PJN
ISSN 1680-5194

PAKISTAN JOURNAL OF NUTRITION

ANSInet
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Pakistan Journal of Nutrition 8 (8): 1251-1257, 2009
ISSN 1680-5194

Effect of Pomegranate (*Punica granatum*) Peels and It's Extract on Obese Hypercholesterolemic Rats

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Abstract: There has been an inverse association between fiber intake and cardiovascular diseases. Dietary supplementation with nutrients rich in antioxidants is associated with inhibition of atherogenic modifications to LDL, macrophage foam cell formation and atherosclerosis. Pomegranates are a good source of polyphenols and other antioxidants. The present study was performed to evaluate the effect of pomegranate peel powder and it's extract on lipids metabolism in hypercholesterolemic male rats. pomegranate peel powder were added to hypercholestrolemic diet by 5, 10 or 15% as dietary fiber supplemented. While pomegranate peel extract were added to hypercholestrolemic diet by 1, 2 or 3% supplemented. Forty adult male rats were assigned to eight groups for four weeks feeding period; group (1) control negative, group (2) control positive hypercholesterolemic rats, groups (3, 4 and 5) hypercholesterolemic rats fed 5, 10 or 15% pomegranate peel powder as dietary fiber supplemented and groups (6, 7 and 8) hypercholesterolemic rats fed 1,2 or 3 % pomegranate peel extract supplemented. At the end of the feeding period, animal's blood were collected for serum lipid measurements. Results showed that hypercholesterolemic rats had highly significant changes in all tested lipids parameters comparing with control negative group. all hypercholestrolemic rats administrated with different levels of pomegranate peel powder (5, 10 and 15%) had significant decrease in food consumption and body weight gain ratio comparing with control positive group. Liver, kidney spleen to body weight ratio and all tested lipid parameters except HDL had highly significant decrease for all hypercholestrolemic rats administrated with different levels of pomegranate peel powder (5, 10 and 15%) or administrated with different levels of pomegranate peel extracts (1, 2 and 3%) comparing with control positive group. In conclusion, the potent antioxidative capacity of pomegranate peel powder or it's extract against lipid peroxidation may be the central link for the antiatherogenic effects of pomegranate peel powder or it's extract on lipoproteins. Moreover, It suggested that, consumption of pomegranate peel powder or it's extract my modify the risk of hypercholesterolemia and it have more potential as a health supplement rich in natural antioxidants.

Key words: Pomegranates, cardiovascular diseases, lipids metabolism

INTRODUCTION

Pomegranate is an important source of bioactive compounds and has been used for folk medicine for many centuries. Pomegranate juice has been demonstrated to be high in antioxidant activity and is effective in the prevention of atherosclerosis. In a previous study, we found that pomegranate peel had the highest antioxidant activity among the peel, pulp and seed fractions of 28 kinds of fruits commonly consumed in China as determined by FRAP (ferric reducing antioxidant power) assay (Li *et al*., 2006).

Major risk factors for atherosclerosis include high plasma LDL concentrations and LDL modifications such as its retention, oxidation and aggregation (Williams and Tabas, 1995). Blood platelet activation also contributes to accelerated atherosclerosis (Aviram, 1992) and (Aviram, 1995). Oxidative modification of LDL is thought to play a key role during early atherogenesis. Oxidized LDL is taken up by macrophages at an enhanced rate via their scavenger receptors (Parthasarathy *et al*., 1986), leading to the formation of lipid-laden foam cells, the hallmark of the early atherosclerosis (Berliner *et al*., 1995).

The lipid peroxidation hypothesis of atherosclerosis (Aviram, 1993a,b; Witztum and Steinberg, 1991 and Aviram, 1993a,b) is supported by evidence of oxidized lipoproteins in atherosclerotic lesions (Aviram *et al*., 1995), by the relatively greater oxidizability of LDL from atherosclerotic patients (Lavy *et al*., 1991) and by the antiatherogenicity of some antioxidants against LDL oxidation (Aviram and Fuhrman, 1998 and Aviram, 1996). The impressive ability of Pomegranate Juice (PJ) to inhibit in vitro and *ex vivo* lipid peroxidation in plasma, as well as in isolated LDL and HDL, was shown in several different oxidative systems including transition metal ions, free radical generators and arterial cells. By more than one assay (TBARS, lipid peroxide and conjugated diene formation) we showed the substantial antioxidative capacity of PJ to scavenge free radicals, a major mechanism of action of some potent natural antioxidants, including vitamin E and flavonoids (Schwenke and Behr, 1998 and Rice *et al*., 1996). The

inhibitory effect of PJ against LDL oxidation was also shared by aqueous extracts of the outer and inner peel of pomegranates. When compared per total polyphenol content (or per weight), the peels were more potent antioxidants than the juice. These fractions may contain different flavonoids from those present in PJ that are more potent antioxidants.

