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Original Article

Role of pomegranate peel on ameliorated hyperglycemia and hypercholesterolemia in experimental rats

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Abstract

Introduction
Pomegranate peels (*Punica granatum*) (contain fiber and antioxidants, which are beneficial to our health. This study aimed to investigate the effects of different concentrations of pomegranate peels on blood glucose, lipid profiles, and some physiological parameters, such as liver and kidney functions, in rats having diabetes and hypercholesterolemia.

Methods
Rats were divided into three main groups: the first main group was the negative control, the second main group was diabetic rats, and the third main group was hypercholesterolemic rats. Second and third main groups were divided into four subgroups (six rats/group) and fed with different diet levels of pomegranate peels (5, 10, and 15%) for 28 days. Body weight gain, feed intake, feed efficiency ratio, and relative weight of some organs were calculated at the end of the experiment. Fasting blood sample was taken for determination of serum glucose, total cholesterol, triglycerides, creatinine, urea, aspartate aminotransferase, and alanine aminotransferase.

Results
There was a significant reduction in both serum total cholesterol and triglycerides in all treated groups with pomegranate peels. The higher peels doses improved liver and kidney functions. However, the highest reduction was achieved by feeding diabetic rats with 15% pomegranate peels.

Conclusion
The study concluded that pomegranate peels ameliorated blood glucose, lipid profiles, liver enzymes, and kidney functions.

Keywords: Blood glucose, kidney function, lipid profile, liver, pomegranate peel

Introduction

Diabetes mellitus is one of the most common metabolic disorders that causes significant morbidity and mortality [1]. WHO[2] defines diabetes as a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Raised blood sugar is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels [2].

Diabetes can be caused by some biological factors, of which insulin resistance and deficiency are both related to hyperglycemia and hyperlipidemia [3].

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The burden of diabetes is increasing globally, particularly in developing countries. The causes are complex but are in large part owing to rapid increases in overweight, obesity, and physical inactivity (WHO, 2011). According to the International Diabetes Federation, 382 million people have diabetes, and patients with diabetes will increase to ~592 million by 2035 [4]. Diabetes is a significant epidemic of chronic metabolic ailment worldwide [5]. It is characterized by an insufficiency of insulin secretion and/or action, insulin resistance, and abnormal metabolism of glucose, lipid, and protein [5,6].

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Plants have always played a significant role in maintaining health and improving the quality of human life; many western drugs owe their origin to plant extracts. Recent years have seen increased interest on the part of consumers, researchers, and the food industry into how food products can help maintain health, and the role that diet plays in the prevention and treatment of many illnesses has become widely accepted [7]. At present, considerable importance is given to functional foods, which, in principle, apart from their basic nutritional functions, provide physiological benefits and play an important role in disease prevention or in slowing down the progression of chronic diseases [8].

Pomegranate belongs to the family Punicaceae. It is native from the area of Iran to the Himalayas in northern India and has been cultivated and naturalized over the entire Mediterranean region since ancient times [9]. Actually, the pomegranate is widely cultivated throughout Iran, India, Mediterranean countries, the drier parts of Southeast Asia, Malaysia, the East Indies, and tropical Africa and, to some extent, in the USA (drier parts of California and Arizona), China, Japan, and Russia [10].

The peel of pomegranate is almost one-half the weights of the whole fruit. It contains flavonoids, phenolic compounds, and a variety of tannins, minerals potassium, sodium, calcium, phosphorus, magnesium, and complex polysaccharides [11].

Hyperlipidemia and hypercholesterolemia are important risk factors for the development of atherosclerosis and coronary artery disease, as reported by Baigent *et al.*[12] and Gielen *et al.* [13]. The main pathogenic blood parameters are increased concentrations of cholesterol bound to low-density lipoprotein cholesterol (LDL-C), Triglycerides (T. Chol), and triglycerides (TG). Conditions of insulin resistance such as impaired glucose tolerance or 'prediabetes' are also characterized by a high risk of cardiovascular diseases [14]. Most therapeutic protocols rely on drugs that belong to the statin family. Statins inhibit the activity of 3-hydroxy-3-methylglutaryl-CoA reductase, which catalyzes the rate-limiting step in mevalonate biosynthesis, a key intermediate in cholesterol metabolism.

This is associated with a decrease in T. Chol, and also a switch from LDL-C to high-density lipoprotein cholesterol (HDL-C) fraction. Despite the significant clinical benefits provided by statins (1), many patients, in particular, those with metabolic syndrome, do not achieve their recommended LDL and HDL-C target goals with statins [14]. Therefore, this study aimed to evaluate the effect of pomegranate peels on blood glucose level, lipids profile, and some physiological parameters such as liver and kidney functions on hypercholesterolemic rats.

