HERBS IN THERAPEUTIC MANAGEMENT OF METABOLIC SYNDROME

Fauzia Bano and Arvind K. Srivastava

Department of Food and Nutrition Era University Lucknow, U.P., India-226003

ABSTRACT

Syndrome X is a combination of different risk factors which are contributory to cardiovascular diseases and type 2 diabetes mellitus. These different clinical manifestations include obesity, hypertension, insulin resistance, dyslipidemia, and cardiovascular complications. In recent years metabolic syndrome is vital cause of death globally. Remedial plants have been identified and used as therapeutic management of different diseases including Syndrome X throughout the world from beginning of human civilization. The present review summarizes the use of few herbs like *Olea europaea (Olives), Momordica charantia (Bitter-gourd),*

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Address for correspondence

Miss. Fauzia Bano Department of Food and Nutrition Era University Lucknow, U.P., India-226003 Email: fauzia0710@gmail.com Contact no: +91-9169630492

Gymnema sylvestre (Gurmar), Enicostema littorale (Chota-chiretta), Cinnamomum zeylanicu (Cinnamon), Garcinia indica (Kokum), Hibiscus rosasinensis (Rose mallow), Emblica officinalis (Indian gooseberry) and their active components for the management of metabolic disorders and also helpful in the regulation of its contributory factors like the regulation of blood sugar level, blood pressure, dyslipidaemia and weight management.

KEYWORDS: Olea europaea, Momordica charantia, Gymnema sylvestre, Enicostema littorale, Cinnamomum zeylanicu, Garcinia indica, Hibiscus rosasinensis, Emblica officinalis, metabolic syndrome.

INTRODUCTION

Metabolic syndrome or Syndrome X is a combination of various hazard factors that aggregately increment the danger of cardiovascular maladies and type 2 diabetes mellitus. Metabolic syndrome is cluster of five different medical condition, however if any three are present, it can also be considered as metabolic syndrome. These medical conditions include central obesity, increased blood pressure, high blood sugar level, high serum triglyceride levels and low HDL levels. The concept of clustering of risk factors is originally given by Prof Reaven in the year 1988, when the term "insulin resistance syndrome" is perceived (1). Metabolic disorder is otherwise called syndrome X, WHO characterize metabolic disorder as a pathologic condition delineated by abdominal obesity, insulin resistance, hypertension, hyperlipidemia. It is regarded as a noncommunicable disease (NCD) that become significant medical problem of present-day world. The pervasiveness of metabolic disorder is progressively normal in urban populace of various nations. The two fundamental parts spreading this issue are – heighten the utilization of high calories and low fibre food and the decrease physical exercises as a result of mechanized transportation and stationary way of life. The commonness of metabolic disorder universally can be generally determined as one fourth of the total population, or one can say over a billion people on the world are presently suffering with metabolic disorder (2).

The prevalence of metabolic syndrome in world depends upon diagnostic criteria as well as sociodemographic and geographical determinants. According to NCEP ATP III criteria, 35% adults in US had diagnosed with metabolic syndrome (30.3% in men and 35.6% in women) this is based on National Health and Nutrition Examination Survey data (3).

The most significant helpful intervention that has been demonstrated successful in management of metabolic syndrome is way of life modification through controlled diet and exercise that focuses on weight reduction. Way of lifestyle modification through exercise and diet brought about an overall deficit of 7% body weight, prompting a 58% decrease in the development of diabetes mellitus and cardiovascular diseases (1).

PATHOPHYSIOLOGY

The pathogenesis of the gathering of hazard factors and its integral components still remain uncertain. There is no accepted fundamental appliance of patho-physiology of metabolic syndrome, although insulin resistance and central obesity plays important role in this (4). Insulin resistance and excess of free fatty acid as a result of improper lipolysis is a most accepted hypothesis for pathophysiology of metabolic syndrome. Insulin rise glucose uptake in liver and muscle, and restrains hepatic gluconeogenesis and lipolysis. Insulin resistance reduced insulin dependent restraint of lipolysis in adipose tissue, prompting to an increase in circulating free fatty acids that further repress the antilipolytic impact of insulin. Free fatty acids obstruct protein kinase initiation in muscle promote to decrease in glucose uptake. They enhance protein kinase activation in liver that stimulates lipogenesis and gluconeogenesis (5). Free fatty acid can repress insulin subordinate glucose in skeletal muscle. Free fatty acid can elevate the production of glucose in liver. And also increase the production of triglyceride, LDL which may cause atherosclerosis. Triglyceride is stored in adipose tissue which releases free fatty acid during lipogenesis by the action of cyclic AMP(3).

