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Metabolic syndrome: risk factors, diagnosis, pathogenesis, and management with natural approaches

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ABSTRACT

Metabolic syndrome (MetS) is a bunch of metabolic defects comprising hypertension, insulin resistance, visceral obesity, fatty liver, and atherogenic cardiovascular diseases. Lifestyle modification is the first step for controlling the MetS progression. If left untreated, MetS is significantly related to a high danger of evolving type 2 diabetes and atherogenic cardiovascular diseases. Thus, MetS is a prominent cause of morbidity and mortality internationally and has been become very important to investigate novel therapies in this context to decrease the heavy burden of the disease. Though, there is no single treatment for MetS and the currently available pharmacotherapy and related comorbidities demand the continued use of multiple drugs that is challenging for patients as the polypharmacy and reduced accordance. There is increasing concern in the use of nutraceuticals in the management of MetS. This review follows MetS with an emphasis on the risk factors and how to control it, epidemiology, pathogenesis, pathophysiology, diagnosis, and treatments. Moreover, the review recaps on the health benefits of natural products in the management of the MetS to give a complete guide to other researchers for new natural products investigation.

Novelty Statement

MetS is significantly related to develop type 2 diabetes and cardiovascular diseases as well as MetS is considered a prominent reason of morbidity and mortality worldwide. Thus, it is critical to explore new treatments in this circumstance. However, there is no single treatment for MetS and the existing pharmacotherapy require the continuous use of numerous drugs that is challenging for patients as the polypharmacy and diminished accordance. There is rising interest in the utilization of nutraceuticals in the management of MetS. Also, the investigation of an efficient approach to manage those complications not studied well, where the authors highlighted this point in our manuscript. We presented in this review a wide information concerning the risk factors, pathophysiology, and diagnosis of MetS. Moreover, this review summarizes the different natural approaches to management MetS. The manuscript is the original study of the authors and the novelty in results is given in different sections.

1. Introduction

Natural foods have attracted much attention nowadays as potential therapeutical agents in the management of metabolic syndrome (MetS). MetS, insulin resistance syndrome (IRS), or syndrome X (Oda, 2018) is frequently defined by the combination of several connected metabolic illnesses of metabolic, environmental and/or genetic origin. It in-

Abbreviations: BP, blood pressure; BMI, body mass index; CAT, catalase; CV, cardiovascular system; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; G, blood glucose; GPX, glutathione peroxidase; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IS, insulin sensitivity; ISR, insulin resistance syndrome; LDL, low density lipoprotein; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MetS, metabolic syndrome; MPO, myeloperoxidase; ND, normal diet; NF-κB, nuclear factor kappa B; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase; STZ, streptozotocin; T2DM, Diabetes mellitus type 2; TG, triglycerides; TNF-α, Tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion protein 1; W, body weight.

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cludes abdominal obesity (Ehrampoush et al., 2016), insulin resistance, dysglycemia (reduced glucose tolerance and/or reduced fasting glucose), atherogenic dyslipidemia (hypertriglyceridemia and/ or low high-density lipoprotein cholesterol), and hypertension (at least three of them) (Gisondi et al., 2018). Previous study conveyed that MetS has inadequate applied investigative or management tools (Oda, 2018). Unfortunately, the subjects having MetS have more risks of developing type 2 diabetes, and atherosclerotic cardiovascular diseases (Franchini et al., 2008). MetS could be the general indicator of adipose tissue illness, is described by an amplified aggregation of activated macrophages and an increase in the number of crownlike structures in adipose tissue (Oda, 2018). The five recognized components of MetS are: waist circumference based on ethnicity to identify abdominal obesity, high blood pressure, impaired fasting blood sugar levels, higher levels of triglycerides, and a reduction in the amount of HDL cholesterol (Fahed et al., 2022).

The prevalence of MetS frequently coincides with the prevalence of obesity and type 2 diabetes, where about one third of US adults have MetS. Nearly 25% of the globe grown population are suffering from MetS, its occurrence is rising in children in Western nations, particularly because of lifestyle alterations (Saklayen, 2018). The global prevalence could be estimated to be about one quarter of the world population. By way of explanation, more than a billion people in the world are now affected by MetS. The prevalence estimates differ depending on the criteria used to define MetS. For example, a national survey in Iran in 2007 showed prevalence of MetS was about 34.7% based on ATP III criteria, 37.4% based on IDF definition, and 41.6% based on ATP III/AHA/NHLBI criteria. In another Middle Eastern country, Tunisia, prevalence was 45.5% based on IDF criteria but 24.3% based on ATP III criteria. But in all the Middle Eastern countries, prevalence was much higher among women than men. The prevalence rose by more than 35% from 1988–1994 to 2007–2012, increasing from 25.3% to 34.2%, among US adults aged 18 years or older (Delvari et al., 2009).

Although diet and exercise are the primary treatments for MetS, pharmaceutical therapy is necessary to control severe obesity, dyslipidemia, type 2 diabetes, and hypertension. The current global drug market is primarily focused on anti-obesity, anti-diabetic (insulin sensitizers, sodium glucose transporter-2 inhibitors, glucagon-like peptide-1 agonists), antiplatelet agents and lipid- dropping, renin-angiotensin system blockers that can be taken alone or in combination (Lim & Eckel, 2014). Our review spotlights on natural remedies that have received a lot of interest in the past 10 years as prospective MetS treatments, notably for overweightness, type 2 diabetes, dyslipidemia, insulin resistance, and nonalcoholic fatty liver disease. Similarly, we summarized *in vitro* and *in vivo* models that give promising conclusions for researchers who concerning about MetS assessment.

2. Materials and methods

2.1. Search strategy

The data in the available literature has been collected from the databases including the Egyptian Knowledge Bank database, ScienceDirect, Scopus, Web of Science, PubMed, Springer, Google Scholar, Emerald, and Elsevier databases. The articles from Database journals were limited to research papers with the keywords “metabolic syndrome” & “risk factors”, “how to control” & “natural sources or, isolated natural compound” or “mechanism of actions/ biological activities” or “clinical surveys” “pathophysiology and diagnosis”. The time of the article published was limited in the period from 1990 to 2020. Articles are selected based on the following criteria: quality criteria during selection of studies and scoping of research, illustrative research article, high reproducibility, inventive potential within natural products, articles in metabolic syndrome and prevalence, articles in foods and metabolic syndrome topic categories, and articles with phytotherapy evidence.

