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Protective Effects of Golden Berry (*Physalis peruviana* L.) Juice against Diabetic Renal Injury in Rats

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Abstract

THE OBJECTIVE of this research was to estimate the kidney-protective properties of golden berry (*Physalis peruviana* L.) fresh juice (GBJ) in rats with streptozotocin (STZ)-induced type 1 diabetes. Thirty male rats were separated into two groups: the control (n=6) and the diabetes (n=24) groups. The diabetic rats were then subdivided into four groups (6 rats each): untreated diabetes, metformin (Met)-treated diabetic, GBJ-treated diabetic, and GBJ + Met-treated diabetic. The treatment duration lasted for eight weeks. The findings demonstrated that GBJ reduced serum glucose levels, ameliorated pancreatic degeneration in both the exocrine and endocrine glands and enhanced serum lipid profile markers. GBJ administration improved serum markers of kidney injury (creatinine and blood urea nitrogen) and mitigated the pathological features of kidney damage induced by STZ. The biochemical analysis further revealed that GBJ decreased oxidative stress levels, as evidenced by reduced malondialdehyde levels, and improved the antioxidant enzymes activity (catalase and glutathione reductase) relative to the diabetic untreated group. Additionally, GBJ improved serum levels of advanced glycation end-products (AGE). GBJ significantly enhanced the effects of Met. Our findings indicate that GBJ can mitigate STZ-induced kidney damage through its antioxidant, antihyperglycemic, and antihyperlipidemic properties. Additionally, GBJ inhibits AGE, thereby contributing to its renoprotective effect.

Keywords: Advanced glycation end-products, Diabetes, Goldenberry, Kidney, Oxidative stress.

Introduction

Diabetes mellitus (DM) is a critical clinical metabolic syndrome induced by a relative or absolute defect or diminished effectiveness of circulating insulin. Globally, it remains a crippling health problem. DM is considered the most prevalent disease of the twenty-one century, and it is occurrence is increasing alarmingly. It was estimated to be 171 million in 2000 and predicted to affect 552 million in 2030 and 693 million in 2045 for all age groups [1,2]. DM is associated with exacerbating declined antioxidant enzyme activities, inducing oxidative stress by forming reactive nitrogen and oxygen species [3,4].

Persistent hyperglycemia stimulates and develops non-enzymatic glycation reaction with lipids, proteins, and nucleic acids, this reaction leads to the formation of advanced glycated end products (AGE) (heterogenous group of chemical compounds), which have a main role in the enhanced inflammation, oxidative stress, and pathophysiology of DM complications. The DM complications` mortality rate is approximately 30 % in diabetic patients [5,6]. Chronic hyperglycemia damages renal tissues and destroys their function, causing diabetic nephropathy (DNP) and developing an end-stage renal disease [7].

The hypoglycemic therapies cannot induce a complete cure and are attributed to mild-to-moderate adverse effects. There is a raised need by DM

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patients to use natural alternatives that have hypoglycemic effects. Natural hypoglycemic products are less costly, efficacious, easily available, and have fewer side effects than medications [8]. Plants have abundant origin of medicinally active compounds, which can be utilized to cure numerous illnesses. In recent years, golden berry (GB), from the Solanaceae family, has been much appreciated by researchers for its impact as a hypoglycemic plant because of its fructose content, which performs a regulatory function in the glucose level of diabetics [9]. The GB (*Physalis peruviana* L.) is a fruit commonly consumed in Egypt and many Arabic countries. It is traditionally utilized as a nutraceutical and curative (antiseptic, diuretic, analgesic, and antispasmodic) plant [10]. GB is one of the functional foods, it is rich in vitamins C, B-complex, A, D, and, E as well as carotenoids, polyphenols, and withanolides [11, 12]. GB also contains phenolic acids (including p-coumaric acids, chlorogenic, caffeic, ferulic, and gallic), flavonoids (as epicatechin, catechin, quercetin, myricetin, kaempferol and rutin), and total phenolic compounds (ranging from 50 to 250 gallic acid equivalents/100 g) [4,13]. GB has anti-inflammatory, antioxidant, and hypoglycaemic actions [4, 14, 15]. GB has antiproliferative activity against renal, prostate, breast, and many cancer cells [11, 16, 17].

Fresh GB juice (GBJ) is considered a functional food. It contains several micronutrients and active constituents that provide physiological benefits. The phenolic compounds in GBJ improve pancreas β-cells [18]. This research was intended to assess the nephroprotective effects of GBJ in streptozotocin-induced nephrotoxic rats. This is explored by researching the ability of GBJ to prevent AGE generation, as well as the formation and development of oxidative stress, as well as comparing the studied impacts of GBJ with the reference drug (metformin (Met).

Material and Methods

Preparation of golden berry juice (GBJ)

Golden berry (GB) (*Physalis peruviana* L.) ripe fruits were purchased from January to April 2023 from Kom Hamada, Al-Buhayrah Government, Egypt. Intact fruits were chosen based on the ripeness degree, which was assessed through the color of fruit (Brilliant orange) (Fig.1) [19] the total titratable acidity (0.92%), and pH of pulp (3.9). Whole GB were washed and dried, then GB pulped were mixed by the blender (Moulinex, France) for 5 min. Filtration was done on the mixture through cheesecloth [20]. The GB juice (GBJ) was freshly prepared for use.

Induction and assessment of diabetes

Following a 12-hour fasting period, rats were administered intraperitoneally (IP) with freshly prepared streptozotocin (STZ) obtained from Sigma-Aldrich (St. Louis, MO, USA) at a dosage of 65 mg/kg body weight [21]. The STZ was dissolved in 0.1 mol/L citrate buffer with a pH of 4.5. To prevent hypoglycemia-induced mortality, STZ-injected rats were provided access to a 5% glucose solution for consumption. Rats exhibiting fasting blood glucose levels exceeding 250 mg/dl after 3 days were identified as having diabetes mellitus (DM) and were included in the experimental procedures [21].

Experimental protocol

The protocol was approved by Regional Centre for Food and Feed, Agricultural Research Centre (ARC), Giza, Egypt (approval No 21529). Male rats (n=50 rats) weighing 200-220 grams were obtained and housed in the animal house, Animal Research Unit, ARC, Giza, Egypt. Rats were fed on a standard diet and housed in standard lab conditions. After 1 week (adaptation period), rats were classified into 2 groups. The first control group (n=7) was rats IP injected with PBS. The second group (n=43), rats after confirmation of DM induction, were classified into 4 subgroups as follows: untreated DM group (n=11). Met-treated DM group (n=11) (Met was dissolved in distilled water and ingested at a daily dose of 600 mg/kg) [22]. GBJ treated DM group (n=11) (GBJ was ingested at a daily dose of 5 ml/kg) [15]. GBJ + Met treated DM group (n=10). After eight weeks of treatment, samples of blood were collected from 6 rats in each group for serum separation and then kept at -20 °C for biochemical analysis [23]. Renal tissue samples were preserved in 10 % neutral-buffered formalin after rinsing with ice-cold saline for histopathological examination.

