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Assessment of the anti-diabetic potential of resveratrol in streptozotocin-induced diabetic animal models through modulation of oxidative stress and inflammation

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ABSRACT

Background: Resveratrol (RES) is well known for its various biological properties, including anti-inflammatory and antioxidant activities, making it a valuable therapeutic approach for treating numerous pathological disorders. Objectives: The aim of this study was to assess the anti-diabetic effects of RES in streptozotocin (STZ)-induced diabetic rats.

Methods: A total of thirty-two male rats, weighing 160-175g, were randomly allocated into four experimental groups (n = 8 per group): normal untreated controls, diabetic controls, diabetic rats receiving resveratrol treatment, and diabetic rats treated with glibenclamide as a positive control. Following completion of the treatment, blood samples were collected for biochemical investigations. Animals were then sacrificed, and renal histopathological analysis was performed to evaluate renal tissue architecture, and IL-6 expression was examined by immunohistochemistry.

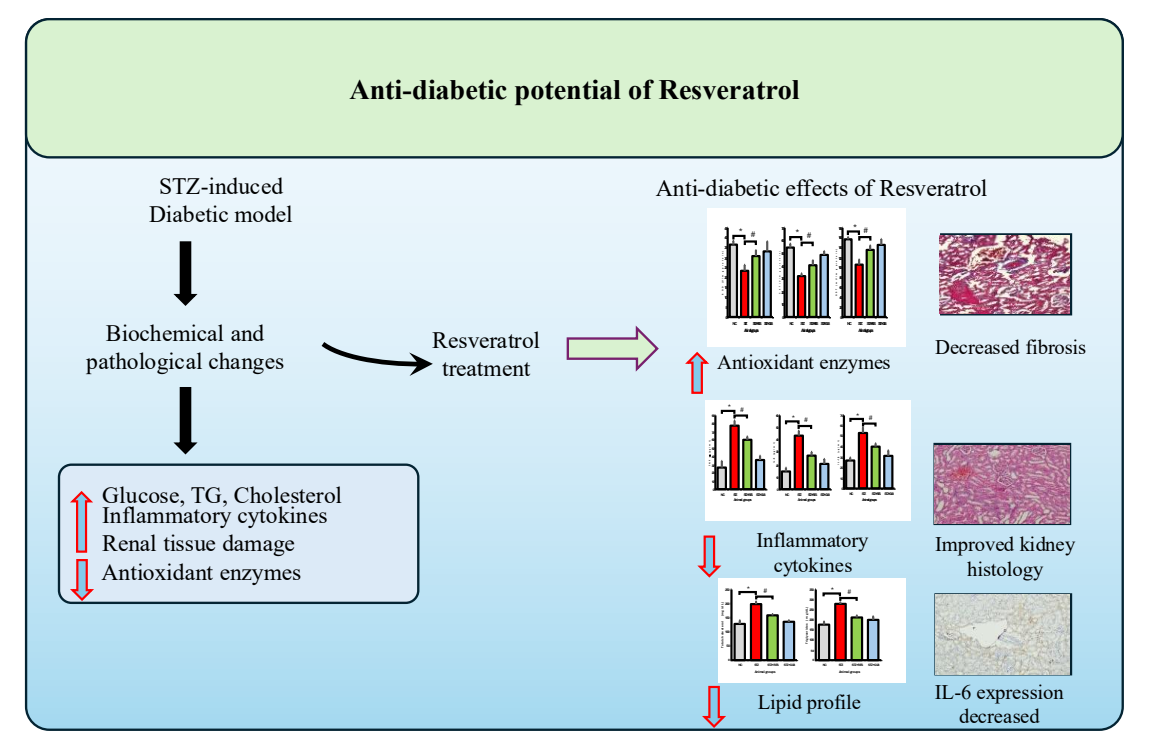
Results: The treatment with RES significantly elevated insulin levels, decreased blood glucose, total triglyceride (TG) and cholesterol (TC) levels, reduced inflammation, lowered the levels of inflammatory markers, and improved the activities of antioxidant enzymes in diabetic rats. RES lessened diabetes-induced renal damage, including inflammation,

congestion, and fibrosis. In addition, RES markedly suppressed interleukin-6 (IL-6) expression in kidney tissues compared with the diabetes control group.

Conclusion: These outcomes suggest that RES is a potent therapeutic agent for diabetes and related complications.

Novelty of the study: This study demonstrates that RES not only improves glycemic control, lipid metabolism, and insulin levels, but also attenuates oxidative stress and inflammation in diabetic rats. Notably, RES protects renal tissue architecture and markedly downregulates IL-6 expression. These findings highlight RES as a multi-target bioactive compound with potential therapeutic in diabetes management.

Key Words: Resveratrol, anti-diabetic potential, oxidative stress, inflammation



Graphical Abstract: Assessment of the anti-diabetic potential of resveratrol in streptozotocin-induced diabetic animal models

INTRODUCTION

Diabetes and its associated complications, including diabetic nephropathy and neuropathy, pose noteworthy public health concerns worldwide. Diabetes is a collection of metabolic disorders that has a major negative effect on the world economy and healthcare. Oxidative stress, beta-cell dysfunction, altered gut flora, hyperglycemia, cellular senescence, genetic predisposition, insulin resistance, epigenetic modifications, cell death, inflammation, cell stress, immunity, haemodynamic abnormalities, and lipotoxicity are among the mechanisms. Numerous organ systems are affected by