3. Discussion

3.1. Risk factors of MetS and How to control it?

- **Lifestyle**: lifestyle has an important role in progression of numerous risk factors of metabolic syndrome, as well as change of some habits could reduce prevalence of this disease. Persons with metabolic syndrome are frequently overweight and have sedentary behavior (Grundy, 2016). A pervious study has been conducted on 8800 adults ≥25 years for approximately seven years and it revealed that every hour spent on TV viewing amplified the risk of cardiovascular mortality by 18% (Dunstan et al., 2010). Moreover, inadequate physical activity or muscular contraction seems to interfere with triglyceride clearance as well as glucose metabolism (Thorp et al., 2010). Several earlier systematic reviews have assessed the consequence of lifestyle interventions on metabolic syndrome (van Namen et al., 2019). These trials aimed to achieve dietary intervention including healthy eating (Pettman et al., 2009), calorie reduction (Oh et al., 2010), reducing fats, carbohydrate, and dairy products (Oh et al., 2011). Besides, induction of exercise intervention including rhythmic dance, aerobics, yoga, and running (Tran et al., 2017). A meta-analysis of six trials reveled reduction of waist circumference by 4.9 cm in 643 participants, triglycerides in nine trials by 11% with 797 participants, and fasting blood glucose by 5% in 10 trials with 816 participants. All studies conveyed decreases in metabolic syndrome prevalence subsequent to the intervention (39%) (van Namen et al., 2019).
- **Diet**: Diet has a major role in progression of MetS (Aron-Wisnewsky & Clément, 2016). The prevalence of MetS was found to be common among subjects who favor omnivores than vegetarian meals (47.55%) in a cross-sectional analysis of 773 subjects. This finding was attributed to the lower levels of glucose and triglycerides in vegetarian diet (Rizzo et al., 2011). Moreover, prolonged consumption of high saturated fat diet concentrations induces deposition of fat and fat-derived lipotoxins in liver, skeletal muscle, and pancreas which develops insulin resistance (Erion & Shulman, 2010). On the contrary, another study was reported that vegetarian foods did not reduce the risk of MetS in vegans (n=1116) relative to pesco-vegetarian (n=2461), lacto-vegetarian (n=4313) and non-vegetarian group (n=85319) in a Taiwanese cohort (Kagawa et al., 2016).
- **Cardiovascular disease (CVD):** Several studies reveled that atherosclerosis increased the incidence of MetS by 2-2.9-fold, while CVD enhanced the MetS frequency by 14.6-fold after 30 years (Magnussen et al., 2010). Recently, a representative sample of adolescent cohort (n = 1516) was evaluated to define the correlation between CVD and MetS incidence, The data showed that raised systolic blood pressure (SBP) was related with a high MetS prevalence risk significantly, whereas diminished levels of SBP and glucose were linked with MetS diminution (Wu et al., 2022). Moreover, newly clinical study was performed on 200 knee osteoarthritis patients to evaluate the link between osteoarthritis, CVD, and MetS. Approximately, 84.8% of patients had full criteria of MetS (Hassan et al., 2022). Hence, early detection and management of these disorders may resist the developing epidemic of MetS.
- **Smoking:** smoking is widely considered as a main risk factor for MetS (Geslain-Biquez et al., 2003). Smokers people have a superior risk of developing MetS than nonsmokers by 1.07–1.66-fold (Nakanishi et al., 2005). Smoking was found to reduce insulin sensitivity, increase cardiovascular risk factor, and upgrade the levels of triglycerides (Cena et al., 2011). Additionally, smoking was reported to induce abdominal obesity in both sex of adolescents. Girls smoking during adolescence (10 cigarettes daily) had a nearly 3.4 cm higher waist circumference as young adults than nonsmoker girls (Saarni et al., 2009). Kawada et al., (Kawada et al., 2010) evaluated the incidence of MetS in smoking workers (n= 2136) after one year.

The results exhibited that the incidence of MetS was greater in current smokers than who did not smoke by 6.3%.

Prolonged smoking of tobacco and nicotine was reported to upgrade the expression levels of leptin hormone that resulted in decreasing the hormone sensitivity and ended by overweight (Perkins & Fonte, 2002). However, A study reported that the leptin levels were lower in smokers compared to nonsmokers (Larsson & Ahren, 1999). Conclusively, the effect of smoking on the leptin hormone was genetically dependent and may affected by age and menopause (Martin et al., 2003).

- **Alcohol:** Heavy alcohol consumption (more than 20 times / months) correlated with the low serum HDL cholesterol level, raised serum triglycerides, higher waist circumference, hyperinsulinemia(Freiberg et al., 2004), as well as incidence of MetS. Contrariwise, mild and moderate consumption of alcohol (1-19 times / month) lowered the levels of insulin, serum lipids, as well as the MetS incidence (n=8,125) (Freiberg et al., 2004).
- **Inadequate sleep:** prolonged period of sleep inadequacy had also believed to be one of MetS risk factors. Insufficient sleep can lead to mental and physical stress besides enhance the incidence of obesity and diabetes (Lam & Ip, 2010). Similarity, Obstructive sleep apnoea was found to decrease the level of HDL besides increase the level of glucose, body weight, insulin resistant, and cardiovascular risk. All these sequences augment the prevalence of metabolic syndrome by 87% (n= 61) compared to control group (35%, n= 43) (Coughlin et al., 2004).
- **Stress:** stressful life events relating to finance, job, relationships, health, and sheltering were self-rated in a random sample of population aged 18–78 years in Western Finland (n= 3,407). Analysis of data reveled those subjects who had suffered from extremely stressful life events related to finance, job, and health or suffered from at least three events in any of the life domains during past 12 months exhibited greater levels of triglycerides, waist circumference, and Body Mass Index (BMI), hence, increase the incidences of MetS (78.69%) compared to those who do not suffer from stress (Pyykkönen et al., 2010).
- **Income**: Unexpectedly, MetS is more common in higher social class population than lower classes (Riediger & Clara, 2011). Occurrence of MetS has been reported to be high among urban subjects relative to rural population by 10% (Mangat et al., 2010), as well another study was found that occurrence of MetS was great in urban as related to rural populations (45.4% vs. 27.6%, n=605) in Mexico (Ramírez-Vargas et al., 2007).
- **Positive family history:** The families with positive history have reveled high susceptibility to MetS than negative families with no history of MetS (42.63%) (Lee et al., 2005).
- **Liver transplantation:** A recent study revealed that incidence of MetS increased shortly after liver transplantation by 46%, 43%, and 49% at 6, 12, and 24 months, respectively (n= 63). Various MetS components were recorded including the raised levels of blood pressure, insulin, and triglycerides (Becchetti et al., 2022). Accordingly, lifestyle adjustments should be recommended after liver transplantation to control various risk factors. Risk factors of metabolic syndrome that are discussed in text are summarized in Fig. 1.

3.2. *Epidemiology*

The incidence of MetS differs all over the world and frequently links with the prevalence of obesity. The variation in MetS prevalence is based on gender, age, and race/ethnicity. MetS was found to affect more than twenty percent of the USA population and around a twenty-five percent of European people. A lower prevalence was recorded in South-east Asia but is speedily progressing towards frequencies close to the western world (Beltrán-Sánchez et al., 2013).

