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Original article

Comparison of the effects of licorice hydroalcoholic extract and glycyrrhizic acid on function, inflammation, oxidative stress, and apoptosis in the liver of diabetic rats

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Abstract

Objective: Inflammation and oxidative stress are important factors in the pathogenesis of diabetes. This study was carried out to determine the effect of licorice (*Glycyrrhiza glabra*) hydroalcoholic extract (Li) and its bioactive compound, glycyrrhizic acid (GA) on liver function markers, inflammatory factors, oxidative stress, and apoptosis regulators in diabetic rats.

Materials and methods: Thirty-six male Wistar rats were randomly divided into 6 groups: diabetic rats, diabetic rats treated with Li (50 and 100 mg/kg), diabetic rats treated with GA (50 and 100 mg/kg), diabetic rats treated with Li and GA, and healthy rats, for 30 days. Administration was done by intraperitoneal injection. Alloxan (240 mg/kg, intraperitoneal injection) was used to induce diabetes. Serum levels of alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), glutathione peroxidase (GPX), and superoxide dismutase (SOD), as well as Bax and BCL2 proteins were measured. Data analysis was done with GraphPad Prism software.

Results: The diabetic control level of serum ALP, ALT, AST, GGT, CRP, TNF-α, IL-1β, IL-6, MDA, 8-OHdG, and Bax proteins was significantly higher compared with the treatment groups ($p \leq 0.001$). The protein levels of GPX, SOD, and BCL2 were significantly up-regulated in the treatment groups compared to diabetic control groups ($p \leq 0.001$). Most variables showed a better result with the 100 mg/kg GA for 30 days.

Conclusion: The present study showed the anti-inflammatory effects of the extract of the root of licorice and the active compound of it, GA, in ameliorating the diabetic-induced hepatic damage in rats.

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Introduction

Diabetes mellitus (DM) is a group of metabolic diseases in which there is an increase in blood glucose (Deepthi et al. 2017). The prevalence of diabetes is increasing, and DM is an important challenge for human health. The prevalence of diabetes mellitus in 2017 was estimated to be 425 million in the age group of 20-79 years and was projected to increase to 642 million in 2040 (Teo et al. 2021). In addition, it has been estimated that almost 46.1% of diabetics will die before the age of 60 (Ogurtsova et al. 2017). There are two main types of diabetes: type 1 (insulin-dependent) and type 2 (non-insulin-dependent) (Roglic 2016). Type 2 DM constitutes approximately 95% of all DM and occurs due to the lack of response to the insulin produced by beta cells of the pancreas, which can lead to a series of complications and death (Zaccardi et al. 2016). It has been reported that DM is closely related to oxidative stress, overproduction of free radicals, and mitochondrial dysfunction (Bhatti et al. 2022). Additionally, hyperglycemia is known to have an impact on lipid and protein metabolism, resulting in alterations of hepatic enzymes and fatty liver diseases (Shojima and Yamauchi 2023). The key mechanisms of DM that cause hepatic injury include the failure of inflammatory response mediated by the pro-inflammatory cytokines (e.g. tumor necrosis factor-α (TNF-α), interleukin-1β (IL)-1β, and IL-6, leading to oxidative damage to the liver (Lempesis and Georgakopoulou 2023). DM, is involved in pancreatic β-cell destruction and apoptosis, can lead to anti-apoptotic protein dysregulations such as BCL2 and BCL-X (Novoselova et al. 2024). Therefore, DM prevention and early identification can prevent serious complications (Huttunen-Lenz et al. 2023. Currently, DM treatment is mainly based on lifestyle modification, oral or injectable hypoglycemic agents, and alternative therapies. Recently, investigations have indicated that herbal medicines could effectively prevent DM progressions and complications (Rayate et al. 2023). Licorice root is a natural sweetener from *Glycyrrhiza glabra* and is beneficial for human health (Elrys et al. 2020). *G. glabra* active component called glycyrrhizin (glycyrrhizic acid) is one of the most frequently used substances in natural medicines (Truong et al. 2024). Its properties have been widely investigated in gastrointestinal disorders, cardiovascular diseases, and respiratory infections (Bazekin et al. 2023; Ghosh and Patra). It also has anti-apoptotic and anti-aging properties (Zhang et al. 2023). But, its role in diabetes complications has not been completely understood. The present study compared the effects of licorice hydroalcoholic extract and glycyrrhizic acid on function, inflammation, oxidative stress, and apoptosis in the liver of diabetic rats.

