Received: 16 December 2018 | Revised: 17 January 2019 | Accepted: 27 January 2019

DOI: 10.1111/jfbc.12803

FULL ARTICLE

WILEY Journal of Food Biochemistry

Phenolic profiles, antihyperglycemic, antihyperlipidemic, and antioxidant properties of pomegranate (*Punica granatum*) peel extract

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Abstract

This work is aimed to evaluate phenolics composition, and in vitro antioxidant activities of hydro-methanol pomegranate (*Punica granatum* L.) peel extract (MPE). In addition, the antihyperglycemic, hypolipidemic, and hepatoprotective effect of MPE in Wister albino rats was compared with standard drugs (glibenclamide and atorvastatin). Total phenolic content and total flavonoid contents in MPE (mg g^{-1}) accounted for 188.9 as GAE and 13.95 as QE, respectively. Phenolic and flavonoids compounds in MPE analyzed by HPLC and revealed the presence of 23 phenolic compounds and 20 flavonoid compounds. For in vivo experiment, 56 rats were distributed into 8 groups. Group 1 was the normal control, while group 2 contained rats orally administrated with 200 mg kg^{-1} MPE daily. Group 3 contained diabetic rats (induced with a single dose of 100 mg/kg b.w. alloxan). Group 4 contained diabetic rats administered daily with 200 mg/kg MPE. Group 5 contained diabetic rats administered orally with a glibenclamide (standard drug for diabetic) at 10 mg/kg daily. Group 6 fed with high fat diet (HFD). Group 7 contained HFD-rats administered orally with 200 mg/kg MPE daily. Group 8 contained HFD-rats administered orally with atorvastatin (used to lower LDL-cholesterol (LDL-C) and fats and to raise HDL-cholesterol (HDL-C) in the blood) at 10 mg/kg daily. The study lasted for 56 days. Administration with MPE 200 mg/kg to both diabetic and hyperlipidemic rats significantly decreased blood glucose, HbA_{1c}, total lipid, total cholesterol, LDL-C, and very low density lipoprotein cholesterol levels, while increased high density lipoprotein cholesterol levels, as well as improved liver and kidney functions, compared with glibenclamide and atorvastatin effects.

Practical applications

Pomegranate peel, constituted about 50% of fruit fresh weight, is rich in bioactive compounds with potent health-promoting activities. The results of the current study stated that MPE is rich in phenolics and flavonoids with powerful antioxidant potential. In addition, MPE showed antihyperglycemic and antihyperlipidemic activities due to the strong antiradical action *via* its antioxidant compounds. MPE enhanced liver and kidney functions when compared to standard drugs in diabetic and hyperlipidemic rats. MPC could be used as a natural material to develop diabetic and hyperlipidemic drugs.

KEYWORDS
agro waste, atorvastatin, by-products, diabetes mellitus, glibenclamide, hydro-methanol extract

1 | INTRODUCTION

Diabetes mellitus (DM), is an abnormally elevated blood sugar level resulting disorder in insulin production and lead to complications in many body systems, significantly participate to cardiovascular morbidity and mortality (Ahmed, Belal, & Salem, 2014; Jyothsna, 2017). Complications of diabetes include blindness, strokes, kidney, and heart failure. Oral antidiabetic or antihyperglycemic drugs are used in treating diabetes. One such drugs is glibenclamide, known as glyburide, and chemically identified as sulfonylureas compound. Chemically it is 5-chloro-N-[2-[4-(cyclohexyl carbamoyl sulfamoyl) phenyl] ethyl]-2-methoxy benzamide. It is used in certain forms against type-2 DM. Drugs are more costly and cause several side effects such as disorder in liver and kidney functions and disturbance in hematological properties. Khalil (2004), Salwe, Sachdev, Bahurupi, and Kumarappan (2015), and Pandarekandy, Sreejesh, Harikumaran Thampi, and Sreekumaran (2017) revealed that those drugs could be replaced by natural bioproducts, which are more safe and cheaper.

Hyperlipidemia or dyslipidemia could be characterized by the elevation of serum lipid parameters including total lipid (TL), triglyceride (TG), total cholesterol (TC), and their blood carting lipoprotein; low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C), as well as the reduction of high density lipoprotein (HDL-C) resulting in the disturbance of lipid metabolism attributable to genetic defect or HFD, and changes in eating habits (Reddy, Venkataiah, Rejeena, & Reddy, 2014).

The elevation of lipid profile parameters is an important risk factor for atherosclerosis and development of coronary artery disease as well as angina pectoris, myocardial infarction, atherosclerosis hypertension, and heart failure leading to death (Movahedian, Zolfaghari, Sajjadi, & Moknatjou, 2010). The continuous administration of lipid-lowering drugs, i.e. atorvastatin and synthetic drugs for diabetes lead to harmful side effects including hepatotoxicity, blood, and lymphatic system disorders and metabolism disorder (Jose, 2016; Nathan et al., 2009).

