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Review

Obesity: The preventive role of the pomegranate (*Punica granatum*)

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ABSTRACT

Obesity represents a rapidly growing threat to the health of populations in an increasing number of countries. Diet intervention has been proposed as one of the strategies for weight loss and weight maintenance. Traditionally, the pomegranate, including its roots, tree bark, fruit juice, leaves, and flowers, has been used to treat some conditions such as diarrhea, hemorrhage, acidosis, and microbial infections. Pomegranate extracts have been found to have strong anti-inflammatory, antioxidant, and even antitumor properties in vivo and in vitro. More recently, positive effects on fat reduction have been shown using the pomegranate and its extracts. Many of the beneficial effects are related to the presence of anthocyanins, tannins, and very high levels of antioxidants, including polyphenols and flavonoids. Many studies have explored the effects of the pomegranate in obesity, and various mechanisms have been proposed as to how these different extracts help in fat reduction. This article provides an overview of the work done addressing the potential benefits of the pomegranate on obesity and assesses the efficacy of intervention by means of the pomegranate and its extracts. Human studies in this field are still limited and need more attention that would help in understanding the preventive and protective roles pomegranate extracts have on obesity.

Introduction

Obesity is one of the most common and important health concerns facing our society today [1]. An increase in the prevalence of obesity in almost all countries in the world has led the World Health Organization to define it as “the global epidemic” [2]. Currently, more than 1 billion adults worldwide are overweight, at least 300 million are clinically obese, and nearly 43 million children younger than 5 y were overweight in 2010 [3]. The Centers of Disease Control and Prevention has reported that during the past 20 y there has been a dramatic increase in the rate of obesity in the United States and more than 60% of the U.S. population is overweight or obese [4,5]. Obesity in other terms is a body mass index of 30 kg/m^2 or greater. The more severe the obesity is, the more serious the medical complications and mortality risks are; hence, the term *morbid*. Morbid obesity affects 3 to 5 million Americans, just over half of whom are women [6–10].

Obesity in adults and in children and adolescents has also gained epidemic proportions and has been associated with premature deaths in adults [11,12]. Childhood obesity affects the developed and developing countries of all socioeconomic groups irrespective of age, sex, or ethnicity [13]. Obese children are susceptible to the development of chronic diseases such as type 2 diabetes and cardiovascular disease [14]. From as early as the development of the fetus, the risk of obesity can be evaluated [15]. The third trimester is a critical period because the number of fat cells starts to increase and a high-caloric diet can stimulate an overproduction of fat cells, thus inducing permanent changes in appetite, neuroendocrine function, and energy metabolism [16]. A dietary intervention at this stage could be adopted as a preventive measure to lower the chances of obesity in the child.

Weight loss in obese persons of any age can decrease the obesity-related medical complications and increase physical function and quality of life [17]. The current therapeutic tools used for weight management are lifestyle interventions, pharmacotherapy, and surgery. Historically, there has been little success in antiobesity drug development because of the low efficiency and undesired side effects [18]. Although surgical weight-loss procedures are on the rise, the occurrence of nutritional deficiencies of micronutrients and macronutrients arising from bariatric surgery has been recognized for decades, but the prevalence and severity depend on the type of surgery [19]. There are several risks associated with the pharmacologic and surgical interventions of obesity, suggesting that a dietary intervention maybe the safest and most cost-effective option for those who are moderately obese [5,20–22]. There are many

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dietary strategies that have been shown to affect energy balance in a manner that results in successful weight loss [23,24].

The pomegranate (*Punica granatum L.*) is a deciduous shrub cultivated throughout Iran, India, the Mediterranean countries, Malaysia, and tropical Africa and to some extent in the United States [25,26]. The extracts from this plant have been used since ancient times to treat many conditions such as parasitic infections, ulcers, diarrhea, dysentery, hemorrhage, microbial infections, and respiratory pathologies [25]. Extracts from the different parts of this plant have been researched for numerous pharmacologic activities, such as antitumor, antibacterial, astringent, antidiarrheal, and antiobesity activities [25]. The pomegranate contains an array of compounds that have been attributed to the antiobesity effects. In this review, we summarize the compounds present in different pomegranate extracts (leaf, seed, flower, and juice) and their potential effects as preventive agents against obesity. The review also focuses on studies conducted in animal models related to obesity and discusses the mechanism of action of these pomegranate extracts.

Composition of the pomegranate

Pomegranate extracts (juice, seed oil, and flower extracts) are known to possess enormous antidiabetic, anti-inflammatory, antioxidant, and antitumor effects in vivo and in vitro [27]. In traditional Chinese medicine, different pomegranate extracts and preparations including the bark, root, and juice of the fruit, especially the dried peels, have been used to treat many conditions [28]. The preparations that are edible are used as fresh juice, canned beverages, jelly and jam, etc., for flavoring and coloring products, and in therapeutic formulas [26]. These pomegranate preparations contain very high levels of antioxidants compared with any other fruit or vegetable, including flavonoids and polyphenols [29,30]. The pomegranate plant contains some important constituents in its entirety. Figure 1 summarizes the beneficial effects of the pomegranate and its extracts and the antiobesity mechanism of the pomegranate constituents.

