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RESEARCH ARTICLE

Ameliorative Effect of Quercetin on Streptozotocin Induced Model Diabetic Kidney Disease

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ABSTRACT

Diabetes mellitus is a serious metabolic disease. Diabetic nephropathy (DN) is a common consequence of diabetes. Quercetin, in particular, has been extensively examined and shown to have positive therapeutic effects on various human diseases, including diabetes. It has significant anti-diabetic benefits, such as lowered blood sugar levels and enhanced insulin sensitivity. It can also prevent and improve nephropathy one of the diabetes complications. This study aims to inspect the prophylactic effect of Quercetin in struggling DN following T1DM development in rats. T1DM was generated in the experimental rats by delivering a single high dose of STZ (65 mg/kg.bw) intraperitoneally, followed by ten weeks of Quercetin therapy. Serum of Diabetic rats showed high levels of urea, creatinine, Na, and K, indicating microvascular issues. Oxidative stress was clearly present, along with an increased inflammatory response. Diabetic rats' kidney tissue showed a significant rise in TNF-α, TGB, and amount of IL-1β. Renal morphological changes were found in all groups following the introduction of T1DM, quercetin significantly improved. Biochemical markers like fasting blood glucose (FBG), insulin, urea, and creatinine can reduce the incidence of TNF-α, IL-6, and TGB. Quercetin professionally protects the kidney and reduces injury of renal tissue via lowering free radical damage and reestablishing glucose homeostasis, suggesting a possible line of therapy for T1DM nephropathy.

***Keywords*:** STZ-induced diabetes; Quercetin; Kidney; Quercetin antioxidant properties

Introduction

A Metabolic syndrome, known as diabetes mellitus, is characterized by increased glucose levels, hyperlipidemia, oxidative damage, and often decreased insulin levels [1]. It affects millions worldwide and is among the top ten causes of death [2]. Type I diabetes is an autoimmune disease marked by immune-mediated damage to the pancreatic beta cells. The resulting insulin deficiency leads to hyperglycemia [3]. Epidemiological studies indicate that childhood obesity, dietary habits, viral infections, and various environmental factors contribute to the development of type 1 diabetes. Reactive oxygen species (ROS) are generated in diabetic patients through glucose auto-oxidation, protein glycosylation, and polyol processes, leading to oxidative stress and β-cell dysfunction [4]. Diabetic kidney disease (DKD) is a major contributor to end-stage renal disease, and due to its complex development and the limited effectiveness of current treatments, it is crucial to delve deeper into the underlying causes [5]. Diabetes mellitus often results in both macrovascular and microvascular complications over time. DKD affects

about one-third of people with diabetes and is essential in the progression to end-stage renal disease (ESRD) [6]. The fundamental causes of diabetic nephropathy (DN) are complex. Research indicates that glucometabolic disturbances, abnormal hemodynamics, and oxidative stress are primary factors involved in DN development [7]. Quercetin (3,3′,4′,5,7-pentahydroxyflavone), a dietary flavonoid and polyphenol found in high amounts in various fruits and vegetables, including capers, figs, cranberries, red onions, radish leaves, asparagus, broccoli, walnuts, and coriander, has the potential to prevent and alleviate diabetic complications such as nephropathy, cardiovascular issues, and neuropathy [8]. It has the potential to avoid and ameliorate diabetic complications such as nephropathy, cardiovascular complications, and neuropathy [9]. It has been suggested that quercetin (QU) is a therapeutic flavonoid that may be used to treat metabolic diseases like diabetes, cancer, and cardiovascular disease [10]. Prior research has demonstrated that the antioxidant and anti-diabetic effect of QU contribute to normal blood glucose levels [11]. Quercetin's antioxidant activity is shown primarily through a variety of methods, involving increased glutathione (GSH) levels, boosted antioxidant signaling pathways, and minimizing oxidative damage brought on by reactive oxygen species (ROS) [7]. Similarly, QU reduces blood glucose by raising insulin secretion, dropping hepatic glucose synthesis, and modifying the function of GLUT4 and insulin receptors [12]. Quercetin is associated with DN modification in mouse models; nonetheless, its protective mechanism remains uncertain [5]. Quercetin may have an antiferroptotic impact on acute kidney injury (AKI) and has the capacity to chelate iron [12]. Quercetin inhibits oxidative stress by controlling the expression of TGF-β1 [13].

Material and Methods

Chemicals

Streptozotocin (STZ) was obtained from Sigma Aldrich, USA. Citrate buffer was obtained from El Gomhorya for drugs trade & medical supplies. Sucrose acquired from El Gomhorya for drugs trade & Medical. Quercetin with purity(95%) supplied by Sigma–Aldrich (St. Louis, MO, USA). The supplier of soy-based saturated phosphatidylcholine was Lipoid GmbH (Ludwigshafen, Germany).

