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NATURAL AGENTS IN THE MODULATION OF METABOLIC SYNDROME

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ABSTRACT

Metabolic syndrome or syndrome X is a profound health issue across the world and a recognized risk elements for both atherosclerosis-related as well as non-atherosclerotic cardiovascular disease. There was remarkable variation in the definition and diagnostic parameters for metabolic syndrome, which represents a chronological advancement in perception about this ailment. Several triggers leading to the primary cause of persistent inflammation variables for metabolic syndrome are pathophysiological. Finding a reliable alternative medication that is ecological and spared from adverse effects, therefore will be a helpful tool in the battle counter to metabolic syndrome. In this set of circumstances, consuming functional foods or making the supposition that natural bioactive compounds (NBCs) exist might have an advantageous effect on controlling body mass, glucose metabolism, and hypertension, as well as endothelial destruction, enhancing lipid profiles, reducing inflammation, and reducing oxidative stress. NBCs like EGCG, curcumin, polyphenols, allicin, barberine, quercetin, hydroxytyrosol, resveratrol etc. shows activity against the risk factors for metabolic syndrome. This review emphasizes the latent activities of NBCs in the modulation of metabolic syndrome, its associates risk determinants, as well as in their prevention.

KEYWORDS: Metabolic Syndrome, Natural bioactive agents, Obesity, Insulin Resistance, Dyslipidemia, Cardiovascular diseases.

INTRODUCTION

The incidence of chronic degenerative non-communicable diseases (CDNCDs) has increase drastically during the past century. This is due to the population's average life expectancy increasing as well as the proliferation of risk factors for unhealthy lifestyles like smoking, drinking too much alcohol, being sedentary, and having poor dietary habits. The metabolic syndrome, one of the most prominent CDNCDs (1).

Obesity, hypercholesteremia, or insulin resistance all are contributory factors to the metabolic syndrome. It begins by identifying individuals who have a higher vulnerability to acquiring type 2 diabetes mellitus and atherosclerotic CVD. Secondly, by considering the interrelationships among the different elements of the metabolic syndrome, we may be able to comprehending the pathophysiology integrating them to the increased probability of heart disease. Thirdly, it contributes to making it more feasible to conduct epidemiological and clinical research on pharmacological, dietary, and preventative treatment methods (2). It's crucial to correctly diagnose patients so that lifestyle and risk factor modifications can be made to improve the disease's outcomes. Metabolic syndrome can be diagnosed whether one or more of its symptoms like abdominal visceral fat, hypertension, impaired insulin sensitivity, and hypercholesteremia are present (3).

Epidemiology of Metabolic Syndrome: Metabolic syndrome is a worldwide issue. Abdominal obesity is allied with the higher probability of metabolic syndrome. Based on several variables, such as gender, ethnic group, age and the criteria used for diagnosis, the disease's prevalence differs throughout various nations and locations. As people age, their risk of developing metabolic syndrome rises. Less than 10% of young adults in their 20s and 40% of seniors in their 60s are affected by metabolic syndrome. The condition can affect schoolchildren, and some of them may even possess more than two of its symptoms (central obesity, insulin resistance, hypertension and dyslipidemia). More than 45 million adult Americans, or more than one-fifth of the population, are affected by metabolic syndrome in the US (4). Depend upon global epidemiological studies, the frequency rate of metabolic syndrome is approximately estimated in

between 20% and 45%, with a roughly increment of 53% by 2035.

Pathophysiology of Syndrome X or Metabolic Syndrome: Abdominal obesity and insulin resistance have been identified as the primary pathophysiologic abnormalities underlying the metabolic syndrome. Since these two risk factors are intricately linked to one another, it is impossible to say which is more important for Metabolic Syndrome etiology and progression. Furthermore, contributing factors like age, ethnicity/race, food, physical inactivity, dysregulation of cytokines originating from adipose tissue, genetics, inflammation, abnormalities in hormone levels, and medications further complicate the pathophysiology of metabolic syndrome (5).