The fruit pomegranate (*Punica granatum*) belong to family Punicaceae. Its native origin is the Middle East and Mediterranean region, and used in many countries as traditional medicine. Pomegranate peels are presumed by-products that became an environmental problem resulted from fruit juice processing (Marchi et al., 2015). Pomegranate peel and white pulp membranes, presented 50%–60% of the total fruit weight as reported by Lansky and Newman (2007). Kanatt, Chander, and Sharma (2010), Gullon, Pintado, Perez-Alvarez, and Viuda-Martos (2016). Pagliarulo, Vito, Picariello, Colicchio, and Pastore (2016) reported that pomegranate peel is well bio-source material rich in bioactive compounds such as phenolics, flavonoids, ellagitannins, proanthocyanidins wherein all of which are potent antioxidants with antibacterial and antifungal activities. Treating potato dry rot disease using pomegranate peel extract (MPE) proved of high efficiency as a fungicide (Elsherbiny, Amin, & Baka, 2016). MPEs had high contents of natural antioxidants than in the fruit's pulp extract or its juice (Li et al., 2006; Yan et al., 2017).

The current study aimed at assessing the phytochemical composition and potential antioxidant activity of hydro-methanol extract of pomegranate peel (MPE), and its in vivo efficiency as an alternative to synthetic hypoglycemia and hypolipidemic drugs in the experimental animals.

2 | MATERIALS AND METHODS

2.1 | Materials

Fruits of pomegranate (*Punica granatum*), Egyptian wonderful variety, were obtained from the local market (Benha city, Egypt) and peeled manually. Folin-Ciocalteu's phenol reagent, standards of a phenolic compound, DPPH (2,2-diphenylpicrylhydrazyl), $ABTS^{\bullet+}$ (2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid), and alloxan hydrate ($C_4H_4N_2O_5$) were purchased from (SIGMA-ALDRICH Co., Louis, Missouri, USA). Solvents and diagnostic kits were of analytical grade. Atorvastatin and glibenclamide were obtained from Egyptian International, Pharmaceutical industries Company (Cairo, Egypt).

2.2 | Preparation of pomegranate peel hydro-methanol extracts (MPE)

Five hundred grams of pomegranate peel were dried under shade for 7 days then pulverized and soaked in 2.5 L of methanol: water (4:1, v/v) for 3 days at room temperature. Extracts were filtered and evaporated under vacuum at 40°C in the dark until turned to semi-dry using rotary evaporator (IKA-WERKE, Germany).

2.3 | Determination of total phenolic compounds

Phenolics were determined according to Singleton and Rossi (1965). One-milliliter extract was added to 5 ml distilled water then 1 ml of Folin-Ciocalteu reagent and 1 ml of sodium carbonate (20%) were added. After standing for 30 min in dark under ambient room temperature, the absorbance was measured using spectrophotometer at 765 nm UV/Vis spectrophotometer (SM1600 UV–vis Spectrophotometers, Azzota, USA). Phenolics in the extracts was expressed as gallic acid equivalent.

2.4 | Determination of total flavonoid compounds

Flavonoids were determined by the aluminum chloride colorimetric method and expressed as quercetin equivalents (Meda, Lamien, Romito, Millogo, & Nacoulma, 2005). One milliliter of diluted extract was mixed with 1 ml of 2% (w/v) methanolic $AlCl_3$, 100 µl 1 M CH_3COOK, and 2.8 ml distilled water and then kept for 30 min at room temperature. Absorbance was measured at 765 nm using UV–vis spectrophotometer (SM1600 UV–vis Spectrophotometers, Azzota, USA).

2.5 | HPLC analyses of phenolic and flavonoid compounds

MPE was dissolved in methanol (1.0 mg/ml) then filtered and injected into YL 9,100 HPLC system (Young YL instruments Co., Ltd, Korea) consisting of YL9150 autosampler, YL9110 quaternary pump, YL9101 vacuum degasser, and YL9160 PDA detector. Separation was on stationary phase YL9131 column compartment C18 column (0.46 × 25 cm) with 20 µl injection volume. The solvent system used was an acetonitrile: water having 1% acetic acid with linear gradient program, starting with 18% acetonitrile then changed to 32% in 15 min, and finally to 50% in 40 min (Prakash, Singh, & Upadhyay, 2007). Retention times and peak areas (λmax = 254 nm) for sample and standard were compared.

2.6 | Determination of antioxidant activity

2.6.1 | DPPH· radical scavenging activity

2,2-diphenylpicrylhydrazyl (DPPH·) antiradical test was performed according to the Blois (1958) with minor modification. DPPH· stock solution was prepared (0.004% w/v) in methanol. One mg ml^{-1} sample was dissolved in methanol and 0.1 ml diluted sample mixed with 3.9 ml stock solution with vigorous shaking. The solution was kept in dark for 30 min then the absorbance was measured at 517 nm using UV–Vis spectrophotometer (SM1600 UV–vis Spectrophotometers, Azzota, USA) against the absorbance of the DPPH. Ascorbic acid was used as a standard reference, and % of DPPH· de-coloration was calculated as follows:

$$\%\ \text{of DPPH}\cdot\ \text{de- coloration} = 100 \times \left(A_2 - A_1/A_2\right)$$

where A_1 is the control absorbance and A_2 is the sample absorbance.

