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Evaluation of Antdiabetic, Hypocholesterolemic of Pomegranate (*Punica Granatum L.*) Juice Powders and Peel Powder Extracts In Male Albino Rats

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Abstract: *Punica granatum L., commonly known as pomegranate and belonging to the family of Punicacceae, is a unique plant. Two varieties of pomegranate including Manfaloty and Wonderful were used in this study. The juice powders (JP) subjected to freeze-drying and peel powder extracts (PPE) of the two varieties were used as hypoglycemic and hypocholesterolemic agents by using albino rats. The juice powder was used in two different concentrations (1 and 1.5 g/kg/day/ rat), meanwhile the peel powder extract was used in only one concentration (0.3 g/kg/day/rat). Results show the effect of JP and PPE on the glucose level of diabetic rats. The superior effect was with G6 rats administrated with 0.3 g MPE/kg/day/rat (Manfaloty peel extract) followed by G9 0.3 g WPE/kg/day/rat (Wonderful peel extract). On the other hand results show the effect of JP and PPE on the level of total cholesterol, LDL, HDL and triglycerides in rats serum as hypocholesterolemic agents. These results show that G5 (HFD+1%cholesterol+300mgMPE/kg /day/ rat) recorded the best results of all the aforementioned experiments, this could be attributed to the phenolic content in peel powder extract of pomegranate.*

Keyword*: pomegranate, juice powder, peel, hypoglycemic, hypercholesterolemia, rats.*

I. Introduction

The pomegranate (*Punicagranatum*L.) is an ancient fruit; it has been widely consumed in various cultures for thousands of years. The use of pomegranate fruit dates back to Biblical times and reports of its therapeutic qualities have echoed throughout the millennia (1).The 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 (2). Actually, the pomegranate is widely cultivated throughout Iran, India, Mediterranean countries, the drier parts of Southeast Asia, tropical Africa, to some extent, in the United States, China, Japan, and Russia (3). The world pomegranate production amounts to approximately 1,500,000 tons (4). In Egypt, annual production of pomegranate is estimated at 64574 tons (5). The peel amounts to approximately 60% of the pomegranate fruit weight (6).

The edible parts of pomegranate fruits are consumed fresh or used for the preparation of fresh juice, canned beverages, jelly, jam, and paste and also for flavoring and coloring beverage products (7, 8). In addition, it is widely used in therapeutic formulas, cosmetics, and food seasonings. Since ancient times, the pomegranate has been regarded as a "healing food" with numerous beneficial effects in several diseases (9). There has been a virtual explosion of interest in the pomegranate as a medicinal and nutritional product because of its multifunctionality and its great benefit in the human diet as it contains several groups of substances that are useful in disease risk reduction. As a result, the field of pomegranate research has experienced tremendous growth (10, 11). The chemical composition of the fruits differs depending on the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions (7, 12, and 13).

The pomegranate peel which is normally considered to be a waste is important antidiarrheal and antidiabetic agent in the Ayurvedic system of medicine. Preclinical studies by (14) have shown that the pomegranate peel extract was effective in decreasing the blood glucose levels in both normal and diabetic mice (alloxan-induced).

Diabetes mellitus (DM) is one of the most crucial chronic diseases of the endocrine pancreas. Its main characteristic is unsuitable hyperglycemia and disordered metabolism of the lipid, carbohydrate, and protein that are caused by insulin deficiency or insulin action or both (15), which contributes to rising in a free radical generation (16). Oxidative stress plays a crucial role in chronic complications of diabetes and it is associated with increased lipid peroxidation (17).

Hypercholesterolemia is generally, associated with an increase in plasma concentrations of low-density lipoprotein (LDL-c) (bad cholesterol) and very low-density lipoprotein (VLDL-c) and /or a decrease in high-density lipoprotein cholesterol (HDL-c) (good cholesterol). Modification of oxidation of LDL-c is thought to

play a key role during early atherogenesis i.e. formation of atheroma inside the walls of blood vessels that finally lead to arteriosclerosis (18).

Several studies on Pomegranate extracts and its active constituents revealed that they have an antioxidant activity by scavenging free radicals, decreasing macrophage oxidative stress and preventing lipid peroxidation in animals as well as increasing plasma antioxidant capacity in elderly humans (19). Studies in rats and mice confirm the antioxidant property of a Pomegranate byproduct extract made from the whole fruit minus, the juice showed a 19% reduction in oxidative stress in mouse peritoneal macrophages, 42% decrease in cellular lipid peroxides content, and 53% increase in reduced glutathione levels (20).

The objective of this work was to Study the chemical composition of the two varieties of Pomegranate "Manfaloty and Wonderful" " and extraction of phenolic compounds from the pomegranate juice powder and peels powder extract as well as study the availability of pomegranate phenolic compounds as hypoglycemic and hypocholesterolemic agents.

II. Materials and Methods

2. 1. Materials

Two varieties of fresh and mature pomegranate (*Punica granatum L.*) "Manfaloty and Wonderful" were obtained from the Horticultural Research Institute, Agriculture Research Centre, Giza, Egypt, in October 2014at their full maturity. The samples were authenticated by Prof. Mohamed Abo El Wafa, Fruits Department, Horticultural Research Institute, Agriculture Research Centre, Giza, Egypt.

Testing chemicals, including Folin-Ciocaltea's reagent, DPPH and Standards of phenolic acids: Gallic acid; Ellagic acid; Quercetin; Caffeic acid Chlorogenic acid; P-coumaric; Vanillic acid and Ferulic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). All others agents and chemicals used in the study were of analytical grade.

2. 2. Preparation of pomegranate juice (PJ):

The pomegranate fruits were washed and cut into four pieces and peeled off. The arils (seed and juice) were separated manually and the pulp (juice) was separated from seed by mechanical press according to the method described by (21). The freshly prepared juice was stored frozen (-20°C) until analyzed.