Preparation of STZ and other different anti-diabetic drugs

Streptozotocin was dissolved in a 0.1M Cool citrate buffering with a pH of 4.5 used by a dose of 65 mg/kg.

Animal model and treatment protocols

The experimental animal unit at Zagazig University's Faculty of Veterinary Medicine supplied 30 male Sprague-Dawley rats aging 8 weeks, weighing between 200 and 250 grams. The University's Veterinary Medicine Faculty. They were housed under conventional laboratory conditions for two weeks. They were kept in an environment with temperatures ranging from 20 to 25°C, 60% relative humidity, they had unlimited access to water and food. The ethics committee of Zagazig University's Faculty of Veterinary Medicine in Egypt examined and approved the research protocol. All procedures were carried out by the laws and established standards (ZU-IACUC/2/F/81/2023, permission number). The study was conducted based

on ARRIVE's instructions. Ten rats were chosen at random as the control group after they had been acclimated to a regular diet for a week. Rats were given an STZ (65 mg/kg, diluted in 0.1 M cold citrate buffer, pH 4.5) intraperitoneally after fasting for the entire night in order to cause type I diabetes [1]. Rats with increased fasting blood glucose levels than 250 mg/dl were fed sucrose for 48 hours in order to stop the release of insulin, and then they were added to the ongoing experiment. Twenty were given a modified technique from earlier research to induce diabetic kidney disease in diabetic rats [14].

The control group consisted of 10 rats who received an intraperitoneal injection of 0.1 M citrate secured saline and phosphate-buffered saline orally once daily for ten weeks. The second group-(STZ)consisted ten rats which were given just one intraperitoneal of 65 mg/kg of STZ diluted in 0.1 M citrate buffer saline to develop diabetes [15]. The third (STZ + QU)-group was 10 rats that were given oral quercetin at a dose of 10 mg/kg for two weeks before the delivery. The induction used only one intraperitoneal injection to treat diabetes of 65 mg/kg of STZ diluted in 0.1 M citrate buffer saline. The rats then get oral quercetin at a dose of 10 mg/kg BW for an additional ten weeks following the onset of diabetes [16].

Blood and tissue samples

Rats were humanely euthanized in airtight containers with 4% fluothane and oxygen inside. We conducted the necropsy after drawing blood from each rat's medial canthus and putting it in tubes devoid of anticoagulant. The remaining sample was then separated from the anticoagulant-free serum using centrifugation (3000 rpm, 4 °C. Two distinct pieces were obtained from the rat kidney after it was extracted and dissected. The supernatant that was left behind after homogenizing a section of tissue in ice-cold phosphate-buffered saline (PBS) was examined to determine the antioxidant status. For histological examination, the residual kidney tissue was kept in a neutral formalin solution that had been buffered with 10%.

Determination of Biochemical Analysis

Glucose levels

The glucose levels were determined using the glucose oxidation method. in the blood while fasting from Sigma-Aldrich (CAT. NO 9001-37-0). A commercial ELISA system from Sigma-Aldrich was used to quantify the levels of insulin (CAT. NO RAB0904).

Kidney function tests

One of the kidney function tests that measures creatinine levels which employs the Colorimetric Kinetic Method kit from Sigma-Aldrich (CAT. NO MAK080), urea measured by using the Colorimetric Kinetic Method by Kit from Sigma-Aldrich (CAT. NO 1.04166).Trace elements measured by Na Kit from Sigma-Aldrich (CAT. NO 262714) and K Kit from Sigma-Aldrich (CAT. NO 244864), Serum level of TGB from Sigma-Aldrich (CAT. NO TGFBMAG-64K-03) , TNF-α from Sigma-Aldrich (CAT. NO. 03-0137-00) and IL-1B from Sigma-Aldrich (CAT.NO.RAB0277).

Determination of the Antioxidant Status

The amount of kidney malondialdehyde (MDA) was measured with an ELISA kit (Cat. No. MBS8807536, My-BioSource, San Diego, CA, USA). Superoxide dismutase (SOD) was determined by using SOD Activity

Assay Kit (MyBioSource, Cat. NO: MBS2707324), glutathione peroxidase (GPx, Biodiagnostic, Catalog NO: GP2524), and catalase (MyBiosource, Catalog No: MBS701908).

