Effects of Pistachios and Their Different Plant Parts on Various Disorders: Evidence about Their Therapeutic Effects on Diabetes Mellitus, Gastrointestinal and Liver Disorders, as well as Blood Pressure

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Abstract

Background: The genus Pistacia is from the family Anacardiaceae, which contains about 70 genera and over 600 species. Various genera of Pistacia are widely spread from the Mediterranean region to the Central Asia, some of which including *Pistacia lentiscus* L., P. atlantica Desf., *P. terebinthus* L., *P. vera* L., and *P. khinjuk*.

Materials and Methods: The present study aims to collect the latest information from databases regarding beneficial effects of pistachio plant parts and nuts.

Results: Different plant parts of pistachios are beneficial for various diseases. The *P. vera* fruit extracts exerted favorable effects on HDL and LDL levels in a rabbit model of atherosclerosis. The oleogum resin, being obtained from *Pistacia lentiscus*, is widely used as an effective therapeutic remedy for curing inflammatory bowel disease in traditional Iranian medicine. Serum glucose levels significantly decreased in diabetic patients who received *P. lentiscus var*. chia gum.

Conclusions: Against this backdrop, in this review article, we aim to investigate beneficial effects of pistachio fruit and its plant parts on different clinical states, such as gastrointestinal disorders, liver diseases, diabetes, and blood pressure.

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1. Introduction

As already stated, the genus *Pistacia* is from the family Anacardiaceae, which contains approximately 70 genera and over 600 species. The species of the genus *Pistacia* are known as evergreen or deciduous resin-bearing shrubs. The trees are known as xerophytic trees that are able to grow 8–10 m in length. Various genera of *Pistacia*, including *Pistacia lentiscus* L., *P. atlantica* Desf., *P. terebinthus* L., *P. vera* L., and *P. khinjuk* are widely cultivated in geographical regions from the Mediterranean basin to the Central Asia [1]. In addition, various *Pistacia* species, including *P. vera* L., *P. khinjuk*, *P. atlantica* Desf., and *P. atlantica* are naturally grown in Iran.

The species *P. atlantica* has three subspecies or varieties that are named *cabulica*, *kurdica*, and *mutica* [2]. *P. vera* is used as the only commercial species, with other species having been often applied as rootstocks for *P. vera.* Iran and the USA are the main pistachio producing countries [1]. Different parts of the *Pistacia* species show various pharmacological activities. Mastic has been introduced as the resin of *P. lentiscus* in many references. In addition to being utilized as a therapeutic remedy, *Pistacia* species are used in the food industry. For instance, pistachio (*P. vera*) nuts are generally consumed as food additives, *P. terebinthus* fruit is used as a snack food or in making coffee-like drinks [3, 4],and the anthocyanin composition of *P. lentiscus* fruit is used as a food colorant. However, a high level of vitamins and minerals was observed in the genus *Pistacia*, being known as secondary metabolites.

In addition to the abovementioned uses of pistachios, pistachio fruit is consumed as an herbal remedy in multiple disease states, such as gastrointestinal and cardiovascular diseases, type 2 diabetes, and a lipid lowering agent both in ancient times and in the present time [5]. In view of the foregoing, we aimed to investigate beneficial effects of pistachio nuts as well as their eatable and non-eatable components on disease states, to be discussed in the next sections of this article.

By and large, this review aims to present a general discribe on phytochemical features, pharmacological activities, and toxicity of the genus *Pistacia.*

2.Materials and Methods

In this review study, relevant articles were collected from databases of PubMed, Scopus, Google Scholar, and Web of Science, which were published from 2000 to January 2020. The search was performed using the keywords of *Pistacia*, diabetes, cardiovascular, obesity, body weight, inflammation, gastrointestinal, liver-derived enzymes, bowel disease, blood pressure, body mass index, and waist circumference. In addition, the conjunctions of “and” and “OR” were utilized to incorporate term usages in the literature review. Accordingly, articles on the effects of pistachio consumption on humans and animals were selected, which totaled 15 articles that were associated with pistachios and human health.

3. Results and Discussion

Beneficial effects of pistachios on gastrointestinal disorders

Pistachio gum plays a central role in treating gastrointestinal disorders. Gastrointestinal diseases affect the gastrointestinal (GI) tract from the mouth to the anus, which include two functional and structural types. Some of these diseases include nausea and vomiting, food poisoning, lactose intolerance, and diarrhea.

Many studies have attributed such a property to pistachio gum [6]. According to research, resins obtained from *P. lentiscus* decreased the severity and size of gastric mucosal injuries at considerable levels, due to pyloric ligation, through the use of aspirin, phenylbutazone, reserpine, and restraint with cold stress via its anti-secretory and cyto-protective activities [7]. Findings of a double-blind placebo controlled trial on humans demonstrated that *P. lentiscus* gum significantly relieved symptoms in patients suffering from functional dyspepsia [8]. Furthermore, *Pistacia* species showed antibacterial activities against *Helicobacter pylori* [9, 10].

Today, nutritional strategies can change the richness and biodiversity of the gut microbiota, so they can be linked to inducing healthier metabolic status. A pistachio-based diet in HFD obese mice influenced seven major phyla of the gut microbiota, including *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *TM7*, *Deferribacteres*, *Actinobacteria*, and *Tenericutes*. In fact, fatty acids, flavonoids, or fibers of the pistachios could modulate the gut microbiota composition. In addition, the pistachio diet can exert effects by enriching potentially beneficial microbes, such as lactic acid bacteria [11]. Additionally, treatment with *P. lentiscus* oil in an trial animal model of colitis hindered the onset and development of acute colitis, with this relatively decreasing the disease-caused weight loss [12]. Rahimi *et al* (2013) reported that in rat models of colitis, an herbal mixture comprised of *P. lentiscus* gum led to decreasing colonic hurm and weakening biochemical markers linked to pathophysiology of irritable bowel syndrome (IBS) [13] (Table 1)

Table 1 Effects of pistachio species on gastrointestinal disorders

Pistachio species	Plant part	Clinical state	P-value	Animal model	Ref.
Pistacia. Lentiscus	Gum	Gastric mucosal injuries ↓	$P < 0.001$	Rats	Al-Said *et al*. (1986)
Pistacia lentiscus	Gum	Functional dyspepsia↓	$P < 0.05$	Humans	Dabos *et al*. (2010)
All *Pistacia* species		*Helicobacter pylori* infection ↓			Paraschos *et al*. (2011); Ramezani *et al*. (2004)
Pistacia lentiscus	Oil	Weight loss-born colitis ↓	$P < 0.05$	Mice	Kim and Neophytou (2009)
Pistacia lentiscus	Gum	Experimental rat IBS↓	$P < 0.001$	Male Wistar-albino rats	Ljubuncic *et al*. (2005)
Pistacia lentiscus	Non-boiled	ALP↓ SGPT↓	$P<0.01$ $P<0.05$	Male Wistar albino rats with CCl4-	Ljubuncic *et al*. (2005)