The soluble polyphenol content in Pomegranate Juice (PJ) varies within the limits of 0.2-1.0%, depending on variety and includes mainly anthocyanins (such as cyanidin-3-glucoside, cyanidin-3,5-diglucoside and delphindin-3-glucoside), catechins, ellagic tannins and gallic and ellagic acids (Narr Ben *et al*., 1996). Pomegranate peel extract had markedly higher antioxidant capacity than the pulp extract in scavenging or preventive capacity against superoxide anion, hydroxyl and peroxyl radicals as well as inhibiting $CuSO_4$ induced LDL oxidation. The contents of total phenolics, flavonoids and proathocyanidins were also higher in peel extract than in pulp extract. The large amount of phenolics contained in peel extract may cause its strong antioxidant ability (Li *et al*., 2006). Dietary supplementation with nutrients rich in antioxidants is associated with inhibition of atherogenic modifications to LDL, macrophage foam cell formation, and atherosclerosis. Pomegranates are a source of polyphenols and other antioxidants (Aviram *et al*., 2000). Edible parts of pomegranate fruit (about 50% of total fruit weight) comprise 80% juice and 20% seeds. Fresh juice contains 85% water, 10% total sugars and 1.5% pectin, ascorbic acid and polyphenolic flavonoids. Pomegranate seeds are a rich source of crude fibers, pectin and sugars. Dried pomegranate seeds contain the steroid estrogen estrone (Heftaman and Bennett, 1996) and (Moneam *et al*., 1988), the isoflavone phytoestrogens genistein and daidzein and the phytoestrogen coumestrol (Sharaf and Nigm, 1964).

This study assessed the effect of pomegranate peel extract on lipid profiles (cholesterol, triglycerides, low density lipoprotein LDL, high density lipoprotein HDL, very low density lipoprotein VLDL and lipid peroxidation) in obese hypercholestrolemic rats.

MATERIALS AND METHODS

Pomegranate used in this research was obtained from local market. Cholesterol (white crystalline powder), bile salt, casein, vitamins, minerals and cellulose were obtained from El-Gomhariya Pharm. and Chem. Ind. Comp., Cairo, Egypt. While starch and corn oil were obtained from local market.

Preparation of pomegranate peel extract: *Pomegranate* fresh peel were washed with water and cut into small pieces and dried by the hybrid solar convective drying system, belonging to the Solar Energy Dept., National Research Center, Dokki, Egypt, at 30-40°C.

Ethanol extraction of Pomegranate dried peel were obtained according to (Bok *et al*., 1999); Dried pomegranate peel weighing 6.7 kg was extracted with 80 L of 95% ethanol for 24 h at 60°C. The extract was filtered and concentrated using a high-capacity evaporator (EYELA Rotary vacuum evaporator N-11; Tokyo Ridadidai Co., Ltd., Japan).

Experimental animals: Forty adult male albino rats Sprague Dawley strain with an average weight of (180 ±220 g) obtained from the Experimental Animal House of Helwan, Egypt. The rats were housed in stainless steel cages with wire mesh bottoms and maintained in temperature and humidity control with 12 h light/dark cycle. All rats were allowed to free access drinking of water and basal diet for seven days adjustment to the laboratory environment. Then rats were randomly divided into 8 groups (each of 5 rats) as follow:

Group 1: Control negative (C-); rats fed on basal diet, the standard casein diet was prepared according to (Reeves *et al*., 1993), protein (13%), fat (4%), salt mixture (3.5%), vitamin mixture (1%), choline (0.2%), cellulose (5%) and the remainder was starch.

Group 2: Control positive (C+); rats fed on hypercholesterolemic diet composed of basal diet + 1 % cholesterol according to (Terpstra *et al*., 2002) + 10 % saturated fat according to (Knapka and Judge, 1974).

Groups 3: Rats fed on hypercholesterolemic diet + Dried pomegranate peel 5%.

Groups 4: Rats fed on hypercholesterolemic diet + Dried pomegranate peel 10%.