2.6.2 | $ABTS^{\bullet+}$ radical scavenging activity

The determination was carried out using cation decolorization assay as described by Re et al. (1999). Stock solutions mixture of 7×10^{-3} M $ABTS^{\bullet+}$ and 2.4×10^{-3} M $K_2S_2O_8$ (1:1, v/v) standing in dark for 12–16 hr then diluted with methanol to give 0.706 absorbances at 734 nm. After 15 min, absorbances of extracts with differed concentrations of 0.1 ml of each mixture with 0.9 ml $ABTS^{\bullet+}$ solution was recorded. Inhibition % being calculated as:

$$\%\ \text{inhibition} = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100$$

where $Abs_{control}$ and Abs_{sample} are the absorbance values of $ABTS^{\bullet+}$ control and sample, respectively.

2.7 | Experimental animals

Healthy adult Wister albino male rats, nearly same age, 160–170 g weight per animal, were obtained from animal farm (Faculty of Veterinary, Benha University, Egypt). Animals were handled according to WHO guidelines and kept under 25°C, 50% relative humidity, and 12 hr light-dark cycle. Free access to water and a standard diet was allowed (Reeves, Nielsen, & Fahey, 1993). Approval from the Research Ethics Committee at Benha University was obtained before the experiment (BU/FA/BIO-4/2017).

Diabetes induction. Intraperitoneal injection was done using alloxan (a single 100 mg/kg body weight dose) for one day. Diabetes occurrence was assured by analysis of blood glucose, which surpassed 200 mg dl^{-1}.

High-fat diet. The basal diet was supplemented with lard (20%), cholesterol (1%), and bile's acid (0.25%).

2.7.1 | Design of the experiment

The experiment was a completely randomized design. Following a two-week acclimatization period, a number of 56 rats were distributed into eight groups (eight treatment) of seven rats each (seven replicates) as performed by El-Hadary and Ramadan (2016).

The eight treatments were as follow:

Group 1 (normal healthy): animals fed with basal diet for the 56-day period.

Group 2: animals fed with basal diet and 200 mg/kg MPE daily through gastric gavages for 56-day period.

Group 3 (diabetic control): animals administrated (after diabetic induction) with 1 ml of distilled water during the 56-day period.

Group 4 (diabetic-MPE group): diabetic animals administered daily with 200 mg/kg MPE through gastric gavages for the 56-day period.

Group 5 (diabetic-glibenclamide group): diabetic animals administered a daily standard aqueous drug for diabetes (glibenclamide) at 10 mg/kg for 56-day period.

Group 6 (HFD group): rats fed with a HFD for 56-day period.

Group 7 (HFD-MPE group): HFD rats were given 200 mg/kg MPE orally through gastric gavages for the 56-day period.

Group 8 (HFD-atorvastatin group): HFD-rats treated daily with the standard drug for antihyperlipidemic (atorvastatin) at 10 mg/kg in aqueous solution through gastric gavages for the 56-day period.

The initial body weight of all animals in each group was determined after the acclimatization period and after 56 days for final body weight.

2.7.2 | Blood collection

Samples of blood were taken using heparinized capillary tubes. Each sample was divided into three tubes. First tube contained the fasting blood collected in a mixture of Na-fluoride + K-oxalate (1/1) at 1 ml blood in 4×10^{-3} g mixture, then centrifuged for 10 min at 2,000 rpm to obtain plasma in which glucose was measured. The second tube contained EDTA for the measurement of glycated hemoglobin (HgA1c). The third tube included the blood left for clotting after centrifuged at 3,000 rpm for 15 min to measure the lipid profile.

2.7.3 | Biochemical assays

Glucose was determined according to Trinder (1969) and HbA1c according to Nayak and Pattabiraman (1981). Lipid profile [TL (total lipids), TG (triglycerides), TC (total cholesterol), and HDL-C (high-density lipoprotein cholesterol)] was determined according to Fossati and Precipe (1982); Finel (1978); Naito and Kaplan (1984), respectively. LDL-C (low-density lipoprotein cholesterol) levels were calculated according to Friedewald Levy, and Fredrickson's (1972) wherein LDL-C = TC-(HDL + TG/5). VLDL-C (very low-density lipoprotein cholesterol) was calculated as TG/5. Liver enzymes (ALT, AST, and ALP) activities were determined according to Reitman and Frankel (1957) and Tietz (1983). Kidney function parameters including urea, uric acid, and creatinine were determined according to Tabacco, Meiattini, Moda, and Tarlip, (1979).

