

Review Article

Nutraceuticals in the Management and Prevention of Metabolic Syndrome

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Abstract

Metabolic syndrome has become a worldwide health problem and it affects a wide variety of population. It is a condition that includes a cluster of disorders such as obesity, diabetes, hypertension, hyperlipidemia etc. mainly due to poor nutrition. In order to deal with this syndrome, researchers have made various interventions in the treatment methods as well in terms of nutrition. The term nutraceutical include nutritional and pharmaceutical aspects that work for the prevention and treatment of diseases and provide health and medicinal benefits. Researchers have identified presence of a wide range of phytoconstituents present in various traditional plants and spices. Certain plants such as *Lagenaria siceraria*, *Trigonella foenum graecum*, *Curcuma longa*, *Vigna mungo* etc. shows excellent properties in curing hypertension, obesity, diabetes and hypercholestromia. The current article reviews the importance of various nutraceuticals that we consume in our daily diet and their contribution in curing the metabolic syndrome.

Keywords: Nutraceuticals; Diabetes; Hypertension; Obesity; Hyperlipidemia

Introduction

Metabolic syndromes such as diabetes mellitus, obesity are rapidly increasing in the westernized world because of poor lifestyle habits favouring fat and sucrose enriched meals and low physical activity or sedentariness. Medical nutritional therapy is an integral component of diabetes mellitus, obesity and metabolic syndrome management. Pharmacological intervention is taken into consideration when diet associated physical exercise and healthy lifestyle is insufficient to control blood glucose, body weight and metabolic profile. In contrast, pharmacological intervention for obesity still remains a controversial issue because of only modest long term efficacy and concern about safety. Obesity is the major underline reason for metabolic syndrome. The worldwide incidence of obesity has been rapidly increasing in the last two decades. According to WHO report, obesity has been classified as a growing epidemic, and if immediate action is not taken, millions of people will suffer from serious weight related disorders. Obesity counts a major health problem and common chronic disease. In health surveys conducted in the United States in 2005, 24.2% of men and 23.5% of women or over one-fifth of the respondents were classified as obese [1]. Obesity mainly arises when there is an imbalance between energy intake, principally stored as triglycerides (food consumption), and energy expenditure (basal metabolic rate and biochemical processes). The excess energy is primarily stored in adipose tissue in the form of triglycerides. When adipose tissue function is compromised during obesity, the excessive fat accumulation in adipose tissue, liver, and other organs predisposes the individual to the development of metabolic changes that increase overall morbidity risks [2]. Hence, the recent recognition of metabolic syndrome and its influence on health has led the researchers to consider the potential drug-food or nutrient-drug interaction here since nutrition therapy and pharmacological intervention are the major components in managing metabolic

syndrome. An interaction is said to take place when the effects of one drug are changed by the presence of another food, drug, and drink or by some environmental chemical agents. Interactions between food and drug may inadvertently reduce or increase the effect of drug, resulting in therapeutic failure (i.e. hyperglycaemia in case of diabetes mellitus) or increased adverse effect (i.e. hypoglycaemia in case of diabetes mellitus). The conventional clinically relevant food-drug interactions are caused by food induced changes in the bioavailability of drugs. Thus, in the field of metabolic disorders where nutrition plays a major role in the overall treatment, the potential influence of food and nutrient intake on drug therapeutic effect may be crucial.

Nutraceutical is defined as a food (or a part of food) that provides medical or health benefits, including prevention or treatment of a disease. Nutraceuticals are found in number of products emerging from (a) food industry, (b) herbal and dietary supplements and (c) pharmaceutical industry. Nutraceuticals covers most of the therapeutic areas that includes disorders related to sleep, digestion, cold and cough, prevention of cancer, blood pressure, pain killers, depression, hyperglycaemia and hypoglycaemia [3].