An increased concentration of the adipose tissue in abdominal area has been related to an elevated incidence of insulin resistance, T2DM, and CVD. (6, 7). Endocrine roles of adipose tissue, is further categorized into two kinds of adipose tissue i.e. brown adipose tissue and white adipose tissue, regulates a number of metabolic pathways that, if changed, might result in a dysfunctional glucose and lipid metabolism (8). Protein 4 (FABP4) that binds fatty acids, adiponectin, leptin, hydroxyl fatty acids (FAHFAs) that are ester of fatty acids and palmitoleate are other substances secreted by WAT that have an impact on the hepatic tissue, skeletal muscles, brain, and pancreas. Because it facilitates the emission of cytokines that are associated with inflammation in the blood, which involve interleukin-6, interleukin-8, and tumor necrosis factor-α, only the previous one is associated with the cardiovascular morbidity, (8, 9,10). In fact, IR, T2DM, metabolic, and CV disorders can be spurred on by the pro-inflammatory chemicals secreted from adipose tissue (11-12). Many researches have indicated that some cytokines that caused inflammation, such as interlukin-1 and interlukin-18, are present in metabolic syndrome and are crucial for the advancement of the atheromatous plaques.

The pathophysiology of metabolic syndrome is significantly influenced by elevated concentration of mono and diacylglycerols in the blood, caused by insulin resistance. Insulin inhibits hepatic gluconeogenesis and lipolysis while elevating the absorption of glucose in muscle and the liver. However, adipose tissue has impaired insulin's capacity to conquer lipolysis during impaired insulin sensitivity, which leads to the transmission of free fatty acid levels to rise and stimulate to reduce antilipolytic effect of insulin (13). Protein kinase is not activated by the muscled due to the presence of FFAs, which results in the less absorption of glucose. They enhance the liver's ability to activate protein kinase, which promotes the gluconeogenesis and lipogenesis. In order to maintain euglycemia, a hyper-insulinemic condition is created overall. The compensation eventually fails, and insulin secretion declines. The pancreas' beta cells are likewise lipotoxic to FFAs, which results in less insulin production.

Accelerated action of sympathetic nervous system (SNS), and the salt reabsorption in the kidneys are additional processes. Because insulin resistance raises serum viscosity, it increases the risk of CVD, inducing a prothrombotic condition, and activating a pro-inflammatory cytokine from adipose tissue (14). An increase levels of FFAs result in more production of apolipoprotein B by the liver, as well as increase synthesis of triglyceride. The lowering in HDL-cholesterol and intensify in low density lipoprotein-cholesterol are the indirect consequences of changes in the lipid metabolism in liver (15).

Research Methodology: The electronic databases Pubmed, Scopus, Google Scholar were searched for the paper (original or review papers) through August 2023. The terms "metabolic syndrome," "natural bioactive compounds," "metabolic changes," "endothelial distruction," "lipid profile," "inflammation," "oxidative stress," "polyphenols" and "alternative medicine" were used. Additionally, we only incorporated English-language papers. Each and every reference were manually selected for the article.

Potential effect of Natural Agents or Bioactive Compounds in modulation of the Metabolic Syndrome

The initial therapeutic strategy implemented in the case of metabolic syndrome is dietary and lifestyle advancement. The therapeutic management of metabolic syndrome comorbidities can actually be aided by a better dietary regime, including a decrease in caloric consumption in cases of overweight and obesity, also a decrease in salt, saturated fats, cholesterol, and simple carbohydrates (16). Other associated factors of metabolic syndrome can be regulated by the dietary modifications; for example, dyslipidemia, hyperglycaemia, and hypertension have been identified to be improved by a minimal consumption of sodium, cholesterol, saturated fatty acids, and simple carbohydrates. Diets with a excessive and a very low-fat substance aggravate atherogenic dyslipidemia; as a result, it's typically advised to consume 25–35% of daily calories as fat.

Metabolic syndrome does not have a single medication that is effective, and the polypharmacy and low

compliance that result from the present pharmacotherapy and related comorbidities make it difficult for patients to take multiple medications for a prolonged duration. Since their impact is unknown what the long-term cardiovascular results and compliance will be, considerable concern in using the naturally available bioactive compounds to decrease the vulnerability and progression of the metabolic syndrome.

Natural bioactive agents have been shown positive impact on managing obesity and a decrease in visceral obesity in various clinical investigations. Catechins and its derivatives are among of the most extensively researched bioactive compounds for their potential anti-obesity activity. As it turns out, these bioactive molecules appear to have two main ways of reducing body weight: raising energy expenditure by activating the sympathetic nervous system, which enhances lipid oxidation, especially in adipose tissue; and lowering intestinal lipid content, which helps people consume less calories (18).