the pathology of diabetes [1]. Diabetes mellitus principally occurs in two main forms. Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β-cells, leading to an absolute insulin deficiency. In contrast, Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin action, generally related to reduced insulin sensitivity [2]. T1DM is an autoimmune disease in which the body's immune system targets and kills the beta cells in the pancreas that produce insulin. This results in insufficient insulin, an essential hormone that controls blood sugar levels and the uptake of glucose by cells. Because of this, people with T1DM must take insulin for the rest of their lives to regulate their blood glucose levels. [3]. It represents around 5–10% of all diabetes cases, with prevalence gradually increasing. On the other hand, T2DM is far more common, representing about 90% of diabetes cases globally [4]. The worldwide occurrence of diabetes continues to intensify at an alarming rate. Reports from the International Diabetes Federation (IDF) estimate that more than 451 million individuals are currently living with diabetes worldwide, with projections representing an increase to almost 693 million cases by the year 2045 [5]. A substantial pathological feature of T2DM is glucolipotoxicity, a combined toxic effect in which elevated free fatty acids (FFAs) and hyperglycemia lead to dysfunction of pancreatic β-cells and insulin resistance, directly linking obesity to the onset of T2DM [6]. In individuals with diabetes, dyslipidemia is a substantial risk factor for cardiovascular disease. High plasma triglyceride levels and elevated low-density lipoprotein (LDL) particles are the hallmarks of diabetic dyslipidemia [7]. In diabetic rats, hepatic and renal dysfunction is indicated by significant abnormalities in serum biochemical biomarker levels and corresponding histopathological changes in tissue architecture [8,9].

Diabetes treatments primarily rely on medications such as metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, and α-glucosidase inhibitors. However, these drugs can have possible side effects, including diarrhea, hypoglycemia, and weight changes [10]. However, treatment that is safe, effective, and has no or fewer side effects is required to manage this pathogenesis. In this regard, natural products and their bioactive constituents have gained significant attention for their potential in the management of diabetes. The plant-derived compounds can exert antidiabetic effects through multiple biological mechanisms. These include improving insulin secretion, enhancing insulin sensitivity, reducing glucose absorption, and protecting pancreatic β-cells from oxidative damage. Research has revealed that active natural products can enhance the efficacy of T2DM treatment and may potentially decrease the quantity of medications required [11-13].

Resveratrol is a polyphenolic compound [Figure 1] and is found in the skin as well as the seeds of grapes. Furthermore, RES is present in various plant foods, specifically in peanuts, tea, and berries [14].

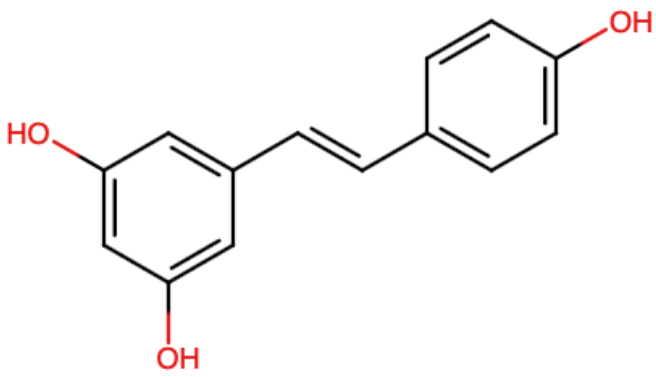


Figure 1. Chemical structure of resveratrol [Drawn on https://www.rcsb.org/search/chemical]

Resveratrol has been widely examined for its therapeutic potential in a variety of diseases, and this natural polyphenolic compound exerts protective effects through multiple biological mechanisms. These include its strong antioxidant activity, its ability to modulate inflammatory pathways, and its regulation of cellular signaling cascades. Through these varied mechanisms, RES helps maintain cellular homeostasis and protect tissues from oxidative damage and inflammation. A previous study reported that RES exerts its effects by suppressing vascular endothelial growth factor (VEGF) expression and p38 phosphorylation, and by increasing endothelial nitric oxide synthase expression, in diabetic rats with concomitant myocardial infarction [15]. Moreover, RES inhibits microglial activation, thereby reducing reactive oxygen species (ROS) production and the activation of signal pathways involved in neuroinflammation [16]. RES also dramatically reduced lysophosphatidylcholine (LPC) induced damage and inflammation, providing additional mechanistic evidence for RES's therapeutic role in arteriosclerosis [17]. A previous investigation confirmed that resveratrol exerted significant protective effects against hepatic impairment and intestinal mucus barrier depletion. RES administration evidently limited body weight gain and fat accumulation, while simultaneously reducing oxidative stress markers and increasing endogenous antioxidant defense systems. Treatment normalized key liver enzyme levels. Histopathological analysis further revealed that RES attenuated liver fibrosis and alleviated hepatic steatosis [18]. Given the protective effects of RES, the current study aimed to explore its antidiabetic potential in diabetic rats using biochemical and histopathological examinations.

MATERIAL AND METHODS

Chemicals/Kits: Commercial assay kits for antioxidant enzymes were bought from Abcam (Cambridge, UK), which also supplied streptozotocin (STZ). Enzyme-linked immunoassay kits for the quantification of inflammatory markers and malondialdehyde (MDA) were obtained from the same manufacturer. Kits for the assessment of tissue fibrosis, including Masson's trichrome as well as Sirius red staining, as well as IL-6 primary antibodies and the horseradish peroxidase (HRP)/diaminobenzidine (DAB) immunohistochemistry detection system, were also sourced from Abcam. All other chemicals, as well as reagents used in the experimental measures, were supplied by specialized local vendors in Saudi Arabia.

Diabetes Model Development and Treatment Plan: A total of 32 rats, each weighing between 160-175g, were obtained from the animal facility of KSU, Saudi Arabia. Throughout the experimental procedure, rats were kept in controlled, standard laboratory conditions. Rats were randomly assigned to four groups (n = 8 per group) for an eight-week treatment period. Group I was assigned as the control group, whereas Group II served as the diabetic control. The STZ solution was freshly prepared by dissolving it in 0.1 M cold citrate buffer (pH 4.5). STZ (55 mg/kg b.w) via intraperitoneal injection was given to rats to develop diabetes [19]. Group III included STZ-induced diabetic rats administered RES orally at 25 mg/kg [20] [Table 1]. Group IV was used as a positive control and received glibenclamide at 5 mg/kg [21].

Table 1. Experimental design showing grouping and treatment regimen of rats.

