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Original Article

Liquiritin Ameliorates Streptozotocin-Induced Gestational Diabetes in Pregnant Rat Model by Inhibiting Inflammation and Oxidative Stress Responses

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ABSTRACT

Aim/Background: Gestational diabetes is a significant medical complication that can develop during pregnancy, characterized by impaired glucose tolerance. This condition poses risks to both the mother and the developing fetus. Effective management of gestational diabetes is crucial to mitigate the potential complications. The current work was aimed at studying the therapeutic roles of the liquiritin on Streptozotocin (STZ)-induced gestational diabetes in pregnant rat models. **Materials and Methods:** The experimental rats with established pregnancies were administered 45 mg/kg of STZ to induce gestational diabetes, followed by an 18-day treatment with liquiritin. After the conclusion of treatments, the changes in body weight, fetal and placental weight, glucose, and insulin levels were evaluated. The concentrations of oxidative stress markers, antioxidants, and inflammatory cytokines in the liver tissues were evaluated using kits. The histological analysis was conducted on both liver and pancreas obtained from the experimental rats. **Results:** The findings of this work indicated that liquiritin at 10, 25, and 50 mg/kg dosages significantly elevated body weight, Hb, and insulin levels, and decreased placental weight, glucose, and HbA_{1c} levels in the gestational diabetes rats. The liquiritin treatment effectively diminished oxidative stress markers, and inflammatory markers, and enhanced the antioxidants in the gestational diabetes rats. The histological analysis of the both liver and pancreas confirmed the beneficial characteristics of liquiritin. **Conclusion:** The findings of this work illustrate that liquiritin considerably mitigates gestational diabetes in pregnant rat models. Thus, it can be a viable therapy option for treating gestational diabetes in the future.

Keywords: Oxidative stress, Glycated hemoglobin, Placenta, Liquiritin, Insulin.

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INTRODUCTION

Gestational diabetes is a type of diabetes that arises during pregnancy and often diminishes following delivery. It is defined by diminished glucose tolerance and/or elevated fasting blood glucose levels, initially identified during pregnancy. This condition arises due to the increased insulin resistance that occurs as a natural consequence of pregnancy, which can become exaggerated in some women.[1] The prevalence of gestational diabetes is estimated to be between 2-12% of all pregnancy cases, contingent upon the demographic and diagnostic criteria employed. Certain risk factors have been identified, including older maternal age, obesity, and a family history of diabetes.[2] Gestational diabetes is linked to several negative consequences for both the mother and the growing fetus. Macrosomia, or excessive fetal growth, can lead to birth injuries such as shoulder dystocia, as well as an increased risk of neonatal hypoglycemia. Gestational diabetes is a significant marker of the mother's eventual onset of permanent Type 2 diabetes and an elevated long-term risk of cardiovascular disease.[3]

Proper management of gestational diabetes, typically through dietary changes and insulin therapy, when necessary, is necessary to mitigate these risks and guarantee the best results for both mother and child.[4] The primary treatment options for gestational diabetes include lifestyle changes, like dietary modifications and exercise, as well as pharmacological interventions. Lifestyle modifications, such as a balanced, nutrient-rich diet and regular physical activity, are often the first-line approach and have been shown to help regulate blood glucose levels and promote healthy fetal growth. When lifestyle changes alone are insufficient, pharmacological therapies may be necessary.[5] Insulin therapy is thought as a gold standard for the pharmacological treatment of gestational diabetes, as it has been demonstrated to be effective

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and safe for both the mother and the fetus. Additionally, the oral medications glyburide and metformin have also been shown to be efficacious in treating gestational diabetes.[6]

While these treatment options are widely used, the potential for adverse effects and the need for continued monitoring and management of the condition highlight the importance of exploring alternative and complementary therapies. One promising area of research is the use of plant-based bioactive compounds, which have been investigated for their ability to improve glucose regulation and insulin sensitivity.[7] For instance, certain phytochemicals found in fruits, vegetables, and herbs have been demonstrated to have antioxidant, anti-inflammatory, and insulin-sensitizing effects that may be beneficial in the management of gestational diabetes.[8] Liquiritin is the major bioactive flavonoid compound majorly found in the licorice. The numerous biological activities of the liquiritin, including cardioprotective, anti-arthritic, anti-sepsis, neuroprotective, anti-inflammatory, and anti-cancer (Wei *et al*., 2017) activities were well reported.[9-14] Furthermore, there is no such data to claim its beneficial properties against gestational diabetes. Consequently, this study was aimed at studying the beneficial roles of the liquiritin on Streptozotocin (STZ)-induced gestational diabetes in pregnant rat models.

MATERIALS AND METHODS

Chemicals

The major chemicals and reagents utilized in this study, such as Liquiritin, Streptozotocin (STZ), etc., were purchased commercially from Sigma Aldrich, USA. The diagnostic kits to evaluate biochemical markers were purchased from LSBio and CusaBio, USA, respectively.

Experimental animals

The present work utilized healthy male Wistar rats, aged 6 to 8 weeks, with a body weight of 220±10 g. The rats were maintained in a controlled laboratory environment for seven days, which were confined in sterile polypropylene enclosures. Stringent cleanliness protocols were upheld during the research duration, and cages and bedding were regularly replaced. Standard temperature and relative humidity were continuously upheld, and a 12 hr light/dark series was instituted. The protocols for the animal assays were validated by the institutional animal ethics committee.

Initiation of gestational diabetes

The experimental rats underwent overnight fasting, and then vaginal swabs were evaluated to assess the estrous phase. Later, female rats with the estrous stage were paired with active male rats (1 male: 2 female ratio) for the mating procedure. Later 24 hr, the presence of sperm in the rat vagina was evaluated to evidence the pregnancy on day 0. Later, pregnant rats were separated from other rats. The non-pregnant rats were removed from further experiments. The rats with pregnancy were then treated with STZ (45 mg/kg) to induce gestational diabetes, while the control animals received an identical volume of buffered saline without STZ.