Histological analysis of the Rats' kidney

Samples from the kidney were preserved using a 10% neutral buffered formalin solution. After that, the tissues were washed with xylene and dehydrated using progressively higher alcohol concentrations, then fixed in paraffin to form blocks that were divided into sections measuring 5 µm. Hematoxylin and eosin (H&E) staining was applied to these sections using the protocol outlined in Suvarna *et al.* [17]. Following staining, the sections were viewed and captured on camera using a light microscope.

Statistical Analysis

The SPSS software, version 10.0.1, and using data analysis was done using an ANOVA with a one-way design, and the Dunc-Kramer test was then used. The cutoff point was set at the 0.05 significance level, according to Jones [18].

Results

The enhanced impact of QU on insulin and FBG

The finding obtained presented that STZ increased the level of FBG level compared to control group (Figure 1a). And decrease the level of serum insulin due to impair of pancreatic β-cell function. On the other hand, STZ induction resulted in a considerably lower FBG level and higher serum insulin levels in diabetic rats with QU. Figure 1b demonstrate role of quercetin in diabetes which decreased blood sugar levels and increased insulin sensitivity.

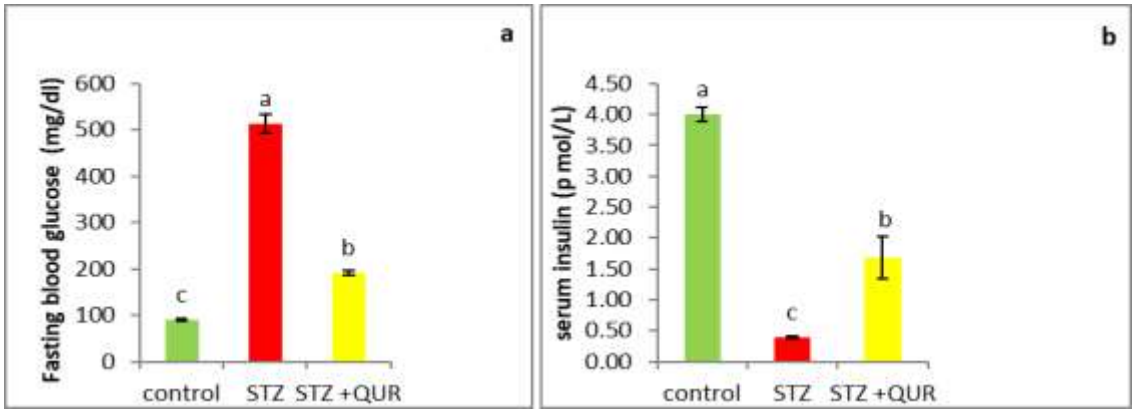

Figure 1. Effect of Quercetin on fasting blood glucose (FBG) (a), serum insulin (b)

The improved effects of QU towards kidney functions tests

Rats given STZ to induce diabetes had higher levels of urea than control rats. Nonetheless, the quercetin group's urea level has significantly decreased. (Figure 2a). Also, level of creatinine increases in rats with diabetes caused by STZ as opposed to controls, On the contrary, there is a notable decline in creatinine level in the quercetin group (Figure 2b). Serum levels of minerals showed that diabetic rats given STZ showed an important rise in sodium (Figure 2c).

However, there is a significant decrease of sodium levels in the quercetin group. The STZ-induced diabetic rats showed a significant rise in potassium levels (Figure 2d). However, there is significant decrease of potassium levels in the group of quercetin.