Group	Description	Treatment / Dose
I	Control group	Rats with free access to rat pellets
II	Diabetic control group	STZ (55 mg/kg b.w) via intraperitoneal injection
III	Diabetic + RES (treatment group) group	RES (25 mg/kg b.w)
IV	Diabetic + Glibenclamide (positive control group)	Glibenclamide (5 mg/kg b.w)

Blood glucose concentrations were measured 48 hrs following STZ injection. Rats showing fasting blood glucose levels above 200 mg/dL were classified as diabetic. All animal handling as well as experimental protocols were conducted and approved by Qassim University (No. QU-J-UG-2-2025-53861).

Evaluation of Fasting Glucose and Serum Insulin Concentrations: Tail vein blood was used to measure fasting blood glucose levels with a standard glucometer. Serum insulin levels were subsequently quantified and analyzed.

Oral glucose tolerance tests (OGTT) performed to Diagnose Diabetes: At the end of the 8-week treatment period, an OGTT was performed after an overnight fast. The rats were orally administered 2 g/kg of glucose. Blood samples were then collected from the tail vein at 0, 30, 60, 90, & 120-minutes following glucose administration to measure blood glucose concentrations.

Determination of Serum Triglycerides and Total Cholesterol: Blood samples were obtained from all experimental rats, then centrifuged to separate the serum. Serum TG and total TC levels were then examined accordingly.

Measurement of malondialdehyde levels: Serum malondialdehyde (MDA) was measured using an Abcam kit. The absorbance of the reaction mixture was recorded by a microplate reader, according to the company's protocol.

TNF-α, IL-6, and IL-1β marker determination: The concentrations of interleukin-1 beta (IL-1β), Tumor necrosis factor-alpha (TNF-α), and IL-6 were measured using ELISA kits. The assays were performed according to the company's instructions, and absorbance readings were used to determine cytokine levels.

SOD, CAT, and GST levels Determination: Kidney tissues of all rats were separately rinsed in phosphate-buffered saline, homogenized, and centrifuged. Antioxidant enzyme activities were subsequently assessed following the manufacturer's protocol.

Histopathological Analysis of Renal Tissue Architecture: Kidney tissue samples were harvested, rinsed in phosphate-buffered saline (PBS), and fixed in 10% formalin for 48 hrs to preserve morphology. Following processing in the Leica tissue processor and paraffin embedding, 5 µm sections were cut and stained with hematoxylin and eosin (H&E) for evaluation of renal tissues. Images were obtained by a high-resolution camera attached to a microscope for subsequent analysis.

Histological Evaluation of Renal Fibrosis by Masson's Trichrome and Sirius Red Staining: Collagen accumulation in tissue samples was assessed using Masson's trichrome and Sirius Red staining, performed according to the manufacturers' protocols. Fibrosis was evaluated under a light microscope. Representative photographs were captured, and the findings were subsequently analyzed.

Expressional Evaluation of IL-6 Protein using Immunohistochemical Methods: An immunohistochemical investigation was performed to estimate IL-6 protein expression using established protocols [22]. Xylene was used to deparaffinize the sections, and these sections were subsequently exposed to 3% H2O2 to suppress intrinsic peroxidase activity. Antigen retrieval was performed in a pressure cooker with sodium citrate–citric acid buffer, followed by incubation of tissues with 5% normal serum for 10 min to block nonspecific binding. The slides were then treated with a primary antibody, IL-6, followed by a secondary biotinylated antibody. After washing with phosphate-buffered saline, the tissue sections were incubated with

streptavidin–peroxidase. Diaminobenzidine (DAB) was then applied as the chromogenic substrate to check the staining reaction, followed by counterstaining with hematoxylin. The stained sections were then examined under a microscope, and characteristic images were captured for further analysis and staining intensity evaluation.

Data Analysis and Statistical Methods: The data are accessible as mean ± standard deviation (SD). Statistical comparisons among the experimental groups were achieved by using one-way analysis of variance (ANOVA). All statistical analyses were performed using SPSS, and p-values < 0.05 were considered statistically significant.

RESULTS

The potential of RES in managing diabetes was evaluated through biochemical and histopathological findings. The results are presented systematically to clearly demonstrate the effects of resveratrol on diabetic conditions.

Effects on blood glucose and insulin levels: In the present study, STZ-induced diabetic rats showed a significant increase in blood glucose levels ($p < 0.05$). However, RES treatment considerably lowered blood glucose levels in diabetic rats ($p < 0.05$) [Figure 2].

Insulin levels were meaningfully reduced in diabetic rats when compared with normal control rat groups ($p < 0.05$). Following RES treatment, a substantial increase in insulin levels was observed ($p < 0.05$) [Figure 2]. Collectively, the outcomes demonstrate the potential of RES to elevate insulin levels and support diabetes management.

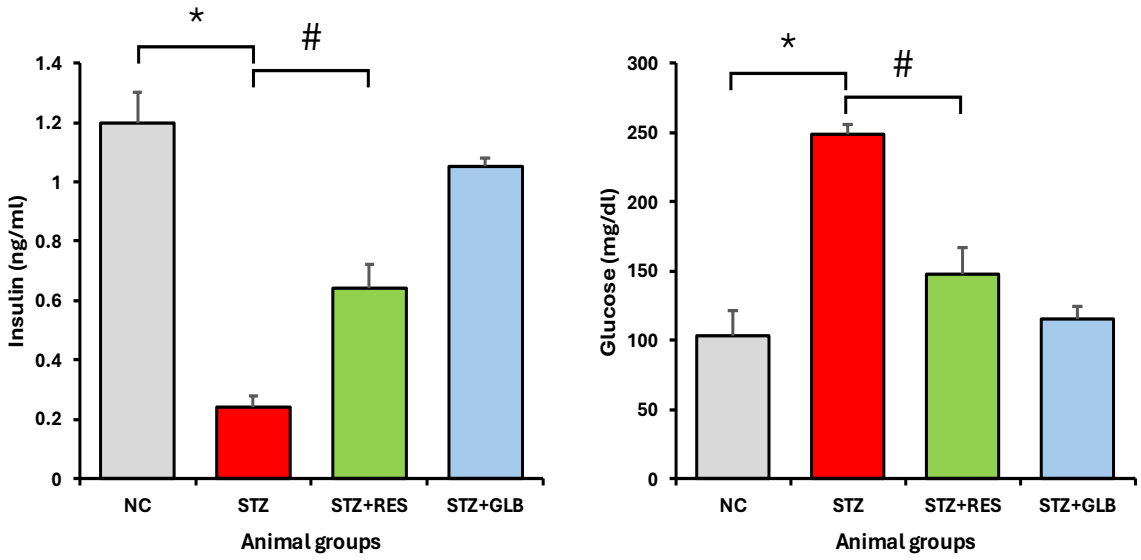


Figure 2. Effect of RES on insulin and blood glucose levels. * $p < 0.05$ designates a substantial difference in body weight between the disease control/Diabetic group and the control; # $p < 0.05$ specifies a significant change between the disease control/Diabetic group and RES-treated STZ-induced diabetic rats.

