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## The value of nutraceuticals in the management of metabolic syndrome

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### Abstract

Metabolic syndrome has become a global health issue that affects a wide range of people. It is a condition characterized by a cluster of ailments, including obesity, diabetes, hypertension, hyperlipidemia, and others, all of which are caused by inadequate nutrition. A nutraceutical is a nutrient that benefits the body physiologically or protects against chronic diseases. Nutraceuticals can help you live longer by improving your health, delaying the aging process, preventing chronic diseases, and supporting the structure and function of your body. Due to the high prices of synthetic drugs, there is a growing demand for cost-effective, affordable, safe, and effective alternative therapies for curing metabolic syndrome-related complications. Nutraceuticals include macronutrients like dietary fibers, sugar, amino acids/proteins, and fatty acids; micronutrients as minerals, vitamin D, folate, and antioxidant vitamins like Vitamin E, Vitamin A, Vitamin C etc; polyphenols including flavonoids, chlorogenic acid, resveratrol and isoflavones, and many bioactive constituents *viz.* benfotiamine,  $\alpha$ -lipoic acid, stanols, policosanol, and fucoxanthin. It was reported that proper consumption of nutraceuticals prevents as well as cures many chronic disorders like obesity, hypertension, Parkinsonism, Alzheimer's disease, allergies, cancer, dental problem, and osteoporosis. Vitamins, amino acids, minerals, anti-oxidants, and other phytochemical constituents are used as vital nutraceuticals that reduce the symptoms of certain diseases caused due to metabolic abnormalities. The current reviews will be of importance for various nutraceuticals that we consume in our daily diet and their contribution to curing metabolic syndrome. Therefore, active research is going on to evaluate the long-term safety, efficacy, and dose schedules of nutraceuticals, functional foods, antioxidant and anti-inflammation phytotherapy for the management of metabolic syndrome and associated disorders.

**Keywords:** Nutraceuticals, phytoconstituents, macronutrients, micronutrients, management

### 1. Introduction

Metabolic syndrome is the coexistence of risk factors of metabolic origin (insulin resistance, hyperinsulinemia, impaired glucose tolerance, type 2 diabetes mellitus, visceral obesity, atherogenic dyslipidemia, high blood pressure) that elevate the risk for cardiovascular disease [1, 2]. A metabolic syndrome is a group of clinical conditions affecting nearly 30% of adults in the Western world where obesity and unhealthy dietary patterns prevail [3]. The worldwide prevalence of metabolic syndromes varies from 7-56% in women (particularly during the post-menopausal period) and 8-43% in men. Visceral fat plays a critical role in the development of dyslipidemia which is linked with a reduction in concentrations of high-density lipoprotein, and enhancement in low-density lipoprotein and triglyceride levels. Preventive strategies for metabolic syndrome are particularly focused on the reduce weight loss through regular exercise and reducing the intake of calories through foods by taking low caloric diets poor in cholesterol and saturated fats [4, 5].

A nutraceutical is a food or component of food that has medicinal or health benefits, such as illness prevention or therapy. Nutraceuticals can be found in a variety of food, herbal, and dietary supplement items, as well as medicinal products [6]. Nutraceuticals also refer to bioactive phytochemicals or natural functional foods that have medicinal properties including health-promoting and disease-preventing abilities [4, 6]. The number of products emerging from pharmaceutical industries, dietary and herbal supplements, and food industries contains nutraceuticals that have therapeutic potential against certain disorders related to blood pressure, digestion, sleep, depression, hypoglycemia, hyperglycemia, and cancer [4]. These compounds work as medicines to have the ability to prevent many metabolic abnormalities. Variation in the metabolic system occurs due to an imbalance between food intake and utilization of energy. Under-utilization of energy by the human body causes the storage of excess energy in adipose tissue in the form of triglyceride.

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Excessive deposition of stored fats in adipose tissue leads to the malfunctioning of different body organs resulting in chronic conditions with an increased risk of death in the affected patient [7]. Nutraceuticals normally contain the required amount of essential nutrients like minerals, vitamins, carbohydrates, proteins, and lipids etc depending on their source [6,8].