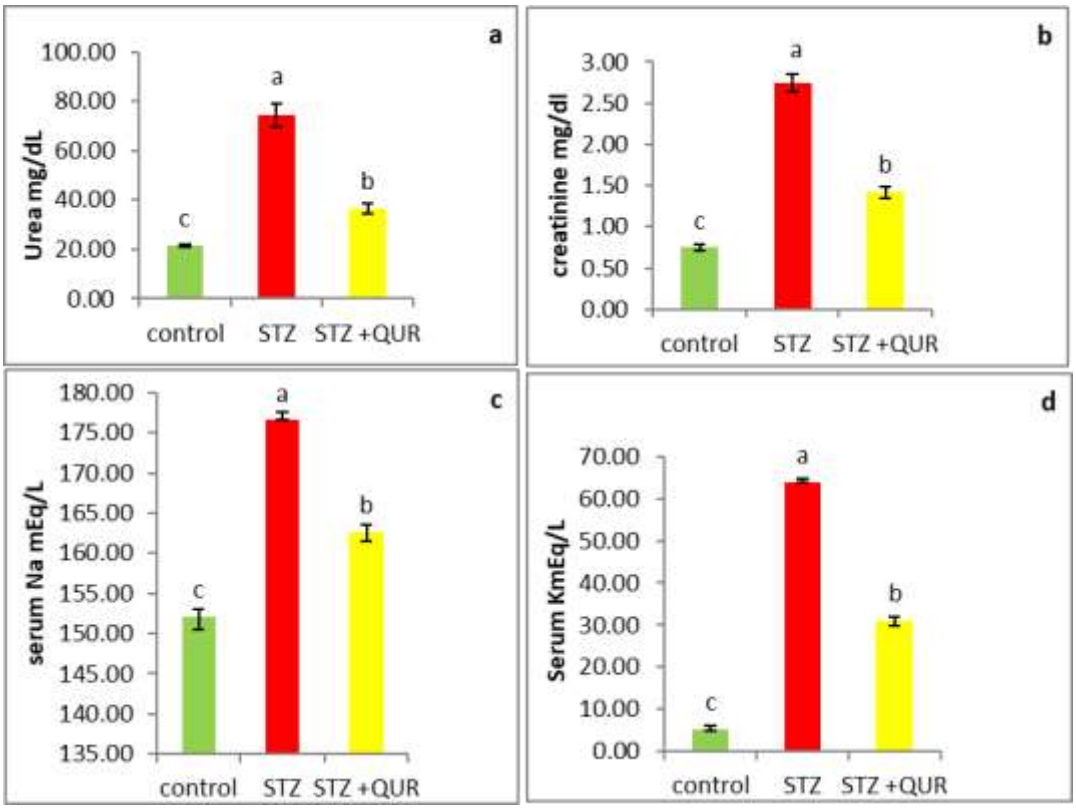

Figure 2. Effect of Quercetin on kidney function urea level (a), creatinine level (b), sodium level (c) and potassium level (d)

The anti-oxidative result of QU on Rat's kidney tissue

To evaluate QU's antioxidative characteristics, kidney tissues were tested for MDA, SOD, GPx, and CAT levels. The results illustrated that STZ therapy increased the amount of Kidney MDA because diabetes increases oxidative stress (Figure 3a). While the kidney levels of SOD, GPx, and CAT decreased (Figure 3b-d). QU therapy improved oxidative capability, as shown by a reduction in kidney MDA levels (Figure 3a) and the rise in the kidney levels of SOD, GPx, and CAT (Figure 3b-d).