Pomegranate fruit

The fruit consists of the peel, seeds, and the arils. The peel makes up about 50% of the fruit, whereas the arils and seeds make up 40% and 10%, respectively. The peel is rich in many compounds such as phenolics, flavonoids, ellagitannins, and proanthocyanidin compounds, complex polysaccharides, and many minerals including potassium, nitrogen, calcium, magnesium, phosphorus, and sodium [26]. Because this is not an edible part of the plant, pharmaceuticals have been produced in different forms such as pills, powders, capsules, vials, etc., for easy consumption. The pomegranate seeds are a rich source of total lipids, and the oil consists of a high concentration of conjugated fatty acids such as linoleic acid (LA) and linolenic acid and other lipids such as punicic acid, stearic acid, palmitic acid, and phytosterols. Minor amounts of conjugated linolenic acid isomers including eleostearic acid and catalpic acid are also found. Phytosterols are found in high concentration in the seed. Other than lipids, decent amounts of proteins, fibers, vitamins and minerals, polyphenols, and isoflavones are present. All these contribute to the overall spectrum of health benefits [31].

The arils of the pomegranate fruit as such or when squeezed for juice extraction consist mainly of fructose and glucose, pectin, citric acid, malic acid, and bioactive compounds such as phenolics and flavonoids. The juice is known to be a rich source of antioxidants from the polyphenols, tannins, and anthocyanins including vitamin C, vitamin E, coenzyme Q10, and lipoic acid. Anthocyanins are the most important group present in the arils or juice, which even give the fruit or juice its color [26]. The levels of antioxidants have been found to be higher than in other natural juices, green tea, and even red wine [26,32–34]. Antioxidants have numerous important biological properties such as anti-inflammatory and antiaging protection against cholesterol oxidation and atherosclerosis. Recent research has also indicated that increased intakes of antioxidants and ω-3 fatty acids can modify the inflammation associated with excess adiposity [14].

Pomegranate leaf extract

Polyphenolic-rich foods have attracted worldwide attention because of their cancer-preventive properties. The pomegranate leaf, like the peels, is rich in polyphenolic compounds including tannins (punicalin, pedunculagan, gallagic acid, ellagic acid and its esters of glucose) and flavonoids. Among the tannins, ellagic acid and punicalgins have aroused great interest, and in recent years most health advantages of the pomegranate have been linked to these tannins [35,36].

Pomegranate flower extract

All parts of the pomegranate fruit are useful, but in the Unani and Ayurvedic systems of medicine, only the flower part has been prescribed for the treatment of diabetes. The pomegranate flower contains different compounds, and the most abundant are the polyphenols (gallic acid [GA] and ellagic acid) and triterpenes (oleanolic, ursolic, maslinic, and asiatic acids). There is also one sterol (daucosterol) and one flavonoid (punicaflavone) that can be separated from the flower. These compounds have shown strong biological activity and medicinal value [37,38].

Antiobesity effect of pomegranate constituents

A wealth of information has indicated that many bioactive compounds from nature are potentially useful in obesity treatments [37]. Obesity is an independent risk factor for many medical conditions such as diabetes, hypertension, coronary heart disease, high cholesterol levels, depression, musculoskeletal problems, and several cancers. Risks are also higher for some non-fatal conditions such as back pain, arthritis, infertility, and, in many Western countries, poor psychosocial functioning [2]. These conditions are placing a great burden on health care resources and health care providers are faced with the challenge of managing this epidemic. With only two drugs (orlistat and sibutramine) on the market [37] approved for long-term use in obesity and conventional weight-management programs showing limited success, there is an interest in alternative strategies for weight management [39]. Obesity is a result of an energy imbalance, where energy intake is greater than energy consumption. The prevention and treatment of this energy imbalance requires modifications not only in lifestyle in terms of physical fitness but also an increased intake of natural foods that help increase energy expenditure by stimulating thermogenesis and fat oxidation [40,41]. Many natural products, including crude extracts and isolated compounds from plants, can induce a decrease in body weight and prevent diet-induced obesity. One natural fruit that is under much research is the pomegranate and its constituents.