Effects of RES on OGTT: Blood glucose levels were determined across different rat groups [Figure 3]. The diabetic group showed significantly elevated blood glucose levels, whereas RES treatment in STZ-induced diabetic rats reduced glucose levels ($p < 0.05$).

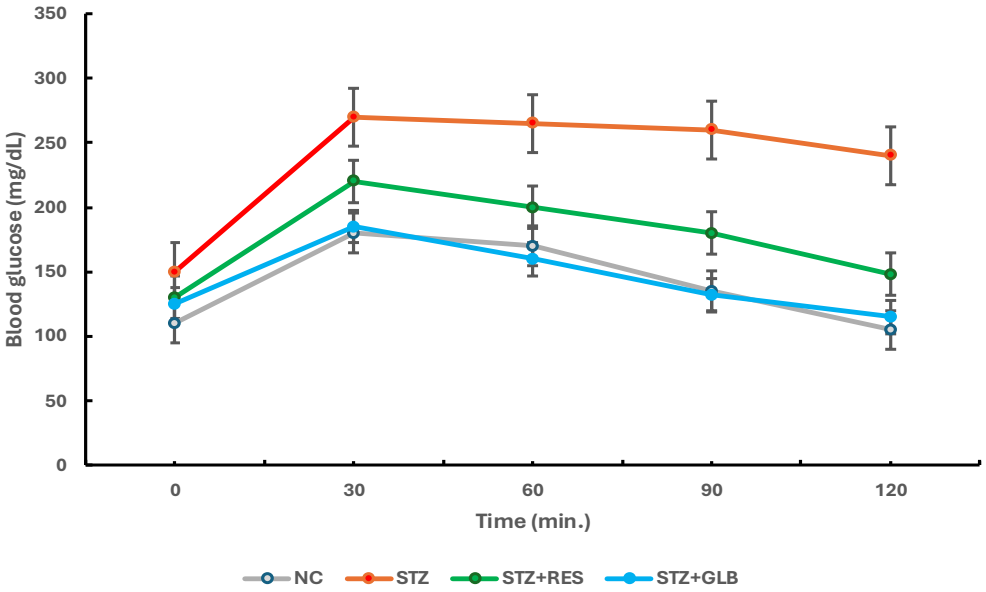


Figure 3. Blood glucose levels were measured, and the role of RES in OGTTs was assessed.

Effect of RES on TG and TC levels: TG and TC levels were assessed in normal, treatment, and diabetic rats. STZ-induced diabetic rats in this study confirmed elevated concentrations of TG and TC, indicating the development of dyslipidemia. Treatment of diabetic rats by RES (25 mg/kg) reduced TG and TC levels in comparison to the disease control group ($p < 0.05$) [Figure 4]. In the positive control group, TG and TC levels remained close to normal, demonstrating the expected protective effect in these animals. Collectively, these results indicate that resveratrol (RES) may help restore lipid balance.

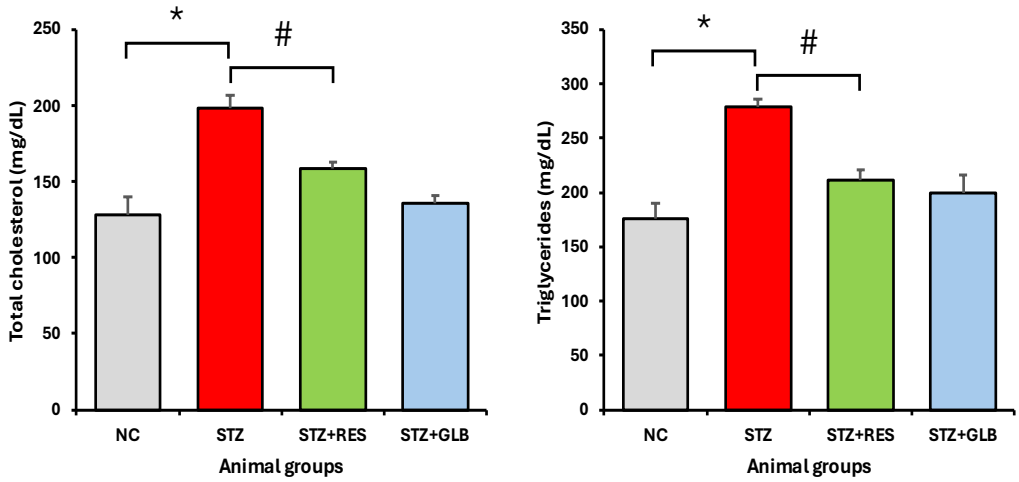


Figure 4. Impact of RES on TG and TC Levels. $p < 0.05$ specifies a noteworthy difference between the diabetic control (DC) group and the normal control (NC) group; #$p < 0.05$ signifies a substantial difference between the diabetic control (DC) group and the RES-treated group (STZ-induced diabetic rats receiving oral resveratrol).

Effects of RES on Lipid Peroxidation and Antioxidant Enzymes: Diabetic rats showed higher levels of MDA than the control group. In contrast, treatment with resveratrol (RES) significantly reduced MDA levels compared with the diabetic control group ($p < 0.05$) [Figure 5].

