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# The Effects of Pistachio (*Pistacia Vera* L.) on Metabolic Syndrome Components: A Comprehensive Review

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**ABSTRACT**

**Introduction**: Pistachio (*Pistacia vera* L.) is a nutrient-dense nut with a healthy nutritional profile and a long history of consumption in the Mediterranean diet and traditional medicine of different countries. Besides drug treatments, dietary modification is also an important and modifiable factor that can affect the prevention and treatment of the metabolic syndrome. This item may benefit metabolic syndrome management when considered in diet planning. This paper aimed to discuss the role of the pistachio in the management of metabolic syndrome.

**Method**: PubMed, EMBASE, and Scopus were searched for data collection using related keywords.

**Results**: A total of 113 articles were included in this review from 220 found documents. The most recent data published were investigated regarding the beneficial effects of pistachios on metabolic syndrome components, including hypertension, hyperlipidemia, obesity, and diabetes mellitus. The profile of nutrients and most important phytochemicals of pistachio were presented. The main mechanisms of action of pistachio in metabolic syndrome are also discussed and summarized in some figures.

**Conclusion**: Based on the results, although pistachio has been less investigated than other nuts, considerable studies provide evidence of its beneficial effects on different components of metabolic syndrome.

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## Introduction

### *Metabolic Syndrome*

Metabolic syndrome is a collection of risk factors, including hypertension, insulin resistance, abdominal obesity, and atherogenic dyslipidemia. The prothrombotic state, pro-inflammatory state, and nonalcoholic fatty liver disease also may be presented in metabolic syndrome (1).

Several definitions of metabolic syndrome are suggested by the World Health Organization, the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Although there are slight differences among definitions, they all overlap in diagnostic criteria, and the main components in all definitions are as explained above (2). Metabolic syndrome patients are diagnosed with at least three of these risk factors: glucose intolerance, hypertension, abdominal obesity, hypertriglyceridemia, decreased HDL, and hypercholesterolemia (3).

Almost one billion people in the world have metabolic syndrome. Lifestyle, nutrition, and socioeconomic factors significantly impact the incidences of metabolic syndrome (4). The prevalence of metabolic syndrome in the Middle East has been estimated in women at about 32.1% to 42.7% and in men at about 20.7% to 37.2% (5).

The pathophysiology of metabolic syndrome is multidimensional, complicated, and incompletely understood. The main factors in the onset and development of metabolic syndrome are persistent oxidative stress, insulin resistance, endothelial dysfunction, chronic inflammation, and neurohormonal activation (6).

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Since metabolic syndrome is multidimensional and results from several pathophysiological processes, no single intervention can address all aspects of this syndrome. Many drugs from different drug classes have been used to treat this disorder, including Biguanides, Thiazolidinediones, insulin, Statins, ACE Inhibitors, Angiotensin II Receptor Blockers, and Antiplatelet Agents. Despite all these medications, current medical treatments have been unable to stop this disorder completely. Comprehensive research projects attempt to develop new herbal and synthetic medications to manage this prevalent syndrome.

Besides drug treatments, lifestyle interventions and dietary modifications are also essential and modifiable factors that can affect the prevention and treatment of metabolic syndrome. In addition, various plants and natural dietary compounds have been used to counteract metabolic syndromes, and the preventive and therapeutic effect of plant-based medications and diets against metabolic syndromes has been shown by research projects (7) (8) (9) (10, 11) (12).

Many studies have shown the effects of some foods, especially nuts, in the treatment and prevention of metabolic syndrome and cardiovascular diseases. Adding nuts to the Mediterranean diet has positively impacted blood lipids and cardiovascular diseases (13).

Epidemiological and clinical studies have shown that nuts consumption (including pistachios, almonds, hazelnuts, Brazil nuts, cashews, pecans, and walnuts) and peanut (legumes ) improves various diseases, including oxidative stress (14) (15), insulin resistance (16), and endothelial dysfunction (17).

Although pistachio has been less investigated than other nuts (walnut, almonds, hazelnut), broad evidence confirms its beneficial effects on risk factors of cardiovascular and metabolic diseases, including hyperlipidemia and insulin resistance, and oxidative stress (18) (19) (20) (21). Therefore, the effects of pistachio on metabolic syndrome should be evaluated, especially regarding associated mechanisms.