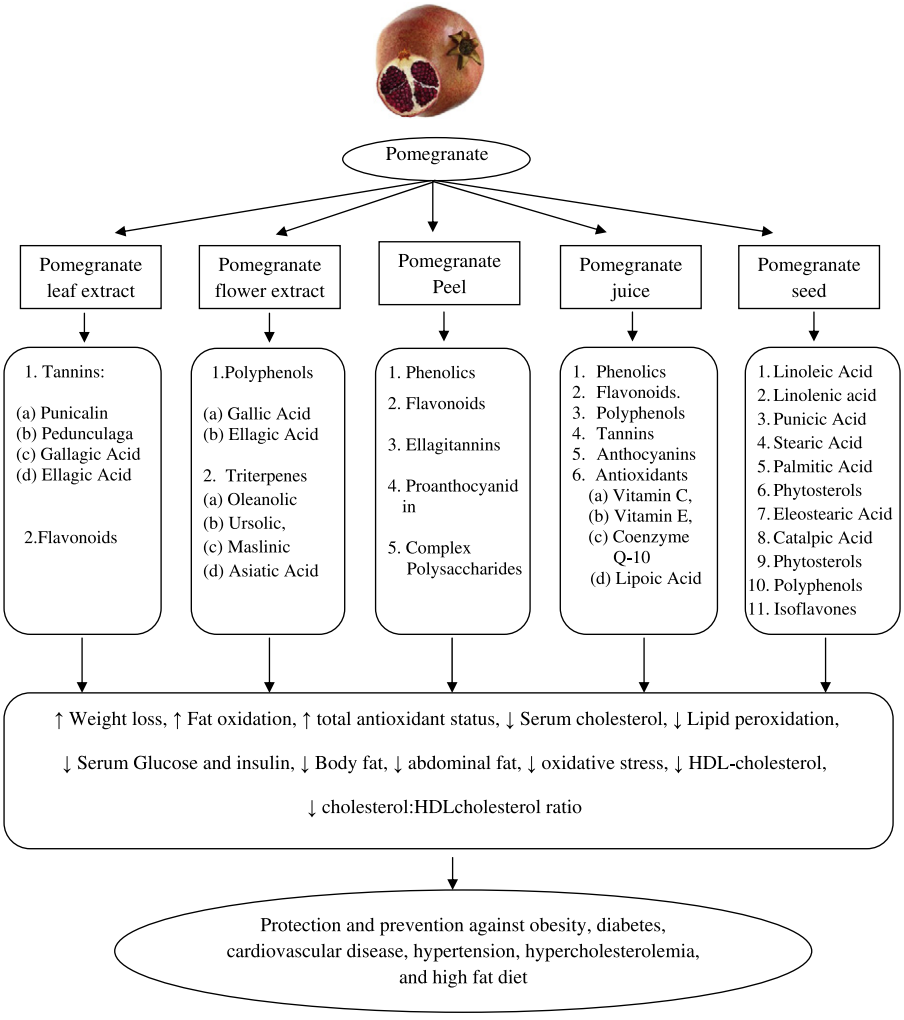

Fig. 1. Beneficial effects and antiobesity mechanism of the pomegranate and its extracts. HDL, high-density lipoprotein.

An early indication for the advantages of the pomegranate and its extracts is seen in ancient Chinese medicine, where it was used to treat acidosis, hemorrhage, diarrhea, helminthiasis, and microbial infections [28]. The effects of the pomegranate and its constituents examined in some animal models of obesity are summarized in Table 1 [27,28,31,34,42–65].

Prevention of obesity by pomegranate seed extracts

Vroegrijk et al. [31] reported that male C57Bl/J6 mice fed on 1 g of pomegranate seed oil per 100 g of a high-fat diet (HFD) for 12 wk resulted in a decreased body weight, which was reflected in a reduced fat mass compared with controls, but there was no difference seen in lean mass between the two groups. The study confirmed previous studies performed in the CD1 mouse strain by McFarlin et al. [42] who found a lower fasting glucose or insulin concentration in animals fed pomegranate seed oil, which was not seen in the study by Vroegrijk et al. This might be due to the different mouse strains and a different fat diet [31,42]. However, Vroegrijk et al. reported that pomegranate seed oil supplementation improved insulin sensitivity in HFD-fed mice, confirming in part the ameliorated glucose intolerance found by Hontecillas et al. [66].

Catalpic acid is a conjugated linolenic acid found primarily in the pomegranate seeds. Hontecillas et al. [66] studied the effect of catalpic acid in C57Bl/67 obese mice. A treatment with 1 g of catalpic acid per 100 g of an HFD for 78 d resulted in improvements of fasting glucose and insulin concentrations compared with the control mice. A decrease in the accumulation of abdominal white adipose tissue in a mouse model of diet-induced obesity was also observed. Catalpic acid also increased high-density lipoprotein (HDL) cholesterol and decreased triacylglycerol levels in plasma [43].

Many other studies have focused on the effects of other conjugated linolenic acids such as fatty acids, making the pomegranate seeds a useful supplement in protecting against obesity and insulin resistance [43,67,68].