2.8 | Statistical analysis

All results were presented as mean ± *SD* of the mean and statistical analyses were carried out with ANOVA using SPSS 13.0 software (SAS, 1996).

3 | RESULTS AND DISCUSSION

3.1 | Extraction yield, total phenolic compounds, total flavonoid compounds, and antioxidant activity of MPE

The extraction yield of MPE was 35.4 g/100 g on a dry weight basis (Table 1). This value is very much around values reported by Li et al. (2006); Shiban Al-Otaibi and Al-Zoreky (2102) and Pagliarulo et al. (2016) who reported that methanol extract yield of pomegranate peel were 31.5%, 45.4%, and 49.9%, respectively. Total phenolic compounds (TPC) was 188.9 mg GAE/g extract residue. These results slightly differed from that obtained by Agourram et al. (2013) and Elsherbiny et al. (2016) who showed that TPC of methanol extract of pomegranate peel, as measured by Folin-Ciocalteu methods were 197.1 and 104.6 mg GAE/g extract, respectively. This may be due to several factors such as the differences in fruit cultivar, extraction procedure, experimental and environmental conditions. Total flavonoid compounds in MPE measured by $AlCl_3$ spectrophotometric methods was 13.95 mg QE/g extract, a value close to that 12.27 mg/g extract reported by Gullon et al. (2016). Phenolic and flavonoid compounds are natural antioxidants originates from several vegetables, fruits, and cereals. Therefore, they had effective scavenging activity against species of oxygen or nitrogen.

TABLE 1 Extracts yield, TPC, TFC, and antioxidant activity of MPE

Parameter	MPE
Yield (%)	35.40 ± 1.44
TPC (mg GAE/g extract)	188.9 ± 0.11
TFC (mg QE/g extract)	13.95 ± 0.95
% Antioxidant activity (DPPH·)	93.97 ± 1.91
% Antioxidant activity ($ABTS^{\bullet+}$)	90.92 ± 1.17

Results of MPE antioxidant activities, shown in Table 1, indicated strong antioxidant capacity with values of 93.9% and 90.9% for DPPH·and $ABTS^{\bullet+}$ methods, respectively. Pagliarulo et al. (2016) reported a value of 94.0% in pomegranate peels and 75.8% in juice. Strong antioxidant capacity of MPE is most probably due to high contents of phenolics (e.g. gallic acid, punicalagin, and ellagic acid) and flavonoids compounds. These natural compounds can donate hydrogen atom, thus quenching the free radicals (Yan et al., 2017). Antioxidants protect the body through neutralization-free radicals, thus lowering risks of infection, acting against degenerative diseases, preventing and managing diabetes, cancer, heart diseases, hypertension, and stroke. Plants rich in phenolics are excellent sources for treating many disorders (Lako et al., 2007).

3.2 | Identification of phenolic and flavonoid compounds in MPE

Table 2 shows that there were 23 phenolic compounds in MPE. The main identified compounds and their contents (mg g^{-1}) were punicalagin (98.0), followed by pyrogallol (45.3), ellagic acid (12.5), *p*-hydroxybenzoic (7.01), catechol (5.96), catechin (3.27), and gallic acid (2.50). These results are in close agreement with those reported by Gullon et al. (2016) and Elsherbiny et al. (2016). Arun, Jayamurthy, Anusha, Mahesh, and Nisha (2017) reported 13 phenolic compounds in ethyl acetate extract of pomegranate peel among which 2.75 mg/g gallic acid and 0.707 mg/g *p*-coumaric acid.

Data presented in Table 3 show the presence of 20 flavonoid compounds in MPE. The main compounds and their contents (mg g^{-1}) were hesperidine (5.04), quercetin (3.51), kaemp-3-(2-*p*-comaroyl) glucose (1.02), naringin (0.94), apig-6-rhamnose 8-galactose (0.71), luteo-7-glucose (0.62), and hespertin (0.52). Zhao, Yuan, Fang, Yin, and Feng (2014) reported the presence of flavonols and flavones in MPE including apigenin, luteolin, kaempferol, myricetin, and quercetin.

TABLE 2 Phenolic compounds in MPE analyzed by HPLC

No	Compound	Retention time (min)	Content (mg g^{-1})
1	Gallic acid	7.43	2.500
2	Pyrogallol	7.74	45.358
3	4-Amino-benzoic acid	8.95	0.084
4	Protocatchuic	9.07	1.987
5	Catechein	9.20	3.275
6	Chlorogenic acid	9.40	1.562
7	Catechol	9.74	5.965
8	Caffeine	10.01	1.339
9	P-hydroxybenzoic	10.18	7.017
10	Caffeic acid	10.49	0.458
11	Vanillic acid	10.57	0.805
12	*p*-coumaric acid	11.74	0.086
13	Ferulic acid	11.99	0.492
14	Iso-ferulic acid	12.43	0.117
15	Rosmarinic acid	12.75	1.173
16	Punicalagin	12.92	98.020
17	Ellagic acid	13.00	12.561
18	Benzoic acid	13.30	0.666
19	α-coumaric acid	13.45	0.268
20	3,4,5-methoxy-cinnamic acid	13.73	0.164
21	Coumarin acid	13.96	0.912
22	Salycilic acid	14.21	0.108
23	Cinnamic acid	14.81	2.500

