

## Original Article

## Effects of punica granatum peel extract and/ or sitagliptin on induced diabetic nephropathy in adult male albino rats

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### ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) represents about 90% of diabetic cases. Diabetic nephropathy (DN) is one of the most serious complications of diabetes. Sitagliptin has an important role in enhancement of the Glucagon-like peptide receptor (GLP-1R) which present in the kidneys, so it may have a role in enhancement of the kidney function in T2DM. Also, Punica granatum peels extract (PGPE) is a herb which has anti-hyperglycemic and antioxidant activities.

**Objective:** This study was designed to investigate the role of PGPE and/or sitagliptin on renal functions in induced diabetes.

**Methodology:** The current study was performed on 60 adult male albino rats. Rats weighing 200 to 250 grams. Rats were divided into: Group I “normal control animals” consists of 20 rats (divided into group 1: normal control and group 2: vehicle received control) 10 rats / each. Group II “Diabetic animals” consist of 40 rats were divided into 4 treated groups: (Diabetic, PGPE, Sitagliptin, sitagliptin and PGPE) 10 rats /each. At the end of experimental period (6 weeks), urinary protein, fasting blood glucose (FBG), urea, blood urea nitrogen (BUN), creatinine, malonyldialdehyde (MDA), tumor necrosis factor alpha (TNF $\alpha$ ), antioxidant enzymes and histopathology of renal tissue were assayed.

**Results:** In diabetic rats there were increased FBG, urea, BUN, creatinine, urinary protein, MDA and TNF $\alpha$  with decreased GSH and SOD. Treatment with PGPE and sitagliptin caused decrease in SFBG, urea, BUN, creatinine, TNF $\alpha$ , MDA and total protein with increase in GSH and SOD.

Histopathological examination of diabetic rats revealed dilated glomerular space and dilated degenerated tubules. Treatment with PGPE and sitagliptin revealed improvement in the glomerular space with less tubular dilatation.

**Conclusion:** Results of the present work showed that combination of PGPE and sitagliptin have synergistic effects for each other and have a better renoprotective effects in diabetic rats.

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### INTRODUCTION

T2DM represents about 90% of all diabetic cases. There is insulin resistance in T2DM [Error! Reference source not found.]. Glucose control can lower the threat of diabetic complications [Error! Reference source not found.]. Diabetic nephropathy (DN) represents a serious long-term complication of DM [Error! Reference source not found.]. It is the major cause of end stage renal disease, accounts about 30–35% incidents of renal alternative therapy globally [Error! Reference source not found.].

Hyperglycemia leads to glomerular hyper filtration; micro albuminuria and eventually end stage renal disease [5]. Hyperglycemia is also known to develop oxidative stress so it's involved in the generation of reactive oxygen species (ROS) which play an important role in the pathogenesis of DN [6]. GLP-1R is present in the kidneys, so it has a role in the modulation of kidney function [7]. Activation of GLP-1R attenuates diabetic renal injury by reduction of kidney inflammation and oxidative stress [8].

Sitagliptin is an oral antidiabetic drug, its main goals is to prolong the effects of endogenous GLP-1 by inhibiting the activity of Dipeptidyl peptidase-IV (DPP-IV) enzyme [9]. PGPE is a herb which is important for treatment of diabetes [10]. The study of **Patil et al.** [11] proved the antihyperglycemic and antioxidant activities of PGPE, due to presence of flavonoids such as ellagitannins, gallic acid and anthocyanins [12].

## MATERIAL AND METHODS

The present study was carried out at the animal house, Physiology department faculty of medicine for girls, Al-Azhar University.

**Experimental drugs:** Streptozotocin, nicotinamide and sitagliptin

**Sitagliptin:** Drug was provided in the form of tablets (50 mg/tablet) and given to the rats in a dose of (10 mg/kg /day) orally via a gastric gavage [13].

### Experimental methodology:

**Induction of T2DM:** Rats were fasted all over the night then, they had been injected by a nicotinamide dissolved in normal saline (110 mg/kg) i.p then after 15 min rats were injected i.p by a streptozotocin (45 mg/kg) dissolved in citrate buffer of pH 4.5. Hyperglycemia was verified via increased blood glucose levels after 72 hours and then on 7<sup>th</sup> days. Those animals with fasting blood glucose greater than 250 mg/dL & raised creatinine level were used for DN study [14-15].