Materials and methods

Pomegranate peel (*Punica granatum* L) was extracted as follows: pomegranates were obtained from the local market. Pomegranate peels were cleaned from impurities and washed with tap water. Pomegranate peels were dried in air dryer oven at 45°C for 48 h, and then the peels were ground in a Multi Mill apparatus and passed through a 0.5-mm mesh sieve to obtain a fine peel powder.

A total of 54 healthy adult male albino rats (Sprague-Dawley strain) whose weight was between 200 and 210 g were obtained from the research institute of Ophthalmology Medical Analysis Department, Giza, Egypt. The animals were kept in single wire cages with wire bottoms under hygienic conditions and controlled laboratory conditions of temperature (25°C), lighting, and ventilation. Food and tap water were provided ad libitum and checked daily.

The basal diet was prepared according to American Institute of Nutrition (AIN, 1993). [15] and Reeves *et al.* [16]. The vitamin mixture and salt mixture were prepared according to American Institute of Nutrition, Committee on Standard Nutritional Studies [17].

Experimental design

Adult male albino rats were fed on a standard diet for 1 week for adaptation; then, they were divided into three groups ($n = 18$). The first group A was fed on standard diet only and served as a control group. The second group B was the diabetic group. Diabetes was induced in normal healthy adult male rats by injection of alloxan 150 mg/kg body weight according to the method described by Desia and Bhide [18]. Six hours after the injection of alloxan, fasting blood samples were obtained by the retro-orbital method to estimate fasting serum glucose. Rats having fasting serum glucose more than 200 mg/dl were considered to have diabetes [19]. Then, they were divided into subgroups as follows: subgroups control B: fed on a basal diet as the positive diabetic control, and subgroups B1, B2, and B3 were fed on basal diet + 5, 10, and 15% pomegranate peel, respectively, replacing an equal amount of starch.

The third group C was the hypercholesterolemic groups. Hypercholesterolemia was induced in normal healthy adult male albino rats by feeding on hyperlipidemia diet (1.5% cholesterol and + 10% lard) as stated by Knapka and Judge[20] for 2 weeks, and then fasting blood sample was obtained to estimate total serum cholesterol and TG level. When insure rats have hypercholesterolemia, then they were divided into subgroups as follows: subgroups control C: hypercholesterolemia as a positive control fed on a basal diet, and subgroups C1, C2, and C3 were fed on basal diet + 5, 10, and 15% pomegranate peel, respectively, replacing an equal amount of starch for 28 days.

At the end of the experiment period, the animals were killed after being fasted (overnight) under anesthetized, and blood samples were collected in dry centrifuge tubes from the hepatic portal vein. The organs (liver, kidney, and spleen) of each animal were quickly removed by careful dissection, washed in a saline solution (0.9%), dried using filter paper, and then rapidly weighed separately to calculate the absolute and relative organ weights. Serum was separated by centrifugation of blood

at 4000 rpm (round/min) for 15 min at room temperature and kept in the plastic vial at −20°C until analysis.

Chemical analysis of peels

Crude protein, fiber, fat, and ash content were determined by using the method described by Official Methods of Analysis, Association of Official Analytical Chemists [21].

Biochemical analysis

The enzymatic colorimetric method was used to determine serum glucose according to Kaplan [22]. Serum cholesterol was determined according to Allain *et al.* [23]. Enzymatic determination of TG in serum was conducted according to Fossatip and Prancipel [24]. Determination of HDL-C according to Burstein [25]. Creatinine was determined according to the method described by Bohmer [26]. Urea was determined according to the method described by Patton and Crouch [27]. Aspartate aminotransferase and alanine aminotransferase activities were measured according to the method described by Reitman and Frankel [28].

The data were expressed as mean ± SD. All variables were tested for normal distribution using the one-way analysis of variance ($P < 0.05$). If the groups showed significant differences, Turkey's multiple comparison tests were performed with Snedecor and Cochran [29]. Statistical analysis was carried out using the program of statistical package for the social sciences (SPSS, windows version 16.0, Chicago, DL-USA), PC statistical software (version 16).

Results and Discussion

Data in Table 1 shows that fiber was 18.10/100 g dried pomegranate peel, which represents approximately half of the recommended daily intake. Dietary fiber that is fundamental and intact in fiber-rich foods (e.g. fruits, vegetables, legumes, and whole grains) is widely recognized to have beneficial effects on health when consumed at recommended levels (25 g/day for adult women and 38 g/day for adult men) [30]. On the contrary, Johansson-Persson *et al.*[31] concluded that high dietary fiber intake helps to prevent the risk of cardiovascular disease.