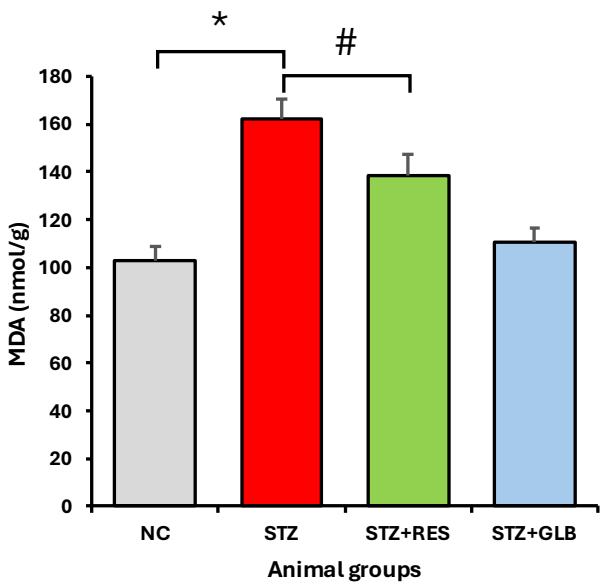


Figure 5. Effect of RES on Malondialdehyde (MDA) Levels. *p < 0.05 designates a substantial increase in MDA levels in the diabetic control (DC) group as compared to the normal control (NC) group. #p < 0.05 represents a substantial reduction in MDA levels in the RES-treated group (STZ-induced diabetic rats receiving oral resveratrol.

The activities of key antioxidant enzymes, including superoxide dismutase (SOD), Glutathione S-transferase (GST), and catalase (CAT), were substantially reduced in diabetic rats compared to controls. Administration of RES to diabetic rats resulted in a significant restoration of these enzyme activities compared with untreated diabetic animals (p < 0.05) [Figure 6]. Overall, these findings indicate that RES exhibits strong antioxidant properties and can mitigate oxidative stress related to diabetes.

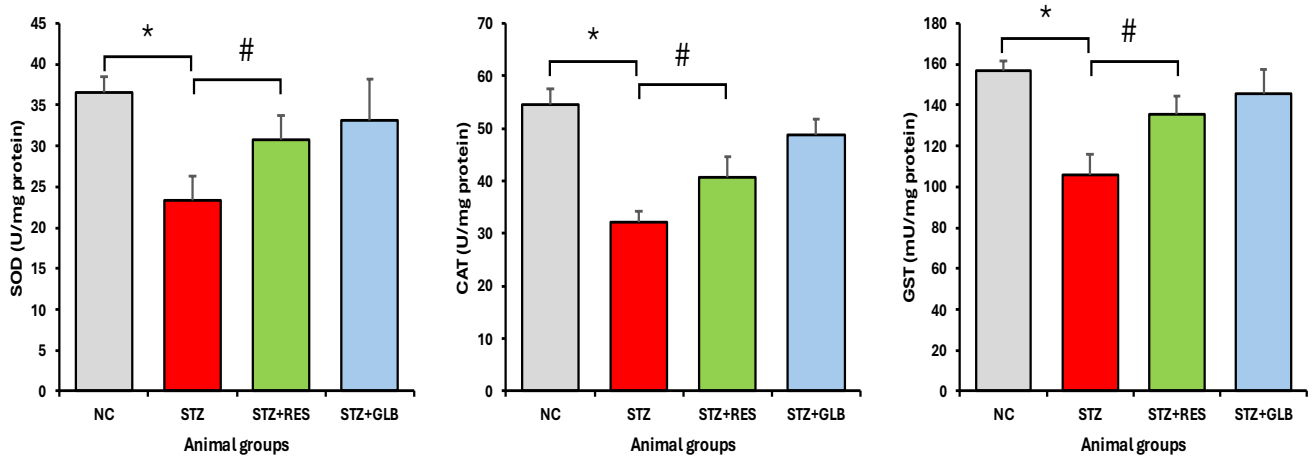


Figure 6. Effect of RES on Antioxidant Enzyme Levels: *p < 0.05 designates a noteworthy decline in antioxidant enzyme activities in the diabetic control (DC) group compared with the NC group. #p < 0.05 characterizes a noteworthy improvement in enzyme levels in the RES-treated group (STZ-induced diabetic rats receiving oral resveratrol), demonstrating the protective effect of RES on antioxidant defense.

Effects of RES on Inflammatory Marker Levels: Diabetic rats showed a noticeable increase in levels of key pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, compared with the normal control group, reflecting a state of inflammation often associated with diabetes. Treatment with resveratrol meaningfully attenuated these elevated cytokine levels ($p < 0.05$) [Figure 7], demonstrating a powerful anti-inflammatory effect. The detected reduction in inflammatory markers suggests that RES may exert its protective effects by modulating inflammatory signaling pathways, such as NF-κB activation, and by countering oxidative stress, which is recognized to exacerbate cytokine production in diabetic conditions. These results underline the therapeutic potential of RES in mitigating inflammation-driven complications

