Understanding the prevalence, progression, and management of metabolic syndrome in Saudi Arabia

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ABSTRACT

متلازمة التمثيل الغذائي (ميتس) لها العديد من الاضطرابات التي تشمل ارتفاع ضغط الدم ، والسمنة البطنية ، وحساسية الأنسولين ، وخلل شحميات الدم. في الآونة الأخيرة ، اكتسبت MetS اهتمامًا متزايدًا بسبب الانتشار العالمي للسمنة. تلعب الأنسجة الدهنية دورًا مهمًا في هذه المتلازمة من خلال إطلاق جزيئات مختلفة تؤثر بشكل كبير على تنظيم الدهون / الأنسولين والإجهاد التأكسدي ووظيفة القلب والأوعية الدموية. يعتبر عامل نخر الورم α (p–α)، وهو السيتوكين الالتهابي ، والأديبونكتين ، وهو بروتين خاص بالأنسجة الدهنية ، من الأديبوكينات الحيوية التي تلعب دورًا مهمًا في التسبب في مرض ميتس. تمت دراسة تأثير المكونات الغذائية على إدارة MetS على نطاق واسع خلال العقود القليلة الماضية. أظهرت هذه المواد الكيميائية الطبيعية المشتقة من النباتات آثارًا مفيدة على السمنة والسكري وأمراض القلب والأوعية الدموية بسبب خصائصها المتنوعة. تنتشر في المملكة العربية السعودية زيادة الوزن ومرض السكري بشكل كبير ، ولكن كانت هناك أبحاث محدودة حول حدوث ميتس في المملكة العربية السعودية. نتيجة لذلك ، في هذه المراجعة ، قمنا بتقييم انتشار MetS في المملكة العربية السعودية وعوامل الخطر المرتبطة بها ، وكذلك استكشاف آليات تطور MetS ودور المواد الكيميائية النباتية الطبيعية في الوقاية من MetS.

Metabolic syndrome (MetS) is characterized by the coexistence of several disorders comprising hypertension, abdominal obesity, insulin sensitivity, and dyslipidemia. In recent times, MetS has gained increased attention due to the global prevalence of obesity. Adipose tissue plays a crucial role in this syndrome by releasing various molecules significantly affecting lipid/insulin regulation, oxidative stress, and cardiovascular function. Tumor necrosis factor-α (p-α), an inflammatory cytokine, and adiponectin, an adipose tissue-specific protein, are considered vital adipokines that play a significant role in the pathogenesis of MetS. The impact of dietary ingredients on MetS management has been extensively studied over the past few decades. These plant-derived natural chemicals have demonstrated beneficial impacts on obesity, diabetes, and cardiovascular disease (CVD) due to their diverse properties. Saudi Arabia has a high prevalence of overweight and diabetes, but there has been limited research on the incidence of MetS in the country. As a result, in this review, we evaluated the prevalence of MetS in Saudi Arabia and its associated risk factors, as well as explored the mechanisms of progression of MetS and the role of natural phytochemicals in the prevention of MetS.

Keywords: metabolic syndrome (MetS), hypertension, insulin resistance, diabetes, obesity, phytochemicals

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Metabolic syndrome (MetS) is a complex metabolic condition characterized by elevated insulin readings, obesity, high blood pressure, and abnormal triglyceride concentrations, all of which increase the risk of developing coronary artery disease (CAD). In 1988, Gerald Reaven first described Syndrome X, which is currently recognized as MS.[1] In addition, other metabolic irregularities, such as microalbuminuria, disturbance in fibrinolysis, and coagulation concerns, have also been associated with this disorder.[2,3] Among the several terms used to describe this syndrome, including MetS, plurimetabolic syndrome, and the deadly quartet, "insulin resistance syndrome" is the most frequently employed term, suggesting that insulin tolerance is a crucial feature underlying this disorder.[4,5] It encompasses a set of potential indicators associated with heart disease and diabetes (Figure 1). Individuals affected by this disorder seem to be susceptible to diabetes, coronary heart disease, and premature mortality.[6]