Nutraceuticals can be organized in several ways depending upon its easier understanding and applications i.e. for academic instruction, clinical trial design, and functional foods. Classification of nutraceuticals on the basis of food sources are as follows [4]:-

- Dietary fibres (fruits, beans, barley, oats)
- Antioxidant vitamins (vitamin C, vitamin E and carotenoids)
- Polyphenols (tea, legumes)
- Spices (clove, garlic, turmeric)

More broadly, they can be classified as:-

- a) Potential nutraceuticals
- b) Established nutraceuticals

A potential nutraceutical can only become an established one after sufficient data on its medicinal and clinical aspects are obtained. Pharmacokinetic interferences often occur as a result of change in drug metabolism. Cytochrome- P450 (CYP-450) system oxidises a broad spectrum of drugs by a number of metabolic processes that can be enhanced or reduced by various drugs (known as inducers or inhibitors). Other factors involved in drug interaction also involve age, sex, patient and administration [5,6].

Curcumin

Curcumin [1, 7- bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5dione], being an active component of turmeric is responsible for the yellow colour and is known to possess multiple pharmacological effects. It is used in the treatment for a wide variety of inflammatory ailments, including obesity and other metabolic diseases. Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which belongs to the family Zingiberaceae. The yellowish compound, curcumin, is known to possess multiple pharmacological effects [7]. Obesity comes with one of the major component and that is inflammation. The chronic and subclinical inflammation is recognized, as being a part in the development of diabetes, and obesity- related atherosclerosis. Adipose tissue is an important initiator of inflammatory response, and which is involved in energy regulation and homeostasis.

Mechanism of Action

Curcumin interacts directly with cyclooxygenase-2 (COX- 2), DNA polymerase, lipoxygenase (LOX), glycogen synthase kinase-3b (GSK-3b), and cytokines (TNF- α). It interacts indirectly with several transcription factors, activator protein1 (AP-1), b-catenin, signal transducer and activator of transcription (STAT) proteins, and peroxisome proliferator- activated receptor c (PPARc) [8]. Adipose tissue is not simply a storage depot for excess calories but it also actively secretes fatty acids and a variety of polypeptides. The adipose tissue consists of adipocytes, immune cells and pre-adipocytes. They secrete leptin, adiponectin and other inflammatory cytokines such as TNF, interleukins 1, 6 [9]. These factors are critically involved in obesity-induced insulin resistance and chronic inflammation.

Safety and Efficacy

Various clinical trials (phase1 and phase 2) dealing with curcumin safety has shown that curcumin is safe and is well tolerated. Doses (500-1200mg/day) were administered in capsules form by patients and safety was assessed. Few developed adverse reactions such as diarrhea, headache, skin rashes and yellow stool. Curcumin has also been reported to inhibit the activity of drug metabolizing enzymes such as CYP-450, glutathione S- transferase, UDP-glucuronosyltransferase [10].

The major obstacle for the clinical development of curcumin is its poor absorption, rapid excretion, and low systemic bioavailability which suggest that the therapeutic potential of oral curcumin is limited.

Lagenaria siceraria

Lagenaria siceraria also known as bottle gourd belonging to

Table 1: Ethanopharmacological uses of *Lagenaria siceraria*.

Sr. No	System	Uses
1	Gastro – intestinal	Aliuretic, purgative, laxative
2	Cardio vascular	Dropsy, diuretic hydropsy
3	Central nervous	Ache(head), emetic, tooth ache, convulsions, insanitary
4	Genito- urinary	Diuretic, litholytic
5	Infections	Sore throat, boils, tumor, tetanus, fever, wound, rheumatism.
6	Respiratory	Asthma, cough
7	Ear, nose, throat	Gum, hoarseness
8	Immunology	Cancer, tumor, tetanus
9	Skin	Pimple, wound, boils, alopecia
10	Metabolism	Refrigerant
11	Poison	Antidote