Adipokines discharged from instinctive fat tissue have been demonstrated to be related with metabolic syndrome and CVD. Leptin is an adipokine that controls vitality homeostasis intervened by the hypothalamus. Obesity enhance leptin levels and higher leptin levels are directly proportional to the development of cardiovascular diseases. Adiponectin has been viewed as a defensive factor against the advancement of diabetes, hypertension, and intense myocardial infarction. An expansion in fat tissue mass associates with decreased adiponectin and higher leptin levels, which finally cause cardiovascular risk. Activation of the renin-angiotensin system (RAS) is a significant neurohumoral pathway adding to the advancement of metabolic syndrome (6).

Different inflammatory markers have been demonstrated to be raised in patients with syndrome X, inflammation plays significant contribution in the pathogenesis of cardiovascular disease. Macrophages inside the fat tissue produce tumor necrosis factor alpha (TNF- α) and its production increments with increment in fat tissue mass. TNF- α causes phosphorylation and inactivation of insulin receptors in the fat tissue just as in smooth muscle cells, the enlistment of lipolysis expanding FFA load, and hinders adiponectin release.

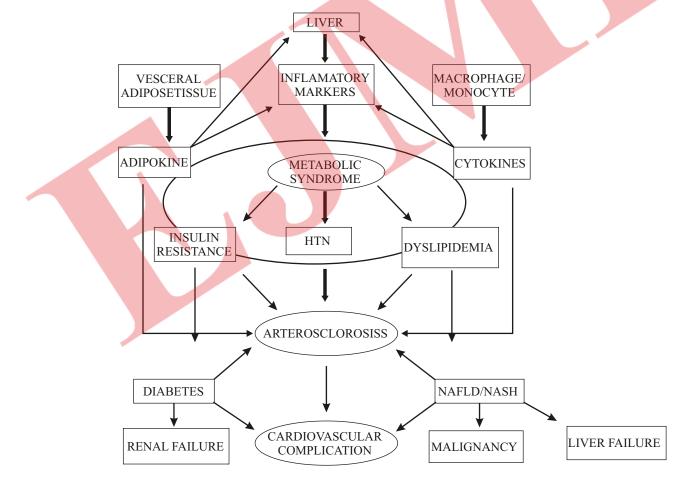


Fig 1: Association of Adipokines, Cytokines, and Inflammatory Markers that Add to the Advancement of Metabolic Disorder and its Complexities. HTN-Hypertension, NAFLD/NASH-Non-alcoholic Fatty Liver Disease /non-alcoholic Steatohepatitis

Elevated serum TNF- α levels are related with obesity and insulin resistance, the two of which are significant segments of syndrome X. Interleukin 6 (IL-6) is a cytokine constructed by adipocytes and insusceptible cells and has complex administrative mechanisms. Production of IL-6 increments with increment in fat and insulin resistance. Different studies have exhibited a relationship between high CRP levels and the advancement of metabolic syndrome, diabetes, and CVD (5).

MECHANISMS UNDERLYING THE SYNDROME X

Insulin resistance - The insulin hormone deals with the proportion of glucose in the blood. In insulin obstruction the body's cells don't react ordinarily to insulin. Glucose can't enter the cells as easily, so it builds up in the blood. This will lead to type 2 diabetes mellitus.

Obesity and increased waist circumference -Obesity is the worldwide outbreak which is a very important aspect in the much more recent endorsement of the metabolic syndrome.