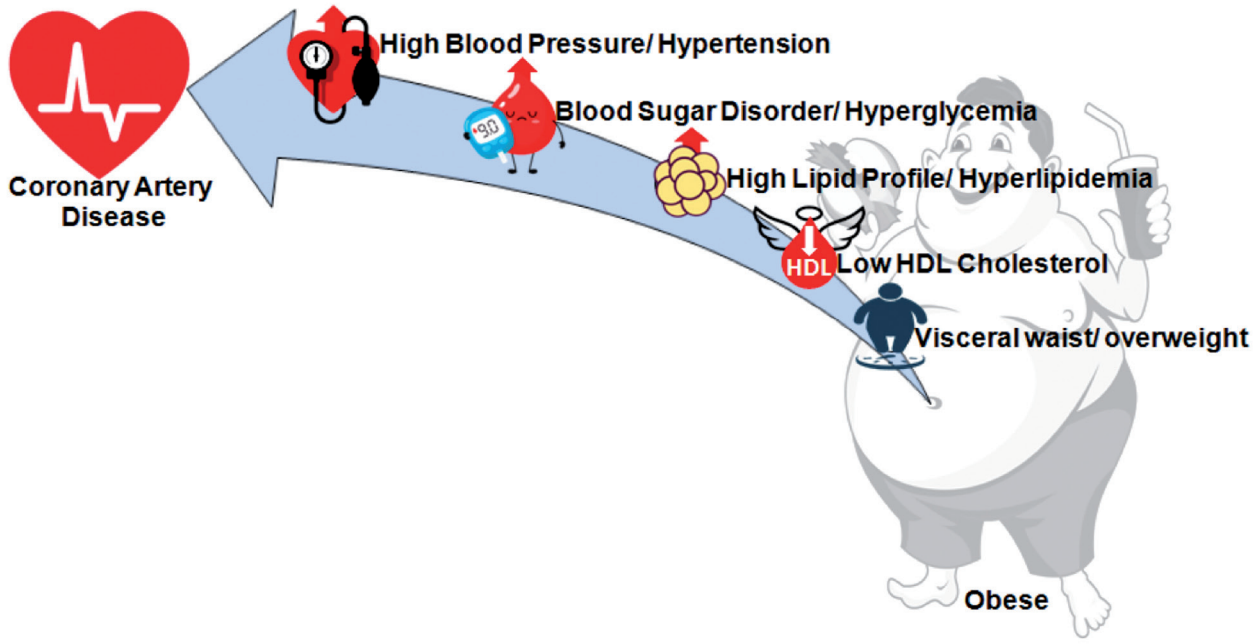

Figure 1 - Overview of metabolic syndrome.

Metabolic syndrome also increases the likelihood of contracting related conditions, such as cancer, renal disease, and psychiatric disorders.[7,8]

The initial widely renowned functional concept for MetS was suggested during a meeting held by the World Health Organization (WHO) around 1988, and several initiatives have been made thereafter to establish a standardized terminology for this condition. A commonly used description of MetS involves the presence of at least 3 of the primary clinical symptoms, namely central obesity, increased fasting blood sugar (FBS) levels, hypertension (high blood pressure, [BP]), increased blood cholesterol levels, and elevated triglyceride levels.[9]

Metabolic syndrome affects approximately one-quarter of the population in many developed nations.[10] While the exact pathogenesis is not fully understood, numerous risk factors have been identified.[11] The prevalence of MetS generally increases with age and shows a gender-specific pattern, primarily affecting males.[11,12] It is indeed strongly and disproportionately linked to a sedentary lifestyle and lack of physical activity. Furthermore, researchers have uncovered a connection between MetS and smoking.[14] The consumption of tobacco has been associated with the development of insulin resistance, aligning with other research findings, as smoking hinders insulin activity and stimulates insulin resistance.[15,16] Therefore, the global incidence of MetS is on the rise. Thus, it is crucial to implement important guidelines and assertive promotional efforts to effectively handle and mitigate the consequences of MetS.

In the present review, our focus encompasses several key aspects related to MetS in Saudi Arabia. We aim to explore the prevalent occurrence of MetS in the country, along with associated risk factors. Additionally, we aim to investigate the mechanisms involved in the progression of MetS. Another important aspect of this review is to examine the potential role of natural phytochemicals in the prevention of MetS. We have taken into account all the components of MetS, such as, central obesity, higher FBS levels, hypertension, and increased blood cholesterol and triglyceride levels, to assess the incidence rate of MetS among Saudi adults. However, we acknowledge that the specific reasons behind the higher incidence of MetS in males compared to females and elderly people have been excluded from this study. To gather relevant information, we utilized

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multiple search engines, including Google search engine, PubMed, science.gov, and Google Scholar. Only refereed or scholarly journals were considered in the selection of articles for this study.

Epidemiology and risk factors of MetS in the Saudi population. Recent findings indicate that a substantial proportion of people seem to be obese. There is a growing concern regarding weight issues in the Arab community, with women being grossly overweight compared to men. Excessive weight has emerged as an epidemic and is acknowledged as a predictive marker for various diet-related diseases, such as MetS, type II diabetes mellitus, hypertension, cerebrovascular disease, and different types of cancer.[17] Besides, abdominal and central obesity are among the principal clinical indicators of MetS. Considering the increasing likelihood and challenges related to MetS, it is important to have a comprehensive awareness of potential confounders to implement basic and accompanying preventive strategies.[18]

Numerous analyses have consistently demonstrated that MetS serves as a significant predictor for the occurrence of CAD.[19,20] Consequently, it is essential to figure out its epidemiology in Saudi Arabia (Figure 2), especially in light of recent evidence suggesting a 5.5% prevalence of CAD in the country.[21] The expanding ratio of MetS is indeed emphasized with the International Diabetes Federation (IDF) reporting that approximately one-quarter of the world's population has developed MetS.[21,22] Metabolic syndrome has been reported to have a prevalence of 12% in the population of the United Arab Emirates (UAE).[23] In Gulf Cooperation Council (GCC) nations, the incidence of MetS spans between 6% and 23.7%.[24] The existing survey suggests that the incidence of MetS in Saudi Arabia is estimated to be 39.8% according to Adult Treatment Panel III (ATP III) standards and 31.6% according to the IDF guidelines (Figure 2).[25]

In a study carries out in 2002, following the guidelines of the World Health Organization, diabetic individuals at King Abdulaziz University Hospital near Jeddah were enrolled as participants. The survey revealed that 56% of the male respondents and 57% of female respondents had MetS. Hypertension was identified as the predominant problem among the participants.[26] According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) concept, research executed over a 5-year period between 1995 and 2000 aimed to include various provinces of Saudi Arabia. The study observed a MetS incidence of around 40% among individuals aged 30-70. Notably,