1.3. Preparation of pomegranate juice powder (JP):

Pomegranate juice was concentrated by using rotary evaporator at 40°C(RV10 basic V; IKA, Staufen, Germany), giving a 73° Brix as recommended by (22) . The concentrated juice was freeze dried using freeze drier evaporator lypholyaizer model labconco, U.S.A, under 46 mbar and - 47°C (23).

1.4. Preparation of pomegranate peel powder (PP):

The pomegranate peels were cut into small pieces and dried in oven at 50oC for 72 h. Dried Pieces were cooled and powdered in a heavy duty grinder and sieved using a 60 mesh sieve and packed and stored at room temperature in a glass jar.

1.5. Determination of Chemical Composition of pomegranate juice powder and peel powder:

Moisture, ash, total carbohydrates, crude protein, crude fiber and ether extract were determined for the juice powder and peel powder of the two varieties of pomegranate (Manfaloty and Wonderful) as described by the (24).

1.6. Preparation of peel powder extracts (PPE):

The pomegranate peel powder (50g) was extracted with 1000 mL of 80% ethanol overnight at 40^{o}C in a shaking water bath. The solutions were filtered through Whatman filter paper No.42 and evaporated to dryness under vacuum with a rotary evaporator (RV10 basic V; IKA, Staufen, Germany) at 40^{o}C.The extract yield was 15%.

1.7. Determination of Total Phenolics of pomegranate juice powder and peel powder extract:

Total phenolic of pomegranate juice powder 'lyophilized" as well as peel powder extracts was determined using the method of (25) and (26). Juice powder was reconstituted by adding water in the ratio of 1:5. Methanol: Water solution (6:4) was prepared as a diluted solution for pomegranate reconstituted juice. The later juice was diluted in the ratio of 1: 100.

Two hundred µl portions of diluted juice extract or 50 mg peel extract/mL water (50 mg/mL) were introduced into test tubes followed by addition of 1000 µl of Folin-Cio- calteu reagent (1:10). Thirty seconds later and just prior to 8 min, 800µL of Na_2CO_3 (7.5%) was added to extracts in tubes. The reaction mixtures were incubated at 24°C for 1h the absorbance was measured by Janway model 6705 spectrophotometer (England) at a λ=765 nm, at room temperature. Total phenolic was calculated from standard Gallic acid

solutions used under the same conditions and concentrations were expressed as mg Gallic acid equivalents (GAE) per g extract.

1.8. Determination of antioxidant activity "DPPH" for pomegranate juice powder and peel powder extract:

The antioxidant capacity of the pomegranate juice powder was determined by the 1, 1-diphenyl-2-picrylhydrazine (DPPH) radical scavenging method as described by (27). 100 µL of diluted pomegranate juice mixed with 2 mL of 0.1 mM DPPH in methanol. The mixture was incubated in the dark for 30 min. The absorbance of the resulting solution was measured at 517 nm by Janway model 6705 spectrophotometer (England).

DPPH radical scavenging activity of peel extract was determined as described by (28). Stock solutions 1 mg peel extract /1mL ethanol (1 mg/ml) was prepared. 2ml of DPPH (80 µg/ml ethanol) solution was prepared and added to 1 ml of extract solution. A positive blank was prepared in the same manner except that respective solvent was added instead of extract. After 30 min of incubation at 37 °C, the absorbance of the solution was recorded by Janway model 6705 spectrophotometer (England) at 517 nm against ethanol. The inhibition of the DPPH radical by the sample was calculated according to the following formula:

DPPH scavenging activity % = {(A blank – A sample) /A blank} × 100

Where, a blank is the absorbance value of the control reaction and A sample is the absorbance value of the sample.

1.9. Fractionation and identification of Phenolic compound:

The polyphenolic compounds of pomegranate juice powde and peel powder extract were fractionated and identified for phenolic compounds by HPLC according to the method described by (29). Identification of individual phenolic compounds was performed on Hewlett- Packard HPLC (Model 1100), using a hypersil C18 reversed- phase column (25 × 4.6 mm) with 5µm particle size. The injection was obtained by means of a Rheodyne injection value (Model 7125) with 50µl fixed loop. The mobile phase was composed of solvent A (4.5% formic acid) and solvent B (80% of acetonitrile and 20% of solvent A). The program began with isocratic elution with 95% A (0-1min); then a linear gradient was used until 16 min, lowering A to 20%; from 17 min to 24 min, and A deceased to 0%. The flow rate was 1 ml min-1, and the runs were integrated at 280 and 320, 360 nm for hydroxycinnamic acid and flavonoid derivatives, respectively. Scanning was performed from 200 to 600 nm. Phenolic compounds were identified by comparing retention times and UVVIS spectra with those of pure standards and the range of calibration curves. The repeatability of the quantitative analysis was ± 4%. The analysis was replicated (n=3), and the contents given as means values, plus or minus the standard deviation. The results were expressed as grams of each compound per total phenolic compounds.

1.10. Biological Experiments:

One hundred and two male Albino rats weighing 180–200 g were obtained from the Research Institute of Ophthalmology, Giza, Egypt. The animals were housed individually in well-aerated cages with a screen bottom and fed a basal diet as described in (30) for 12 days as an adaptation period. The salt mixture and vitamin mixture were prepared as described in (31) and (30) respectively. Temperature and humidity were maintained at 25°C and 60% respectively, food and water were given *ad libitum*.