## Material & Method

PubMed, EMBASE, and Scopus were searched for data collection using the following keywords with *pistacia vera* L: “metabolic syndrome,” Hypertension or “blood pressure,” or hypotensive or antihypertensive, diabetes or insulin or hyperglycemia or hypoglycemic or antidiabetic or antihyperglycemic or “blood glucose,” overweight or obesity or anti-obesity, dyslipidemia or "high triglyceride" or hypertriglyceridemia or hyperlipidemia or "high cholesterol" or hypercholesterolemia, Atherosclerosis or atherogenic, In total, 220 articles were found, of which 113 were included in this review without time limitations.

### *Pistacia Vera* L.

The pistachio (*Pistacia vera* L.) is one of the most popular tree nuts worldwide, with universal importance for its nutritional, economic, and health Properties (22) (23) (24) (25).

The genus of *Pistacia* systematically fits into the family of Anacardiaceae. This family contains about 20 species; five are more popular, including *P. lentiscus, P. vera, P. terebinthus, P. atlantica,* and *P. khinjuk* (26). *Pistacia vera* L. (pistachio) is the only species that gives edible nuts with commercially acceptable sizes in this genus. Other species include *P. cabulica, P. atlantica*, *P. falcata*, *P. kinjuk, P. chinensis*, *P. integerrima*, *P. kurdica*, *P. terebinthus P. mutica*, *P. lentiscus*, *P. palaestina*, are used mostly for oil extraction, forestry, and wood production (27).

Pistachio is a native and ancient plant of the Middle East (13). The evidence of pistachio consumption back to 7000 B.C. This plant is cultivated in the United States, the Middle East, and Mediterranean countries. Iran and the United States are the two main producers and exporters of pistachio (26). Iran is an important source of germplasm of pistachio and has several male genotypes and more than 70 genotypes and cultivars of female pistachios. The most popular types of pistachios in Iran are Ahmad Aghaei, Akbari, Koaleghoochi, Ouhadi, Qazvini, and Shah Pasand Damghan (27). Pistachio is mainly used as a tasty snack or an ingredient in the food industry, which is beneficial for the human diet and is rich in nutrient content (22).

Pistacia species have numerous traditional uses. Different parts of *P. lentiscus, P. vera*, *P. khinjuk, P. atlantica,* and *P. terebinthus* have been used in traditional Iranian medicine (TIM) as useful medicines for a wide range of purposes like antiseptic, tonic, antihypertensive, aphrodisiac, management of gastrointestinal, dental, liver, respiratory tract and urinary tract disorders and diabetes (26). Meanwhile, the fruit kernel of *P.*

*vera* is used as a tonic in cardiac, stomach, hepatic, and brain diseases (28).

*P. vera* nut has a special profile of nutrients. Pistachios are rich in protein (about 20% of total weight) with almost 2% of L-arginine. L-arginine is a precursor of NO as an endogenous vasodilator, which has a crucial role in vascular tonicity (29). Pistachios contain sufficient amounts of all essential amino acids based on the WHO-recommended essential amino acid pattern (30). The ratio of the essential amino acid (essential amino acid: total amino acid) in pistachios is 39.1, higher than almost all nuts (walnuts, almonds, hazelnuts, and pecans). Compared to other tree nuts, pistachios have the highest content of branched-chain amino acids (1·262 g valine, 1·599 g leucine, and 0·932 g isoleucine per 100 g) (31).