Prevention of obesity by pomegranate leaf extracts

Leaf extracts have shown free radical scavenging activity and antioxidant effects in vitro [69]. The nutritional and antioxidant characteristics of the pomegranate leaves have increased recent interest in their use as a beneficial source of secondary metabolites. They have even been developed into a series of commercial products such as green tea and other teas consumed in China

Table 1
Effects of different pomegranate extracts on obesity

Plant part	Extract	Dose	Alone/combination	Duration	In vivo study	Results	References
PSO	xanthigen	PSO 300 mg	brown seaweed extract 300 mg	16 wk	obese premenopausal women	↑ weight loss and resting energy expenditure, ↓ body and liver fat content	[54]
	punicic acid	PSO 400 mg	alone	4 wk	hyperlipidemic patients	↓ HDL-C, ↓cholesterol/HDL-C, ↓ TG	[56]
	punicic acid	PSO 1%	alone	12 wk	HFD-fed male C57Bl/J6 mice	protects against HFD-induced weight gain and fat mass gain, e.g., obesity and insulin resistance	[31]
	linolenic acid	PSO 1%	safflower oil	2 wk	Otsuka Long-Evans Tokushima fatty rats	↑ hepatic TG accumulation	[57]
	punicic acid	0%, 0.12%, and 1.2%	alone	3 wk	C57BL/6N mice	↑ IgG and IgM, serum TG, phospholipid levels	[58]
	conjugate linolenic acid	61.79 mg/d	alone	14 wk	wild-type CD-1 mice	↓ body weight, leptin, insulin, ↑ plasma adiponectin concentration	[42]
	catalpic acid	1%	alone	4 wk	C57BL/6J and diabetic obese mouse	↓ fasting plasma glucose and insulin concentrations, abdominal white adipose tissue, plasma TG levels, ↑ PPAR-α and its responsive genes, HDL-C	[43]
Pomegranate extract	polyphenols	—	green tea extract, ascorbic acid	3 mo	patients with T2DM	↓ oxidative stress, lipid peroxidation	[116]
PFE	oleanolic acid, ursolic acid, oleic acid	500 mg/kg	alone	6 wk	ZDF rats	↓ liver weight, hepatic TG contents, lipid droplets, ↑ PPAR-α	[59]
	oleanolic acid, ursolic acid, gallic acid	500 mg/kg	alone	6 wk	ZDF rats	↓ cardiac fibrosis by modulating cardiac ET-1 and NF-κB signaling	[60]
	oleanolic acid	500 mg/kg	alone	6 wk	ZDF rats	↓ circulating lipid and inhibiting cardiac fatty acid uptake, ↓ fatty acid oxidation	[44]
PLE	ellagic acid, tannic acid	800 mg · kg^{-1} · d^{-1}	alone	5 wk	HFD-fed mice	↓ body weight, energy intake, adipose pad weight percentage, serum, TC, TG, glucose levels TC/HDL-C ratio, intestinal fat absorption, pancreatic lipase activity	[28]
PFRE, PJ, PSO	—	PJ 50 mL, PSO 1%, PFRE 500 mg/kg	alone	24 h	obese Zucker rats	PFRE or PJ: ↓expression of vascular inflammation markers, TSP, cytokine TGF-β1, ↑ plasma nitrate and nitrite, eNOS expression	[34]
Pomegranate byproducts (whole pomegranate fruit after juice preparation)	gallic acid	51.5 μg · kg^{-1} · d^{-1}, 50 μm/L	alone	—	apoE-deficient mice, J774A.1 macrophage cell line	↓ cellular lipid peroxide content, ↓ cellular total peroxide content oxidized LDL uptake	[61]
Pomegranate extracts from peels, arils, flowers	phenolics	200 μg/d	alone	3 mo	atherosclerotic apoE-deficient mice, J774A.1 macrophage cell line	↓ atherosclerotic lesion area, serum lipids, glucose levels, oxidized LDL uptake	[27]
PJ	gallic acid	gallic acid 2600 ppm/d	alone	4 wk	patients with T2DM	↓ oxidative stress, ↑ protection of HDL against oxidation	[62]
	gallic acid	200 μg	alone	4 wk	C57BL/6 mice	↓ peritoneal macrophages, TG content, TG biosynthesis rate	[63]
	polyphenols	31 μL	alone	11 wk	apoE-deficient mice	↓ LDL susceptibility to aggregation and retention, ↑ activity of serum paraoxonase, ↓ size of atherosclerotic lesions, ↓ uptake of oxidized LDL and native LDL	[48]
	polyphenols	PJ 31 μL/d	alone	2 mo	apoE-deficient mice	↓ macrophage cholesterol content, plasma lipid peroxide, macrophage oxidative stress, showed antiatherosclerotic activity	[64]
	tannins, anthocyanins	PJ 50 mL/d	alone	3 y	atherosclerotic patients with carotid artery stenosis	↓ serum lipid peroxidation, systolic blood pressure, carotid intima–media thickness, ↑ total antioxidant status	[55]
	flavonoid	PJ 40 g/d	alone	8 wk	healthy diabetic patients	↓ TC, LDL-C, LDL-C/HDL-C, TC/HDL-C	[51]
	polyphenols	PJ 50 mL/d	alone	24 wk	hypercholesterolemic $LDLR^{-/-}$ mice	↓ progression of atherosclerosis	[47]
PJ	polyphenols	75 μmol/L	alone	90 min	J774.A1 macrophage-like cell line	↓ cellular uptake of oxidized LDL, ↓ cellular cholesterol biosynthesis	[49]