	aqueous extract of leaves	SGOT↓ Bilirubin level ↓	*P*<0.01 *P*<0.05	induced hepatotoxicity	
Pistacia lentiscus	Gum	Total cholesterol↓ LDL↓ Total cholesterol/HDL↓ Lipoprotein (a) ↓ apoA-1↓ apoB↓ SGOT↓ SGPT↓	*p* = 0.002 *p* = 0.001 *p* = 0.018 *p* = 0.002 *p* < 0.001 *p* < 0.001 *p* = 0.039 *p* =0.005	93 women and 40 men, all aged over 50	Marinou *et al*. (2010)
Pistacia vera	Seeds	Atherosclerosis-derived hypercholesterolemia↓			Harandi *et al*. (2018)
Pistacia vera	Seeds	Total cholesterol ↓ HDL↑ Total cholesterol/HDL ratio ↓ LDL/HDL ratio↓ TG↓ LDL↓	p<0.04 p<0.09 p<0.01 p<0.02 NS NS	10 patients with moderate hypercholesterolemia	Edwards *et al*. (1999)
Pistacia vera	Seeds	Body weight Cholesterol ↓ TNF-α ↓ *Firmicutes* ↑ *Bacteroidetes* ↓ *Proteobacteria* ↓ *TM7* ↑	NS *P*<0.05 *P*<0.05 *P*<0.05 *P*<0.05 *P*<0.05 *P*<0.05	Obese male C57BL/6J (B6) mice	Wien *et al*. (2010)

		Deferribacteres ↑ *Actinobacteria* ↑ *Tenericutes* ↑	*P*<0.05 *P*<0.05 *P*<0.05		
Pistacia vera	Seeds	Body weight → Body mass index → Waist circumference → Cholesterol → HDL → LDL →	*P*=0.05 *P*=0.05 *P*=0.05 *P*=0.05 *P*=0.05 *P*=0.05	Non-diabetic overweight/obese adults n=100	Foster *et al*. (2012)
Pistacia vera	Seeds	LDL ↓ HDL ↑ Body weight → Body mass index → Waist circumference →	*P*<0.05 *P*<0.05 P=0.38 P=0.13 P=0.23	60 adults with mild dyslipidemia	Collaboration (2010)
Pistacia vera	Seeds	Body weight → Waist circumference → Fat body mass →	P=0.96 P=0.72 P=0.29	30 healthy French women; age range of 23-49	Rahimi *et al*. (2013)
Pistacia terebinthus	Fruit	Total cholesterol↓ TG↓ VLDL↓ LDL↓ HDL↑	P<0.01 P<0.01 P<0.01 P<0.01 P<0.001	Hypercholesterolemic rabbits	Bakirel *et al*. (2004)
Pistacia integerrima	Aqueous extract of galls	SGPT↑ SGOT↑ ALP↑	P<0.01 P<0.01 P<0.01	CCl4-treated rats	Khan *et al*. (2004)
Pistacia integerrima	Methanolic extract of bark	Anti-nociceptive and analgesic, anti gastrointestinal motility effect	*p*<0.05	Balb-C mice	Banno *et al*. (2006)

Pistacia lentiscus	Gum	TNF-α ↓ MIF↑ IL-6→ MCP-1→ GSH→	*P* = 0.028 *P* = 0.026 NS NS NS	Patients with established moderately active CD	Fernandez-Banares *et al*. (1999)
Pistacia lentiscus	Gum	CDAI↓ IL-6↓ CRP↓ TAP↑	*P* = 0.05 *P* = 0.027 *P* = 0.028 *P* = 0.036	Patients with established moderately active CD	Gupta *et al*. (1997)

Abbreviations used in this table are listed below:
ALP: alkaline phosphatase, apoA-1: Apolipoprotein A-1, apoB: Apolipoprotein B, CCl4: carbon tetrachloride-4, CD: Crohn's disease, CDAI: CD activity index, CRP: C-reactive protein, GSH: intracellular antioxidant glutathione, HDL: high density lipoprotein, IBS: Irritable bowel syndrome, IL-6: Interleukin 6, LDL: low density lipoprotein, MCP-1: monocyte chemotactic protein-1, MIF: macrophage migration inhibitory factor, *SGOT:* serum glutamic oxaloacetic transaminase, *SGPT:* serum glutamic pyruvic transaminase, TAP: total antioxidant potential, TG: triglyceride, TNF-α: tumor necrosis factor α, VLDL: very low density lipoprotein. ↓: decreased, ↑: increased, →: no change, NS: not significant

Effects of pistachios on liver-derived enzymes and other serum biochemical parameters

P. lentiscus leaves were reported to have protected the liver against carbon tetrachloride-(CCL4) in a rat model of hepatotoxicity via attenuating the level of bilirubin as well as balancing the reaction of liver-derived enzymes (14). Another study showed that hepatic fibrosis, mild cholestasis, and depletion of reduced glutathione were improved by the long-term administration of an aqueous form of pistachio leaf extract in healthy rats [15]. According to research, treatment with *P. lentiscus* var. *chia* gum reduced liver-derived enzymes as well as hypolipidemic effects in healthy subjects for 18 months [16]. In a study, mastic triterpenes exerted antioxidant and anti-atherogenic effects, thereby leading to a considerable increase in intracellular GSH and downregulation of CD36 expression [17]. Accordingly, CMG compounds could mediate as a PPARα agonist to improve serum lipid metabolism [18]. According to research, Oleanonic acid is one of the mastic compounds identified as a PPARγ agonist. This compound

can regulate insulin-mediated gene expression, being associated with PPARγ. In fact, triterpenoid compounds exert their beneficial effects by increasing insulin secretion through pancreatic β-cells [19] .

In a rabbit model of atherosclerosis, extracts of *P. vera* fruit were able to exert beneficial effects on high density lipoprotein (HDL) and low density lipoprotein (LDL) levels [20]. Although, the extract of *P. vera* hulls is rich in phenolic compounds, Harandi *et al* (2020) reported that the hydro-alcoholic extract of pistachio hulls reduced the survival of liver cancer cells (HepG2) in an in vitro study [21]. In a study in which pistachio nuts were consumed for a period of three weeks, a positive change was recorded in lipid profiles in sicks with moderate hypercholesterolemia, yet it reduced triglyceride (TG); however, LDL concentrations did not considerably decrease [22]. In addition, hypolipidemia was found to be associated with *P. terebinthus* fruit treatment in hypercholesterolemic rabbits [23]. Due to their antioxidant properties, some *Pistacia* species demonstrated anti-hepatotoxic effects in rats fed by a hydro-ethanolic extract of *Pistacia* gum. In a rat model of CCL4-induced hepatoxocity, the level of serum glutamic pyruvic transaminase (*SGPT*) in the animals that received *P. vera* gum extracts (0.5 and 1 g/kg) decreased. Nonetheless, no effect was reported on the level of serum glutamic oxaloacetic transaminase (*SGOT*). These observations might be due to the presence of flavonoids, saponins, and hydrotannins, indicating that the ethanolic extract of *P. vera* gum show a protective activity versus liver hurm in the rat model of hepatic injury [24]. Furthermore, the aqueous extract of *Pistacia integerrima* was found to be effective in treating CCL4-induced liver injury in rats [25]. The *Pistacia integerrima* leaf extracts proved to have anti-nociceptive and analgesic effects in mice, with no considerable acute toxicity after oral administration [26]. In addition, the bark extract of this plant had analgesic and anti-gastrointestinal motility effects [27] (Table 1).