Figure 2 - Epidemiology of metabolic syndrome in Saudi Arabia.

reduced high-density lipoprotein (HDL) cholesterol seemed to be the most unifying criterion in this population.[27]

Furthermore, several studies have indicated that the rising frequency of MetS is proportional to aging, approaching 47.4% among men and 61.8% among women in the age cohort of 60 to 70 years. This aligns with the growing incidence of CAD observed in older individuals. Moreover, it is expected that the incidence of MetS will continue to rise in the coming decades due to the significant increase in overweight cases among Saudi adults. Similar trends have been observed in the United States, where statistics revealed a 23.5% increase in age-adjusted occurrence among females and a 2.2% increase among males between 1994 and 2000.[28] The risk factors linked to MetS extend beyond CAD, diabetes, and high blood pressure; instead, various studies observed a connection between MetS and related diseases, such as fatty liver, polycystic ovarian syndrome, sleep-disordered breathing, and severe kidney diseases.[29]

Using the equivalent criteria, several minor investigations conducted in the urban areas of Saudi Arabia revealed an incidence rate of 31.4%, specifically among men,11 and a rate of 35.3% among the entire population.[10] A similar study carried out in Jeddah, province of the western region, comprising healthy National Guard employees and their families, used the same criteria and reported a MetS occurrence of 21%.[30] Notably, reduced HDL cholesterol levels were recognized as one of the most prevalent factors in these trials.

The composition of the individual's diet is a significant determinant in the progression of MetS. Diets that are low in monounsaturated fats and high in carbohydrates have been criticized as they may lead to an increase in triglyceride concentrations and a decrease in HDL cholesterol levels, worsening dyslipidemia associated with MetS.[31] Furthermore, dyslipidemia observed in residents may indeed be linked to insulin resistance and an increased incidence of diabetes mellitus (DM), which has been mentioned to affect approximately 25% of the Saudi population in recent studies.[32] Despite the established connection between obesity and a higher incidence of MetS, studies have revealed that even among adults with average body mass, there is a noteworthy overall incidence of MetS, reaching 21.4%.

Meanwhile, Al-Qurashi et al[33] investigated age-related variations in heart rates among Saudi children and adults. Finding that heart rate variability (HRV) was substantially reduced in obese Saudi male university students compared to their counterparts with average body weight.[34] Besides, studies have shown that short-period high-intensity interval training, as opposed to moderate-intensity continuous training, can have an impact on HRV in physically inactive people.[35] Alkahtani et al[36] investigated the impact of different kinds and intensities of moderate cardiovascular strength training on HRV in Arab men.

Research suggests that engaging in regular physical activity, such as walking more than 150 km per month or biking over 100 km per month at speed exceeding 20 km/h, may provide cardiac autonomic benefits through strength training, particularly among Arab males. However, Alassiri et al[37] found that placing smartphones in a shirt pocket had negative effects on HRV in both normal-weight and obese medical graduates. The study also showed that smartphone placement magnified the impact of adiposity on sympathetic stimulation. Furthermore, prolonged use of dipping tobacco was not found to be related to irreversible abnormalities in heartbeat and hypertension, as indicated through a case analysis of 101 adult men; however, it induced a rapid, irregular heartbeat.[38] Among younger individuals, the consumption of chocolates had also not been associated with fluctuations in cardiac rhythm.[39]

A comprehensive study performed on a national community group of 53,370 participants in Saudi Arabia has revealed that impaired glucose metabolism has reached pandemic percentages in the country. Nearly one-third of the inhabitants were observed to be influenced by the impairment, while an alarming 50% of individuals were uncertain on their disease status.[40] Importantly, pre-diabetes in Saudi youth is associated with several factors, such as dyslipidemia, a relatively low overall antioxidative state, obesity, and physical inactivity compared to those with normoglycemia.[41] A recent study has revealed that the prevalence of uncontrolled FBS is higher among Saudi people with diabetes, with risk variables including older age, male gender, high BP, smoking, and overweight. In addition, unregulated hyperglycemia has been associated with dyslipidemia.[42]

Pathways leading to MetS. Being overweight has reached pandemic proportions globally, affecting both developed and underdeveloped nations, mainly attributed to factors like the consumption of fast food, unhealthy lifestyles, and socioeconomic situations. Individuals with MetS may have a genetic predisposition towards obesity and exhibit pro-inflammatory responses. Adipose tissues release countless autoimmune components (adipokines) into the bloodstream, including tumor necrosis factor-α (TNF-α), leptin, adiponectin, resistin, monocyte

chemoattractant protein-1, adipocyte-type fatty acid binding protein, and so on. Metabolic syndrome is strongly related to oxidative stress and inflammation, with TNF-α overexpression in adipose tissue being linked to obesity-related insulin resistance, as reported by Hotamisligil et al.[41]

The identification of the immunological properties of adipocytes has contributed to a better pharmacological understanding of the development of MetS. Specifically, adipokines secreted from the abdominal adipose tissue have been associated with both MetS and cardiovascular disease (CVD).[43] Adiponectin, an anti-inflammatory and anti-atherogenic adipokine, possesses properties that reduce cardiovascular responses and the proliferation of smooth muscle cells.[44] It has been identified as a preventive element against the progression of hyperglycemia, high BP, and severe myocardial infarction.[45] Additionally, adipose tissue produces angiotensin II (Ang II) through the enzymatic conversion of angiotensin, and increased synthesis of Ang II has been correlated with overweight and insulin resistance.[46] Meanwhile, Ang II stimulates nicotinamide adenine dinucleotide phosphate oxidase through the type 1 receptor, contributing to the formation of reactive oxygen species (ROS).[47]