**Experimental plant material:** Fruits was cut into portions. Then, the peels were cut into small pieces and leave to be dried until complete dehydration. Dried peels were grounded into powder which was stored at 5 °C till used. It was suspended in warm distilled water (100 mg/1 ml) and was given to the rats orally via a gastric gavage in a dose (200 mg/kg/day) [16-17].

**Experimental design:** Rats were divided into 6 equal experimental groups.

**Group I (Normal control):** Received ordinary rat chow.

**Group II (Control citrate buffer):** Were injected i.p with sodium citrate buffer pH4.5 (vehicle received).

**Group III (Diabetic):** T2DM.

**Group IV (Diabetic plus PGPE):** PGPE treated group (started one week after induction of DM) for 6 weeks.

**Group V (Diabetic plus sitagliptin):** Sitagliptin treated group (started one week after induction of DM) for 6 weeks.

**Group VI (Diabetic treated with sitagliptin and PGPE):** Received sitagliptin & PGPE (started one week after induction of DM) for 6 weeks.

**Experimental protocol:** At the end of the experimental period, rats were put in a metabolic cage for 24 hours to collect urine samples to detect total protein level (It has a feeder chamber located

outside the cage that contains a feeder drawer that slides out for easy filling. This set-up prevents the urine from getting contaminated with the food. The cages have a water bottle support and spillage collection tube designed to prevent water from entering the cage and contaminating the urine). Then rats were fasted for 12 hours, blood samples were taken from retro-orbital plexus using heparinized capillary tubes under light ether anesthesia. It was introduced at the inner canthus of the eye and advanced gently along the sides of the globe into the venous plexus. The serum was prepared according to [18] & used for estimation of: Fasting serum Glucose (FSBG), urea, blood urea nitrogen (BUN) and creatinine.

**Tissue samples:** after sample collection, rats were sacrificed by cervical dislocation. Kidneys were excised, left kidney of each rat was rapidly dissected and washed with saline and fixed in 10% formalin for histopathological examination. Tissue homogenate of the right kidney: the supernatant was estimated for: Malonyldialdehyde (MDA), Tumor necrosis factor alpha (TNF $\alpha$ ), glutathione (GSH) and superoxide dismutase (SOD). At the end of experimental period, all samples was subjected to the following investigations: Measurement of SFBG [19], urea and BUN [20], creatinine [21], GSH [22], SOD [23], MDA [24], TNF $\alpha$  [25] and total protein in urine [26].

### Histopathological examination of the kidney:

Kidneys were fixed in 10% formalin then dehydrated, embedded in paraffin, sectioned to 3–5  $\mu$ m thickness, deparaffinized and rehydrated. Hematoxylin and Eosin (H&E) dyes were used to stain the kidney tissues. The slides were then observed under light microscope [27].

### Statistical Analysis

Data were coded and entered using the statistical package for social science version16 (SPSS, 16) for windows. Quantitative data were expressed by using mean and standard error (S.E). Comparing between groups was done using one-way analysis of variance (one-way ANOVA) for comparison of quantitative data of more than 2 groups. The level of significance was taken at p value of  $\leq 0.05$ .

## RESULTS

**Biochemical results:** Table (1) & figs. (1 and 2): Induction of DM caused significant increase in SFBG, urea, BUN, creatinine TNF $\alpha$ , MDA and total protein with significant decrease in GSH and SOD versus control groups. Treatment with PGPE, sitagliptin or PGPE and sitagliptin simultaneously caused significant decrease in SFBG, urea, BUN, creatinine, TNF $\alpha$ , MDA and total protein with significant increase in GSH and SOD versus diabetic group.

**Table (1): Changes in different parameters among the studied animals groups: Serum fasting blood glucose, urea, blood urea nitrogen, creatinine, Tumor necrosis factor alpha level, Malonyldialdehyde, glutathione, Superoxide dismutase and 24 hours protein in urine**