the family Curcubitaceae is extensively grown in India and other tropical and sub tropical regions of the world. Bottle gourd has certain potent nutraceutical and therapeutic functions and they include phytoconstituents, minerals, vitamins, fibre etc. Certain parts of the plant is used to treat disorders such as headache, baldness etc. *L. siceraria* is reported to exhibit cardio protective, antihyperlipidemic, antioxidant, and antihyperglycemic, analgesic, anti-inflammatory, immnuomodulatory and hepatoprotective functions in humans [11]. Different varieties of *L. Siceraria* are known to exist; the sweet variety is generally used as vegetable and for the preparation of sweets and pickles, while the wild variety is preferred for medicinal use. Drinking one or two glasses of raw bottle gourd juice in the morning on an empty stomach is one particular practise in India to deal with obesity associated disorders. Table 1 enlists the Ethanopharmacological uses of *Lagenaria siceraria*

Mechanism of Action

A study showed that *Lagenaria siceraria* reduces total cholesterol, triglycerides (TG) and low density lipoproteins (LDL) levels. This study involved fifty subjects in the age group of 40- 60 years and participating subjects were asked to consume freshly prepared *L. siceraria* juice for about 90 days in an empty stomach. Daily attendance was recorded and maintained during the study period. During the study period, the parameters such as kidney functioning, body weight and BMI were measured and monitored. At the end of the study, feedback and viewpoints of participating subjects were recorded. Hence, the results showed that there was an improvement in high density cholesterol levels (HDL) and a reduction in low density cholesterol levels. A marginal decrease in fasting glucose and total cholesterol was seen [12].

Kidney functioning evaluation showed that there was a decrease in urea level with a considerate improvement in uric acid level. There was no significant change in the BMI and the body weight of subjects. At the end of study a positive feedback was obtained [13]. The observed results are listed below:-

- o It helped in digestion and relieved constipation.
- o Relief from headache and other body pain was experienced.
- o Subjects felt more energetic and lighter.

- o Subjects felt that *L.siceraria* was much beneficial and was highly acceptable.

Trigonella foenum-graecum

Fenugreek (*Trigonella foenum-graecum* L. Leguminosae) is one of the oldest medicinal plants mostly used as spice. It is known to originate in India and Northern Africa. This herb is known to have diverse medicinal uses. It includes wound healing, bust enhancement, as an aphrodisiac and promote of lactation weaning mothers. A number of important chemicals with medicinal values have been found in fenugreek seeds and leaves. Medicinal values of Fenugreek lie in three important chemical constituents and they are: (a) steroidal sapogenins; (b) galactomannans and (c) isoleucine [14]. These constituents seem to work in a synergistic way to produce health effects and have placed fenugreek among the mostly known “nutraceuticals”. Fenugreek seed is an important source of steroidal sapogenins such as diosgenin which are used extensively by pharmaceutical and nutraceutical industries. Diosgenin is used as a raw precursor for the production of steroidal drugs and hormones such as testosterone, glucocorticoids and progesterone. It was studied that these steroidal sapogenins are effective agents for the treatment of hypocholesterolemia, a disorder often related to diabetes. Fenugreek being an important source of diosgenin is widely used as an alternative for its production. Galactomanans are major polysaccharide components found in fenugreek seeds. They are considered unique due to 1:1 or 1:2 ratio of galactose to mannose (Gal: Man) molecules. This high ratio of galactose substitution helps galactomanans to absorb water allowing them to form highly viscous solutions at relatively low concentrations resulting in reduced glucose absorption within the digestive tract. This property offers a unique opportunity for its use to control caloric intake by targeted group of consumers. It aids to help in the control of type 2 diabetes. The amino acid isoleucine is a precursor which is known to regulate the secretion of insulin. Most hypoglycaemic and anti- hyperglycaemic effects of fenugreek is attributed to gastrointestinal effect of dietary fibres and systemic effects of amino acids like 4-hydroxy isoleucine present in the seed.

Mechanism of Action

In human studies, the mechanism of action in the reduction of the plasma glucose and increased insulin receptors remains unclear. Fenugreek seeds also lower serum TGs, total cholesterol and LDL cholesterol. These effects are mainly because of constituent's sapogenins, which increase cholesterol excretion enzyme [15].