Table 2 shows the effect of feeding diabetic rats and hypercholesterolemic rats with diets containing some levels of pomegranate peel on feed intake (FI), feed efficiency ratio (FER), and body weight gain. FI in hypercholesterolemic groups showed a nonsignificant difference in C3 (15% peel) when compared with the positive control group. However, diabetic groups B3 (15% peel) showed a significant increase when compared with the positive control group. These results were in agreement with those reported by Dikmen *et al.* [32], who reported that pomegranate peel was able to reduce FI in diabetic and hypercholesterolemic rats. Moreover, this is in agreement with Mohammed[33] and Labib and Hossin[34] who reported a decrease in feed consumption in diabetic and hypercholesterolemic rats treated with pomegranate peel.

The results of FER increased in most groups. This was in accordance with those reported by El-Dein *et al.*[35] who reported that FER increased in hypercholesterolemic and diabetic rats treated with pomegranate peel, whereas these results were not similar to that recorded by Oluremi *et al.*[36] and Al-Rawahi *et al.* [37]. The results of body weight gain in our study increased in hypercholesterolemic groups and decreased in diabetic groups, especially in 15% peel group. This was in agreement with Chao *et al.*[38] who reported a significant decrease in body weight gain ratio in diabetic rats treated with pomegranate peel. Moreover, this is in agreement with Labib and Hossin[34] who reported a significant increase in body weight gain compared with positive control in hypercholesterolemic rats. The obtained results were in agreement with those reported by Youssef *et al.* [39]. The increase in fiber intake might be associated with improvements in body weight. Moreover, enhancement of body weight may be owing to the biological function of pomegranate polyphenols including ellagic and tannic acids, which increase total serum protein and protein synthesis in the body [33].

Table 3 shows the effect of feeding different levels of pomegranate peel on the relative weight of the organs in

Table 1: Chemical composition of dried pomegranate peel (g/100 g)

Material	Constituents					
	Protein (g)	Fat (g)	Fiber (g)	Ash (g)	T. Carb. (g)	Total (g)
Pomegranate peel	15.91	7.56	18.10	15.67	42.76	100

Table 2: Effect of some levels from pomegranate peel on feed intake, feed efficiency ratio, and body weight gain of diabetic or hypercholesterolemic rats

Parameters	Groups								
	A (negative)	B (positive)	B1 (5%)	B2 (10%)	B3 (15%)	C (positive)	C1 (5%)	C2 (10%)	C3 (15%)
FI (g/day)	14.32±0.56^{b}	14.32±0.91^{b}	12.64±0.87^{c}	14.44±0.83^{b}	15.36±0.86^{a}	9.67±0.72^{b}	8.54±0.83^{b}	8.38±0.84^{b}	9.78±0.86^{b}
FER	0.14±0.002^{c}	0.11±0.003^{e}	0.19±0.006^{a}	0.17±0.003^{b}	0.12±0.004^{d}	0.10±0.001^{d}	0.10±0.001^{d}	0.13±0.002^{b}	0.11±0.004^{c}
BWG (g/period)	42.27±1.22^{c}	92.70±1.32^{a}	90.96±1.3^{b}	86.04±0.43^{c}	66.45±0.44^{d}	29.12±1.84^{e}	28.28±0.99^{e}	30.12±0.98^{e}	33.17±0.96^{b}

Data are expressed as mean±SD. Values within a row having different superscripts are significantly different ($P \leq 0.05$). BWG, body weight gain; FER, feed efficiency ratio; FI, feed intake.

alloxan-induced diabetic rats. The obtained data illustrated in diabetic rats a gradual decrease of relative kidney weight, spleen weight, heart weight, and liver weight with the increase of supplement level. The statistical analysis showed a low significant correlation between treatments and organ ratio compared with positive control. This may be owing to peels' polyphones, which increased the antioxidant capacity against the free radical in some organs. These results are similar to those of Oluremi *et al.* [36]. Data also showed that hypercholesteremic rats had a gradual decrease in relative kidney weight, heart weight, and liver weight; however, spleen weight increase in C1 and C2, whereas decreased in C3. The statistical analysis showed a low significant correlation between treatment and organ ratio compared with positive control.

On the contrary, the supplemented diabetic groups had a significant decrease in the liver, kidney, and feeding rats decreased heart on pomegranate peel. This may be owing to peels' polyphones, which increased the antioxidant capacity against the free radical in some organs. These results are similar to those of Oluremi *et al.* [36].