The study on Liquiritin administration in pregnant rats aimed to control litter and cage effects, using a stratified randomization process. The study ranked rats based on glucose levels and distributed equal numbers of mild, moderate, and severe diabetic rats across groups. However, the study also addressed concerns about blinding in the allocation process, treatment administrators, and outcome assessors. It suggested that randomization should have been conducted by an independent researcher to minimize selection bias. The study also standardized environmental factors such as light cycle, diet, temperature, and humidity. The study should clarify whether pups were randomly selected per litter, housed in cages, and if environmental standardization was strictly followed.

Experimental groups

Group, I rats received only saline, without STZ and/or liquiritin (Control). Group II rats were administered only with STZ to induce Gestational Diabetes (GDM). Group III-V rats were administered with STZ and subsequently treated with liquiritin at 10, 25, and 50 mg/kg concentrations (GDM+Liquiritin). The liquiritin treatment was delivered orally for 18 days. Following the conclusion of treatment, rats were euthanized, and samples were obtained for future analysis. The body weight of the rats was analyzed on the 0, 9th, and 18th day. The placental tissues and fetus were collected and weighed carefully.

Analysis of biochemical markers

The commercial glucometer (Roche) was utilized for the assessment of blood glucose levels. The commercial assay kit (Sigma-Aldrich) was employed to measure insulin concentration in the rats. The concentrations of Hemoglobin (Hb) and glycated Hemoglobin (HbA_{1c}) were measured by using the commercial kits (Elabscience, USA).

Oxidative stress-associated markers

The concentrations of Glutathione (GSH), Glutathione Peroxidase (GPx), Catalase (CAT), Superoxide Dismutase (SOD), and Malondialdehyde (MDA) in the liver of the experimental rats were assessed utilizing commercial diagnostic kits by strictly following the manufacturer's specifications (CusaBio, USA).

Analysis of inflammation-associated cytokines

The Interleukin (IL-6), IL-1β, and TNF-α concentration in the liver tissues of both control and experimental rats were evaluated using commercially available test kits. All tests were conducted in triplicate according to the manufacturer's protocols (Abcam, USA).

Histopathological analysis

Following surgical extraction from the experimental rats, both liver and pancreas were rinsed with buffered saline, dehydrated with graded ethanol, and then fixed in paraffin. The paraffinized liver and pancreas were then subsequently cut into 5 µm diameter. The liver and pancreas tissue sections were subsequently stained using hematoxylin and eosin and examined microscopically for histological alterations.

Statistical analysis

All the data were depicted as mean±SD of three replicate studies, analyzed using GraphPad Prism software. A one-way ANOVA and Tukey's *post hoc* assay were utilized for group comparisons, with $p<0.05$ denoting significance.

RESULTS

Effect of liquiritin on the body weight, fetus, and placental weights of experimental rats

The data indicated that rats subjected to gestational diabetes induction exhibited a substantial decrease in body weight and fetal weight and subsequently increased the placental weights compared to pregnant rats without gestational diabetes induction (Figure 1). Whereas, the oral administration of liquiritin at varying dosages (10, 25, and 50 mg/kg) significantly augmented the body weight and fetal body weight in the gestational diabetes rats (Figure 1). Furthermore, the liquiritin also diminished the placental weights in the gestational diabetes rats.