Groups Parameters	G I Control group			G II Control + Buffer group			G III Diabetic group			G IV Diabetic +Punica group				G V Diabetic +sitagliptin group				G VI Diabetic +punica & sitagliptin group)			
	Mean ±SEM	Mean ±SEM	p vs. G I	Mean ±SEM	P vs. G I	P. vs. G II	Mean ±SEM	P vs. G I	P vs. G II	P vs. G III	Mean ±SEM	P vs. G I	P vs. G II	P vs. G III	Mean ±SEM	P vs. G I	P vs. G II	P vs. G III			
SFBG (mg/dl)	102.50 ±4.92	101.00 ±2.22	0.90	507.43 ±7.29	0.001* A	0.001* b	156.57 ±11.27	0.001* A	0.001* b	0.001* C	158.86 ±11.84	0.001* a	0.001* b	0.001* C	121.43 ±7.46	0.13	0.10	0.001* c			
Urea (mg/dl)	26.66 ±4.96	29.29 ±0.59	0.54	80.08 ±3.68	0.001* a	0.001* b	43.60 ±1.59	0.001* A	0.001* b	0.001* c	52.17 ±2.68	0.001* a	0.001* b	0.001* C	39.43 ±1.86	0.001* A	0.001* b	0.02* c			
BUN (mg/dl)	14.77 ±1.11	15.28 ±0.74	0.73	37.71 ±1.16	0.001* a	0.001* b	20.63 ±0.62	0.001* A	0.001* b	0.001* c	22.87 ±0.70	0.001* a	0.001* b	0.001* C	17.11 ±1.42	0.11	0.22	0.001* c			
Creatinine (mg/dl)	0.70 ±0.03	0.70 ±0.06	1.00	1.83 ±0.02	0.001* a	0.00* b	0.92 ±0.09	0.07	0.07	0.001* c	1.13 ±0.14	0.001* a	0.001* b	0.001* C	0.91 ±0.07	0.09	0.09	0.001* c			
TNFα (pg/g. tissue)	23.42 ±1.79	19.77 ±0.41	0.44	95.26 ±5.32	0.001* a	0.001* b	56.00 ±3.94	0.001* A	0.001* b	0.001* c	55.33 ±1.88	0.001* a	0.001* b	0.001* C	52.91 ±2.28	0.00* A	0.001* b	0.001* c			
MDA (nmol / g. tissue)	11.68 ±0.69	11.22 ±0.25	0.85	54.88 ±3.24	0.001* a	0.001* b	23.90 ±1.52	0.001* A	0.001* b	0.001* c	27.40 ±1.06	0.001* a	0.001* b	0.001* C	21.33 ±1.34	0.001* A	0.001* B	0.001* c			
GSH (mmol / g. tissue)	66.45 ±4.56	59.65 ±1.46	0.14	23.53 ±3.02	0.001* a	0.001* b	45.56 ±3.20	0.001* A	0.001* b	0.001* c	47.87 ±1.78	0.001* a	0.01* b	0.001* C	57.01 ±3.28	0.03* a	0.54	0.001* c			
SOD (U/g.tissue)	5.87 ±0.17	5.53 ±0.21	0.30	1.45 ±0.19	0.001* a	0.001* b	4.05 ±0.10	0.001* A	0.001* b	0.001* c	4.09 ±0.21	0.001* a	0.001* b	0.001* C	4.83 ±0.31	0.001* A	0.02* b	0.001* c			
Total protein in urine (mg/day)	2.73 ±0.32	3.07 ±0.22	0.65	37.28 ±0.39	0.001* a	0.001* b	27.68 ±0.65	0.001* A	0.001* b	0.001* c	25.58 ±0.57	0.001* a	0.001* b	0.001* c	22.20 ±0.55	0.001* A	0.001* b	0.001* c			

Values are represented as mean ± SEM and statistically evaluated using one way ANOVA followed by Bonferroni's post hoc test, a= statistically significant compared to corresponding value in G I (Control group) (p<0.05), b= statistically significant compared to corresponding value in G II (Control + Buffer group) (p<0.05), c= statistically significant compared to corresponding value in G III (Diabetic group) (p<0.05), N=10 animals.