	polyphenols	14 μL	alone	24 h	human coronary endothelial cells	↓ LDL oxidation, ↑ eNOS	[46]
	flavonoid	PJ 40 g	alone	8 wk	patients with T2DM	↓ TC, LDL-C, LDL-C/HDL-C, TC/HDL-C	[52]
	potent antioxidants	50 mL	alone	3 mo	patients with NIDDM	↓ serum lipid peroxides, cellular peroxides, oxidized LDL uptake, ↑ glutathione	[50]
	phenolics	50 mL/d	alone	4 wk	patients with T2DM	↓ basal serum oxidative stress, ↑ HDL-associated PON1 arylesterase, paraoxonase, lactonase activities	[65]
	antioxidants	240 mL/d	alone	4 wk	adolescents with metabolic syndrome	improvement in endothelial function	[53]

↑, increased; ↓, decreased; apoE, apolipoprotein E; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; IgG, immunoglobulin G; IgM, immunoglobulin M; LDL-C, low-density lipoprotein cholesterol; $LDLR^{-/-}$, low-density-lipoprotein receptor deficient; NF-κB, nuclear factor-κB; NIDDM, non–insulin-dependent diabetes mellitus; PFE, pomegranate flower extract; PFRE, pomegranate fruit extract; PLE, pomegranate leaf extract; PJ, pomegranate juice; PON1, paraoxonase 1; PPAR, peroxisome proliferator-activated receptor; PSO, pomegranate seed oil; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triacylglycerol; TGF, transforming growth factor; TSP, thrombospondin; ZDF, Zucker diabetic fatty

and also been included in nutrition supplement capsules in the USA. Some studies have focused on the effects of pomegranate leaf extracts (PLEs) on obesity. Lei et al. [28] investigated the antiobesity effects of the pomegranate leaf in a mouse model of HFD-induced obesity. These mice were treated with PLE at a dose of 800 mg/kg for 5 wk. The oral administration of PLE at a dose of 800 mg/kg decreased not only the body weight and various adipose pad weight percentages but also serum total cholesterol triacylglycerol, glucose levels, and the total cholesterol/HDL cholesterol ratio. The PLE also decreased the dyslipidemia of obesity and cardiovascular risk factors from a decrease in abdominal fat pad weight percentage compared with control mice. Food intake was also lower in PLE-treated obese mice, similar to sibutramine-treated obese mice. Tannic acid and ellagic acid are thought to be responsible for the activity [28].

Prevention of obesity by pomegranate flower extracts

Evidence for body weight management has also been presented by many studies using pomegranate flower extracts (PFEs). Huang et al. [44] analyzed the effects of PFEs on abnormal cardiac lipid metabolism. Because triacylglycerol accumulation and increased fatty acid oxidation lead to cardiac dysfunction in diabetic hearts, Zucker diabetic fatty rats were treated with PFE 500 mg/kg; PFE is a traditional antidiabetic medicine. The PFE was administered for 6 wk, resulting in a corrected abnormal cardiac lipid metabolism by the activation of peroxisome proliferator-activated receptor-α (PPAR-α), lower circulating lipids, and an inhibition of cardiac uptake. PPARs are known to be central modulators of lipid and carbohydrate metabolism [44].

Aviram et al. [27] also analyzed in vivo and in vitro the mechanism of action of pomegranate fruit parts, i.e., the peel, arils, seeds, and flower. All extracts were shown to possess antioxidative properties in vitro and the PFE consumption resulted in lower serum lipids and glucose levels by 18% to 25% [27].

Obesity is predictive of the presence of fibrosis, which progresses to advanced liver diseases. Non-alcoholic fatty liver diseases, hypertriglycerides, and increased free fatty acids are present in most patients with type 2-diabetes and the metabolic syndrome [45,70]. The oleanolic acid and ursolic acid present in PFEs have antihyperlipidemic properties [71–73]. GA, also found in PFEs, is known to correct HFD-induced hyperlipidemia and fatty liver in mice [74]. Xu et al. [45] investigated the effects of PFE on hepatic lipid accumulation in Zucker diabetic fatty rats with severe fatty liver disease. Male Zucker lean and Zucker diabetic fatty rats were treated with PFE 500 mg/kg for 6 wk, which resulted in a decrease in the hepatic triacylglycerol content and fatty droplets but did not alter the hepatic total cholesterol content. The maximum effects were observed in Zucker diabetic fatty rats compared with Zucker lean rats [45].