Diabetes Mellitus is a complex metabolic disorder characterized by  $\beta$ -cell dysfunction, impaired insulin signaling, insulin resistance leading to abnormal carbohydrate and lipid metabolism, higher risk of oxidative stress ultimately causes micro and macrovascular complications such as retinopathy, neuropathy and nephropathy. These complications consequently decrease the quality of life with increase in the rate of mortality [9-11]. According to literature reports from studies conducted at various research institutes the forecast is that the expected ratio of people suffering from diabetes mellitus in 2030 will increase to 4.4%. Further, studies reported and indicated that the use of plants phytochemicals, polyphenolic compounds, and other antioxidant compounds may decrease the chances of type 2 diabetes mellitus [12]. Hypertension is another metabolic disorder, which occurs as a consequence of the interaction between genetic variability and the environment. The optimal combination of micro- and macro-nutrients is vital for the treatment and prevention of hypertension-related to vascular complications [13].

## 2. Metabolic syndrome

Metabolic syndrome is an assemblage of interrelated abnormalities like insulin resistance, hyperglycemia, obesity, dyslipidemia, and hypertension in which the chances of cardiovascular disorder and diabetes mellitus are increased [14-16]. The metabolic syndrome is a multifactorial risk factor for cardiovascular disease and type 2 diabetes. Atherogenic dyslipidemia, high blood pressure, insulin resistance, high glucose, a pro-thrombotic state, and a pro-inflammatory state all are part of metabolic syndrome [18]. In the United States and around the world, metabolic syndrome and its associated chronic diseases are major public health concerns. About 34% of individuals in the United States have metabolic syndrome, [19], and 9.3% of the population (29.1 million) has diabetes. Over the next 5–10 years, metabolic syndrome is linked to an increased risk of cardiovascular disease and type 2 diabetes mellitus [21]. Heart disease is responsible for one out of every four deaths in the United States each year, amounting to around 610,000 deaths each year [22]. Cardiovascular disease (hypertension, heart disease, and stroke) and diabetes cost the United States \$650 billion per year in direct and indirect costs in 2003, and are expected to cost \$1.96 trillion by 2023 [23]. Obesity, Insulin resistance, Dyslipidemia and Hypertension are the different metabolic syndrome parameters [17].

### 2.1 Insulin Resistance

The etiology of metabolic syndrome is thought to be aided by an increase in circulating free fatty acids caused by insulin resistance. Insulin inhibits lipolysis and hepatic gluconeogenesis while increasing glucose absorption in muscle and liver. Insulin resistance in adipose tissue reduces insulin's ability to inhibit lipolysis, resulting in an increase in circulating free fatty acids, which further reduces insulin's antilipolytic effect [25]. Insulin resistance is the major cause for type 2 diabetes mellitus development characterized by hyperglycemia due to high free fatty acids flux. Pancreatic  $\beta$

cells secretory function is enhanced at the primary stage to compensate the insulin level for the maintenance of euglycemia and with the progress of continuous resistance, decompensation occurred. Insulin resistance in skeletal muscles decreased the transportation of glucose into myocytes and ultimately decreased glycogen synthesis, while in the liver insulin resistance stimulates the continuous synthesis of lipid [15, 18]. Tyrosine phosphorylation is reduced due to the accumulation of lipids in skeletal muscle, which inhibits the activation of phosphoinositide 3-kinase [17]. Lipid accumulation may be a consequence of increased fatty acid delivery to tissues where energy intake outstrips storage capacity. It was also described that mitochondrial dysfunction is also involved in the severity of insulin resistance due to the defective process of mitochondrial oxidative phosphorylation [15, 16, 18]. Free fatty acids are mainly derived from triglyceride stores in adipose tissue, released via the action of cyclic adenosine monophosphate during lipolysis as a result of fasting, this process is initiated by catecholamines [17, 19-21].