Measurements of serum glucose and lipid profiles

Glucose and lipid profiles (total cholesterol (T Chol), triglycerides (TG), and high-density lipoprotein cholesterol (HDLC)) levels were measured using the procedure of colorimetric kits (BioMerieux, France). Very low and low-density lipoprotein cholesterol (VLDLC and LDLC) were calculated with a standard equation.

Measurements of the renal function

Creatinine (Cr) and blood urea nitrogen (BUN) were measured in serum by the procedure of colorimetric standard kits (Roche Cobas Diagnostic, USA).

Histopathology examination and quantitative scoring of renal lesions

Renal and pancreas specimens, after fixation, were prepared following the standard technique and then stained with hematoxylin and eosin (H&E stain) [24].

At 200 x magnification, the histopathological grading of the renal lesions was categorised on a 4-point rating according to the occurrences of the following: degenerative lesions, inflammatory

changes, hydronephrosis, and vascular changes (hemorrhage and congestion) (0 score demonstrate normal renal tissues, 1 mild lesion, 2 moderate, 3 severe focal lesions, and 4 severe lesions) [25]

Measurements of the redox status and advanced glycation end products (AGE)

Serum malondialdehyde (MDA) (LS-F28018), catalase (CAT) (LS-B5636), and glutathione reductase (GR) (LS-B11952) were assessed through ELISA LSBio kits (LifeSpan Biosciences, USA) as described in the kits' procedure. The serum AGE level was determined as per the procedure's protocol of the Sandwich LSBio (LifeSpan Biosciences, USA) ELISA kit LS-F39268.

Statistical tests

Data were displayed as mean ± SD. One way analysis of variance (ANOVA) was used to compare whether there are any statistically significant differences between the means across the experimental groups. If the variation between group means is significantly larger than the variation within groups, it suggests a significant difference between the means of the groups. ANOVA was followed by the least significant difference (LSD) test in order to compare the experimental groups' means in pairs. The SPSS program version 27 for the window was utilized in performing the statistical tests.

Results

Impact of GBJ and/or Met on mortality in DM rats

Following 8 weeks of the experiment, the % mortality in DM rats' group was significantly higher relative to the control rats (24.45% and 14.29%, respectively). The DM group treated with Met exhibited a reduction in the % mortality relative to the DM group treated with GBJ (18.17% and 36.36%, respectively). Adding GBJ to Met resulted in a more pronounced decline in % mortality (10%) relative to the group treated with either Met alone (18.18%) or GBJ alone (36.36%) (Table 1).

Impact of GBJ and/or Met on glucose level in DM rats

The glucose level in DM rats' group was significantly higher relative to the control rats ($p \leq 0.001$). Following 8 weeks of treatment with Met, GBJ, and GBJ + Met, significant reduction in glucose levels were observed relative to the DM group ($p \leq 0.001$). The DM group treated with Met exhibited a significant reduction in serum glucose level relative to the DM group treated with GBJ ($p \leq 0.001$). Conversely, adding GBJ to Met resulted in a significant decline in serum glucose levels relative to the group treated with either Met alone or GBJ alone ($p \leq 0.01$ and $p \leq 0.001$, respectively). Interestingly, DM treatment with GBJ successfully augmented the hypoglycemic effect of Met, leading to a normalization of glucose level, there was no significant change relative to the control rats (Fig. 2).

Impact of GBJ on pancreatic histopathological changes in DM rats

The pancreatic sections of control rats showed normal pancreatic acini lined with normal acinar cells filled with zymogen granules and normal β islets of Langerhans (Figures 3A & 4A). DM rats' pancreatic sections showed severe necrosis of β islets of Langerhans associated with marked fibroblastic cell proliferation and marked inflammatory cells consisting of eosinophils, lymphocytes, and macrophages (Figures 3B & 4B). In the treated DM rats with Met, it showed a noticeable decrease in pancreatic degeneration within the endocrine portion, with normal pancreatic acini (Figures 3C & 4C). In the treated DM rats with GBJ, it showed a remarkable decrease in pancreatic degeneration of the exocrine glandular acini or the endocrine portion (Figures 3D & 4D). In treated DM rats with GBJ + Met, it showed a marked decrease in pancreatic degeneration within the endocrine portion with normal islets of Langerhans (Figures 3E & 4E).

Impact of GBJ and/or Met on lipid profile levels in DM rats

In the DM group, there were substantial increases in serum levels of T Chol, TG, LDLC, and VLDL along with a significant decline in HDLC, relative to the control rats ($p \leq 0.001$). After 8 weeks of treatment with Met, GBJ, and GBJ +Met, there were substantial decrease in the T Chol, TG, LDLC, and VLDL levels along with a substantial rise in HDLC level relative to the DM group ($p \leq 0.001$). The hypolipidemic effects of both Met and GBJ were similar, as indicated by the absence of statistically significant alterations in the serum levels of lipid profile markers between the Met and GBJ groups. Interestingly, treatment of DM with GBJ successfully augmented the lipid-lowering effect of Met, leading to a normalization of different lipid levels, there was no substantial change relative to the control rats (Table 2).

Impact of GBJ and/or Met on renal function in DM rats

The serum levels of Cr and BUN in STZ-induced DM group were significantly elevated relative to the control rats ($p \leq 0.001$). Following 8 weeks of treatment with Met, GBJ, and GBJ +Met, significant reductions in Cr and BUN levels were observed relative to the DM group ($p \leq 0.001$). Adding GBJ to Met induced a significant reduction in serum Cr and BUN levels relative to the group treated with Met alone and the group treated with GBJ alone ($p \leq 0.01$). Interestingly, treatment of DM with GBJ successfully augmented the renoprotective effect of Met, leading to a normalization of different kidney function

markers, there was no substantial change relative to the control rats (Table 3).

Impact of GBJ on renal histopathological changes in DM rats

The renal section of control rats showed normal renal glomeruli and tubules (Figures 5A & 6A). In DM rats' renal sections showing congestion of blood capillaries, a severe degree of tubular degenerative changes associated with the appearance of proteins within the lumen of the renal tubules (Figures 5B & 6B). In DM treated rats with Met, the renal section showed decreased renal degeneration with mild vacuolation of renal tubular epithelium. In contrast, the high power of the renal section showed normal renal parenchyma (Figures 5C & 6C). In DM treated rats with GBJ, the renal section showed eosinophilic degenerative changes within the renal tubular epithelium. In contrast, the high power of the renal section showed normal renal parenchyma with mild congestion of the renal blood capillaries (Figures 5D & 6D). In DM treated rats with GBJ + Met, the renal section showed a marked decline in tubular degenerative changes with a marked decrease in proteinous material within the lumen of the renal tubules. In contrast, the high power of the renal section showed normal renal parenchyma (Figures 5E & 6E).