Excess visceral adiposity in the abdominal cavity is a risk factor for cardiovascular disease, insulin resistance, and the metabolic syndrome [75]. In search of antiobesity compounds from natural sources, de Melo et al. [39] evaluated the effects of the oleanolic acid commonly present in the PFE, which exhibits a wide range of pharmacologic and biochemical effects. To combat obesity, HFD-induced obese mice were treated with oleanolic acid 10 mg/kg daily for 7 d, which resulted in significant decreases in body weight gain (11.11%, $P < 0.05$) and visceral abdominal fat (1.28-fold). Blood glucose levels were also observed to decrease to the extent of 31%. Many plant metabolites in fruits and vegetables have medicinal actions without any nutritional role [39]. These metabolites should be explored

further for their preventive properties and any possible treatments for metabolic diseases such as obesity.

Prevention of obesity by pomegranate juice

Several studies have also evaluated the effects of pomegranate juice (PJ) on adiposity and diabetes because these conditions go hand in hand. Other extracts of the pomegranate plant (e.g., PLE, seed oil) may not always be available, thus adding more importance to the research involving the PJ and the mechanism of action of the PJ constituents. It has been documented that patients who are overweight are at greater higher risk for type 2 diabetes and hypertension [33,42]. PJ is known to be rich in antioxidants, and the levels have been found to be higher than those in other natural juices. These antioxidants have been demonstrated to protect against cholesterol oxidation and have antiaging effects [46,47,76]. Dramatic increases in serum low-density lipoprotein (LDL), triacylglycerols, and total cholesterol are symptoms of hyperlipidemia occurring in obesity and can be induced by the secondary effect of diabetes [77]. Stowe [33] reviewed the effect of PJ on blood pressure and cardiovascular health and found antiatherosclerotic, antihypertensive, antioxidant, and anti-inflammatory effects in human subjects and mouse models.

Aviram et al. [48,78] demonstrated the ability of polyphenols and flavonoids to inhibit LDL oxidation by protecting LDL against cell-mediated oxidation. The effect of PJ on cholesterol accumulation in macrophages, on cellular oxidation stress, and on cholesterol biosynthesis in a J774.A1 macrophage-like cell line has recently been reported [49]. Cells treated with PJ (polyphenol 75 mmol/L) for 90 min at 37°C showed a 40% decrease in the degradation of oxidized LDL. A decrease of 50% in the rate of macrophage cholesterol synthesis was also observed compared with controls, as was a decrease of oxidative stress. Rosenblat et al. [50] also reported that the consumption of PJ by diabetic patients led to a decrease in oxidative stress in the patients' serum and the macrophage uptake of oxidized LDL.

Some constituents have also been tested individually and in combination. The effects of GA, LA, and their mixture on the ability to ameliorate hyperlipidemia in C57BL/6 mice fed an HFD have been studied [74]. The HFD obese mice treated with the test compounds (1% of diet) at the end of 7 wk showed body weight decreases of 12.8%, 6.8%, and 12.20% for GA, LA, and GA + LA, respectively, compared with HFD control mice. With obesity being a common risk factor for fatty liver disease in children and adults, decreases in liver weight and plasma glucose levels are of significant importance for the advancement of liver disease. Significant decreases with the supplementation of GA, LA, and GA + LA have been seen in total cholesterol, triacylglycerols, HDL cholesterol, and LDL cholesterol compared with HFD-fed mice. These results suggest that GA, LA, and their mixture have effective lipid-lowering actions and may protect patients against diseases that occur from hyperlipidemia [74].

Esmaillzadeh et al. [51,52] demonstrated the effect of PJ in 22 diabetic patients who were fed concentrated PJ 40 g/d for 8 wk. After consumption, significant decreases were seen in total cholesterol, LDL cholesterol/HDL cholesterol, and total cholesterol/HDL cholesterol.

A study by Cerda et al. [79] investigated the effects of 6% punicalagin found in PJ in female rats for 37 d. An intake of 4800 $mg \cdot kg^{-1} \cdot d^{-1}$ had a lowering effect on the food consumption and body weight of the animals. These results clearly indicate the potent, beneficial effects of PJ to help curb obesity and modify heart disease risk factors in hyperlipidemic patients [79].