Safety/ Adverse Effects

Fenugreek is generally considered safe and is well tolerated, but there are certain side effects associated with the same. Caution in using fenugreek is warranted in patients known to be allergic to it or who are allergic to chicken peas because of cross reactivity. The known side effects include dizziness, transient diarrhea, and flatulence. Blood glucose levels needs to be checked during the beginning of supplementation. Decreased body weight has also been reported due to decrease in T3 levels. Because of fenugreek containing coumarin derivatives, there is a theoretical risk of increased prothrombin time which in turn increases risk of bleeding. Fenugreek should be avoided during pregnancy due to its uterine stimulating properties observed in animal studies [16].

Potential Drug Interaction

Toxicological evaluation of 60 diabetic patients who took powdered fenugreek seeds at a dose of 25g per day for 24 weeks disclosed no clinical hepatic or renal toxicity and no haematological abnormalities. Fenugreek being rich in fibre can interfere with the absorption of oral medications in the gut because of its mucilaginous and highly viscous nature. Concomitant use of fenugreek with other hypoglycaemic agents might also lower serum glucose levels more than expected; hence the level should be monitored closely at regular intervals. When used along with laxatives, mineralocorticoids, diuretics fenugreek may precipitate hypokalemia. [16,17].

Emblica officinalis

Emblica officinalis also known as Amla belong to the family Euphorbiaceae is the most important medicinal plant in Indian medicines. It is extremely nutritious and is a chief dietary source of vitamin C, amino acids, and minerals. Entire parts of the plant are used for medicinal purposes, particularly the fruit. The fruit is known to treat ailments such as fever and cold. It also acts as an anti inflammatory, diuretic, hair and liver tonic, refrigerant, stomachic and as a digestive. It prevents peptic ulcer and dyspepsia.