Sex-related differences in MetS prevalence are not stable, for example, the incidence of metabolic syndrome was higher in men than woman (3.9%; n=5775), while the prevalence was lower in men than woman in another group (2.7%; n=1514) (Ford, 2005). This variety may be due to work nature, lifestyle, and body fat (Gu et al., 2005; Kozan et al., 2007). There are also sex and race-based variants in MetS prevalence. Investigation of NHANES (National Health and Nutrition Examination Survey) records gathered between 1988 and 1994 in USA reveled that the incidence of MetS is higher in Hispanic women relative to Hispanic men by 26% and higher in African-American by 57% compared to African-American men (Rochlani et al., 2017). Besides, risk factors of MetS were found to be affected with the race. For



Fig. 1. Risk factors of metabolic syndrome. CVD; cardiovascular disease.

example, dyslipidemia is more frequent in Caucasians, insulin resistance in Hispanics, and hypertension in African-Americans (Grundy, 2008).

MetS also is highly age dependent, as expected, the prevalence of MetS increase after sixth or seventh decades (Deepa et al., 2007). Following to the criteria from NCEP-ATP III (The National Cholesterol Education Program-Adult Treatment Panel III), the incidence of MetS in USA increased by 35-37% in group aged 60-69 years relative to those aged 20–29 years at least 70 years (Eckel et al., 2005). However, may factors accelerate the incidence of MetS including diabetes, overweight, and CVD (Jeppesen et al., 2007).

3.3. Theories of metabolic syndrome pathogenesis

Obesity has become a global epidemic due to sedentary lifestyles, high-powered fast-food environments, and other obesogenic socioeconomic environments. Individuals may acquire MetS due to a genetic susceptibility to obesity and proinflammatory responses. We concise the different theories of MetS in the following text.

- **Adipose tissues inflammation**

Numerous humoral substances, including tumor necrosis factor-α (TNF-α), leptin, and adiponectin, are produced by adipose tissue (Oda, 2018). Obesity-related metabolic abnormalities are characterized by an increase in crown-like structures made up of activated macrophages accumulating around an enlarged dead adipocyte. TNF-adipose expression also directly contributes to the connection between insulin resistance and obesity (Oda, 2018). The metabolic effects of obesity are dependent on the penetration of macrophages into adipose tissue, which is characterized by an increase in the crownlike constructions but not by an increase in adipocyte mass (Cai et al., 2022).

- **Cross talks between signaling systems.**

Obesity and hypertension may be connected by interactions between the insulin and renin-angiotensin signaling systems (Kamei et al., 2006). Insulin resistance and endothelial dysfunction as well as insulin resistance and inflammation have reciprocal relationships (Kanda et al., 2006). The renin-angiotensin-aldosterone system (RAAS) in the cardiovascular system (CV) is unusually triggered the MetS, a complex metabolic and vascular condition that is linked to increased CV morbidity and mortality. As a result, Angiotensin II and insulin signaling interact extensively in both insulin-sensitive and CV tissues, establishing a relationship between insulin resistance and CV disease (Kamei et al., 2006).

- **Cell stress**

Stress in the mitochondria, nucleus, and endoplasmic reticulum may also be contributing factors to MetS (Zhou et al., 2012). Oxidative stress is a state where there is an imbalance between the creation and inactivation of reactive oxygen species (ROS). In many physiological systems, ROS are crucial and when cells are under oxidative stress, they can become dysfunctional (Dandona et al., 2005). In this context, MDA levels, a by-product of unsaturated fatty acid peroxidation, were increased in patients with MetS (Monserrat-Mesquida et al., 2020). Furthermore, it was also reported that MPO levels progressively increase with MetS (Sladoje et al., 2017). CAT and SOD activities have lower levels in plasma from patients with MetS as compared to patients without MetS (Sheikhansari et al., 2019). Hyperglycemia and hyperlipidemia have been linked to an increase in ROS generation and oxidative damage, which has been linked to the development of insulin resistance, altered endothelial dysfunction and energy metabolism, and the emergence of vascular problems in patients with MetS (Okon et al., 2007).

- **Autonomic dysfunction and leptin resistance**

The underlying causes of MetS also include leptin resistance and autonomic nervous system dysfunction (Roberts & Sindhu, 2009). It has been extensively studied how the autonomic nervous system (ANS) contributes to insulin resistance and obesity. Since most of these processes exhibit a bi-directional effect, the precise mechanisms behind this relationship have not yet been fully understood. Both the short-term and long-term regulation of body weight depend heavily on the ANS. Particularly, the sense of fullness, which is caused by stomach distension and the release of gut hormones, is primarily responsible for the short-term management of body weight. The activation of vagal afferents has recently been identified as an early stage in the control employed by gut hormones on nutrient supply to the intestine by regulating food intake and stomach emptying, but vagal activity is also engaged in this latter route (Semenkovich, 2006). The development of obesity has thus been thought to be significantly influenced by gut hormones and vagal afferent neurons (Roberts & Sindhu, 2009).

- **Lipid disposition in skeletal muscle**

Skeletal muscle is essential for maintaining the body's general glucose homeostasis and preventing the malfunction of adipose tissue. Recent studies have shown that oxidative stress, aberrant lipid accumulation, and mitochondrial dysfunction are all associated with insulin resistance in skeletal muscle (Sacramento et al., 2017). Reduced estrogen receptor expression in the muscles of women and female mice is associated with glucose intolerance and obesity. Mice lacking the muscle-specific estrogen receptor exhibit altered mitochondrial shape and compromised mitochondrial fission dynamics (Ehrampoush et al., 2016).

- **Hepatic steatosis**

Independent of obesity, liver stored fat exhibits an extremely substantial connection with all MetS components (Kotronen & Yki-Jarvinen, 2008). MetS was predicted by gamma glutamyltransferase (Lee et al., 2007) and alanine aminotransferase (Hanley et al., 2005). Hepatic insulin resistance and type 2 diabetes have been related to hepatic lipids, according to research (Perry et al., 2014). MetS considerably augments the risk of hepatic fibrosis and steatosis, indicating that MetS should be considered an additional independent risk factor for hepatic fibrosis alongside other recognized etiologies. Using population estimates based on surveys, 26% of the population had steatosis, 7.5% had fibrosis, and 3.3% had fibrosis without steatosis (Gangireddy et al., 2022).