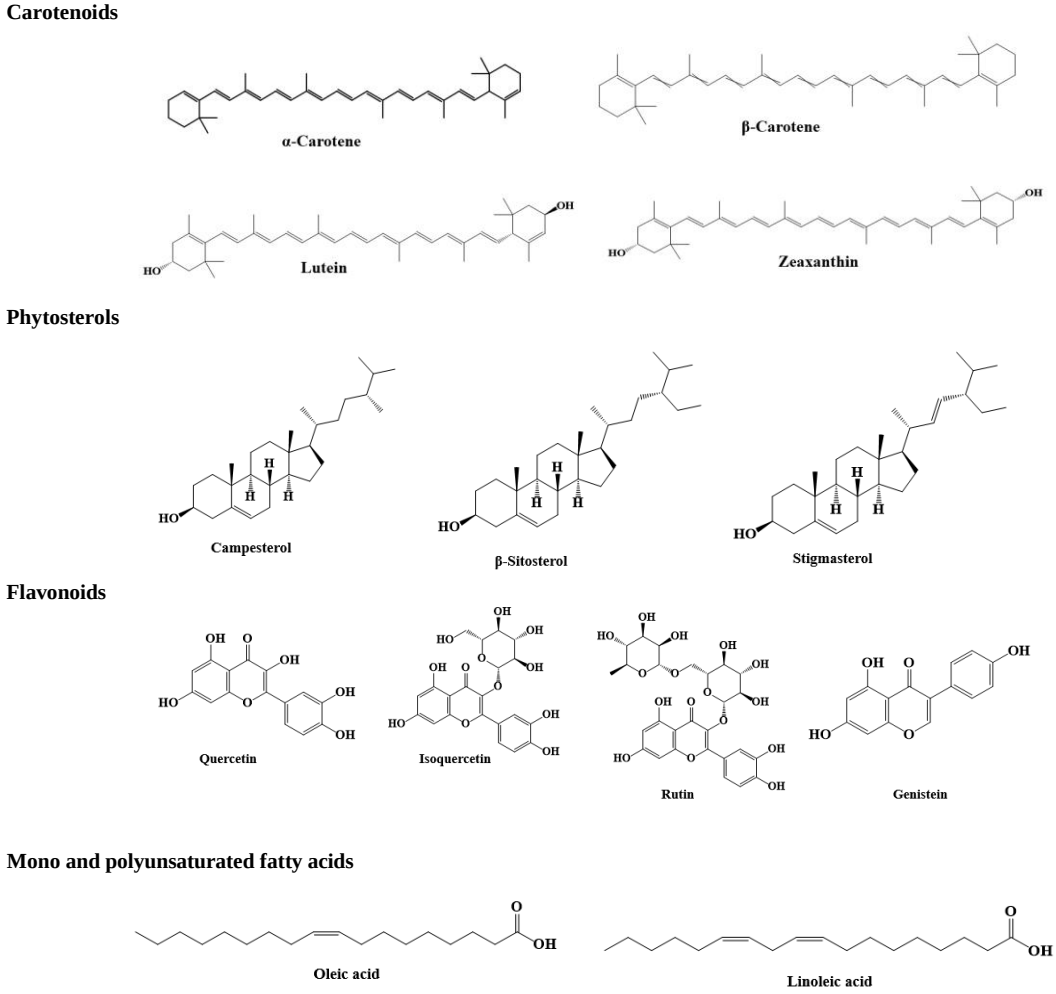


**Figure 1.** Main pharmacologically active compounds of *Pistacia vera* L. and their chemical structure

Pistachio is a rich source of monounsaturated (53.5%) and polyunsaturated (29.1%) fatty acids and contains small amounts of saturated fatty acids (11%). Hence, the ratio of unsaturated fatty acids to saturated fatty acids in pistachio is high. Such a ratio makes pistachio optimal for improving the lipid profile (32). Several studies have implied that unsaturated fatty acids prevent insulin resistance and diabetes development, while saturated fatty acids promote insulin resistance (33) (34, 35). Oleic and linoleic acids comprise more than 60% of the total fatty acids content of pistachios and are known for their hypoglycemic, cardioprotective, hypocholesterolemic, and anti-inflammatory effects (35) (36). The total content of omega-6 and omega-3 fatty acids in pistachio are 13.2% and 0.25%, respectively (37).

Pistachios have 0.3% weight of soluble fiber and 10% of insoluble fiber (27). Among all nuts, only almonds have comparable content of fiber (13% of Weight) (31). Compared to other nuts, pistachios are considered a good source of vitamins C and A, folic acid, thiamin, pyridoxine, and other vitamins of group B, except vitamin B12 (38). For example, 100g of pistachios provides 0.87mg and 1.7mg of thiamin (50% of the RDA) and pyridoxine (exceeding the total RDA) respectively. Pistachios also provide high amounts of vitamin K (approximately 13.2mg/100g, equivalent to 50% of the RDA). A higher dietary intake of vitamin K lowers the risk of diabetes and some other chronic diseases (31) (39) (40).

