Review

Physicochemical properties and health benefits of pistachio nuts

A comprehensive review

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Abstract: The genus of Pistacia plant systematically fits into the family of Anacardiaceae. Pistachios contain protein, carbohydrate, dietary fibers, fat, folic acid, vitamin K, magnesium and potassium, gama-tocopherols, phytochemicals, and polyphenols**.** Collectively, these constituents have been shown to possess antioxidant and anti-inflammatory functions to improve overall health when consumed as a healthy diet. We searched the following keywords within the literature databases: pistachio, heart disorders, lipids, weight, antioxidants, and allergy. Further searching theses keywords, we have found 50 articles in PubMed, 40 articles in ISI web of knowledge and 30 articles in Google Scholar. We have selected 100 articles, among them 80 articles were used as the references of this review**.** In the current article, we have discussed the most recent data published regarding the regulatory effects of pistachios on several clinical states such as heart related disorders, hyperlipidemia, hypertension, vascular stiffness and endothelial and gut functions, weight management, glucose metabolism, kidney function and finally allergies.

Keywords: Lipids, weight, cardiovascular disease, antioxidants, allergies, renal disorder, diabetes mellitus

Introduction

The genus Pistacia fits into the family of Anacardiaceae. This genus contains 13 or more species and among them *Pistacia vera* L. (pistachio) is the only species that is commercially important [1]. Although pistachios are widely cultivated in Mediterranean countries, their probable origin is central and southeastern parts of Asia. Remnants of pistachios have been found in Yahya in the Soghum valley of southeastern Iran from the sixth millennium BC [2]. The fruits of pistachios have been included in the human diet from the prehistoric times. In addition to therapeutic potentials, these fruits have been taken by ancient people for their nutritional properties [3]. Pistachio kernels are most frequently used as snacks, either in crude, roasted and salted or flavored forms. Pistachios are also sometimes consumed as a folk remedy for some illnesses. The pistachio as a tree is amongst the oldest flowering nut trees that are native to the Middle-East region of the world. Since pistachios tolerate hot and dry type of climate, these trees are grown in different parts of the world such as the Middle East and Mediterranean areas, as well as in other countries with similar climates. They found valued for their nutritional composition along with storage life. Thus, pistachios were a favorable "lightweight food" which were also popular among early explorers and traders, especially on long journeys [3]. Pistachios are grown in the raceme form, like grapes and almonds. This nut is surrounded by a fleshy shaft which ripens at the end of summer. Pistachio fruit hulls become rosy and their inner shells break naturally along their

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stiches. The nut possesses a hard outer shell, accounting for approximately half of the pistachio weight. The pistachio seed has a thin skin and light green flesh with a unique flavor. Both the United States (especially the State of California) and Iran are of the greatest pistachio producers globally, so that each of the countries produces several hundred million pounds of pistachio, annually. During the 1980s, little was known about the health impacts of the pistachios on risk of chronic diseases. While dietary guidelines recommended a lower fat diet, the health benefits of the fat components of nuts was not appreciated. According to the healthy eating recommendations, food industry has developed fat-reduced foods, and most of the subjects changed their diet by lowering the intake of nuts in the context of low-fat diets. It is now well established that, once nuts are consumed, they are heart healthy and can be used as a dietary strategy to lessen the consumption of saturated fatty acids (SFA) and correspondingly induce the intake of both monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) [4, 5]. Pistachios contain several constituents such as protein (20%), carbohydrate (27%), dietary fibers (10% in the form of insoluble forms and 0.3% soluble forms), fat [45%, including 5.9% saturated fatty acids (SFA), 23.3% monounsaturated fatty acids (MUFAS), and 14.4% polyunsaturated fatty acids (PUFAS)], and other minerals like, magnesium, potassium, manganese, calcium, vitamins (A, B and C) especially vitamin K, and phytochemicals varying from phytosterols lutein (xanthophylls carotenoid), gama-tocopherol, to polyphenols [6, 7]. Amongst different species of pistachio, nutrient composition of Asian pistachio including Ohadi, Mumtaz and Ahmad Aghaei that are mostly cultivated in Kerman region may show some differences in both level and type of fatty acids, protein, sugar, and mineral elements. The main frequent types of fatty acids in Asian pistachio are oleic acid (60.2% – 64.8%) and linoleic acid (21.95% – 26.24%) [8]. Collectively, these constituents may synergistically improve heart function, glycemic control, and regardingly maintain the weight, when are consumed along with a healthy diet [4, 5]. The nutrient content of different forms of pistachio including dry, roasted/salted and raw are presented in Table I.