2.10.1. Experimental Design

The rats were divided into two main groups:

(I) Diabetic group (Π) hypercholesterolemia group

The group of rats "diabetic group" was extended up to 4 weeks. This main group contained 54 rats, thus divided into 9 groups of rats, each one contains (6 rats) as recommended by (32). All the diabetic rats were fed on basal diet. The groups were classified as (G1) Control basal diet, (G2) diabetic control, (G3) diabetic injected with 20 units insulin, (G4) diabetic +1g Manfaloty juice powder/kg b.w, (G5)Diabetic +1.5g Manfaloty juice powder/kg b.w, (G6) Diabetic + 0.3g Manfaloty peel extract/kg b.w, (G7) Diabetic+ 1g Wonderful juice powder/kg b.w,(G8) Diabetic + 1.5g Wonderful juice powder/kg b.w,(G9) Diabetic + 0.3g Wonderful peel extract/kg b.w.

Diabetes was induced in overnight fasted animals by a single intraperitoneal injection of alloxan monohydrate dissolved in 5% w/v normal saline at a dose of 150 mg/kg b.w. The dose of alloxan was injected periodically for 3 days. Five days later, blood samples were collected from the eye plexuser by a fine capillary glass tube. The samples were centrifuged for 10 min at 3000 rpm and the serum was collected, blood glucose level was measured. The rats with blood glucose level ≥300 mg/dL were considered to be diabetic as recommended by (33). Serum glucose, serum total cholesterol, HDL, and LDL - cholesterol, and triglycerides (TG) were determined by using the diagnostic kits.

The second main group of hypercholesterolemia experiment contained 48 rats,the experiment was extended up to 6 weeks. The animals were distributed into 8 groups, each containing 6 rats as recommended by (34). One of the experimental groups was fed on the basal diet and used as the normal control (G1). The other seven groups were allowed to fed a high fat diet +1 % cholesterol. Rats of 6 groups were administered with the pomegranate juice powder or peel powder extract by stomach tube .Such groups were classified as (G2) which fed on high fat + 1 % cholesterol diet;(G3) HFD + 1% cholesterol + 1g Manfaloty juice powder/kg b.w, (G4) HFD + 1 % cholesterol + 1.5g Manfaloty juice powder/kg b.w, (G5) HFD +1% cholesterol + 0.3gManfaloty peel extract/kg b.w, (G6) HFD + 1% cholesterol + 1gWonderful juice powder/kg b.w, (G7) HFD + 1% cholesterol + 1.5g Wonderful juice powder/kg b.w, (G8) HFD + 1% cholesterol + 0.3g Wonderful peel extract/kg b.w.

2.10.2. Histopathological studies

Portions of pancreatic and liver tissues were dissected out and fixed at 10% buffered neutral formal saline and processed. After fixation, tissues were embedded in paraffin. Fixed tissues were cut at 5 µm and stained with hematoxylin and eosin. The sections were estimated under microscopically according to (35).

1.11. Statistical Analysis

Results were statistically analyzed by the least significant differences (L.S.D) at the level of probability procedure according to (36).

III. Results and Discussions

3.1. Chemical composition of pomegranate juice powder and peel powder

Result in Table (3) show the chemical composition of pomegranate juice powder "lyophilized" and peel powder for the two of pomegranate varieties "Manfaloty and Wonderful". The juice powder of the two varieties had only total carbohydrate those recorded 100% on dry weight basis. Meanwhile, the peel powder of the two varieties had a different amount of chemical composition. All the results were in significant difference. Manfaloty peel powder had higher amounts of protein, fiber, and fat than Wonderful peel powder, lower the ash content of Wonderful peel powder was higher than the Manfaloty peel powder. Our results are in coincide with the result of (37) who reported that pomegranate peel powder had high nutritive value, those contains important raw materials like crude fibers, protein, and carbohydrates.

3.2. Total phenolic content and antioxidant activity of the two varieties of pomegranate Juice powder and peel powders extracts:

Results in Table 4 show the phenolic content of the two varieties (Manfaloty and Wonderful) pomegranate juice powder and peel powder extract, the phenolic content was determined as g Gallic acid/ 100g dried pomegranate. Results were insignificant difference among the two varieties of pomegranate (Manfaloty and Wonderful) for juice powder "lyophilized" and peel powder extract. Peel powder extract of the two varieties had higher total phenols than the juice powder "lyophilized" of the corresponded varieties. However, the phenolic content of peel powder extract of Manfaloty varieties was superior to the other phenolic content that amounted as 27.79g Galic acid/100 g dried sample. Moreover, the juice powder of Manfaloty variety had a higher amount of total phenols 3.13g Galic acid/100g dried sample than Wonderful pomegranate juice powder. Our results are in agreement with the results of (38) who found that the total Phenolic contents commercially grown in South Africa included Wonderful and Ganesh was 18.9 and 29.5 g Galic acid/100g dry weight. In addition (39) found that the lyophilized pomegranate juice had 2.5g Galic acid/100g dried sample.

Results in Table 4 show also the antioxidant activity of the two varieties of pomegranate Manfaloty and Wonderful, results show that the peel powder extract of Manfaloty pomegranate had the highest value of antioxidant activity (87.07%) which is in direct proportion with the total phenolic content of peel powder extract. In contrast, the antioxidant activity of wonderful juice powder "lyophilized" recorded the lowest value that amounted to 30.84%. (40) Reported that the antioxidant activity as DPPH scavenging free radical activity reaction was clearly related to the total phenolics of juice powder "lyophilized" or peel powder extracts.

3.3. Identification of phenolic compounds for pomegranate juice powder and peel powder extract:

Phenolic compounds of the two varieties of pomegranate (Manfaloty and Wonderful) of their juices powder "lyophilized" and peel powder extract (g/100g dried sample) were identified by HPLC, results are shown in Table (5). In particular, the phenolic acid gallic acid, ellagic acid, quercetin, caffeic acid, chlorogenic acid, P-coumaric, Vanillic acid and Ferulic acid were identified with values ranging from 0.001 to 0.20 g/100g lyophilized juice and from 0.0010 to 0.52 g/100g peel powder extract (PPE). Results show that the pomegranate juice powder "lyophilized" and pomegranate peel powder extract were rich in gallic acid followed by chlorogenic acid. Meanwhile, Vanillic acid and P-coumaric were found in small amounts. So, the phenolic acids present in pomegranate juice or peel can be divided into two groups: (1) hydroxybenzoic acids, mainly gallic

acid and ellagic acid and (2) hydroxycinnamic acids, principally caffeic acid, chlorogenic acid, and *p*-coumaric acid (12). Our results are in agreement with the result of (41), (42) and (43).