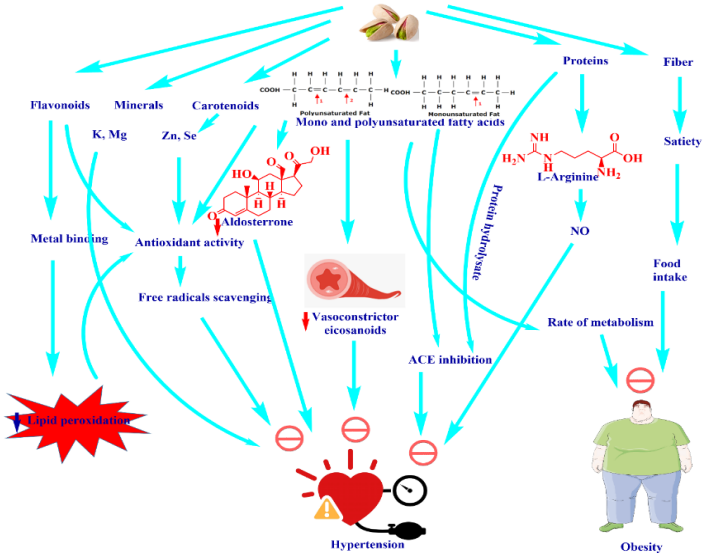


**Figure 2.** The possible mechanism of actions of pistachio on hypertension and obesity.

Pistachios are rich in main minerals, including potassium, magnesium, calcium, copper, and manganese. This mineral profile may have a beneficial role in lowering blood pressure. Pistachios also provide selenium and zinc, which have established antioxidant effects (38).

Pistachios contain large amounts of phenolic compounds. The flavonoids, including flavonols, flavanols, flavanones, anthocyanins, and isoflavones, are the main class of phenolic compounds of pistachio that reach 16–70 mg/100g of pistachios depending on the variety (41) (27) (37).

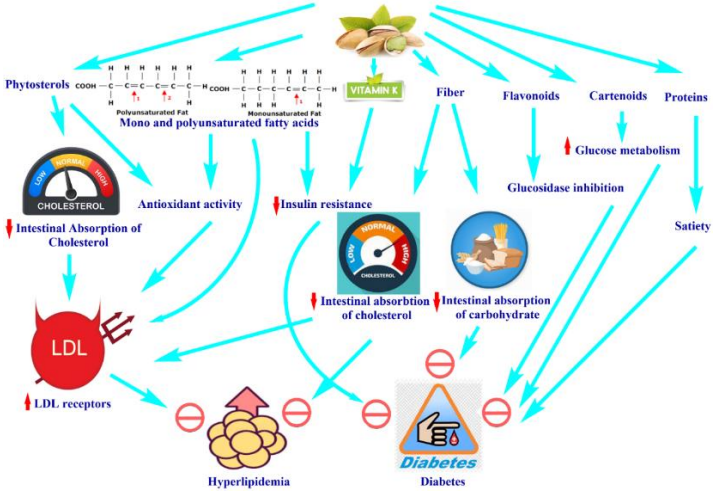


**Figure 3.** The possible mechanism of actions of pistachio on hyperlipidemia and diabetes.

Pistachio flavonoids (polyphenols) are bio-accessible and available for absorption in the stomach and intestine. The amount of polyphenol compounds in roasted pistachios is the same as in raw pistachios (42, 43). These phenolic compounds have important antioxidant, cardioprotective, and vasoprotective properties (44). For example, Anthocyanidins significantly bind to metals and inhibit metal-induced lipid oxidation, playing a vital role in the antioxidant properties of pistachio phenolic compounds (45).

Pistachios have 2790mg/Kg of phytosterol, including campesterol, stigmasterol, and b-sitosterol) which is the highest among nuts. Walnut, almond, and hazelnut have between 1130 to 1990mg/kg of phytosterol (including D5-avenasterol, sitosterol, stigmasterol, and campesterol) (46).

Several studies have indicated that phytosterols dose-dependently reduce plasma levels of cholesterol (46).

In addition, pistachios contain significant amounts of lutein and zeaxanthin (10) (xanthophyll carotenoids), while other nuts do not have significant amounts of these xanthophyll carotenoids (31) (47). Zeaxanthin is concentrated in the retina and protects the retina from phototoxic damage and age-related macular degeneration as a potent antioxidant (47).

As mentioned above**,** the benefits of nuts in managing cardiovascular diseases and dysmetabolic conditions, such as obesity and diabetes mellitus, were shown in epidemiological and clinical studies (48) (49). Accordingly, the US Food and Drug Administration (7) and the American Heart Association have recommended the continuous consumption of nuts in the general population's diet to prevent the risk of metabolic syndrome and cardiovascular diseases (31).