Pistachios and inflammatory bowel disease (IBD)

The oleogum resin (OR), as a component of *Pistacia lentiscus* (*P. lentiscus*), being also called “Mastaki”, is widely used as an effective therapeutic remedy in curing inflammatory bowel disease (IBD) in traditional Iranian medicine[6]. Inflammatory bowel disease (IBD) is a term used for two conditions (Crohn's disease and ulcerative colitis) specified by chronic inflammation of the gastrointestinal (GI) tract. Treatment with OR was reported to improve both the onset and development of the disease, thereby inhibiting weight loss in colitis models [7, 28-35]. Additionally, generation processes of pro-inflammatory mediators, including nitric oxide (NO) and prostaglandin E2 from their cellular sources, are limited by OR. Analyses based on western blotting and reverse transcription polymerase chain reaction (RT-PCR) confirm that OR (from *P. lentiscus)* is able to down-express persuadable nitric oxide synthase (iNOS) and cyclooxygenase-2 (Cox-2) at both protein and mRNA levels. In addition, research shows that OR contains hydroxyl radicals with potent scavenging properties, yet it scavenges NO and superoxide radicals very weakly (31). OR (at an oral dose of 500 mg/kg) has been reported to adequately reduce severity of gastric mucosal damage caused by pyloric ligation, aspirin, phenylbutazone, and reserpine in rat models [7]. Furthermore, in a four-week treatment of Crohn’s disease (CD) patients with OR (6 caps/d, 0.37 g/cap), the protein level of tumor necrosis factor α (TNF-α) decreased, while the macrophage migration inhibitory

factor (MIF) remarkably increased. This fact may somehow confirm that random migration and/or oriented chemo-attraction of monocytes/macrophages to inflamed regions were restricted. This restricted migration of monocytes/macrophages may help attenuate clinical aspects of IBD due to the decreased infiltration of these cell types inside the inflamed bowel. According to the latest studies, an alteration is yet to be observed in the levels of interleukin 6 (IL-6), chemokine (C-C motif) ligand 2 (CCL2), and intracellular antioxidant glutathione (GSH). This may change OR effects, as an immune-modulatory factor, on peripheral blood mononuclear cells (PBMCs). In fact, this may be realized either via inhibition of TNF-α expression or stimulation of its activity [36]. In another study of OR effects (6 caps/d, 0.37 g/cap) on CD patients, a remarkable reduction was reported in the CD activity index (CDAI), through which a comparison was made with pretreatment status of the disorder. Accordingly, the plasma levels of IL-6 and c-reactive protein (CRP) considerably decreased; in addition, the total antioxidant potential (TAP) significantly decreased in the studied patients. Surprisingly, none of the patients or controls experienced considerable side effects [37].

The results of a double-blind clinical trial on patients experiencing symptomatic and endoscopically proven duodenal ulcers showed that symptomatic relief was achieved in 80% of patients treated with OR and in 50% patients treated with a placebo ($P < 0.01$). In this study, the patients received either OR or a placebo for a two-week period. Besides, endoscopical findings showed that 70% of patients treated with OR were cured, while this rate amounted to 22% in patients who only received placebo treatment. The variation in healing caused by the therapy protocols was considerably significant ($P < 0.01$). OR, in addition to being tolerated well by patients, was associated with no side effect. These investigations confirmed the fact that OR is effectively involved in improving ulcer-related healings [36-42] (Table 1).

In general, given the underlying action mechanisms of these plant products, the combination of OR with other plant remedies can be beneficial for the effective multiple reactions involved in IBD. Plant sources of OR include *Pistacia lentiscus*, *Bunium persicum*, *Solanum nigrum*, *Plantago ovata*, *Boswellia*, *Solanum nigrum*, *Plantago ovate*, and *Commiphora mukul* [34]. According to the data existing in the literature, *Pistacia lentiscus* is more effective in treating IBD, with no harmful side effects observed [34]. Some other studies demonstrated that beneficial effects of OR on IBD are exerted through various pathways. These pathways include NO production inhibition [29], immunomodulatory properties [30], antimicrobial [29] and anti-inflammatory activities [32, 33], as well as inducing clinical remission [38, 39]. In general, these data indicate that the the effects of OR on various features of IBD are required to be examined more accurately in further studies. In addition, obesity can be caused by the interaction of gut microbes and metabolic disorders. In general, gut microbes in obese patients can induce inflammation in adipose tissue and increase macrophage infiltration. Rock *et al* (2020) reported that pistachio consumption in high-fat diet-fed mice surprisingly increased butyrate-producing bacteria, such as the genera *Allobaculum* and *Dorea*. Butyrate helps maintain normal differentiation in epithelial colonocytes. Moreover, in some models of inflammatory bowel diseases, colitis decreased with an increase in probiotic *Lactobacillus* in a pistachio diet [43].

Effects of pistachios on lowering the glycemia index

Diabetes mellitus (DM), especially type 2 diabetes mellitus (T2DM), is a global disorder. In fact, it is mostly believed that diabetes mellitus is related to obesity and lack of physical activity. T2DM is one of the leading causative factors for cardiovascular disorders and other chronic states. Thus, this clinical state is turning into a serious public health complication in different populations [44, 45]. Consumption of nuts has an inverse correlation with an increased risk of T2DM, mainly due to their being rich in several beneficial components, such as fibers, healthy fats, antioxidants, and anti-inflammatory compounds [46-51].

The protein hydrolysate derived from *P. vera* regulates the blood glucose level. Mohamadi *et al* (2019) reported that pistachio protein lysates had a strong effect on the blood glucose level in rats with a high-sugar diet and type 1 diabetes [52]. Besides, the results showed that hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) decreased significantly after 8 weeks. Hern´andez-Alonso *et al* (2014) investigated the consequence of pistachio supplmentation on glucose metabolism and insulin resistance. In their research, 54 prediabetic subjects went on two diets, including a pistachio-supplemented diet and a control diet, each for 4 months. Participants assigned to the pistachio diet were supplemented with 57 g/day of pistachios. In that study, chronic consumption of pistachios reduced fasting glucose and insulin levels, thereby improving insulin resistance. In addition, consumption of pistachios increased gastric hormone levels, such as glucagon-like peptide-1 (GLP-1), which enhanced the secretion of insulin and inhibited glucagon release [53]. Solute Carrier Family 2 Member 4 (SLC2A4) protein expression occurred on the surface of lymphocytes in both prediabetic subjects and those with impaired glucose metabolism. Besides, a snack of pistachio nuts significantly reduced HbA1c and FBG concentrations. Accordingly, in a double-blind, placebo-controlled, randomized trial, 48 diabetic patients with type 2 diabetes were equally separated into two groups of A and B. In group A, patients consumped 25 g of a pistachio nut snack twice a day for 12 weeks, and group B was supplemented with a control meal without nuts. According to the results, the snack of pistachios had favorable efficacy on glycemic control, so it was considered a desirable supplement in type 2 diabetic patients [54].