Mechanism of Action

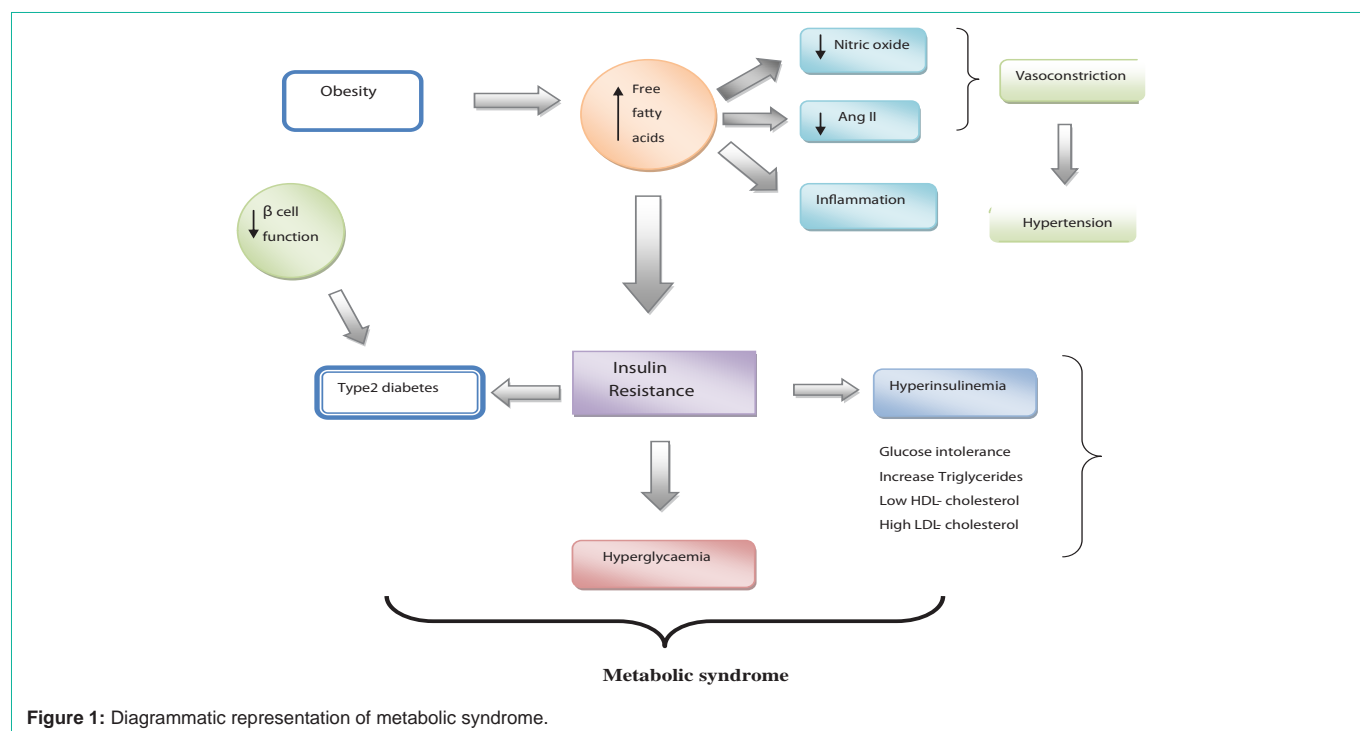
Increased level of lipids such as cholesterol and triacylglyceride in serum as well as in liver is significantly decreased by the administration of *E. officinalis*. Peroxisome proliferator-activated receptors (PPAR α) regulate the transcription of genes involved in lipid and cholesterol metabolism. The oral administration of *E. officinalis* significantly increases the hepatic PPAR α protein level [18]. It indicated that *E. officinalis* may prevent age-related hyperlipidaemia through attenuating oxidative stress in the ageing process. Treatment with *E. officinalis* also shows significant reduction of total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), LDL and a significant increase in high-density lipoprotein levels. In view of the above results, it is recommended that addition of *E. officinalis* to the currently available hypolipidemic therapy would offer significant protection against atherosclerosis and coronary artery disease.

Murraya koenigii

The leaves of *Murraya koenigii* are widely used as a spice for flavouring food and as such it appears to be without any side effects and toxicity. *Murraya koenigii* belongs to the family Rutaceae [19]. According to ayurveda, various parts of plants have been used in folk medicines for the treatment of hypertension, hepatitis, rheumatism, cough, hysteria, skin eruptions and poisonous bites. The stems are very popular for cleaning teeth and gums. Furthermore, the plant is also known to have antioxidant, anti tumor, anti inflammatory, anti hyperglycaemic, hypoglycaemic and hypolipidemic effects. Clinical studies were preformed on *Murraya* leaves to evaluate hypoglycaemic activity. The findings suggested leaves to be used as an adjunct in dietary therapy and only of the important constituent being carbazole alkaloid [20].

Mechanism of Action

The antidiabetic effect of *Murraya koenigii* is due to increase in hepatic glycogen concentration and decrease in concentration of glycogen phosphorylase and gluconeogenic enzymes. It exhibits



antioxidant activity by free radical scavenging activity. It is also known to induce apoptosis in human myeloid cancer cells and also a time dependent anti-proliferative in acute lymphoid and chronic myeloid leukemic cell lines. It is a inhibitor of lipoxygenase.

Vigna mungo

Vigna mungo is also known as black gram or black lentil. Grain legumes are the important source of food proteins. The leguminosae are the most important family in Dicotyledonae. These grams are the richest source of proteins and amino acids for human as well as animal nutrition [21].

Beneficial effects of black gram are:

Cardiovascular disease: The frequent intake along with a saturated fat poor diet can help in controlling the lipid homeostasis and consequently reduce the risk of CVD. The legume high fibre content, low glycemic index and the presence of minor components such as phytosterols, saponins, oligosaccharides etc. are considered the main responsible agents for this property.