According to International Nut & Dried Fruits, almonds and walnuts were the most consumed tree nuts in 2019. These two nuts' estimated worldwide consumption was 30% and 20%, respectively. The next ranks were Cashews, pistachios, and hazelnuts, with 18%, 15%, and 11% of worldwide consumption, respectively (20, 50). Although the studies conducted on pistachios are less than other nuts (almonds, walnut, and hazelnut), the accumulating evidence supports the beneficial effects of pistachios on cardiovascular risk factors, especially the lipid-lowering property of this nut (20)(51). Accordingly, in 2010, the US food guide recommended the consumption of pistachio to improve diabetes, metabolic syndrome, and cardiovascular diseases (51).

As mentioned earlier, pistachio has a healthier nutritional profile than other nuts, with low-fat content mainly composed of unsaturated fatty acids, high dietary fiber, and vegetable protein. Pistachio also has rich content of phytochemicals, such as carotenoids and phenolic compounds, and suitable minerals, especially potassium, which makes pistachio a powerful food for improving endothelial function, lipid and glucose homeostasis, obesity, and oxidative stress (20).

In this review article, a variety of *in vitro*, *in vivo*, and clinical studies was investigated to present an updated report about the effects of *P. vera* L. on the prevention and treatment of different aspects of metabolic syndrome, including diabetes, hypertension, hyperlipidemia, and obesity.

***The Effects of Pistachio on Hypertension***

Hypertension is a major risk factor for numerous diseases and the world's number one cause of death (40). Several studies have shown an inverse relationship between blood pressure and nut consumption (52) (20, 53).

Several studies have also found that pistachios benefit blood pressure (20) (54). In a recent one-blind randomized crossover trial in 2021, the administration of Iranian pistachios (50g for 12 weeks) to 48 diabetic patients significantly reduced systolic blood pressure. The diastolic blood pressure of these patients did not change significantly (55). Similar results were achieved in a Spanish randomized clinical trial conducted on 54 prediabetic patients. Systolic blood pressure was reduced significantly after four months of administration of pistachios (57 g/day), while there were no significant changes in diastolic blood pressure (54).

In addition, a randomized, cross-over clinical trial on 28 patients with dyslipidemia who received a diet with 10% of the total energy from pistachios for four weeks showed a significant reduction in systolic blood pressure and non-significant changes were observed in diastolic blood pressure. In this study, a decrease in peripheral vascular dilation was also observed in patients who received higher doses of pistachios

(a diet with 20% of energy as pistachios) (56). Another randomized, crossover, controlled feeding trial conducted showed a decrease in systolic blood pressure in 30 patients with type 2 diabetes (3.5 ± 2.2 mm Hg) after administration of a diet containing 20% energy from pistachios for four weeks. The most significant reduction was recorded during sleep (−5.7 ± 2.6mm Hg) (57).

On the other hand, three controlled trials demonstrated as a secondary outcome that supplementation with pistachios does not have significant effects on both systolic or diastolic blood pressure (58-60).

Nevertheless, a recent meta-analysis of 20 clinical trials showed that pistachios have the most potent effect on reducing blood pressure among all nuts and therefore, despite the small number of studies, there is more supporting evidence in favor of the blood pressure-lowering effect of pistachios.

Regarding the mechanism of the antihypertensive action of pistachio, arginine can be considered one possible mechanism. As mentioned earlier, pistachios are rich in L-arginine, which produces nitric oxide. Nitric oxide acts as an antiplatelet and a vasodilator, and the lack of nitric oxide causes endothelial dysfunction and increases the risk of cardiovascular diseases. Therefore, via nitric oxide production, pistachios can show a vasodilatory action. In agreement with this hypothesis, administering 40 grams of pistachios daily for three months in 60 adults with mild dyslipidemia improves endothelial function and vascular stiffness via a reduction in brachial-ankle pulse wave velocity and carotid-femoral pulse wave velocity (61).

The angiotensin-converting enzyme (ACE) inhibitory effect of pistachio is another mechanism of its blood pressure-lowering activity. The protein hydrolysates can exhibit pharmacological activities. For example, proteins derived from plant food sources have shown antihypertensive effects (62). Pistachio proteins are hydrolyzed to release bioactive peptides that inhibit ACE. Sequential hydrolysis by pepsin and trypsin provided polypeptides with ACE inhibitory activity ($IC_{50}$ 0.87 ± 0.04 mg/ml), which also reduced diastolic and systolic blood pressure (16 and 22mmHg respectively) 4h after oral administration (63).

A similar study explored the potential of pistachio to release bioactive peptides with ACE inhibitory effects. The total soluble proteins were extracted from the ground and hydrolyzed at different intervals using chymotrypsin and trypsin. A 24h digestion time showed the highest ACE-inhibition activity (62).