It has been established that most pistachio varieties, among other nuts, have a low glycemic index. Thus, they are proposed to be used for their possible effectiveness in lowering postprandial glycaemia and insulinaemia, with this potentially enabling them to reduce the risk of DM. Consumption of pistachios, either alone or in combination with other foodstuffs, has been shown to affect postprandial glycaemia [55, 56]. Pistachios exert minimal effects on postprandial glycaemia when used alone. Following the addition of pistachios (around 56 g) to other foodstuffs with a high glycemic index (e.g. pasta, parboiled rice, and instant mashed potatoes), the total postprandial glycemic response of the combination decreased by 20–30% in a dose-dependent manner [55]. An investigation of 20 subjects suffering from metabolic syndrome, who were treated with 85.04 g of pistachios and bread, showed a decrease in postprandial glycaemia levels; however, the diet increased the glucagon-like peptide compared to the subjects who received bread alone [56].

In several clinical investigations, beneficial effects of pistachio supplementation were

studied on glucose concentrations, which produced inconsistent results [57]. In a study, a Mediterranean diet was administered to 32 healthy young men (mean age of 22, within range 21-24) without any lipid defects for 4 weeks. Following that period of having the diet, participants received the same Mediterranean diet with the only exception that it contained pistachios for 4 weeks instead of the monounsaturated fat content, which constituted about 20% of the daily caloric intake. Furthermore, fasting blood samples and brachial endothelial functions were assayed at the baseline and after each diet. Finally, the Mediterranean diets were compared to each other, and the pistachio diet significantly reduced the glucose level ($P < 0.001$).

The effects of the American Heart Association Step I diet combined with the supplementation of 42 or 70 g/day of pistachios were compared to those of a control diet (the American Heart Association Step I itself without any supplementation) on Chinese subjects suffering from metabolic syndrome, in a randomized parallel-group study. The results of the study showed no considerable difference in fasting plasma glucose or insulin levels between the two groups when compared to the baseline values. Accordingly, the blood glucose levels increased significantly in the control group in week 12, but not in the pistachio group [58]. In another similar study, 60 subjects with confirmed metabolic syndrome were randomly divided into two groups of salted and unsalted pistachio diets (20% energy) as well as a control diet for a 24-week period. Accordingly, a significant reduction was observed in glucose levels, yet blood insulin levels consistently remained unchanged. In fact, pistachios contain fibers and healthy fats, but they have a low content of carbohydrates. This could in part explain that the effect of pistachios on glucose metabolism may be due to their rich carotenoid content [59]. Based on the results of another randomized controlled study, the intake of 75 g/day of mixed nuts, including pistachios, in 117 T2DM patients for a three-month period (as a replacement for a carbohydrate-rich diet), compared to the intake of healthy whole-wheat muffins, or a half portion of both showed a remarkable reduction in the HbA1c level even though the subjects were in oral anti-diabetic therapy. Moreover, an improvement was observed in total cholesterol in the subjects who were taking statins [60]. Additionally, positive effects were observed on glucose metabolism in fasting or postprandial conditions. However, more accurate studies are required to be conducted to evaluate long-term effects of diets containing pistachios on insulin resistance and secretion, or diabetes control. Many researchers reported that nuts be able to lower the risk of insulin resistance in T2DM patients.

The anti-diabetic effect of Chios Gum Mastic (CGM) is rather a novel observation, yet few studies have supported the notion to date. Evidence regarding the glucose lowering activity of CGM was initially provided by Triantafyllou *et al* (2007) who demonstrated that glucose levels decreased significantly in the low-dose studied group in male subjects [16].

Serum glucose levels in T2DM patients who received *P. lentiscus* var. *chia* gum for 12 months decreased considerably in men ($p = 0.003$); however, glucose level changes were not observed in women [16] (Table 2).

Table 2 Effects of pistachios on lowering the glycemia index

Effect on disorders	P-value	Type of patients	Pistachio species	Plant part	Ref. number
Glycemic index↓	$P < 0.01$	10 healthy volunteers (3 males, 7 females); aged 48.3±6.4; BMI: 28.0±4.8 kg/m^2	*Pistacia vera*	Seeds	Sari *et al*. (2010)
Postprandial glycaemia↓	$P < 0.05$	Men and women aged 40–65 and BMI of 430 kg/m^2, with metabolic syndrome	*Pistacia vera*	Seeds	Gulati *et al*. (2014)
FBS↓	$P < 0.001$	32 healthy young men (mean age 22 y, range 21–24)	*Pistacia vera*	Seeds	Jenkins *et al*. (2011)
BG/ Insulin →	$P < 0.05$	Metabolic syndrome	*Pistacia vera*	Seeds	Phillips *et al*. (2005)
BG↓ Insulin →	$P < 0.04$ $P = 0.7$	Metabolic syndrome	*Pistacia vera*	Seeds	Segura *et al*.(2006)
FBS ↓ **HbA1c →** **Insulin ↓** **Total cholesterol →** **GLP-1↑** **SLC2A4 ↓** **Systolic blood Pressure →** **Diastolic blood Pressure →**	p < 0.001 p=0.14 p < 0.001 p=0.15 P < 0.01 P < 0.05 p=0.22 p=0.75	54 pre-diabetic subjects; aged between 25 and 65; fasting plasma glucose levels between 100 and 125 mg/dL; BMI: 28.2, 29.6 kg/m2	*Pistacia vera*	Seeds	Zhou *et al*. (2009)
FBS ↓ **HbA1c ↓** **Systolic BP ↓**	P < 0.05 P < 0.05 P < 0.05 P=0.10	48 diabetic patients; aged 53±10	*Pistacia vera*	Seeds	Salehi-Abargouei *et al*. (2013)

Diastolic BP → BMI ↓	P < 0.05				
Systolic BP ↓ Diastolic BP → BMI→	P < 0.04 P=0.11 P=0.05	30 well-controlled type 2 diabetic adults; aged: 56.1±7.8	*Pistacia vera*	Seeds	Burns-Whitmore *et al*. (2017)
HbA1c↓ Total cholesterol↑	p < 0.001	117 T2DM patients	Mixed nuts (including pistachios)	Seeds	Myers & Champagne (2007)
BG in men↓ BG in women→	*p* = 0.003 NS	133 humans (93 women and 40 men) aged over 50	*Pistacia lentiscus* var. *chia*	Gum	Marinou *et al*. (2010)

Abbreviations used in this table are listed below:

BG: Blood Glucose, BMI: Body mass index, FBS: Fasting blood suger, HbA1c: Glycated hemoglobin A1c, T2DM: Type 2 diabetes mellitus, ↑: increased, ↓: decreased, →: not changed, NS: Not significant

Pistachio regulatory effects on blood pressure

Several studies have reported that pistachios, among nuts, have the highest level of potassium, amounting to approximately 10,053 mg/kg (8% of the daily value) [61, 62]. Potassium is the main intracellular cation, and body organs are in high demand of it for normal cellular activities and vascular tone in blood pressure (BP) [63]. Clinical studies have reported that increased potassium intake might possibly help control BP in normal and hypertensive subjects [64, 65].

