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Original Article

Schaftoside Attenuates Myocardial Ischemia/Reperfusion Injury in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus, a chronic metabolic disorder defined by persistent hyperglycemia, is a foremost global health issue. A significant complication of diabetes is the heightened risk of cardiovascular diseases. **Objectives:** The current work was planned to disclose the cardioprotective properties of the schaftoside against Myocardial Ischemic Reperfusion Injury (MIRI) in diabetic rats. **Materials and Methods:** The rats were treated with 60 mg/kg Streptozotocin (STZ) to induce diabetes and underwent to the MIRI induction procedure. The rats were orally treated with the schaftoside at 50 and 100 mg/kg of concentrations. Upon completion of treatment, body weight, Fasting Blood Glucose (FBG) level, glycated Haemoglobin (HbA_{1c}) level, and tissue injury marker levels were estimated. The concentrations of oxidative stress markers, lipid profile markers, myocardial injury markers, and pro-inflammatory markers were studied utilizing commercial kits. The histological investigation was performed on the pancreas extracted from the experimental rats. **Results:** The findings of this work demonstrated that schaftoside at dosages of 50 and 100 mg/kg markedly diminished FBG, HbA_{1c}, and tissue marker enzyme concentrations in diabetic rats with MIRI. The concentrations of oxidative stress markers and myocardial injury markers were considerably diminished by the schaftoside in the rats with MIRI. The schaftoside treatment effectively regulated the lipid profile marker levels and reduced pro-inflammatory cytokines in the diabetic rats with MIRI. The histological analysis of the pancreas confirmed the beneficial activities of schaftoside. **Conclusion:** The results of this study highlight that schaftoside alleviated the MIRI-induced complications in the diabetic rats. Thus, it has the potential to function as a potential therapeutic agent to treat cardiovascular complications in the context of diabetes.

Keywords: Myocardial injury, Diabetes Mellitus, Schaftoside, Glycated Haemoglobin, Cardiac Troponin-I.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic condition marked by increased blood glucose due to the body's failure to adequately secrete or utilize insulin, the hormone that regulates blood sugar. This condition can be caused by a decrease in pancreatic insulin secretion or a lack of insulin responsiveness in the body's cells.[1,2] The global prevalence of diabetes has been on the increase, with an estimated 9.3% of the population affected in 2019, up from 171 million incidences in 2000, and it is projected to reach 439 million by 2030. The disease imposes a significant health burden, as it is connected with a high risk of several macrovascular and microvascular complications. These complications can lead to significant morbidity, mortality, and economic costs for healthcare systems.[3] One of the most significant and burdensome cardiovascular comorbidities associated with diabetes is Myocardial Ischemic Reperfusion Injury (MIRI), a condition that arises from the complex interplay between the metabolic dysregulation of diabetes and the consequences of cardiac ischemia and subsequent reperfusion. Diabetes, particularly the non-insulin-dependent (type 2) variety, is defined by a state of insulin resistance and hyperglycemia, which can have direct deleterious effects on the cardiovascular system. This metabolic disturbance, coupled with the often co-existing cluster of risk factors for cardiovascular disease, can lead to a heightened state of oxidative stress and endothelial dysfunction.[4] The overproduction of free radicals and inflammatory factors in the diabetic state can promote the onset of atherosclerosis, thereby increasing the risk of myocardial ischemia.[5] When a myocardial infarction occurs in a patient with diabetes, the damage inflicted during the ischemic event is often exacerbated by the subsequent reperfusion of the

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affected tissue. The reintroduction of oxygenated blood can result in further tissue injury and cell death, a phenomenon known as ischemic reperfusion injury. This is thought to be due to the ROS accumulation, the activation of pro-inflammatory signaling, and the disruption of normal cellular metabolism.[6] It has already been demonstrated the heightened prevalence of cardiovascular diseases in diabetic patients. The underlying mechanisms are multifaceted, involving metabolic disturbances, small vessel disease, autonomic neuropathy, and insulin resistance, all of which can participate in the onset of a distinct diabetic cardiomyopathy.[7] The burden of cardiovascular comorbidity in diabetes is substantial, both in terms of the personal impact on the individual and the wider societal and economic implications. Diabetic patients are at a significantly high risk of cardiovascular-related morbidity and mortality, underscoring the critical need for effective interventions and prevention strategies.[8]

The primary treatment approaches for diabetes-associated myocardial ischemic injury include glycemic control, management of associated risk factors, and targeted pharmacological therapies. Glycemic control is essential, as sustained hyperglycemia is a key driver of oxidative stress and endothelial dysfunction, which participate in the onset of cardiovascular complications. However, achieving optimal glycemic control can be challenging, particularly in advanced stages of the disease.[9] Pharmacological interventions, such as the use of anti-diabetic drugs like metformin, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors, have shown promising results in decreasing the risk of cardiovascular problems in diabetic patients.[10] Despite these advancements, the management of diabetic cardiomyopathy and associated myocardial ischemic injury remains a significant challenge. The complex interplay of multiple pathways, including oxidative stress, inflammation, and metabolic disturbances, necessitates a multifaceted approach to effectively prevent and treat these complications. In this context, the exploration of plant-derived bioactive compounds has gained increasing attention.[11]

The application of plant bioactive compounds in the management of diabetes-associated myocardial ischemic injury presents several advantages. The multifaceted mechanisms of action of these plant-based compounds, targeting various pathways participated in the onset of diabetic cardiomyopathy, offer a promising opportunity to address the complex nature of this condition.[12] Schaftoside is a major flavonoid compound found extensively in several herbal plant species, including *Eleusine indica, Scutellaria baicalensis*, and *Glycyrrhiza uralensis*. The several biological activities of the schaftoside was well reported, including its anti-seizure,[13] neuroprotective,[14] anti-melanogenic,[15] antineuroinflammatory,[16] anti-cholesterol,[17] and antihyperlipidemic[18] effects. In addition, it has been highlighted that schaftoside alleviated the fibrosis, myocardial hypertrophy, and cardiac metabolic imbalances in mice model.[19] However, its protective effects against myocardial injury during diabetic condition was not assessed yet. The present study was focused at assessing the cardioprotective properties of the schaftoside against MIRI in diabetic rats.

MATERIALS AND METHODS

Chemicals

The primary chemicals including schaftoside, streptozotocin, etc., were purchased from Sigma Aldrich, USA. The diagnostic kits for the estimation of biochemical markers were procured from Elabscience, Abcam, and MyBioSource, USA, respectively.