Quantitative scoring of renal histopathological lesions demonstrated a significant raise in the DM group relative to the control group ($p \leq 0.001$). All the treated groups with Met, GBJ, and GBJ+ Met exhibited a significant decrease in renal histopathological lesion scores relative to the DM group ($p \leq 0.001$). Adding GBJ to Met induced a significant decline in renal histopathological lesions score relative to the DN treated with Met alone and the group treated with GBJ alone ($p \leq 0.05$ and $p \leq 0.01$, respectively). Interestingly, treatment of DM with GBJ successfully augmented the renoprotective effect of Met, leading to a normalization of renal histopathological lesions score, there was no significant change relative to the control rats (Fig. 7).

Impact of GBJ and/or Met on redox state concentrations in DM rats

Results in Table 3 demonstrate that DM induced significant oxidative stress in rats, as evidenced by a significant raise in serum MDA level and significant declines in CAT and GR activities ($p \leq 0.001$). However, treating DM rats with Met, GBJ, or GBJ + Met prevented DM-induced oxidative stress, as evidenced by the significant reduction in serum MDA level and the significant elevate in CAT and GR activities ($p \leq 0.001$) relative to the DM untreated rats. Adding GBJ to Met resulted in a significant reduction in serum MDA level and significant increases in CAT and GR activities relative to the group treated with Met alone and the group treated with GBJ alone ($p \leq 0.05$ and $p \leq 0.01$, respectively). Interestingly, treatment of DM with GBJ successfully augmented the effect of Met, leading to a normalization of redox state markers, there was no significant change relative to the control rats (Table 4).

Impact of GBJ and/or Met on serum advanced glycation end products (AGE) in DM rats

The AGE level in the serum of DM rats were significantly greater than those of control rats ($p \leq 0.001$). After 8 weeks of treatment with Met, GBJ, or GBJ + Met, the AGE in treated DM rats was statistically decreased relative to the DM untreated rats ($p \leq 0.001$). Adding GBJ to Met resulted in a significant decline in AGE levels relative to the group treated with Met alone and the group treated with GBJ alone ($p \leq 0.05$ and $p \leq 0.01$, respectively). Interestingly, treatment of DM with GBJ successfully augmented the reduction of AGE effect of Met, leading to a normalization of serum AGE, there was no significant change relative to the control rats (Fig. 8).

Discussion

The STZ is a well-established method for inducing hyperglycemia in animal models, mimicking key features of Type 1 DM [26]. It exerts its diabetogenic effect by triggering an autoimmune-like response leading to selective destroying of pancreatic β-cells. This induced loss of insulin secretory capacity and degranulation of pre-existing insulin stores, ultimately driving hyperglycemia [27]. In our study, STZ injection in rats was a reliable approach to establishing a diabetic model. We observed a significant increase in glucose levels following STZ administration. Notably, the GBJ and Met treatment successfully reversed hyperglycemia but did not restore blood glucose levels to the normoglycemic range. The antihyperglycemic effect observed with GBJ was inferior to that of Met, the standard drug. In contrast, supplementing Met with GBJ augmented Met's glucose-lowering effect, leading to a normalization of glucose levels (control group level). Previous studies have reported similar findings, where treatment with the ethanolic extract ethyl acetate subfraction resulted in decreased glucose levels and even normalization in DM treated rats [28].

The ingestion of GB positively mitigates hypercholesterolemia induced by a high-cholesterol diet [29]. The present study's findings demonstrated a cholesterol-lowering effect of GBJ in diabetic rats. Results from both human and animal investigations highlighted the anti-inflammatory properties of phytosterols, alongside their established role in reducing cholesterol. The treatment with GBJ not only lowered serum glucose in diabetic animals but also improved the health of key organs. Microscopic examination (histopathology) revealed that pancreatic and kidney tissues showed signs of improvement after treatment. Uncontrolled DM, both type 1 and type 2, can severely destroy the kidneys,

leading to end-stage renal disease in a worrying 30% of diabetics. This complication starts with high blood sugar (hyperglycemia) directly harming the kidneys, causing them to malfunction and structurally change [30]. The current study using STZ-DM rats demonstrates that sustained hyperglycemia and elevated levels of BUN and creatinine promote the progression of DM renal disease. This association is clinically mirrored by the observation that increased blood urea levels coinciding with hyperglycemia serve as an indicator of kidney damage in diabetic patients [31]. The findings of this study align with previous experimental data demonstrating elevated BUN and serum creatinine levels in diabetic rat models, which are recognized indicators of progressive kidney damage [28, 32]. Besides, a previous study indicates that the ethyl acetate fraction from GB protects against cisplatin-induced kidney damage by improving kidney tissue structure (histology) [33]. Dietary supplementation with GB fruit or peels at 5% and 10% concentrations led to a significant reduction in serum levels of uric acid, creatinine, and urea relative to the DM group [34].

Different signalling pathways inside the kidney get thrown off balance, contributing to key features of diabetic nephropathy like oxidative stress and inflammation [30]. Our study findings indicate that administering GBJ induced a notable decline in MDA levels and a rise in CAT and GR levels relative to diabetic rats. Prior research has linked the renoprotective effect of GB to the extract's antioxidant and antifibrotic properties [35]. GB exhibits an exceptionally high antioxidant capacity [36]. The nephroprotective efficacy of GB stems from its ability to scavenge free radicals. This leads to an enhancement in the antioxidant defense system and a reduction in the kidney's vulnerability to oxidative stress [34, 37]. The ascorbic acid content in GBJ (46 mg/100 g) surpassed that found in most fruit juices such as pear, apple, and peach [38]. The presence of phenolic compounds in GBJ holds significant promise for preventing or treating DM complications. GBJ exhibited high levels of total phenolics, with a full phenolic content of 6.3 mg, which is equivalent to caffeic acid per 100 g of juice [39]. Phenolic compounds kaempferol, quercetin, and myricetin were identified in GBJ [40]. These phytochemicals have been noted for their antioxidant properties, which aid in preventing oxidative damage [41].

AGEs are molecules with the potential to pose a hazard to human health via their toxicity [42]. AGE is formed when reducing sugars spontaneously react with the amino groups of proteins. This non-enzymatic process, which is accelerated in diabetes, contributes significantly to the development of kidney complications related with DM disease [43, 44]. High blood sugar levels observed in conditions like DM and cellular stress from oxidative damage both significantly contribute to the development of AGE [45]. The primary processes that impede AGE development include reducing active dicarbonyl compounds, inhibiting the development of ROS, preserving protein structure, and facilitating AGE degradation [42]. Ne-(carboxymethyl) lysine (CML), a molecule belonging to the harmful AGE family, has been linked to increased cholesterol accumulation in the kidneys of individuals with type 2 DM. This suggests that AGE may play a role in developing diabetic nephropathy by interfering with the internal mechanisms that regulate cholesterol levels within cells [46]. Preventing the accumulation of lipids triggered by AGE could offer a kidney-protective strategy against the progression of diabetic nephropathy [46]. This study uniquely demonstrates, for the first time, that GBJ can effectively reduce levels of AGE in the STZ-induced DM rats. This finding suggests that preventing the formation of AGE by GBJ could hold promise as a strategy to protect the kidneys from the progression of diabetic nephropathy. Laboratory studies utilizing simulated glycation reactions, known as "*in vitro* glycation assays," have demonstrated that polyphenol compounds like caffeic acid, catechin, and anthocyanins can hinder the formation of harmful AGE and offer protection against their damaging effects [47, 48]. Combining GBJ with the drug Met significantly improved its ability to lower blood glucose and AGE. This promising finding warrants further clinical studies to confirm its potential in reducing diabetic complications, offering hope for improved patient outcomes.