To collect useful and the most related information regarding the role of pistachios on the health, various disease states, blood lipid/lipoprotein levels, antioxidants and anti-inflammatory markers, body mass index (BMI) and food allergies, we searched the following keywords in the database: pistachio, heart disorders, lipids, BMI, antioxidants, anti-inflammatory markers and allergy. Based on searching by these keywords, we have found 50 articles in PubMed, 40 articles in ISI web of knowledge and 30 articles in Google Scholar. Amongst them, 80 articles have been indeed selected and 54 were used for this review.

Table I. The nutrient content of dry, roasted/salted and also raw pistachio per 1 ounce.

	US pistachios* (roasted/salted) 28 g, 1 oz (49 kernels)		Iranian pistachios (roasted/salted) 28 g, 1 oz (49 kernels)	
	Absolute value	%DV	ɔsolute value	%DV
Total Energy(kcal)	159.89		181.87	
Total fat (g)	12.7	20%	15.1	23%
Protein(g)	5.9	12%	6.1	12%
Total Carbohydrate(g)	8.1	3%	5.3	2%
Fiber(g)	2.8	11%	3.1	12%
Potassium, K(mg)	285		220	
Calcium, Ca (mg)	30		35.7	4%
Magnesium, Mg (mg)	31		0.64	4%
Iron, Fe (mg)	1.14	6%	0.62	
Zinc, Zn (mg)	0.66		<0.28	0%
Vitamin C (mg)	0.9	2%	1.5	8%
Folate (μg)	14		9.1	
Vitamin A (μg)	43.8	1%	3.9	
Alpha-tocopherol (mg)	0.62		<0.28	0%
Saturated fat(g)	1.5	8%		
Monounsaturated fat(g)	6.7			
Polyunsaturated fat(g)	3.8			
Cholesterol (mg)	0	0%		
Carotene, beta(μg)	44			
Carotene, alpha(μg)	0			
γ-Tocopherol(mg)	6.64			
Flavonoids (mg)	5.10			
Total phenols (mg)	470			
Lutein + zeaxanthin (μg)	329			
Total phytosterols (mg)	61–82		4	
Linoleic acid (18 : 2) (g)	3.7		0.06	
Linolenic acid (18 : 3) (g)	0.07			
Trans-fat (g)	0		<0.02	

*United States (American) pistachio daily value (percent %).
Data from references [8, 32, 38, 70–71].

Advantages of pistachio consumption on heart-related disorders, endothelial function and arterial stiffness

Cardiovascular diseases (CVDs) are amongst the leading causes for disability and death in industrial countries and in most developing countries. Over the past three decades, it has been well documented that both initiation and further development of atherosclerosis, as the pathological basis of CVD, was resulted from some of several abnormalities in the metabolism of lipoproteins, oxidative stress, chronic inflammation, and susceptibility to thrombosis [9–11]. Both the epidemiological- and clinical-based investigations have consistently claimed the significant cardiovascular benefits of tree nuts and peanuts, including pistachios [12, 13]. The cardio-protective properties of tree nuts and peanuts were found to be associated with several constituents such as the unsaturated fatty acid profile and bioactive constituents/phytochemicals [12, 13]. The oxidized Low-Density Lipoprotein (LDL)-cholesterol [14] and end products of lipid peroxidation are elevated within the atherosclerotic plaques [15]. They play a fundamental part in the development and further progression of atherosclerosis [14, 15]. During the past two decades, multiple clinical investigations have examined the beneficial effects of nuts consumption on CVDs outcomes and have reported their marked and valuable benefits [12, 13].