Experimental rats

Healthy Sprague-Dawley rats, 7-8 weeks aged, and weighing 200±10 g, were procured from an institutional animal facility for this study. Rats were caged in sterile polypropylene enclosures under air conditions of 22-24ºC with 12-hr light/dark series. Throughout the duration of the trials, the rats were granted access to pellet food and drinking water. All rats were acclimatized to the laboratory for one week before the commencement of the investigations.

Induction of MIRI in diabetic rats

The experimental rats were allocated into four groups: group I was control; group II was MIRI-induced diabetic rats; group III: MIRI + 50 mg/kg of schaftosdie-treated rats; group IV: MIRI + 100 mg/kg of schaftoside-treated rats. The rats in the control group were sham-operated and provided with a standard diet. The rats in the remaining groups were induced with diabetes and MIRI. Following a 12-hr fast, the rats administered 60 mg/kg streptozotocin. Following a 3-day period, the Fasting Blood Glucose (FBG) levels of the rats were assessed using a glucose meter. A FBG level over 15 mmol/L signified the effective onset of the diabetes.

To induce the MIRI, rats were sedated using 3% pentobarbital sodium. The trachea was dissected and exposed, followed by the insertion of the tracheal tube to establish a connection with small-animal ventilator for ventilation. The thoracic cavity was incised, revealing the heart. The left anterior descending branch of the coronary artery was occluded with silk thread for 30 min. The myocardial cyanosis, along with a 0.1 mV elevation of the ST segment in lead II or T-wave peaking, indicated effective ligation. Following 30 min of ligation, the ligation thread was released, and reperfusion was performed for 120 min. The reddening of the ischemic myocardium and the elevation of the ST segment or the decline of the T wave indicated effective reperfusion. In sham group, the coronary artery remained unligated for a duration of 120 min.

Analysis of body weight and FBG

The body weight and FBG was assessed in the experimental rats. FBG levels were assessed utilizing an Accu-Chek glucometer (Roche, USA). The body weight was accurately determined using an advanced electronic weighing scale.

Analysis of biochemical markers

The tissue injury indicators, including Aspartate Transaminase (AST) and Alanine Transaminase (ALT) were assessed in the serum of the experimental rats with commercial diagnostic kits. The tests were performed with three replicates following the instructions of the kit's manufacturer (Elabscience, USA). The glycosylated Hemoglobin A1c (HbA_{1c}) and Fasting Insulin (FINS) were assessed with commercial kits in accordance with the manufacturer's suggested methods (Abcam, USA).

Analysis of oxidative stress biomarkers

The biomarkers of oxidative stress in the serum of the experimental rats were evaluated utilizing assay kits. The concentrations of Superoxide Dismutase (SOD), Myeloperoxidase (MPO), and Malondialdehyde (MDA) were evaluated utilizing the commercial kits. The tests were done in triplicate using the manufacturer's indicated guidelines (MyBioSource, USA).

Analysis of lipid markers

The lipid profile markers, comprising Triglycerides (TG), Total Cholesterol (TC), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL) in the experimental rats were evaluated with commercial diagnostic kits following the manufacturer's guidelines (Elabscience, USA).

Analysis of cardiac injury biomarkers

The concentrations of cardiac injury biomarkers Cardiac Troponin I (cTnI) and Creatinine Kinase-MB (CK-MB) in the serum of experimental rats were analyzed using commercial kits. The manufacturer's instructions (MyBioSource, USA) were adhered to for these assays.

Analysis of inflammation-associated cytokines

The Interleukin (IL-6) and Tumor Necrosis Factor-α (TNF-α) concentrations in the cardiac tissue homogenates of both control and experimental rats were assessed using commercially available test kits. All tests were performed in triplicate in accordance with the manufacturer's guidelines (Elabscience, USA).

Histopathological analysis

Subsequent to surgical extraction from the experimental rats, the pancreas tissues were cleaned with buffered saline, dehydrated with ethanol, and subsequently fixed in paraffin. The paraffin-embedded tissue was then cut into 5 μm slices. The pancreas sections were stained with hematoxylin and eosin and microscopically evaluated for histological changes.

Statistical analysis

All statistical tests were conducted using Graphpad software. The results are presented as a Mean±SD of three replicates. The values are studied using one-way ANOVA and Tukey's *post hoc* test, with $p<0.05$ as significant.

RESULTS

Effect of schaftoside on the body weight and FBG in the experimental rats

The effects of schaftoside on body weight and FBG concentration in the experimental rats were evaluated, as illustrated in Figure 1. The MIRI-induced diabetic rats displayed a remarkable diminution in body weight and a subsequent elevation in FBG concentration compared to the sham-operated rats. Notably, schaftoside at a dosages of 50 and 100 mg/kg remarkably decreased FBG level and elevated the body weight in rats with MIRI (Figure 1).

Effect of schaftoside on biochemical markers in experimental rats

Figure 2 illustrates the effect of schaftoside on the liver function biomarkers ALT, AST, HbA_{1c} and FINS concentrations of the experimental rats. The diabetic rats with MIRI displayed an increased ALT, AST, HbA_{1c}, and FINS concentrations in their serum. Whereas, the schaftoside treatment at 50 and 100 mg/kg concentrations substantially diminished the concentrations of ALT, AST, HbA_{1c} and FINS in the MIRI-induced diabetic rats.

Effect of schaftoside on oxidative stress biomarkers in experimental rats

The effect of schaftoside on the oxidative stress biomarkers MDA, MPO, and SOD concentrations in the serum of rats were presented Figure 3. The findings demonstrated a substantial increase in MDA and MPO concentrations and reduced SOD concentration in the serum of diabetic rats with MIRI. Interestingly, the schaftoside at 50 and 100 mg/kg of concentrations remarkably reduced the MDA and MPO levels and consequently elevated SOD concentration in the diabetic rats with MIRI.

Effect of schaftoside on lipid markers in experimental rats

Lipid marker levels were evaluated in the serum of the rats, and finding are revealed in Figure 4. The diabetic rats with MIRI exhibited increased TG, TC, and LDL levels and diminished HDL concentration in their serum relative to the sham group. Nevertheless, the 50 and 100 mg/kg of schaftoside to the MIRI-induced rats exhibited a considerable decrease in the TG,

TC, and LDL concentrations, along with an increase in HDL concentration in their serum (Figure 4).

Effect of schaftoside on the cardiac injury biomarkers in the experimental rats

The cardiac injury markers cTnI and CK-MB were assessed in the serum of experimental rats, with the results displayed in Figure 5. The diabetic rats with MIRI demonstrated a significant increase in their serum cTnI and CK-MB levels relative to the control group. Nonetheless, the schaftoside at dosages of 50 and 100 mg/kg significantly diminished both cTnI and CK-MB concentrations in the serum of diabetic rats with MIRI.