Conclusion

The current study suggested that GBJ might protect against diabetic kidney damage by reducing oxidative stress and AGE. Additionally, combining GBJ with the common diabetes medication Met appeared to increase its protective effect against kidney damage. These findings highlight the potential of GBJ as a natural product, potentially useful alongside traditional medications, for managing DM and its complications. However, further clinical studies are crucial to confirm these promising results.

Conflicts of interest

Authors declared no conflict of interests.

Funding statement

No funds.

Fig. 1. Golden berry (GB) (*Physalis peruviana* L.) ripe fruits [19].

TABLE 1. Impact of GBJ and/or Met on mortality in DM rats.

Experimental groups	Number of animals At zero time	Number of animals and (% mortality) 8 weeks after DM induction
Control	7	6 (14.29%)
DM	11	6 (24.45%)
DM+ Met	11	9 (18.18%)
DM+ GBJ	11	7 (36.36%)
DM+ GBJ + Met	10	9 (10%)

TABLE 2. Impact of GBJ and/or Met on lipid profile levels in DM rats.

Experimental groups	T Chol (mg/dl)	TG (mg/dl)	HDLC (mg/dl)	LDLC (mg/dl)	VLDLC (mg/dl)
Control	86.78 ± 5.09	111.05 ± 9.94	56.38 ± 6.79	8.20 ± 2.34	22.21 ± 1.99
DM	121.95 ± 10.79 $^{a\#}$	172.50±10.43$^{a\#}$	32.30 ± 4.27$^{a\#}$	55.15 ± 9.79$^{a\#}$	34.50 ± 2.09$^{a\#}$
DM+ Met	100.02 ± 6.17 $^{a\^{}, b\#}$	130.13 ± 10.08 $^{a\^{}, b}$	47.41 ± 2.56$^{a\^{}, b\#}$	26.58 ± 2.78$^{a\#, b}$	26.03 ± 2.02$^{a\^{}, b}$
DM+ GBJ	97.80 ± 6.30 $^{a\^{}, b\#}$	128.42 ± 9.82 $^{a\^{}, b\#}$	48.18 ± 4.94$^{a\^{}, b\#}$	23.94 ± 4.79$^{a\#, b}$	25.68 ± 1.96$^{a\^{}, b}$
DM+ GBJ + Met	86.92 ± 2.79 $^{b\#,c\^{},d*}$	112.30 ± 10.13$^{b\#, c\^{},}$	55.46 ± 4.45$^{b\#, c\^{}, d}$	9.04 ± 2.19$^{b\# c\#, c}$	22.46 ± 2.03$^{b\#, c\^{},}$

Values are the mean ± SD (n = 6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{*}p \leq 0.05$, $^{\^{}}p \leq 0.01$, $^{\#}p \leq 0.001$).

TABLE 3. Impact of GBJ and/or Met on renal function in DM rats.

Experimental groups	Cr (mg/dl)	BUN (mg/dl)
Control	0.21 ± 0.03	47.73 ± 6.92
DM	0.60 ± 0.11$^{a\#}$	78.54± 5.40$^{a\#}$
DM+ Met	0.35 ± 0.03$^{a\#, b\#}$	59.65±2.88$^{a\#, b\#}$
DM+ GBJ	0.47 ± 0.03$^{a\#,b\#,c\^{}}$	67.97 ± 4.79$^{a\#, b\#, c\^{}}$
DM+ GBJ + Met	0.22 ± 0.02$^{b\#, c\#, d\#}$	44.07 ± 3.08$^{b\#, c\#, d\#}$

Values are the mean ± SD (n = 6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{\^{}}p \leq 0.01$, $^{\#}p \leq 0.001$).

TABLE 4. Impact of GBJ and/or Met on redox state concentrations in DM rats.

Experimental groups	MDA (nmol/mL)	CAT (U/L)	GR (U/L)
Control	91.68 ± 8.49	6.60 ± 0.40	68.33 ± 8.07
DM	390.45 ± 49.82$^{a\#}$	2.85± 0.34$^{a\#}$	33.67 ± 3.98$^{a\#}$
DM+ Met	159.40 ± 13.24$^{a\#, b\#}$	5.29 ± 0.69$^{a\#, b\#}$	56.68 ± 2.73$^{a\#, b\#}$
DM+ GBJ	149.03 ± 8.76$^{a\#, b\#}$	5.60 ± 0.54$^{a\#, b\#}$	58.67 ± 3.08$^{a\#, b\#}$
DM+ GBJ + Met	119.67 ± 9.11$^{b\#, c\^{}, d*}$	6.24 ± 0.41$^{b\#, c\^{}, d*}$	66.66 ± 5.43$^{b\#, c\^{}, d*}$

Values are the mean ± SD (n = 6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{*}p \leq 0.05$, $^{\^{}}p \leq 0.01$, $^{\#}p \leq 0.001$).

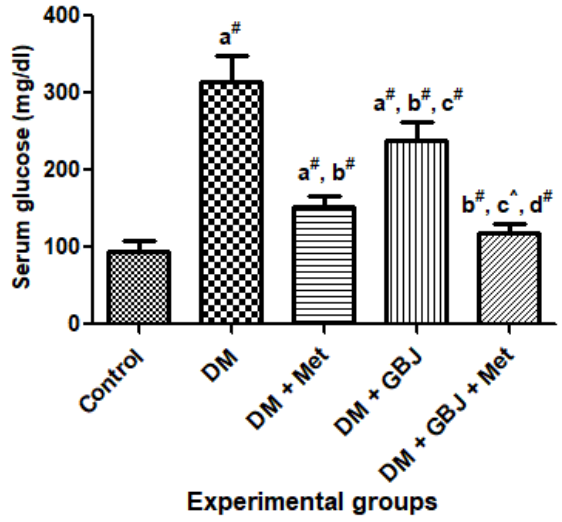

Fig. 2. Impact of GBJ and/or Met on serum glucose level in DM rats.

Values are the mean ± SD (n=6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{\wedge}p \leq 0.01$, $^{\#}p \leq 0.001$).