Table 4 shows the effect of feeding diabetic rats on different levels of pomegranate peel on serum glucose level. Serum glucose decreased gradually in diabetic rats, after two weeks of feeding rats on the supplemented diet with different levels of pomegranate peel. The decrease was increased with the increase of supplement level. Blood glucose was lower in all groups compared with the positive control group. Group B3 had a lower value compared with other groups (15% pomegranate peel).

These results are in agreement with those reported by Youssef *et al.*[39] and Najafzadeh *et al.* [40], who reported that pomegranate peel had marked protection, as it brought down the level of blood sugar. Chau *et al.*[41] suggested that glucose-lowering effects that are most often associated with viscous fiber lie in the soluble dietary fiber content of peels.

Serum T. Chol and serum TG levels in hypercholesterolemic rats fed different doses of pomegranate peels are present in Table 5. The data in this table showed a gradual decrease in all parameters, except HDL-C, which increased with increase in the concentration of pomegranate peels in the supplemented diets. T. Chol and TG

Table 3: Effect of some levels from pomegranate peel peels on the relative weight of the organs in diabetic and hypercholesterolemic rats

Parameters	Groups								
	A (negative)	B (positive)	B1 (5%)	B2 (10%)	B3 (15%)	C (positive)	C1 (5%)	C2 (10%)	C3 (15%)
Liver relative weight	5.92±0.05^{a,b}	7.33±0.22^{a}	5.22±0.08^{b,c}	5.26±0.12^{c}	5.48±0.17^{b,c}	8.34±0.18^{a}	6.12±0.43^{b}	6.58±0.87^{b}	5.02±0.03^{c}
Kidney relative weight	0.98±0.01^{b}	1.78±0.44^{a}	0.98±0.04^{b}	0.92±0.06^{b}	1.05±0.16^{b}	1.78±0.02^{a}	1.15±0.33^{b,c}	1.27±0.19^{b}	0.9±0.03^{c}
Spleen relative weight	1.43±0.18^{a}	0.95±0.10^{b}	0.68±0.03^{c}	0.60±0.05^{c}	0.65±0.03^{c}	0.76±0.19^{c}	1.03±0.12^{b}	1.00±0.01^{b}	0.53±0.02^{c}
Heart relative weight	0.75±0.19^{a}	0.75±0.14^{a}	0.68±0.09^{b}	0.74±0.04^{b}	0.67±0.01^{b}	0.76±0.15^{a}	0.64±0.04^{d}	0.67±0.03^{c}	0.77±0.08^{a}

Data are expressed as mean±SD. Values within a row having different superscripts are significantly different ($P \leq 0.05$).

Table 4: Effect of feeding different doses of pomegranate peel on glucose level in diabetic rats (mg/dl)

Feeding period	Groups				
	A (negative)	B (positive)	B1 (5% peel)	B2 (10% peel)	B3 (15% peel)
1 Week	98.50±1.12^{e}	388.20±2.34^{a}	372.20±1.99^{b}	352.20±2.42^{c}	276.40±1.18^{d}
2 Weeks	92.20±1.13^{e}	361.40±2.33^{a}	355.30±1.01^{b}	334.20±1.13^{c}	255.30±1.19^{d}
3 Weeks	90.70±1.11^{e}	327.20±2.05^{a}	318.20±1.56^{b}	288.50±1.98^{c}	238.60±1.73^{d}
4 Weeks	89.80±0.98^{e}	288.30±1.18^{a}	276.20±1.33^{b}	237.50±1.05^{c}	200.61±1.33^{d}

Table 5: Effect of feeding rats on a hypercholesterolemic diet containing some levels of pomegranate peels on lipid profile (mmol/l)

Lipid profile	Groups				
	A (negative)	C (positive)	C1 (5%)	C2 (10%)	C3 (15%)
Total cholesterol (mg/dl)	78.3±0.78^{k}	204.55±1020^{a}	139.46±2.62^{e}	134±6.15^{f}	130.48±9.24^{f}
Triglycerides (mg/dl)	97.68±1.76^{i}	123.70±2.18^{a}	70.91±6.74^{d}	69.00±2.85^{d}	62.10±4.72^{e}
HDL-C	60.58±3.62^{a}	28.38±5.33^{b}	43.55±1.64^{c}	52.08±4.16^{c}	53.48±1.94^{c}
LDL-C	20.86±2.74^{a}	154.03±8.07^{i}	83.30±3.71^{g}	65.97±8.48^{e}	67.05±4.97^{e}
VLDL	7.92±0.19^{c}	24.20±0.64^{a}	13.16±0.76^{b}	12.42±0.94^{b}	13.80±0.57^{b}