Diabetes: Because of low glycemic index and high content of indigestible fibres, dry legumes are claimed to maintain glycemic control in diabetes individuals. Moreover, black grams also help to prevent insulin resistance which represents Type 2 diabetes.

Overall weight and obesity: Despite their content of lipids, starch and proteins, dry legumes help in maintaining a regular body weight, and this is because of their satiety effects, thus limiting overall food daily intake.

Mechanism of Action (in weight control and obesity)

Various studies suggest that proteins are more satiating than carbohydrates or fats. In this respect, an increased gram protein

intake may have weight loss benefits, and it also has credits to the lower extent of kidney workload of plant proteins compared to animal proteins. [22]. A specific direct action of black grams on α amylase protein inhibitors has been considered for its potential use in prevention of obesity and weight loss. To prove these studies were carried out on normal, obese and diabetic subjects by oral administration of wheat α amylase inhibitor have shown delayed carbohydrate absorption, a reduction in peak postprandial plasma glucose concentrations with no malabsorption or other symptoms. More recently, the binding parameters of the association between wheat α amylase inhibitors and porcine pancreas α amylase and the high thermal stability of the proteins inhibitor have confirmed the potentially for its use as a nutraceutical molecule.

Camellia sinensis

Tea can be grouped into three main types, black, oolong, and green tea. Green tea (*Camellia sinensis*) is one of the popular beverages in the world and has been extensively studied for its preventive effects. Green tea is characterised by the presence of poly phenolic compounds known as catechins along with epigallocatechin-3-gallate (EGCG) being the most abundant and most well studied. Green tea has been reported to have preventive effects against a number of chronic diseases including heart disease, neurodegenerative disease and cancer. An early indication for the benefits of green tea for weight management is seen in Chinese tradition, where green tea is said to wash out fat. Green tea leaves contain three main components which act upon human health and they are:-

- o Xanthine bases (Caffeine and theophylline)
- o Essential oils
- o Polyphenolic compounds

Certain study models mentioned below help in understanding

Table 2: Marketed preparation of Nutraceuticals.

Nutraceutical	Marketed preparation	Pre clinical studies	Clinical studies	Side effects (in humans)	Side effects (in animals)
Curcumin	Mervia	Wister rats and female Swiss mice were fed turmeric (1% and 5%) along with its extract in their diet for 90days.	Administration of curcumin for 4 months at a dose of 3600-8000 mg/day	Only few showed minor GI infections, nausea and diarrhea.	Rats didn't show any adverse effects, while mice showed some evidence of hepatotoxicity.
Fenugreek	Available in the form of seeds and powder.	Weanling rats were fed with fenugreek seeds for 90days.	Diabetic patients were given fenugreek seed powder at a dose of 25mg/day for 24weeks.	No clinical hepatic or renal toxicity was observed.	No significant hematological hepatic or histopathological changes were seen.
Vitamins-Chromium	Chromium polynicotinate	-	A non controlled open label trial of chromium polynicotinate was performed in type2 diabetes patients for 10months.	A decrease in fasting glucose, fatigue, and frequent urination was observed.	-
Vitamins-Magnesium	Available in the form of tablets.	-	Magnesium supplements were given to diabetic patients for glycemic control. A decrease in fasting glucose and an increase in insulin levels were seen.	-	-
Vitamin- vitamin E	-	-	Vitamin E was examined for glucose control in one of the control trial, with the dose of 100-1600 mg/ day for 2-4months.	-	-
Amla	Amla C, amla candy, amla juice, Chvanprasha	Extracts of <i>E.officinalis</i> were given to diabetic rats and it resulted in reversing neuropathic pain by modulating oxidative stress.	Normal and diabetic patients were given 2 to 3g/per day of <i>E. officinalis</i> . It improved high density lipoprotein and cholesterol.	None	None

the mechanism of action of green tea in hypertension, obesity etc. and some remain uncertain [23,24].