TABLE 3 Flavonoids in MPE analyzed by HPLC

No	Compound	Retention time (min)	Content (mg g^{-1})
1	Apigenin-6-arbinose 8-glactoside	11.46	0.353
2	Apigenin-6-rhamnose 8-glactoside	12.14	0.719
3	Naringin	12.39	0.944
4	Luteo-7-glucoside	12.46	0.622
5	Rutin	12.49	0.265
6	Hesperidine	12.52	5.047
7	Quercetrin-3-O-glucoside	12.58	0.189
8	Kamp.3,7-di rhamoside	12.75	0.323
9	Apigenin.7-O-neohespiroside	12.96	0.329
10	Quercetrin	13.27	3.519
11	Apigenin-7-glucoside	13.48	0.780
12	Kaemp-3-(2-*p*-comaroyl) glucoside	14.25	1.024
13	Quercetin	14.30	0.215
14	Acacetin7 neo hesperside	14.41	0.342
15	Naringenin	14.57	0.089
16	Hesperetin	14.86	0.523
17	Acacetin 7-O-rutinoside	14.91	0.121
18	Rhamentin	15.51	0.351
19	Apegnin	15.58	0.107
20	Kampferol	15.78	0.106

3.3 | Effect of treatment with MPE on the body weight, glycated hemoglobin (HbA_{1c}), and blood glucose

At zero time, there were no significant differences between all treatments for all groups regarding the initial body weight. Results in Table 4 show a significant decrease in the final body weight in diabetic rats compared with healthy control group. Treatment with MPE (200 mg/kg) ameliorated the final body weight in diabetic and normal rats after 56 days. This may be due to phenolic and flavonoid compounds in the administered extract. However, administration of glibenclamide (10 mg kg^{-1}) increases the final body weight in diabetic rats compared with the normal control as well as in a diabetic group. These results are in agreement with Khalil (2004), who reported that pomegranate peel hydro-extract improved the body weight of diabetic rats after 4 weeks attributed to antidiabetic activity.

Alloxan selectively destroys the pancreatic insulin secreting β-cells, leaving less active cells and resulting in a diabetic state. Alloxan-induced diabetes is characterized by a severe loss in body weight, and this reduction is due to the loss or degradation of structural proteins, as the structural proteins, which are known to contribute to body weight. This effect is evident by the high level of glucose in animals (Khalil, 2004).

Table 4 contains results and also shows a very high significant ($p \leq 0.001$) elevation in the final body weight of hyperlipidemic rats (group 6) compared with the normal control. Increased weight of hyperlipidemic rats may be due to increased caloric intake. The treatment with 10 mg/kg atorvastatin (group 8) or 200 mg/kg MPE (group 7) in hyperlipidemic rats caused an increase in the body weight when compared with normal control. However, these values were decreased when compared with hyperlipidemic rats (group 6). Such results may be due to the inhibition of pancreatic lipase activity or the reduction of intestinal fat absorption; however, improvement in the obesity had occurred as revealed by Hasona, Ahmed, Alghassab, Alghassab, and Alghabban (2016).

Fasting blood sugar and HbA_{1c} results are presented in Table 4. A significant ($p \leq 0.001$) augmentation in fasting blood glucose and HbA_{1c} levels in the diabetic group (296.6 mg dl^{-1} and 11.7%, respectively), as compared with the normal control (84.6 mg dl^{-1} and 5.26%, respectively) was recorded. Administration with MPE (200 mg/kg) or glibenclamide (10 mg kg^{-1}) in diabetic rats for 56 days reduced blood glucose levels (121.6 and 101.6 mg dl^{-1}, respectively), and decreased HbA_{1c} (6.56% and 5.98%, respectively). The aforementioned data are in harmony with those reported by Khalil (2004), Ahmed et al. (2014), and Salwe et al. (2015) who noted pomegranate leaves and fruit peels protect pancreas from damage and increase beta cells resulting in overflow of insulin, increasing the regeneration of beta cells and insulin receptor.