Materials and Methods

Animals

In this work, 36 adult male Wistar rats were prepared and sent to Basic Sciences Laboratory of Payam Noor University of Mashhad, Iran. They received standard rat chow and water *ad libitum* in the cages under normal condition with regard to light-dark cycle (12hr/12hr), temperature (22 ± 2 ºC), and humidity. Also, all experiments were performed 10 days after the accommodation of the animals to adapt to the environment.

Plant preparation and chemical extraction

First, licorice plants (*G. glabra*) were collected from agricultural fields around Mashhad, Iran. The roots were separated, dried, and subjected to hydroalcoholic extraction using the Soxhlet method (De Castro & Priego-Capote, 2010). The hydroalcoholic solvent consisted of 70% ethanol in water, which was used to efficiently extract bioactive compounds from the roots.

Onset of diabetes

A single intraperitoneal dose of alloxan monohydrate induced type 1 diabetes, with a concentration of 240 milligrams per kilogram (mg/kg), after 16-hour fasting (Macdonald Ighodaro et al. 2017).

Glucose determination

Glucose levels were measured by blood collection from the tail vein using a lancet to prick the skin, test-strip, and glucometer device model IGM-0002A (Korea EasyGluco). Diabetes was diagnosed as glucose levels more than 200 mg/dL (Ahmad and Ahmad 2018).

Experimental design

Following diabetes induction, rats were randomly assigned into experimental groups to evaluate the hepatoprotective and anti-inflammatory effects of licorice hydroalcoholic extract and glycyrrhizic acid. The study design included healthy and diabetic controls, as well as groups receiving different doses of licorice extract or glycyrrhizic acid, in order to systematically assess their effects on liver function, oxidative stress, inflammation, and apoptosis. Treatments were administered intraperitoneally for 30 days according to previously reported protocols (Yahya et al. 2024; Sil et al. 2015; Jani et al. 2021). Rats were randomized into 6 groups consisting of 6 rats each: Group 1 (normal saline control) received an intraperitoneal injection of sterile normal saline; Group 2 (diabetic control group) was administered intraperitoneal injection of sterile normal saline (diabetic); Group 3 (diabetic treatment group): intraperitoneal injection with 50 mg/kg licorice hydroalcoholic extract (Li) (Jani et al., 2021); Group 4 (diabetic treatment group): intraperitoneal injection with 100 mg/kg licorice hydroalcoholic extract (Li); Group 5 (diabetic treatment group): intraperitoneal injection with 50 mg/kg glycyrrhizic acid (GA); and Group 6 (diabetic treatment group): intraperitoneal injection with 100 mg/kg glycyrrhizic acid (GA).

Sample collection

At the end of the experiment, the animals were anesthetized with diethyl ether. Then, the hearts were opened, and blood was withdrawn from the left ventricle using a 2 ml syringe. Samples were kept in standard tubes and were placed in a 35°C incubator. These tubes were then allowed to coagulate and then spun for 12 min at 5000 rpm. The clots were taken out, and the serum was transferred and stored in a -80°C freezer. The liver was homogenized in water with a T25 digital ULTRA-TURRAX tissue homogenizer for 2 min at 5000 rpm (IKA, Germany). To prevent the degradation of enzymes and proteins, all steps were carried out at 4°C, and 0.5 mM of phenylmethanesulfonyl fluoride solution was used as a cellular protease inhibitor.