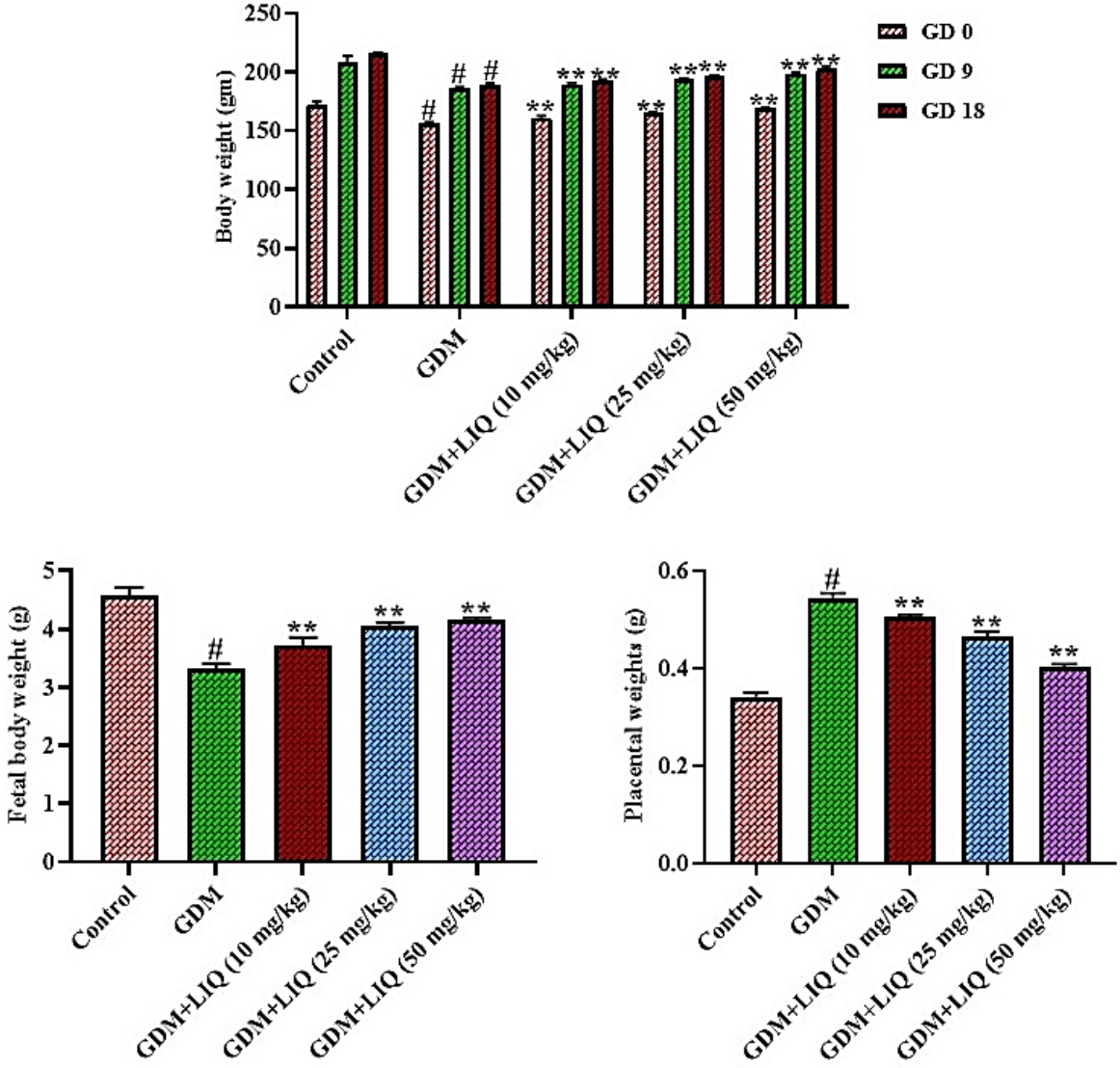

Figure 1: Effect of liquiritin on the body weight, fetus, and placental weights of the experimental rats. The findings are revealed as a mean±SD of three replicate studies. Each data undergoes statistical analysis by one-way ANOVA and Tukey's *post hoc* tests. Note: '#' reveals that the results are significant at $p<0.01$ in comparison to the control group (Group I); '**' reveals that the results are significant at $p<0.05$ in comparison to the gestational diabetes-induced group (Group II).

Effect of liquiritin on insulin and blood glucose in experimental rats

The present findings highlighted that pregnant rats with gestational diabetes exhibited a considerable increase in blood glucose and subsequent reduction in insulin concentrations in comparison to normal pregnant rats without gestational diabetes (Figure 2). Interestingly, the treatment with liquiritin at 10, 25, and 50 mg/kg concentrations effectively reduced the blood glucose and subsequently increased the insulin concentrations in the pregnant rats with gestational diabetes.

Effect of liquiritin on Hb and HbA_{1c} in experimental rats

Both Hb and HbA_{1c} concentrations were evaluated in the serum of experimental rats, with findings illustrated in Figure 3. The pregnant rats with gestational diabetes demonstrated a drastic reduction in Hb concentration and an elevation in HbA_{1c} concentration than the control. However, the liquiritin treatment at 10, 25, and 50 mg/kg concentrations considerably elevated the Hb level and diminished the HbA_{1c} concentration in the gestational diabetic rats.

Effect of liquiritin on oxidative stress-associated markers in experimental rats

The result of liquiritin on oxidative stress was assessed by quantifying the levels of MDA and antioxidants in the liver of experimental rats. The present results indicated a marked elevation in MDA levels, alongside the reduction in GSH, GPx,

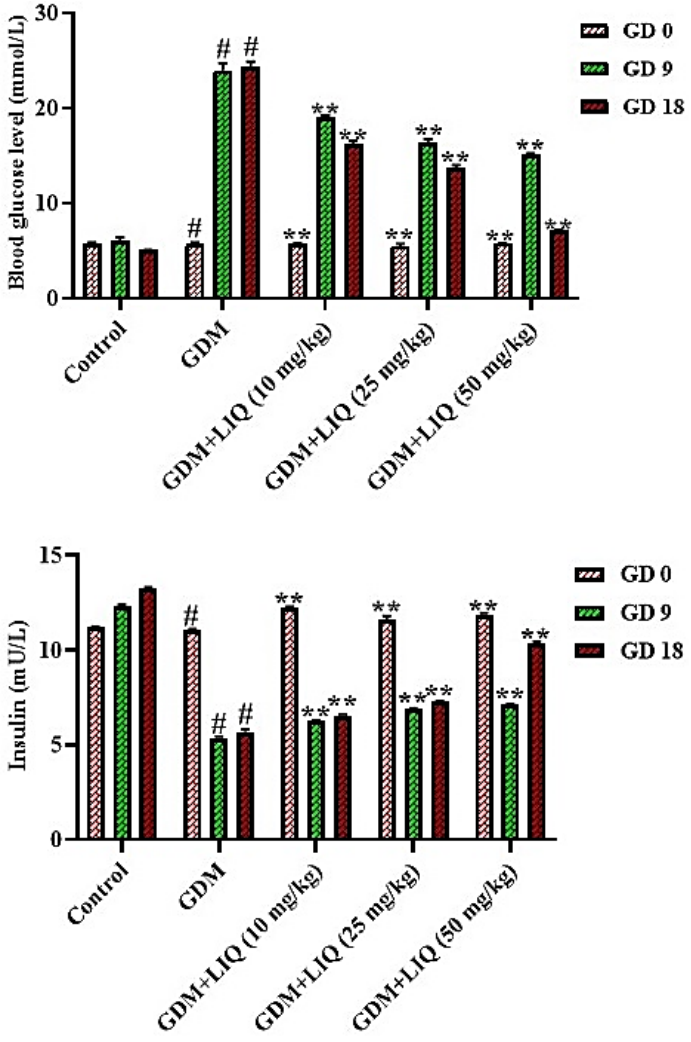

Figure 2: Effect of liquiritin on the insulin and blood glucose levels in the experimental rats. The findings are revealed as a mean±SD of three replicate studies. Each data undergoes statistical analysis by one-way ANOVA and Tukey's *post hoc* tests. Note: '#' reveals that the results are significant at $p<0.01$ in comparison to the control group (Group I); '**' reveals that the results are significant at $p<0.05$ in comparison to the gestational diabetes-induced group (Group II).