Hyperlipidemia, hypertension, diabetes, and obesity are of well-known risk factors associated with coronary arterial disease [10]. Some of other extensive epidemiological studies have demonstrated an effective link between nuts intake and related risk of Coronary Heart Disease (CHD). In a study 34,486 postmenopausal women have been enrolled in Iowa Women's Health Study (IWHS) for examination of the possible association between diet and CHD [14], by employing a 127-item Food Frequency Questionnaire (FFQ). The initial findings of this investigation were as similar as those of the Adventist Health Study (AHS) and a 15-year follow-up found remarkable reductions in total mortality of CHD in subjects who were frequent consumers of nuts as well as peanut butter. Moreover, results of one study which was undertaken on a number of 86,016 women in the Nurses' Health Study (NHS) [16] and findings of another investigation on 22,071 men enrolled in the Physician's Health Study [15] were in agreement with the AHS results which reported an inverse fashion of relationship between nut intake and CHD outcomes. West and co-workers enrolled 28 adults suffering from dyslipidemia and treated with pistachios. They further found a reduction in peripheral vascular constriction and reported that pistachios reduced the hemodynamic load which may lower the risk of CVD [17]. During the past decade, Gebauer and colleagues performed a study on 28 patients who had LDL cholesterol > 2.86 mmol/L. When the participants of the study consumed three isoenergetic diets supplemented with pistachios in a healthy diet for four weeks, it markedly lowered the CVD risk factors in a dose-dependent pattern [18]. A recent randomized parallel-group study reported that, daily consumption of 80 g (in-shell) of pistachio (equivalent to 40 g or 1.5 oz shelled pistachios) for 3 months in 60 adults showing mild dyslipidemia not only improved glycemic and lipid parameters, but also resulted in improvements in vascular stiffness and endothelial function [brachial artery flow-mediated vasodilation (BAFMD), and carotid-femoral and brachial-ankle pulse wave velocity][19]. In another randomized, crossover, controlled feeding study on 30 adults with type 2 diabetes, the pistachio diet (20% of total energy for 4 weeks) significantly reduced total peripheral resistance, increased cardiac output and improved some measures of heart rate viability. The systolic ambulatory blood pressure was also significantly reduced [20]. As evidenced by several studies, pistachio could have positive effects on cardiac health and vascular disorders through specific mechanisms described above.

The advantageous effects of pistachio on lipids/lipoproteins

Many clinical nutritional investigations have explored the effects of nuts on blood lipids, lipoproteins and/or their respective apolipoproteins, to date. Many of these investigations were short-term and have frequently compared the nut-supplemented diets with nut-free diets to evaluate the outcomes of nuts on changes in blood lipid profile in either healthy subjects or patients who had moderate hypercholesterolemia [21].

Two studies reported significant decrease in triglyceride (TG) levels [18, 22]. Gebauer and colleagues reported that supplementation of a healthy diet with pistachio nuts has beneficially affected both lipids and lipoproteins in a dose-dependent manner [18]. Previous studies revealed that, inclusion of pistachios to the diet have benefited lipid/lipoprotein profile [23–25]. Kay *et al.,* demonstrated that a pistachio-rich diet has decreased oxidized-LDL compared to the control diet [26]. Li and colleagues examined 70 overweight and obese individuals who were receiving approximately 230 calories from pistachios or pretzels as an afternoon snack for 12 weeks and reported a considerably lower TG level in the pistachio group compared to the pretzel group. They have claimed that pistachio has not significantly affected the TC, HDL and LDL levels [27].

Two other independent studies also showed the pistachio effects on lowering LDL after further consumption for three weeks [28, 29]. Altogether, these trial studies have proposed the positive effect of pistachio consumption on blood lipid/lipoprotein profiles when other sources of calories are replaced by pistachios in either usual or reduced-fat, controlled-energy diets [22, 29]. Sari and colleagues conducted an investigation on 32 healthy young men and reported that a pistachio-rich diet reduced LDL, TC, and TG in addition to the TC/HDL and LDL/HDL ratios [22].

Kocyigit and co-workers examined 24 healthy men and 20 healthy women for three weeks and reported that following a pistachio treatment (as 20% of the daily energy intake) has significantly reduced the mean plasma levels of TC, TG, TC/HDL and LDL/HDL ratios while has increased the HDL level, thereby favorably affecting the HDL:TG ratio. The LDL level was also reduced, but it was not significant [23]. About the effect of pistachio on the lipid profile, the results of researches are controversy. Although most of the reports showed a decrease in TG and LDL, some of them showed no effect.

Antioxidant and anti-inflammatory effects of pistachios

Like several other nuts, pistachios are considered as a rich source of antioxidants, such as lutein, b-carotene, and gamma-tocopherol in addition to selenium, flavonoids, and proanthocyanidins [30], thereby exhibiting a high *in vitro* antioxidant capacity [23, 31, 32].