TABLE 4 Effect of treatment with MPE on the body weight, HbA_{1c}, and blood glucose in normal, diabetic, and hyperlipidemic rats

G	Treatment	Initial body weight (g)	Final body weight (g)	HbA_{1c} (%)	Glucose (mg dl^{-1})
1	Control (normal)	162.4 ± 2.51^{a}	195.1 ± 4.88^{de}	5.26 ± 0.23^{e}	84.67 ± 6.28^{de}
2	MPE (200 mg/kg)	167.0 ± 2.51^{a}	198.8 ± 4.88^{de}	5.04 ± 0.23^{e}	76.62 ± 6.28^{e}
3	Diabetic	164.6 ± 2.51^{a}	143.7 ± 4.88^{f}	11.7 ± 0.23^{a}	296.6 ± 6.28^{a}
4	Diabetic + MPE (200 mg/kg)	165.3 ± 2.51^{a}	185.7 ± 4.88^{e}	6.56 ± 0.23^{cd}	121.6 ± 6.28^{c}
5	Diabetic + glibenclamide (10 mg/kg)	165.1 ± 2.51^{a}	225.6 ± 4.88^{b}	5.98 ± 0.23^{d}	101.6 ± 6.28^{cd}
6	Hyperlipidemia	164.3 ± 2.51^{a}	276.9 ± 4.88^{a}	7.02 ± 0.23^{bc}	138.3 ± 6.28^{b}
7	Hyperlipidemia + MPE (200 mg/kg)	163.9 ± 2.51^{a}	223.1 ± 4.88^{bc}	6.47 ± 0.23^{cd}	105.0 ± 6.28^{c}
8	Hyperlipidemia + Atorvastatin (10 mg/kg)	164.5 ± 2.51^{a}	208.8 ± 4.88^{cd}	6.27 ± 0.23^{d}	115.0 ± 6.28^{c}

Note. Values with same letter(s) have no significant difference ($p \leq 0.001$).

Fasting blood glucose level and HbA_{1c} in hyperlipidemic rats group 6 exhibit a significant ($p \leq 0.001$) increment of 138.3 mg dl^{-1} and 7.02% compared with the normal control 84.6 mg dl^{-1} and 5.26. Administration of 10 mg/kg atorvastatin (group 8) or 200 mg/kg MPE (group 7) in hyperlipidemic rats ameliorate the blood glucose levels. MPE caused antidiabetic mechanism by powerful reactive oxygen scavenger through its antioxidant compounds such as punicalagin, ellagic acid, gallic acid, and other phenolic compounds. These compounds may lower glucose levels, fight cell damage and reduce insulin resistance deficiency, lipid peroxidation, and oxidative stress, as stated by Banihani, Swedan, and Alguraan (2013) who showed that pomegranate peel possesses anti-diabetic activity.

3.4 | Impact of treatment with MPE on lipid profile

The profile of serum lipids in normal, diabetic, and hyperlipidemic rats is shown in Table 5. Serum TL, TC, TG, LDL-C, and VLDL-C levels were significantly ($p \leq 0.001$) increased in rats-fed HFD (group 6) and in diabetic rats (group 3). On the contrary, significant ($p \leq 0.001$) decrements in HDL-C occurred when compared with control normal. These results agree with Salwe et al. (2015), who noticed significant increase in TC, TG, and significant decrement in HDL-C levels in streptozotocin-induced diabetic rats.

Administration of 200 mg/kg MPE or 10 mg/kg glibenclamide for 56 days improved the profile of serum lipids (TL, TC, TG, LDL-C, and VLDL-C) since their levels decreased when compared with diabetic rats (group 3). A significant ($p \leq 0.001$) increase in HDL-C levels was noted when compared with diabetic rats (group 3). These results agree with Movahedian et al. (2010), who reported that diabetic rats treated with ethanol MPE or glibenclamide for one month showed a decrease in TC, TG, and LDL-C levels, but an increase in HDL-C compared to control rats.

Administration of MPE (200 mg/kg) or atorvastatin (10 mg/kg) in rats fed HFD ameliorates serum lipid parameters (TL, TC, TG, LDL-C, and VLDL-C), where their levels were significantly ($p \leq 0.001$) decreased when compared with hyperlipidemic rats (group 6). On the contrary, a significant ($p \leq 0.001$) increase in HDL-C level was recorded when compared with hyperlipidemic rats (group 6).

The performance of MPE or atorvastatin in exhibiting antihyperlipidemic activity could be due to the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase, which regulates the synthesis of