3.4. Effect of pomegranate juice powder "lyophilized" and peel powders extracts on the level of serum glucose, total cholesterol, LDL and HDL in diabetic rats.

The effect of pomegranate juice powder as well as pomegranate peel powder extract for the two varieties of pomegranate " Manfaloty and Wonderful" on the level of serum glucose, total cholesterol, LDL and HDL in induced diabetic rats was measured, results are shown in Table 6. Significant differences are shown throughout the results in Table 6. The highest value of serum glucose was with G2"diabetic group rats" that recorded 330.35 mg/dl. This value decreased up to121.55 mg/dl for G3 diabetic rats injected with 20 units insulin /kg/day followed by G6 diabetic rats administration with 300 mg Manfaloty peel extract "MPE" that recorded 128.41mg/dl. Result show also that, the group of rats administration with 1.5g Manfaloty juice powder/ kg/day "G5" could reduce the level of glucose better than G4 those recorded 136.43 and 144.80mg/dl respectively. Moreover, the groups of rats administrated with pomegranate Wonderful varieties either juice powder or peel powder extract (G7, G8 and G9) had lees effective in lowering glucose level than those rats administrated with pomegranate Manfaloty varieties, those included G4, G5 and G6. The antidiabetic activity of the peel of *Punica granatum* might be attributed to the presence in them of tannins, flavonoids "Quercetin" and phenolic glycosides, known to be natural antioxidants (44), which protect the existing β-cells (which escaped alloxanization) from dying by their free radical scavenging action (45). The peel of *Punica granatum* has been reported to possess the highest antioxidant activity among the parts of pomegranate (46). Leaves and fruit peel extracts of *Punica granatum* decreased the elevated blood sugar levels. The possible mechanism for this anti-diabetic action of leaves and fruit peel extracts of *Punica granatum* may be improving glycemic control and insulin secretion from pancreatic beta cells in diabetic rats (32). The hypoglycemic, antioxidant and hypolipidemic effect of leaves and fruit peel extract could be due to the presence of phytochemicals such as alkaloids, flavonoids, saponins, and tannins. (47) Reported that, fruit peel of *Punica granatum* has the most antioxidant content followed by flowers, leaves, and seeds. This could be the reason for better activity of fruit peel extract than the leaves extract (48).

It is reported by (49) that aqueous extracts of *Punica granatum* peel at dose of 430 mg/kg b.w lowered blood glucose levels in alloxan-induced diabetic rats after 4 weeks of daily administration. Preclinical studies have shown that oral treatment with gallic acid, an important constituent of pomegranate possesses antidiabetic effects in streptozotocin-induced diabetic animals (50) and (51). The main compounds that present antidiabetic properties are polyphenols, which may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues (52).

Result in Table 6 also show the level of total cholesterol (mg/dl), LDL level as mg/dl and HDL level as (mg/dl) for the different groups of rats, those diabetic groups either treated with insulin or administration with MJP or MPE as well as those had WJP or WPE with different concentration for 4 weeks. Results show that the levels of total cholesterol and LDL were increased in diabetic rats "G2" meanwhile, the level of HDL was decreased for the mentioned group "G2" compared with the normal control "G1". All the results were in significant difference. Results show that administration of MJP, WJP "juice powder" or MPE, WPE "peel powder extract" at all doses for 28 days significantly reduced the total cholesterol and LDL levels and significantly increased the HDL level as compared with diabetic rats. Peel powder extract 300mg/kg/day was significantly better than juice powder either 1g or 1.5g/kg/day for both varieties Manfaloty or Wonderful. However, G6 of rats those administrated with 300mg Manfaloty peel extract was the best group for lowering total cholesterol and LDL levels and increasing HDL level. The standard group of rats "G3" those diabetic rats injected with 20 units insulin/kg/day was better than all the extracts of pomegranate.

The level of serum lipids are usually raised in diabetes and such an elevation represents a risk factor for coronary heart disease (53) and (54). Since lipid abnormalities accompanied with premature atherosclerosis is the major cause of cardiovascular diseases in diabetic patients, therefore ideal treatment for diabetes, in addition to glycemic control, should have a favorable effect on lipid profile (55), (56), (57) and (58). Free reactive oxygen species generated due to sustained hyperglycemia causes lipid peroxidation (48).

3.5. Effect of pomegranate juice powder* and peel powders extracts on the serum total cholesterol, LDL, HDL and triglyceride of hypercholesterolemic rats.

Results in Table (7) show the different groups of rats administrated with pomegranate juice powder (lyophilized) or pomegranate peel powder extracts for the two varieties of pomegranate with high fat diet + 1% cholesterol, compared with the two control groups of rats "G1" basal diet and "G2" group of rats had high fat diet + 1% cholesterol. All the results were in significant difference. The group of rats G5 and G8, those administrated with 300mg Manfaloty peel powder extract (MPE) and Wonderful peel powder Extract (WPE) were better than the corresponded group of rats G3, G4, G6 and G7 those administrated with juice powder

"lyophilized" for the different varieties of pomegranate" Manfaloty or Wonderful " as lowering total cholesterol, LDL and triglyceride, G5 the group of rats administrated 300mg MPE/kg b.w/day recorded the best results for total cholesterol, LDL, and triglyceride, this group showed increasing the level of HDL. Our results in agreement with the results of (34) who reported that administration of hydroethanolic extract from *Punica granatum* peel showed marked antihyperlipidemic effects in high lipid diet fed rats. They also found that Pomegranate extract decreased serum cholesterol, triglycerides, LDL, while increasing serum HDL levels in high lipid diet fed rats in comparison to saline-treated rats. On the other hand, (50) found that oral administration of gallic acid (20 mg/ kg b.w) significantly decreased serum total cholesterol, triglyceride, LDL-cholesterol, urea, uric acid, creatinine and at the same time markedly increased plasma insulin, C-peptide, and glucose tolerance level.