An investigation indicated the beneficial effects of pistachios on the serum levels of antioxidants in 44 males and females who consumed a diet which provided 20% of their energy from pistachios for three weeks [23]. Kay and colleagues showed that the pistachio-enriched diets have elevated the serum levels of antioxidants [26]. Sari and co-workers demonstrated that a pistachio-enriched diet decreased serum interleukin-6 (IL-6), and overall oxidant status. However they reported no significant alteration in either C-reactive protein or Tumor Necrosis Factor alpha (TNF- α) levels [22]. In another 24-wk randomized controlled trial study, the unsalted pistachios (20% energy) were given daily to 60 individuals who were suffering from the metabolic syndrome. This remedy has significantly improved high-sensitivity C-reactive protein (hs-CRP), adiponectin, tumor necrosis factor (TNF)-α, and thiobarbituric acid reactive substances (TBARS) in the patients [33]. Results of an *in vitro* study in a cell model of human intestinal epithelial cells showed that a hydrophilic extract (HPE) obtained from Sicilian pistachio nut (rich in proanthocyanidins) decreased prostaglandin (PG)E2 production, IL-6 and IL-8 release, and cyclooxygenase (COX)-2 expression. HPE has also considerably inhibited the induction of para cellular permeability and further reduced NF-κB activation [34]. In another *in vitro* study, extracts of the leaf and fruit of pistachio showed strong antioxidant and anti-inflammatory activities in the ORAC assay [35]. *In vivo* pretreatment with aqueous and organic extracts from *pistacia lentiscus* in rat exhibited anti-inflammatory gastric mucosal damages in a dose-dependent manner [36]. In a randomized, crossover, controlled feeding study in type 2 diabetic patients who received diets containing pistachios, no positive effect has been found regarding inflammatory markers and endothelial function [37]. As listed above, most of the studies favor positive effects for pistachio by reducing inflammation and modulating oxidative stress.

Effects of pistachio on gut microbiota composition

Pistachios are rich in dietary fiber (2.8 g fiber per ounce) that 80% of them is insoluble [38]. A healthy microbiota composition contains bacteria, viruses and fungi in gut which emerges from microbial fermentation of significant amounts of fiber [39]. Microbiota improves health through the fermentation of fiber to beneficial end products, especially butyric acid, and modulation of phyto-chemicals [40]. Pistachio hull polysaccharides (PHP) have been demonstrated to possess a considerable prebiotic capability as similar as insulin and increase the production of acetate, propionate and butyrate [41]. A recent randomized crossover clinical trial in prediabetic subjects who consumed a pistachio-supplemented diet (57 g/d of pistachios) showed modulation of urinary metabolites related to gut microbiota [42]. In another randomized crossover human feeding study [0, 1.5 or 3 servings/d of the nuts (almond and pistachio)] pistachio consumption for 18 days improved the gut microbiota composition by increasing the number of potentially beneficial butyrate-producing bacteria [39]. Thus, pistachio could balance the gut microbiota based on findings of various studies.

Benefits of pistachios on weight control

Both of the epidemiologic- and clinical-based investigations have shown that moderate consumption of nuts may aid weight control [43, 44]. According to a 24-wk randomized control trial, a single food intervention with pistachios (20% of energy) has significantly decreased waist circumference [33]. In another study, pistachios were consumed as a portion-controlled daily snack (53 g) in a 12-week weight reduction diet and compared with refined carbohydrate snacks such as pretzels. It was observed that changes in BMI were more considerable in the pistachio groups [27]. The mechanisms by which pistachios promote weight loss are likely stronger satiety signals and lower metabolizable energy [45]. So, pistachio consumption might help in weight reduction.

Effect of Pistachio on Glucose Metabolism and Insulin Resistance

According to a recent meta-analysis in pre-diabetic and type 2 diabetics people, intake of 50 to 57 g/d of pistachio or uptake of 20% of the daily caloric from pistachios for a period of 1 to 4 months decrease fasting blood glucose, insulinemia, HOMA-IR, and fructosamine, but has no significant effect on HbA1c level. Modulation of insulin sensitivity through specific changes in miRNA and increasing the PI3K-AKT signaling pathway were also observed. The mechanisms for these effects might be related to the synergism between high PUFA, MUFA, polyphenols and carotenoids in pistachio [46, 47]. In streptozotocin-induced diabetic rats, *pistacia lentiscus* extract (125 mg/kg b.w.) showed antidiabetic activity which was similar to that observed following glibenclamide therapy (0.91 g/L). The potential mechanism of α-amylase inhibition was confirmed by *in vitro* studies [48]. However, in two other studies in diabetic patients [37] and obese subjects [27] who consumed diets supplemented with pistachio no changes were found in fasting glucose and insulin. Therefore, pistachio extract might be effective on glucose control via modifying insulin signaling cascade.