Mechanism of action

The exact etiology of obesity remains unclear but seems to be a complex combination of nutritional, genetic, and environmental factors [80]. Over the years, consumption of the pomegranate has grown tremendously because of the reported health benefits and recent research. Different mechanisms have been proposed to explain the antiobesity effects of the different constituents of the pomegranate. Evidence for body weight management by suppressing energy intake using the pomegranate has been shown in several studies, in particular the study by Lei et al. [28]. Lei et al. demonstrated dual antiobesity effects of the pomegranate extract: 1) an inhibition of lipase activity and 2) the suppression of energy intake. Obese mice have greater triacylglycerol absorption from the intestine than normal mice, and dietary fat is not directly absorbed from the intestine unless acted on by pancreatic lipase [28,81]. Orlistat, a clinically proved medicine, inhibits pancreatic lipase, decreasing the absorption of dietary fat in the blood and increasing fat excretion in the feces [28,82]. It has been reported that the effect of the pomegranate extract on energy intake is similar to orlistat, and the active compounds (ellagic acid and tannic acid) present in the extract decreases hyperlipidemia by inhibiting pancreatic lipase activity in vitro and increasing fecal fat excretion [28]. The pomegranate extract also works like sibutramine, an appetite suppressant used in clinics; similarly, the pomegranate extract has been observed to markedly decrease the calorie intake of mice fed an HFD but not of those fed a normal diet. The mechanism by which the appetite in obese mice is decreased is not known and needs further research, but the dual action of the pomegranate extract on obese mice has clearly been demonstrated [28]. Similar findings have been demonstrated in different animal models. For example, McFarlin et al. [42] reported that the consumption of pomegranate seed oil (61 mg/d) for 14 wk and an HFD resulted in decreases of body weight, leptin, insulin, and increased adiponectin compared with controls. Fu et al. [83] reported the association of a low plasma level of adiponectin with the development of obesity, insulin resistance, and cardiovascular disease. The decrease in body weight was assumed to be mediated by the leptin–adiponectin pathway because leptin and adiponectin are closely related to body weight and composition [83,84].

The composition of the human gut microbiota has been linked to health improvement and the development of various diseases. Beneficial bacteria, known as *probiotics*, such as bifidobacteria and lactobacilli, function as a barrier against pathogens, stimulate the host immune system, prevent food allergies and tumors, produce vitamins, metabolize cholesterol and other lipids, and increase mineral bioavailability [36,85,86]. Conversely, an overgrowth of deleterious bacterial species causes chronic and acute bowel diseases and has been associated with aging, cancer, obesity, and Alzheimer's disease [87,88]. Dietary substrates influence the gut microbiota by enhancing the growth of beneficial bacteria or causing their depletion. Most health benefits of the pomegranate are known to be caused by the presence of ellagitannins, mainly punicalgins and ellagic acid. At the pH levels of the small intestine and under physiologic conditions, punicalagins are known to undergo partial hydrolysis to yield ellagic acid [89]. The consumption of pomegranate products leads to a significant accumulation of ellagitannins in the large intestines, where they interact with complex gut microflora. Two cell-based studies by Bialonska et al [36,90] reported the pomegranate byproducts and punicalagins inhibit the growth of pathogenic *Clostridia* species, *Pseudomonas*

aeruginosa, and *Staphylococcus aureus*. It was also observed that probiotic lactobacilli and most bifidobacteria were not affected, whereas the growth of *Bifidobacterium breve* and *Bifidobacterium infantis* was significantly increased under treatment, as was the production of short-chain fatty acids in media inoculated with human fecal microflora. A similar growth increase was seen in the feces of rats fed with a pomegranate extract [91]. Probiotics are commonly consumed as part of fermented foods with specially added active live cultures, such as in yogurt, soy yogurt, or as dietary supplements. The manipulation of the gut microbiota using probiotics may provide novel therapeutic treatments for different conditions, including obesity [92].

The PPARs are the central modulators of lipid and carbohydrate metabolism. Hsu and Huang [93] reported that some seed oils activated PPAR-γ in mice, which resulted in an alteration of adiposity, lower leptin levels, and an increase in adiponectin when fed an HFD. In contrast, the catalpic acid found in pomegranate seed oil has been demonstrated to decrease abdominal fat deposition, improve glucose tolerance, and upregulate adipose PPAR-α in two models of obesity [66]. An overexpression of PPAR-α, which is known for its triacylglycerol-lowering effects, was also demonstrated by Huang et al. [94] in Zucker diabetic fat rats, and PPAR-α agonists have been used for more than 40 y for the treatment of dyslipidemia [94,95]. Aasum et al. [96] treated experimental diabetic mice with PPAR-α agonists, which normalized the circulating fatty acid and triacylglycerol levels and decreased myocardial fatty acid oxidation by 50%. These findings suggest that pomegranate extract and seed oil have PPAR-α activators that help correct the abnormalities of lipid metabolism.