### 2.2 Obesity

Abdominal obesity is the major cause of metabolic syndrome, which leads to insulin resistance, inflammation, and oxidative stress. It was also reported that despite the obesity importance, in the model, normal body weight patients also have insulin resistance which is known as metabolically obese usually with high-fat deposits in visceral adipose tissue. And it was described that free fatty acids flux from increased visceral adipose tissue to the liver through the splanchnic circulation expected, on the other hand, high abdominal subcutaneous fat enhance the systematic circulation lipids derived products, which ultimately affects the liver metabolism [15, 22].

### 2.3 Hypertension

Hypertension is a significant modifiable risk factor for cardiovascular disease [23, 24]. Lowering blood pressure reduces myocardial infarction risk by 20–25%, stroke risk by 35–40%, and heart failure risk by roughly 50% [24, 25]. Interrelation of hypertension development and insulin resistance is well reported. Insulin has vasodilator activity in a healthy person and has a role in the reabsorption of sodium by acting on renal receptors. But during insulin resistance vasodilation effect is lost with continuous sodium reabsorption. In addition, Free Fatty Acids also acts as a vasoconstrictor. Hyperactivity of beta cells might cause Hyperinsulinemia which ultimately enhanced the activity of the sympathetic nervous system and contribute to hypertension development [19, 22].

### 2.4 Inflammatory

Based on different research reports, insulin resistance do not only leads to the development of hypertension, glucose intolerance, hyperlipidemia etc but it is also accompanied by many other alterations which make metabolic syndromes more drastic like high level of pro-inflammatory cytokines, mitochondrial dysfunction, production of free radicals, high level of prothrombotic factors, increase apo B and C-III, homocysteine, uric acid, serum viscosity, non-alcoholic fatty liver disease, asymmetric dimethylarginine, white blood cell count, obstructive sleep apnoea, the presence of microalbuminuria, and polycystic ovarian disease are all associated with insulin resistance [15, 19, 22].

## 2.5 Dyslipidemia

In a healthy person, the secretion and binding of insulin with their receptors suppress the synthesis and secretion of very low-density lipoprotein from the liver. In insulin resistance, due to the high flux of free fatty acids, the liver produces high amount of very low-density lipoprotein and the production of hepatic triglyceride increased [17]. Metabolic syndrome could be diagnosed with hypertriglyceridemia in the insulin-resistant and the other most important metabolic change is the decreased production of high-density lipoprotein cholesterol. These metabolic changes enhance the risk of cardiovascular disorders. Due to hyperproduction of triglyceride the low-density lipoprotein composition is adapted which is attributable to relative depletion of phospholipids and cholesterol both esterified and un-esterified cholesterol. It was found that the modification in the composition of low-density lipoprotein is an independent risk factor for Cardiovascular disease [15, 19, 22].

## 3. Nutraceuticals against Metabolic Syndromes

### 3.1 Fibers

Based on solubility, fibers are of two types Soluble and insoluble. The chances of diabetes decrease by 21% if the patient takes two meals of grains per day [26, 27]. Soluble dietary fibers play a vital role in maintaining insulin sensitivity and controlling blood pressure. Insoluble fibers have more potential to improve type 2 diabetes as compared to soluble fibers. For men and women, the daily intake of fiber is 26 to 38 g/day [24, 26, 28].

### 3.2 Proteins and Amino Acids

Taking 1.2 to 1.6-gram protein/kg/day recovers the dietary deficiencies and weight problems. Obese patients who suffered from diabetes and blood sugar levels improved by the use of valine, leucine, and isoleucine [17]. In those patients who suffered from high cholesterol levels, the use of lupin protein with a diet for twenty-eight days reduces the level of bad cholesterol [29]. Evidence currently indicated that diabetic patients require a similar amount of protein as the general population which is about 0.86 g/Kg per day. Excessive protein intake contributes to the pathogenesis of diabetic nephropathy that should be avoided in spite of the fact that proteins play an important role in stimulating the secretion of insulin [6, 30]. Some evidence suggested that increased serum cholesterol levels and nephropathy can be managed in a better way by eating vegetable protein rather than animal proteins [6].