Pistachio and Kidney Function

The oil obtained from the aerial parts of pistachio is rich in unsaturated fatty acids (oleic + linoleic = 73%) and saturated fatty acids (palmitic + stearic = 25.8%). This essential oil has been reported to show antioxidant, anti-inflammatory, antimicrobial, antifungal and antiatherogenic activities [49]. Thus, pistachio extracts could have ameliorative effects in acute renal failure (ARF) by alleviating inflammation and reducing ROS (reactive oxygen species) production [50]. According to a recent study on rabbits, pistachio fatty oil extract was confirmed as a safe nutrient with no toxic effects on liver and renal functions [49]. The nephroprotective effects of different doses (10, 50 and 100 mg/kg/p.o) of the hydroalcoholic extract of pistachio on rats was also proved. The pistachio extract showed protective effects in renal function through reducing the serum levels of creatinine, urine volume, urine glucose and blood urea nitrogen (BUN) and increasing creatinine clearance. The kidney structural damage was also reduced by attenuated oxidative stress and inflammation [50]. Another animal study revealed protective effects of the hydroethanolic extract of pistachio leaf against gentamicin-induced nephrotoxicity. These rats orally treated with 200, 400, and 800 mg/kg of the hydroethanolic extract of *P. atlantica* leaf, showed a significant increase in catalase (CAT), superoxide dismutase (SOD) and vitamin C and also a reduction in the serum levels of creatinine (Cr), urea, uric acid, malondialdehyde (MDA), protein carbonyl (PC), tumor necrosis factor-α (TNF-α) protein, and the gene expression of TNF-α [51]. The pistachio ethanolic extract has also shown effective impact on proximal tubular cells through reducing E-cadherin expression and particles size of calcium oxalate monohydrate (COM) crystals [52]. Animal studies also revealed the positive effect of pistachio extract on kidney functions which may pave the way for more practical human studies in future.

Food allergy reactions are elicited by pistachios

Allergy to peanut and tree nuts is defined by a high frequency of life-threatening anaphylactic reactions that typically persists during lifetime [53]. A clinical association between peanut and tree nuts allergies was reported. However, the prevalence of multiple nut sensitivities exhibited discrepant findings. Based on the findings of two groups that assessed subjects from specialty allergy clinics, the prevalence of nut allergies has been reported between 35% to 40% [54]. However, in the general population, there is only 2.4% prevalence for peanut and tree nut allergies [55].

Allergy to the other tree nuts, like cashews, walnuts, almonds, pistachios, hazel nuts, and pecans was considered to be a public health problem within the most countries [56]. Similar to other tree nuts, pistachios can also sensitize the immune system and is considered a source of food allergens [57–59]. The most frequent allergens which have been described are Pis v1, 2S albumin; Pis v 2, 11S globulin subunit, Pis v 3, vicillin, Pis v 4, a manganese superoxide dismutase, Pis v 5, and 11S globulin subunit [57–59]. Three of these five identified allergens are globulins, and one is an albumin storage protein that is common in other tree nuts as well. Fernandez and co-workers reported that pistachios have several allergens that are protein in nature and can trigger type I hypersensitivity reactions [60]. Parra and colleagues described three adult cases of anaphylaxis to the pistachio protein allergens [61]. A rare case (one in a young child) of an oral allergic syndrome characterized by itching and localized swelling in the mouth and pharynx after consumption of pistachios was reported in Italy. The allergic reactions most often took place in response to ingestion of either dry pistachios alone, or when pistachio-containing foods are taken. An allergic reaction was confirmed by skin-prick and specific IgE tests. Interestingly, an adult will experience a reaction only if the oral mucosa was eroded (as might occur if the shell was broken by the teeth) [62].

Noorbakhsh and colleagues claimed that exposure to pistachios causes related allergic reactions and, in pistachio allergic individuals, these reactions may result in

Table II. Summary of human studies on the effects of pistachio on health.