Cardiovascular diseases (CVDs), being partially caused by hypertension, are considered the major risk factors for mortality worldwide. Accordingly, hypertension consider as one of the most recurrent leading causes of CVDs [66, 67], the main causative factor of 7 million deaths per year worldwide. Positive modifications in lifestyle have been reported to be effective in controlling BP [67]. Among these modifications, nutritional conditions play a particularly important role in limiting and controlling BP [68]. Some specific dietary modalities, including Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets are likely to significantly reduce BP [69], having become promising regimens for lowering the risk of CVDs [70]. Foodstuffs with a compact and dense nature, such as unprocessed nuts, are

among the main candidates of healthy foods. Raw nuts contain a high diversity of nutrients and phytochemicals with little amounts of sodium, which can be require to control BP [71]. Some prospective longitudinal studies claimed that subjects receiving nuts on a daily basis faced lower risks of hypertension and CVD risk factors than those not regularly consuming nuts [72, 73].

An investigation, in which 1,652 adults from 21 RCTs were assessed, showed that systolic BP (SBP) was controlled by nuts. In addition, it showed that pistachios had significant effects on reducing SBP. In contrast, almonds, walnuts, cashews, mixed nuts, peanuts, and soy nuts showed no significant effect on reducing SBP. Surprisingly, in individuals not suffering from T2DM, pistachios affected SBP more significantly. However, Sauder *et al* (2014) demonstrated that systolic ambulatory BP decreased significantly in a pistachio diet. In this randomized trial, participants with well-controlled T2DM consumed a moderate-fat diet (33% fat) containing pistachios (20% of total energy) for 4 weeks. In addition, replacing low-fat snacks with pistachios led to increasing heart rate variability and decreasing ambulatory blood pressure in adults with well-controlled T2DM [74].

In this study, diastolic BP (DBP) was not affected by other nuts, while pistachios controlled DBP in 1,652 male adults. Researchers claim that pistachios alone or in combination with other nuts significantly minimize DBP, whereas other nuts fail to do so. A recent randomized clinical trial was done on the outcomes of the daily 42 g of pistachio consumption compared to the control group for a four-month period on cardiometabolic factors. Accordingly, the pistachio group experienced a notable lowering in the body mass index (BMI) and waist circumference, as well as a reduction in both systolic and diastolic blood pressure [43]. In addition, in subjects without a history of T2DM, only pistachios were able to decrease DBP, similar to SBP. According to the results of the abovementioned investigation, only pistachios exhibited a unique tendency to reduce both SBP and DBP; however, mixed nuts lowered only DBP, with nut consumers without T2DM having experienced no reduction in SBP. Moreover, when T2DM patients were eliminated from statistical data analysis, only pistachios significantly reduced both SBP and DBP [72, 73].

As mentioned above, pistachios include MUFAs and a rich content of phytosterols, being highly effective in controlling BP. The presence of a variety of compounds, including lutein, b-carotene, and g-tocopherol in pistachio nuts, has been proved to affect inflammatory mediators and oxidative states, including CRP and IL-6 [75]. This in turn causes a reduction in oxidized LDL cholesterol and further improves total antioxidant status, all of which being well recognized as factors involved in mediating the endothelial function. Nuts are considered the major source of arginine, a member of the amino acid family [75], serving as a precursor for endogenous nitric oxide, i.e. a known potent vasodilator that acts via second intracellular cyclic guanosine 5'-monophosphate [76]. These facts are the main purposes for minimizing the effects of nuts on BP [77, 78]. These observations were made with limitations that must be considered when interpreting the findings; accordingly, the reasons for the inconsistency observed could be differences in the duration of interventions, inclusion criteria (age range and health status), exclusion criteria (diseases, clinical states, and therapy protocols), amounts of pistachios consumed, and the type of recommendations given to the subjects [57, 79-

81]. According to the results of this study, consumption of nuts reduced BP, and in particular SBP. Besides, it appeared that pistachios were more effective in reducing SBP and DBP than other nuts.

Pistachios and anthropometric indices

Overweight and obesity, being among the most important problems in the world, have negative impacts on the quality of life and community health. Human body shape provides important information about health and disease risks, such as cardiovascular diseases, diabetes mellitus, and all-cause mortality [82]. Moreover, nutritional disorders are considered among the most important factors associated with overweight, obesity, and underweight.

Body mass index (BMI) is the most prevalent factor used to assess anthropometric indices. BMI is evaluated based on a person's weight and height [83] . In a randomized controlled study, 100 subjects were prescribed with regular consumption of 42 g of pistachios in a four-month behavioral weight loss intervention. According to the results, there was no significant difference in weight changes, with a greater reduction observed in BMI in the pistachio group [43]. In another study, the effect of daily consumption of pistachios, as an afternoon snack, was investigated on body weight and BMI. Accordingly, the pistachio-supplemented group, with overweight or obesity, consumed 53 g/d of pistachios and showed a significant reduction in BMI [84].

Waist circumference and body weight are considered good indices of body fat, especially one's internal fat deposits. In fact, pistachios contain small amounts of saturated fatty acids (SFA) and more than 80% of unsaturated fatty acids, mostly monounsaturated fatty acids (56%). Hence, anti-hyperlipidemic effects of pistachios depend on their fatty acid content [43]. In a study, 30 healthy French women consumed 56 g of pistachios as an afternoon snack [85]. Among the women who consumed pistachios, no significant effect was observed on body weight, but their waist circumference decreased. As a matter of fact, consuming pistachios increases levels of proteins and unsaturated fatty acids, thereby increasing energy as well as the risk of weight gain and obesity. Nevertheless, the satiety value of nuts has been considered as a factor for nut consumption not associated with weight gain. Wang *et al* (2012) reported that the daily ingestion of 42 g of pistachios was not significantly effective in increasing the waist-to-hip ratio and weight gain [86]. In another crossover study, 48 healthy college-aged female students were supplemented with 20% of energy from pistachios in a 10-week treatment period, yet their body weight did not change despite the dietary energy they received. In addition, total MUFA, total PUFA, insoluble dietary fibers, gamma-tocopherol, and copper were all significantly higher than those of the control [87]. It is worth noting that regular pistachio consumption is linked to increased dietary fiber and decreased consumption of sweets, with positive effects on anthropometric indices.

4. Conclusion

In conclusion, the information on the databases about pistachios and their different plant parts indicated their essential role in exerting therapeutic effects in various clinical states. Beneficial effects of pistachios have been well documented on several gastrointestinal disorders, such as IBS, dyspepsia, and the like. In addition, their effects have been reported on controlling critical levels of liver-derived enzymes (SGOT, SGPT), especially after liver toxicity. Several clinical trials have reported that

inflammatory bowel disease responds to the therapy with pistachios and their different parts, specifically their resin. Although some clinical studies reported positive effects of pistachio supplementation on balancing glucose levels in diabetic patients, there were some inconsistencies; thus, the results must be documented more accurately. Pistachios contain nutrients and significantly attenuate blood pressure (either systolic or diastolic) that is the leading cause of cardiovascular diseases. According to the facts reviewed in this article, it is recommended that more accurate investigations be performed with more subjects in clinical trials to more accurately assess the effects of pistachio nuts and their various plant parts on controlling the aforementioned clinical states. In addition, it is required that adverse effects of pistachios and their plant parts on subjects consuming them be studied well.