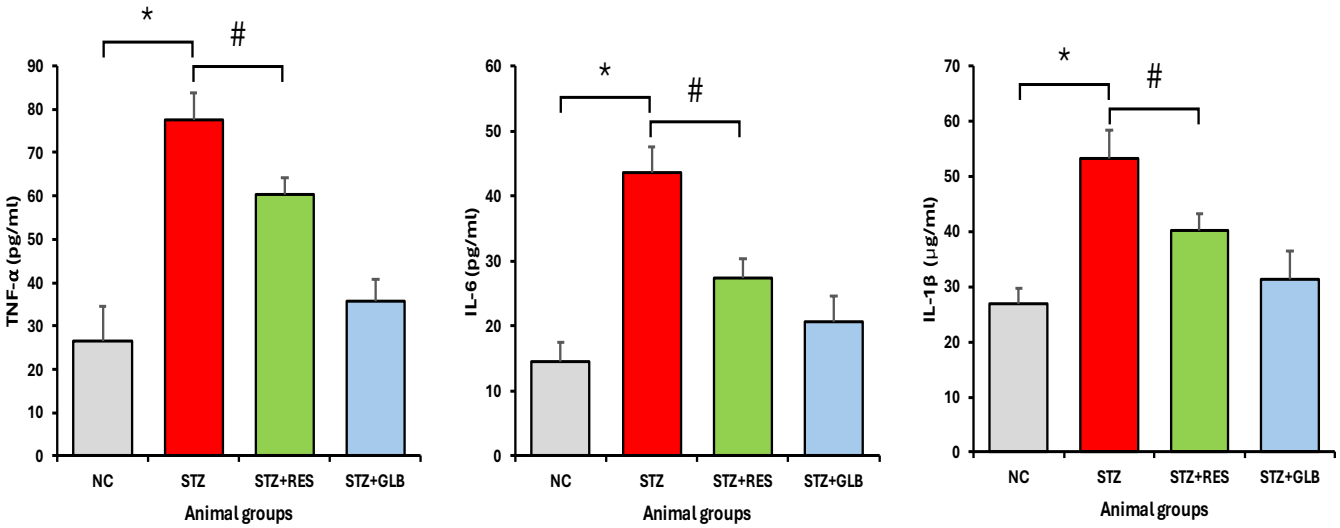


Figure 7. Impact of RES on Antioxidant Enzyme Levels. *$p < 0.05$ indicates a substantial increase in inflammatory markers in the DC group when compared to the NC group. #$p < 0.05$ characterizes a noteworthy reduction in inflammatory markers in the RES-treated group (STZ-induced diabetic rats receiving oral resveratrol), demonstrating the protective effect of RES on antioxidant defense.

The Effect of RES on Renal Tissue Architecture: Normal histological features and intact architecture were observed in the renal tissue of the control group. Kidney tissue samples of diabetic rats induced by STZ exhibited pathological alterations, including congestion, inflammation, fibrosis, and hemorrhage. RES administration in diabetic control rats induced by STZ led to a notable improvement in renal histology, including reduced inflammation, congestion, hemorrhage, and fibrosis [Figure 8]. Moreover, the renal tissue architecture was normal in the positive control and RES-only treated groups.

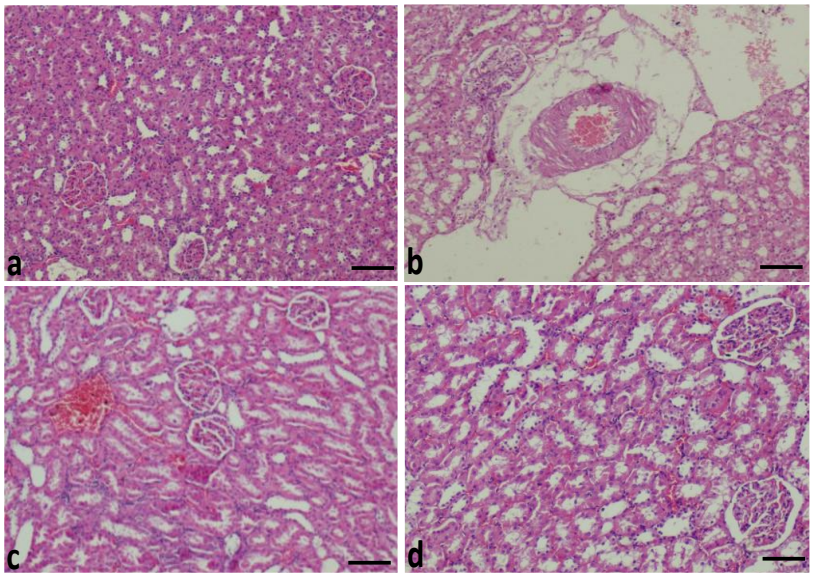


Figure 8. Histological examination of renal tissue architecture. (a) Normal control rats revealed intact renal tissue with normal histological features. (b) STZ-induced diabetic rats (disease control) exhibited noticeable structural changes in renal tissues. (c) Diabetic rats treated with resveratrol exhibited reduced tissue damage. (d) The positive control rats showed normal renal tissue, similar to the control group. Original magnification: 100X; scale bar: 50 µm.

Impact of RES on Renal Tissue Fibrosis: Fibrosis was not observed in the renal tissues of control rats following Masson trichrome staining. Collagen fiber bundles were detected in STZ-induced diabetic rats, whereas reduced fibrosis was noted in RES-treated diabetic rats [Figure 9].

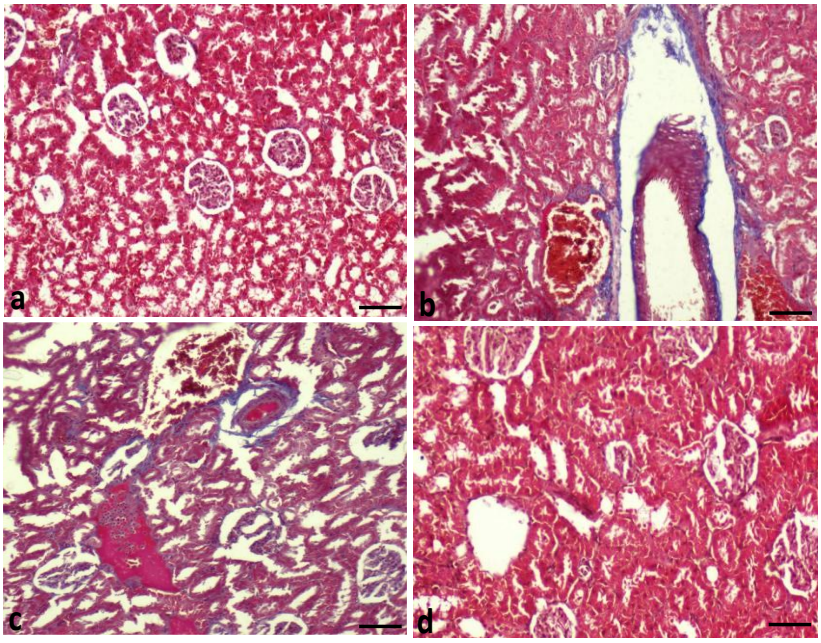


Figure 9. The fibrosis examination of renal tissue**.** (a) Normal control rats revealed no fibrosis. (b) STZ-induced diabetic rats (disease control) exhibited noticeably high fibrosis. (c) Diabetic rats treated with resveratrol exhibited reduced fibrosis. (d) The positive control rats treated with glibenclamide demonstrate no fibrosis, similar to the control group. Original magnification: 100X; scale bar: 50 µm.