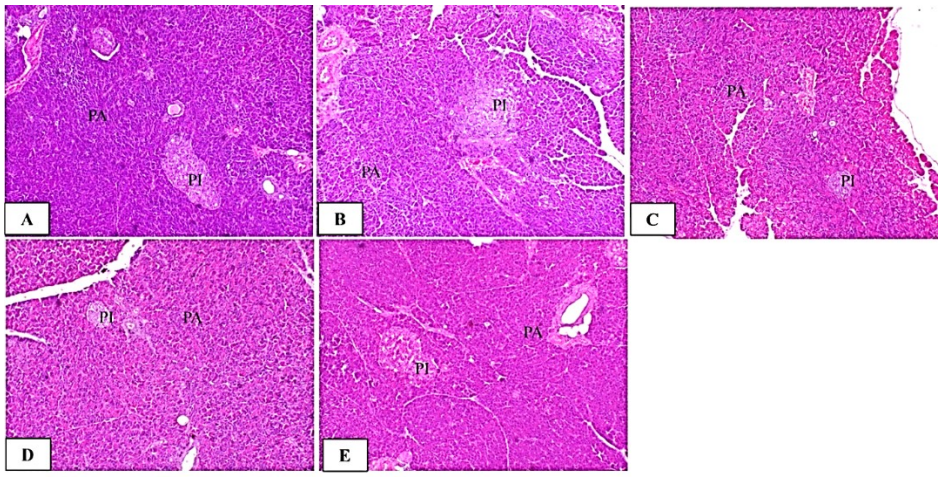

Fig. 3. Impact of GBJ on pancreatic histopathological changes in STZ- induced diabetic rats (Bar = 200 µm, H&E staining).

PA: Pancreatic acini. β islets of Langerhans (PI). The pancreatic section of control rats showed normal PA and normal β islets of Langerhans (PI) **(Photo A)**. In DM rats, the pancreatic section shows PI necrosis and PA degeneration **(Photo B)**. In DM rats treated with Met, the pancreatic section showed a noticeable decrease in pancreatic degeneration within the endocrine portion (PI) with normal PA **(Photo C)**. In DM rats treated with GBJ, the pancreatic section showed a remarkable decrease in pancreatic degeneration within the endocrine portion (PI) and normal PA **(Photo D)**. In DM rats treated with GBJ+ Met, the pancreatic section showed a marked decrease in pancreatic degeneration within the endocrine portion (white arrows) **(Photo E)**.

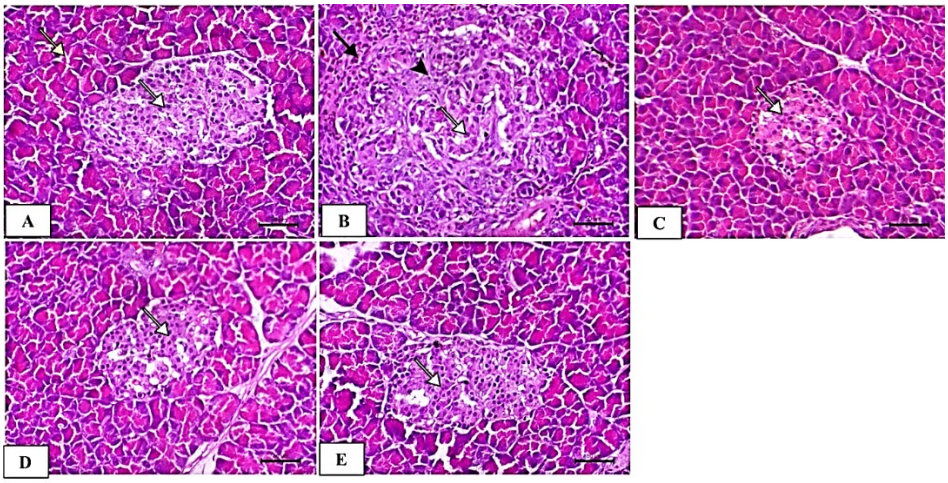

Fig. 4. Impact of GBJ on pancreatic histopathological changes in STZ- induced diabetic rats (Bar = 50 µm, H&E staining).

Pancreas of control rats showing the normal pancreatic acini lined with normal acinar cells filled with zymogen granules (yellow arrow) and normal β islets of Langerhans (white arrow) **(Photo A)**. In DM rats' pancreatic section showing severe necrosis of β islets of Langerhans (white arrow) associated with marked fibroblastic cell proliferation (black arrowhead) and marked inflammatory cells consisting of eosinophils, lymphocytes, and macrophages (black arrow) **(Photo B)**. In DM rats treated with Met, the pancreatic section showed a noticeable decrease in pancreatic degeneration within the endocrine portion (white arrow), with normal pancreatic acini **(Photo C)**. In DM rats treated with GBJ, the pancreatic section showed a remarkable decrease in the pancreatic degeneration of the exocrine glandular acini or the endocrine portion (white arrow) **(Photo D)**. In DM rats treated with GBJ + Met, the pancreatic section showed a marked decrease in pancreatic degeneration within the endocrine portion with normal islets of Langerhans (white arrow) **(Photo E)**.

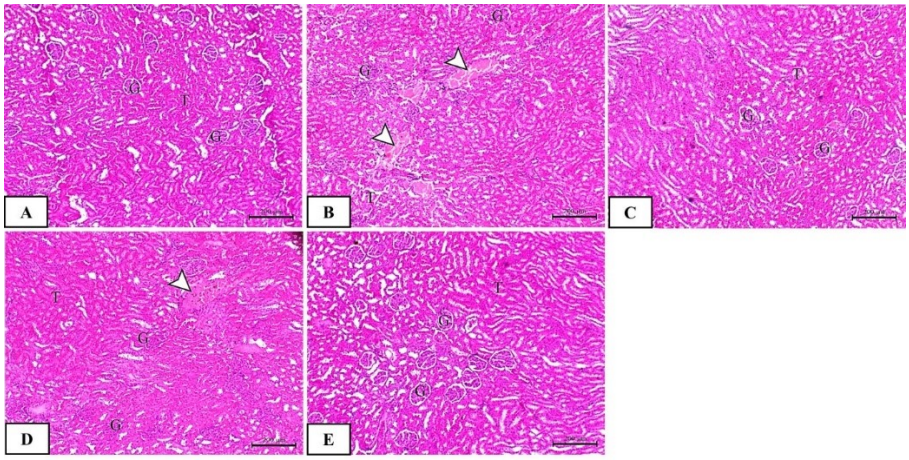

Fig. 5. Impact of GBJ on renal histopathological changes in STZ-induced diabetic rats (Bar = 200 µm, H&E staining).

G: renal glomeruli and T: renal tubules. The renal section of control rats showed normal renal glomeruli and tubules **(Photo A)**. In DM rats' the renal section showed tubular degenerative changes and congestion of the renal blood capillaries (white arrowheads) **(Photo B)**. In DM rats treated with Met, renal section showed normal renal parenchyma **(Photo C)**. In DM rats treated with GBJ, the renal section showed normal renal parenchyma with mild congestion of the renal blood capillaries (arrowhead) **(Photo D)**. The renal section showed normal renal parenchyma in DM rats treated with GBJ+ Met **(Photo E)**.