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Conflicts of interest

None!

Abbreviations

The abbreviations used in this study are listed below:

Blood pressure (BP), Body mass index (BMI), Carbon tetrachloride-4 (CCL4), Cardiovascular diseases (CVDs), CD activity index (CDAI), Chemokine (C-C motif) ligand 2 (CCL2), Chios Gum Mastic (CGM), C-reactive protein (CRP), Crohn's disease (CD), Cyclooxygenase-2 (Cox-2), Diabetes mellitus (DM), Diastolic blood pressure (DBP), Dietary approaches to stop hypertension (DASH), High density lipoprotein (HDL), Inflammatory bowel disease (IBD), Intracellular antioxidant glutathione (GSH), Irritable bowel syndrome (IBS), Low density lipoprotein (LDL), Macrophage migration inhibitory factor (MIF), Monounsaturated fatty acid (MUFAs), Nitric oxide (NO), Nitric oxide synthase (iNOS), Oleogum resin (OR), Randomized controlled trials studies (RCTs), Reverse transcription polymerase chain reaction (RT-PCR), Solute Carrier Family 2 Member 4 (SLC2A4), Saturated fatty acid (SFA), Serum glutamic oxaloacetic transaminase (*SGOT*), Serum glutamic pyruvic transaminase (*SGPT*), Systolic blood pressure (SBP), Total antioxidant potential (TAP), Traditional Iranian Medicine (TIM), Triglyceride (TG), Tumor necrosis factor α (TNFα), Type 2 diabetes mellitus (T2DM)

References

1- Kole C. Wild crop relatives: Genomic and breeding resources: Cereals: Springer Science & Business Media; **2011**.

2- Mozaffarian V. A dictionary of Iranian plant names: Latin, English, Persian: Farhang Mo'aser; **1996**.

3- Durmaz G, Gökmen V. Changes in oxidative stability, antioxidant capacity and phytochemical composition of Pistacia terebinthus oil with roasting. Food chemistry. **2011**;128(2):*410-4*.

4- Gogus F, Ozel M, Kocak D, Hamilton J, Lewis A. Analysis of roasted and unroasted Pistacia terebinthus volatiles using direct thermal desorption-GCxGC–TOF/MS. Food chemistry. **2011**;129(3):*1258-64*.

5- Nadimi AE, Ahmadi Z, Falahati-Pour SK, Mohamadi M, Nazari A, Hassanshahi G, et al. Physicochemical properties and health benefits of pistachio nuts. International Journal for Vitamin and Nutrition Research. **2020**;90(5-6):*564-574*.

6- Rahimi R, Shams-Ardekani MR, Abdollahi M. A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. World J Gastroenterol. **2010**;16(36):*4504-14*.

7- Al-Said MS, Ageel A, Parmar N, Tariq M. Evaluation of mastic, a crude drug obtained from Pistacia lentiscus for gastric and duodenal anti-ulcer activity. Journal of ethnopharmacology. **1986**;15(3):*271-8*.

8- Dabos KJ, Sfika E, Vlatta LJ, Frantzi D, Amygdalos GI, Giannikopoulos G. Is Chios mastic gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial. Journal of ethnopharmacology. **2010**;127(2):*205-9*.

9- Ramezani M, Khaje-Karamoddin M, Karimi-Fard V. Chemical Composition and anti–helicobacter pylori activity of the essential oil of pistacia vera. Pharmaceutical biology. **2004**;42(7):*488-90*.

10- Paraschos S, Magiatis P, Gousia P, Economou V, Sakkas H, Papadopoulou C, et al. Chemical investigation and antimicrobial properties of mastic water and its major constituents. Food chemistry. **2011**;129(3):*907-11*.

11- Terzo S, Mulè F, Caldara GF, Baldassano S, Puleio R, Vitale M, et al. Pistachio consumption alleviates inflammation and improves gut microbiota composition in mice fed a high-fat diet. International journal of molecular sciences. **2020**;21(1):*365*.

12- Kim H-J, Neophytou C. Natural anti-inflammatory compounds for the management and adjuvant therapy of inflammatory bowel disease and its drug delivery system. Archives of pharmacal Research. **2009**;32(7):*997-1004*.

13- Rahimi R, Baghaei A, Baeeri M, Amin G, Shams-Ardekani MR, Khanavi M, et al. Promising effect of Magliasa, a traditional Iranian formula, on experimental colitis on the basis of biochemical and cellular findings. World Journal of Gastroenterology: WJG. **2013**;19(12):*1901-11*.

14- Janakat S, Al-Merie H. Evaluation of hepatoprotective effect of Pistacia lentiscus, Phillyrea latifolia and Nicotiana glauca. Journal of Ethnopharmacology. **2002**;83(1):*135-8*.

15- Ljubuncic P, Song H, Cogan U, Azaizeh H, Bomzon A. The effects of aqueous extracts prepared from the leaves of Pistacia lentiscus in experimental liver disease. Journal of Ethnopharmacology. **2005**;100(1):*198-204*.

16- Triantafyllou A, Chaviaras N, Sergentanis TN, Protopapa E, Tsaknis J. Chios mastic gum modulates serum biochemical parameters in a human population. Journal of ethnopharmacology. **2007**;111(1):*43-9*.

17- Dedoussis GV, Kaliora AC, Psarras S, Chiou A, Mylona A, Papadopoulos NG, et al. Antiatherogenic effect of Pistacia lentiscus via GSH restoration and downregulation of CD36 mRNA expression. Atherosclerosis. **2004**;174(2):*293-303*.

18- Georgiadis I, Karatzas T, Korou L-M, Katsilambros N, Perrea D. Beneficial health effects of Chios gum mastic and peroxisome proliferator-activated receptors: indications of common mechanisms. Journal of medicinal food. **2015**;18(1):*1-10*.