Biochemical analysis

Various biological parameters were determined in the blood serum. Liver function was evaluated by measuring alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST) (De Castro and Priego-Capote, 2010), and gamma-glutamyl transferase (GGT). The inflammatory status was determined by the levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6. Oxidative stress was determined using levels of malondialdehyde (MDA), glutathione peroxidase (GPX), and superoxide dismutase (SOD) activity. Special kits and the ELISA method (ELISA Reader-State Fax 2100-American) were used for all measurements. Protein expression of Bax and Bcl-2 was quantified to study the regulation of apoptosis. The assays of 8-hydroxy-2'-deoxyguanosine (8-OHdG) were used to measure DNA oxidative damage (De Castro & Priego-Capote, 2010).

AST measured by Pars Azmoon kit based on IFCC standard method; ALP with Pars Azmoon kit by kinetic method (p-nitrophenyl phosphate substrate); GGT with Pars Azmoon kit by kinetic assay (γ-

glutamyl-p-nitroanilide substrate); TNF-α, IL-1β and IL-6 with special kit (KalaZist, Iran) and ELISA method; CRP by latex immunoturbidimetric assay; MDA: by Lipid peroxidation kit (Kiazist, Iran) by using TBARS: Thiobarbituric Acid Reactive Substances assay; 8-OHdG by ZellBio kit; SOD by SOD Assay Kit (Karmania Pars Gene, Iran), GPX by Glutathione peroxidase assay kit (Navand Salamat Co, Iran); BCL2 kit, Code: CSB-E08854r and BAX kit: Code: CSB-EL002573RA (Cusabio, China) by Sandwich Elisa method.

Statistical analysis

All statistical evaluations and comparisons have been done by examining the data using the GraphPad Prism software (version 10.4.1). The values of the mean are given as the mean ± standard deviation (SD). Statistically significant differences are $p<0.05$, $p<0.01$ and $p<0.001$. In the event that the data sets had more than one factor, both one-way and two-way analysis of variance were utilized. In the following step, multiple comparisons were carried out using Tukey's post hoc test, which is described in the captions of the Figures.

Results

Serum liver markers and glucose levels

The levels of fasting blood sugar FBS (Figure 1A) and liver enzymes such as ALT, ALP, and AST (Figure 1B, C, and D) were significantly raised after induction of diabetes as compared to the non-diabetic control group (NS) ($p<0.0001$). These results indicate the occurrence of severe hyperglycemia and liver damage caused by diabetes. All treated groups (hydroalcoholic extract of Licorice (Li), glycyrrhizic acid (GA), and Li ± GA) had a significant reduction in the above-mentioned indicators after 30 days of intervention versus the diabetic control group.. Both doses of glycyrrhizic acid showed considerable therapeutic benefits, but in most cases (particularly in Figure 1B and D), there was no significant difference between 50 and 100 mg/kg, indicating that lower dose had the greatest effect. Both compounds may have antidiabetic and hepatoprotective effects in the animal model. A significant plasma GCT rise was seen in Figure 1E (diabetes induction) compared to NS (control) group ($p<0.0001$). After 30 days, the diabetic group had significantly higher GCT levels ($p<0.0001$) compared to the hydroalcoholic extract of licorice (50 and 100 mg/kg). GCT reduction by licorice groups was dose-dependent, but about glycyrrhizic acid was not dose-dependent.