Other possible mechanisms for the antihypertensive effect of pistachios, besides those mentioned above, have been directly tested in animal and human studies.

Meanwhile, various studies have shown that antioxidants can lower blood pressure (64) (65, 66). Antioxidants by scavenging free radicals protect nitric oxide and improve endothelial function and have some potential inhibitory effects on NADPH oxidase. (67, 68).

Pistachio is among the top 50 foods with high antioxidant activity (31) because of its phenolic compounds (69) and several other antioxidants, such as α-tocopherol, β-carotene, phylloquinone, chlorophyll, lutein, selenium, zinc, and phytoestrogens. The prominent antioxidant activity of pistachio is probably due to the synergistic action of these components (27, 70).

In addition, pistachio contains significant amounts of several minerals such as potassium, magnesium, calcium, copper, and manganese and this profile of minerals can contribute to the blood pressure-lowering effect of the pistachio (38).

Pistachio is also a rich source of fatty acids (53.5% of monounsaturated fatty acids (43) and 29.1% of polyunsaturated fatty acids) that exhibit antihypertensive activity via several mechanisms. ω-3 polyunsaturated fatty acids compete with ω-6 fatty acids for common metabolic enzymes and thereby decrease the production of vasoconstrictor eicosanoids. Polyunsaturated fatty acids also reduce ACE activity, enhance endothelial nitric oxide generation, decrease plasma aldosterone levels and activate the parasympathetic nervous system (71, 72).

### *The Effect of Pistachio on Blood Lipid Profile*

Hyperlipemia is an established risk factor for cardiovascular diseases. Although nuts contain high-fat content, they have a favorable effect on blood lipids due to the presence of unsaturated fatty acids and other bioactive compounds. Growing evidence shows that nut consumption, including pistachios, improves lipid profiles and weight management (31).

In animal studies, it has been shown that pistachio can improve blood lipids and ameliorate oxidative stress. In hyperlipidaemic rats (rats with a high-cholesterol diet), eight weeks of administration of pistachio significantly decreased triglycerides and increased total antioxidant activity (73). In a rabbit model of atherosclerosis, short-term administration of the pistachios cyclohexane and methanolic extracts showed beneficial effects on aortic intimal thickness, LDL- cholesterol, and HDL-cholesterol (74).

Recently, it has been shown that three weeks of administration of the pistachio hydroalcoholic extract to diabetic rats significantly improve the lipid profile, inflammation process, and oxidative stress via increasing total antioxidant capacity and reducing lipid peroxidation (75). Also in hypercholesterolemic rabbits, oral administration of pistachio extract significantly increased HDL level compared to the control group. In the most recent study, dietary pistachio has beneficially altered fatty acid profiles in streptozotocin-induced diabetic rats (76).

In clinical studies, pistachio supplementation has been associated with improving lipid profile, increasing low-density lipoprotein, decreasing total cholesterol, and decreasing low-density lipoprotein in both hypercholesterolemic patients and healthy individuals (77) (78) (20).

A systematic review of epidemiological evidence also showed that pistachio supplementation improves plasma lipid profile (79). A recently published meta-analysis has shown that comparing different types of nuts, pistachio, and walnut are more effective in lowering total cholesterol, triglycerides, and LDL cholesterol (80). Then, a systematic review and meta-analysis of randomized controlled trials revealed that pistachios might improve lipid profiles and prevent cardiovascular and metabolic diseases (81). According to the most recent meta-analysis of randomized controlled trials about nuts and blood lipid profiles, pistachio consumption may lower TC levels (82).

It can be concluded that the consumption of pistachios can improve plasma lipid profile and lipoprotein particle size and thereby may help to decrease the risk of cardiovascular disease. The mechanism of action of tree nuts and pistachios on lipid profile is unknown, but some possibilities can be considered. The plant sterols may contribute to the lipid-lowering effect of plant-based diets. In the intestinal lumen, the phytosterols compete with dietary cholesterol for absorption (83). Reducing cholesterol absorption from the intestinal lumen increases endogenous cholesterol synthesis. Thus, LDL receptors are up-regulated and removed from circulation, reducing plasma LDL (83). Pistachios contain 214mg/100g of phytosterol, including stigmasterol, campesterol, and b-sitosterol, the highest phytosterol content among nuts. According to the dose-response relationship, about 200g of pistachios should be consumed daily to reduce plasma cholesterol. As polyunsaturated fatty acids and other compounds affect blood lipid levels, smaller pistachios can also reduce cholesterol levels (84). Pistachios contain high amounts of polyphenols, which can neutralize reactive oxygen species (ROS), scavenges free radicals, and enhance endogenous antioxidant contents (85). The antioxidant activity of pistachios could reduce oxidative stress and protect against diseases related to free radical overproduction, including hyperlipidemia and atherosclerosis. In a randomized double-blinded study in pre-hypertensive patients, daily supplementation of 640mg anthocyanins (one of the polyphenols of pistachio) for four weeks significantly increased HDL-cholesterol levels (86).