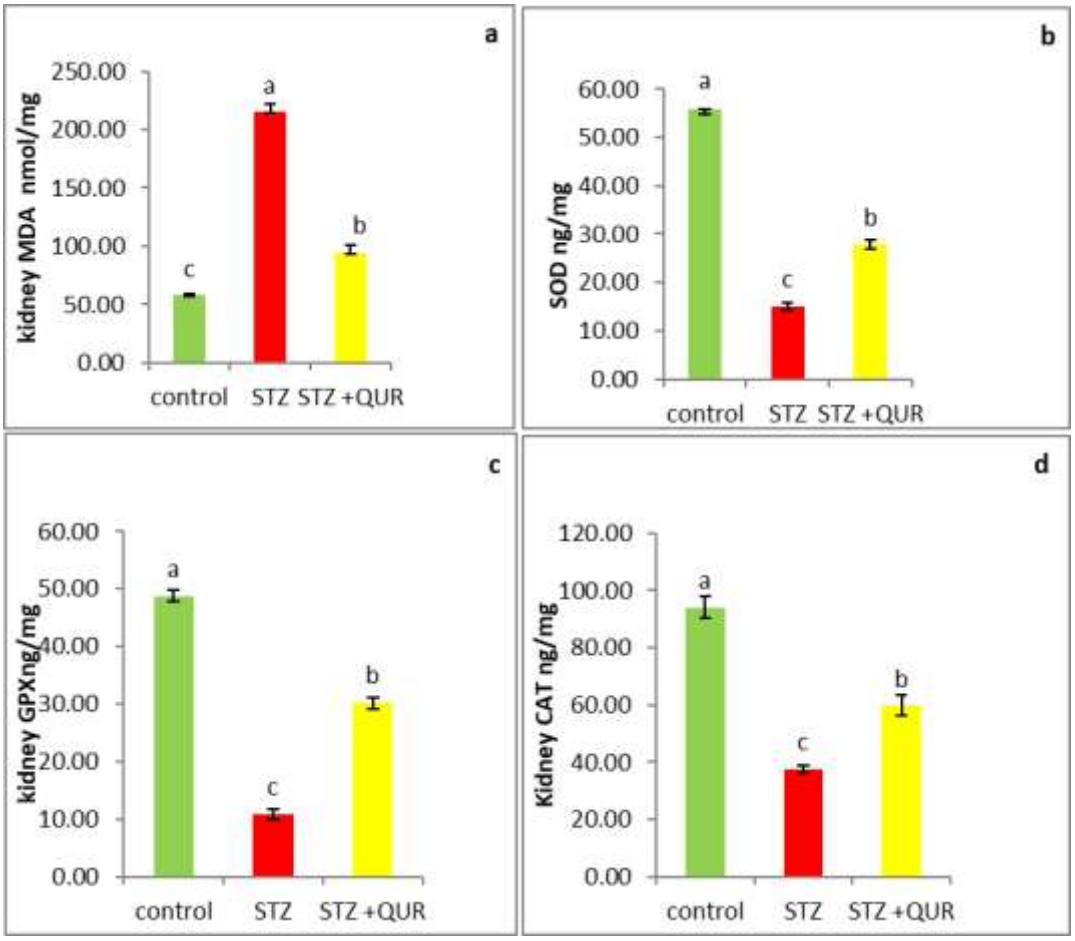

Figure 3. Effect of Quercetin on the renal oxidant/antioxidant: malondialdehyde (MDA, a), superoxide dismutase (SOD, b), glutathione peroxidase (GPX, c) and catalase (CAT, d).

Influence of QU on STZ-induced inflammatory mediators

Determining if the QU treatment's regulatory mechanism on ROS formation was connected to a shift in the blood levels of inflammatory mediators prompted by STZ administration. STZ therapy considerably elevated serum levels of IL-1β and TNF-α (Figure 4a–b). When STZ was administered to diabetic rats, QU significantly reduced serum TNF-α and IL-1β levels (Figure 4a- b).

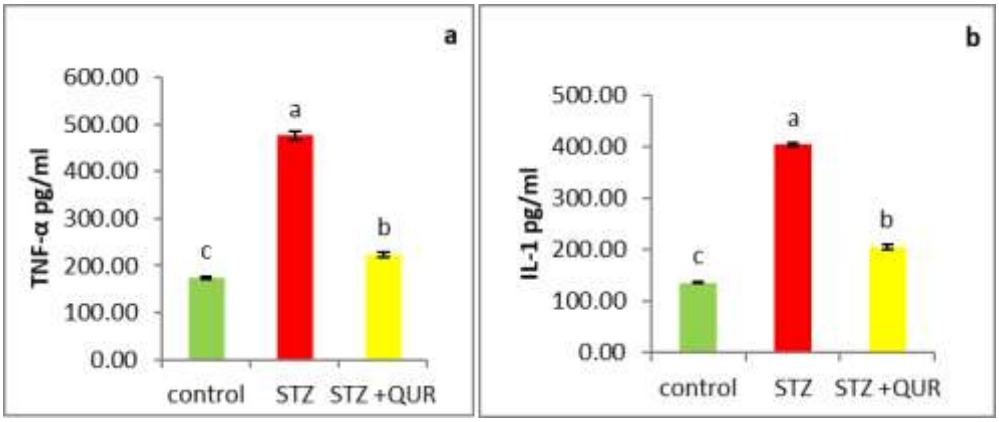

Figure 4. Effects of Quercetin on STZ-induced inflammatory mediators: tumor necrosis factor (TNF-α, a) and interleukin 6 (IL-6, b).

The consequences of QU on TGFβ1 biomarker of glomerular damage induced by STZ

STZ administration led to a considerable increase in the serum levels of TGFβ1, while in STZ induced diabetic rats with QU therapy reduced serum TGFβ1 levels (Figure 5).

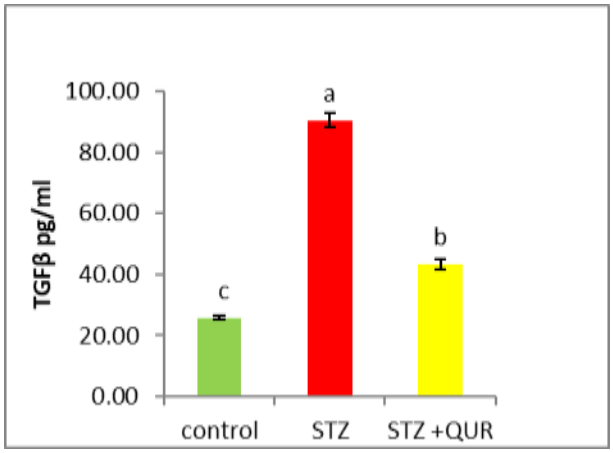

Figure 5. Effect of Quercetin on the transforming growth factor beta (TGF-β)

Effectiveness of QU on renal tissue histological alterations in rats with diabetes