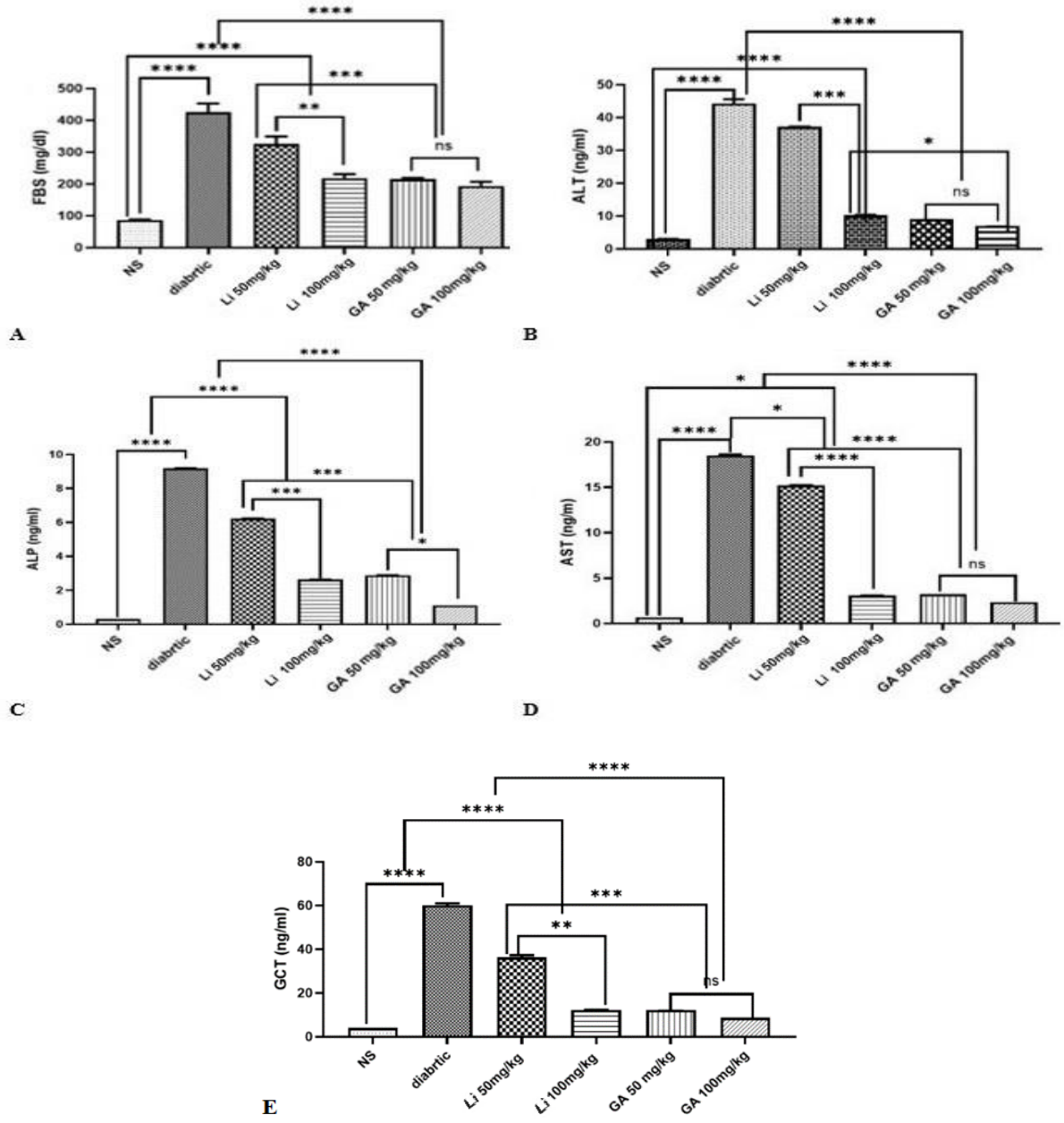

Figure 1. Effect of licorice hydroalcoholic extract (Li) and glycyrrhizic acid (GA) on FBS (Fasting blood sugar) and serum alanine aminotransferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) in control (Normal saline: NS) and diabetic rats (six rats per group). The data are shown as Mean ± SD. Significant differences are marked by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns: no significant difference.

Inflammatory markers

Diabetes induction led to significant increases in plasma levels of IL-1β, IL-6, and CRP compared to the NS group (Figures 2A, B, and D), but not significant changes in TNF-α (Figure 2C). These data suggest that diabetic mice had systemic inflammation. Treatment with hydroalcoholic licorice extract (50 and 100 mg/kg) and glycyrrhizic acid (50 and 100 mg/kg) for 30 days significantly reduced IL-1β, IL-6, and CRP levels compared to the diabetic group. The licorice extract with the 100 mg/kg dose having a stronger effect. Only the high dose of licorice extract significantly reduced TNF-α. These findings suggest that licorice extract has higher anti-inflammatory benefits than glycyrrhizic acid.