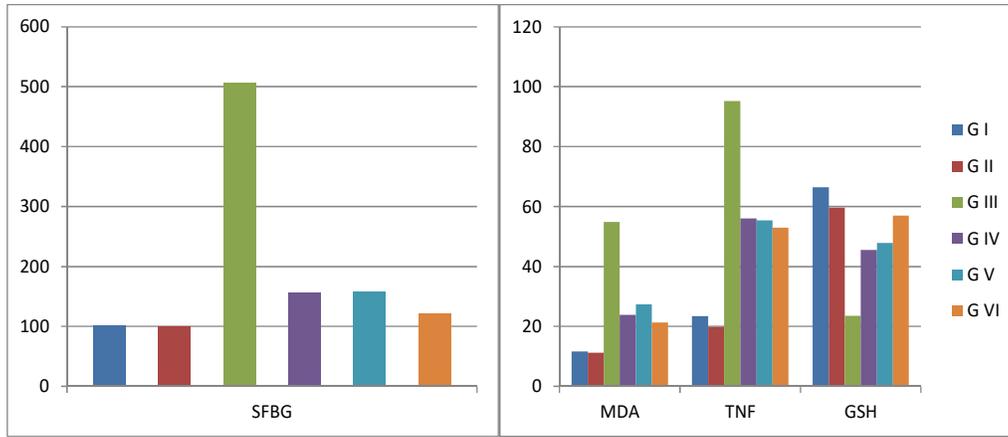


Figure (1): Changes in different parameters among studied animals groups: Serum fasting blood glucose (SFBG), Malonyldialdehyde (MDA), Tumor necrosis factor alpha level (TNF $\alpha$ ) and glutathione (GSH).

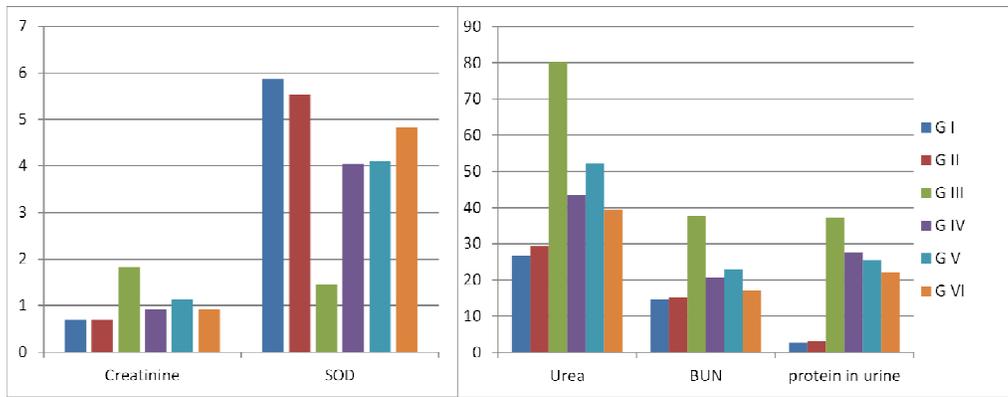


Figure (2): Changes in different parameters among studied animals groups: Superoxide dismutase (SOD), urea, blood urea nitrogen (BUN), creatinine and 24 hours protein in urine.

**Histopathology :** Control groups revealed normal tubular and glomerular structures(Fig.3).Diabetic rats revealed dilated glomerular space and dilated degenerated tubules (Fig.4).Diabetic rats treated by

either PGPE or sitagliptin revealed some improvement in the glomerular space and most tubules (Figs. 5 and 6). Diabetic rats treated by both PGPE & sitagliptin revealed the best results (Fig.7).

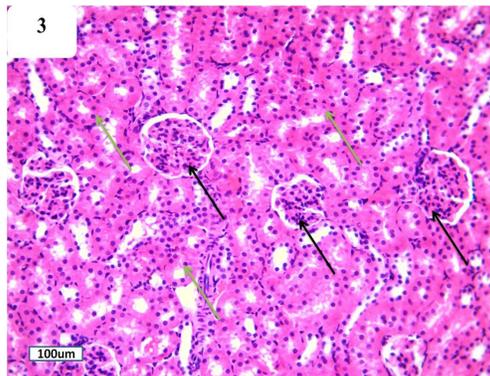


Fig. 3: Histopathological examination of control and control buffer group was similar: A photomicrograph of a section in a control rat kidney: showing the normal histological structure of the cortex, containing the glomeruli (black arrows) and renal tubules (green arrows) (H&E X200).