Certain amino acids including glutamine derivatives, alanine and arginine, may influence pancreatic  $\beta$ -cell function (eg, insulin secretion) [31]. Human studies report that consumption of dairy products rich in branched-chain amino acids (leucine, isoleucine, and valine) or whey/casein protein is associated with improved diabetic parameters (eg, fasting insulin levels) among obese and type 2 diabetes mellitus individuals [31, 32]. When human subjects with hypercholesterolemia consumed lupin protein (25 g/day) with a mixed diet for 28 days, their plasma levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol decreased [33].

### 3.3 Sugar

Fruit juice, fructose, and sucrose are the main ingredients of sugary beverages [24, 34]. Scientists concluded that people

who take or consume two meals of these sugars per day have a high chance of developing chronic disease and metabolic changes as compared to those people who take less amount of these sugars [35].

### 3.4 Fatty Acids

Fats have an important role to play in metabolism. Levels of lipid, blood sugar, the sensitivity of insulin, and bp are those metabolic problems that are recovered by the use of unsaturated fatty acids like mono, omega 3, and 6. The use of a diet that is a rich source of linoleic acid like 9 and 11 cis trans-isomer has greater potential to improve the metabolic profile and sensitivity of insulin within the liver and adipose tissue of the body [6].

According to many studies, saturated and trans-fatty acids have negative effects on metabolic health [26, 27, 36, 37]. But Unsaturated fatty acids, such as monounsaturated fatty acids and omega-3/omega-6 polyunsaturated fatty acids, help to improve metabolic parameters (eg, blood pressure, lipid profile, glycemic control, and insulin sensitivity) [26, 27, 36, 37].

### 3.5 Vitamins

For the prevention of diabetes, it is necessary to use proper anti-oxidant in diet which prevents many complications like neural dysfunction and kidney failure. For example, retinol which is also called vitamin A has an important role as an immune enhancer and acts as an anti-inflammatory by decreasing the level of adipocytokines. From the previous study, it was concluded that the use of an antioxidant-rich diet helps to prevent diabetes by improving the metabolic system and also decrease the incidence of cardiovascular disease [6]. Ascorbic acid (Vitamin C) is a water-soluble vitamin that acts as an antioxidant by directly scavenging the reactive oxygen species and prevents the propagation of chain reactions leading to reduced protein glycation [38]. Ascorbic acid supplementation replenishes the vitamin C levels in ascorbic acid-deficient type 2 diabetes mellitus patients without improving insulin resistance or endothelial dysfunction [39].

Vitamin E, a fat-soluble vitamin also functions as an antioxidant and a reduced level of this vitamin has been associated with a higher incidence of diabetes. Studies also suggested that diabetic patients have decreased levels of antioxidants, and that diabetic patients require increased antioxidants because of increased production of free radicals in hyperglycemic patients [40]. Vitamin D is a fat-soluble vitamin and plays defensive functions against diabetes. In type 2 diabetes mellitus, the patients suffer from many complications like insulin resistance, insufficient excretion of insulin, and the inflammation of secretory cells. From experiments, it was concluded that vitamins have the potential to improve the functioning of the pancreas and induce the production of insulin from the islet cells. Vitamins also stimulate the receptors of insulin and regulate their calcium influx, acting as an anti-inflammatory by reducing the production of cytokines which are inflammatory mediators [41].

### 3.6 Minerals

Minerals is an important dietary supplement that is obtained from food also called trivalent chromium. A diabetic patient may have lower levels of chromium [42]. Studies suggested that chromium supplementation increases the sensitivity to insulin and an improvement in glucose tolerance has been

seen in patients with type 2 diabetes mellitus. The American Diabetes Association reported inconclusive evidence regarding the chromium supplementation benefits in diabetes [43]. It is an important and 4<sup>th</sup> crucial mineral in our body that contributes almost more than 300 metabolic activities which include reproduction, growth, production of cellular energy, RNA, DNA, and protein synthesis. Magnesium has an important role in treating many diseases like constipation, migraine, pre-eclampsia, and asthma. The magnesium in a dose concentration of 368 mg/day shows the potential efficacy against the treatment of hypertension. The level of magnesium decreases in the diabetic patient as compared to healthy individuals. Those patients who suffered from type 2 diabetes mellitus are suggested to use a supplement of magnesium, thereby curing insulin sensitivity and metabolic activity [6].