Epigallocatechin gallate (EGCG) is a natural biologically active agent abundantly occur in a green tea. According to an array of clinical studies (19-22), EGCG consumption is linked to a remarkable decrease in abdominal obesity, BMI, and intra-abdominal fat. These activities have frequently been investigated in relation to caffeine use, which appears to work in combination with EGCG to reduce body weight (23). It seems that EGCG can increase AMPK activity. AMP-activated protein kinase (AMPK) contributes to decreased fat production, increased fat breakdown, and improved insulin sensitivity, all of which leads to reduced body weight. Coffee contains a significant amount of chlorogenic acid, which appears to work by modulating the PPAR, the receptor in charge of lipid metabolism, it can also help intercept the buildup of visceral fat and uncontrolled body weight (24, 25).

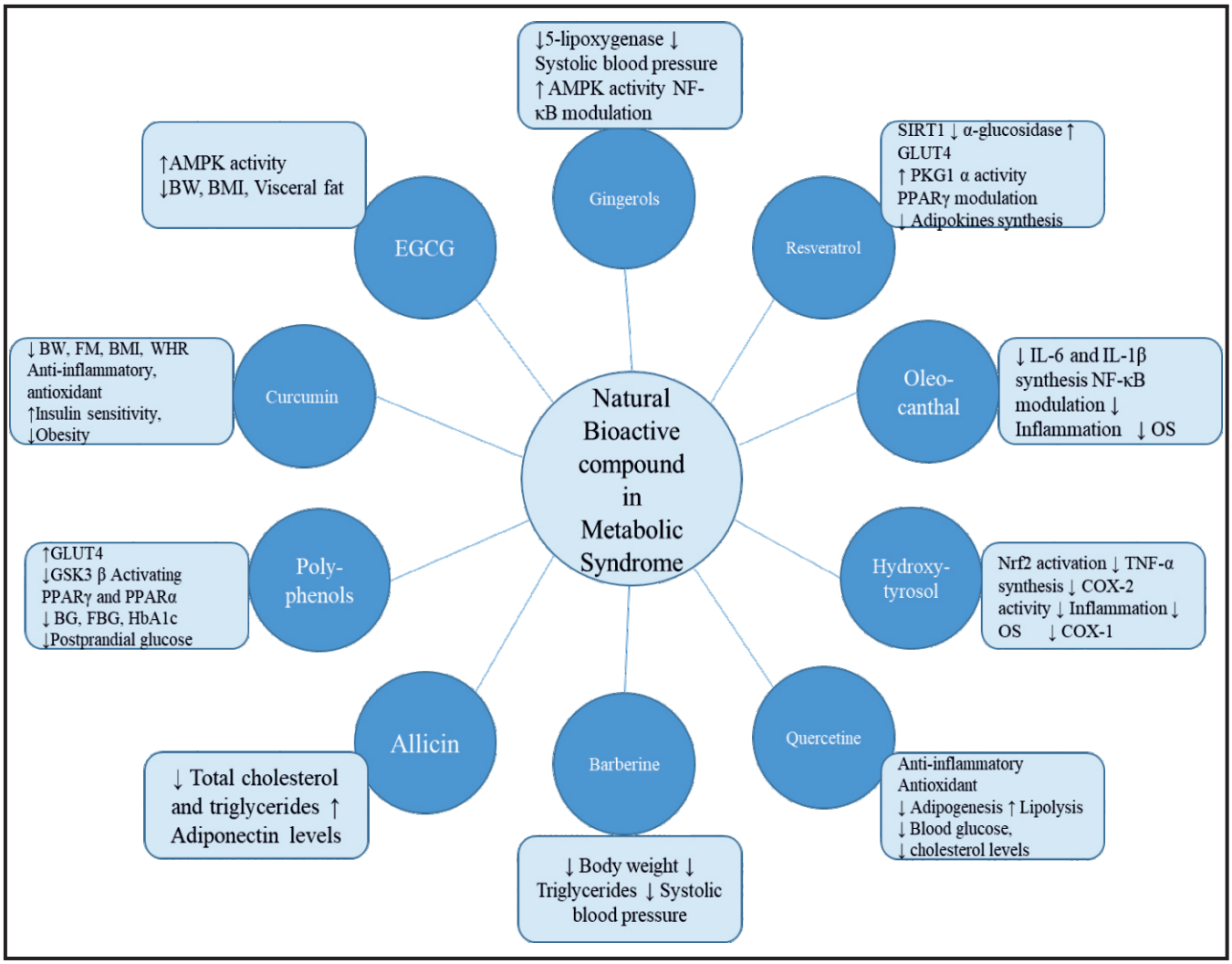

Fig. 1: The Impact of Naturally Occurring Bioactive agents on the Metabolic Syndrome

MUFAs, PUFAs, fibre, folate, calcium, magnesium, and potassium are all present in nuts, making them useful foods. Their impact on body weight management appears to be brought about by a rise in satiety (26-28).