Dyslipidemia - Elevation in cholesterol and total lipid levels blood is known as dyslipidemia. Elevation in free unsaturated fat transition to the liver also expanded creation of apo B – containing triglyceride rich low-density lipoprotein.

Glucose intolerance - The deterrent in the activity of insulin in the metabolism of glucose remembers the insufficiency for the limit of the hormone to overcome the generation of glucose by the liver and kidney, and intervention in glucose take-up and digestion in insulin sensitive tissue for example muscles and fat tissue.

Hypertension - Is a long-haul ailment where circulatory strain in the supply routes is diligently raised.

Different appearances - Smoking, sedentary way of life and non-alcoholic fatty liver disease (NAFLD) can likewise deliver a large number of the significant criteria of the disorder (6).

Herbs Use for the Management of Metabolic **Syndrome**

Analeptic herbs have been recognized and used traditionally throughout the whole world from the beginning of human civilization. Metabolic syndrome is one of vital cause of deaths worldwide in modern years. Medicinal herbs and natural products have been claimed to be fruitful in suppression of metabolic syndrome (7). Natural herbs and alternative medicine are claimed to be advantageous for management of diabetes, obesity and cardiovascular diseases. In this review beneficial and clinical effects of Olea europaea (Olives), Momordica charantia (Bitter-gourd), Gymnema sylvestre (Gurmar) and Enicostema littorale (Chota-chiretta), Cinnamon zeylanicum (cinnamon), Emblicaofficinalis (gooseberry), Hibiscus rosa sinensis (hibiscus), and Garciniaindica (kokum) have been highlighted.

Olea europaea (Olives)

Olea europaea belongs to family Oleaceae often known as Olives and are generally found in Mediterranean regions. Recent clinical studies show the beneficial role of olives and oleuropein on different human malady including metabolic syndrome. Abdominal adiposity and weight gain have been intercepted by Oleuropein in animal models.

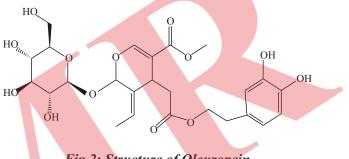


Fig 2: Structure of Oleuropein

Oleuropein suppress mitochondrial action during adipogenic differentiation and expression of gene involved in adipogenesis. Oleuropein hinder Proliferator-activated receptor gamma 2 (PPAR γ 2), the fatty acid-binding protein 4 (FABP-4) geneand the lipoprotein lipase (LPL) (8). In another study by Drira et al 2011 (9) on 3T3-L1 adipocytes, it was observed that inhibition of transcription factors PPAR-y, C/EBPa, SREBP1c occurred after the addition Oleuropein. In glucose tolerance test, there is a huge lessening in glucose levels of nicotinamide and streptozotocin induced co-diabetic hypertensive rats Oleuropein has ability to decrease serum LDL, TC and serum triglycerides while it also increases serum HDL levels (10-12). In another study it was found that Oleuropein stimulate the LDL-R receptor in the liver and proliferate the gene expression which is associated with the combination, up-take, transport, digestion and elimination of triglycerides (13). Oleuropein has also cardioprotective, and antioxidant activity, this suppress the oxidative stress related with ischemia reperfusion injuries in isolated rat hearts. This shows remarkable decline in glutathione, oxidized glutathione and thiobarbituric acid reactive substances TBARS)(14).

Momordica charantia (Bitter gourd)

Momordica charantia belongs to family Cucurbitaceae and is principally utilized in Asian nations as useful nourishment and medication. Charantin, isolated from M. charantia shows dynamic yet noteworthy decline in blood glucose levels in ordinary hares (15). Watery concentrate from unripe products of M. charantia

invigorate insulin discharge from segregated β -cell of large hyperglycaemic mice (16). Histological studies show that acetone extract of *M. charantia* does recuperation of β -cell of the islet of Langerhans of pancreas at various stages (17). Acetone concentrate of *M. charantia* cause decline in glucose and serum cholesterol levels in alloxan-prompted diabetic rodents, clearly demonstrates changes in urinary metabolite profile on STZ-instigated type 1 diabetic rodents. This show noteworthy lessening in blood glucose level and furthermore deals with the modified metabolic procedures (18).