19- Janakat S, Al-Merie H. Evaluation of hepatoprotective effect of Pistacia lentiscus, Phillyrea latifolia and Nicotiana glauca. Journal of ethnopharmacology. **2002**;83(1-2):*135-8.*
20- Marinou KA, Georgopoulou K, Agrogiannis G, Karatzas T, Iliopoulos D, Papalois A, et al. Differential effect of Pistacia vera extracts on experimental atherosclerosis in the rabbit animal model: an experimental study. Lipids in health and disease. **2010**;9(1):*73.*
21- Harandi H, Majd A, Falahati-Pour SK, Mahmoodi M. Anti-cancer effects of hydro-alcoholic extract of pericarp of pistachio fruits. Asian Pacific Journal of Tropical Biomedicine. **2018**;8(12):*598-603*.
22- Edwards K, Kwaw I, Matud J, Kurtz I. Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia. Journal of the American College of Nutrition. **1999**;18(3):*229-32.*
23- BAKIREL T, ŞENER S, BAKIREL U, KELEŞ O, ŞENNAZLI G, GÜREL A. The investigation of the effects of Pistacia terebinthus L. upon experimentally induced hypercholesterolemia and atherosclerosis in rabbits. Turkish Journal of Veterinary and Animal Sciences. **2004**;27(6):*1283-92.*
24- Parvardeh S, Niapoor M, Hosseinzadeh H. Hepatoprotective activity of Pistacia vera L. gum extract in rats. Journal of Medicinal Plants. **2002**;4(4):*27-34.*
25- Khan M, Malik S, Shad A, Shafi M, Bakht J. Hepatocurative potentials of Pistacia integerrima in CCl4-treated rats. Sarhad Journal of Agriculture (Pakistan). **2004**;20(2):*279-285.*
26- Ahmad S, Ali M, Ansari SH, Ahmed F. Phytoconstituents from the galls of Pistacia integerrima Stewart. Journal of Saudi Chemical Society. **2010**;14(4):*409-12.*
27- Ismail M, ur Rahman S, Zada A, Abbas M, Ali T, Niaz U. Analgesic, anti GIT motility and toxicological activities of Pistacia integerrima Stewart ex Brandis bark in mice. Journal of Medicinal Plants Research. **2012**;6(14):*2827-31.*
28- Watt K, Christofi N, Young R. The detection of antibacterial actions of whole herb tinctures using luminescent Escherichia coli. Phytotherapy research. **2007**;21(12):*1193-9.*
29- Yoshikawa M, Morikawa T, Oominami H, Matsuda H. Absolute stereostructures of olibanumols A, B, C, H, I, and J from olibanum, gum-resin of Boswellia carterii, and inhibitors of nitric oxide production in lipopolysaccharide-activated mouse peritoneal macrophages. Chemical and Pharmaceutical Bulletin. **2009**;57(9):*957-64.*
30- Chevrier MR, Ryan AE, Lee DY-W, Zhongze M, Wu-Yan Z, Via CS. Boswellia carterii extract inhibits TH1 cytokines and promotes TH2 cytokines in vitro. Clinical and diagnostic laboratory immunology. **2005**;12(5):*575-80.*
31- Zhou L, Satoh K, Takahashi K, Watanabe S, Nakamura W, Maki J, et al. Re-evaluation of anti-inflammatory activity of mastic using activated macrophages. in vivo. **2009**;23(4):*583-9.*
32- Fan AY, Lao L, Zhang R-X, Wang L-B, Lee DY-W, Ma Z-Z, et al. Effects of an acetone extract of Boswellia carterii Birdw.(Burseraceae) gum resin on rats with persistent inflammation. Journal of Alternative & Complementary Medicine. **2005**;11(2):*323-31*.
33- Banno N, Akihisa T, Yasukawa K, Tokuda H, Tabata K, Nakamura Y, et al. Anti-inflammatory activities of the triterpene acids from the resin of Boswellia carteri. Journal of ethnopharmacology. **2006**;107(2):*249-53*.
34- Kiela PR, Midura AJ, Kuscuoglu N, Jolad SD, Sólyom AM, Besselsen DG, et al. Effects of Boswellia serrata in mouse models of chemically induced colitis. American Journal of Physiology-Gastrointestinal and Liver Physiology. **2005**;288(4):*G798-G808.*
35- Bhattacharya S, Chaudhuri SR, Chattopadhyay S, Bandyopadhyay SK. Healing properties of some Indian medicinal plants against indomethacin-induced gastric ulceration of rats. Journal of Clinical Biochemistry and Nutrition. **2007**;41(2):*106-14.*
36- Kaliora AC, Stathopoulou MG, Triantafillidis JK, Dedoussis GV, Andrikopoulos NK. Alterations in the function of circulating mononuclear cells derived from patients with Crohn's disease treated with

mastic. World journal of Gastroenterology. **2007**;13(45):*6031-3036.*

37- Kaliora AC, Stathopoulou MG, Triantafillidis JK, Dedoussis GV, Andrikopoulos NK. Chios mastic treatment of patients with active Crohn's disease. World journal of Gastroenterology. **2007**;13(5):*748-53.*

38- Madisch A, Miehlke S, Eichele O, Mrwa J, Bethke B, Kuhlisch E, et al. Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. International journal of colorectal disease. **2007**;22(12):*1445-51.*

39- Gupta I, Parihar A, Malhotra P, Gupta S, Lüdtke R, Safayhi H, et al. Effects of gum resin of Boswellia serrata in patients with chronic colitis. Planta medica. **2001**;67(05):*391-5.*

40- Gupta I, Parihar A, Malhotra P, Singh G, Lüdtke R, Safayhi H, et al. Effects of Boswellia serrata gum resin in patients with ulcerative colitis. European journal of medical research. **1997**;2(1):*37-43.*

41- Al-Habbal MJ, Al-Habbal Z, Huwez FU. A Double-Blind Controlled Clinical Trial of Mastic and Placebo in the Treatment of Duodenal Ulcer. Clinical and experimental pharmacology and physiology. **1984**;11(5):*541-4.*

42- Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana J, Navarro E, Martinez-Salmeron J, Garcia-Puges A, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. The American journal of gastroenterology. **1999**;94(2):*427-33.*

43- Rock CL, Zunshine E, Nguyen HT, Perez AO, Zoumas C, Pakiz B, et al. Effects of pistachio consumption in a behavioral weight loss intervention on weight change, cardiometabolic factors, and dietary intake. Nutrients. **2020**;12(7):*2155*.

44- Collaboration ERF. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. The Lancet. **2010**;375(9733):*2215-22.*

45- Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. **2010**;87(1):*4-14.*

46- Rajaram S, Sabaté J. Nuts, body weight and insulin resistance. British Journal of Nutrition. **2006**;96(S2):*S79-S86.*

47- Jenkins DJ, Hu FB, Tapsell LC, Josse AR, Kendall CW. Possible benefit of nuts in type 2 diabetes. The Journal of nutrition. **2008**;138(9):*1752S-6S*.

48- Ros E. Health benefits of nut consumption. Nutrients. **2010**;2(7):*652-82.*

49- Damavandi RD, Eghtesadi S, Shidfar F, Heydari I, Foroushani AR. Effects of hazelnuts consumption on fasting blood sugar and lipoproteins in patients with type 2 diabetes. Journal of Research in Medical Sciences. **2013**;18(4):*314-21*.

50- Kochar J, Gaziano JM, Djoussé L. Nut consumption and risk of type II diabetes in the Physicians' Health Study. European journal of clinical nutrition. **2010**;64(1):*75-9.*

51- Pan A, Sun Q, Manson JE, Willett WC, Hu FB. Walnut consumption is associated with lower risk of type 2 diabetes in women. The Journal of nutrition. **2013**;143(4):*512-8.*

52- Mohamadi M, Mirzahosseini-pourranjbar A, Bagheri-Hosseinabadi Z, Dini A, Amiri M, Shojaei A, et al. Protein hydrolysate derived from Pistachio vera regulates blood glucose level in streptozotocin-diabetic and high-sugar diet-fed rats. Pistachio and Health Journal. **2019**;2(3):*1-16.*

53- Hernández-Alonso P, Salas-Salvadó J, Baldrich-Mora M, Juanola-Falgarona M, Bulló M. Beneficial effect of pistachio consumption on glucose metabolism, insulin resistance, inflammation, and related metabolic risk markers: a randomized clinical trial. Diabetes care. **2014**;37(11):*3098-105.*

54- Parham M, Heidari S, Khorramirad A, Hozoori M, Hosseinzadeh F, Bakhtyari L, et al. Effects of pistachio nut supplementation on blood glucose in patients with type 2 diabetes: a randomized crossover trial. The review of diabetic studies: RDS. **2014**;11(2):*190-196.*

55- Kendall C, Josse A, Esfahani A, Jenkins D. The impact of pistachio intake alone or in combination with high-carbohydrate foods on post-prandial

glycemia. European journal of clinical nutrition. **2011**;65(6):*696-702*.