3.4. Pathophysiology of metabolic syndrome

A crucial aspect of metabolic syndrome's pathophysiology is adipose tissues that have the ability of mobilization and lipid storage. Due to its capacity to release a significant number of bioactive mediators that regulate a variety of signaling cascades, known as adipokines, it has lately been recognized as an functioning endocrine organ that has a crucial function in the incorporation of systemic metabolism (Ouchi et al., 2011). As an illustration, different fatty deposits (visceral and subcutaneous) have varying capacities for metabolism and release varied adipocytokines (Mendonca et al., 2015). Diverse cell types make up the various adipose tissue depots (structural support, functional and immunological). Additionally, blood arteries serve a dual purpose by transporting inflammatory mediators to distant regions while also supplying nutrients and oxygen (Ouchi et al., 2011). Catabolic mechanisms like lipolysis are associated with inflammation (Maury & Brichard, 2010). Increased lipolysis in the enlarged adipose tissue causes a significant flow of free fatty acids (FFA) into the portal vein. Once in the liver, FFA enhance the production of extremely low-density lipoproteins (LDL), glucose, and triglycerides. This condition is accompanied with dyslipidemias, which are characterized by lowering High density lipoprotein (HDL), cholesterol and an increase in LDL (Mendonca et al., 2015). FFA also decrease muscle insulin sensitivity, which inhibits glucose uptake. An increase in blood sugar levels and, to a lesser degree, FFA leads to increased pancreatic insulin secretion, which causes hyperinsulinemia. Hyperinsulinemia can cause increased sodium absorption and sympathetic nervous system activity, both of which may increase

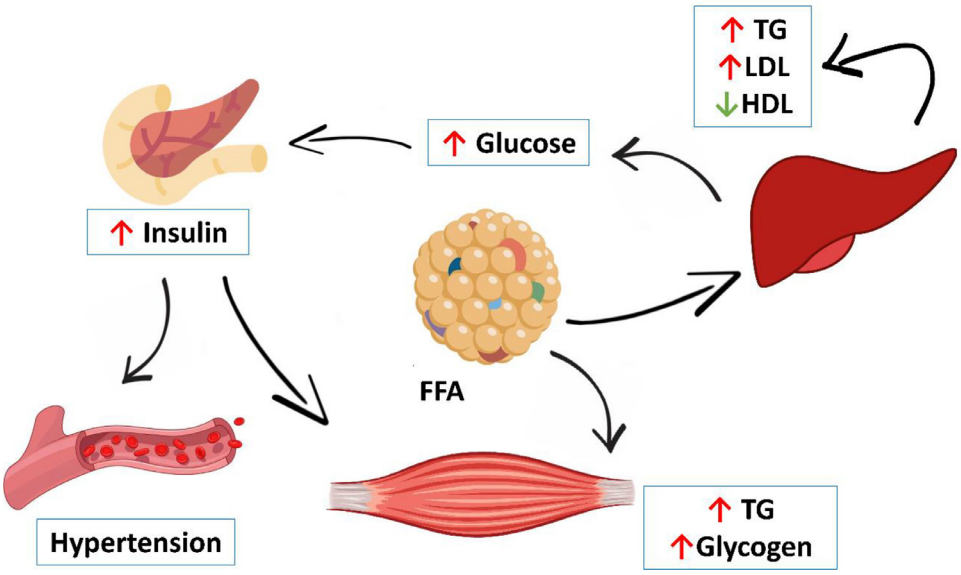


Fig. 2. Pathophysiology of metabolic syndrome. FFA, free fatty acid; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

blood pressure (Cohen & LeRoith, 2012). The high FFA-induced pro-inflammatory state overlaps with and feeds into the insulin resistance. Insulin resistance and lipolysis in adipose tissue are further exacerbated by the increased TNF-α and IL-6 release by adipocytes and macrophages. On the other hand, IL-6 and other cytokines also promote muscle insulin resistance, VLDL synthesis, and hepatic gluconeogenesis (Maury & Brichard, 2010). Additionally, the prothrombotic condition, another feature of this disease, is brought on by the liver's elevated production of fibrinogen, plasminogen activator inhibitor (PAI-1), and C-reactive protein (Cowey & Hardy, 2006). According to several studies, each element of the MetS shares in the growth of numerous processes, including angiogenesis, insulin resistance, the manufacture of adipocytokines, and oxidative stress, which increase the danger of developing chronic diseases like cancer or worsen the prognosis of these same complications (Braun et al., 2011). Pathophysiology of metabolic syndrome is illustrated in Fig. 2.

3.5. *Causes of metabolic syndrome*

- **Genetic causes of obesity**

Studies on twins, adoptees, and relatives have shown that genetic variables are liable for 60% of the alteration in body mass index (BMI(. Calorie intake and energy spending, which are both impacted by genetic variables, are used to calculate BMI (Min et al., 2013). Despite compelling evidence that family history influences the onset and progression of obesity (Han and Lean, 2106), research has made only little improve in determining the basic genetic origins of the condition in the general population. More than 30 distinct genes have been found to date to have significant influence on its pathogenesis; nevertheless, only 10% of the population is affected by these genetic alterations, leading to obesity. However, genetic research has shed a lot of light on the pathogenesis of obesity. These findings have drawn attention to the hypothalamus' crucial role as the body's principal sensor of body fat and plasma adipokines as well as the basic controller of caloric consumption and energy spending. Adipose tissue leptin serves as a vital link between the deposition of the peripheral fat and the expression of hypothalamus proopiomelanocortin (POMC) in neurons (Cowey & Hardy, 2006). The anorectic response and fat deposit are produced by the stimulation of the melanocortin receptors 3 and 4 (MC4R and MC3R) by the melanocortin peptides produced by posttranslational processing of POMC (Farooqi, 2009). Both autosomal dominant and recessive obesity have been linked to MC4R gene loss of function mutations. Additionally, case reports of people with obesity and mutations in the POMC and MC3R genes have been published (Cinti et al., 2005). Leptin also blocks the orexigenic pathway by inhibiting neurons in the arcuate nucleus that produce agouti-related peptide (AGRP) and neuropeptide Y (NPY) (Gropp et al., 2005). Mice with leptin (ob/ob) or leptin receptor (db/db) deficiencies are obese, have insulin resistance, and have hyperinsulinemia However, paradoxically, to stimulate weight loss in either mice or people, physiological leptin levels must be 20 to 30 times higher (Abou Ziki & Mani, 2016). This implies that leptin's primary function is to maintain a healthy weight by preventing weight loss. Most people with typical obesity have high leptin levels, except for rare individuals who have homozygote mutations in the leptin gene. Since obesity and metabolic syndrome are complicated features brought on by a mix of genes and gene-environment interaction, genetic association study have been the main method utilized to find the disease-causing genes (Laakso, 2004).

- **Non genetic causes of metabolic syndrome:**

In experimental research on mice fed diets rich in sucrose or fructose, hyperinsulinemia has been linked to the other symptoms of the syndrome in people. Supporting the function of hyperinsulinemia in the development of metabolic syndrome, which includes the emergence of high levels of triglycerides, hypertension, hypertriglyceridemia, and decreased high-density lipoprotein. Significant associations between insulin and the other variables were still apparent after accounting for baseline obesity, fat distribution, and weight growth (Farooqi et al., 2003). The underlying MetS causes discussed in text are summarized in Fig. 3.