Study	Subject	Design	Intervention	Main Findings
West SG et al. (2012) [17]	Twenty-eight adults with dyslipidemia	Randomized, crossover, controlled-feeding study	Diet containing 10% or 20% of energy from pistachios (on average, 1 or 2 serving per day) (4 weeks)	↓ Systolic blood pressure, peripheral vascular constriction and heart rate. ↑ Cardiac output.
Gebauer SK et al. (2008) [18]	28 individuals with LDL cholesterol > or = 2.86 mmol/L	Randomized crossover controlled-feeding study	1 serving/d of a pistachio diet (1 PD; 10% of energy from pistachios), 2 servings/d of a pistachio diet (2 PD; 20% of energy from pistachios)(4 weeks)	↓ TC/HDL-C, LDL C/HDL-C and non-HDL cholesterol/HDL cholesterol. 2 PD: ↓ TC, LDL-C, non-HDL -C, apo B, apo B/apo A-I, and plasma SCD
Sauder KA et al. (2014) [20]	30 adults with type 2 diabetes	Randomized, crossover, controlled feeding study.	A moderate-fat diet (33% fat) containing pistachios (20% of total energy) (4 weeks)	↓ Total peripheral resistance, and systolic ambulatory BP. ↑ Cardiac output.
Sari I et al. (2010) [22]	32 healthy normolipidemi young men	Prospective crossover trial	Mediterranean diet in which pistachio was added by replacing the monounsaturated fat content (20% of daily caloric intake)(4 weeks)	↓ Glucose, LDL-c, TC, TG, TC/HDL-C, LDL-C/HDL-C and, serum interleukin-6, total oxidant status, lipid hydroperoxide, and MDA. ↑ Endothelium-dependent vasodilation, and SOD
Sheridan MJ et al. (2007) [24]	15 subjects with moderate hypercholesterolemia (serum cholesterol greater than 210 mg/dL)	Randomized crossover trial	Four weeks of dietary modification with 15% caloric intake from pistachio nuts	↓ TC/HDL-C, LDL C/HDL-C, B-100/A-1 ↑ HDL-C
Edwards K et al. (1999) [72]	Ten patients with moderate hypercholesterolemia.	Controlled, randomized crossover design	Dietary modification with 20% caloric intake from pistachio nuts (3 weeks)	↓ TC, TC/HDL-C, LDL-C/HDL-C ↑ HDL-C
Kocyigit A et al. (2006) [23]	24 healthy men and 20 healthy women	Randomized controlled trial	Dietary modification (substituting pistachio nuts for 20% of their daily caloric intake) (3 weeks)	↓ TC, TC/HDL-C, LDL-C/HDL-C, and MDA ↑ HDL-C, AOP, AOP/MDA
Kay CD et al. (2010) [26]	28 hypercholesterolemic adults (LDL-cholesterol >or=2.86 mmol/L)	Randomized, crossover controlled-feeding study	A lower-fat control diet with 1 serving/d (i.e. 32-63 g/d; energy adjusted) of pistachios (1 PD; 10% energy from pistachios) or with 2 servings/d (63-126 g/d; energy adjusted) of pistachios (2 PD; 20% energy from pistachios)	↑ Plasma lutein, alpha-carotene, and beta-carotene ↓ Serum oxidized-LDL

(Continued on next page)

Table II. (Continued)

Study	Subject	Design	Intervention	Main Findings
Li Z et al. (2010) [27]	59 obese subjects	Randomized controlled trial	Isocaloric weight reduction diet(500 cal per day less than resting metabolic rate) included an afternoon snack of either 53 g (240 cal) of salted pistachios or 56 g of salted pretzels (220 cal)	↓ TG, BW
Aldemir M et al. (2011) [28]	17 married male patients with ED	Prospective crossover trial	100 g pistachio nuts diet (3 weeks)	↓ TC, LDL ↑ HDL
Kasliwal RR et al. (2015) [19]	60 adults with mild dyslipidemia	Open label, randomized parallel-group study	lifestyle modification (LSM) alone or LSM with consumption of 80 g (in-shell) pistachios(equivalent to 40 g or 1.5 oz shelled pistachios) daily (3 months)	↓ LDL, TC/HDL, FBS, cfPWV, Left and average baPWV, and BAFMD ↑ HDL
Gulati S et al (2014) [33]	60 individuals with themetabolic syndrome	Randomized control trial	A standard diet and exercise protocol with unsalted pistachios (20% energy) daily (24 weeks)	↓ WC, FBS, TC, LDL, hs-CRP, TNF-α, FFAs, TBARS and adiponectin levels.
Ukhanova M et al. (2014) [39]	34 healthy volunteers	Randomised, controlled, cross-over feeding studies	0, 1.5 or 3 servings/d of pistachio or almond(18 days)	↑ Number of potentially beneficial butyrate-producing bacteria ↓ Number of lactic acid bacteria
Hernández- P et al (2017) [42]	39 prediabetic subjects	Randomized crossover clinical trial	A pistachio-supplemented diet (PD, 50% carbohydrates, 33% fat, including 57 g/d of pistachios daily) (4 months)	↓ Gut microbiota metabolites (hippurate, p-cresol Sulfate, and dimethylamine), cis-aconitate, TMAO
Hernández- P et al (2017) [47]	49 subjects with prediabetes	Randomized crossover clinical trial	A pistachio-supplemented diet (PD, 50% carbohydrates, 33% fat, including 57 g/d of pistachios daily)(4 months)	↓ miR-192 and miR-375