TABLE 5 Impact of treatment with MPE on lipid profile

G	Treatment	TL	TC	TG	HDL-C	LDL-C	VLDL-C
1	Control (normal)	468.0 ± 8.95^{e}	148.0 ± 3.94^{ef}	162.9 ± 3.00^{cd}	54.93 ± 1.03^{b}	60.48 ± 3.69^{f}	32.59 ± 0.62^{cd}
2	MPE (200 mg/kg)	475.4 ± 8.95^{e}	143.7 ± 3.94^{f}	155.6 ± 3.00^{d}	61.99 ± 1.03^{a}	50.58 ± 3.69^{g}	31.13 ± 0.62^{d}
3	Diabetic	648.9 ± 8.95^{b}	190.3 ± 3.94^{b}	188.2 ± 3.00^{b}	40.36 ± 1.03^{e}	112.35 ± 3.69^{b}	37.64 ± 0.62^{b}
4	Diabetic + MPE (200 mg/kg)	495.7 ± 8.95^{c}	165.6 ± 3.94^{cd}	169.6 ± 3.00^{c}	48.93 ± 1.03^{c}	82.76 ± 3.69^{d}	33.94 ± 0.62^{c}
5	Diabetic + glibenclamide (10 mg/kg)	490.2 ± 8.95^{c}	159.0 ± 3.94^{de}	168.8 ± 3.00^{b}	49.72 ± 1.03^{d}	75.57 ± 3.69^{d}	33.77 ± 0.62^{b}
6	Hyperlipidemia	696.8 ± 8.95^{a}	271.8 ± 3.94^{a}	285.5 ± 3.00^{a}	29.30 ± 1.03^{f}	185.3 ± 3.69^{a}	57.26 ± 0.62^{a}
7	Hyperlipidemia + MPE (200 mg/kg)	528.1 ± 8.95^{d}	172.3 ± 3.94^{c}	192.4 ± 3.00^{b}	40.03 ± 1.03^{d}	93.84 ± 3.69^{c}	38.49 ± 0.62^{b}
8	Hyperlipidemia + Atorvastatin (10 mg/kg)	452.4 ± 8.95^{e}	154.5 ± 3.94^{ef}	170.3 ± 3.00^{c}	49.70 ± 1.03^{c}	70.86 ± 3.69^{e}	34.02 ± 0.62^{c}

Note. Values with same letter(s) have no significant difference ($p \leq 0.001$).

cholesterol, and may inhibit the intestinal absorption of cholesterol, obstructive with lipoprotein production, leading to decreased of LDL-C and TC. The methanol extract of *Punica granatum* flower, rich in antioxidants, decreased LDL-C, prevented the oxidation of LDL-C, reduced TG levels due to the inhibition of lipolysis, and increased HDL-C. This was associated with decreased intestinal absorption of TG by the inhibition of pancreatic lipase (Sarker et al., 2012).

Hyperlipidemic may be attributed to free radicals and oxidative stress. The anti-hyperlipidemic activity of MPE may be related to the presence of phenolics and flavonoids compounds which scavenged free radicals by hydrogen-donating capacity of phenolic group that play apart in neutralizing free radicals and protect the body against oxidative stress (Mahmud, Bachar, & Qais, 2011).

3.5 | Changes in liver enzymes in rats treated with MPE, glibenclamide, and atorvastatin

Data presented in Table 6 show a significant ($p \leq 0.001$) increment in liver enzymes (AST, ALT, ALP, and TB) levels in the hyperlipidemic group treated with atorvatatin (10 mg/kg) compared with normal control and hyperlipidemic rats control (group 6), as well as a significant increment in liver enzymes levels in rats treated with glibenclamide (group 5) compared to normal control. Atorvastatin hepatotoxicity can cause a hepatocellular pattern of injury with marked elevations in serum aminotransferase levels (De Marzio & Navarro, 2013).

Diabetes could cause chronic liver diseases including hepatocellular carcinoma. The glibenclamide hypoglycemia drug decreases blood glucose and insulin resistance but increases insulin penetration into the cells and insulin secretion. At the same time, it is hepatotoxicity, abnormally elevates liver enzymes, increases the oxidative stress, all of which are reflected manifested in elevated malondialdehyde activity of hepatic and pancreatic tissues, cirrhosis, and chronic liver dysfunction (Lee et al., 2014). The acquired results in a Table 6 indicated a significant increments in liver enzymes (AST, ALT, ALP, and TB) levels in control diabetic rats (group 3) and control hyperlipidemic rats (group 6) compared to normal control. The increment in the liver enzymes activities may be attributed to the leakage from liver cells into the bloodstream, which in turn causes hepatotoxic effects of alloxan as stated by Lee et al. (2014).

The obtained results of the impact of MPE on liver enzymes in diabetic rats (group 4) and hyperlipidemic rats (group 7) exhibited a significantly ameliorate in liver enzymes levels (Table 6) when compared to control diabetic rats (group 3) and control hyperlipidemic rats (group 6). These results were in agreement with Sadeghipour et al. (2014) and Hasona et al. (2016), who observed that hydro-ethanol extract from *Punica granatum* peel decreased the serum LDL, AST, and ALT in hyperlipidemic rats compared to healthy control as well as protect liver damage including fatty change in hepatocyte and congestion.

3.6 | Kidney function biomarkers

A significant increment was noted in the serum urea, creatinine, and uric acid levels in hyperlipidemic group treated with 10 mg/kg atorvastatin (group 8) and in hyperlipidemic rats control (group 6) compared with the normal control (Table 7). These results agree with Ghirlanda et al. (1993), who noted that the end products of atorvatatin over load the kidneys, causing membrane alteration with consequent renal failure. The mean values of serum urea, creatinine, and uric acid levels in control diabetic rats (group3) and in diabetic rats treated with glibenclamide (10 mg/kg) were higher than those of the non-diabetic control group.