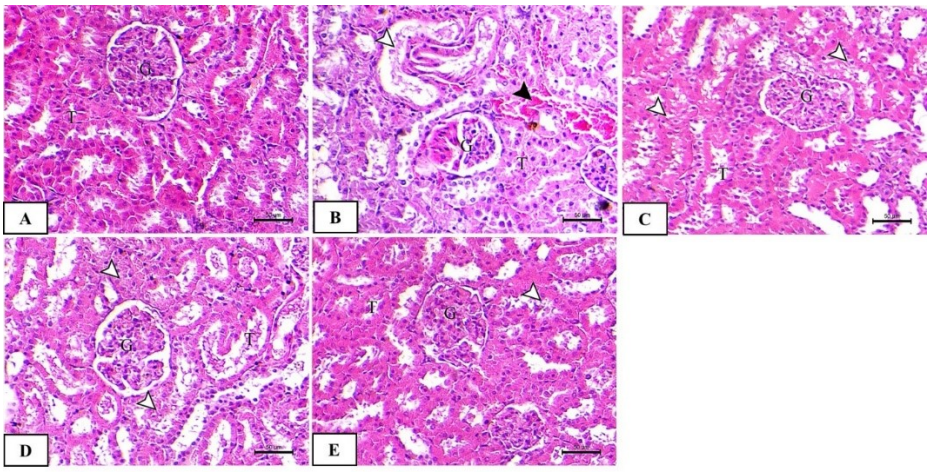

Fig. 6. Impact of GBJ on renal histopathological changes in STZ-induced diabetic rats (Bar = 50 µm, H&E staining).

G: renal glomeruli and T: renal tubules. The renal section of control rats showed normal renal glomeruli and tubules **(Photo A)**. In DM rats' the renal section showed congestion of blood capillaries (black arrowhead) and a severe degree of tubular degenerative changes associated with the presence of proteins within the lumen of the renal tubules (white arrowhead) **(Photo B)**. In DM rats treated with Met, the renal section showed decreased renal degenerative with mild vacuolation of the renal tubular epithelium (arrowheads) **(Photo C)**. In DM rats treated with GBJ, the renal section showed eosinophilic degenerative changes within the renal tubular epithelium (arrowheads) **(Photo D)**. In DM rats treated with GBJ + Met, the renal section showed a marked decline in tubular degenerative changes with a noticeable decline in proteinous material within the lumen of the renal tubules (arrowhead) **(Photo E)**.

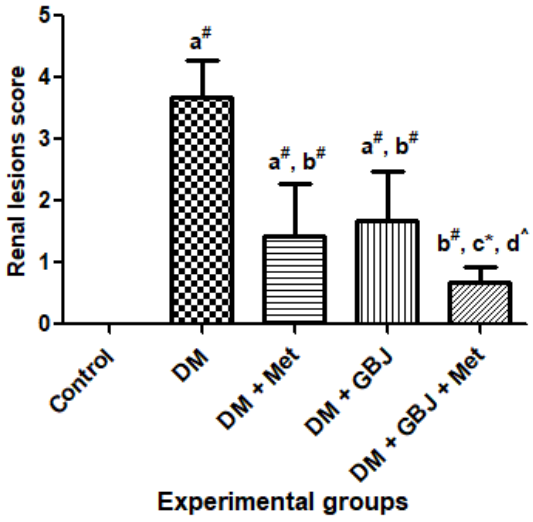

Fig. 7. Scores of renal histopathological lesions.

Values are the mean ± SD (n = 6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{*}p\leq0.05$, $^{\wedge}p\leq0.01$, $^{\#}p\leq0.001$).

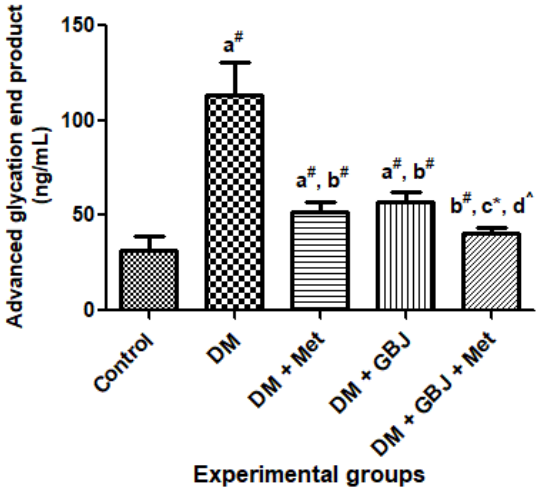

Fig. 8. Impact of GBJ and/or Met on serum advanced glycation end product in DM rats.

Values are the mean ± SD (n = 6). [a] Significant DM relative to control. [b] Significant relative to DM. [c] Significant relative to DM+ Met. [d] Significant relative to DM+ GBJ. ($^{*}p \leq 0.05$, $^{\wedge}p \leq 0.01$, $^{\#}p \leq 0.001$).

References

1. Whiting, D.R., Guariguata, L., Weil, C. and Shaw, J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res. Clin. Pract.*, **94**(3), 311–321(2011).
2. Cho, N.H., Shaw, J.E., Karuranga, S., Huang, Y., da Rocha Fernandes, J.D., Ohlrogge, A.W. and Malanda, B. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.,* **138**, 271–281 (2018).
3. Caturano, A., D'Angelo, M., Mormone, A., Russo, V., Mollica, M. P., Salvatore, T., Galiero, R., Rinaldi, L., Vetrano, E., Marfella, R., Monda, M., Giordano, A. and Sasso, F. C. Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications. *Current Issues in Molecular Biology,* **45**(8), 6651–6666 (2023).
4. Erman, F., Kaya, T., Aydin, S., Erman, O. and Yilmaz, O. The protective effects of goldenberry (*Physalis peruviana* L.) extract against the oxidative and destructive effects of type I diabetes in rats. *Fresenius Envir. Bulletin*, **29**(5), 3344–3353 (2020).
5. Indyk, D., Bronowicka-Szydełko, A., Gamian, A. and Kuzan, A. Advanced glycation end products and their receptors in serum of patients with type 2 diabetes. *Sci. Rep.*, **11**(1),13264(2021).
6. Khalid, M., Petroianu, G. and Adem, A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. *Biomolecules,* **12**(4),542 (2022).
7. Wu, T., Ding, L., Andoh, V., Zhang, J. and Chen, L. The Mechanism of Hyperglycemia-Induced Renal Cell Injury in Diabetic Nephropathy Disease: An Update. *Life (Basel, Switzerland),* **13**(2), 539 (2023).
8. Alam, S., Sarker, M. M. R., Sultana, T. N., Chowdhury, M. N. R., Rashid, M. A., Chaity, N. I., Zhao, C., Xiao, J., Hafez, E. E., Khan, S. A. and Mohamed, I. N. Antidiabetic phytochemicals from medicinal Plants: Prospective Candidates for New Drug Discovery and Development. *Frontiers in Endocrinology,* **13**, 800714 (2022).
9. Erman, F., Kirecci, O.A., Ozsahin, A.D., Erman, O., Kaya, T. and Yilmaz, O. Effects of *Physalis peruviana* and *Lupinus albus* on malondialdehyde, glutathione, cholesterol, vitamins and fatty acid levels in kidney and liver tissues of diabetic rats. *Prog. Nutri.*, **20**(Suppl1), 218–230 (2018).
10. Singh, N., Singh, S., Maurya, P., Arya, M., Khan, F., Dwivedi, D.H. and Saraf, S.A. An updated review on Physalis peruviana fruit: Cultivational, nutraceutical and pharmaceutical aspects. *Indian J Natural Products Resources*, **10**(2), 97–110 (2019).
11. Xu, Y., Wijeratne, E., Babyak, A., Marks, H., Brooks, A., Tewary, P., Xuan, L., Wang, W., Sayers, T. and Gunatilaka, A.A.L. Withanolides from aeropXuonically grown *Physalis peruviana* and their selective cytotoxicity to prostate cancer and renal carcinoma cells. *J. Na.t Prod.*, **80** (7), 1981–1991(2017).
12. Etzbach, L., Pfeiffer, A. and Schieber, A. Characterization of carotenoid profiles in goldenberry (*Physalis peruviana* L.) fruits at various ripening stages and in different plant tissues by HPLC-DAD-APCI-MSn. *Food Chem*, **245**, 508–517(2018).
13. Areiza-Mazo, N., Robles, J., Zamudio-Rodriguez, J.A., Giraldez, L., Echeverria, V., Barrera-Bailon, B., Aliev, G., Sahebkar, A., Ashraf, G.M. and Barreto, G.E. Extracts of *Physalis peruviana* protect astrocytic cells under oxidative stress with rotenone. *Front. Chem.*, **6**, 276(2018).