Effect of schaftoside on pro-inflammatory cytokines in experimental rats

The inflammatory cytokine concentrations were evaluated in the heart tissues of the rats, with findings illustrated in Figure 6. The MIRI-induced diabetic rats demonstrated a substantial elevation in both TNF-α and IL-6 concentrations relative to the control group. Interestingly, the schaftoside treatment at 50 and 100 mg/kg of concentrations markedly reduced the TNF-α and

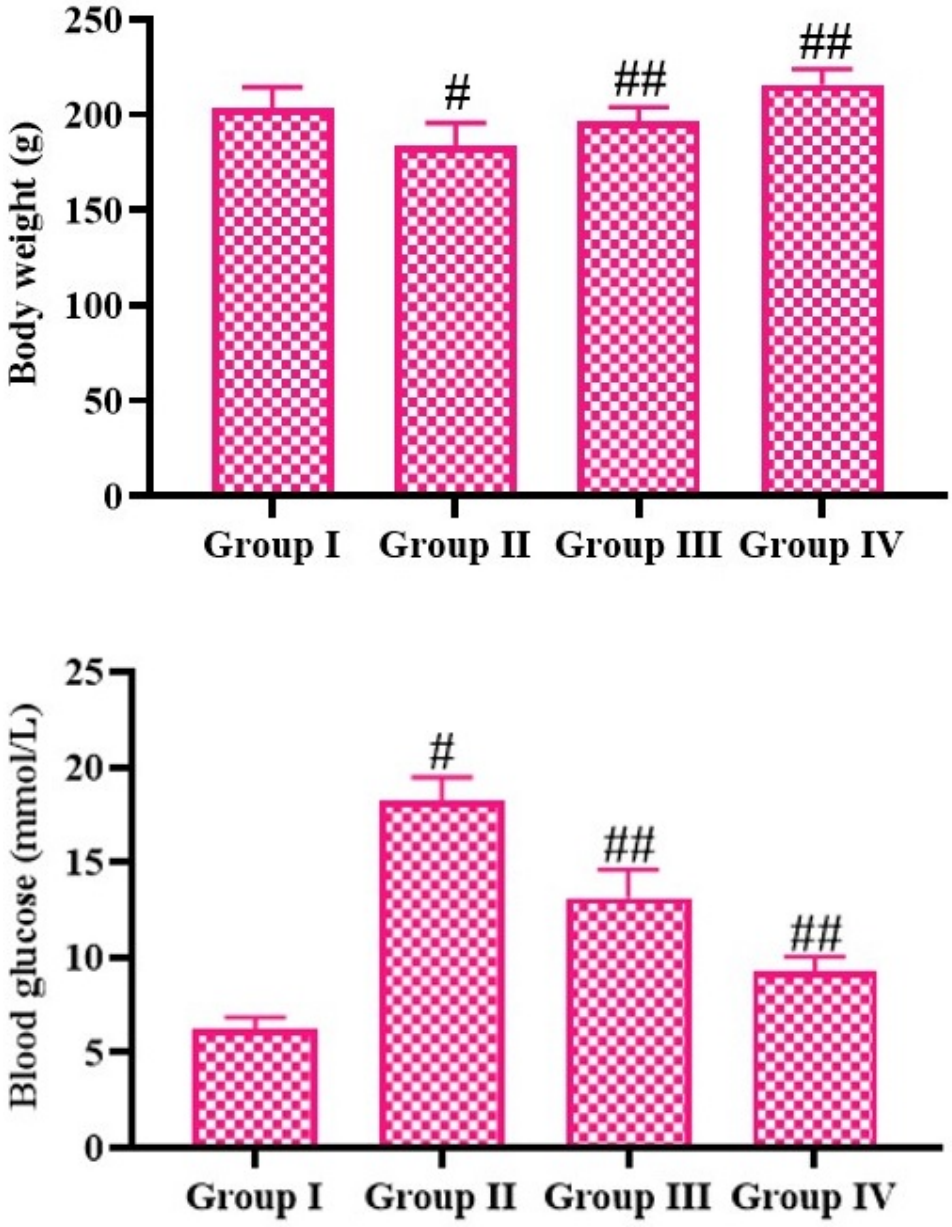

Figure 1: Effect of schaftoside on the body weight and FBG in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