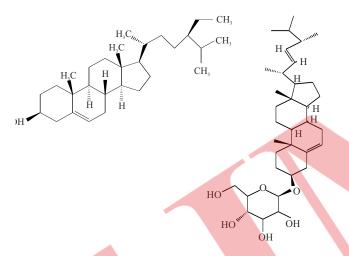


Fig 3: Chemical Structure of Charantin (B-sitosterol Glucoside And 5, 25-stigmastadienol Glucoside)

Enicostemma littorale (Chota-chiretta)

Enicostemma littoralecommonly is commonly known as Chota-chiretta in India. Swertiamarin is a secoiridoid glycoside found in members from the family Genetianaceae, is gotten from loganic acid by mevalonic acid pathway (19). Swertiamarin shows glucose homoestasis alongside restraint of sugar using compounds in-vitro and in-vivo ponders (20). In another investigation is was discovered that Swertiamarin altogether brings down the fasting blood glucose, glycosylated hemoglobin (HbA1c), TC, triglyceride, LDL and furthermore increase the plasma insulin, HDL levels as opposed to STZprompted diabetic rodents (21). In silico study performed by Vaidya et al., (2013) (22) clearly shows that swertiamarin have anti-diabetic activity through hindrance of glycogen phosphorylase-an at pyridoxal phosphate restricting site with its docking vitality of -7.01 kcal/mol. Upadhyay and Goyal (23) outlined the adequacy of E. littorale two times every day for 3 months for repressing distinctive entanglement emerging T2DM in patients (n=84). Blood glucose levels were altogether diminished in T2DM patients. This examination additionally shows

huge decrease in urine sugar level, postprandial glucose, systolic circulatory strain, just as pulse. This treatment likewise shows huge decrease in serum creatinine, cholesterol and triglyceride levels alongside a noteworthy increment in serum HDL levels.

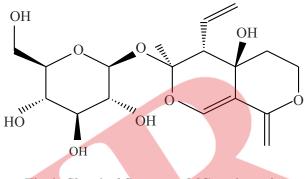
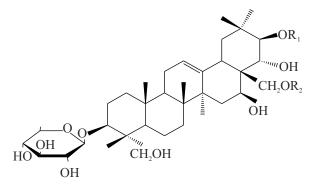


Fig 4: Chemical Structure Of Swertiamarin

Gymnema sylvestre (Gurmar)

Gymnema sylvestre is a member of the family Asclepiadaceae which is usually found in southern and focal India and Sri Lanka. The major bioactive parts of G. sylvestre are a gathering of oleanane type triterpenoid saponins known as gymnemic acid (24) The ethanolic concentrate of Gurmar causes decline in glucose level in ordinary rodents. Another investigation by Persaud (1999) (25) shows that alcoholic concentrate of G. sylvestre animate insulin from HIT-T15, MIN6 and RINm5F β-cells and from islets without some other upgrade. In one study Sugihara et al (2000) (26) have shown the anti-hyperglycemic impact of unrefined saponin portion and triterpenic glycosides (gymnemic acids I-IV and gymnemasaponin V) isolated from the methanolic separate from the leaves of G. sylvestre on STZ-induced diabetic mice. Kang et al (2013) (27) have also demonstrated hypoglycaemic action of G. sylvestre separates on oxidative and cell reinforcement status in diabetic rodents. The G. sylvestre removes displayed solid cell reinforcement movement in the measures, including TBA (56%), SOD-like (92%) and ABTS (54%).