Macrophages present in adipose tissue release TNF-α, and its synthesis increases with the expansion of the volume of adipose tissue. A TNF-α stimulates lipolysis, increases the burden of free fatty acids (FFAs), and suppresses the production of adiponectin by phosphorylating and deactivating insulin receptor sites in adipose tissue and smooth muscle cells.[48] Elevated levels of TNF-α in the blood have been associated with both overweight and insulin intolerance, which are crucial attributes of MetS.[49]

Inflammatory mediators and adherence factors, along with increased NO synthesis, and NF-κB activation, have been implicated in the development of both atherogenesis and endothelial dysfunction.[50] In conjunction with TNF-α concentrations, which trigger the synthesis of interleukin-6 (IL-6) and serve as the main controller of C-reactive protein (CRP) synthesis, CRP concentrations increase in the conditions of obesity, insulin resistance, and CVD, while adiponectin levels decrease.[51] Plasma CRP concentrations were closely connected with concentrations of adhesion factors, contributing to endothelial dysfunction and promoting intimal-medial thickening.[52] CRP boosts LDL absorption and also induces macrophages to secrete cytokines.[53] Both atherosclerosis and diabetes result in an increase in plasma lipids and adhesion molecules, which are released in response to cytokines via NF-κB activation.[54,55]

Numerous studies provide evidence that adipokine-induced NF-κB stimulation contributes to insulin resistance and dysregulated insulin secretion.[56] This process produces cytokines that have considerable effects on β-cell function, as well as glucose and insulin regulation. As previously stated, increased levels of TNF-α are related to insulin sensitivity in both hepatic and muscular tissues.[57] Diabetic individuals often exhibit higher concentrations of TNF-α, IL-6, and CRP.58 Additional NF-κB-induced cytokines include IL-1β and γ-interferon that counteract insulin signaling and suppress glucose-stimulated insulin release.[59] Furthermore, glucose, FFAs, and insulin serve essential functions in the pathogenesis of MetS, notably by triggering the NF-κB system.

The framework illustrated in Figure 3 highlights different potential pathways, implying that the progression of MetS is governed by adipose tissue density and its complex interactions with inflammatory adipokines, predominantly TNF-α, as well as the defensive properties of adiponectin.[60-62] Inflammatory adipokines promote the generation of superoxide (a type of ROS), inflammatory mediators, and adhesion components through NF-κB stimulation, thereby exacerbating pathological mechanisms such as LDL oxidation, dyslipidemia, insulin resistance, glucose intolerance, endothelial dysfunction, and atherogenesis. Further, elevated levels of serum FFAs, glucose, and insulin stimulate NF-κB, which in turn contributes to various mechanisms associated with pathological changes in MetS. In contrast, adiponectin mitigates NF-κB activation, thereby suppressing both oxidative stress and systemic cytokine synthesis.[63] This protective effect of adiponectin helps safeguard against the emergence of long-term complications, including CAD, BP, and type II DM.

Phytochemicals in the management of MetS. Phytochemicals refer to beneficial compounds found in plant-based extracts, spices, herbs, and essential oils, which have been shown to offer preventive health benefits beyond basic nutrients. Numerous active ingredients derived from these sources have demonstrated potential in managing MetS (Table 1). However, it is important to note that while the advantages of these nutritional supplements are being studied, they are not recommended as a substitute for the currently prescribed pharmacological treatments for MetS. Phytochemicals can be classified based on their dietary resources, such as fiber-rich food (fruits, beans, barley, and oats), vitamins with antioxidant properties (vitamin C, vitamin E, and carotenoids), polyphenolic compounds (tea and legumes), and seasonings (clove,