In addition, nuts are an excellent food source for managing metabolic syndrome because they have a favorable impact on the modulation of lipid and glucose metabolism (29). Further research has determined the role the curcumin, the naturally occurring phenol found in *Curcuma longa*, plays an important role in managing pathways related with obesity. In addition to the low-calorie diet, curcumin use accelerates weight loss, resulting in decreased FM%, BMI, and body circumferences. (30-32).

Turmeric, one of the NBCs, that have been constantly investigated for its anti-inflammatory, anti-diabetic and antioxidant characteristics, and it come into sight to have a significant regulatory role on diabetes and insulin resistance. Curcumin is one of the important natural bioactive agents that shows anti-inflammatory, antioxidant and have modulatory activities on T2DM and insulin resistance (33, 34). Additionally, the anti-inflammatory and anti-lipolytic activities of its antihyperglycemic role have been linked to a decrease in circulation of fatty free acids (FFAs) levels and TNF-α, respectively (35-37).

Natural Bioactive Compounds	**Source**	**Pathways**	**References**
EGCG (Epigallocatechin gallate)	Green Tea (*Camellia sinensis*)	↑Enhance AMPK activity ↓Body Weight, BMI and Visceral fat	21, 22
Curcumin	*Curcuma longa*	↓Adipocytes differentiation ↑ Preadipocytes apoptosis ↓Body Weight, BMI and Waist Hip Ratio Anti-inflammatory, antioxidant ↓Leptin, ↑adiponectin ↑Insulin sensitivity, ↓Obesity	32, 63, 64
Polyphenols	Cinnamon (*Cinnamomum zeylanicum*)	Antithrombotic activity, Anti-inflammatory, ↑Insulin sensitivity ↑GLUT4 ↓ Blood Glucose, Fasting blood sugar, HbA1c ↓PP glucose levels ↑ Insulin sensitivity TRPA1 activation ↑ Vasorelaxation ↓GSK3 β Activating PPARγ and PPARα	65, 66-68
Allicin	Garlic *(Allium sativum)*	Increase Anti-inflammatory and Antioxidant activities, Decrease Hypercholesteremia and Triglycerides levels and increase Adiponectin levels	39, 70
Barberine	*Rhizoma coptidis*	Increase Insulin sensitivity, decrease Systolic blood pressure, ↓ Body weight and Triglycerides	47
Quercetin	Onions *(Allium cepa)*, Grapes, Red wine	↓ Adipogenesis ↑ Lipolysis ↓ Blood glucose, ↓ cholesterol levels Modulation of PPARγ increases the activity of AMPK ↓ Obesity ↑ GSH synthesis Catalase, and increase GSH peroxidase modulation of SOD activities Decrease Inflammation	56,71
Olive Oil (Extra Virgin)	Olive *(Olea europaea)*	Increase activity of eNOS Increase synthesis of NO and NF-κB Decrease Oxidative Stress and Endothelial damage Decrease Blood Pressure	72-75,45, 76, 77
Hydroxytyrosol		Decrease activity of Nrf2 Decrease synthesis of TNF-α Reduced activity of COX-2 & COX-1 and OS Decrease inflammation	