3.6. In vitro *and* in vivo *models for MetS*

A primary therapeutic method for metabolic diseases has been to identify and treat each symptom or disorder separately. This leads to several drugs being advised to patients with MetS. To investigate these drugs to be effective in the management of MetS several *in vitro* assays could be applied. In this context, angiotensin-converting (ACI) and renin (RI) enzyme inhibitors are routinely used to treat hypertension caused by metabolic disorders. ACI and RI are not only lower blood pressure but can also slow the course of heart and kidney damage in diabetics (Lillich et al., 2021). Anti-diabetic agents including α-glucosidase and α-amylase inhibitors are effective in lowering blood glucose (BG) and hemoglobin A1c (HbA1c) levels (Bianchi et al., 2007). Obesity could be treated with gastrointestinal lipase inhibitors (Bianchi et al., 2007).

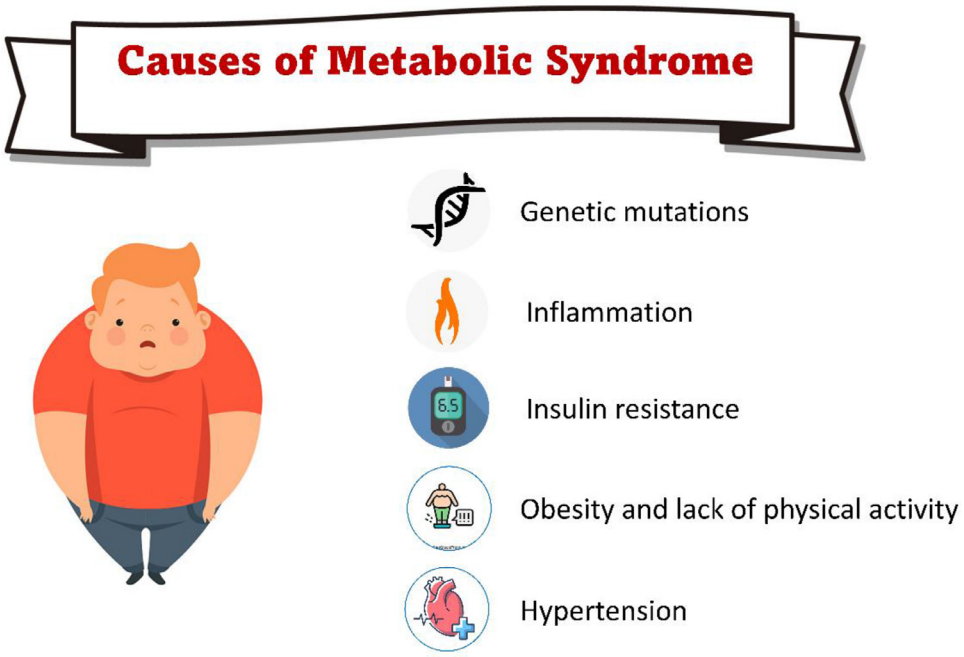


Fig. 3. Causes of metabolic syndrome (MetS).

Anti-inflammatory agents will have the capacity to influence the multiple factors as blood pressure, lipid and triglyceride levels, and insulin signaling in MetS, type 2 diabetes and nonalcoholic fatty liver. So, testing anti-inflammatory *in vitro* using enzyme inhibition assays (Hotamisligil, 2006; Lillich et al., 2021).

Several animal models could be used to induce MetS and its complications including obesity, insulin resistance, inflammation, oxidative stress, and dyslipidemia (Ren & Xu, 2015). Different experimental models could be used as male mice or rats were fed with atherogenic diet or chronic high fat diet feeding in different composition (40, 58, 60%) for 8 to 20 weeks (He et al., 2012; Sciarretta et al., 2012; Xu et al., 2013). For example, mice were fed a 45% high fat diet for 20 weeks to induce metabolic syndrome, as shown by obesity, glucose intolerance, dyslipidemia, and insulin resistance. Additionally, 60% high fructose diet-induced insulin resistance, and sometimes STZ-induced diabetes mellitus (DM) could be employed in the laboratory setting with a high fat diet to induce murine model of MetS (Xu et al., 2013). Where, the different findings in MetS murine animal model could be attributed to the differences in diet composition, time course of diet feeding, animal gender and age (Ren & Xu, 2015).

To clarify the incidence of MetS and understand the underling pathophysiology of it, several *in vitro* and *in vivo* models were used**.** The data were summarized in Supplementary file (**Tables S1&S2)**.

3.7. Diagnosis of MetS

The International Diabetes Federation (IDF) recommend is against diagnosing MetS in children younger than 10 years old. If a child owns at least three of the risk factors for MetS-a high waist circumference, high blood pressure, insulin resistance, and dyslipidemia they are said to be at least 15 years old (Yuan et al., 2019). The IDF recommended applying the same criteria for the MetS diagnosis to teenagers older than 15 years old, as shown in in Supplementary file (**Table S3)**. Besides, MetS was found to induce several histopathological and morphometric alterations that were confirmed in different *in vivo* modules; including extensive fibrosis as well as steatohepatitis in the liver of male C57BL/6J mice when feed on a high saturated fat diet (HF) for 9.5 months as a model of metabolic syndrome (DeLeve et al., 2008). Moreover, deposition of lipid vacuoles, inflammatory cell infiltration and fibrosis were detected after administration of HF diet in male rats for 8 weeks as well as a damage of intestinal microvilli and crypts (Lasker et al., 2019). Several biochemical measures and biomarkers **(**Fig. 4**)** could be used in the diagnosis of MetS, where these markers provide a useful and predictable to allow the diagnosis of MetS in the majority cases (Taskinen, 1993).

3.8. Management of metabolic syndrome (MetS)

3.8.1. Dietary patterns

- **Energy-restricted diets**

Dietary treatments for preventing obesity and its associated comorbidities that most frequently used are energy restriction diets. They consist of individualized diet plans that provide lesser calories than the total amount of energy consumed by a particular person (de la Iglesia et al., 2016). A hypocaloric diet causes a negative energy balance, which leads to a loss of body weight (de la Iglesia et al., 2016). As a result of the lipolysis procedure required to deliver energy substrate, fat is mobilized from various bodily compartments to reduce body weight.

- **Omega-3 fatty acids enriched diets**

Human physiology depends on the omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish, algae, and fatty fish are their main nutritional sources, but humans can also make them from α-linolenic acid (Fleming & Kris-Etherton, 2014). These positive effects are believed to be primarily caused by these essential fatty acids' capacity to lower levels of plasma TG (Lopez-Huertas, 2012). The pro-inflammatory cytokines IL-6 and tumor necrosis factor-alpha (TNF), as well as plasma C-reactive protein (CRP), have also been associated to decreased plasma levels in people who consume more n-3 PUFA (Maiorino et al., 2016).