Groups 5: Rats fed on hypercholesterolemic diet + Dried pomegranate peel 15%.

Groups 6: Rats fed on hypercholesterolemic diet + pomegranate peel extract 1%.

Groups 7: Rats fed on hypercholesterolemic diet + pomegranate peel extract 2%.

Groups 8: Rats fed on hypercholesterolemic diet + pomegranate peel extract 3%.

Each diet was prepared with equal in nutritional value to control casein diet. Food consumption was recorded every other day and body weight was recorded weekly throughout the feeding period which lasted for eight weeks. At the end of the experiment rats (4 weeks) fasted overnight and Blood samples were collected from the aortic vein into clean dry centrifuge tubes and were stored at room temperature for 15 min, put into a

refrigerator for 2 h, then centrifuged for 10 min at 3000 rpm to separate serum. Serum was carefully aspirated and transferred into dry clean Wasserman tubes by using a Pasteur pipette and kept frozen at (-20°C) till analysis, while organs was removed then washed in saline and weighed after dried with filter paper.

The analytical methods of serum

Determination of total cholesterol: Serum cholesterol was determined according to the enzymatic method described by Allain *et al.*,1974 .

Determination of triglycerides: The triglycerides in serum were colorimetrically determined according to Wahlefeld, 1974.

Determination of High Density Lipoprotein (HDL) cholesterol: The HDL-c was determined according to Albers *et al.*, 1983.

Determination of Very Low Density Lipoprotein (VLDL) cholesterol: The concentration of VLDL-c was estimated according to the Fridewald's equation Fridewald *et al.*, 1972.

$$VLDL\text{-}c = triglycerides/5$$

Determination of Low Density Lipoprotein (LDL) cholesterol: According to Fridewald *et al.*, 1972, low density lipoprotein cholesterol can be calculated as follows:

$$LDL\text{-}c = Total\ cholesterol - (HDL\text{-}c) - (VLDL\text{-}c).$$

Determination of lipid peroxidation: Peroxidation was determined by measuring the amount generated of Thiobarbituric Acid–reactive Substances (TBARS) (Buege, 1978) and lipid peroxides (El-Saadani *et al.*, 1989).

Statistical analysis: The obtained data were statistically analyzed according to SAS, 1996.

RESULTS AND DISCUSSION

Dietary supplementation with nutrients rich in antioxidants is associated with inhibition of atherogenic modifications to LDL, macrophage foam cell formation, and atherosclerosis. Pomegranates are a source of polyphenols and other antioxidants (Aviram *et al* ., 2000). The present study designed to evaluate the effect of pomegranate peels and it's extract on food consumption, body weight gain, organs to body weight ratios, lipid profiles (total cholesterol, triglycerides, low density lipoprotein LDL, high density lipoprotein HDL, very low density lipoprotein VLDL and lipid peroxidation) and atherogenic index.

From the data in Table 1 and Fig. (1 and 2) it could be observed that, rats fed on hypercholestrolemic diet without supplementation (control positive) had significant increase in food consumption and body weight gain ratio comparing with rats fed on basal diet (control negative). Moreover, all hypercholestrolemic rats administrated with different levels of pomegranate peel powder (5, 10 and 15%) had significant decrease in food consumption and body weight gain ratio comparing with control positive group. While there were no significant differences between all hypercholestrolemic rats administrated with different levels of pomegranate peel extract (1, 2 and 3%) and positive control group in food consumption and body weight gain ratio. The results are agreement with Ludwing (2000) who found that increased consumption of fiber is associated with decreased body weight and reduction in other cardiovascular risk factors.

Table 1: Effect of pomegranate peel powder and it's extract on food consumption and body weight Gain ratio (mean + SE)

Parameter	Food consumption	Body weight
Treatment	gm/day	Gain ratio
Negative control	19.47	23.56±0.65^{c}
Positive control	25.57	57.09±0.72^{a}
Peel 5%	20.2	38.28±0.61^{bc}
Peel 10%	19.9	22.77±0.86^{c}
Peel 15%	18.83	21.15±0.98^{ac}
Extract 1%	24.65	49.98±0.72^{b}
Extract 2%	24.54	47.65±0.67^{b}
Extract 3%	23.32	51.34±0.97^{a}

*Values with the same letters indicate non-significant difference ($p<0.001$) and vice versa

From the data in Table 2 and Fig. 3, it could be indicated that rats fed on hypercholestrolemic diet without supplementation (control positive) had significant increase in liver, kidney spleen to body weight ratio comparing with rats fed on basal diet (control negative). Moreover, it could be observed that, liver, kidney spleen to body weight ratio had significant decrease for all hypercholestrolemic rats administrated with different levels of pomegranate peel powder (5, 10 and 15%) or administrated with different levels of pomegranate peel extracts (1, 2 and 3%) comparing with control positive group. The results are agreement with Chidambara *et al.* (2002) who reported that liver of different groups support the protective effects exhibited by the extract of pomegranate peel.