### 3.7 Conjugated Linoleic Acid and Coenzyme Q10

Conjugated linoleic acid and the natural retinoid phytyanic acid, trigger the retinoid X receptor that make a heterodimer with Peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), seem to be PPAR- $\gamma$  agonistic. Both have insulin-responding characteristics in diabetic rats [44]. It is an important nutrient, has anti-oxidant potential and coenzyme activities which shows an important role in the production of energy in mitochondria. It decreases the resistance of systemic vessels; improves the cardiac condition and manage blood pressure by phosphorylation. This coenzyme has the potential to improve left heart failure and also increase the synthesis of energy from mitochondria. Studies revealed reduced levels of coenzyme Q10 in various metabolic disorders like diabetes mellitus, atherosclerosis, hyperlipidemia, hypertension, and chronic heart diseases. Coenzyme Q10 also decreases with increasing age and this coenzyme has potential efficacy for the treatment of hypertension [45]. An adequate amount of coenzyme Q10 is essential for oxidative reduction processes and play important role in preventing the peroxidation of low-density lipoprotein. In patients with hypercholesterolemia, reduced coenzyme Q10 levels are associated with increased arterial stiffness that can be improved by supplementation with diets containing coenzyme Q10 [46].

### 3.8 Polyphenols

Polyphenols are plants derived natural antioxidant compounds found in fruits, whole grains, vegetables, legumes, cereals, coffee, tea, and wines. To date, thousands of polyphenolic compounds have been identified from plant foods and these include flavonoids, phenolics, polymeric lignans, and stilbenes [47]. There are two main types of polyphenols which include flavonoids and non-flavonoids. Phenol and stilbenes are the component of non-flavonoids. The role of polyphenol is very important because of their number of properties including anti-oxidant activity. It also decreases the chances of fatty liver by inhibiting lipogenesis. It is a rich source of diet protecting from many chronic diseases like osteoarthritis, cancer, and diabetes. Due to its anti-oxidative activity, it reduces the chances of oxidative stress [48].

It is an important antioxidant and quencher of free radicals which got attention for its pivotal role in improving cardiovascular function by inhibiting oxidative stress and preventing cardiovascular diseases in humans [49, 50]. It is obtained from tomato and their products. It is a lipophilic,

unsaturated, biologically active non-pro-vitamin which is also called carotenoid A. Lycopene also present in many other fruits like Papaya, Apricots, Grapefruit, Guava, and watermelon [51]. Lycopene has anti-hypertensive activity reducing the lipid level and blood pressure. A dose of >12 mg/day effectively lowers the systolic blood pressure in population with increased systolic pressure particularly among Asians [52]. Curcumin is an active component of turmeric which belongs to zingiberoside family. It has a number of therapeutic actions and with the yellow color of turmeric is thought to be due to its active component. Curcumin contains 3-methoxyphenyl-4-hydroxy which is used for the cure of many diseases. It shows anti-inflammatory activity and also has the potential to treat many metabolic diseases like diabetes and obesity [53].