In addition, pistachios are rich in fiber (0.3% of soluble fiber and 10% of insoluble fiber), which could improve lipid profile via inhibiting intestinal absorption of cholesterol (27).

The last possible mechanism is related to the presence of unsaturated fatty acids. Pistachio is a unique source of fatty acids (53.5% of monounsaturated fatty acids, 29.1% of polyunsaturated fatty acids, and small amounts of saturated fatty acids). Some studies have indicated that such a rich acid profile is associated with increased levels of LDL receptors on mononuclear cells that lower total and LDL cholesterol and increase HDL cholesterol (32) (87).

### *The Effect of Pistachio on Obesity*

Obesity is a risk factor for dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease (30). Nuts, including pistachios, contain high-fat levels and are considered energy-dense foods. The long-term intake of high amounts of nuts may increase the risk of obesity. However, some epidemiological studies have provided considerable evidence that the balanced

consumption of nuts is not associated with weight gain and obesity (88, 89).

Compared to other nuts, pistachios have a relatively low-fat content (mainly from polyunsaturated and monounsaturated fatty acids) and higher amounts of fiber (90). Regular consumption of pistachios does not cause weight gain. Wang et al. showed that pistachios supplementation (42 or 70g/day) for 12 weeks in 90 patients with metabolic syndrome did not cause weight gain or increase in waist-to-hip ratio (60). Likewise, evaluating the effects of pistachios (20% dietary Energy) in 60 patients with metabolic syndrome for 24 weeks showed no significant change in body weight. However, a significant decrease was observed in waist circumference (91). On the other hand, Parham et al. reported a significant reduction in BMI after daily consumption of pistachio (50g for 12 weeks) compared to the control diet (92).

A recent study showed that the consumption of pistachios (44 grams daily) does not cause weight gain in healthy women (93). A recent systematic review and meta-analysis of 11 randomized controlled trials, including 1593 subjects, showed that a diet with pistachios reduces BMI with no significant effects on body weight and waist circumference (94).

Despite their high energy content, numerous explanations have been proposed as to why consuming pistachios does not lead to being overweight. Some studies have shown that the fat content of nuts is less absorbed than the fat in other foods (95). In the intestine, pistachios cannot absorb fat contained in their cell walls (90). In some interventions, the fat measured in the stool increased during pistachio consumption compared to before the intervention (13) (23).

Pistachios contain polyunsaturated fatty acids, which are easily oxidized compared to saturated fatty acids and have higher thermogenic effects, increasing the metabolism rate (50, 90).

Another mechanism is related to the fiber content of the pistachio. Fiber content is important because clinical and epidemiological investigations have demonstrated that fiber intake is inversely associated with weight gain (96, 97). Pistachios also have a high protein content (21%), which increases satiety and decreases food intake. The process of chewing can also reduce hunger sensations (90). Moreover, pistachios have a low glycemic index, maintaining a satiety status (98). A recent randomized controlled pilot study has shown that the satiety effect of pistachio is similar to biscuits, and pistachio consumption does not cause weight gain (99). In a more recent randomized controlled trial study on 60 overweight and obese women, consumption of pistachio and milk for a month similarly affects the maintenance of satiety in overweight people (100). Due to the importance of satiety regulation on body-weight management, more clinical trials are needed in the future to establish this effect of pistachio.

***The Effect of Pistachio on Diabetes***

The prevalence of obesity and lifestyle changes have increased the prevalence of diabetes and made diabetes mellitus one of the most common diseases worldwide. Diabetes is the leading risk factor for the development of cardiovascular disease. Diabetes is characterized by insulin resistance, hyperglycemia, and impaired insulin secretion (101, 102).