From the data in Table 3 and Fig. 4, it could be observed that rats fed on hypercholestrolemic diet without supplementation (control positive) had significant increase in total cholesterol, triglycerides and high density lipoprotein HDL cholesterol comparing with rats fed on basal diet (control negative). Moreover, all

Table 2: Effect of pomegranate peel powder and it's extracts on organs/body weight ratio (mean ± SE)

Treatment/Parameter	Liver /B.W. ratio	Kidney/B.W. ratio	Spleen/B.W. ratio
Negative control	3.22± 0.23^{b}	0.96±0.049^{b}	0.43±0.039^{b}
Positive control	4.94±0.24^{a}	1.09±0.048^{a}	0.66±0.038^{a}
Peel 5%	3.68±0.29^{b}	0.89±0.046^{b}	0.39±0.034^{b}
Peel 10%	3.46±0.34^{b}	0.83±0.054^{b}	0.40±0.037^{b}
Peel 15%	3.65±0.46^{b}	0.94±0.049^{b}	0.44±0.039^{b}
Extract 1%	3.68±0.29^{b}	0.89±0.046^{b}	0.39±0.035^{b}
Extract 2%	3.46±0.34^{b}	0.88±0.045^{b}	0.40±0.036^{b}
Extract 3%	3.65±0.46^{b}	0.84±0.049^{b}	0.47±0.033^{b}

* Values with the same letters indicate non- significant difference (p<0.001) and vice versa

Table 3: Effect of pomegranate peel powder and it's extracts on serum total cholesterol, HDL and triglycerides (mean + SE)

Treatment/ Parameter	Total cholesterol mg /dl	Triglycerides mg/dl	HDL gm /dl
Negative control	67.33±4.89^{C}	62.33±3.54^{C}	31.27±5.30^{B}
Positive control	154.33±5.13^{A}	124.33± 3.70^{A}	41.93±5.53^{A}
Peel 5%	92.33±4.76^{B}	66.00± 3.46^{C}	38.40±5.18^{AB}
Peel 10%	96.00±4.11^{B}	62.00± 3.69^{C}	36.93±5.53^{AB}
Peel 15%	97.67±4.52^{B}	52.00±3.99^{C}	41.50±5.98^{A}
Extract 1%	75.00± 3.66^{C}	86.33±4.78^{B}	41.40±5.18^{A}
Extract 2%	69.00± 3.89^{C}	82.00±4.11^{B}	42.93±5.53^{A}
Extract 3%	70.00± 3.92^{C}	83.67±5.12^{B}	40.50±5.98^{A}

*Values with the same letters indicate non -significant difference (p<0.001) and vice versa

Table 4: Effect of pomegranate peel powder and it's extracts on serum LDL, VLDL lipid peroxidation and atherogenic index (mean ± SE)

Treatment/ Parameter	LDL mg /dl	VLDL mg/dl	Lipid peroxidation mg /dl	Atherogenic Index
Negative control	23.60± 1.89^{C}	12.47±0.68^{C}	3.35±0.25^{B}	2.15^{B}
Positive control	87.53±1.97^{A}	24.87±0.77^{A}	5.29±0.21^{A}	3.68^{A}
Peel 5%	40.73±1.85^{B}	13.20±0.69^{C}	3.40±0.36^{B}	2.41^{B}
Peel 10%	46.67±1.97^{B}	12.40±0.84^{C}	3.25±0.27^{B}	2.59^{B}
Peel 15%	45.77±2.13^{B}	10.40±0.59^{C}	3.77±0.33^{B}	2.35^{B}
Extract 1%	16.33±1.85^{D}	17.27±0.79^{B}	2.40±0.26^{C}	1.81^{C}
Extract 2%	9.67±1.97^{D}	16.40±0.67^{B}	2.25±0.23^{C}	1.61^{C}
Extract 3%	12.77±2.13^{D}	16.73±0.64^{B}	2.27±0.36^{C}	1.71^{C}