Sheybaniasl et al. (2014) noted interaction effects between oxidative stress and each of diabetes, liver disease, vascular disorders, and renal damage. Diabetes can damage the blood vessels in kidneys leading to the abnormal renal function represented by a reduction in glomerular filtration and a rise in serum urea and creatinine (Bamanikar, Bamanikar, & Arora, 2016).

Data presented in Table 7 show a significant decrease in serum urea, creatinine and uric acid levels in rats treated with MPE in diabetic rats (group 4) and hyperlipidemic rats (group 7) when compared with diabetic control and hyperlipidemic control rats. MPE alleviated the diabetic renal complication by glomerular tuft and tubular epithelium cells as concluded by Ahmed et al. (2014).

TABLE 6 Changes in liver enzymes in normal, diabetic and hyperlipidemic rats treated with MPE, glibenclamide, and atorvastatin

G	Treatment	AST	ALT	ALP	TB
1	Control (normal)	20.00 ± 2.50^{e}	31.33 ± 1.94^{ed}	90.14 ± 3.91^{e}	0.84 ± 0.06^{cd}
2	MPE (200 mg/kg)	19.33 ± 2.50^{e}	28.00 ± 1.94^{ed}	89.50 ± 3.91^{e}	0.82 ± 0.06^{d}
3	Diabetic	37.67 ± 2.50^{d}	50.00 ± 1.94^{c}	130.14 ± 3.91^{c}	1.11 ± 0.06^{c}
4	Diabetic + MPE (200 mg/kg)	24.00 ± 2.50^{ed}	32.67 ± 1.94^{ed}	95.02 ± 3.91^{de}	0.89 ± 0.06^{cd}
5	Diabetic + glibenclamide (10 mg/kg)	46.00 ± 2.50^{c}	58.67 ± 1.94^{b}	149.2 ± 3.91^{b}	1.33 ± 0.06^{b}
6	Hyperlipidemia	64.00 ± 2.50^{b}	68.00 ± 1.94^{b}	162.1 ± 3.91^{b}	1.50 ± 0.06^{b}
7	Hyperlipidemia + MPE (200 mg/kg)	31.33 ± 2.50^{ed}	43.33 ± 1.94^{d}	102.1 ± 3.91^{d}	0.91 ± 0.06^{cd}
8	Hyperlipidemia + Atorvastatin (10 mg/kg)	193.3 ± 2.50^{a}	205.3 ± 1.94^{a}	381.4 ± 3.91^{a}	3.97 ± 0.06^{a}

Note. Values with same letter(s) have no significant difference ($p \leq 0.001$).

TABLE 7 Effect of treatment with MPE on Kidney function biomarkers

G	Treatment	Urea	Creatinine	Uric acid
1	Control (normal)	28.40 ± 1.78^{e}	0.92 ± 0.08^{c}	3.20 ± 0.19^{e}
2	MPE (200 mg/kg)	24.44 ± 1.78^{e}	0.87 ± 0.08^{c}	3.18 ± 0.19^{e}
3	Diabetic	45.87 ± 1.78^{bc}	1.50 ± 0.08^{b}	4.06 ± 0.19^{d}
4	Diabetic + MPE (200 mg/kg)	34.25 ± 1.78^{d}	1.03 ± 0.08^{c}	3.49 ± 0.19^{e}
5	Diabetic + glibenclamide (10 mg/kg)	41.41 ± 1.78^{c}	1.67 ± 0.08^{b}	7.26 ± 0.19^{b}
6	Hyperlipidemia	49.09 ± 1.78^{b}	1.60 ± 0.08^{b}	5.88 ± 0.19^{c}
7	Hyperlipidemia + MPE (200 mg/kg)	33.79 ± 1.78^{d}	1.04 ± 0.08^{c}	4.45 ± 0.19^{d}
8	Hyperlipidemia + Atorvastatin (10 mg/kg)	62.68 ± 1.78^{a}	2.40 ± 0.08^{a}	8.34 ± 0.19^{a}

Note. Values with same letter(s) have no significant difference ($p \leq 0.001$).

4 | CONCLUSION

The hydromethanol MPE is rich in phenolic and flavonoid compounds, thus it had a powerful antioxidant activity, which may be due to the synergistic effect of phenolic components. In the present study, MPE showed antihyperglycemic and antihyperlipidemic activities by powerful reactive oxygen scavenger through its antioxidant compounds. In addition, MPE enhanced liver and kidney functions when compared to standard drugs in diabetic and hyperlipidemic rats.

COMPLIANCE WITH ETHICS REQUIREMENTS

This article does not contain any studies with human subjects.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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How to cite this article: El-Hadary AE, Ramadan MF. Phenolic profiles, antihyperglycemic, antihyperlipidemic, and antioxidant properties of pomegranate (*Punica granatum*) peel extract. *J Food Biochem*. 2019;e12803. https://doi.org/10.1111/jfbc.12803