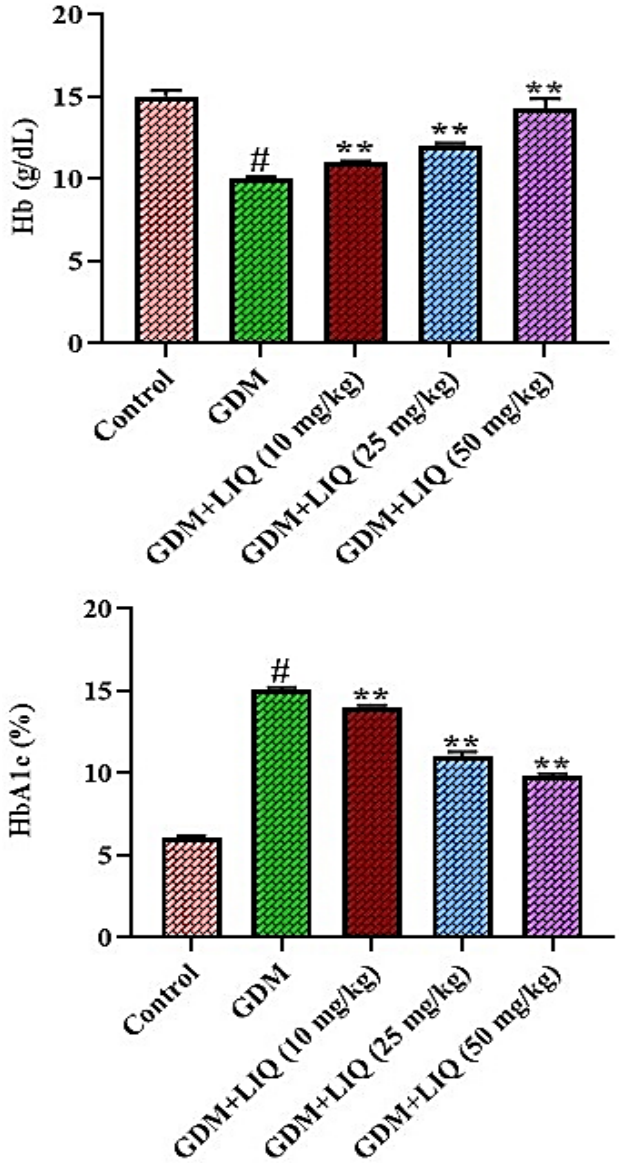

Figure 3: Effect of liquiritin on Hb and HbA_{1c} in experimental rats. The findings are revealed as a mean±SD of three replicate studies. Each data undergoes statistical analysis by one-way ANOVA and Tukey's *post hoc* tests. Note: '#' reveals that the results are significant at $p<0.01$ in comparison to the control group (Group I); '**' reveals that the results are significant at $p<0.05$ in comparison to the gestational diabetes-induced group (Group II).

CAT, and SOD concentrations in the liver tissues of gestational diabetes rats, relative to the control rats (Figure 4). Captivatingly, the different concentrations (10, 25, and 50 mg/kg) of liquiritin treatment markedly decreased MDA levels and subsequently increased the antioxidants in gestational diabetes rats.

Effect of liquiritin on inflammatory cytokines in experimental rats

The present findings indicated a significant increase in the IL-6, IL-1β, and TNF-α concentrations in the liver of the rats with gestational diabetes when compared with control (Figure 5). However, the treatment of varying dosages of liquiritin (10, 25, and 50 mg/kg) significantly diminished the concentrations of IL-6, IL-1β, and TNF-α in the liver of the gestational diabetes rats.

Effect of liquiritin on liver and pancreas histology of the experimental rats

The findings of the histopathological study of both the liver and pancreas are represented in Figures 6 and 7. Both liver and pancreas from control rats exhibited no inflammatory signs and exhibited normal cellular architecture. Conversely, the livers of rats with gestational diabetes displayed significant inflammatory cell infiltration and hepatocyte injury. The pancreas of the rats with gestational diabetes exhibited inflammatory cell infiltrations, constriction of islet cells, and enlarged adipose tissue. Fascinatingly, the histological alterations in both the liver and pancreas were remarkably alleviated by 10, 25, and 50 mg/kg of liquiritin, as demonstrated by the reduction in pancreatic lesions, inflammation, and tissue damage in the tissues of gestational diabetes rats.

DISCUSSION

Gestational diabetes is a disorder marked by glucose intolerance that commences or is initially identified during pregnancy. This disorder is a growing global health concern, linked to numerous short-term and long-term complications for both mother and child. One crucial aspect of understanding and managing gestational diabetes is the analysis of maternal body weight, fetal,