*Values with the same letters indicate non- significant difference (p<0.001) and vice versa

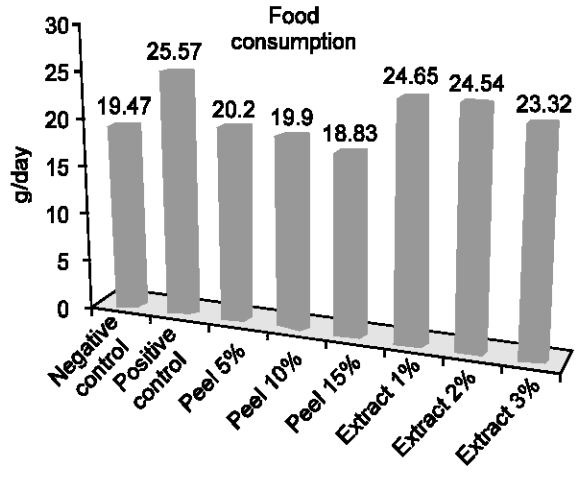

Fig 1: Effect of pomegranate peel powder and its extract on food consumption (g/day)

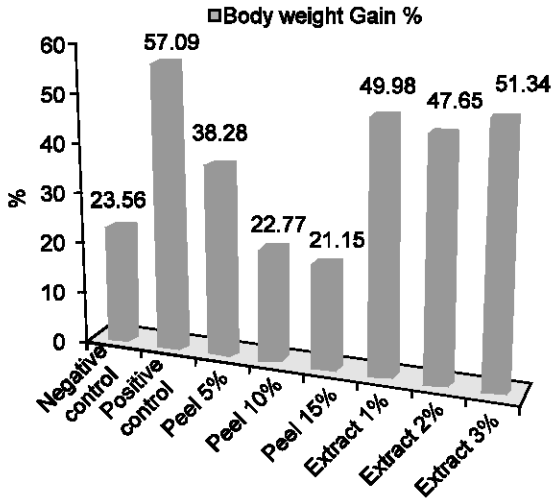

Fig. 2: Effect of pomegranate peel powder and its extract on body weight gain ratio

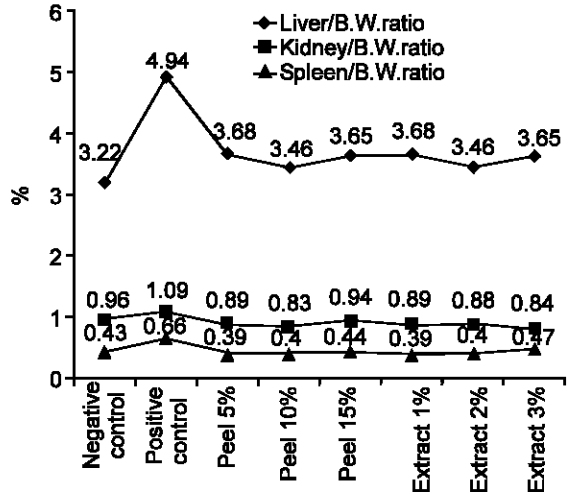

Fig. 3: Effect of pomegranate peel powder and its extract on organs/body weight ratio

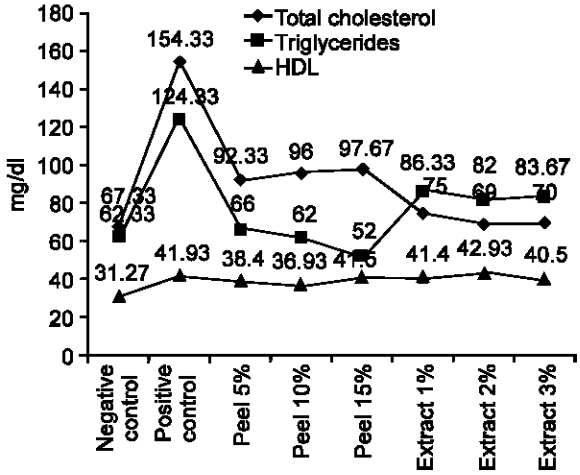

Fig. 4: Effect of pomegranate peel powder and its extract on total cholesterol, triglycerides and high density lipoprotein