Epidemiological and interventional studies have shown that nut consumption is conversely related to the risk of diabetes mellitus (103, 104). Pistachio, among nuts, has a low carbohydrate index with a positive effect on glucose metabolism in fasting and postprandial status (50, 105).

In clinical studies, the effect of pistachio has been evaluated on fast plasma glucose, insulin, and postprandial glycemia (106) (19). In a randomized, cross-over study conducted on 20 patients with metabolic syndrome, the consumption of 85g of pistachios along with bread increased glucagon-like peptide (GLP) levels and reduced postprandial glycemia in comparison to patients who consumed bread alone (19). Four weeks of supplementation with a Mediterranean diet supplemented with 20% of energy intake as pistachios significantly decreased fasting plasma glucose compared to the control group (58). In another study conducted on 60 subjects with metabolic syndrome, 24 weeks of consumption of a pistachios diet (20% energy) significantly decreased plasma glucose levels but did not change plasma insulin levels (98).

Recently, in a study conducted by Feng on 59 Chinese women suffering from gestational diabetes mellitus or impaired glucose tolerance, the administration of 42g of pistachios could significantly reduce postprandial glucose and

GIP and increase GLP-1 levels. Therefore, pistachios can improve the impaired glucose tolerance of patients with gestational diabetes mellitus (107). Finally, a systematic review analyzed the results of four studies in pre-diabetic and type 2 diabetic patients, daily administration of 50-57g of pistachio, decreased plasma insulin levels, fasting blood glucose, HOMA-IR, and fructosamine, but did not change HbA1c levels (108).

Although many studies have shown the beneficial effect of pistachios on impaired glucose tolerance and diabetes mellitus, more studies with longer study duration are necessary to evaluate the effects of pistachio consumption on insulin resistance and HbA1c.

Several mechanisms can explain the beneficial effects of pistachios in diabetic conditions. Pistachios have a high fiber content, which can decrease carbohydrate absorption (97, 109). Pistachio has healthy fats, low available carbohydrate content, and a high protein content (21%), reducing appetite and food intake. In addition, the pistachio is a nut with high carotenoid content to improve glucose metabolism.

A longitudinal study of 1389 healthy subjects has shown that higher levels of total plasma carotenoids are associated with a lower risk of developing diabetes mellitus or impaired fasting glucose (43).

Pistachio also has some flavonoids (quercetin-3-O-rutinoside, genistein, isoquercetin, rutin, and quercetin), which can impact enzymes responsible for the regulation of carbohydrate digestion and glucose metabolism (110). Administration of quercetin to streptozotocin-diabetes-induced rats increased hexokinase, decreased glucose-6-phosphatase, and decreased fructose-6-bisphosphate activities that improve glucose homeostasis (111). In a recent study, five metabolites isolated from the fruit of *P. vera* showed an inhibitory effect on α-amylase and α-glycosidase enzymes. The best inhibitors against the α-amylase were pistachionic acid, tirucallol, and masticadienolic acid based on the IC50 values (112).

The synergistic effects of different compounds present in pistachios, including unsaturated fatty acids, flavonoids, and carotenoids, can improve glucose metabolism. Ribeiro et al. showed that the synergism between these compounds could modulate specific miRNA and increase insulin sensitivity via the PI3K-AKT signaling pathway. (108) More research projects should be conducted to join these preliminary findings to the clinical studies and confirm pistachio's role in treating and preventing diabetes mellitus.

## Conclusion

Compared to other nuts, pistachio has a healthier nutritional profile with low-fat content, remarkable content of minerals, a high source of vegetable protein and dietary fiber, an excellent source of vitamins, rich composition of phytochemicals, including phenolic compounds, carotenoids, and phytosterols. The results showed the positive effects of pistachios on patients with hypertension, diabetes, obesity, metabolic syndrome, and dyslipidemia. Antioxidant activity, improving endothelial function, inhibiting ACE and cholesterol absorption, glucosidase inhibition, decreasing food intake, and preventing insulin resistance are possible mechanisms of action of pistachio on metabolic syndrome.For the treatment of metabolic syndrome and its components, pistachio can be useful with dosages ranging from 30 to 100g per day. However, the dosage range used in most trials is 42-45g per day, and the lowest effective dose has been proposed to be 35g of pistachios per day. Although available data support the inclusion of pistachios in the diet of all patients with metabolic syndrome, more clinical trials are needed for a more definitive conclusion and determination of the optimum dosage.

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## Conflict of Interest

The authors declare not to have any conflicts of interest.

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