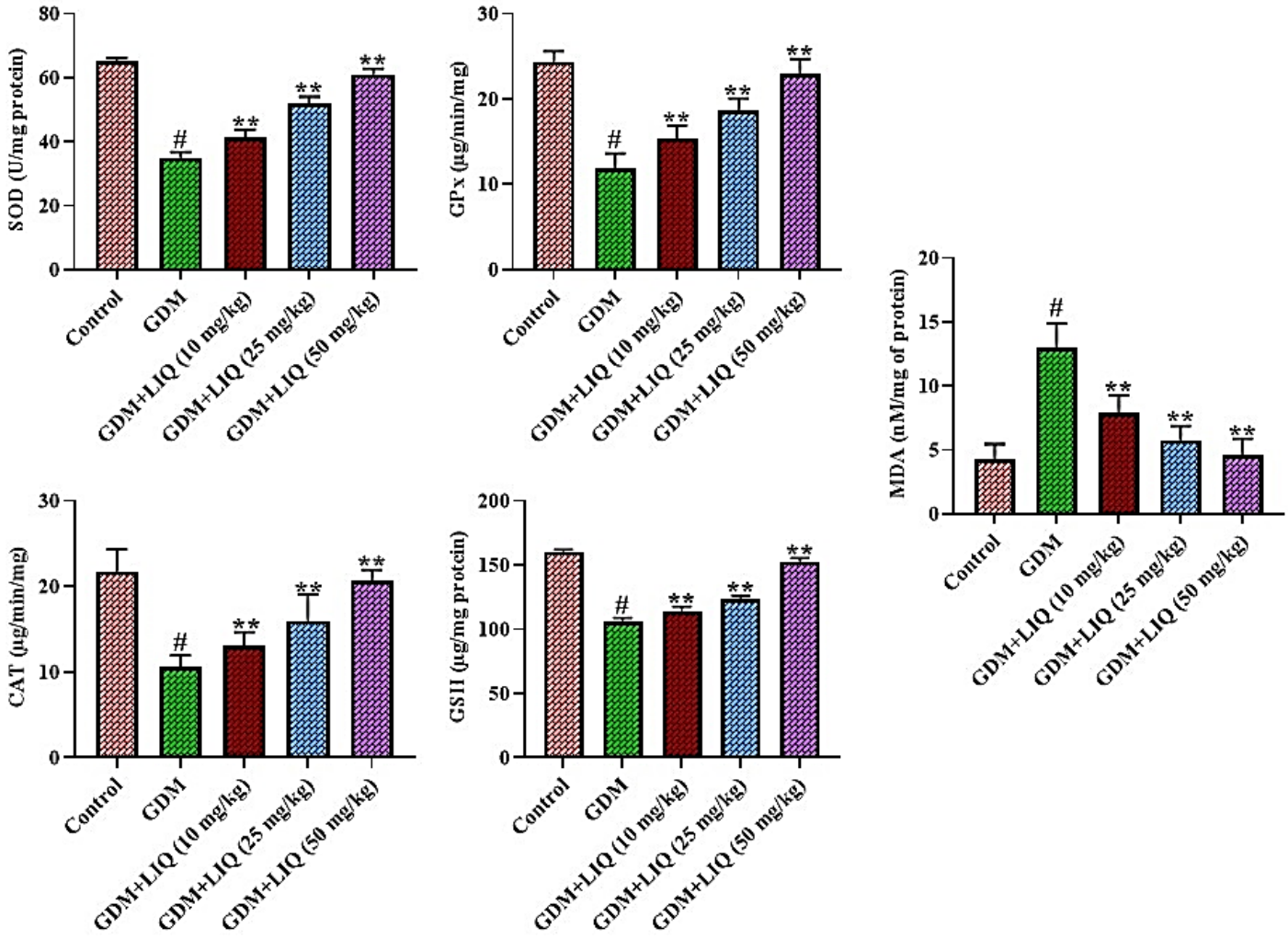

Figure 4: Effect of liquiritin on the oxidative stress-associated marker levels in the experimental rats. The findings are revealed as a mean±SD of three replicate studies. Each data undergoes statistical analysis by one-way ANOVA and Tukey's *post hoc* tests. Note: '#' reveals that the results are significant at $p<0.01$ in comparison to the control group (Group I); '**' reveals that the results are significant at $p<0.05$ in comparison to the gestational diabetes-induced group (Group II).

and placental weights.[15] The weight of the mother is a crucial determinant in the onset of gestational diabetes. Gestational diabetes affects 2 to 12% of pregnant women, potentially resulting in macrosomia, shoulder dystocia, delivery complications, neonatal hypoglycemia, and elevated perinatal mortality. The overwhelming majority of women with gestational diabetes are overweight or obese, and the increased body mass index of these women may, at least in part, explain the complications associated with gestational diabetes.[16] Fetal body weight is another important consideration in gestational diabetes. Maternal obesity and gestational diabetes have been associated with elevated risks of excessive birth weight in offspring. This may result in difficulties including shoulder dystocia, birth trauma, and elevated rates of cesarean delivery. Monitoring fetal growth and weight through ultrasound is crucial to treat gestational diabetes.[17] Placental weight is also closely linked to gestational diabetes. The placenta plays a critical role in regulating fetal development, and alterations in placental function can participate in the onset of gestational diabetes and its associated complications.[18] The current findings indicated that gestational diabetes rats exhibited a substantial decrease in body weight and fetal body weight and subsequent elevation in placental weights. Whereas, the treatment of liquiritin at various concentrations significantly augmented body weight and fetal body weight and reduced the placental weights in the gestational diabetes rats.

Gestational diabetes poses a considerable health risk, linked to numerous metabolic and cardiovascular issues for both mother and fetus. Proper management of gestational diabetes, including the analysis of blood glucose and insulin is crucial to ensure the well-being of the mother and child.[19] Routine screening of glucose levels is typically advised for pregnant women since