Table 1: Natural Bioactive Compound in the modulation of Metabolic Syndrome

Oleocanthal		Reduce synthesis of interlukin-6 and interlukin-1β and decrease activity of NF-κB Decrease Inflammation and oxidative stress Decrease COX-2 and iNOS	
Gingerols, Shogaols, Parasols	Ginger *(Zingiber officinale)*	Increase anti-inflammatory activities Reduce Cyclooxygenase-2, and 5-lipoxygenase activity Decrease systolic blood pressure Increase activity of AMPK and NF-κB modulation Reduce Endothelial damage and BP	78-80
Resveratrol	Grapes *(Vitus vinifera)*	↓ Adipogenesis ↑ Lipolysis ↓Insulin resistance, ↓Body mass index Increase activation of SIRT1 and AMPK Decrease activity of α-glucosidase ↑ GLUT4 ↑ PKG1 α activity PPARγ modulation ↓ Adipokines synthesis ↓ Inflammation ↑ PKG1 α activity ↓ OS ↓ BP	81-83, 54, 84-85
Charantin	Bitter gourd *(Momordica charantia)*	↓ Blood Glucose level ↓Serum Cholesterol levels	89, 90
Swertiamarin	Chota-chiretta *(Enicostemma littorale)*	↓ Fasting blood glucose, HbA1c, ↓TC, LDL, triglycerides ↑ Plasma insulin, HDL	91, 92
Gymnemic acid	Gurmar *(Gymnema sylvestre)*	↑ MIN 6 ↓ Hyperglycemic effect	93, 94
Garcinol, Hydroxycitric acid, Anthocyanins	Kokum *(Garcinia indica)*	Antidiabetic effect, Cardioprotective effect, Anti-obesity activity ↑ SREBP1c, SREBP2c	95
Tannins, Flavonoids Proanthocyanidin	Rose mallow *(Hibiscus rosasinensis)*	↑ Ratio of TC/HDL ↑ Ratio of LDL/HDL Anti-diabetic activity	96
Gallic acid, Ellagic acid, E mblicanin A & B	Amla *(Emblica officinalis)*	Cardio protective activity ↓ ChREBP expression ↓ FAS and HMGCR	97-98

Cont. Table 1: Natural Bioactive Compound in the modulation of Metabolic Syndrome

Another bioactive compound, Allicin which is found in garlic (*Allium sativum*), have medicinal properties as it possesses antioxidant and antithrombotic properties. Different studies shows that garlic improves insulin sensitivity and also lowers total cholesterol and triglyceride levels (38, 39). Berries like strawberries, red fruits, blackberries, blueberries, or raspberries contain natural bioactive agents, including anthocyanins and flavonoids (40). Since lipotoxicity is reduced, it would seem that anthocyanins are responsible for their hypoglycemic activities. However, anthocyanins function by activating AMPK, which increases the amount of GLUT4 transporters, increases the absorption of glucose, and inhibits gluconeogenesis. In addition, PPAR, CPT1A (carnitine palmitoyltransferase-1A) and acyl-coA oxidase are the genes that modulate the hepatic lipid metabolism by the influence of AMPK (41-42). Additionally, it appears that anthocyanins stimulate the secretion of the GLP-1, which in turn stimulates the release of insulin.

Olives are abundant in natural polyphenolic substances like as oleuropein, hydroxytyrosol, and tyrosol, which

have a number of beneficial properties. Extra virgin olive oil (EVOO) has been recently gained a scientific attention, as it contains free radical scavenging quality and anti-inflammatory characteristics. The anti-inflammatory and antioxidant qualities of the polyphenols hydroxytyrosol and oleocanthal aid in delaying the onset of chronic degenerative non-communicable diseases (CDNCDs). The stimulation of Nrf2, a factor contributing in the production of phase two enzymes which are involved in detoxification, is one way by which hydroxytyrosol might appear to execute the body's endogenous defences (43). Both in vivo and in vitro investigations have demonstrated that hydroxytyrosol suppresses the activity of cyclooxygenases (COX)-2 and increases the generation of cytokines that promote inflammation, including TNF-α (44). Oleocanthal exhibited a primary anti-inflammatory effect comparable to that of ibuprofen (an anti-inflammatory medication) because of its capacity to prevent the activation of COX-1 and COX-2 enzymes, which in turn contributes to the production of inflammatory prostaglandins in a dose-related approach. Preadipocytes expression of genes linked to inflammation can be altered by oleocanthal. As a matter of fact, the research contends that oleocanthal appears to reduce NF-κB activation, which reacts to incendiary response and controls the synthesis of cytokines and adipokines (45, 46). By the regulation inflammatory reactions at the adipose tissue level, as suggested by this research, oleocanthal may be able to reduce the persistent low-level inflammatory condition of obesity-related illnesses and metabolic syndrome.