- **Moderate-high protein diets**

Improvement in glucose homeostasis (Heer & Egert, 2015), potential reduction in blood cholesterol levels (Layman et al., 2009), lowering of blood pressure (Pedersen et al., 2013), maintenance of lean body mass or decreased risk of cardiometabolic disease (Daly et al., 2014).

- **High meal frequency pattern**

Professionals are currently using the pattern of progressively more frequent meals in weight loss and weight control therapies

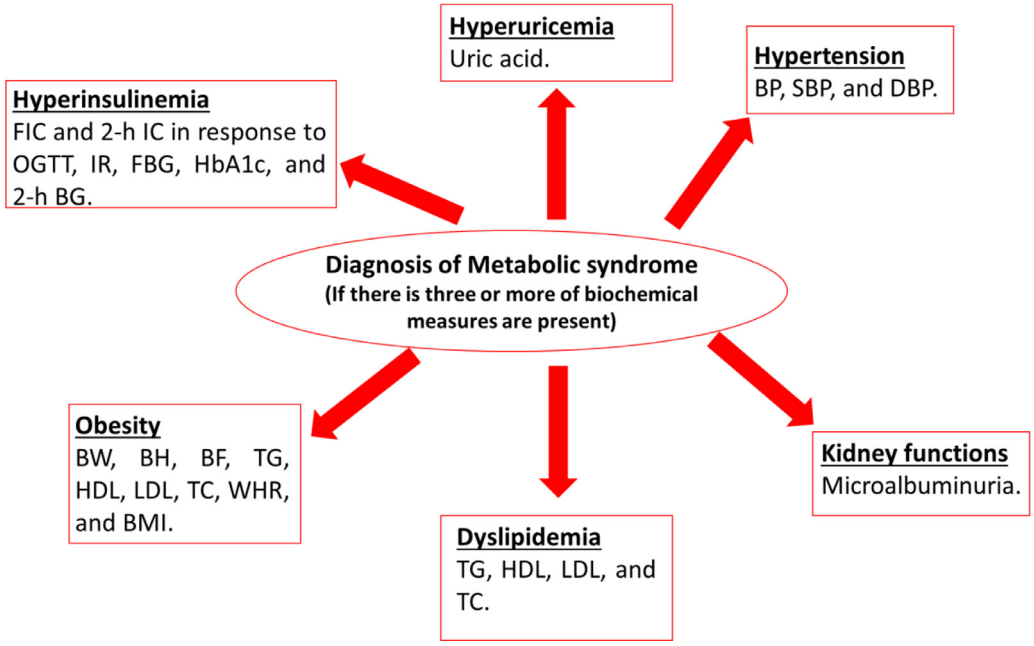


Fig. 4. Diagnosis of metabolic syndrome. BW; body weight, BH; body height, BF; body fats, HbA1C; hemoglobin A1C, HDL; high density lipoprotein, LDL; low density lipoprotein, TC; total cholesterol, WHR; waist: hip ratio, BMI: body mass index, BP; blood pressure, DBP; diastolic blood pressure, FIC; Fasting insulin concentration, 2-h IC; 2 hours insulin concentration after OGTT; oral glucose tolerance test, FBG; fasting blood glucose, IR; insulin resistance test, 2-h BG; 2 hours blood glucose after meals, SBP; systolic blood pressure, TG; triglycerides.

(Schwarz et al., 2011). The goal is to break up the overall number of daily calories into smaller, more frequent meals.

3.8.2. Single nutrients and bioactive compounds

- **Ascorbate**

Since humans cannot generate vitamin C, also known as ascorbic acid or ascorbate, it is a necessary nutrient. It is a water-soluble antioxidant that is mostly present in plants (pepper, kale), citrus fruits (lemon, orange), and fruits (Juraschek et al., 2012). This vitamin has been linked to several positive effects, including anti-inflammatory and antioxidant characteristics, as well as the prevention or treatment of CVD and type 2 diabetes (Michels & Frei, 2013).

- **Hydroxytyrosol**

A phenolic substance called hydroxytyrosol (3,4-dihydroxyphenylethanol) is mostly present in olives (Frei et al., 2012). It is regarded as one among nature's most important antioxidants and the olive oil's strongest antioxidant (Vilaplana-Perez et al., 2014). Hydroxytyrosol has the capacity to prevent macrophage oxidation of low-density lipoprotein-cholesterol (LDL-C) (Bulotta et al., 2014). This phenolic molecule is also thought to have cardiovascular protective properties. By decreasing the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) (Giordano et al., 2015), it has anti-atherogenic effects.

- **Quercetin**

The main flavanol obviously found in vegetables, red wine, green tea, and fruits is quercetin (Nabavi et al., 2015). Quercetin has been linked to numerous advantageous outcomes that may help with MS improvement. Among them, its antioxidant ability needs to be emphasized because it has been shown to reduce lipid peroxidation and boost

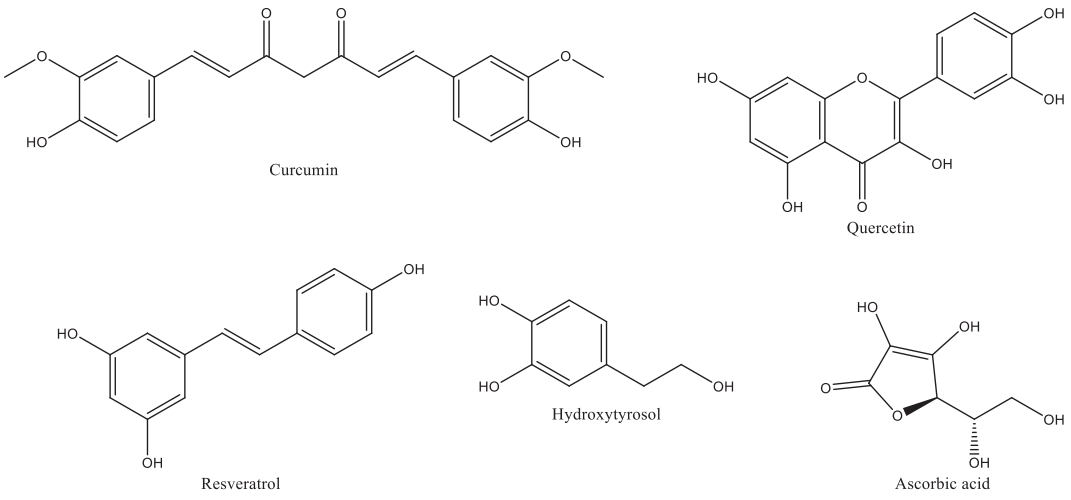


Fig. 5. Structures of compounds used in the management of metabolic syndrome (MetS).