Cinnamomum zeylanicu (Cinnamon)

Cinnamomum zeylanicu is commonly known as Cinnamon and used by various cultures the world over. The volatile oils isolated from the leaf, and bark establish that barks have diverse in substance arrangement, they may change in their pharmacological impacts (28). There are three fundamental segments which are acquired from bark of Cinnamomum zevlanicu are trans-cinnamaldehyde, eugenol, and linalool, which speak to 82.5% of the complete composition. Cinnamomum zeylanicu have various advantageous wellbeing impacts, for example, calming properties, hostile to microbial movement, decreasing cardiovascular malady, boosting intellectual capacity and diminishing danger of colonic disease (29). Another investigation shows that cinnamon extracts help in decreasing body weight in high fructose sustained animals. The non-enzymatic cell reinforcement like liver GSH and liver nutrient C levels are outstandingly decreased by high fructose diet. The organization of cinnamon concentrate would upgrade the action of these cancer prevention agents. Supplementation of cinnamon concentrate build the action of liver cell reinforcement compounds (SOD, CAT, GPX and GST) which are decline in fructose nourished animals (30).

Garcinia indica (Kokum)

Garcinia indica belongs to family Guttiferae and is commonly known as kokum. The *Garcinia indica* possesses antioxidant effects (31, 32), anticlastogenic effect (33), antiglycation activity (34), antibacterial activity, antifungal activity (35), gastroprotective effect [34], neuroprotective effect, antidiabetic effect (33), cardioprotective effect (36) and anti-obesity activity (37). The kidney weight indicated a noteworthy increment in high fructose fed rats and the kokum extract decrease the kidney weight. The mRNA expression of transcription factors such as SREBP1c and SREBP2 have been increased in high fructose fed animals, these up-regulation in highly balanced by feeding of kokum extract (33).

Hibiscus rosasinensis (Rose mallow)

Hibiscus rosasinensis belongs to family Malvaceae. It contains tannins, steroids, alkaloids, saponins, phenols, flavonoids, and proanthocyanidin. The *Hibiscus rosa sinensis* flowers reveals various pharmacological activities such as free radical scavenging activity (38), anti-inflammatory, antipyretic, antibacterial (39), antispermatogenic, androgenic (40), anticonvulsant (41), anti-tumor (42) and anti-diabetic (43). The ratio of TC/HDL, LDL/HDL have been found increased in high fructose fed rats whereas the extracts of Hibiscus flowers showed highest lipid lowering activity on these

rats. The non-enzymatic cell reinforcements in kidney, for example, GSH and nutrient C decline on high fructose diet in rodents when treated with Hibiscus separate degree of these cancer prevention agent were expanded (30).

Emblica officinalis (Indian gooseberry)

Emblica officinalis have a place in the family Euphorbiaceae and is commonly known as Indian gooseberry or Amla. Amla is one of the most extravagant well spring of vitamin C, amino acids and minerals (44). Pharmacological research provides details regarding amla uncovers its pain relieving, (45) hostile to tussive (44) against atherogenic (46) adaptogenic (47) cardio (48) gastro (49) nephro, neuro, defensive and anticancer properties. Amla is additionally answered to have chemo preventive (50) radio, chemo and immunomodulatory (51) free radical rummaging (52) cell reinforcement, calming (53)hostile to mutagenic activities. In one study which is done by khristi Vincentaben S 2016 high fructose diet fed animals shows increase in serum glucose, triglyceride and cholesterol levels which is significantly decrease by administration of amla extract. Amla shows lipid lowering activities. In this study, gene expression of carbohydrate and lipid metabolism was also evaluated. One transcription factor which is involved in lipogenesis is ChREBP is increase by high fructose diet, Amla shows highest regulatory effect on ChREBP expression. The gene involved in triglyceride and cholesterol synthesis was FAS and HMGCR was significantly increases in high fructose diet fed animals. Amla extract shows inhibitory effect (30).

CONCLUSION

This review mainly summarizes the beneficial effects of *O. europaea, M. charantia, G. sylvestre, E. littorale, Emblica officinalis, Cinnamomum zeylanicum, Garcinia indica, Hibiscus rosasinensis* and their active components in therapeutic management of the causative factors of metabolic syndrome that includes high blood glucose level, high blood pressure, dyslipidaemia and obesity. The limited results presented of clinical and preclinical studies clearly provide evidence of the potential benefits of these herbs and their active components in the therapeutic management of metabolic syndrome and needs further investigation.

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