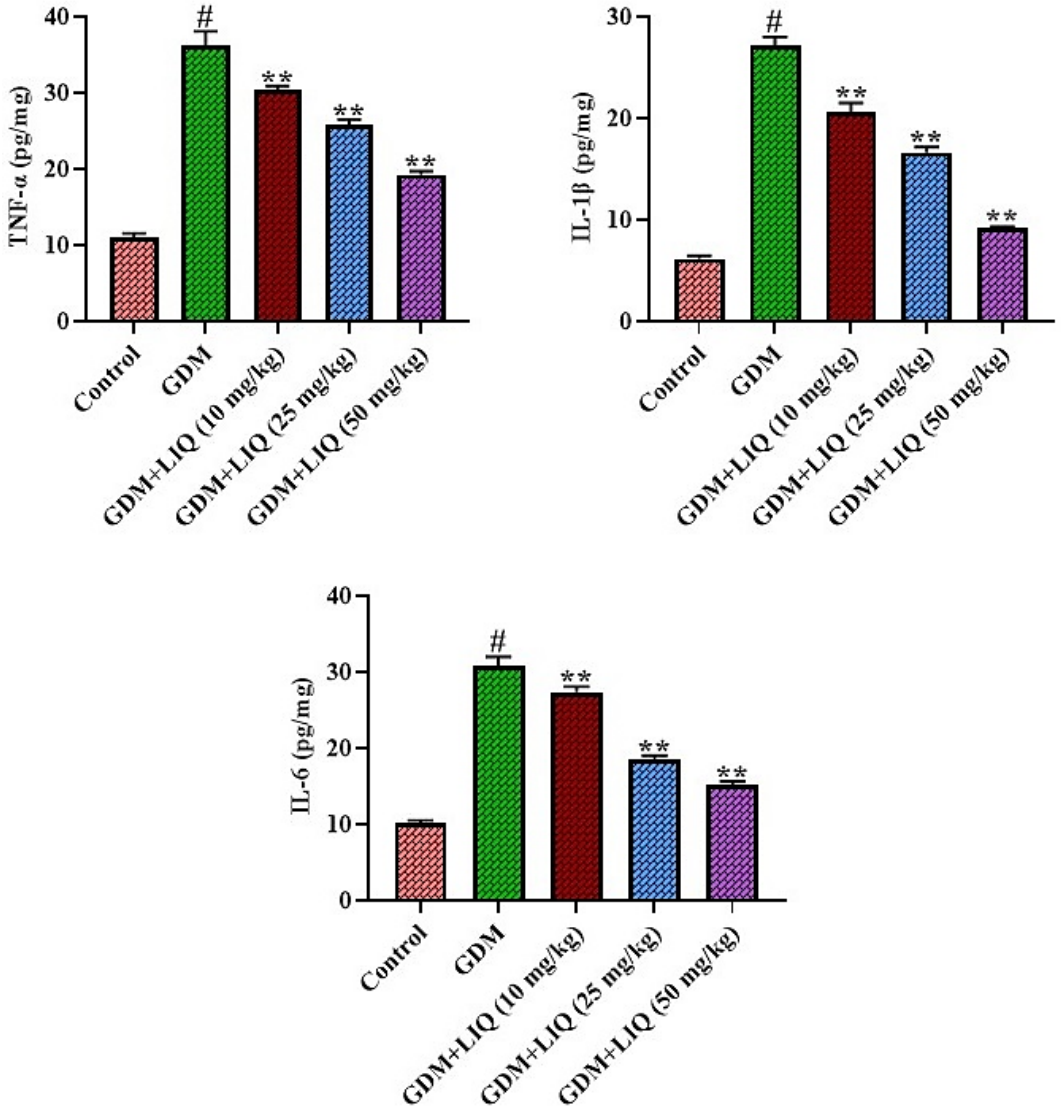

Figure 5: Effect of liquiritin on the inflammatory cytokine levels in the experimental rats. The findings are revealed as a mean±SD of three replicate studies. Each data undergoes statistical analysis by one-way ANOVA and Tukey's *post hoc* tests. Note: '#' reveals that the results are significant at $p<0.01$ in comparison to the control group (Group I); '**' reveals that the results are significant at $p<0.05$ in comparison to the gestational diabetes-induced group (Group II).

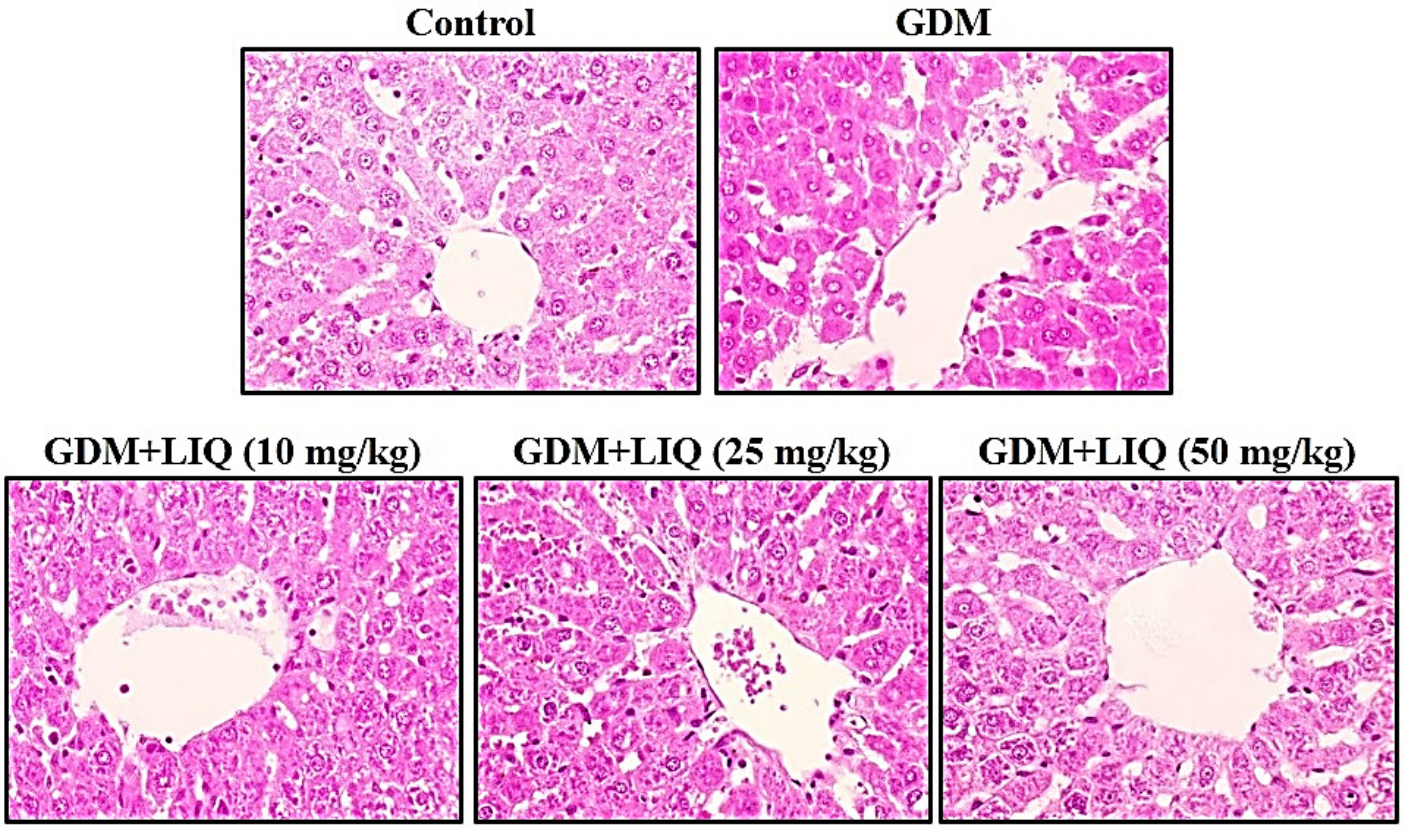

Figure 6: Effect of liquiritin on the liver histopathology of the experimental rats. Group I: the liver tissues from healthy pregnant rats exhibited no signs of inflammation and demonstrated normal cellular architecture. Group II: The livers of the rats with gestational diabetes displayed significant inflammatory cell infiltration and hepatocyte injury. Groups III-V: The histological alterations in the liver tissues were significantly alleviated by the treatment with 10, 25, and 50 mg/kg of liquiritin, respectively as demonstrated by the reduction in adipose size, inflammation, and hepatocyte damage in the liver tissues of gestational diabetes rats.