Fibrosis was not observed in the renal tissues of control rats following Sirius red staining. Collagen fiber bundles were detected in diabetic rats, whereas reduced fibrosis was noted in RES-treated diabetic rats [Figure 10].

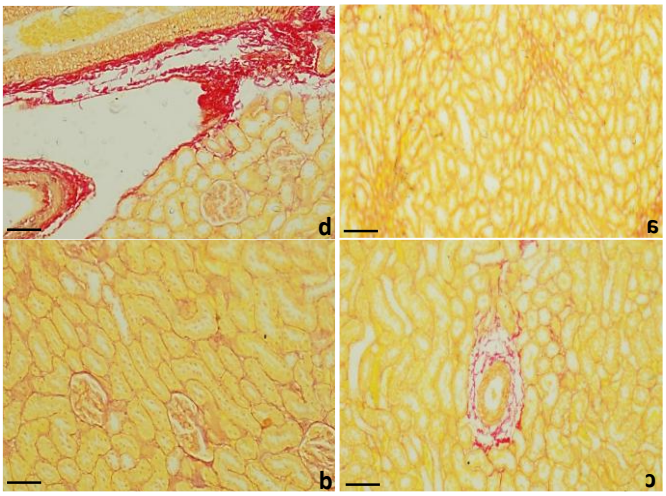


Figure 10. The fibrosis examination of renal tissue: (a) Normal control rats revealed no fibrosis. (b) STZ-induced diabetic rats (disease control) showed noticeably high fibrosis. (c) Diabetic rats treated with resveratrol displayed reduced fibrosis. (d) The positive control rats treated with glibenclamide showed no fibrosis, similar to the control group. Original magnification: 100X; scale bar: 50 µm.

The Effect of RES on IL-6 protein expression: Renal IL-6 expression was evaluated by immunohistochemistry (IHC) in different groups. No IL-6 expression was observed in control renal tissues. However, cytoplasmic IL-6 expression was strongly detected in diabetic rats, while RES treatment in diabetic rats notably decreased IL-6 protein expression. Moreover, positive control showed no detectable IL-6 expression [Figure 11]. These findings indicate that Res has anti-inflammatory potential.

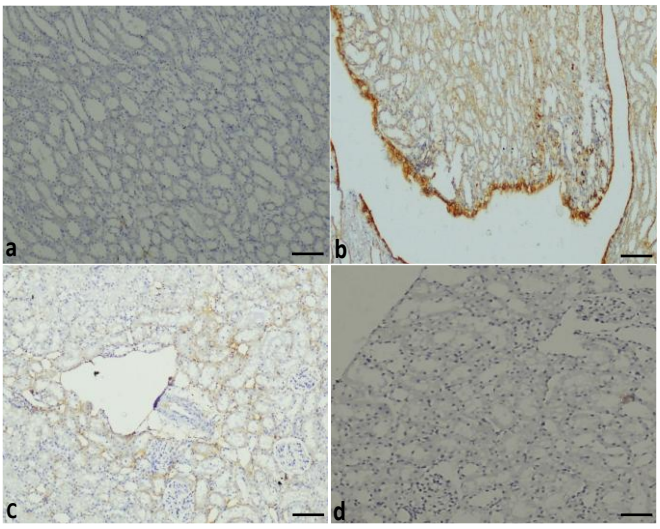


Figure 11. The IL-6 protein examination of renal tissue: (a) IL-6 protein expression was not observed in the renal tissues of control rats; (b) IL-6 protein expression was detected in cytoplasm as brown color in diabetic rats; (c) reduced IL-6 protein was noted in RES-treated diabetic rats; (d) Diabetic rats treated with glibenclamide (positive control) showed no IL-6 protein, similar to the control group. Original magnification: 100X; scale bar: 50 µm.

DISCUSSION

In this study, streptozotocin administration in the diabetic group led to a noticeable decline in insulin levels, accompanied by a significant increase in blood glucose concentrations. This alteration mirrors the characteristic β-cell cytotoxicity caused by STZ, which impairs insulin secretion and thereby disrupts glucose homeostasis. The resultant hyperglycemic state induces diabetes in the experimental model and offers a basis for evaluating the therapeutic effects of interventions such as resveratrol on pancreatic function as well as glycemic control. These outcomes are in line with prior studies that have reported similar findings [19]. In the current study, RES administration markedly lowered blood glucose levels and elevated insulin levels in diabetic rats, in contrast to the diabetes control rats. Thus, these findings indicate that RES effectively manages hyperglycemia while improving insulin secretion. This dual effect supports the potential antidiabetic effects of RES, suggesting that RES may improve glycemic control by protecting pancreatic β-cell function. A previous study reported that rats with STZ-induced diabetes had profound hyperglycemia, increased fasting blood glucose, and serum insulin. However, RES treatments caused a substantial decrease in these diabetic parameters [23]. Another study reported that administration of kaempferol-3-rhamnoside enhanced glycolytic enzyme activity, dropped fasting blood glucose levels, and increased insulin concentrations [24].

Oxidative stress occurs when natural antioxidant defenses are inadequate to counteract the reactive byproducts, chiefly ROS, produced during normal metabolism [25]. These ROS can cause significant damage to cellular components and are involved in the development and progression of various pathological conditions. The imbalance between ROS production and antioxidant defense mechanisms underlies much of the cellular and tissue damage observed in chronic diseases.