14. Sathyadevi, M., Suchithra, E.R. and Subramanian, S. *Physalis peruviana* Linn. fruit extract improves insulin sensitivity and ameliorates hyperglycemia in high-fat diet low dose STZ induced type 2 diabetic rats, *J. Pharm. Res.*, **8**(4), 625-632 (2014).

15. Kinasih, L.S., Djamiatun, K. and Al-Baarri, A.N. Golden berry (*Physalis peruviana*) juice for reduction of blood glucose and ameliorate of insulin resistance in diabetes rats. *J. Gizi. Pangan.*, **15**(1),37-44(2020).

16. Peng, C., You, B., Lee, C., Wu, Y., Lin, W., Lu, T. Chang, F. and Lee, H.Z. The roles of 4β-Hydroxywithanolide E from *Physalis peruviana* on the Nrf2-antioxidant system and the cell cycle in breast cancer cells. *Am. J. Chin. Med.*, **44** (3),617–636 (2016).

17. Park, E., Sang-Ngern, M., Chang, L. and Pezzuto, J.M. Physalactone and 4β- Hydroxywithanolide E isolated from Physalis peruviana inhibit LPS-induced expression of COX-2 and iNOS accompanied by abatement of Akt and STAT1. *J. Nat. Prod.*, **82**(3), 492–499(2019).

18. Hameed, A., Galli, M., Adamska-Patruno, E., Krętowski, A. and Ciborowski, M. Select Polyphenol-Rich Berry Consumption to Defer or Deter Diabetes and Diabetes-Related Complications. *Nutrients,* **12**(9), 2538 (2020).

19. Bayas-Morejon, A., Tigre-Leon, A., Tapia-Verdezoto, M. and Flores-Ribadeneira, F. Antibacterial activity of golden berry (*Physalis peruviana*) extract against *escherichia coli*spp. Isolates from meats in Ecuador. *Int. J. Curr. Pharm. Res.*, **12**(2), 115-118 (2020).

20. Shahein, M.R., Atwaa, E.H., Radwan, H.A., Elmeligy, A.A., Hafiz, A.A, Albrakati, A. and Elmahallawy, E.K. Production of a yogurt drink enriched with golden berry (*Physalis pubescens* l.) juice and its therapeutic effect on hepatitis in rats. *Fermentation*, **8**, 112(2022).

21. Furman B. L. Streptozotocin-Induced Diabetic Models in Mice and Rats. *Current protocols,* **1**(4), e78 (2021).

22. Derkach, K., Zakharova, I., Zorina, I., Bakhtyukov, A., Romanova, I., Bayunova, L. and Shpakov, A. The evidence of metabolic-improving effect of metformin in Ay/a mice with genetically induced melanocortin obesity and the contribution of hypothalamic mechanisms to this effect. *PLoS ONE*, **14**(3), e0213779 (2019).

23. Cavani, F., Ferretti, M., Smargiassi, A. and Palumbo, C. PTH (1-34) effects on repairing experimentally drilled holes in rat femur: novel aspects - qualitative vs. quantitative improvement of osteogenesis. *Journal of Anatomy,* **230**(1), 75–84 (2017).

24. Feldman, A. T. and Wolfe, D. Tissue processing and hematoxylin and eosin staining. *Methods in Molecular Biology (Clifton, N.J.),* **1180**, 31–43 (2014).

25. Antar, S.A., Abdo, W., Taha, R.S., Farage, A.E., El-Moselhy, L.E., Amer, M.E., Abdel Monsef, A.S., Abdel Hamid, A.M., Kamel, E.M., Ahmeda, A.F. and Mahmoud, A.M. Telmisartan attenuates diabetic nephropathy by mitigating oxidative stress and inflammation, and upregulating Nrf2/HO-1 signaling in diabetic rats. *Life Sci.,* **291**,120260 (2022).

26. Wu, J. and Yan, L. Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity. *Diabetes Metab. Syndr. Obes.,* **8**, 181–188(2015).

27. Lenzen, S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*, **51**(2), 216–226(2008).

28. Ezzat, S. M., Abdallah, H.M.I., Yassen, N.N., Radwan, R.A., Mostafa, E.S., Salama, M.M. and Salem, M.A. Phenolics from *Physalis peruviana* fruits ameliorate streptozotocin-induced diabetes and diabetic nephropathy in rats *via* induction of autophagy and apoptosis regression. *Biomedicine Pharmacother*, **142**,111948 (2021).

29. Ramadan, M. F. *Physalis peruviana* pomace suppresses high-cholesterol diet-induced hypercholesterolemia in rats. *Grasas y Aceites*, **63**(4), 411–422(2012).

30. Jin, Q., Liu, T., Qiao, Y., Liu, D., Yang, L., Mao, H., Ma, F., Wang, Y., Peng, L. and Zhan, Y. Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. *Frontiers in Immunology,* **14**, 1185317 (2023).

31. Ullah, W., Nazir, A., Israr, H., Hussain, S. and Farooq, M. Assessment of Serum Urea and Creatinine Levels in Diabetic Patients History: Assessment of Serum Urea and Creatinine Levels in Diabetic Patients. *BioScientific Review,* **5**(3), (2023).