The protective role of the fruit peel could be related to its flavonoids and polyphenolic contents, which possess antioxidative activity (59) Moreover, the juice of *Punica granatum* is also known to prevent atherosclerosis, which further supports its antiatherogenic potential (60). It is reported that addition of pomegranate juice to simvastatin in a macrophage cell culture model system improves the statin ability to inhibit cellular cholesterol biosynthesis and to protect the cells from oxidative stress. These effects could be related to the antioxidant hydrolysable tannin punicalagin and to the phytosterol β-sitosterol, which are both present in pomegranate (61) .Moreover, phytosterols of pomegranate consumption decreased serum cholesterol levels in dyslipidemic patients, as well as their cardiovascular risk (62) and (63).

As a result, it may be concluded that pomegranate peel extract possesses antilipidemic activities in high lipid diet fed rats and that the pomegranate peel extract may be of use as an antidyslipidemic agent. It is concluded that the plant should be considered as an excellent candidate for future studies on dyslipidemia(34).

3.6. Histological examination

3.6.1. Effect of pomegranate juice powder and peel powder extracts on histopathology of the pancreas in normal and diabetic rats.

Histological examination of pancreas of the control basal diet "G1 group of rats demonstrated normal histological pattern (Fig1). Examination of Pancreas sections of the diabetic rats "G2" injected with alloxan revealed vacuolation of cells of islets of Langerhans (Fig2). Pancreas of rats of "G3" diabetic rats treated with 20 units insulin /kg b.w/day showed regeneration of beta cells (Fig3). Moreover, examination of the pancreas of diabetic rats administration with 1.5g MJP/kg b.w/day "G5" showed the islets of Langerhans with well-organized beta cells (Fig4). Sections from the pancreas of diabetic rats after administrated with pomegranate peel powder extract in a dose of 300mgMPE/kg b.w/day showed improvement in pancreatic damage and there was marked improvement in islets structure. Our results are in accordance with the results of (64).

3.6.2. Effect of pomegranate juice powder and peel powder extracts on histopathology of the liver in normal and hypercholesterolemic rats.

Histological examination of the liver of the basal diet "control group of rats G1" showed normal histological pattern (Fig6). The hypercholesterolemic rats G2 "high fat diet" impairment of the normal structural organization of hepatic lobules in many areas and deposition of large lipid droplet in cells (Fig7). Examination of liver of high-fat diet rats administrated with 1.5g MJP/kg b.w/day "G4" showed marked improvement from change caused by cholesterol except of few residual cells with fine lipid droplets (Fig8). The section from the liver of high-fat diet rats administrated with Manfaloty peel extract in a dose of 300mgMPE/kg b.w/day"G5" showed more improvement in histological structure and showed an almost normal structure with a regular arrangement of hepatic cell cords and exhibited a reduction in fat accumulation (Fig9). Our results are in agreement with the results of (65).

IV. Conclusions

The peel powder extracts have higher phenolic content and antioxidant activity than the juice powder for the two varieties of pomegranate, the results indicate that pomegranate juice powder and peel powder extract may be considered a good source of natural compounds with significant antioxidant activity which can be attributed to the high percentages of the main constituents or to synergy among their different components, especially phenolic acids, flavonoids, and tannins**.** Therefore they have an important role as hypoglycemic and hypocholesterolemic agents.

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Table (1) Composition of basal and different diabetic diets (g/100g diet)

Ingredient	(G1) control basal diet	(G2) diabetic control	(G3) diabetic treated with insulin	(G4) diabetic + 1g MJP/kg b.w	(G5) diabetic + 1.5gMJP/kg b.w	(G6) diabetic + 300mg MPE/kg b.w	(G7) diabetic + 1g WJP/kg b.w	(G8) diabetic + 1.5g WJP/kg b.w	(G9) diabetic + 300mg WPE/kg b.w
Starch	62	62	62	61	60.5	61.7	61	60.5	61.7
Casein*	18	18	18	18	18	18	18	18	18
Corn oil	10	10	10	10	10	10	10	10	10
Cellulose	5	5	5	5	5	5	5	5	5
Vit- Mix	1	1	1	1	1	1	1	1	1
Salt-Mix	4	4	4	4	4	4	4	4	4
Pomegranate juice powder	-	-	-	1	1.5		1	1.5	
Pomegranate peel powder extract	-	-	-			0.3			0..3

* Casein contained 90% protein.

Table (2) Composition of basal and different HF diets (g/100g diet)

Ingredient	(G1) control basal diet	(G2) HFD +1%cholesterol	(G3) HFD +1%cholesterol +1g MJP/kg b.w	(G4) HFD +1%cholesterol +1.5g MJP/kg b.w	(G5) HFD +1%cholester+300mgMPE/kg b.w	(G6) HFD +1%cholesterol+ 1gWJP/kg b.w	(G7) HFD +1%cholesterol +1.5g WJP/Kg b.w	(G8) HFD +1%cholesterol +300mg WPE/kg b.w
Starch	62	47.62	46.62	46.12	47.32	46.62	46.12	47.32
Casein*	18	18	18	18	18	18	18	18
Corn oil	10	8	8	8	8	8	8	8
Cellulose	5	5	5	5	5	5	5	5
Vit- Mix	1	1	1	1	1	1	1	1
Salt-Mix	4	4	4	4	4	4	4	4
Beef Tallow	-	15	15	15	15	15	15	15
Cholesterol	-	1	1	1	1	1	1	1
Cholinbitartarate	-	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Cholic acid	-	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Pomegranate juice powder			1	1.5		1	1.5	
Pomegranate peel powder extract					0.3			0.3

*Casein contained 90% protein.