Table 1
Natural approaches in metabolic syndrome treatment

Plant	Scientific name	Dose	Active principle	Therapeutic effects	Reference
Aloe vera	*Aloe barbadensis* Miller	- Extract of *A. vera* (32 mg/kg) - Leaf pulp from *A. vera* (500 mg/kg) - Gel of *A. vera* (10 ml/kg)	Anthraquinones (chromone, barbaloin, aloeemodin-9-anthrone, lsobarbaloin, and anthrone-C-glycosides). Saponins. Vitamins. Minerals. Enzymes (peroxidases, lipases, alkaline phosphatases, cellulases, catalases, and amylases).	↑IS; ↓G; ↓LDL; ↓TG.	(Shakib et al., 2019)
Avocado	*Persea americana*	- Avocado fruit (300 mg/kg, taken orally for 8 weeks). - Avocado seed (300 and 600 mg/kg). - Avocado oil (4 mL/kg for 3 months). - Avocado leaves extract (10 mg/kg, for 8 weeks).	Fatty acids, minerals, phenolics, vitamins, and carotenoids.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Tabeshpour, Razavi, et al., 2017)
Barberry	*Berberis vulguris*	-Fruits (30 mg/kg/day for six weeks).	Isoquinoline alkaloids (berberine, acanthine, bargustanine, berbamine, berlambine, and palmatine). Aesculetin. Ascorbic acid. Caffeic acid. Pectin. Tannins.	↓BP; ↓LDL; ↓TG.	(Tabeshpour, Imen-shahidi, et al., 2017)
Bitter melon	*Momordica charantia*	-A drink of freshly prepared bitter melon fruit.	Alkaloids, steroidal saponins known as charantins, peptides that resemble insulin, and triterpenoids of the cucurbitane type.	↑IS; ↓G; ↓LDL; ↓TG.	(Chaturvedi, 2005; Fernandes et al., 2007; Leung et al., 2009)
Cinnamon	*Cinnamomum cassia-Cinnamomum verum*	-Bark (1.5 – 6 g/day).	Polyphenol type-A polymers.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Anderson et al., 2009; Crawford, 2009; Qin et al., 2010)
Curcumin	*Curcuma longa* (Turmeric plant)	- Rhizomes (1 g/kg body weight).	Phenolics. Terpenoids. Curcuminoids including curcumin, demethoxy curcumin and bisdemethoxy curcumin.	↓BP; ↓LDL; ↓TG.	(Bulboacă et al., 2016)
Drumstick	*Moringa oleifera*	100 - 200 mg/kg.	Vitamins, minerals, carotenoids, n-benzyl thiocarbamate, glucomoringin, kaempferol, niazinin, and niazimicin.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Khan et al., 2017)
Fenugreek	*Trigonella foenum-graecum*	10 – 20 g/day.	High neutral and soluble fiber content. Seeds also contain alkaloid namely trigonelline, and steroidal saponins.	↑IS; ↓G; ↓LDL; ↓TG. The fibers; which slows gastric emptying, thus decreasing post-prandial blood glucose levels. Trigonelline, potentially reduces glycosuria.	(Srinivasan et al., 2018), (Kassaian et al., 2009)
Garlic	*Allium sativum*	- Garlic extract (5 and 10 ml/kg, po). - Garlic powder (15 mg/kg, for three weeks). -Garlic oil (100 mg/kg).	Allicin, allylcysteine, ethylcysteine, and propylcysteine.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Hosseini & Hosseinzadeh, 2015)
Ginger	*Zingiber officinale*	-Ginger ethanolic extract (800 mg/kg). -Ginger ethanolic extract (400 mg/kg).	Terpenes. Oleoresin, also known as ginger oil. Oils that are volatile range from 1% to 3%. Pungent non-volatile components oleoresin.	↓G; ↓LDL; ↓TG.	(Rahmani & Aly, 2014), (Li et al., 2012)
Argel	*Solenostemma argel*	Ethanolic extract and its fractions; dichloromethane and *n*-butanol.	Pregnane glycoside (Stemmoside C)	↓G; ↓LDL; ↓TG.	(El-Shiekh et al., 2019a) (El-Shiekh et al., 2019b)
Ginkgo	*Ginkgo biloba (G. biloba)*	500 mg/kg.	Biflavonoids, flavonoids, terpenoids, polyphenols, and organic acids. Ginkgolides.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Eisvand et al., 2020)
Grape seed	*Vitis vinifera* L. (Vitaceae)	150 and 300 mg/day.	Procyanidins make up about 90% of the polyphenols, with the remaining 7% being various polyphenol chemicals.	↓BP; ↓LDL.	(Peng et al., 2005), (Quesada et al., 2009)
Hawthorn	*Crataegus laevigata, Crataegus monogyna, Crataegus curvisepala (Crataegus oxyacantha) and Crataegus tanacetifolia.*	1200 mg of hawthorn extract per day.	Polyphenols, mainly flavonoids and procyanidins.	↓BP; ↓LDL	(Guo et al., 2008), (Tadić et al., 2008), (Kocyildiz et al., 2006)

(*continued on next page*)

Table 1 (*continued*)

