curcumin inhibited TNF- α , IL-1 β , IL-6 and COX-2 gene expression at an IC₅₀ of 2 μ M and also showed a reduction in secreted IL-6 and PGE2 at IC₅₀ ~20 μ M in adipocytes¹³⁹. Dietary curcumin improved inflammation and diabetes associated with obesity¹⁴⁰. In high-fat fed obese and leptin-deficient *ob/ob* mice, curcumin reduced macrophage infiltration of white adipose tissue, increased adipose tissue adiponectin production and decreased hepatic NF- κ B activity, hepatomegaly and other markers of hepatic inflammation¹⁴⁰. Curcumin and other curcuminoids prevented lipid accumulation in the liver and epididymal adipose tissues in high fat-fed Sprague-Dawley rats, possibly by altering fatty acid metabolism¹⁴¹.

An extract of turmeric decreased LDL oxidation and lowered oxidation of erythrocyte and liver membranes in rabbits on a high saturated fat and cholesterol diet¹⁴². Interestingly, curcumin did not show any hypoglycaemic activity in streptozotocin-induced diabetic rats⁶¹, suggesting it may have a therapeutic potential in type II but not type I diabetes. Early studies showed anti-thrombotic responses by curcumin in normal mice, possibly by suppressing thromboxane-2 production¹⁴³. In humans, a longer-term study with 30 healthy subjects given turmeric extract equivalent to 20 mg curcumin for 60 days also showed decreased peroxidation of both HDL and LDL cholesterol¹⁴⁴. The biological activity of curcumin in humans has been extensively reviewed, although evidence on the symptoms of metabolic syndrome is limited¹⁴⁵.

Black mustard or Rai (*Brassica nigra*), black pepper or Kali Mirchi (*Piper nigrum*) and nutmeg or Jaiphal (*Myristica fragrans*)

Black mustard, black pepper and nutmeg are some of the other spices sparingly examined for possible therapeutic effects in the symptoms of metabolic syndrome in experimental diseased animals. Mustard showed hypoglycaemic effect in rats in a study to test its effect on the enzymes of carbohydrate metabolism^{61,100}. The mucilage (soluble fibre) of mustard at 5%, 10% and 15% in the food improved post-prandial glucose concentrations and insulinaemia in normal rats⁶¹.

Black pepper supplementation (0.25 or 0.5 g/kg body weight) in high fat-fed rats lowered concentrations of thiobarbituric acid reactive substances and conjugated dienes, maintained superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase concentrations and reduced glutathione concentrations in the liver, heart, kidney, intestine and aorta compared to control rats¹⁴⁶. Black peppers also showed potential in obesity by increasing thermogenesis and fat oxidation¹⁴⁷.

An *in vitro* study suggests that meso-dihydroguaiaretic acid isolated from the nutmeg plant may act as an enhancing agent in intracellular insulin signalling, possibly through the inhibition of PTP1B activity¹⁴⁸. An extract of nutmeg seeds prevented lipid abnormalities and atherosclerosis in hypercholesterolaemic rabbits^{149,150}.

Health benefits of Indian spices: how strong is the evidence?

The quality of evidence for health benefits can be categorised into different levels. As an example, the evidence for cinnamon bark has been reported under the following levels⁷¹: A: very strong scientific evidence from systematic reviews or meta-analysis; B1: strong scientific evidence from one or more randomised controlled trials; B2: good scientific evidence from one or more randomised controlled trials of limited size or methodology; C: fair scientific evidence from one or more cohort studies or outcome studies or case control studies; D: weak scientific evidence from case series; E: indirect evidence from case reports or expert opinion or laboratory studies; and F: historical or traditional evidence.

This provides an evaluation on each study and possible clinical indication; for example, the randomised clinical trials of 60-79 patients using cinnamon for diabetes^{75,82} have been both classified as level B1, a smaller clinical trial of 25 patients¹⁵¹ is classified as level B2, while a case report of a chronic carrier of *Salmonella enteritidis* showing improvement after consumption of cinnamon bark is classified as level E⁷¹. A thorough evaluation of all evidence for therapeutic effectiveness of spices in the metabolic syndrome is not possible for this review. However, the evidence for individual spices would appear to be level B for cinnamon to lower blood glucose concentrations or insulin resistance, for turmeric to improve the lipid profile, for hydroxycitrate from tamarind to reduce obesity and for garlic to reduce blood pressure.

Similarly, the potential of therapeutic interventions to harm the patient can be categorised into levels as follows⁷¹: 1a: very strong scientific evidence from systematic reviews or randomised clinical trials; 1b: strong scientific evidence from outcome studies, cohort studies or case control studies; 1c: good scientific evidence from one or more case series; 2: fair scientific evidence from case reports; 3: *in vitro* scientific evidence from studies on animals, insects, micro-organisms or cell cultures; 4: indirect evidence based on scientific theory or expert opinion; and 5: no available evidence.

In general, spices are generally recognised as safe (GRAS) by the United States Food and Drug Administration, when used in therapeutic doses. Some studies have reported minor adverse effects, usually gastrointestinal complaints with spices used as therapeutic agents.

The development of more active nutraceuticals and purified products from herbal medicines raises the controversial issues of patents and protection of intellectual property¹⁵². This issue is very relevant to India, as shown by the discussions on the Traditional Knowledge Digital Library (<http://www.tkdil.res.in/tkdil/langdefault/common/home.asp?GL=Eng>), a searchable database of more than 230,000 formulations taken from ancient texts on Indian systems of medicine - Ayurveda, Unani, Siddha and Yoga - in Hindi, Sanskrit, Arabic, Persian and Urdu¹⁵³. Since spices are a part of herbal medicines, these issues become relevant to this review.

Safety and toxicity

Herbal medicines, including spices, have the potential to produce adverse effects, especially when used in concentrated forms. Further, these products may interact with other herbal products as well as drugs¹⁵⁴. Although spices are regularly consumed in the diet by many populations, their use as nutraceuticals in a concentrated form needs further investigation for efficacy and toxicity. Nutraceuticals may tend to show fewer adverse effects compared to prescription drugs or herbal remedies, but the lack of documentation does not necessarily mean they are safe. Other safety issues include variability in biologic potency in different crops, contamination and use of the incorrect plant species¹⁵⁵. In addition, it is extremely difficult to guard against consumer fraud in this unregulated industry. Very limited regulation can lead to problems including unreliable herb quality, the marketing of secret formulas with unsubstantiated

claims, the proliferation of unqualified practitioners and the possibility of deliberate adulteration of the product. Even with the ban imposed on claims that a food can cure a disease in the United States, European Union and Australia, consumers are still being lured into buying the products by "marketing strategies"¹⁵⁶. Stronger regulation of this industry is essential to ensure that the same high standards of preparation, quality control and management are enforced as with conventional pharmaceutical products. Stricter regulations will bring modern scientific techniques and intellectual rigour to traditional herbal medicine.

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