Normal physiological levels of ROS function as essential signaling molecules and are implicated in maintaining homeostasis [26]. Both ROS and reactive nitrogen species (RNS) play dual roles, with their influence varying with concentration. In STZ-induced hyperglycemia, the oxidation of overproduced NADH exerts a heavy electron load on the mitochondrial electron transport chain, leading to increased ROS production [27]. Oxidative stress arises when the generation of ROS, such as the superoxide anion ($O_2^{\bullet-}$), exceeds the antioxidant defenses' capacity to counteract them, leading to potential damage to cellular components [28]. In this study, the results demonstrated that RES treatment in diabetic rats markedly reduced MDA levels and restored antioxidant enzyme activities compared with the diabetes group. Hence, these outcomes indicate that RES possess strong antioxidant properties. This effect supports its potential antidiabetic activity, suggesting that RES may improve antioxidant potential by reducing oxidative stress. A prior study reported that diabetes considerably decreased kidney CAT activity. However, treatment by RES was reported to successfully stop this decline in enzyme activity in both tested groups. Further, RES had a protective effect on SOD, in contrast to the diabetic/saline group, consistent with CAT results [29]. Moreover, RES has been reported to exhibit antioxidant activity by increasing the activities of antioxidant enzymes and the levels of nonenzymatic antioxidant compounds [30-31]. RES reduces oxidative stress and promotes mitochondrial biogenesis by maintaining normal Mn-SOD function and regulating glycolipid metabolism [32].

Inflammation plays a crucial role in the pathogenesis of diseases, significantly contributing to the development and progression of pathological conditions.

Inflammation plays a critical role in the pathogenesis of DM, exacerbating insulin resistance and impairing insulin responsiveness in insulin-sensitive tissues [33]. Persistent inflammatory responses also cause β-cell dysfunction and reduced insulin secretion, further accelerating the progression of DM. TNF-α, as well as nuclear factor kappa B (NF-κB), serve as key mediators of insulin resistance and pancreatic β-cell dysfunction, thereby contributing to lipid metabolism disorders and DM pathogenesis [34]. In patients with DM, long-term hyperglycemia activated a variety of inflammatory signal pathways as well as inflammatory mediators, caused in aggravating the development of diabetes complications, and ultimately led to damage of various organs [35]. In the present investigation, diabetic rats showed elevated levels of inflammatory markers compared with the control group. Furthermore, treatment with RES resulted in a clear reduction in these inflammatory biomarkers. These outcomes are consistent with prior reports showing that diabetic rats exhibit increased levels of inflammatory mediators. The same study found that RES exacerbated these inflammatory alterations, consistent with our findings [23]. The anti-inflammatory properties of RES have been established in diabetic animals through the downregulation of proinflammatory proteins/genes [31, 36-37]. Moreover, Resveratrol reduces the inflammatory state and the damage associated with diabetic retinopathy via PON1 [38]. Another recent study reported that treatment with S. commune polysaccharides meaningfully lowered blood glucose levels, reduced inflammatory markers, and restored the expression of GLUT4 and GLP-1R [39]. There are many reports that have evidenced the possible health-beneficial role of natural products and bioactive compounds [40-43].

H&E staining of kidney tissues from diabetic rats revealed numerous structural anomalies. These changes included noticeable infiltration of inflammatory cells, vascular congestion, and fibrosis. Additionally, degenerative changes in renal tubular epithelial cells, as well as disruption of normal glomerular architecture, were noticed, demonstrating substantial renal damage linked with diabetic conditions.

Previous studies have also reported that STZ-induced diabetes induces similar pathological alterations in renal tissues [40]. In the current study, results indicate that RES-treated diabetic rats have significantly reduced tissue alterations as compared with the diabetic group. These findings indicate that RES can maintain tissue architecture. A recent study reported that RES-pretreatment significantly reduced kidney tissue injury and improved renal function in diabetic nephropathy rats [44]. Immunohistochemical findings showed that IL-6 protein levels were notably higher in diabetic control rats. However, RES treatment decreased the expression of this inflammatory marker. Collectively, this study supports previous investigations confirming the protective effects of RES, including reductions in inflammation and oxidative stress in diabetic rats. In this regard, earlier studies have shown that TNF-α expression was elevated in diabetic animal groups. However, treatment with natural compounds was found to decrease the expression of this protein [40]. RES treatment at 25 mg/kg significantly improved glycemic control by lowering blood glucose and elevating insulin levels in STZ-induced diabetic rats, showing a clear dose-dependent trend. It also ameliorated dyslipidemia by reducing total cholesterol and triglycerides, which correlated with decreased oxidative stress and enhanced antioxidant enzyme activities. RES exhibited notable anti-inflammatory effects, as evidenced by reduced inflammatory markers and suppression of IL-6 expression in renal tissues. Overall, the findings highlight RES as a potent agent that mitigates diabetes-related metabolic and renal complications by coordinating the modulation of key biomarkers.

CONCLUSION

In this study, diabetic rats were used to evaluate the efficacy of RES in treating diabetes and associated complications. The data show that RES improves lipid

profiles, lowers oxidative stress markers, and improves kidney function. RES also has anti-inflammatory properties and is shown to reduce inflammatory marker levels. Additionally, it lessens fibrosis, inflammation, and congestion, all of which contribute to the preservation of renal tissue architecture. From a wider perspective, the results of this research have noteworthy implications for the development of functional foods and nutraceuticals. In terms of future applications, resveratrol could be developed as a dietary supplement or functional food ingredient to support metabolic health, chiefly for individuals at risk of developing diabetes. The link between Functional Food Science and Resveratrol lies in its role as a bioactive compound that provides health benefits beyond basic nutrition. Its inclusion in functional foods highlights how specific compounds can be leveraged to support disease prevention and overall health. However, further research is essential to clarify the exact molecular mechanisms underlying its modulatory effects, optimize dosage and bioavailability, and authenticate its efficiency and safety through well-designed clinical trials.

Abbreviations: **Abbreviations:** CAT: catalase; FFAs: free fatty acids; GST: glutathione S-transferase; IL-1β: interleukin-1 beta; LDL: low-density lipoprotein; MDA: malondialdehyde; OGTT: oral glucose tolerance test; PBS: phosphate-buffered saline; RES: resveratrol; SOD: superoxide dismutase; STZ: streptozotocin; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TG: triglyceride; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor

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