One mechanism reported by several groups is related to the pomegranate being one of the richest sources of antioxidants. The antioxidant activity of pomegranate constituents has been the subject of many studies conducted in vivo and in vitro [26,29,97–99]. The antioxidant activity is related to the diverse phenolic compounds present in the pomegranate, including the punicalagin isomer, ellagic acid, and anthocyanins. These compounds are known for their free radical-scavenging properties and inhibit lipid oxidation in vitro [100,101]. Tzulker et al. [102] suggested punicalagin as one of the major phytochemicals contributing to the total antioxidant capacity of PJ, with anthocyanin playing a minor role. Cerda et al. [79,103] demonstrated the role of punicalagin in female rats, which resulted in significant decreases in food consumption and the body weight of animals. Aviram et al. [48] and de Nigris et al. [34,46] demonstrated the antioxidative effect of PJ extract against lipid peroxidation in whole plasma and isolated lipoproteins. The pomegranate extract and juice are also effective in increasing vascular endothelial nitric oxide synthase and plasma nitric oxide levels, in turn increasing the response to acetylcholine in a resistance artery in vitro, thus suggesting a clinical application in the metabolic syndrome [34,46,48]. Aviram et al. [48] showed a decreased oxidation of HDL and LDL in humans after a 1-y consumption of PJ. A randomized control clinical trial conducted in 2008 in 30 adolescents with the metabolic syndrome; one group consumed natural grape juice 18 mL $\cdot$ kg^{-1} $\cdot$ d^{-1} and the other group consumed natural PJ 240 mL $\cdot$ kg^{-1} $\cdot$ d^{-1} for 1 mo. This study showed an improvement in endothelial function in the subjects, suggesting the importance of consuming diets rich in antioxidants by obese patients [53].

Obesity is a low-grade chronic inflammatory condition and the pomegranate constituents manifest important pharmacologic effects such as anti-inflammatory antioxidant effect and effects related to carbohydrate and lipid metabolism [39,72,104–109]. Obesity has been associated with adipocyte-derived inflammatory mediators; among these, interleukin-6 (IL-6) has a primary effect on metabolism through several mechanisms. IL-6 affects adipose tissue-specific gene expression, triacylglycerol release, lipoprotein lipase downregulation, and insulin sensitivity [110]. Constituents from the pomegranate have been described to decrease IL-6 production and thus decrease symptoms of obesity [111].

Many studies in humans have demonstrated that obesity is associated with an inflammatory state that in turn induces oxidative stress [112–117]. An exposure to increased levels of reactive oxygen species has been shown to facilitate adipocyte differentiation in vitro [112,118]. Childhood obesity is growing at an alarming rate, with an increased prevalence of metabolic risk factors such as high circulating triacylglycerols, low LDL, and an increase in inflammatory biomarkers (C-reactive proteins and IL-6) [118]. Sen and Simmons [112] demonstrated that antioxidant supplementation in pregnant rats resulted in a decreased adiposity and normalized glucose tolerance in the offspring as young as 2 wk. Inflammation and oxidative stress are known to play a key role in the development of obesity. Thus, providing foods with a high antioxidant capacity in addition to a hypocaloric diet is crucial for the treatment and prevention of obesity.

The cause of obesity is an imbalance between energy intake and energy expenditure. The consumption of thermogenic ingredients could also be a tool for obesity management in the future. The consumption of caffeine and catechin polyphenols in tea has been shown to increase energy expenditure, the metabolic rate, and fat oxidation [119,41]. In the pomegranate, the effects of xanthigen, a constituent in the seed oil, was studied for its thermogenic effects in obese non-diabetic female volunteers with non-alcoholic fatty liver disease by Abidov et al. [54]. They reported that xanthigen promoted weight loss and decreased the body and liver fat content in obese non-diabetic women. They also found that xanthigen increased resting energy expenditure, suggesting that it may be a promising food supplement in the management of obesity [54].

Conclusions

Pomegranate is a food that can be beneficial to the human body because many studies have demonstrated its potential beneficial effects. The PJ and pomegranate extracts have a long history of safety, and various pomegranate constituents have been developed as botanical dietary supplements to provide an alternative and easy form for consumption [120]. Different studies have demonstrated the safety of pomegranate dietary supplements in rats, but there have not been many studies evaluating their safety in humans. One such study concerned the 4-wk supplementation of 710 or 1420 mg of an ellagitannin-enriched pomegranate polyphenol extract in 64 overweight individuals with an increased waist size and no chronic disease, and it was observed to be safe and well tolerated [55,103,121]. In general, pomegranate dietary supplements are safe, with no adverse effects reported in any human subjects. Keeping the health benefits of the pomegranate in mind, the routine supplementation of PJ or extracts may prevent or even correct obesity, diabetes, and cardiovascular diseases [120]. However, as indicated in this review, decreasing energy intake, the intestinal absorption of dietary fats by inhibiting pancreatic lipase, and oxidative stress and inflammation might be important mechanisms for the antiobesity effects of pomegranate food as a whole. The relation of pomegranate constituents to thermogenesis has not been studied with more constituents of the pomegranate

other than xanthigen found in seed oil, and future work should investigate a link between the two. The antiobesity action of the pomegranate also has been hypothesized to be caused by the stimulation of probiotic bacteria, but further human studies on the potential of the pomegranate as a probiotic would be very useful [28]. Furthermore, a therapeutic index of all constituents must be established in dietary and commercialized forms (pills, capsules, etc.) to have a complete understanding of the potential benefits of the pomegranate for the prevention of obesity and related disorders.

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