The histology of the interstitial tissue, renal tubules, and glomeruli was typical in the control group Control –ve group (Figure 6a) showed normal histology of glomeruli, renal tubules and interstitial tissue. While STZ group (Figure 6b,6c) revealed focal tubular necrosis that represented by hypertrophied renal tubular epithelium with prominent vacuolization and pyknotic nuclei. Also, dilated tubular lumina, congested interstitial renal vasculatures were observed. Moreover, some glomerular corpuscles exhibited mesangial sclerosis or glomerulosclerosis which accompanied

with thickening of capsular basement membrane. In the other hand, there are improvement the majority of renal tubules & glomerular tufts in treated STZ group by QUR (Figure 6d). But, some atrophied glomeruli, mild degenerative change in the few numbers of tubular epithelium, and interstitial round cells infiltration were noticed in some examined sections of treated STZ group by QUR.

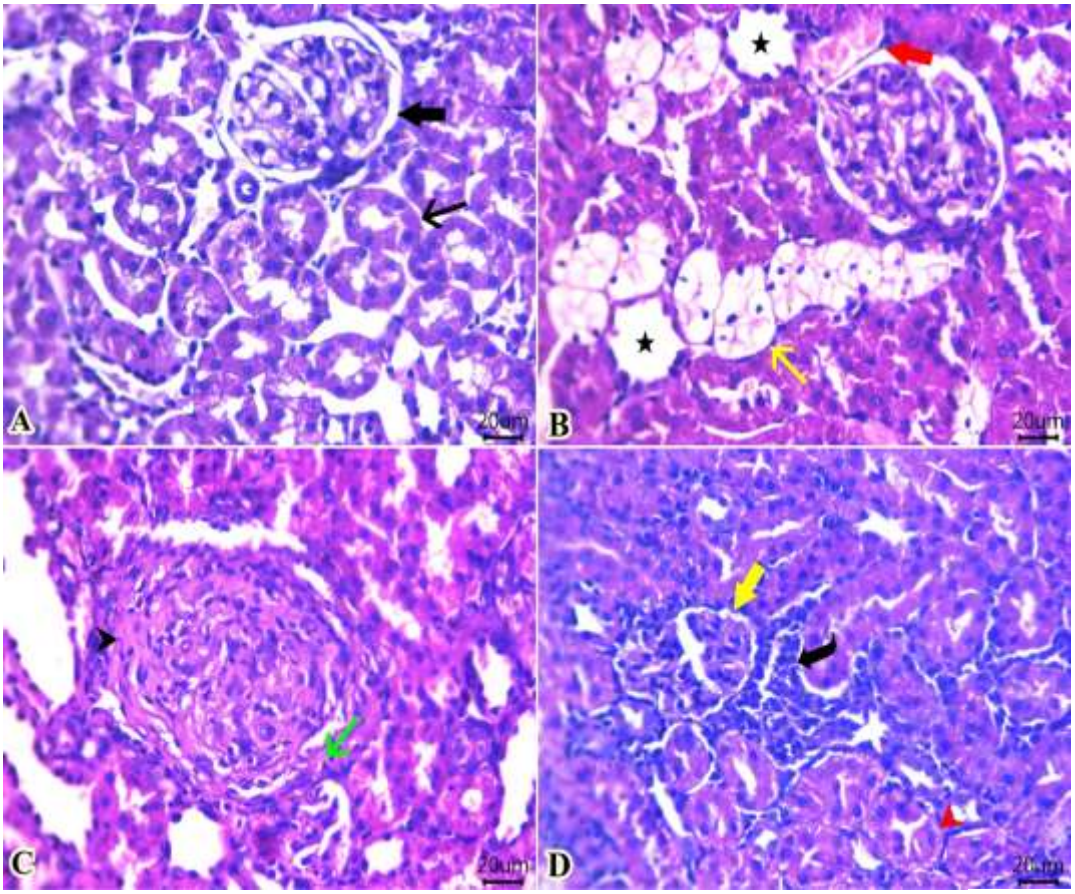

Figure 6. Photomicrograph of H&E-stained sections from rat kidney **(Scale bar 20 µm)** showing: **a.** normal histology of glomeruli **(closed arrow)**, renal tubules **(open arrow)** and interstitial tissue in Control –ve group. **b, c.** focal tubular necrosis with prominent vacuolization and pyknotic nuclei **(yellow open arrow)**, dilated some tubular lumina **(stars),** congested interstitial renal vasculature **(red closed arrow)**, and glomerulosclerosis **(black arrowhead)** accompanied with thickening of capsular basement membrane **(green open arrow)** in STZ group. **d.** some atrophied glomeruli **(yellow closed arrow),** mild degenerative change in few numbers of tubular epithelium **(red arrowhead)**, and interstitial round cells infiltrations (**curved arrow)** in treated STZ group by QUR.