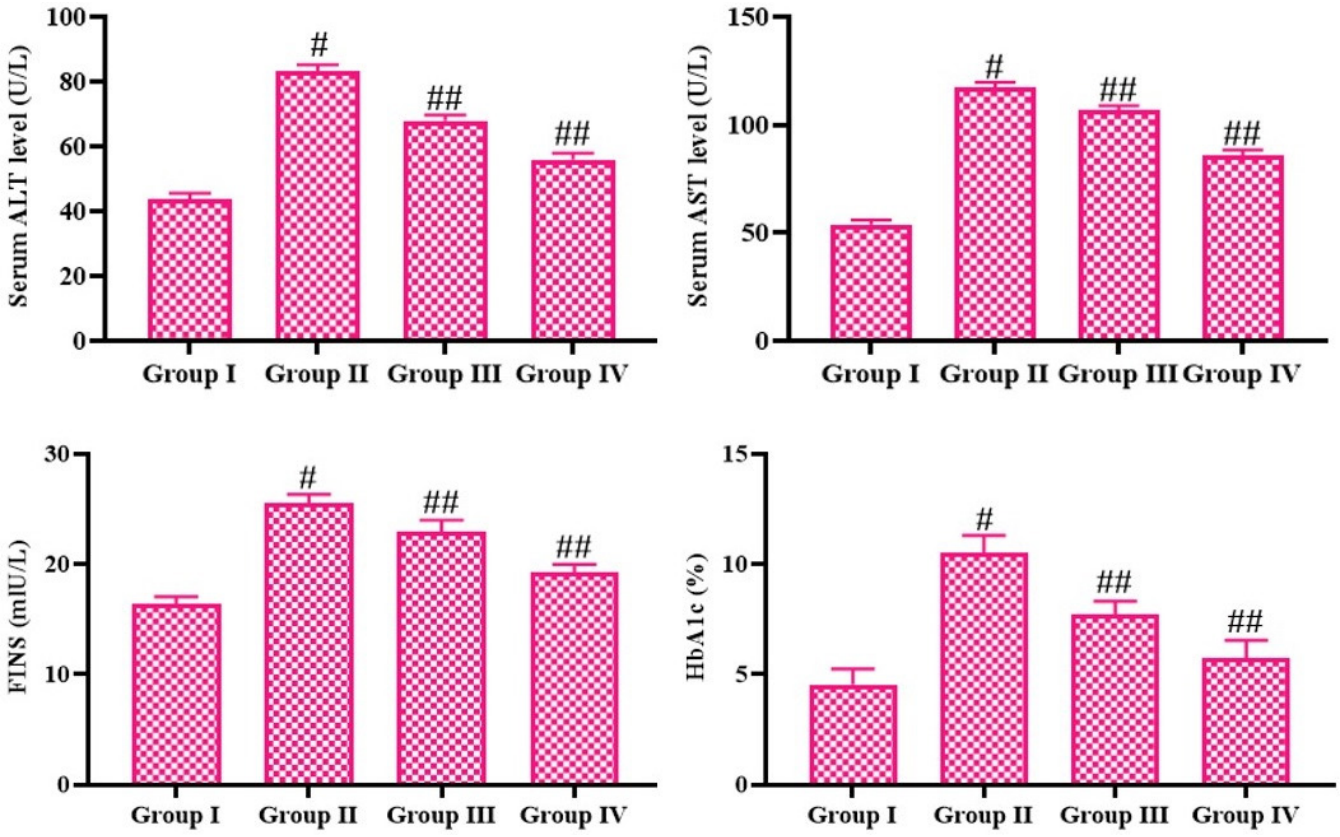

Figure 2: Effect of schaftoside on the biochemical marker levels in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

IL-6 concentrations in the MIRI-induced rats, demonstrating its anti-inflammatory capabilities.

Effect of schaftoside on pancreatic tissue histopathology of experimental rats

Figure 7 illustrates the results of a histopathological study of the pancreas from the experimental rats. The pancreatic tissues from sham-operated rats displayed no indications of inflammation and revealed a normal cellular structure. Whereas, the pancreas tissue of diabetic rats with MIRI displayed increased inflammatory cell infiltration, islet cell shrinkage, and adipose tissue hypertrophy. Interestingly, the histopathological alterations in the pancreas tissue of the MIRI-induced diabetic rats were remarkably diminished by 50 and 100 mg/kg of schaftoside treatment.

DISCUSSION

Diabetes mellitus, a chronic metabolic condition marked by sustained hyperglycemia, represents a significant global health issue. A significant complication of diabetes is the heightened risk of cardiovascular disease.[20] The underlying mechanisms that link diabetes and cardiovascular disease are complex and multifaceted.[21] Despite the introduction of new therapies, the high cardiovascular morbidity and mortality related with diabetes remains a significant challenge. This has encouraged researchers to develop alternative strategies, including the use of plant-derived bioactive compounds, which have shown encouraging results in the treatment of cardiovascular problems in diabetes.[22] Diabetes mellitus and cardiovascular disease are intimately linked, with MIRI posing significant risks for diabetic individuals. The analysis of FBG, HbA_{1c}, and FINS levels in the serum of diabetic rats subjected to MIRI is crucial for understanding the underlying mechanisms and potential therapeutic interventions. FBG levels provide an immediate overview of glycemic control, reflecting the body's ability to regulate blood sugar. HbA_{1c}, on the other hand, offers a more comprehensive assessment of long-term glycemic management, as it measures the average blood glucose over a period of 2-3 months. FINS level can shed light on insulin resistance, a hallmark of type-2 diabetes, and its role in the onset of MIRI.[23] Abnormal glucose counter regulation, characterized by impaired glucagon response and delayed insulin clearance, has been observed in insulin-dependent diabetes mellitus. This alteration in glucose homeostasis can exacerbate the detrimental effects of MIRI, leading to increased oxidative stress and further insulin resistance. Additionally, chronic heat stress has been shown to induce hyperinsulinemia in various animal models, potentially contributing to the metabolic dysregulation observed in diabetic individuals with cardiovascular complications.[24] Understanding the interplay between glycemic control,

insulin resistance, and MIRI is crucial for developing targeted interventions. By analyzing these key biomarkers in the serum of diabetic rats subjected to MIRI, researchers can gain valuable insights into the pathophysiological conditions underlying this comorbid condition, paving the way for potential therapeutic methods.[25] The present findings demonstrated that MIRI-induced diabetic rats exhibited increased FBG, FINS, and HbA_{1c} levels in their serum. Interestingly, the schaftoside treatment considerably decreased the concentrations of FBG, FINS, and HbA_{1c} in the rats with MIRI.

MIRI is a complex pathophysiological process that occurs when blood supply to the heart is temporarily interrupted and then restored, leading to further damage to the myocardium. This injury is particularly problematic in the context of diabetes, as the condition is related with high oxidative stress and dysregulated cellular signaling pathways. To better understand and manage this condition, the analysis of specific serum biomarkers plays an essential role in understanding the pathogenesis and guiding the management of the MIRI in diabetic condition.[26] ALT and AST are enzymes that are typically found at low concentrations in the blood, but their levels can increase significantly when myocytes are damaged, indicating the presence of tissue injury.[27] MDA, a byproduct of lipid peroxidation, offers as a marker of oxidative stress and can provide insights into the degree of oxidative injury occurring in the myocardium during ischemia-reperfusion injury.[28] MPO, an enzyme released by activated neutrophils, is a marker of inflammation and can be used to assess the inflammatory response to the injury.[29] SOD, an antioxidant enzyme, plays a pivotal role in mitigating oxidative stress and its levels can reflect the body's attempt to counteract the damaging effects of free radicals during ischemia-reperfusion injury.[30] The analysis of these biomarkers in the serum of diabetic rats subjected to MIRI can provide valuable information about the underlying pathophysiological processes, the extent of tissue damage, and the body's response to the injury. This knowledge can inform the development of more potential strategies and therapeutic techniques to treat this complex condition in the context of diabetes. In this work, we found the increased ALT, AST, MDA, and MPO concentrations and a subsequent reduction in SOD concentration in the serum of diabetic rats with MIRI. However, the treatment with the schaftoside remarkably decreased the ALT, AST, MDA, and MPO levels and elevated the SOD level in the diabetic rats with MIRI.