Table (3) Chemical Composition of pomegranate juice powder and peel powder for the two varieties "Manfaloty and Wonderful" on dry weight basis (g/100g).

Components	Juice powder*		Peel Powder		LSD (P≥0.05)
	Manfaloty	Wonderful	Manfaloty	Wonderful	
Crude protein	___	____	$3.83^{a} \pm 0.15$	$3.16^{b} \pm 0.05$	0.2
Crude fibers	____	____	$14.66^{a} \pm 0.11$	$12.73^{b} \pm 0.05$	0.2
Crud fat	____	____	$3.06^{a} \pm 0.05$	$2.46^{b} \pm 0.05$	0.13
Total ash	____	____	$2.86^{b} \pm 0.05$	$3.36^{a} \pm 0.05$	0.13
Total carbohydrates	$100^{a} \pm 0$	$100^{a} \pm 0$	$75.7^{c} \pm 0.14$	$78.4^{b} \pm 0.13$	0.27

Table(4). Total phenolic content of pomegranate juice powder and peel extract

	Juice powder*		Peel powder extract		LSD (P≥0.05)
	Manfaloty	Wonderful	Manfaloty	Wonderful	
Total phenols g/100 dry weigh	$3.13^{c} \pm 0.01$	$2.50^{d} \pm 0.15$	$27.79^{a} \pm 0.42$	$19.78^{b} \pm 0.83$	0.09
Antioxidant activity %	$35.16^{c} \pm 0.53$	$30.84^{d} \pm 0.39$	$87.07^{a} \pm 0.71$	$79.81^{b} \pm 0.31$	0.98

* Freeze dried pomegranate juice.

Table (5) Identification of phenolic compounds for the two varieties of pomegranate juice powder and peel powder extract (g/100g dried sample).

*

Phenolic compounds	Juice Powder*		Peel powder extract	
	Manfaloty	Wonderful	Manfaloty	Wonderful
Galic acid	0.20	0.017	0.520	0.490
Ellagic acid	0.013	0.008	0.042	0.036
Qurecetin	0.050	0.042	0.055	0.035
Caffeic acid	0.02	0.02	0.031	0.022
Chlorogenic acid	0.069	0.062	0.513	0.478
P-coumaric	0.002	0.0026	0.012	0.015
Vanillic acid	0.001	0.001	0.0015	0.0010
Ferulic acid	0.067	0.058	0.154	0.096
Total	0.422	0.2106	1.3285	1.173

lyophilized pomegranate juice.

Table. (6) Effect of pomegranate juice powder*and peel powders extracts on the level of serum glucose, total cholesterol, LDL and HDL in diabetic rats.

Groups	Glucose (mg/dl)	Total cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
G1: Control (basal diet)	$92.71^{i} \pm 0.09$	$89.17^{i} \pm 0.57$	$29.85^{i} \pm 0.17$	$47.10^{a} \pm 0.64$
G2: Diabetic	$330.35^{a} \pm 0.59$	$131.85^{a} \pm 0.49$	$81.77^{a} \pm 0.32$	$30.87^{i} \pm 0.61$
G3: Diabetic injected with 20 units insulin /kg/day	$121.55^{h} \pm 0.17$	$96.30^{h} \pm 0.18$	$31.62^{h} \pm 0.18$	$45.40^{b} \pm 0.38$
G4: Diabetic +1g MJP/kg/day	$144.80^{c} \pm 0.51$	$120.27^{c} \pm 0.47$	$48.95^{c} \pm 0.57$	$35.89^{g} \pm 0.47$
G5: Diabetic +1.5g MJP/kg/day	$136.43^{e} \pm 0.37$	$112.12^{e} \pm 0.33$	$42.87^{e} \pm 0.42$	$38.32^{e} \pm 0.79$
G6: Diabetic +300mgMPE/kg/day	$128.41^{g} \pm 0.49$	$101.07^{g} \pm 0.63$	$32.92^{g} \pm 0.58$	$43.30^{c} \pm 0.67$
G7: Diabetic +1g WJP/kg/day	$150.93^{b} \pm 0.40$	$122.87^{b} \pm 0.75$	$51.57^{b} \pm 0.41$	$36.40^{f} \pm 0.47$
G8: Diabetic +1.5g WJP/kg/day	$139.75^{d} \pm 0.50$	$117.65^{d} \pm 0.74$	$45.67^{d} \pm 0.61$	$32.92^{h} \pm 0.47$
G9: Diabetic + 300mg WPE/kg/day	$130.82^{f} \pm 0.37$	$105.42^{f} \pm 0.59$	$36.42^{f} \pm 0.25$	$40.72^{d} \pm 0.47$
LSD($P \geq 0.05$)	0.63	0.78	0.60	0.41

MJP (Manfaloty juice powder), MPE(Manfaloty peel extract), WJP (Wonderful juice powder), WPE (Wonderful peel extract).

* lyophilized pomegranate juice.

Table (7) Effect of pomegranate juice powder* and peel powders extracts on the serum total cholesterol, LDL, HDL and triglyceride of hypercholesterolemic rats.