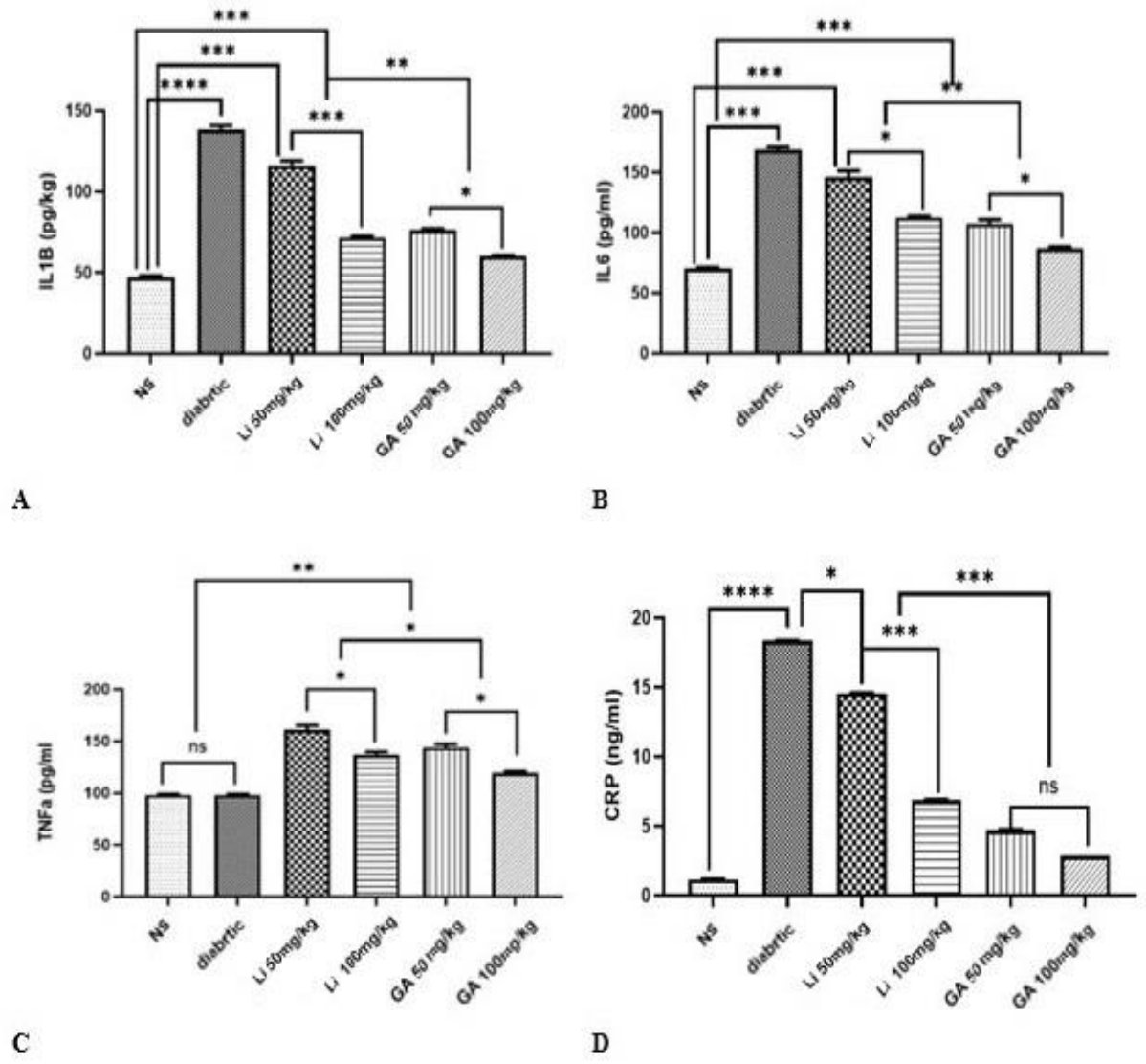

Figure 2. Effect of licorice hydroalcoholic extract (Li) and glycyrrhizic acid (GA) on inflammatory indicators: Interleukin 1B (IL1B), Interleukin 6 (IL6), Tumor necrosis factor (TNF-α) and C-Reactive Protein (CRP) in six rats per group. Control (Normal saline: NS), The data are presented as Mean ± SD. Significant differences are marked by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns: no significant difference.