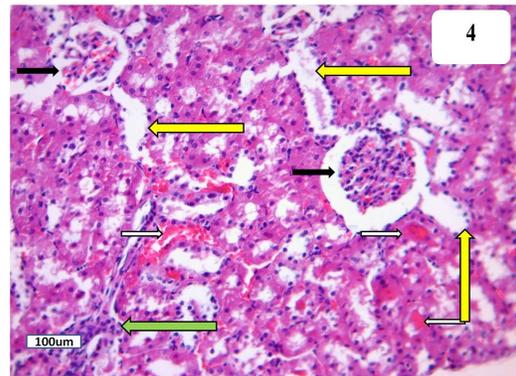
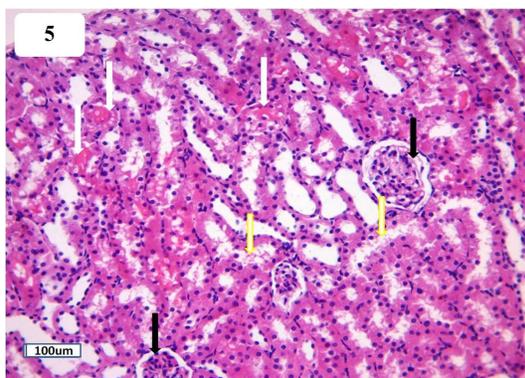
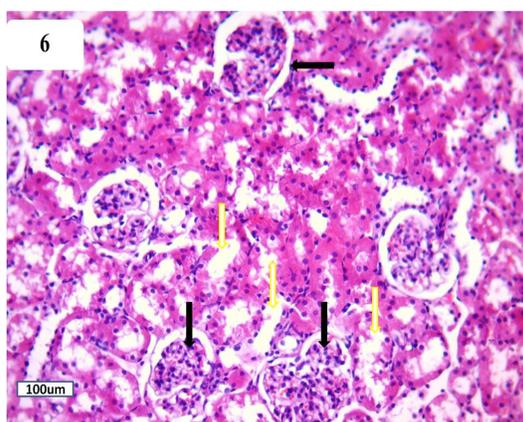


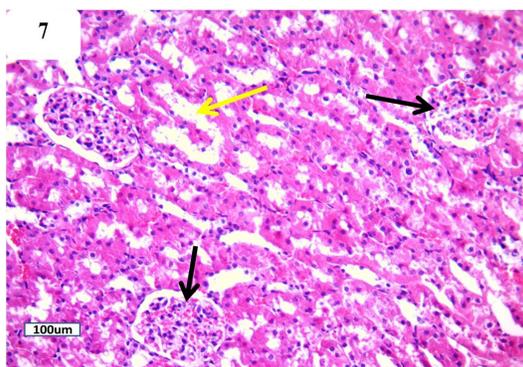
Fig. 4: A photomicrograph of a section in a diabetic rat kidney: showing mononuclear cell infiltration (green arrow), dilatation in the glomerular space (black arrow), vacuolated cytoplasm of the renal tubules (yellow arrows) and hemorrhage inside many tubules (white arrows) (H&E X 200).



**Fig. 5: A photomicrograph of a section of diabetic adult male rat kidney treated with Punica granatum peels extract (PGPE):** showing decrease in the glomerular space (black arrows), but hemorrhage inside some tubules (white arrows) and vacuolated cytoplasm of some renal tubules (yellow arrows) are still present (H&E X 200).



**Fig. 6: A photomicrograph of a section of diabetic adult male rat kidney treated with sitagliptin:** showing decrease in the glomerular space (black arrows) but some dilated renal tubules with vacuolated cytoplasm (yellow arrows) are still observed (H&E X 200).



**Fig.7: A photomicrograph of a section of a diabetic adult male rat kidney treated with Punica granatum peels extract (PGPE) and sitagliptin:** showing decrease in the glomerular space (black arrows), but vacuolated cytoplasm of some renal tubules (yellow arrow) is still noted (H&E X 200).

## DISCUSSION

In the present study, there was a significant increase in SFBG in diabetic group versus control groups. In agreement with our results [28] increased glucose level in diabetic rats.

Streptozotocin (STZ) after administration is rapidly enters into the pancreatic beta cells and leads to breakage of DNA strands [29-30]. STZ leads to generation of ROS which leads to DNA fragmentation in the pancreatic B-cell islets by increasing  $H_2O_2$  production [31]. Alterations of the damaged pancreatic islets due to induction of diabetes, is accompanied by increased blood glucose [32-33].

In the present study, there was a significant increase of urea, BUN, creatinine and total protein in diabetic group versus control groups. The effect of Streptozotocin-nicotinamide (STZ-NIC) could be proved by the present work histopathological finding. The kidney sections showed dilated glomerular space, dilated degenerated tubules and vacuolated cytoplasm of many renal tubules. In agreement with our results [34] increased total protein, BUN, urea and creatinine levels in diabetic rats. The histopathological findings were in consistence with the study of [35 - 36] who found dilated glomerular space, increased vacuolization of the cytoplasm and dilated degenerated tubules.