it aids in identifying those at risk of significant hyperglycemia. Once diagnosed, the mother is taught self-monitoring of blood sugar with a blood glucose meter, and the number and timing of measurements are agreed upon individually.[20] Analyzing glucose and insulin concentrations in gestational diabetes is important for several reasons as it allows healthcare providers to monitor the effectiveness of the treatment plan, which typically involves dietary modifications, physical activity, and potentially insulin or oral medication. The analysis of these concentrations can offer useful insights into the underlying pathophysiological mechanisms of gestational diabetes.[21] In this study, the results indicated that gestational diabetes rats exhibited a considerable increase in blood glucose and subsequent diminution in insulin concentrations in comparison to normal pregnant rats. However, the liquiritin treatment effectively diminished the blood glucose and subsequently increased the insulin concentrations in the gestational diabetes rats.

Hb and HbA_{1c} are two crucial biomarkers that offer useful data for the diagnosis and management of gestational diabetes. Hb is a protein located in RBCs that facilitates the transport of oxygen throughout the body. In individuals with diabetes, including those with gestational diabetes, the Hb molecules can become glycated, meaning they have glucose attached to them. This process, known as glycation results in the formation of HbA_{1c}.[22] HbA_{1c} serves as a significant indicator for evaluating long-term glycemic regulation in diabetic individuals. It offers a more thorough representation of an individual's typical blood glucose levels over the past 2-3 months, in contrast to a solitary blood glucose measurement.[23] In the context of gestational diabetes, analyzing both Hb and HbA_{1c} can provide critical information for diagnosis, treatment, and monitoring. Hb levels can help identify anemia, a common complication in pregnant women, while HbA_{1c} can help assess the effectiveness of dietary and lifestyle interventions, as well as the need for pharmacological treatment.[24] The importance of analyzing Hb and HbA_{1c} in gestational diabetes is well-documented in the literature. The present findings found a significant reduction in Hb level and an elevation in HbA_{1c} concentration in the gestational diabetes rats. The liquiritin markedly elevated the Hb level and diminished the HbA_{1c} level in the gestational diabetic rats.

Oxidative stress, characterized by an imbalance between ROS production and the body's antioxidant defenses, is a critical element in the pathophysiology of gestational diabetes and its related hepatic problems.[25] The analysis of specific biomarkers of oxidative stress can provide valuable insights into the role of oxidative stress in the liver tissues of individuals with gestational