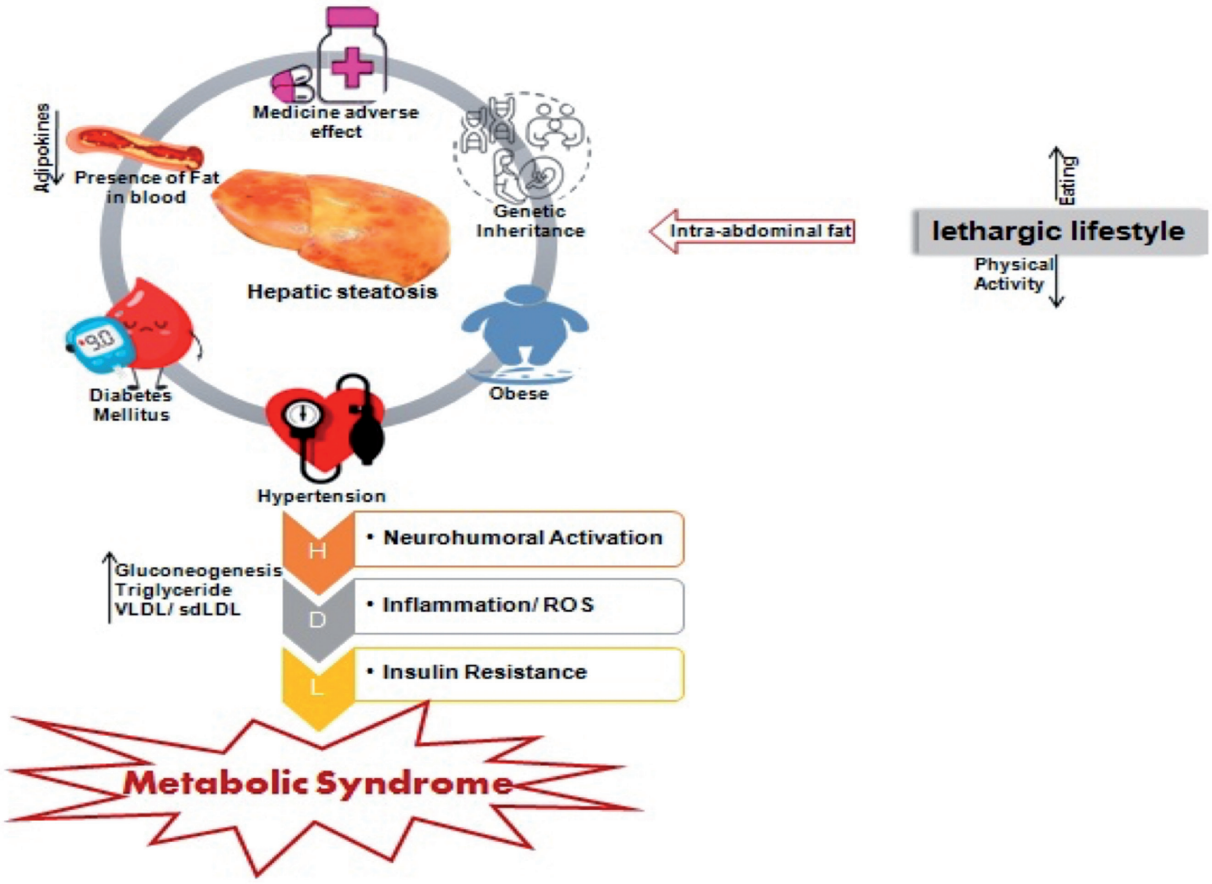

Figure 3 - Mechanisms resulting in the clinical signs of metabolic syndrome.

garlic, and turmeric).[64] In this section, we will discuss the naturopathic remedies that have been investigated thus far and have shown promising results in preventing MetS.

I. Monounsaturated fatty acids (MUFAs). Monounsaturated fatty acids constitute fats that contain single unsaturated carbon in their chain. Dietary MUFAs can be derived from a variety of sources including animal products in westerners' meals and extra virgin olive oil comprising oleic acid in the southern European nations.[65] Additional origins of MUFAs include vegetable oils and nuts including macadamia nuts, hazelnuts, and pecans.[66]

Olive oil against MetS. The latest clinical researches have shown that olive oil can decrease the probability of obesity. After one year of therapy, people who adopted a Mediterranean routine supplemented with excess virgin olive oil and regulated minimal fat meal exhibited a reduced body mass index (BMI) and waist circumference, according to a systematic random assignment study trial.[67] According to an analysis, olive oil intake can minimize the incidence of MetS and central obesity olive oil has phenolic substances that inhibit the breakdown of lipids and carbohydrates (CHO), as well as the assimilation and retention of macronutrients.[68-70] Furthermore, the phenolic components of olive oil, mainly extra virgin olive oil, possess an oxidative action that helps reduce the oxidative load, that is elevated in obese patients.[71]

II. Polyunsaturated fatty acids (PUFAs). Polyunsaturated fatty acids are lipids that have more than 2 unsaturated carbon in their chain and were categorized into 2 categories. First is Blue fish, eggs, flaxseed and walnuts enriched omega-3 fatty acids (alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid) and second is omega-6 fatty acids (linoleic acid, arachidonic acid, and docosapentaenoic acid) primarily found in vegetable oils, nuts and seeds.

Omega fatty acids against MetS. Omega-3 fatty acids (docosahexaenoic acid (DHA]) were obtained mainly from fish (Atlantic mackerel, Atlantic salmon), rice (Oryza sativa), and flaxseed (Linumusitatissimum).

Table 1 - Accessible natural metabolic syndrome remedies.