In 2016 [37] proved that diabetes can decrease the glomerular filtration rate by damaging the renal blood vessels. So, less BUN, creatinine and urea filtered out as they are excreted in the urine. Increased serum creatinine may be due to damaged muscles [38]. Recently [39] suggested that diabetes weakens the glomerular filtration barrier, leads to glomerular damage and increased glomerular permeability to protein leading to albumin leakage. Also, [40] found that T2DM causes a marked decrease in the tubular brush border thickness. The renal tubular structural abnormalities could disturb the normal fluid uptake leading to proteinuria.

In the present study, diabetic group showed significant increase of  $TNF-\alpha$  and MDA. Significant decrease in SOD and GSH versus control groups. In agreement with this result [41 - 42] increased  $TNF-\alpha$  and MDA with decreased SOD and GSH levels in diabetic rats.

Oxidative stress is one of the most basic causes of chronic complications of T2DM. It leads to production of many oxidative intermediates, resulting in exacerbated oxidative damage [39].

SOD is the first barrier to free radical and one of the most important antioxidant enzymes which convert superoxide radicals into the hydrogen peroxide. Also, GSH protects cells from oxidative damage; it helps

glutathione peroxidase in scavenging free radicals. So, their levels decrease in oxidative stress<sup>[43-44]</sup>.

TNF- $\alpha$  is an inflammatory cytokine which is secreted from the macrophages. TNF- $\alpha$  suppresses insulin secretion in DM<sup>[45]</sup>. Free radicals over production cause DNA damage especially strand breakage and base alterations, which induce cell cycle arrest or apoptosis. Inflammation develops as a response to OS-induced damage involving activation of the nuclear factor kappa B (NF- $\kappa$ B) pathway in the renal cells. Chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and interleukins<sup>[46]</sup>. These pro-inflammatory adhesion molecules and chemokines attract monocytes, macrophages, and T lymphocytes, which infiltrate kidney tissue, resulting in activation of TNF- $\alpha$  signaling. Therefore, aggravation of kidney lesions<sup>[47]</sup>. TNF- $\alpha$  has a role in regulating apoptosis and inflammatory processes in diabetes<sup>[48]</sup>. In addition, increased level of TNF- $\alpha$  could be due to lipids dysfunction, especially increased triglyceride (TG) in adipose cells causing its secretion from macrophage cells<sup>[49]</sup>.

Lipid peroxidation is a marker of oxidative stress, in which polyunsaturated fatty acids (PUFAs) interact with free radicals, leading to formation of MDA, which causes negative effects as cell necrosis and inflammation. Administration of PGPE caused significant decrease in SFBG versus diabetic group while SFBG remained significant higher than control groups.

Similar changes were recorded by<sup>[50]</sup> who found that PGPE caused a significant decrease in SFBG versus diabetic group.

The hypoglycemic effect of PGPE related to its active substances (polyphenols and flavonoids) which have the properties of increasing insulin secretion, promoting glucose uptake by muscle or adipose tissues, regenerating pancreatic beta cell, decreasing glucose absorption from the intestine and glucose production from the liver<sup>[51]</sup>. PGPE leads to increase insulin levels by increasing either pancreatic secretion of insulin or its release from the bound form<sup>[52]</sup>.

Administration of PGPE extract showed significant decrease in urea, BUN, creatinine and total protein levels versus diabetic group. However, levels of urea, BUN and total protein remained significant higher than control groups, while the creatinine returned almost back to control groups.

These results were in agreement with the finding of<sup>[53-54]</sup> who found that PGPE cause decrease on serum creatinine, BUN, and urea. Administration of PGPE causes a significant decrease in total protein<sup>[17]</sup>.

In kidney sections, PGPE treated animals showed moderate renal improvement, in glomerular space and most tubules. Some tubules dilated, others still vacuolated and hemorrhage was noted inside them.

The histopathological findings were in consistence with the study of<sup>[55-56]</sup> who found significantly reduced vacuolar degeneration of tubules of the kidney and reduction of the thickened basement membrane in diabetic rats treated with PGPE.

The protective effect of PGPE on the creatinine and urea could be attributed to its antioxidant effect as ROS has been found to be involved in the impairment of glomerular filtration rate<sup>[57]</sup>.

The present study demonstrated that administration of PGPE induced a significant decrease in TNF- $\alpha$  and MDA. Significant increase in GSH and SOD levels versus diabetic group, while TNF- $\alpha$  and MDA levels remained significantly higher than the control groups. However, GSH and SOD levels remained significantly lower than the control groups. These results were in agreement with the finding of<sup>[53-55]</sup> who recorded that administration of PGPE leading to reduction of TNF- $\alpha$  and MDA levels with significant increase in GSH and SOD levels.