(↑ =increase ↓ = decrease) Total cholesterol/high-density lipoprotein ratio (TC/HDL-C),low-density lipoprotein/high-density lipoprotein ratios (LDL-C/HDL-C), apolipoprotein B100 to apolipoprotein A1 ratio (B100/A1),low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), superoxide dismutase (SOD), total cholesterol (TC), triacylglycerol (TG), stearoyl-CoA desaturase activity (SCD), malondialdehyde (MDA), antioxidant potential (AOP), antioxidant potential to malondialdehyde ratio (AOP/MDA), body weight (BW), erectile dysfunction (ED), brachial artery flow-mediated vasodilation (BAFMD), carotid-femoral pulse wave velocity (cfPWV), brachial-ankle pulse wave velocity (baPWV), fasting blood sugar (FBS), waist circumference (WC), high-sensitivity c-reactive protein (hs-CRP), free fatty acids (FFAs), tumor necrosis factor (TNF)-α, thiobarbituric acid reactive substances (TBARS), trimethylamine N-oxide (TMAO), miRNAs related to glucose and insulin metabolism (miR-192 and miR-375)

Table III. Summary of Experimental Studies On the Effects of Pistachio on Health.

Study	Sample	Intervention	Main Findings
Gentile C et al. (2015) [34]	A cell model of IBD, consisting of interleukin (IL-1β)-exposed human intestinal epithelial cells.	Differentiated human epithelial colorectal adenocarcinoma cells were pre-incubated with HPE or PPF and then were exposed to IL-1β.	↓ (PG)E2, IL-6 and IL-8, (COX)-2 expression, paracellular permeability and NF-κB activation
Remila S et al. (2015) [35]	Macrophages of melanoma (B16F10) and mammary (EMT6) cell lines exposed to ATP or H2O2	The antioxidant activity was assessed using the ORAC test, Anti-inflammatory activity was examined by measuring the secretion of interleukin-1β	Leaf extract (100 μg/mL) showed significant anti-inflammatory activity, compared to ASA. Leaf and fruit extracts inhibited the growth of B16F10 cells.
Dellai A et al. (2013) [36]	In vivo investigation (carrageenan-induced paw edema assay and HCl/ethanol-induced gastric lesions in paw rats)	The aqueous, chloroformic, ethyl acetate and methanolic leaves extracts of Pistacia lentiscus (50, 100 and 200 mg/kg) given intraperitoneally	↓ Gastric lesions in a concentration related manner, inflammation, and gastric mucosal damages
Mehenni C et al (2016) [48]	Experimentally paracetamol-induced liver damage. (streptozotocin-induced diabetic rats)	Mice were pretreated with the same dose of PL or PF extract (125 mg/kg b.w.) or a combination of both (PL/PF 63/63 mg/kg b.w.)	Significant protection against paracetamol-induced hepatic necrosis + ↓ α-amylase
Djerrou Z et al. (2011) [49]	12 white male New Zealand rabbits	PLFO was applied to tested rabbits (PLFO group) via rectal route, once daily 5-day per week, for six consecutive weeks at the dose of 1 ml/Kg body weight.	↓ AST and ALT ↑ Fasting glucose level
Ehsani V et al. (2017) [50]	Gentamicin-induced nephrotoxicity rats	Nephrotoxicity was induced in rats by intraperitoneal injection of gentamicin (100 mg/kg/day for 7 days). Hydroalcoholic extract of pistachio (10, 50 and 100 mg/kg/p.o) was administered. (7 days)	↓ Serum creatinine, urine volume, urine glucose and BUN ↑ Creatinine clearance
Heidarian E et al. (2017) [51]	Forty Gentamicin-induced nephrotoxicity rats	They received gentamicin (120 mg/kg, i.p.). Also orally treated with 200, 400, and 800 mg/kg of P. atlantica leaf hydroethanolic extract (7 days)	↑ CAT, SOD, vitamin C, and HDL-C ↓ Cr, urea, uric acid, MDA, PC,TG, TC, LDL, VLDL,TNF-α, the gene expression of TNF-α, and kidney lymphocyte infiltration
Cheraft-Bahloul N et al. (2017) [52]	In vitro study. Human Kidney [HK]-2 cells were incubated with and without COM in the presence or absence of PLEF.	PLEF incubated with COM crystals on proximal tubular cells.	↓ Hydrogen peroxide, COM concentration, particles size ↑ E-cadherin expression