Data are expressed as mean±SD. Values within a row having different superscripts are significantly different ($P \leq 0.05$). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 6: Effect of some levels from pomegranate peels on liver functions in diabetic and hypercholesterolemic rats

Liver enzymes	Groups								
	A (negative)	B (positive)	B1 (5%)	B2 (10%)	B3 (15%)	C (positive)	C1 (5%)	C2 (10%)	C3 (15%)
AST (U/l)	18.06±1.07^{f}	32.10±0.10^{a}	27.10±0.22^{b}	23.40±0.10^{b}	21.30±0.30	37.25±5.82^{a}	37.25±7.22^{a}	35.10±4.92^{a}	26.12±0.51^{b,c}
ALT (U/l)	9.51±0.94^{h}	29.40±2.50^{a}	24.00±2.52^{a}	21.80±3.25^{b}	17.30±1.1037.52	16.10±1.10^{a}	15.93±1.25^{a}	14.43±1.21^{c}	12.80±0.48^{d}

Data are expressed as mean±SD. Values within a row having different superscripts are significantly different (P≤0.05). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 7: Effect of some levels from pomegranate peels on kidney functions in diabetic and hypercholesterolemic rats

Kidney function	Groups								
	A (negative)	B (positive)	B1 (5%)	B2 (10%)	B3 (15%)	C (positive)	C1 (5%)	C2 (10%)	C3 (15%)
Creatinine (mg/dl)	0.67±0.33^{g}	0.75±0.9^{a}	0.65±0.10^{b}	0.60±0.10^{b}	0.56±0.20^{b}	1.88±0.12^{a}	1.71±0.15^{b}	1.47±0.10^{c}	1.40±0.72^{d,f}
Urea (mg/dl)	14.70±0.90^{h}	26.60±2.20^{a}	23.10±0.80^{c,d}	21.10±0.90^{c}	22.10±1.20^{b}	47.35±0.10^{a}	40.10±0.10^{a}	37.10±0.30^{b}	34.20±0.10^{b}

Data are expressed as mean±SD. Values within a row having different superscripts are significantly different (P≤0.05).

levels (mg/dl) were increased significantly ($P < 0.05$) for rats fed on hypercholesterolemia diet (group C), compared with (group A) the negative control. T. Chol and TG of groups C1, C2, and C3 decreased significantly ($P < 0.05$) when compared with group C. The statistical analysis showed a significant decrease in T. Chol and TG of all treated groups with different doses of nutritional peels when compared with control positive group. These results are in agreement with those reported by Adler *et al.*[42] and Allain [43], who reported that pomegranate peel decreased blood lipid profiles.

The results of this study showed a decrease in TG and Very low density lipoprotein (VLDL) in all groups. However, LDL and T. Chol decreased in some groups. The best result was found in the group fed 15% peel. HDL increased in all groups. These results were in agreement with those of Esmaillzadeh *et al.* [44], who found significant reductions were recorded in T. Chol and LDL-C, whereas no change in HDL-C was noticed in hypercholesterolemic and rats. They concluded that concentrated pomegranate peel consumption might modify the risk factors in hyperlipidemic patients and their inclusion may be beneficial. Moreover, a study of Bagri *et al.*[45] found that the administration of pomegranate peel extract resulted in a significant reduction in cholesterol, TG, and LDL-C in compression with hypercholesterolemic control and a significant increase in the level of HDL-C. Fenercioglu *et al.*[46] indicated that the Polyphenol-rich antioxidant supplement containing pomegranate extract has an important antagonizing effect on oxidative stress and lipid peroxidation in patients with type 2 diabetes mellitus and might be beneficial in preventing cardiovascular complications in hypercholesterolemic rats. They showed a decrease in LDL and an increase in HDL in hypercholesterolemic and diabetic rats.

Table 6 shows the effect of feeding different levels of pomegranate peel on liver functions in alloxan-induced diabetic rats. We can see that the aspartate aminotransferase level and alanine aminotransferase level decreased gradually when the supplement level increased when compared with the positive control group. Chau *et al.*[47] proved that pomegranate peel is rich in polyphenols, which exhibit antioxidant and anti-inflammatory capacities *in vitro*.

Table 7 indicated that creatinine and urea levels in both diabetic control group B and hypercholesterolemic control group C increased compared with the healthy control group A. A gradual decrease of serum creatinine and urea was observed as the feeding dose of pomegranate peel increased. These results are in the same line with Adler *et al.*[42] and Youssef *et al*. [39].

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Conflicts of interest
There are no conflicts of interest.

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