Discussion

Diabetes is characterized by long-term hyperglycemia and modified lipid, protein, and carbohydrate metabolism caused by impaired Creation of insulin, activity, or both [19]. Diabetic renal failure is a diabetic complication that affects 56.7% of people with diabetes. Diabetic kidney disease is a diabetic complication that affects 56.7% of diabetic individuals. Caused by many factors including old age, longer duration since diagnosis of diabetes, obesity, hypertension, diabetic retinopathy, diabetic foot ulcers, non-traumatic lesser-extremity amputations, ischemic heart disease, stroke, insulin use (either alone or

combined with oral glucose-lowering medications), and poorer HbA1c control [20]. One of the greatest typical long-term consequences of diabetes is DN, and approximately half of patients will likely acquire DPN at some point throughout their illness [21]. Inflammation, one unique pathophysiological mechanism in diabetes mellitus requires ongoing monitoring: the development of DN. The present study's outcomes supported the development of DKD by an elevation in levels of serum creatinine, and urea. These outcomes were in keeping with those previously reported by Rahmani *et al.* [22]. According to reports, glucose fluctuations are a separate risk factor for the emergence of disorders related to metabolism that underlie diabetes mellitus (DN) and have been connected to the etiology of problems throughout the prediabetic era [23]. Both podocyte and tubular cell lifetime and function have been affected by hyperglycemia, which explains the relationship. According to Liu and Tang, hyperglycemia-induced apoptosis of podocytes has been related with proteinuria, renal fibrosis, and chronic renal impairment [24]. This research proposes investigate the benefits of quercetin as prophylactic and management of oxidative stress, glycemic management, and renal function in diabetic rats. In this study, the STZ (65 mg/kg.bw) was used for the induction of type I diabetes and DKD in rats. Whereas STZ is toxic to islet β cells, Large doses of STZ can destroy most islet β cells and produce T1DM [22].

Quercetin is a kind of polyhydroxy flavonoid which is present in the fruits, leaves, and flowers of a wide variety of food plants, such as apples, onions, cabbage, and lettuce. It was shown in a prior investigation to decrease blood glucose levels while preserving pancreatic β-cell counts and insulin sensitivity in rats and mice given an artificial version of diabetes [25]. Its reduction of aldose reductase, an enzyme that uses the polyol route to convert glucose to sorbitol, is another important feature [25]. Ojo et al. 2021demonstrated that a four-week quercetin dose dramatically lowered blood sugar levels in an STZ-induced model of diabetes [26]. When quercetin was administered to diabetic mice, the FBG levels decreased significantly, which was beneficial. The decrease in FBG level, which was statistically significant, shows that quercetin might possess a reaction on the kidney that is protective without requiring insulin. receptor-dependent mechanism. In our investigation, it was found that quercetin stimulates the release of insulin and decreases blood glucose levels. Prior studies have demonstrated quercetin's impact on blood glucose levels [27, 28]. Quercetin improved insulin being published by repairing β cells of the Langerhans islets destroyed by STZ [29].

Notably, the quercetin significantly alleviated kidney damage and dysfunction signals, as seen through a decrease in urea and creatinine in diabetic mice. These findings are consistent with a prior study that found quercetin to have a significant effect on improving kidney function in diabetic nephropathic rats [25].

Decrease the level of sodium (Na) in the diabetic group compared to the control. Lower serum sodium levels represent that the kidneys are unable to store sodium and chloride. Haemodilution, which occurs the reduction in salt levels may potentially be attributed to excessive water intake or enhanced endogenous water production. The reversed potassium increases appeared to be related to decreased K excretion, which was exacerbated by the

disclosure of intracellular potassium (K) into the bloodstream caused by gentamicin- inflicted lesions in the renal tubular epithelium. Quercetin brings the level close to normal [30, 31]. Quercetin lowers the amount of (TGF)-β, and in our investigation, the diabetes group showed an increase in TGF-β1 relative to the control group. The activation of the MAPK pathway is associated with elevated levels of extracellular matrix protein and hepatic growth factor (TGF)-β1 among individuals with DN [32].