56- Kendall C, West S, Augustin L, Esfahani A, Vidgen E, Bashyam B, et al. Acute effects of pistachio consumption on glucose and insulin, satiety hormones and endothelial function in the metabolic syndrome. European journal of clinical nutrition. **2014**;68(3):*370-5*.

57- Sari I, Baltaci Y, Bagci C, Davutoglu V, Erel O, Celik H, et al. Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: a prospective study. Nutrition. **2010**;26(4):*399-404*.

58- Wang X, Li Z, Liu Y, Lv X, Yang W. Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. Nutrition journal. **2012**;11(1):*20*.

59- Gulati S, Misra A, Pandey RM, Bhatt SP, Saluja S. Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: a 24-wk, randomized control trial. Nutrition. **2014**;30(2):*192-7*.

60- Jenkins DJ, Kendall CW, Banach MS, Srichaikul K, Vidgen E, Mitchell S, et al. Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes care. **2011**;34(8):*1706-11*.

61- Segura R, Javierre C, Lizarraga MA, Ros E. Other relevant components of nuts: phytosterols, folate and minerals. British Journal of Nutrition. **2006**;96(S2):*S36-S44*.

62- Phillips KM, Ruggio DM, Ashraf-Khorassani M. Phytosterol composition of nuts and seeds commonly consumed in the United States. Journal of agricultural and food chemistry. **2005**;53(24):*9436-45*.

63- Myers VH, Champagne CM. Nutritional effects on blood pressure. Current opinion in lipidology. **2007**;18(1):*20-4*.

64- Braschi A, Naismith DJ. The effect of a dietary supplement of potassium chloride or potassium citrate on blood pressure in predominantly normotensive volunteers. British journal of nutrition. **2008**;99(06):*1284-92*.

65- Chang H-Y, Hu Y-W, Yue C-SJ, Wen Y-W, Yeh W-T, Hsu L-S, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. The American journal of clinical nutrition. **2006**;83(6):*1289-96*.

66- Jones DW, Hall JE. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and evidence from new hypertension trials. Hypertension. **2004**;43(1):*1-3*.

67- Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadifard N, et al. The Isfahan cohort study: rationale, methods and main findings. Journal of human hypertension. **2011**;25(9):*545-53*.

68- 68. Kokkinos P, Panagiotakos DB, Polychronopoulos E. Dietary influences on blood pressure: the effect of the Mediterranean diet on the prevalence of hypertension. The Journal of Clinical Hypertension. **2005**;7(3):*165-72*.

69- Bazzano LA, Green T, Harrison TN, Reynolds K. Dietary approaches to prevent hypertension. Current hypertension reports. **2013**;15(6):*694-702*.

70- Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases—incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. **2013**;29(4):*611-8*.

71- Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. Journal of hypertension. **2006**;24(2):*215-33*.

72- Martínez-González MÁ. The SUN cohort study (Seguimiento University of Navarra). Public health nutrition. **2006**;9(1a):*127-31*.

73- Djoussé L, Rudich T, Gaziano JM. Nut consumption and risk of hypertension in US male physicians. Clinical Nutrition. **2009**;28(1):*10-4*.

74- Sauder KA, McCrea CE, Ulbrecht JS, Kris-Etherton PM, West SG. Pistachio nut consumption modifies systemic hemodynamics, increases heart rate variability, and reduces ambulatory blood pressure in well-controlled type 2 diabetes: a randomized trial.

Journal of the American Heart Association. **2014**;3(4):*e000873*.

75- Ros E, Tapsell LC, Sabaté J. Nuts and berries for heart health. Current atherosclerosis reports. **2010**;12(6):*397-406.*

76- Bode-Böger SM, Böger RH, Alfke H, Heinzel D, Tsikas D, Creutzig A, et al. L-Arginine induces nitric oxide–dependent vasodilation in patients with critical limb ischemia. Circulation. **1996**;93(1):*85-90.*

77- Schutte AE, Van Rooyen JM, Huisman HW, Mukuddem-Petersen J, Oosthuizen W, Hanekom SM, et al. Modulation of baroreflex sensitivity by walnuts versus cashew nuts in subjects with metabolic syndrome. American journal of hypertension. **2006**;19(6):*629-36.*

78- Sheridan MJ, Cooper JN, Erario M, Cheifetz CE. Pistachio nut consumption and serum lipid levels. Journal of the American College of Nutrition. **2007**;26(2):*141-8.*

79- Wien M, Bleich D, Raghuwanshi M, Gould-Forgerite S, Gomes J, Monahan-Couch L, et al. Almond consumption and cardiovascular risk factors in adults with prediabetes. Journal of the American College of Nutrition. **2010**;29(3):*189-97.*

80- Foster GD, Shantz KL, Vander Veur SS, Oliver TL, Lent MR, Virus A, et al. A randomized trial of the effects of an almond-enriched, hypocaloric diet in the treatment of obesity. The American journal of clinical nutrition. **2012**;96(2):*249-54.*

81- West SG, Gebauer SK, Kay CD, Bagshaw DM, Savastano DM, Diefenbach C, et al. Diets Containing Pistachios Reduce Systolic Blood Pressure and Peripheral Vascular Responses to Stress in Adults With DyslipidemiaNovelty and Significance. Hypertension. **2012**;60(1):*58-63.*

82- Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics. **2015**;33(7):*673-89.*

83- Wells JC, Treleaven P, Cole TJ. BMI compared with 3-dimensional body shape: the UK National Sizing Survey. The American journal of clinical nutrition. **2007**;85(2):*419-25.*

84- Li Z, Song R, Nguyen C, Zerlin A, Karp H, Naowamondhol K, et al. Pistachio nuts reduce triglycerides and body weight by comparison to refined carbohydrate snack in obese subjects on a 12-week weight loss program. Journal of the American College of Nutrition. **2010**;29(3):*198-203.*

85- Carughi A, Bellisle F, Dougkas A, Giboreau A, Feeney MJ, Higgs J. A randomized controlled pilot study to assess effects of a daily pistachio (Pistacia vera) afternoon snack on next-meal energy intake, satiety, and anthropometry in French women. Nutrients. **2019**;11(4):*767.*

86- Wang X, Li Z, Liu Y, Lv X, Yang W. Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. Nutrition journal. **2012**;11(1):*1-6.*

87- Burns-Whitmore B, Bushnell A, Towne A, Roy S, Hall L. Pistachio Consumption at 20% of Energy Does Not Significantly Change Body Composition. Blood Pressure or Blood Lipids but Improves Diet Quality in Free-Living, Healthy College-Aged Women Food Nutr J: FDNJ-130 DOI. **2017**;10:*2575-7091*.