The plant *Rhizoma coptidis* Insulin sensitivity, lipid levels, and body weight all improve when berberine is administered. Equivalent to thiazolidinediones and metformin, berberine acts by downregulating lipogenesis- related genes and activating genes involved in energy utilisation. Berberine also has an insulin-sensitizing effect that is mediated through adipocyte pivoting of the adenosine monophosphate-associated protein kinase. Research on humans with metabolic syndrome has demonstrated a decrease in lipid levels, waist circumference, together with systolic blood pressure, particularly in females (47-49).

Quercetin being demonstrated to have an anti-inflammatory and free radical scavenging characteristics (50-51). 60 participants in an in vivo trial found that an 8-week treatment of 500 mg/day of quercetin substantial reduced levels of IL6 and C-reactive protein (CRP).

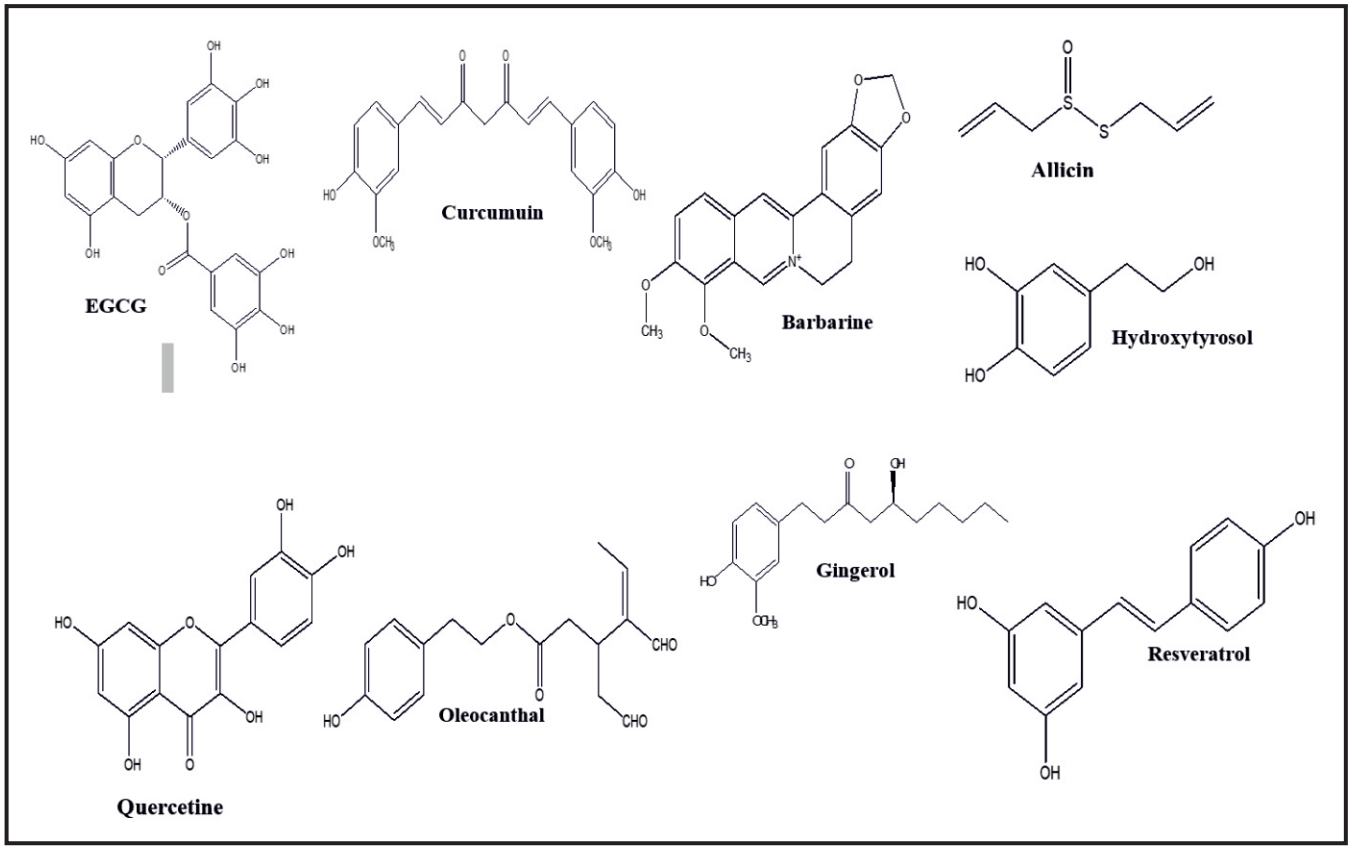

Fig. 2: Structure of Bioactive compound in the modulation of Metabolic Syndrome

Additionally, quercetin appears to decrease the gene expression for inducible nitric oxide synthase (iNOS) and COX-2 (52). Quercetin may strengthen the body's barriers system against free radicals by encouraging the production of glutathione (GSH), regulating the catalase gene expression, superoxide dismutase (SOD), and GSH peroxidase (53).