Diabetes is a complex metabolic condition that has a profound impact on several physiological systems, including cardiovascular system. One of the most serious issues connected with diabetes is the onset of MIRI, which can lead to significant myocardial damage and impaired cardiac function.[31] In this context, the

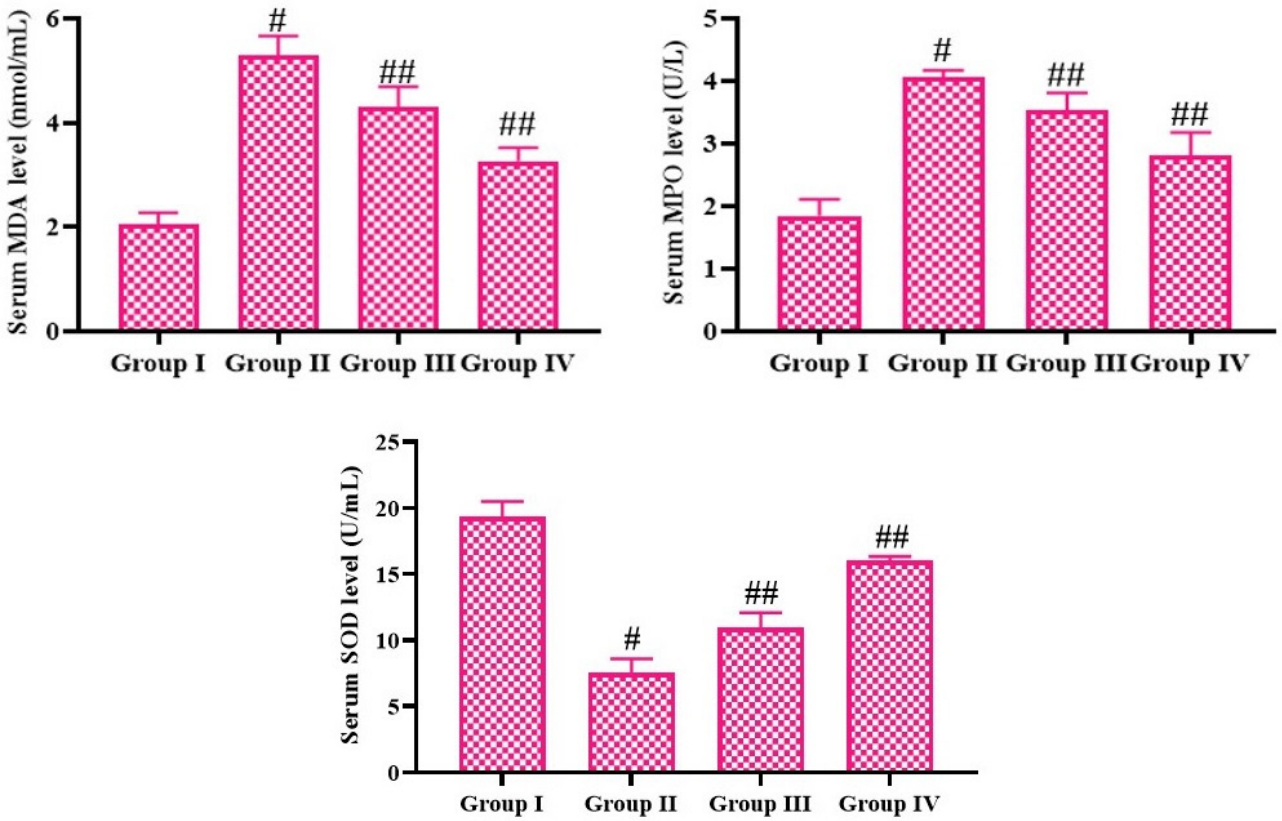

Figure 3: Effect of schaftoside on the oxidative stress markers in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

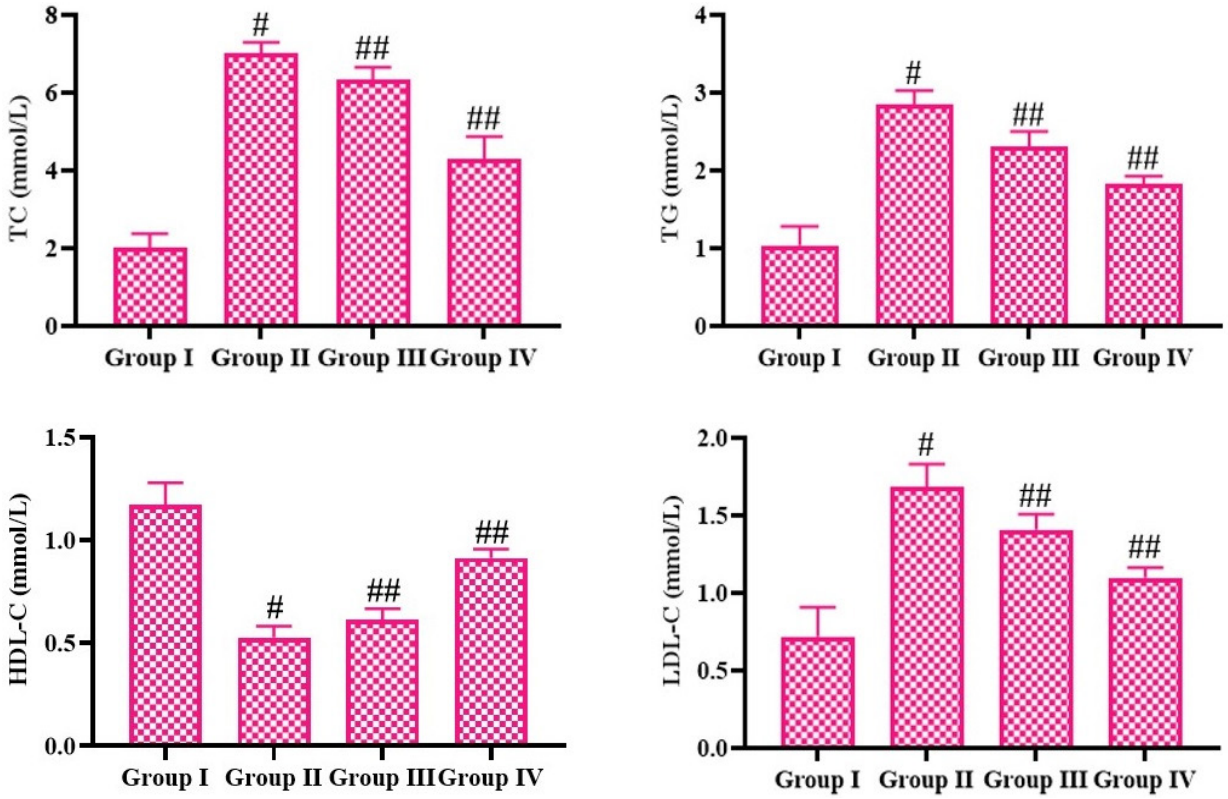

Figure 4: Effect of schaftoside on the lipid marker levels in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