Plant	Scientific name	Dose	Active principle	Therapeutic effects	Reference
Hazelnut	*Corylus avellena* L	3 g/kg of the extract.	oleic Acid, Palmitoleic Acid, Thiamine and Linoleic Acid.	↓G; ↓LDL; ↓TG	(Mercanligil et al., 2007), (Di Renzo et al., 2019), (Jenkins et al., 2011)
Hoodia	*Hoodia gordonii*	-	A steroidal pregnane glycoside.	↓W	(MacLean & Luo, 2004), (Shukla et al., 2009), (Graf et al., 2010)
Hot pepper	*Capsicum annuum*	250 μg: 1 g of food	Capsaicin, Dihydrocapsaicin and Nordihydrocapsaicin.	↑IS; ↓G; ↓LDL; ↓TG.	(Marrelli et al., 2016), (Zheng et al., 2017), (Villarroya et al., 2017)
Rosella	*Hibiscus Sabdariffa*	500 and 1000 mg/kg of HSE extract for 6 weeks.	Polyphenols, flavonoids (including anthocyanins, delphinidin, hibiscetin, quercetin and gossypetin, protocatechuic acid, alkaloids, L-ascorbic acid, carotenoids, anisaldehyde, galactose, mucopolysaccharides, pectins, polysaccharides, and stearic acid.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Perez-Torres et al., 2013)
Lowbush blueberry	*Vaccinium angustifolium* Aiton	Daily portions consisted of 100 g of whole bilberries and the nectar of 50 g of crushed lingonberries every other day, with a puree of 100 g of blackcurrants or strawberries and 0.7 dl of chokeberry or raspberry juice on alternating days.	Polyphenols, which have a high antioxidant capacity, exceeding that of vitamin C or E by 4- to 5-folds.	↓BP; ↓G; ↓W	(Shaughnessy et al., 2009), (Kalea et al., 2010), (Kalea et al., 2009)
Mango	*Mangifera indica*	25 – 500 mg/kg of body weight / day for a period of 30 days.	Mangiferin	↓LDL; ↓TG.	(Fomenko & Chi, 2016)
Mangosteen pericarp	*Garcinia mangostana*	50 mg/kg α-mangostin or 200 mg/kg peel extract that contains 25.7% α-mangostin.	Xanthones as gartanin, α- and γ-mangostin.	↑IS; ↓G; ↓LDL; ↓TG.	(Tousian Shandiz et al., 2017)
Olive	*Olea europaea* Linn.	51 mg/day	Oleuropein.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Katagiri et al., 2007)
Onion	*Allium cepa*	900 mg/day for 12 weeks.	Flavonoids, phenolic acids, organosulfur compounds, anthocyanins, quercetin glycosides, S-methlycysteine sulfoxide and S-allylcysteinesulpoxide.	↑IS; ↓G; ↓TG.	(Jakobs et al., 2006), (Srinivasan et al., 2018)
Oregano	*Origanum vulgare* L.	600 mg/day for six weeks.	Carvacrol, Thymol, Quercetin, Luteolin, Rosmarinic acid, Diosmetin, Biochanin A, Naringenin and Apigenin.	↓G; ↓LDL; ↓TG.	(Bagetta et al., 2020), (Cho et al., 2012), (Valentová et al., 2007)
Red clover	*Trifolium pratense* L.	308, 615, and 1.538 mg/kg.	Isoflavones biochanin A, genistein, daidzein, and formononetin.	↑IS; ↓G; ↓LDL; ↓TG.	(Mueller & Jungbauer, 2008)
Rosemary	*Rosmarinus officinalis* L.	200 mg / kg.	Polyphenols.	↑IS; ↓G; ↓BP; ↓LDL; ↓TG.	(Hassani et al., 2016)
Russian tarragon	*Artemisia dracunculus*	6 g/day.	4,5-Di-*O*-caffeolquinic acid, davidigenin, 6-demethoxy-capillarison and 2′,4′-dihydroxy-4-methoxydihydrochalcone.	↑IS; ↓G.	(Ribnicky et al., 2006), (Logendra et al., 2006)
Saffron	*Crocus sativus* L.	50 mg/ kg.	Crocin (crocetinglycoside), crocetin and safranal.	↑IS; ↓G; ↓BP; ↓LDL.	(Razavi & Hosseinzadeh, 2017)
Silymarin	*Silybum marianum (milk thistle)*	25 mg/kg/day.	Flavonolignans (70–80%) containing silibinin, isosilybin, silychristin, and silydianin.	↓BP; ↓G; ↓W.	(Tajmohammadi et al., 2018)

BP; blood pressure, G; blood glucose, IS; insulin sensitivity, LDL; low density lipoprotein, TG; triglycerides, W; body weight.

antioxidant enzymes containing glutathione peroxidase (GPX), catalase, and superoxide dismutase (SOD) (Vinayagam & Xu, 2015).

Additionally, TNF-α, NF-κB, and mitogen-activated protein kinases (MAPK), as well as decreased expression of IL-6, IL-1, IL-8, or monocyte chemoattractant protein-1 (MCP-1), have all been connected to this polyphenol's anti-inflammatory effects (Cheng et al., 2019; Chuang et al., 2010; Yahfoufi et al., 2018).

- **Resveratrol**

Red grapes and their derivatives, such as red wine and grape juice, are the main source of the phenolic chemical resveratrol (3,5,4′-trihidroxiestilben). It has demonstrated anti-inflammatory, antioxidant, and cardioprotective properties, plus anti-obesity, anti-diabetic, and anti-obesity capacities (Leonard et al., 2003). According to reports, resveratrol's antioxidant benefits work via scavenging radicals caused by metals, superoxide, and hydroxyl ions as well as by antioxidant actions in cells that produce reactive oxygen species (ROS) (de la Iglesia et al., 2016).

The structures of compounds used in the management of MetS are shown in Fig. 5.

3.8.3. Natural approaches in metabolic syndrome treatment

A multi-drug treatment or polypharmacy is a major difficulty for the treatment of patients with MetS because of poor patient compliance, drug-drug interactions, and side effects including anti-hypertensive, anti-diabetic, and lipid lowering agents, as well as heart failure, and anti-obesity drugs. Reduction of LDL-C and inhibition of intestinal cholesterol absorption are common treatments for patients with MetS (Grundy, 2006). For example, blueberry anthocyanins, and polyphenols that reduce plasma ghrelin concentrations and enhance blood glucose tolerance could be used in the management of MetS (Rebello et al., 2015). Also, ginseng that aid in lowering the choles-



Fig. 6. Natural products used in the management of metabolic syndrome (MetS).

terol and LDL-C by inhibition of β-hydroxy-β-methylglutaryl-CoA reductase (Sotaniemi et al., 1995). Bergamot juice has significant effects on metabolic markers, as atherogenic lipoproteins, subclinical atherosclerosis, and plasma lipids (Toth et al., 2016). Mulberry leaf extract has impact on MetS by decreasing postprandial glucose, triglycerides, LDL-C and increasing HDL-C (Kojima et al., 2010). Natural products and different phytoconstituents used for the management of metabolic syndrome were summarized in Table 1 and are concise in Fig. 6.

4. Conclusions

The MetS, one of the main health hazards of the modern era, is characterized by the presence of many dysmetabolic events, such as Diabetes mellitus type 2 (T2DM), obesity, hypertension, dyslipidemia, and cardiovascular problems. In reality, because of the spread of the Western way of life over the world, even the MetS, which first originated in the West, is now a global issue. Once diagnosed, it is extremely important to respond promptly through the adoption of a healthier lifestyle and pharmacological interventions. Given that natural compounds have been used extensively and successfully for medical and health purposes throughout the course of human evolution, we have concentrated our attention in this review on natural bioactive components derived from plant extracts, spices, herbs, and essential oils that have shown promise in the treatment of patients with MetS. The introduction of such dietary supplements may constitute a therapeutic option with significant promise for the management of MetS and prevention of the start of several complicated multifactorial diseases, including cardiovascular diseases, diabetes, obesity, and cancer.

4.1. Future research directions

First, the pharmaceutical strategy necessitates the use of medications that can individually target each dysmetabolic process, such as statins, ACE inhibitors or angiotensin receptor blockers, ezetimibe, metformin. So, the identification of bioactive molecules interacting with many targets is a helpful strategy for improving patient compliance and boosting medication effectiveness. Second, the effects of metabolic syndrome on the thyroid and heart functions and to investigate efficient approach to manage those complications should be investigated.

Author Contributions

Salma Mostafa Mohamed, Riham A. El-Shiekh, and Alaa F. Bakr; collected the data and wrote the paper draft. Shimaa Ramadan Emam, Mostafa Abbas Shalaby, and Hossni A. El-Banna; corrected the draft. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analyzed during this study are included in this published article.

Supplementary materials

Supplementary Information: See supplementary file (Tables S1-S3).

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.focha.2023.100335.

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