A polyphenol, resveratrol (3,5,4′-trihydroxystilbene), is derived from natural herbs notably in grapes, dry fruits or nuts as well as its derivatives like wine. It is a sirtuin pathway activator, that controls a number of cellular processes including metabolism, oxidation, along with aging. It has benefit in reducing adipogenesis and promoting lipolysis via a variety of methods and also prevents cyclooxygenase, with the resulting antioxidant activity (54). Investigations on individuals suffering from NAFLD and IR have produced encouraging findings (55). In fact, the investigations on the application of resveratrol in individuals with metabolic syndrome has revealed that it increases insulin sensitivity, glucose tolerance, total weight, and body mass index. Additionally, resveratrol has antioxidant properties that counteract reactive oxygen and nitrogen species (56-57).

Numerous epidemiological studies have looked closely at omega-3 polyunsaturated fatty acids (PUFAs), especially in regards to their preventive impact on metabolic syndrome-related symptoms (58). Eicosapentaenoic acid and docosahexaenoic acid are two particular PUFAs that are rich in fish oils and have drawn a lot of attention, leading to important preventive recommendations for society (59).

Sulforaphane is another phytochemical that comes from the Brassica family, which includes broccoli. Because of its antioxidant and anti-inflammatory qualities, it has been shown to offer potential therapeutic benefits for metabolic syndrome. It has been demonstrated to offer protection against a range of illnesses, conditions like type 2 diabetes mellitus, hyperlipidemia, and hypertension— each of which is significant contributory factors for the metabolic syndrome (60- 62).

The relevance of the polyherbal formulation's application in Metabolic Syndrome:

Approximately 80% of Asians, based upon estimates from the World Health Organization (WHO), receive their primary medical care from complementary and alternative medicine., partly due to the fact that the majority of population in developing countries can hardly afford basic health services. Metabolic syndrome has numerous etiologies; hence no single therapy can reverse the condition. Lifestyle modifications are the core component of risk-adverse persons' prevention and management. Those with high levels of risk determinanats, on the other hand, are the recipients of pharmaceutical treatment directed at managing individual symptoms (86).

The underlying mechanisms that allow for the synergistic therapeutic effect of polyherbal formulations include the modulation of the different targets or same targets in different mechanisms, which when combined increase activities; the modulation of transporters and enzymes to enhance the bioavailability of oral drugs; neutralization of detrimental effects; and the circumvention of drug resistance mechanisms (87). Multiple chemical constituents in only one herb or in combination with other herbs exhibit synergism, suggesting that these constituents may be useful as therapeutics for a range of disease targets. This is thought to be more logical and effective in treating diseases with multiple targets and serves as the foundation for polyherbal therapy (88).

CONCLUSION

As a consequence of stress, the synthesis of superoxides, abnormalities in lipid metabolism, and rises in impaired insulin sensitivity, the intricate nature of the metabolic syndrome is becoming more and more pronounced every day. The primary form of treatment and prevention for metabolic syndrome is regarded as changing one's lifestyle worldwide because pharmaceutical therapy is not a complete solution.

It is unquestionably obvious that natural bioactive agents play a beneficial contribution in the medical oversight of syndrome X and its associated concomitant conditions. In actuality, their hypothesis presents a number of positive outcomes, particularly over a long period of time, including body weight management, improved carbohydrate and lipid metabolisms, blood pressure management, endothelium protection, and eventually the reduction in oxidative stress and a persistent low-grade inflammatory state. Even though the possible advantages to health of several natural bioactive agents which have been already received extensive research, more clinical studies with larger population are still required to fully understand the unique mechanisms of action that can be used to regulate metabolic pathways. In order to achieve the positive benefits outlined in the research, it is required to develop worldwide norms for a natural bioactive compound's minimum effective dose and their period of assumption.

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