Origin	Compound	Mechanism	References
Date palm (*Phoenix dactylifera L.*)	Carotenoids and phenolics	Anti-hyperglycemic, antioxidant and anti-inflammatory, inhibited lipid peroxidation, cardioprotective effect	86,88–90,92,93
Olive oil (*Oleaeuropaea L.*)	Oleuropein, hydroxytyrosol and tyrosol	Inhibit lipid and cholesterol breakdown, control obesity, possess oxidative action	68,69,71
Honey (Apismellifera)	Flavonoids, phenolic acids, and phenolic acid derivatives	Anti-obesity effects, reduce cardiovascular risk factors, decline in blood glucose levels	96,98,137
Sorghum (*Sorghum bicolor L.*)	Phenolic compounds, 3-deoxyanthocyanidins 3-DXA & tannins	Anti-hyperglycemic, prevent CVD, anti-cancer and anti-inflammatory, control obesity	99–102
Barley (*Hordeumvulgare*)	Whole Grain (Fiber/Vitamin B)	Improve digestion and appetite, control obesity, blood triglycerides, anti-hyperglycemic	119,120
Turmeric (*Curcuma longa*)	Curcumin	Anti-inflammatory and antioxidant, prevent cancer, reduce heart disease risk, control obesity, anti-hyperglycemic	103–105
Garlic (*Allium sativum*)	Garlicin	Anti-hyperglycemic, antioxidative and anti-platelet, total cholesterol and triglyceride, anti-inflammatory properties	128–130
Cinnamon (*Cinnamomumverum*)	Inner bark (peel)- polyphenols and flavonoids	Anti-hyperglycemic, anti-inflammatory properties, anti-thrombotic, lipid-lowering properties, anti-cancer effects, control BP	106,107
Barberry/Rhizomacoptidis (*Berberis vulgaris*)	Berberine	Anti-hyperglycemic and anti-bacterial, prevent CVD, control lipoproteins and triglycerides levels, control systolic BP, lowering cholesterol level	138–140
Green tea (*Camellia sinensis*)	Catechins, L-theanine, and caffeine	Anti-diabetic and antioxidant, degrade lipoproteins, prevent CVD, anti-obesity and effective on MetS	81–83
Fish (*Atlantic mackerel, Atlantic Salmon*), Rice (*Oryza sativa*), Flaxseed (*Linumusitatissimum*)	Omega-3 fatty acid (Docosahexaenoic acid [DHA])	Effective on MetS, anti-inflammatory and antioxidant, prevent CVD, reduce triglycerides, lower BP	72–74

DXA: deoxyanthocyanidins, CVD: cardio vascular disease, Bp: blood pressure

Numerous demographic investigations have been carried out to examine the preventive impact of omega-3 long-chain PUFA in MetS-related disorders.[72] Polyunsaturated fatty acids have been shown to reduce lipogenesis and promote fatty acid metabolism in adipose tissue and liver by regulating critical signaling molecules such as activated peroxisome proliferator receptors and sterol regulatory element binding protein.[73,74] Although there is a positive influence on different factors related to metabolic syndrome, the long-drawn-out evidence on the treatment of serious cardiovascular consequences using PUFAs has not yet been validated. Furthermore, animal research demonstrates that omega-3 stimulates insulin sensitivity and inhibits zazvisceral fat buildup.[75] Various systematic experimental studies indicate that omega-3 intake provides beneficial hypolipidemic impacts, decreases pro-inflammatory cytokine concentrations, and improves glycemia.[76] Higher omega-3 dosage and a reduced omega-6/omega-3 proportion have been related to a decreased incidence of MetS in animal and human studies.[77,78]

III. Polyphenols. Polyphenols constitute antioxidant-rich bioactive components present mainly within plant-based diets.[79] Polyphenols were divided into 2 categories based upon their molecular arrangements namely flavonoids (catechins) and non-flavonoids namely phenolic acids (ellagic acid), stilbenes (resveratrol), lignans (pinoresinol), and others (oleuropein and hydroxytyrosol). Majority of these possess mitochondrial impacts and have been known to be associated with MetS modulation.[80]

Green tea against MetS. Green tea (*Camellia sinensis*), a member of the *Theaceae* family, is a famous drink that has recently been widely researched for its therapeutic properties. Green tea is defined by the existence of polyphenolic constituents called catechins, along with the most prominent and widely researched epigallocatechin-3-gallate (EGCG). Green tea has

EGCG, which acts as an antioxidant and suppresses LDL degradation. The experts used a unique perspective on this issue, examining the effectiveness of EGCG-rich green tea catechins on body mass and body fat in adults. After a 12-week administration with encapsulated green tea, obese polycystic female subjects (median BMI 30.5 kg/m^2) dropped 2.4% of their body mass, while control subjects were put on body fat. These optimistic data lacked scientific proof of the variance between groups, which could be attributed to differential responses in various patients, as well as changes in metabolism caused by polycystic ovarian syndrome, particularly compared to normal obese individuals.[81,82] Green tea catechins have been shown in both animals and humans to have antidiabetic, cardioprotective, and antiobesity properties. Furthermore, long-regulated human testing would help in determining the appropriate dosage for protection, monitoring, and cure of MS.[83]

Date palm against MetS. The date palm (*Phoenix dactylifera*) is a type of flowering plant in the palm family *Arecaceae*. *Arecaceae* representing a traditional food staple in Arab nations and are a religious priority for Muslims around the world.[84] The Gulf countries produce more than 90% of the world's date palm plants.[85] Experimental model research revealed that Aseel dates possess antihyperglycemic abilities.[86] The date fruit exhibited a particular blocker of glucosidase and was reported to reduce blood glucose more than acarbose within half an hour after intake, attributed to its elevated level of 13 phenolic components.[87] In addition, it has been found to be advantageous in the management of diabetes and a variety of related health complications.[88] Studies in the Kingdom of Saudi Arabia demonstrated antidiabetic abilities in diabetic rats, and random controlled experiments in healthy people revealed that dehydrated dates decrease the glycemic index of white bread and the Tamersit type reduce blood glucose.[89,90] Subsequent animal and laboratory investigations indicated that date fruit suppresses blood sugar readings substantially higher than acarbose (a glucosidase inhibitor used for the treatment of diabetes mellitus).[87,91] Date palm fruits contain considerable nutritional and pharmacological potential, as well as bactericidal, antifungal, and antiproliferative capacities.[92] Al-Yahya et al,[93] investigated the cardioprotective efficacy of liquid date extract (Ajwa variety) ex vivo and in vivo, determining that it increased cardiomyoblast cell multiplication by approximately 40%, reduce endogenous antioxidant intake, and suppressed lipid peroxidation.