Although diabetic peripheral neuropathy (DPN) is a complex process with multiple underlying causes, persistent hyperglycemia is the main source of metabolic complications and is essential for the extreme oxidative stress associated with diabetes. Increased oxidative stress brought on by hyperglycemia is mostly responsible for auto-oxidative glycosylation and advanced glycation end products. This affects the polyol pathway's increasing activity, which causes sorbitol accumulation, elevated intracellular osmolarity, and oxidative stress [33]. Sciatic nerve dysfunction is believed to be a result of oxidative stress acting as a metabolic trigger. Thus, examinations of diabetic rats have shown that Improved cellular reactive oxygen species (ROS) lead to protein nitration and membrane lipid peroxidation., and DNA degradation, all of which are connected to the emergence of oxidative stress and inflammation [13]. According to Wang et al.2020 and Khan et al. 2022, Malondialdehyde (MDA) levels dramatically rose in rats with streptozotocin-induced diabetes, although the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) declined [33, 34]. In addition, previous research has demonstrated that a three-week quercetin dosage can lower lipid peroxide Measures in rats and reduce oxidative stress in the brain by increasing antioxidant enzyme levels [26].Our research conducted in STZ-diabetic rats found that ROS in T1DM significantly elevated levels of inflammatory cytokines, including TNF-α, IL-1β, and IL-6 Phases. However quercetin reduces inflammatory cytokines in diabetic rats' renal tissue and lowers TNFα and IL-1β levels in the sciatic nerve [32].

Conclusion

Quercetin could potentially offer improved therapeutic benefits for controlling type I diabetes and related kidney complications, since it may effectively alleviate renal oxidative stress, hyperglycemia, and hyperlipidemia.

Authors' contributions

The idea for the study was provided by each author; D.H., M.F.D., and S.I.K. helped with the design, carried out the tests, and conducted the data analysis. The experiments were carried out and the data was examined by H.M.E. and M.M.L. The manuscript was written, reviewed, and edited by D.H. M.M.L. edited, examined, and carried out statistical analysis on the text. Every author has viewed and authorized the completed manuscript.

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Availability of data and materials

Upon reasonable request, the corresponding author can supply the datasets used and/or evaluated during the current study.

Declarations

Ethics approval

The research protocol was reviewed and agreed to by the Faculty's Ethics Committee of Veterinary Medicine at Zagazig University in Egypt. All procedures were carried out in accordance with applicable laws and regulations (ZU-IACUC/2/F/81/2023). The paper was conducted in accordance with the ARRIVE recommendations.

Competing interests

The authors have disclosed no material issues of interest.

Consent for publication

Not applicable.

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الملخص العربي

التأثير التحسيني للكرستين على نموذج جرذان مستحدث بها مرض الكلى السكري بواسطة مادة الاستربتزيتوسين

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اعتلال الكلية السكري (DN) هو نتيجة شائعة لمرض السكري. واستخدم الكرستين على نطاق واسع وأظهر أن له تأثيرات علاجية إيجابية على العديد من الأمراض التي تصيب الإنسان، بما في ذلك مرض السكري. له فوائد كبيرة مضادة لمرض السكري، مثل خفض مستويات السكر في الدم وتعزيز حساسية الأنسولين. ويمكنه أيضًا منع وتحسين اعتلال الكلية أحد مضاعفات مرض السكري. تهدف هذه الدراسة إلى فحص التأثير الوقائي الكرستين في مقاومة DN بعد تطور T1DM في الفئران. تم توليد T1DM في فئران التجارب عن طريق إعطاء جرعة واحدة عالية من 65) STZ مجم/كجم من وزن الجسم) داخل الصفاق، تليها عشرة أسابيع من العلاج بالكرستين. أظهر مصل الجرذان المصابة بداء السكري مستويات عالية من اليوريا والكرياتينين والصوديوم والبوتاسيوم، مما يشير إلى وجود مشاكل في الأوعية الدموية الدقيقة. كان الإجهاد التأكسدي موجودًا بشكل واضح، إلى جانب زيادة الاستجابة الالتهابية. أظهرت أنسجة الكلى لدى الجرذان المصابة بداء السكري ارتفاعًا ملحوظًا في TNF-α وTGB وكمية IL-1β. تم العثور على تغيرات شكلية كلوية في جميع المجموعات بعد إدخال T1DM، وتحسن الكيرسيتين بشكل ملحوظ. يمكن للعلامات البيوكيميائية مثل جلوكوز الدم الصائم (FBG)، والأنسولين، واليوريا، والكرياتينين أن تقلل من حدوث TNF-α، وIL-6، وTGB. الكرستين يحمي الكلى بشكل احترافي ويقلل من إصابة أنسجة عن طريق تقليل أضرار الجذور الحرة وإعادة توازن الجلوكوز، مما يشير إلى خط علاج محتمل لاعتلال الكليه T1DM