analysis of key lipid markers plays a pivotal role in understanding the onset and potential treatment strategies for this condition. Analyzing these lipid markers in the serum of MIRI-induced diabetic rats can provide valuable insights into the underlying metabolic disturbances and cardiovascular complications. TC and LDL levels are often elevated in diabetic individuals, contributing to the development of cardiovascular disorders. Similarly, elevated TG levels are commonly observed in diabetes and are related with an elevated risk of cardiovascular complications. In contrast, reduced levels of HDL, the "good" cholesterol, are often observed in diabetic individuals, further exacerbating the cardiovascular risk.[32] Analyzing these lipid markers in the serum of MIRI-induced diabetic rats has several applications. These measurements can help to understand the mechanisms underlying the progression of diabetes and associated insulin resistance, which are key participants in the onset of MIRI. Additionally, the analysis of these lipid markers can offer valuable insights into the potential therapies targeting the lipid metabolism and signaling cascades to mitigate the adverse effects of MIRI in the context of diabetes.[33] In this work, the findings illustrated that the diabetic rats with MIRI exhibited increased concentration of TG, TC, and LDL and diminished HDL in their serum. Whereas, the schaftoside treatment to the MIRI-induced diabetic rats exhibited a considerable diminution in the TG, TC, and LDL and elevation in HDL in their serum.

MIRI is a significant concern in diabetic patients, often leading to further cardiac complications. The analysis of cTnI and CK-MB levels in the serum of diabetic rats with induced MIRI can provide valuable insights into the pathophysiology and potential diagnostic markers for this condition.[34] cTnI is a highly specific and sensitive biomarker for myocardial damage. In patients with chronic kidney disease, elevated troponin levels have been shown to be indicator of high risk of mortality and cardiovascular disorders. This is especially relevant in the context of diabetic patients, as the incidence of cardiovascular disease is high in this population.[35] The level of cTnI in the blood is elevated in both primary and secondary cardiac disorders, making it a valuable indicator of cardiac abnormalities. In addition to its diagnostic utility, cTnI has also been projected as a prognostic indicator of disease severity and risk of adverse outcomes.[36] On the other hand, CK-MB, a cardiac-specific isoenzyme, is also a well-established biomarker for myocardial injury, as its release into the bloodstream is a hallmark of cardiomyocyte necrosis. Its presence in the serum, along with cTnI, can provide a more insights into myocardial injury in the context of diabetic MIRI.[37] The analysis of these two cardiac biomarkers in the serum of diabetic rats with induced MIRI can contribute to understand the pathogenesis of this condition and its potential diagnostic and prognostic implications. The present findings evidenced that diabetic rats with MIRI exhibited an increased serum cTnI and

CK-MB levels relative to the control. However, the schaftoside treatment significantly decreased both cTnI and CK-MB concentrations in the serum of diabetic rats with MIRI.

MIRI can lead to significant tissue injury and impaired heart function, particularly in the context of diabetes, which is a major risk factor. A critical aspect of the pathogenesis of MIRI is the inflammation, which is defined by the inflammatory cytokine release, like TNF-α and IL-6.[38] TNF-α is a pivotal inflammatory cytokine that plays an essential role in the inflammatory response to MIRI. It has been shown to participate in the development of myocardial dysfunction by stimulating myocyte hypertrophy, inducing apoptosis, and altering the extracellular matrix.[39] IL-6 is another important inflammatory cytokine that is elevated in response to MIRI. IL-6 has been implicated in the activation of autophagy and the development of cachexia in skeletal muscle, which may also have implications for cardiac activity.[40] The assessment of serum TNF-α and IL-6 in animal models of MIRI and diabetes can offer valuable insights into the underlying