Honey against MetS. Honey is a naturally pleasant material that comes under the Apidae family, manufactured by Apismellifera bees from flower nectar, fluids from vital plant components, or by-products of plant-sucking bugs on live plant live segments (Codex Alimentarius Commission, 2001). Honey's medicinal benefits were dependent on anti-oxidant and anti-inflammatory capabilities of its polyphenols and flavonoids concentration. Hussein and colleagues observed that Gelam honey administered at 1 or 2 g/kg body weight for a time period of seven days inhibited NF-κBpathways in a Carrageenan-induced paw oedema model in rats leading to a decline in COX-2 and TNF-α.[94] In another investigation, Ranneh and coworkers reported that stingless bee honey (SBH) inhibited LPS-induced chronic subclinical systemic inflammation (CSSI) and oxidative stress in rodents. Stingless bee honey also suppressed NF-B, p65, and p38 MAPK function while enhancing Nrf2 activity in the liver, kidney, heart, and lungs.[95] Nemoseck et al,[96] found that honey had antiobesity effects in 2011. Within that study, the investigators observed that rodents administered 20% carbohydrate derived from clover honey feed, gained considerably less body weight and exhibited a marked decrease in adipose pad compared to rats administered an isoenergetic feed of liquefied sucrose.[96] In 2008, Yaghoobi et al[97] study that honey has the ability to reduce cardiovascular risk factors. In 2011, Romero-Silva et al[98] observed that rats who receive a 20% hypocaloric honey diet do not have an increase in blood pressure compared to untreated rats.

Sorghum against MetS. Sorghum (*Sorghum bicolor L.*), an African grain and representative of the *Poaceae* family, may possess nutritional and metabolic benefits that could strengthen human well-being.[99] Grains with a seed coat and a colored forehead have a significant level of phenolic acids, 3-deoxyanthocyanidins (3-DXA), and proanthocyanidins (tannins) within sorghum varieties.[100] Molded sorghum flour can dramatically decrease lipogenesis by lowering the expression of fatty acid synthase genes, promote insulin sensitivity, and suppress inflammatory cytokines such as tumor necrosis factor alpha.[101] The current survey has discovered that compressed sorghum has antiobesogenic and anti-inflammatory properties in obese Wistar rats on a high-calorie diet.[102]

Curcumin against MetS. Curcumin is obtained from the turmeric family (*Curcuma longa*) which is widely known in Southeast Asia. Diferuloylmethane (a polyphenol compound) the effective component, has been recognized to possess anti-inflammatory and

antioxidative characteristics. Curcumin also inhibits the obesity-related Wnt/-catenin pathway and stimulates the receptor activated by the gamma peroxisome proliferator in liver stellate cells.103 Potential advantages of MetS include unfavorable consequences for obesity, favorable impact on insulin sensitization, and inhibition of inflammatory mechanisms. Curcumin [1, 7- bis (4-hydroxy-3-methoxyphenyl)-1, 6- heptadiene-3,5dione], an effective component of turmeric, appears to be responsible for the yellow coloring and has been recognized to possess a wide variety of therapeutic properties. It is used to cure a wide range of chronic disorders, such as weight gain, as well as other metabolic disorders.[104] The inflammation process is a crucial component of obesity. The persistent and subacute inflammatory response is recognized as a characteristic of the progression of diabetes and obesity-related atherosclerosis. Adipose tissue is an important source of systemic inflammation and is involved in energy metabolism and homeostasis.[105]

Cinnamon against MetS. Cinnamon (*Cinnamomumverum*), a family of *Lauraceae*, obtained from the peel of a plant. The anti-thrombotic, insulin sensitizing, lipid-lowering, anti-inflammatory and antioxidant characteristics of cinnamon extracts and polyphenols were effective in MS. Cinnamon phytochemicals exhibit insulin-like properties, and numerous investigations have shown that they improve glycemic balance and cholesterol profiles. Ziegenfuss et al,[106] reported in a nonrandomized experiment that cinnamon extract was linked with benefits in fasting plasma glucose, hypertension, and body mass in community with metabolic syndrome. Although not all pharmacological routes of this activity have been identified, research in rodent models predicts that cinnamon compounds can influence gene expression to promote glucose uptake (GLUT 4) and insulin signaling.[107]

IV. Dietary fibers. Dietary fibers have been intimately connected to the management and therapy of many metabolic syndrome symptoms. Randomly selected research have demonstrated that fiber-rich diets and separated fibers, both soluble and insoluble possess a significant impact on overweight, heart disease, and type II diabetes.[108,109] Fiber-rich foods promote glycemic tolerance in type 2 diabetes 110 lowers LDL cholesterol in hypercholesterolemia, and promote to long-term weight maintenance.[111-114] Increased cereal intake, a source of both insoluble and soluble fibers, has been linked to a lower incidence of metabolic syndrome, cardiovascular disease, and indicators of systemic inflammation in epidemiological studies.[115-117] Whole-grain diets have also been linked to a lower risk of metabolic syndrome.[108,109,118]

Barley against MetS. Barley (*Hordeum vulgare*), a staple grain and representative of the *Poaceae* family, cultivated mainly in Saudi Arabia, appear to have higher glucan than different grains such as oatmeal, rye and wheat. Its properties lower postprandial blood sugar levels and promote appetite, promote glucose intolerance, and decrease visceral fat deposition by decreasing abnormal insulin production.[119] In vivo and human investigations have similarly shown that barley supplementation minimizes blood triglyceride concentrations.[120]