### 4. Value of Nutraceuticals in metabolic syndrome

Many important nutraceuticals which show anti-obese properties have the potential to manage the excess weight in obese people. Important nutraceuticals like fibers of psyllium, charantia, Momordica, conjugated linoleic acid, and Capsaicin all of these have anti-obesity activities. In routine, if we use the combinations of vitamin C, Sylvester G, Fenugreek, Glucomannan, and Chitosan, these nutraceuticals in the diet have the potential to reduce the extra fat from obese patients. People suffered from complexity because obesity becomes a psychological issue in our society otherwise, obesity should be easy to manage with nutraceuticals even without any exercise. Obesity occurs in people who consumed less energy while the intake of their energy is more, so this imbalance between intake and consumption process causes obesity, hence it can be prevented through dietary supplementation [54]. In diabetes mellitus there is an abnormal level of glucose in the blood as the synthesis of insulin is not adequate. Omega 3 fatty acid also called docosahexaenoic acid which is an important insulin-resistant modulator may be very useful in this process when deployed early. The important nutraceutical component is Lipoic acid which has anti-oxidative activity and is very effective for the treatment of diabetes. In hyperlipidemic cases, the level of lipid is decreased by using the fibers of psyllium. If the level of magnesium in our body is enough, the chances of diabetes will decrease because it improves the sensitivity of insulin. In some diabetic patients, diabetes control should be done by the use of vitamin D, calcium and chromium picolinate. Many other plants like cinnamon and bitter melon also have been shown to be effective for the treatment of diabetes [6, 54].

Different flavonoids like flavonols, flavones, and flavanones are present in berries, apples, red wine, cherries, grapefruits, onion, and black grapes. Other flavonoid derivatives like flavone glycosides ginkgo, quercetin and hesperidins are all important for the treatment of cardiovascular disorder. The important role of flavonoids is stops the aggregation of platelet and their thickness. It strengthens the vessels and provides potential to small capillaries, hence provides nutrients and oxygen to all cells [54], thus, preventing joint disorder which mostly affects obese patient. The joint problem also occurs due to an imbalance between intake of diet and their usage. Chondroitin sulphate and Glucosamine both have an important role in the management of osteoarthritis as both possess anti-inflammatory activity by regulating the expression of genes, hence producing nitric oxide and prostaglandin E2 [55].

Alzheimer's disease is an abnormality of mental health, commonly characterized by memory loss. Many nutraceuticals play an important role in the management of the disease. In Huntington, Parkinson's and Alzheimer's disease oxidative free radicals are produced in high concentration. Due to the anti-oxidant properties of nutraceuticals, they prevent the progression of these diseases and it was reported that the chances of Alzheimer's disease decrease on taking the antioxidants. Mostly these antioxidants are obtained from our food like vitamin C and E. Another important antioxidant is alpha-lipoic acid which also has the potential to prevent this disease. The basic arrangements of cell membranes in the brain occur by phospholipids. Many neurotransmitters like dopamine, epi, and norepinephrine, acetylcholine, and serotonin all have an important role in the transfer of message and gave a signal to the brain so phosphatidylserine helps them in their function and enhance the metabolism of the cell. By all these, they have an important role in the management of Alzheimer's disease by reducing the symptoms of memory loss<sup>[56]</sup>.

### 5. Conclusion and Recommendations

A metabolic syndrome is a complex group of diseases affecting a large population and a serious international common cause of morbidity and mortality. A wide range of factors contributes to the development of this condition among which insulin resistance due to increased free fatty acids flux is a more prevalent pathophysiological mechanism. The present review article mainly focused on the role of nutraceuticals in the treatment and management of a variety of metabolic complications. From an extensive literature study, the present review concluded that nutraceuticals are effective in treating a variety of disorders including metabolic disorders. However, continued exploration of underlying pathophysiologic mechanisms and exploration of therapeutic targets for a syndrome that, if left untreated, has potentially catastrophic outcomes. A place for nutraceuticals in clinical practice is emerging, but important pharmaceutical and clinical issues need to be addressed by further research. The potential nutraceuticals should be evaluated further to study their mechanism responsible for the beneficial effect in metabolic syndrome.

### 6. Ethical approval

Not applicable

### 7. Consent to participate and Consent to publish

Not applicable

### 8. Availability of data

The data that support this review are available in the manuscript.

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Article searching, selection process, data extraction,

preparing the draft manuscript, revising the manuscript, finalizing the manuscript, and communicating it to the journal were the contribution of the author.

### 12. Conflict of Interest

Not available

### 13. Financial Support

Not available

### 14. References

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