Oxidative stress and antioxidants

Diabetic mice showed increased MDA and 8-OHdG plasma levels and decreased SOD and GPX antioxidant activities compared to the NS group (Figure 3A–D; p<0.0001), indicating increased oxidative stress and DNA damage. Compared to the diabetes group, a 30-day treatment with hydroalcoholic extract of licorice (50 and 100 mg/kg) and glycyrrhizic acid (50 and 100 mg/kg) significantly reduced MDA and 8-OHdG levels and increased SOD and GPX activity. Licorice extract dose-dependently affected most indices, with 100 mg/kg causing a stronger effect.. Both compounds have significant antioxidant and protective action against diabetes-induced oxidative damage.

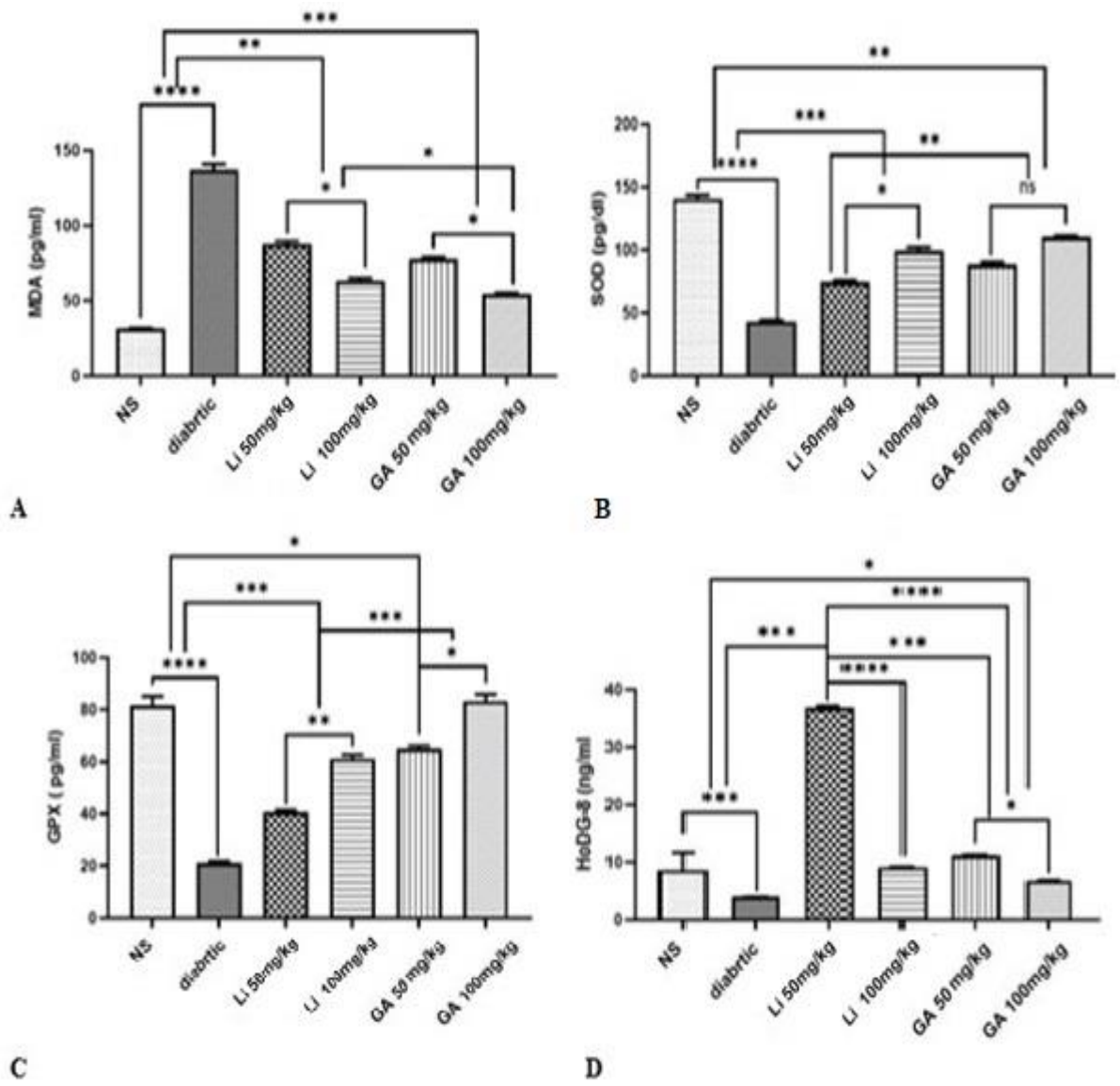

Figure 3. Effect of licorice hydroalcoholic extract (Li) and glycyrrhizic acid (GA) on oxidative stress markers: Malondialdehyde (MDA), Superoxide dismutase (SOD), glutathione peroxidase (GPX), and 8-hydroxy-2'-deoxyguanosine (8-OHdG) were measured across research groups (six rats per group). The data are presented as mean ± SD. Significant differences are marked by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns: no significant difference.