(↑ = increase ↓ = decrease) inflammatory bowel diseases (IBD), hydrophilic extract from Sicilian pistachio nut (HPE), polymeric proanthocyanidin fraction (PPF), cyclooxygenase (COX)-2, prostaglandin (PG)E2, nuclear factor-κB (NF-κB), acetylsalicylic acid(ASA), pistacia lentiscus leaves (PL) and fruits (PF), pistacia lentiscus fatty oil (PLFO), aspartate transaminase (AST) and alanine transaminase (ALT), blood urea nitrogen (BUN), catalase (CAT), superoxide dismutase (SOD), high-density lipoprotein cholesterol (HDL-C), creatinine (Cr), malondialdehyde (MDA), protein carbonyl (PC), triglyceride (TG), total Cholesterol (TC), low-density lipoprotein cholesterol(LDL) very low-density lipoprotein cholesterol (VLDL), tumor necrosis factor-α (TNF-α), calcium oxalate monohydrate (COM), pistacia lentiscus ethanolic fruit extract (PLEF).

co-sensitivities with other tree nuts, such as cashews and almonds. The taxonomical classification of pistachios seems to be involved in predication of allergenic cross-reactivity [63]. Pistachios are most frequently consumed within the pistachio cultivation parts in Iran rather than other parts and it appears that allergic people in such regions are more exposed to pistachio allergens during their lifetime [63]. In an investigation on 122 allergic children, 92% of the patients with a peanut allergy, tree nut allergy, or both of them showed elevated IgE levels to more than one tree nut, while 37% of the patients were reactive to the allergens and showed elevated IgE levels for more than a nut [64]. Noorbakhsh's research team evaluated allergy symptoms to other nuts including cashews, almonds, and peanuts in pistachio allergic individuals. They found that allergic reactions to cashews and almonds in people living in pistachio cultivation areas were more than those observed in other people [63]. The fewer number of peanut allergic patients in the pistachio-rich areas might be, at least in part, due to the fact that these people do not consume this nut. It could also be related to the limited IgE cross-reactivity between pistachios and peanuts, as the authors claimed [63]. Several studies proposed that there might possibly be some common allergens between various tree nuts. As an example, a study on 142 allergic patients who were exhibiting allergy to peanuts indicated that 50% of them had positive results for skin tests to almonds, 40% to cashews, 30% to pistachios, 26% to Brazil nuts, and 21% to hazelnuts [65]. Multiple tree nut allergies which were observed in allergic patients are probably due to the presence of common IgE epitopes in homologous tree nut allergens [66]. The CAP-inhibition (complex absorbing potential) studies demonstrated a remarkable cross-reactivity between pistachios and cashews; this was also present between pistachios and other types of dried fruits obtained from taxonomically unrelated botanical families [67]. It has been reported that peanuts are serologically IgE cross-reactive with pistachios. Hazelnuts, cashews, Brazil nuts, pistachios, and almonds together constitute a group of moderately cross-reactive tree nuts [68]. These findings are in contradiction with a previous investigation which reported a cross reactivity between peanuts and almonds [69]. Food allergy reactions caused by pistachio have been proved for years and are indicated as one of the negative effects of pistachio.

Table II and III demonstrate the effects of pistachio nut on hearth related diseases, blood lipid and glucose levels, antioxidant and anti-inflammatory status, weight control, renal function and gut microbiota based on different human and animal studies.

Conclusions

Overall, this review article showed that for a long period of time pistachios constitute a part of the human diet. A large body of evidences obtained from clinical studies demonstrated that pistachios reduce oxidative and inflammatory stress, heart diseases, blood lipids/lipoproteins, and obesity. Additionally, pistachios can also function as a prebiotic. However, pistachios may act as a food allergen for some individuals. Thus, dietary recommendations encourage consuming pistachios as part of a healthy dietary pattern to reduce chronic disease risk. However, individuals and healthcare professionals must be mindful of any potential nut allergy. In this review article, we discussed all of the health benefits of pistachio nuts regarding different diseases based on the latest results of both human and animal studies. Findings of *in vivo* and *in vitro* studies of pistachio extract were also included. No published article was found regarding the effects of Asian pistachio on health in Asian population and this might be the limitation of our study. Also molecular mechanisms have not been discussed in this review. More detailed data about the nutrient composition of pistachio nuts especially Asian species are needed in future research for exploring more sophisticated mechanisms of action of pistachio with a deep look into cellular pathways. Also, a metaanalysis about pistachio in different disorders could be helpful for getting the best results.

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Conflict of interest

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