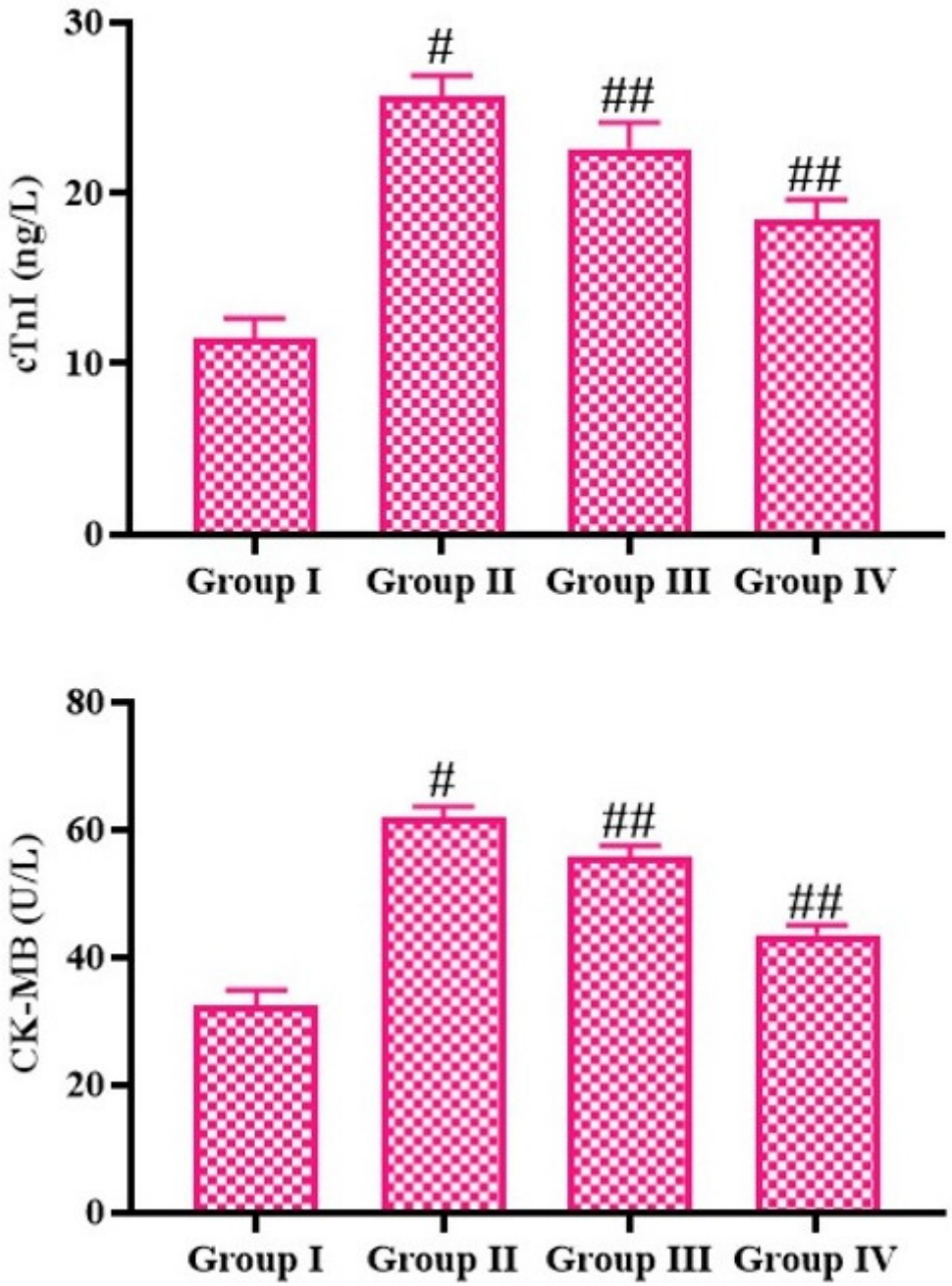

Figure 5: Effect of schaftoside on the cardiac injury biomarker levels in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

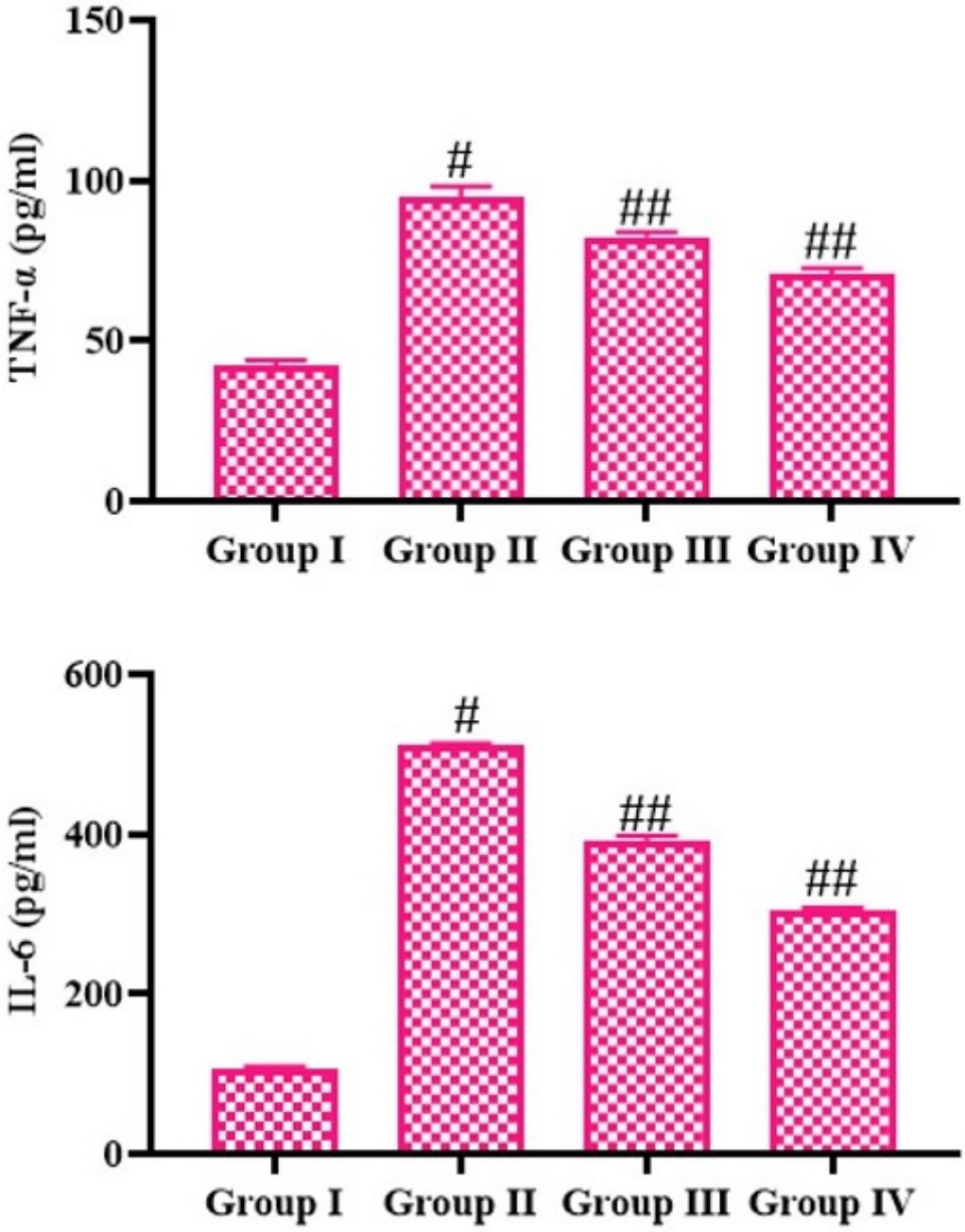

Figure 6: Effect of schaftoside on pro-inflammatory cytokines in the experimental rats. Each bar represents the mean±SD of three replicate tests, with statistical analysis performed using Graphpad software. Data are evaluated using one-way ANOVA and Tukey's post hoc analysis. An asterisk '#' indicates statistical significance at $p<0.01$ compared to the control group (Group I); '##' indicates statistical significance at $p<0.05$ in relation to the MIRI-induced diabetes group (Group II).

pathological mechanisms and the potential therapeutic options. Additionally, the modulation of the inflammation, through the inhibition of pro-inflammatory cytokines or the activation of anti-inflammatory pathways, may signify the promising therapeutic option to mitigate the adverse effects of MIRI, particularly in the context of diabetes.[41] The findings of this work has demonstrated that the MIRI-induced diabetic rats exhibited a considerable increase in both TNF-α and IL-6. Captivatingly, the schaftoside remarkably diminished the TNF-α and IL-6 levels in the MIRI-induced diabetic rats, highlighting its anti-inflammatory effects.