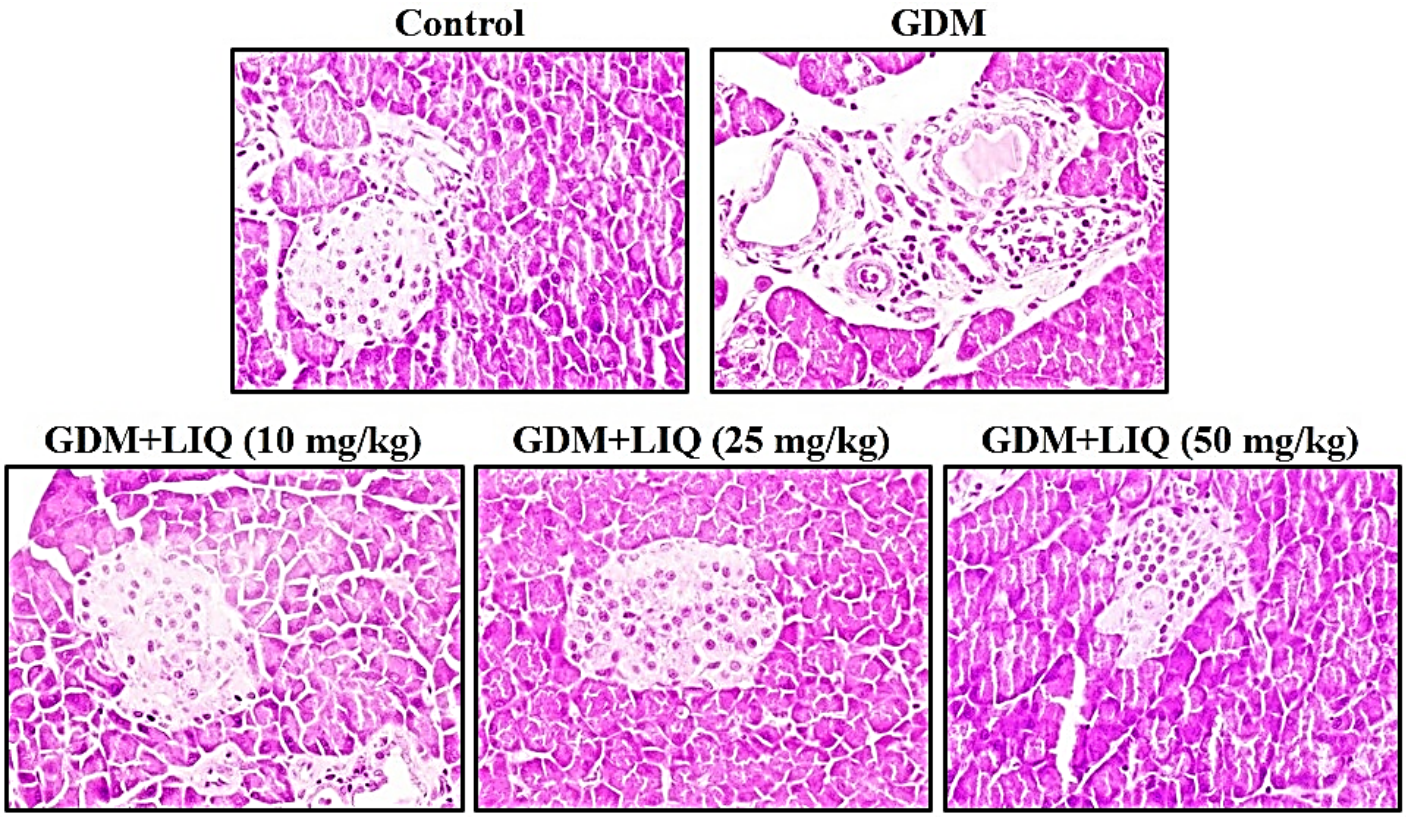

Figure 7: Effect of liquiritin on the pancreas histopathology of the experimental rats. Group I: the pancreas tissues from healthy pregnant rats exhibited no signs of inflammation with normal cellular arrangements. Group II: The pancreas of the rats with gestational diabetes exhibited increased infiltration of inflammatory cells, constriction of pancreatic islet cells, and enlarged adipose tissue. Groups III-V: The histological abnormalities in the pancreatic tissues were considerably decreased by the treatment with 10, 25, and 50 mg/kg of liquiritin, as indicated by the reduction in pancreatic lesions and inflammatory signs in the pancreas of rats with gestational diabetes.

diabetes. MDA, a byproduct of lipid peroxidation, is a commonly utilized marker of oxidative stress and may be increased in the livers of persons with gestational diabetes.[26] GSH, an important antioxidant, and its related enzymes, such as GPx and CAT, play a critical role in the body's protection against oxidative damage. SOD, a major antioxidant enzyme that catalyzes the transformation of superoxide radicals to H_2O_2 and O_2, is another key marker of the antioxidant response to oxidative stress.[27] Numerous studies have investigated the relationship between oxidative stress and gestational diabetes, highlighting the importance of these biomarkers in understanding the underlying mechanisms and potential therapeutic interventions.[28,29] The elevated ROS generation and the subsequent imbalance in the antioxidant system can contribute to various pathological changes, including liver dysfunction, in individuals with gestational diabetes.[30] In this study, the present results indicated a marked elevation in MDA levels, alongside the decrease in GSH, GPx, CAT, and SOD concentrations in the liver tissues of the rats with gestational diabetes. However, the liquiritin treatment successfully diminished MDA level and subsequently increased the antioxidant concentrations in rats with gestational diabetes, which proves its antioxidant effects.

It has been highlighted the close relationship between inflammation and the pathogenesis of diabetes, including gestational diabetes. Inflammatory cytokines, like TNF-α and IL-6, have been shown to diagnose the onset of type-2 diabetes, and anti-inflammatory interventions have been found to lower glycemia and potentially diminish diabetic risks. In the context of gestational diabetes, the presence of an ongoing cytokine-induced acute-phase response has also been implicated in the disease.[31] The liver is a key organ involved in glucose metabolism and homeostasis, and it is known to be a source of TNF-α, IL-6, and IL-1β. During gestational diabetes, these pro-inflammatory markers may be augmented in the liver, contributing to insulin resistance and dysregulated glucose regulation.[32] Obesity and insulin resistance, which are common precursors to gestational diabetes, are also connected with increased concentrations of these pro-inflammatory cytokines. The influx of cytokines from the expanding adipose tissue can create an imbalance between cytokines that promote insulin sensitivity, such as adiponectin and leptin, and those that promote inflammation, leading to the onset of insulin resistance and glucose intolerance.[33] The mechanisms by which inflammation participates in the pathogenesis of gestational diabetes are multifaceted. Cytokines can interfere with insulin signaling pathways, impairing the anti-inflammatory properties of insulin and further perpetuating the inflammatory

state. Chronic overnutrition and oxidative stress may also play major roles in triggering the inflammatory cascade, facilitating the onset of gestational diabetes.[34] Therefore, understanding these underlying mechanisms is critical to developing useful diagnostic and therapeutic methods to address this significant health challenge. The present findings indicated a significant increase in the IL-6, IL-1β, and TNF-α concentrations in the liver tissues of the gestational diabetes rats. Interestingly, the treatment with liquiritin significantly reduced these inflammatory cytokine concentrations in the liver of gestational diabetes rats which evidences its anti-inflammatory properties.

CONCLUSION

The findings of this work demonstrate that liquiritin considerably mitigates gestational diabetes in rats. Rats with gestational diabetes exhibited increased body weight, Hb, and insulin levels, reduced placental weight, glucose, and HbA_{1c} levels following treatment with liquiritin. Moreover, the liquiritin treatment reduced oxidative stress by enhancing antioxidants and inflammatory conditions by enhancing and reducing inflammatory cytokines in rats with gestational diabetes. Thus, it can be a viable therapy option for treating gestational diabetes in the future. Additionally, it is important to perform more work to have a detailed understanding of the benefits of liquiritin on gestational diabetes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

STZ: Streptozotocin; **GDM:** Gestational Diabetes Mellitus; **ROS:** Reactive Oxygen Species; **Hb:** Hemoglobin; **HbA_{1c}:** Glycated Hemoglobin; **MDA:** Malondialdehyde; **GSH:** Glutathione; **GPx:** Glutathione Peroxidase; **CAT:** Catalase; **SOD:** Superoxide Dismutase; **TNF-α:** Tumor Necrosis Factor-alpha; **IL-6:** Interleukin-6; **IL-1β:** Interleukin-1 beta; **IAEC:** Institution Animal Ethics Committee; **RIPA:** Radioimmunoprecipitation Assay; **BSA:** Bovine Serum Albumin; **TBST:** Tris-Buffered Saline with Tween; **ELISA:** Enzyme-Linked Immunosorbent Assay; **NF-κB:** Nuclear Factor Kappa B; **MAPK:** Mitogen-Activated Protein Kinase; **SD:** Standard Deviation; **ANOVA:** Analysis of Variance; **RBC:** Red Blood Cells; **USA:** United States of America.

ETHICAL STATEMENTS

The research study was carried out obeying Institution Animal Ethics Committee (IAEC No. Huabh20221203X), Ethics Committee: Affiliated Hospital of Hebei University.

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