Apoptotic regulators

In this study, diabetes induction resulted in significant apoptotic changes at the plasma level, including increased BAX and decreased BCL2 compared to the control group (NS) (Figure 4; p<0.0001). The data show that diabetes activates the cellular apoptotic process. Hydroalcoholic licorice extract (Li) and glycyrrhizic acid (GA) treatment for 30 days decreased BAX and significantly increased BCL2 levels, preventing apoptosis. Both medications at 100 mg/kg were more effective at regulating these markers. Licorice and glycyrrhizic acid reduce diabetes-induced apoptosis and protect cell viability.

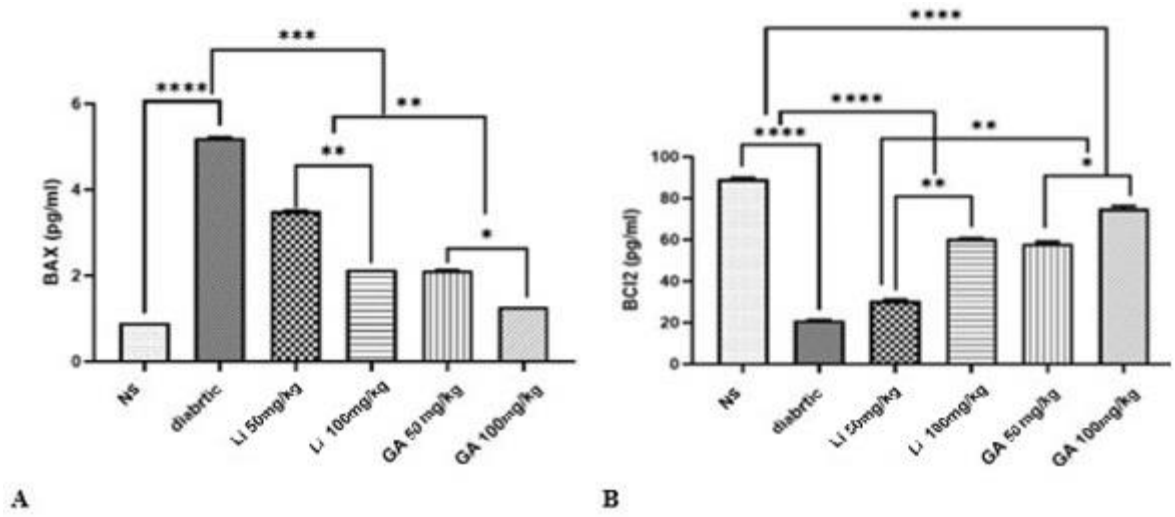

Figure 4. Effect of licorice hydroalcoholic extract (Li) and glycyrrhizic acid (GA) on apoptotic regulators Bcl-2 associated X-protein (BAX) and B-cell lymphoma 2 (BCL2). The data are presented as mean ± SD. Significant differences are marked by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns: no significant difference.