The anti-inflammatory effects of PGPE happen via inhibition of cell signaling pathways including suppression of cyclo-oxygenase-2 and inducible nitric oxide expression, inhibition of activation of NF $\kappa$ B and inhibition of phosphorylation of mitogen-activated protein kinase (MAPKs) proteins<sup>[58]</sup>. Phenolic compounds due to their redox properties contribute to the antioxidant activities of PGPE. They prevent decomposition of hydroperoxides into free radicals and neutralize lipid free radicals<sup>[59]</sup>. On contrary to our results<sup>[60]</sup> found that PGPE supplementation showed insignificant improvement in the activity of SOD and MDA, this may be due to different method in preparing the extract.

Administration of sitagliptin showed significant decrease in SFBG versus diabetic group, however level of SFBG remained significant higher than control groups. In agreement with our results<sup>[61]</sup> reported that sitagliptin caused decreased glucose level.

Sitagliptin is a DPP-IV inhibitor which improves glucose level by stimulating insulin secretion results from GLP-1R activation in the pancreas. GLP-1 can inhibit glucagon secretion in a glucose-dependent manner by its effect on pancreatic alpha cells and, thereby improving glycemic control with decrease the risk of hypoglycemia<sup>[62-63]</sup>.

Administration of sitagliptin showed a significant decrease in urea, BUN, creatinine and total protein versus diabetic group. However, levels of urea, BUN, creatinine and total protein remained significant higher than control groups. Similar changes were recorded by<sup>[64-65]</sup> who reported that sitagliptin caused a significant decrease in urea, BUN, creatinine and total protein levels versus diabetic group.

In kidney sections of sitagliptin treated rats showed improvement of the glomerular spaces and most tubules versus diabetic group, but some tubules still dilated and others degenerated. The histopathological findings were in consistence with the study of <sup>[47]</sup> who found that diabetic rats treated with sitagliptin showed improvement in the morphological changes and the infiltration of inflammatory cells.

Sitagliptin has renoprotective effects via the anti-inflammatory and anti-oxidant actions <sup>[66]</sup>. It also might be associated with the attenuation of podocyte injury <sup>[67]</sup>. Sitagliptin reduces albuminuria by controlling of blood sugar <sup>[68-69]</sup>. Also, it has been shown to inhibit renal tubular sodium reabsorption so increase the glomerular pressure and reduce the albuminuria <sup>[70]</sup>. On contrast to our results <sup>[71, 72, 73]</sup> reported that sitagliptin has no effect on the creatinine, urea and BUN levels. This might be related to the extremely high urinary concentrations that result from rapid renal elimination of the drug as seen in rodents.

Administration of sitagliptin showed a significant decrease in TNF- $\alpha$  and MDA, significant increase in GSH and SOD versus diabetic group, while TNF- $\alpha$  and MDA remained significant higher than control groups, however GSH and SOD remained significant lower than control groups. In agreement with these results <sup>[73-73]</sup> found that administration of sitagliptin caused a significant decrease in TNF- $\alpha$  and MDA, significant increase in GSH and SOD versus diabetic group.

Sitagliptin treatment decreased the proinflammatory cytokine genes expression such as TNF- $\alpha$  in the kidney of diabetic rat <sup>[75]</sup>. Renal cyclic adenosine monophosphate (cAMP) production is up regulated by sitagliptin through elevating circulatory stromal cell-derived factor-1a. Another mechanism is that sitagliptin elevates active GLP-1, which is known to up regulate cAMP. Increased cAMP has antioxidative effects and reduces reactive oxygen species, which are a major cause of DN <sup>[Error! Reference source not found.]</sup>.

There was no previous studies discussed the effect of combined PGPE and sitagliptin. Therefore, the obtained results reflect the cumulative effects of both PGPE and sitagliptin with their underlying mechanism of action. Concomitant administration of PGPE and sitagliptin showed significant decrease in SFBG, urea, BUN, creatinine, total protein, MDA and TNF $\alpha$ . Significant increase in GSH and SOD versus diabetic group. SFBG, BUN and creatinine returned almost back to control groups, while urea, total protein, MDA and TNF $\alpha$  remained significantly higher than that of control groups. SOD remained significantly lower than that of control groups. GSH returned back to control buffer group but remained significantly lower than control group. Co-

administration of PEPE and sitagliptin induced the best improvement of the histopathological results of renal tissues where the histopathological picture of the kidney tends to be normal. However, some renal tubules still having vacuolated cytoplasm.