Histopathological analysis of the pancreatic tissue in diabetic rats is crucial for understanding the underlying pathological changes associated with the development and progression of the disease. Gross examination of the pancreas in diabetic rats often reveals atrophic changes, congestion, and edema, in contrast to the normal appearance of the pancreas in healthy control animals. Microscopic examination of the pancreatic

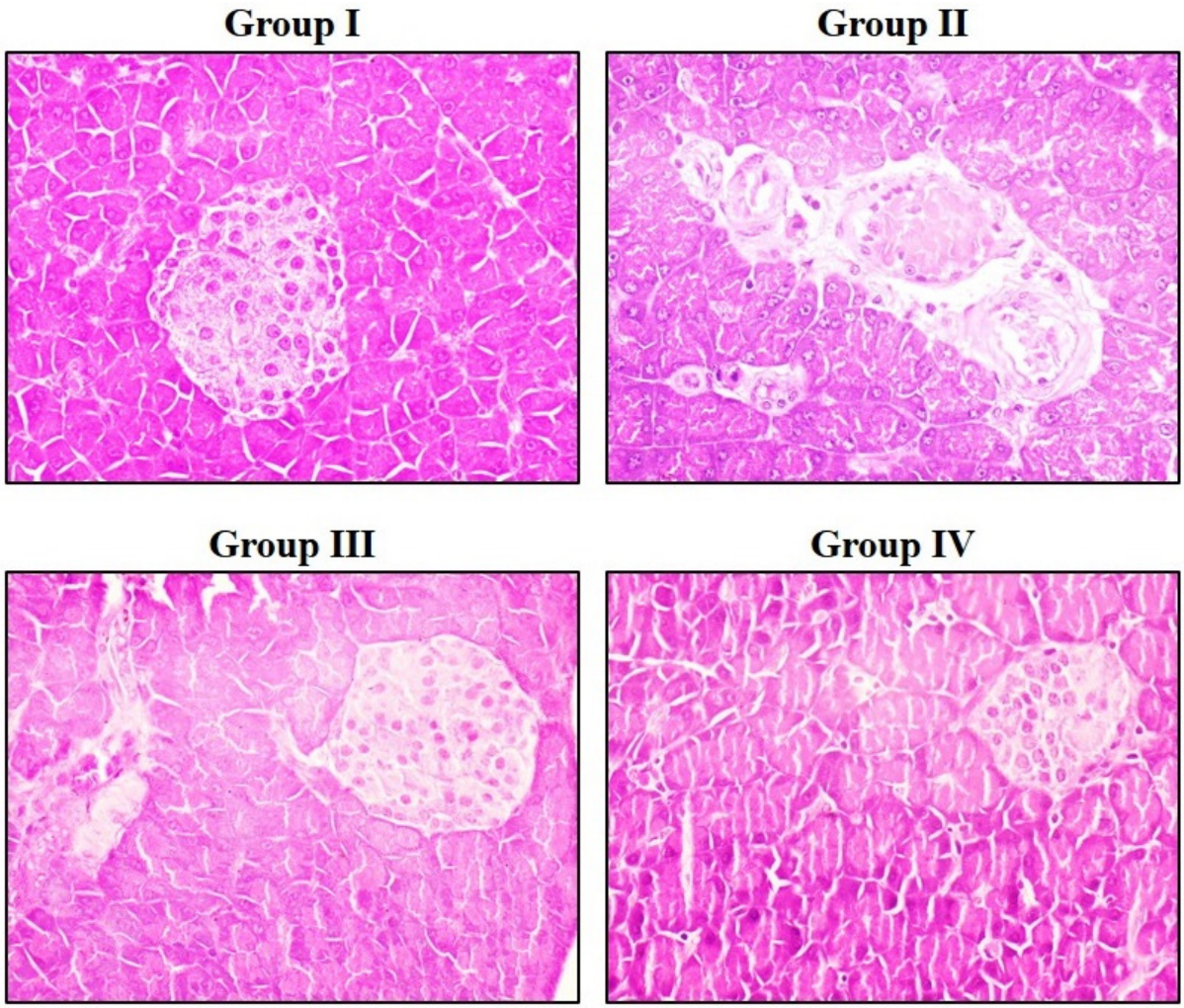

Figure 7: Effect of schaftoside on the pancreatic tissue histopathology of the experimental rats. The pancreatic tissues from control rats exhibited no signs of inflammation and revealed a normal cellular structure (Group I). The pancreas tissue of diabetic rats with MIRI displayed increased inflammatory cell infiltration, islet cell shrinkage, and adipose tissue hypertrophy (Group II). The histological changes in the pancreas tissue of the diabetic rats with MIRI were remarkably diminished by the 50 and 100 mg/kg of schaftoside treatment, respectively (Groups III and IV, respectively).

tissue further elucidates the specific cellular and structural changes. The islets of Langerhans, which are responsible for insulin production, typically show a reduction in size, number, and cellular components in diabetic rats compared to healthy controls. Additionally, necrotic and degenerative changes are commonly observed in the pancreatic tissue of diabetic rats, indicating the severe damage to the insulin-producing beta cells.[42] These histopathological findings are consistent with the reported metabolic changes observed in streptozotocin-induced diabetic rats. Furthermore, the histopathological changes in the pancreas can be used to evaluate the efficacy of potential therapeutic interventions for diabetes. In this work, the histopathological alterations in the pancreas tissue of the MIRI-induced diabetic rats were effectively reduced by the schaftoside treatment, which evidences the therapeutic effects of schaftoside.

CONCLUSION

The findings of this study demonstrate that schaftoside treatment alleviated the MIRI-induced complications in the diabetic rats. The diabetic rats with induced MIRI exhibited reduced FBG, tissue injury markers ALT and AST, FINS, HbA_{1c}, and oxidative stress markers following treatment with schaftoside. Moreover, the schaftoside treatment effectively regulated the lipid markers, and reduced the cTnI and CK-MB levels in the diabetic rats with induced MIRI. The concentrations of pro-inflammatory cytokines were also reduced the schaftoside treatment in the diabetic rats with MIRI. Thus, it has the potential to function as a talented therapeutic agent to treat cardiovascular complications in the context of diabetes. Additionally, it is essential to perform additional studies to have a more precise understanding of the salutary benefits of schaftoside on cardiovascular complications in diabetes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MIRI: Myocardial ischemic reperfusion injury; **FBG:** Fasting blood glucose; **HbA_{1c}:** Glycated haemoglobin; **AST:** Aspartate transaminase; **FINS:** Fasting insulin; **MPO:** Myeloperoxidase; **MDA:** Malondialdehyde; **cTnI:** Cardiac troponin I; **CK-MB:** Creatinine kinase-MB.

FUNDING

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ETHICAL STATEMENTS

Affiliated hospital of Beihua University (REC-47/05/1200).

SUMMARY

Diabetes mellitus, a chronic metabolic condition marked by increased hyperglycemia, represents a significant global health issue. A significant complication of diabetes is the heightened risk of cardiovascular disease. The findings of this study demonstrate that schaftoside treatment alleviated the MIRI-induced complications in the diabetic rats. Therefore, it has the potential to function as a talented therapeutic agent to treat cardiovascular complications in the context of diabetes.

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