V. Lycopene against MetS. Lycopene is carotenoids prevalent mostly in tomatoes, in addition to melon, papaya, and red grapefruits. Lycopene concentration varies across distinct periods of ripening process; therefore ripe tomatoes exhibit high lycopene contents.[121] Multiple researches have demonstrated lycopene as a significant ingredient in the management and therapy of MetS attributed to its strong antioxidant and lipid-lowering effects. Lycopene has been demonstrated in research on animals and humans to lessen blood pressure, atherosclerotic burden, and strengthen blood anti-oxidant capability, in addition to its anti-obesity function, to enhance sensitivity to insulin, to decrease hyperglycemia,and to strengthen the lipid profile.[80,122-126] Furthermore, a research comprising 2500 MetS subjects revealed that greater blood lycopene concentrations were related with a lower mortality rate.[127]

VI. Organosulfur compounds (OSCs). The garlic family (*Allium sativum*), a prevalent condiment, has therapeutic benefits due to its antioxidant and antiplatelet properties. Garlic's anti-inflammatory properties are attributed to the organosulfur active ingredients in its extracts. Crude garlic improves insulin responsiveness in fructose-fed rats, according to Padiya et al,[128] and could, in fact, have comparable consequences in humans. Reinhart et al,[129] reported that garlic ingestion reduces total cholesterol and triglyceride levels in a meta-analysis of randomized and non-randomized investigations contrasting the influence of garlic on blood lipids. Gomez-Arbelaez et al,[130] illustrated the consequence of the old garlic extract on adiponectin thresholds in individuals with MetS in another study. Apionectin levels were found to increase after 12 weeks of incorporating old garlic extract. Garlic is a natural biologically active remedy for MetS because such substances have an antioxidant response due to thiol groups that allow combat against ROS-mediated inflammatory responses. Garlic administration has been

demonstrated in various experimental trials to minimize MetS disorders such as high blood pressure enhance lipid profile, waistline measurement, and fasting blood glucose.[131-133]

VII. Alkaloids. Natural molecules derived from herbal medicines were accountable for exerting therapeutic influence on human wellbeing, with aporphine alkaloids being of significant relevance.[134] Aporphine alkaloids exhibit a wide range of therapeutic effects, including anti-insulin resistance, anti-hyperlipidemia, anti-hypertension, anti-diabetic, anti-obesity, anti-oxidants and anti-inflammatory.[134–136] These aporphine alkaloids have beneficial impacts on the various risk variables associated with metabolic syndrome.

Berberine against MetS. Berberine is an isoquinoline derivative alkaloid derived from the Berberry/ Rhizomacoptidis (Berberis vulgaris) of the Ranunculaceae family. It is widely used in China owing to its antibacterial and diabetes prevention characteristics. Animal studies have demonstrated that berberine improves body mass, reduces triglyceride levels, and enhances insulin susceptibility in insulin-resistant subjects. Berberine works by enhancing the activation of genes involved in energy consumption while suppressing the activation of genes associated with lipogenesis.[138] It also exerts insulin-sensitizing effects, analogous to metformin and thiazolidinediones, primarily by stimulating adenosine monophosphate-activated protein kinase (AMPK) in adipocytes.[139] Human investigations conducted on individuals with MetS have revealed a reduction in waistline measurement, serum triglyceride levels, and systolic BP, with a stronger impact observed in women.[140] Research suggests that berberine mainly targets adipose tissue and exerts various effects on adipocytes. It inhibits the differentiation of mouse 3T3-L1 preadipocytes into mature fat cells, lowers leptin and resistin secretion, intensifies adiponectin mRNA expression, and modulates glucose and lipid metabolism through multiple pathways involving AMPK-p38 MAPK-GLUT4 signaling, JNK pathway and peroxisome proliferator-activated receptor-alpha (PPARα).138

In conclusion, to sum up, individuals with MetS have a higher risk of developing diabetes and CVD. The most effective treatment strategy for managing MetS is lifestyle modification, with an emphasis on achieving a modest weight and engaging in regular physical exercise. Overall, lifestyle modifications, including regular training, a balanced diet, and smoking cessation, should be suggested to people diagnosed with MetS. Public health statistics and behavioral patterns clearly indicate that a lack of awareness is a major contributing factor to obesity; therefore, it is essential to implement community health initiatives aimed at addressing the obesity burden. Metabolic syndrome represents a widespread global health concern and a potential risk factor for both atherosclerosis and non-atherosclerotic CVDs. The considerable differences observed in the defining parameters and diagnostic criteria of MetS suggest a contextual shift in the conceptual understanding of this disorder. The main underlying factors contributing to MetS appear to be numerous stressors that result in chronic inflammation. Conventional therapies targeting specific features of MetS are constrained by a wide range of factors. Firstly, there are only a limited number of drugs that have been proven to have a compelling influence on long-term outcomes, making treatment choices complicated. Furthermore, the continuous pattern of factors related to MetS often necessitates the utilization of different drugs, such as statins, which can increase the risk of drug-related complications and side effects in patients. In this scenario, the production of readily accessible phytochemicals with limited adverse impacts could offer possibilities for the introduction of innovative therapeutics.

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