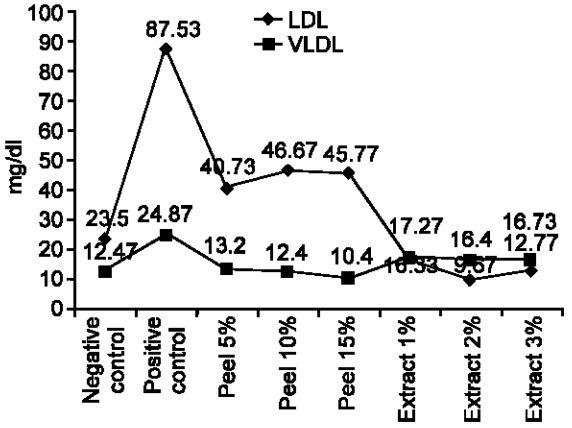

Fig. 5: Effect of pomegranate peel powder and its extract on high density lipoprotein and low density lipoprotein

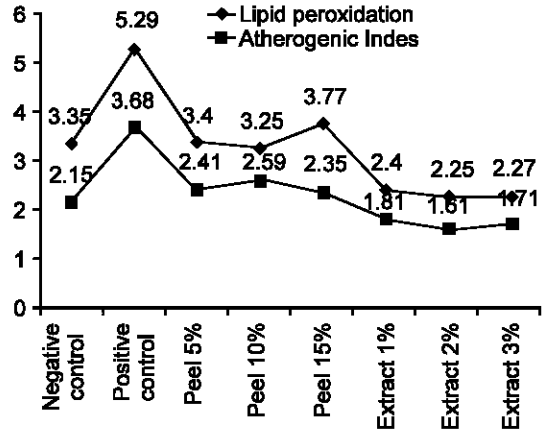

Fig. 6: Effect of pomegranate peel powder and its extract on lipid peroxidation and atherogenic index

hypercholestrolemic groups administrated with different level of pomegranate peel powder (5, 10 and 15%) or administrated with pomegranate peel extract (1, 2 and 3%) had significant decrease in serum total cholesterol and triglycerides comparing with control positive. Moreover, there were no significant differences in high density lipoprotein HDL between all hypercholestrolemic groups with or without administration by pomegranate peels powder or it's extracts. The results are agreement with Esmaill *et al.* (2006) who reported that consumption of concentrated pomegranate juice for type II diabetic patient with hyperlipidemia significant reduction were seen in total cholesterol ($p>0.006$) and had no significant changes in serum HDL.

From the data in (Table 4) and Fig. (5 and 6), it could be indicated that rats fed on hypercholestrolemic diet without supplementation (control positive) had significant increase in serum low density lipoprotein LDL, very low density lipoprotein VLDL, lipid peroxidation and atherogenic index comparing with rats fed on basal diet (control negative). Moreover, all hypercholestrolemic groups administrated with different level of pomegranate peel powder (5, 10 and 15%) or administrated with pomegranate peel extract (1, 2 and 3%) had significant decrease in serum low density lipoprotein LDL, very low density lipoprotein VLDL, lipid peroxidation and atherogenic index comparing with control positive. The results are agreement with (Aviram *et al.*, 2000) who reported that Dietary supplementation

with nutrients rich in antioxidants is associated with inhibition of atherogenic modifications to LDL, macrophage foam cell formation and atherosclerosis. Pomegranates are a source of polyphenols and other antioxidants and with Li *et al.* (2006) who reported that Pomegranate peel extract appeared to have more potential as a health supplement rich in natural

antioxidants than the pulp extract. Also the results are agreement with Esmaill *et al*. (2006) who found that consumption of concentrated pomegranate juice for type II diabetic patient with hyperlipidemia that have significant decrease in low density lipoprotein cholesterol LDL-c and LDL-c/high density lipoprotein cholesterol (HDL-c) ($p>0.001$) and it are agreement with Rosenblat *et al*. (2006) who reported that pomegranate juice consumption resulted in a significant reduction in serum lipid peroxides and thiobarbituric acid reactive substances (TBARS) by 56% and 28% respectively.

Conclusion: We showed the antiatherogenic capabilities of pomegranate peel powder and it's extracts in obese hypercholestrolemic rats. The potent antioxidative capacity of pomegranate peel powder or it's extract against lipid peroxidation may be the central link for the antiatherogenic effects of pomegranate peel powder or it's extract on lipoproteins. Moreover, It suggested that, consumption of pomegranate peel powder or it's extract my modify the risk of hypercholesterolemia and it have more potential as a health supplement rich in natural antioxidants.

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