## CONCLUSIONS

The result of the present study showed that combination of PGPE and sitagliptin have synergistic effects for each other compared to monotherapy and have a better renoprotective effects in diabetic rats. The concomitant administration of PGPE along with sitagliptin not only attenuated the glucose homeostasis but also showed significant improvement in renal functions, inflammatory and antioxidant markers. So, it is recommended that: PGPE is worthy of further investigations as they are safe and effective for modulating DM and its complications (DN). Additional clinical trials are needed to support the use of sitagliptin and PGPE as preventive or therapeutic agents in patients with DN.

## Conflicts of interest

There are no conflicts of interest.

## Acknowledgment

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## الملخص العربي

آثار مستخلص قشر الرومان و / أو السيتاجلبتين على اعتلال الكلية السكري المستحدث في ذكور الفئران البيضاء البالغة

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### ملخص البحث:

**الخلفية:** داء السكري من النوع الثاني يمثل حوالي 90 ٪ من حالات مرض السكري. اعتلال الكلية السكري هو واحد من أخطر مضاعفات مرض السكري. السيتاجلبتين له دور مهم في تعزيز مستقبلات الببتيد الشبيهة بالجلوكاجون الموجودة في الكلى، لذلك قد يكون له دور في تعزيز وظيفة الكلى في النوع الثاني من الداء السكري. أيضا مستخلص قشر الرومان عشب له أنشطة مضادة لفرط سكر الدم ومضادات الأكسدة.

**الهدف:** تم تصميم هذه الدراسة للتحقيق في دور مستخلص قشر الرومان و / أو السيتاجلبتين على وظائف الكلى في مرض السكري المستحدث.

**الطرق:** تم إجراء الدراسة الحالية على 60 فأر من ذكور الفئران البيضاء البالغين. فئران تزن 200 إلى 250 جرام. تم تقسيم الفئران إلى: المجموعة الأولى "حيوانات التحكم الطبيعية" تتكون من 20 فأر (مقسمة إلى مجموعة 1: التحكم الطبيعي و مجموعة 2: محلول السيترات الصابطة) 10 فئران / لكل منهما. المجموعة الثانية "الحيوانات المصابة بالسكري" تتكون من 40 فأر تم تقسيمها إلى 4 مجموعات معالجة: (السكري، مستخلص قشر الرومان، السيتاجلبتين، مستخلص قشر الرومان و السيتاجلبتين معا) 10 فئران / لكل منهما. في نهاية الفترة التجريبية (6 أسابيع)، البروتين البولي، السكر في الدم صائم، اليوريا، نيتروجين اليوريا في الدم، الكرياتينين، عامل الإجهاد التأكسدي، عامل نخر الورم ألفا والانزيمات المضادة للأكسدة قد تم تقييمهم والتشريح المرضي للأنسجة الكلوية.

**النتائج:** في الفئران المصابة بداء السكري كانت هناك زيادة السكر في الدم صائم، اليوريا، نيتروجين اليوريا في الدم، الكرياتينين، البروتين البولي، عامل الإجهاد التأكسدي و عامل نخر الورم ألفا مع انخفاض مستويات الجلوتاثيون و سوبروكسيد ديسموتاز. تسبب العلاج باستخدام مستخلص قشر الرومان و السيتاجلبتين في انخفاض السكر في الدم صائم، اليوريا، نيتروجين اليوريا في الدم، الكرياتينين، عامل الإجهاد التأكسدي، عامل نخر الورم ألفا والبروتين الكلي مع زيادة في الجلوتاثيون وسوبروكسيد ديسموتاز.

**الاستنتاجات:** كشف الفحص النسيجي للفئران المصابة بداء السكري عن وجود مساحة كيببية متوسعة وأنابيب متدهورة متضخمة. كشفت الفئران التي عولجت بمستخلص قشر الرومان و السيتاجلبتين تحسن في مساحة الكيببي مع توسع أنبوبي أقل. أظهرت نتائج العمل الحالي أن الجمع بين مستخلص قشر الرومان و السيتاجلبتين لهما آثار تآزرية لبعضهما البعض ولهما تأثيرات أفضل على الكلى في الفئران المصابة بداء السكري.

**الكلمات المفتاحية:** مضادات الأكسدة، فلافونيدات، حماية الكلى، نيكوتيناميد، استربتوزوتوسين.

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