Groups	Total cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	Triglyceride (mg/dl)
G1	$90.14^{g} \pm 0.28$	$28.93^{g} \pm 0.05$	$51.30^{a} \pm 0.40$	$45.78^{g} \pm 0.14$
G2	$150.73^{a} \pm 0.42$	$102.63^{a} \pm 0.18$	$32.34^{e} \pm 0.74$	$92.66^{a} \pm 0.43$
G3	$120.96^{c} \pm 0.77$	$65.79^{c} \pm 0.61$	$39.80^{c} \pm 0.71$	$57.34^{c} \pm 0.65$
G4	$115.21^{e} \pm 0.84$	$60.23^{e} \pm 0.90$	$42.24^{b} \pm 0.32$	$54.50^{e} \pm 0.94$
G5	$95.93^{g} \pm 0.34$	$40.33^{g} \pm 0.24$	$48.79^{a} \pm 0.13$	$48.53^{g} \pm 0.22$
G6	$131.17^{b} \pm 0.84$	$72.97^{b} \pm 0.88$	$37.69^{g} \pm 0.20$	$64.88^{b} \pm 0.19$
G7	$118.32^{e} \pm 0.70$	$67.59^{c} \pm 0.76$	$40.64^{d} \pm 0.15$	$59.67^{c} \pm 0.53$
G8	$101.94^{f} \pm 1.11$	$50.39^{f} \pm 0.38$	$45.62^{c} \pm 0.27$	$52.00^{f} \pm 0.63$
LSD($P \geq 0.05$)	1.00	0.74	0.75	0.97

G1: Control (basal diet), G2: HFD+1%cholesterol, G3: HFD+1%cholesterol++1g MJP/kg b.w /day, G4: HFD+1%cholesterol++1.5g MJP/kg b.w /day, G5: HFD+1%cholesterol+300mgMPE/kg b.w /day, G6:HFD+1%cholesterol+1gWJP/kg b.w /day, G7: HFD+1%cholesterol+1.5gWJP/kg b.w /day and G8: HFD+1%cholesterol+300mg WPE/kg b.w /day.

* lyophilized pomegranate juice

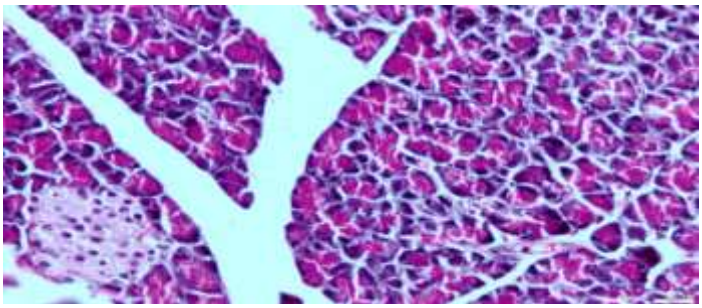


Fig (1) Pancreas of rat from G1"control basal diet, healthy rats" showing no histopathological changes (H & E X 400).

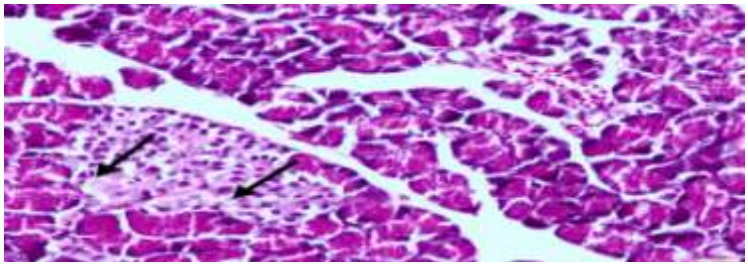


Fig (2): Pancreas of rat from G2 "Diabetic rats, injected with alloxan" showing vacuolation of cells of islets of Langerhans (H & E X 400).

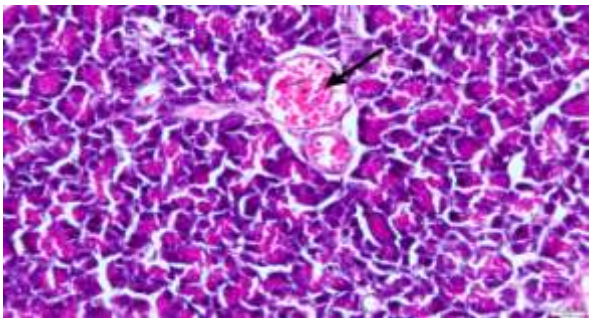
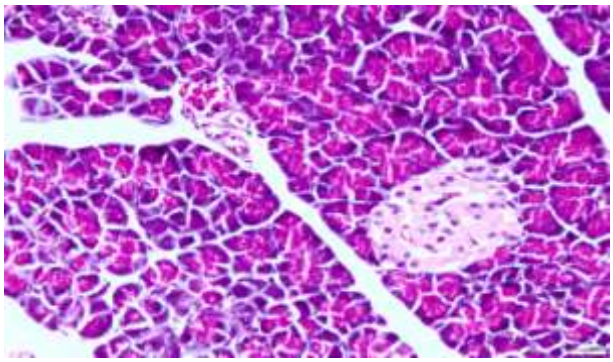


Fig (3) Pancreas of rats from G3 "Diabetic rats treated with 20 units insulin /kg b.w/day showing regeneration of beta cells and acinar looked normal with increased number of beta cells. (H & E X 400).



Fig(4) Pancreas of rats from G5 "Diabetic rats administration with 1.5g MJP/kg b.w/day" showing the islets of Langerhans with well-organized beta cells. (H & E X 400).