Mechanism of Action

Action on blood pressure: When studied in older women in China, it was found that consumption of green tea for about 120 ml/day or more for one year significantly reduces the risk of developing hypertension. However, other studies do not support a hypotensive effect of green tea. Green tea consumption has also been inversely associated with the development and progression of atherosclerosis [25].

Action on Cardiovascular disease: There is limited data available on green tea support a potential association between green tea and beneficial properties in relationship to risk factors for cardiovascular disease According to epidemiological studies, consumption of green tea is related to reduction of cardiovascular risks. The mechanism of action for these effects is not well-defined.

The effect of green tea on cardiovascular function has been proved by a number of studies conducted and these studies relate green tea to be working through action related to LDL- cholesterol oxidation. Oxidation of LDL – cholesterol leads to an increase in risks of cardiovascular disorders and atherosclerosis. Green tea acts as an antioxidant due to epigallocatechin-3-gallate and inhibits oxidation of LDL- cholesterol. Investigators approached this topic from a different point of view and studied the effect of green tea catechins supplementation rich in EGCG on body weight and body fat in humans. It was observed that there was a 2.4% body weight reduction in obese female patients (median BMI of 30.5kg/m²) with PCOS, following a 12-weeks supplementation with encapsulated green tea; while the control group gained weight. This promising findings lack statistical support for the between group variations, possibly because of different response in different patients clubbed with degree of obesity and changes in metabolism due to PCOS when compared to healthy but overweight subjects [25,26].

In another study, tea catechins enriched oolong tea were embedded into a dietary regime, it was observed that after a 12-weeks supplementation to overweight but otherwise healthy subjects showed significant reduction in body weight and body fat as compared to the control group (diet only). Thus we have evidence that green tea catechins can contribute to lifestyle changes which are related to weight management also the subjects who had been following their usual lifestyle while taking green tea catechins showed a noteworthy reduction in body weight and body fat. In this study, anti-obesity effects of green tea catechins is correlated with improvements in cardiovascular risk factors like systolic blood pressure and LDL cholesterol in a relatively large (n = 240) population, hence this study is of special value. 78 obese females (BMI 30.8) were given 12 weeks of supplementation with only 27mg of caffeine and 491mg catechins, decrease in 0.12kg body weight and 0.05kg body fat were observed. Significant results were obtained with moderately overweight subjects and not obese, hence the duration of obesity and extent in future studies should be more tightly controlled [26].

Action on improved glucose intolerance: Decreased rate of diabetes was seen in subjects with habit of consuming >6 cups of green tea per day compared to those who drank less than one cup a week, in an epidemiological study conducted in Japan. Additional support was garnered from a cross-sectional study which showed green tea consumers had less impaired fasting glucose. However close association between green tea consumption and glucose tolerance was not found. The consumption of oolong tea containing 386 mg epigallocatechin gallate (EGCG) decreased plasma glucose and fructosamine levels in twenty type-II diabetics. Plasma glucose and insulin was found to decrease in healthy volunteers consuming green tea extract (300mg EGCG) for 12 weeks. These subjects experienced light weight loss which could have affected insulin sensitivity rather than EGCG. Green tea beverage consumption in Asia results in high EGCG ingestion. Green tea catechins have been proven to show anti-diabetic, cardioprotective and anti-obesity effects in both animals and humans. Further controlled long term human studies would help to

decide the optimal dose for prevention, management and treatment of metabolic syndrome [27].

Marketed preparations: Marketed preparations of the above mentioned spices, herbs, etc. are available in the market in the form of tablets, capsules, powder etc. Below is the Table 2 that mentions the marketed preparation [28-30].

Conclusion

With this changing lifestyle, individuals are more prone to disorders such as diabetes, hypertension and obesity etc. These disorders are known to be silent killers. In order to prevent the wide spread of these disorder, researchers have understood the importance of nutraceuticals and their benefits on health. The potential nutraceuticals should be evaluated further to study their mechanism responsible for the beneficial effect in metabolic syndrome.

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