32. Wu, X., Huang, Y., Zhang, Y., He, C., Zhao, Y., Wang, L. and Gao, J. Efficacy of tripterygium glycosides combined with ARB on diabetic nephropathy: a meta-analysis. *Bioscience reports,* **40**(11), BSR20202391. (2020).

33. Ahmed, L. Renoprotective effect of Egyptian cape gooseberry fruit (*Physalis peruviana* L.) against acute renal injury in rats. *Scientific World J.*, **2014**, 273870 (2014).

34. Zakaria, R., Abelbaky, M. S. and Abo-Raya, A. O. Effect of golden berry (*Physalis peruviana*) fruits and its peels on acute hepatotoxicity with diabetic rats. *Egypt. J. Appl. Sci.,* **35**(11),158–171(2020).

35. El-Gengaihi, S. E., Hamed, M.A., Khalaf-Allah, A.M. and Mohammed, M.A. Golden berry juice attenuates the severity of hepatorenal injury. *J. Diet. Suppl.*, **10**(4), 357–369(2013).

36. Guiné, R. P. F., Gonçalves, F.J.A., Oliveira, S.F. and Correia, P.M.R. Evaluation of phenolic compounds, antioxidant activity and bioaccessibility in *Physalis peruviana* L. *Inter. J. Fruit Sci.*, **20**(S2), S470–S490 (2020).

37. Abdel Moneim, A. E. and El-Deib, K. M. The possible protective effects of *Physalis peruviana* on

carbon tetrachloride-induced nephrotoxicity in male albino rats. *Life Sci. J.*, **9**(3),1038–1052(2012).

38. Belitz, H. D. and Grosch, W. *Food Chemistry.* Springer-Verlag, Berlin, pp. 84–189(1999).
39. Ramadan, M. F. Enzymes in Fruit Juice Processing. *Enzymes in Food Biotechnology: Production, Applications, and Future Prospects*, pp. 45–59 (2019).
40. Häkkinen, S. H., Kärenlampi, S.O., Heinonen, I.M., Mykkänen, H.M. and Törronen, A.R. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *J. Agri. Food Chem.*, **47**(6), 2274–2279(1999).
41. Wang, I. K., Lin-Shiau, S. Y. and Lin, J. K. Induction of apoptosis by apigenin and related flavonoids through cytochrome c release and activation of caspase-9 and caspase-3 in leukaemia HL-60 cells. *Eur. J. Cancer,* **35**(10),1517–1525 (1999).
42. Song, Q., Liu, J., Dong, L., Wang, X. and Zhang, X. Novel advances in inhibiting advanced glycation end product formation using natural compounds. *Biomed. Pharmacother.,* **140,** 111750 (2021).
43. Khalid, M., Petroianu, G. and Adem, A. Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. *Biomolecules,* **12**(4), 542 (2022).
44. Mengstie, M.A., Chekol Abebe, E., Behaile Teklemariam, A., Tilahun Mulu, A., Agidew, M. M., Teshome Azezew, M., Zewde, E. A. and Agegnehu Teshome, A. Endogenous advanced glycation end products in the pathogenesis of chronic diabetic complications. *Frontiers in molecular biosciences,* **9**, 1002710 (2022).
45. Dozio, E., Caldiroli, L., Molinari, P., Castellano, G., Delfrate, N.W., Romanelli, M.M.C. and Vettoretti, S. Accelerated AGEing: The Impact of Advanced Glycation End Products on the Prognosis of Chronic Kidney Disease. *Antioxidants,* **12**, 584 (2023).
46. Yuan, Y., Sun, H. and Sun, Z. Advanced glycation end products (AGEs) increase renal lipid accumulation: A pathogenic factor of diabetic nephropathy (DN). *Lipids in Health and Dis.,* **16**(1), 1–9(2017).
47. Cao, X., Xia, Y., Zeng, M., Wang, W., He, Y. and Liu, J. Caffeic acid inhibits the formation of advanced glycation end products (AGEs) and mitigates the AGEs- induced oxidative stress and inflammation reaction in human umbilical vein endothelial cells (HUVECs). *Chem. Biodivers,* **16** (10), e1900174 (2019).
48. Wu, Q., Tang, S., Zhang, L., Xiao, J., Luo, Q. and Chen, Y. The inhibitory effect of the catechin structure on advanced glycation end product formation in alcoholic media. *Food Function,* **11**(6),5396–5408(2020).

التأثيرات الوقائية لعصير التوت الذهبي لحماية الكلى في الجرذان المصابة بالسكري

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المستخلص:

هدفت هذه الدراسة الي تقييم خصائص عصير الحرنكش الطازج في وقاية الكلي في الجرذان المصابة بداء السكري من النوع الأول الناجم عن الاستربتوزوتوسين. تم تقسيم ثلاثين من الجرذان الذكور إلى مجموعتين: المجموعة الضابطة (عددهم = 6) ومجموعة السكري (عددهم = 24). تم بعد ذلك تقسيم الجرذان المصابة بداء السكري إلى أربع مجموعات (6 جرد لكل مجموعة) كالتالي: مجموعة السكري غير المعالجة، مجموعة السكري المعالجة بعقار الميتافورمين (ميتا)، مجموعة السكري المعالجة بعصير الحرنكش، ومجموعة السكري المعالجة بالميتا وعصير الحرنكش. واستمرت مدة العلاج لمدة ثمانية أسابيع. أظهرت النتائج أن عصير الحرنكش أحدث انخفاضاً في مستويات الجلوكوز في الدم، تحسناً في أنسجة الغدد الصماء وغير الصماء في البنكرياس، وتحسناً في دلائل الدهون في الدم. أحدث عصير الحرنكش تحسناً في مقاييس الكلى (نيتروجين اليوريا في الدم والكرياتينين)، وتخفيف الخصائص المرضية لتلف الكلى الناجم عن الاستربتوزوتوسين. واوضح التحليل الكيميائي الحيوي أيضًا أن عصير الحرتكش أحدث انخفاضاً في مستويات الإجهاد التأكسدي، كما يتضح من انخفاض مستويات المالونديالدهيد، وتعزيز نشاط الإنزيمات المضادة للأكسدة (الكتاليز والجلوتاثيون المختزل) مقارنة بمجموعة السكري غير المعالجة. بالإضافة إلى ذلك، أحدث عصير الحرنكش تحسناً في مستويات المنتجات النهائية لتسكر بروتينات الدم المتقدمة. وعزز عصير الحرنكش بدرجة معنوية تأثيرات عقار الميتا. تشير النتائج إلى أن عصير الحرنكش يمكن أن يقي من تلف الكلى الناجم عن الاستربتوزوتوسين من خلال خصائصه المضادة للأكسدة، الخافضة لسكر الدم، والخافضة لارتفاع الدهون. بالإضافة إلى ذلك، يثبط عصير الحرنكش المنتجات النهائية لتسكر بروتينات الدم المتقدمة مما يساهم في تأثيره الوقائي للكلي.

الكلمات الدالة: المنتجات النهائية لتسكربروتينات الدم المتقدمة، السكري، الحرنكش، الكلي، الاجهاد التاكسدي.