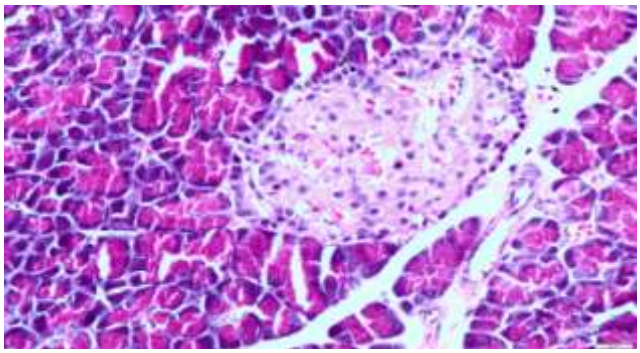


Fig (5) Pancreas of rats from G6 "Diabetic rats administration with 300mgMPE/kg b.w/day showing revealed improvement in pancreatic damage and there was marked improvement in islets structure. (H & E X 400)**.**

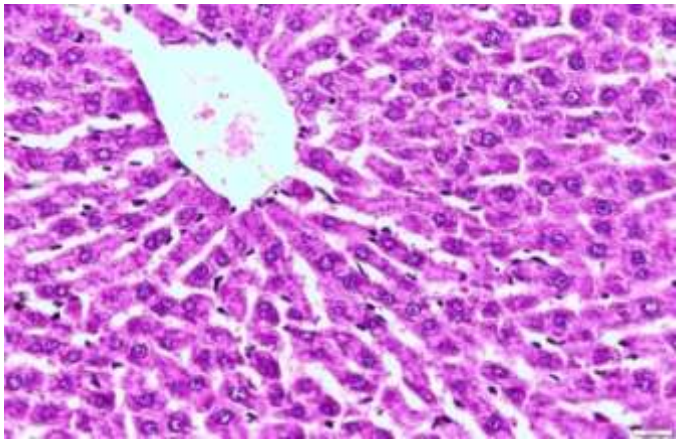


Fig (6) Liver of rats from G1 "control basal diet, healthy rats" showing the normal histological structure of hepatic lobule (H & E X 400).

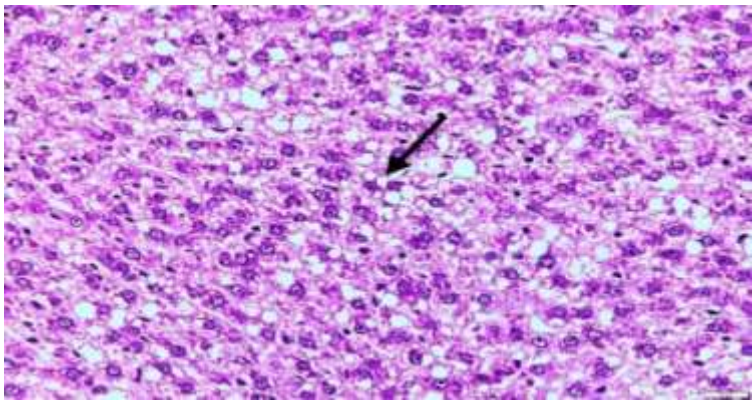


Fig (7) Liver of rats from G2" high fat diet+1%cholesterol" showing foci of lipid droplets deposition within hepatocytes and the neighboring cells showed vacuolar degeneration(H & E X 400).

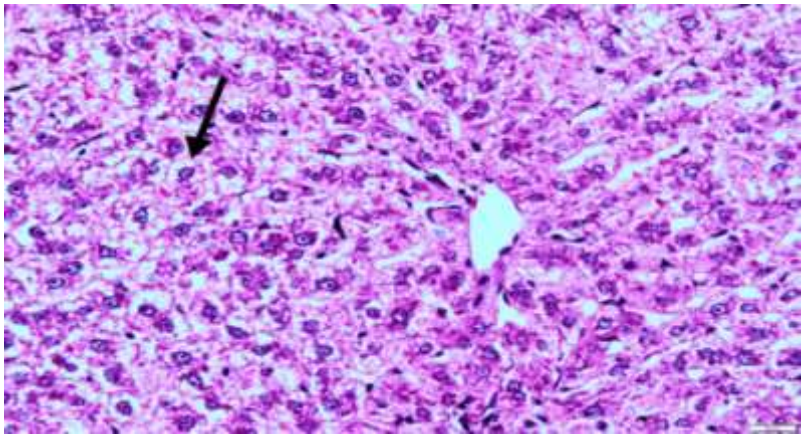


Fig (8) Liver of rats from G4" high fat diet+1%cholesterol+1.5g MJP/kg b.w/day moderate improvement from degenerative changes except presence of few residual cells with lipid droplets (thin black arrows) or scattered dark apoptotic cells(dotted arrows) and some showed bile duct proliferation(H & E X 400).

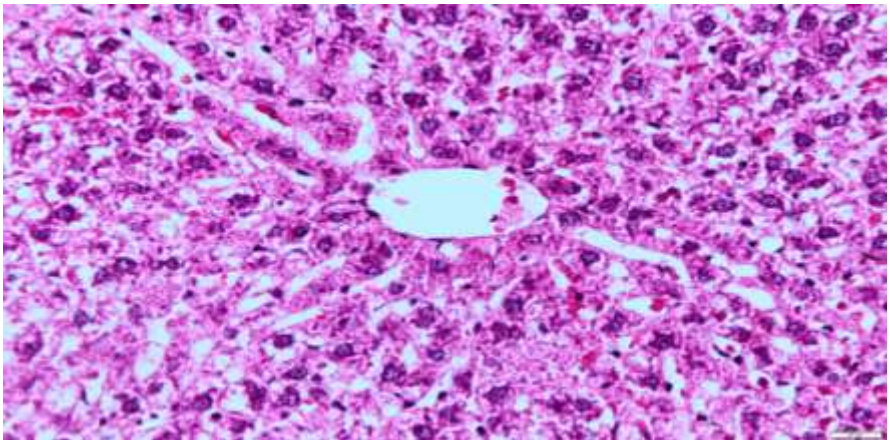


Fig (9) Liver of rats from G5" high fat diet+1%cholesterol+300mgMPE/kg b.w/day" almost normal structure with a regular arrangement of hepatic cell cords around the central vein, hepatocytes showed rounded and vesicular nuclei indicating active cells. Hepatic sinusoids between the cells showed normal appearance (H & E X 400).