Discussion

The induction of sustained hyperglycemia significantly, increased oxidative stress,. This pathological state was evidenced by elevated liver enzymes (ALT, AST, ALP, and GGT), increased blood glucose, decreased antioxidant capacity (GPx and SOD), and elevated markers of lipid peroxidation and DNA damage (MDA and 8-OHdG). Furthermore, the altered apoptotic balance—characterized by increased Bax and decreased Bcl-2—confirmed the activation of mitochondrial cell-death pathways.

Administration of *G. glabra* hydroalcoholic extract and glycyrrhizic acid (GA) over 30 days significantly ameliorated these metabolic and cellular impairments. Both interventions demonstrated potent hepatoprotective, antioxidant, and anti-inflammatory activities, effectively attenuating systemic inflammation (IL-1β, IL-6, TNF-α, and CRP) and normalizing liver function and glycemic levels. Notably, GA exhibited a robust therapeutic profile, with most effects—including blood glucose regulation, liver enzyme reduction (ALT, ALP, AST), and GCT modulation—reaching a therapeutic plateau at 50 mg/kg, with no significant additional benefit at 100 mg/kg. In contrast, the hydroalcoholic extract displayed efficacy, suggesting that the complex profile of bioactive compounds within the whole extract may provide additive or synergistic benefits.

In conclusion, these results demonstrate that both *G. glabra* extract and its primary constituent, glycyrrhizic acid, serve as powerful protective agents against diabetes-induced systemic injury. By reinforcing endogenous antioxidant defenses, stabilizing hepatocyte membranes, and regulating apoptotic pathways, these interventions effectively mitigate the multi-faceted damage associated with chronic hyperglycemia. GA, in particular, acts as a highly effective agent, achieving maximal protective responses at lower dose (50 mg/kg).

Recently, the examination of medicinal plants and their effective components have gained special importance in metabolic disease prevention such as DM (Kumar et al. 2021). Glycyrrhizin, as the active component of the licorice root, has been shown to have diverse pharmacologic properties including anti-microbial, anti-inflammatory, and immunomodulatory activities (Huan et al. 2021). The hepatoprotective activities of glycyrrhizic

acid have been also reported through diverse mechanisms (Hua et al. 2019; Li et al. 2019). ALT, AST, ALP, and globulin are well-established indicators of liver function, with ALT and AST being the most sensitive markers for detecting chemically induced hepatic injury (Ahn 2023). In the present study, serum levels of these markers were markedly elevated in diabetic control rats compared with healthy controls, confirming liver dysfunction associated with diabetes. Treatment with either licorice hydroalcoholic extract or glycyrrhizin significantly reduced ALT, AST, ALP, and globulin levels, indicating improved liver function. These findings are in line with previous reports by Saleem et al. (2011), who demonstrated the hepatoprotective effect of licorice root extract in mice, and Yahya et al. (2024), who observed similar protective effects in rats. Together, these results reinforce the potential role of licorice-derived compounds in mitigating diabetes-related hepatic injury.

Apoptosis is a natural cellular process responsible for the removal of aged, damaged, or potentially harmful cells. Disruptions in this process contribute to the development of various disorders (Sang et al. 2025). Increasing evidence suggests a close relationship between hyperglycemia, oxidative stress, and diabetes-related complications, including hepatic tissue dysfunction (Mohamed et al., 2016). In such conditions, apoptosis of hepatocytes is markedly enhanced, leading to progressive liver injury. Among the key regulators of apoptosis are BCL-2 and BAX. In our study, BCL-2 expression was highest in healthy rats but significantly reduced in diabetic rats (Chen et al. 2019). Conversely, BAX expression was lowest in healthy animals and markedly elevated in diabetic groups. Treatment with licorice and glycyrrhizin significantly modulated the expression of both proteins compared with diabetic controls. These findings align with those of Jani et al. (2021), who demonstrated that administration of licorice and glycyrrhizin improved liver architecture in diabetic rats. Similarly, Sil et al. (2015) reported that glycyrrhizin 50 mg/kg reduced apoptosis in a rat model of metabolic syndrome. C-reactive protein (CRP) is a systemic inflammatory biomarker synthesized by the liver in response to cytokines including IL-6 and TNF-α (Rizo-Téllez et al. 2023). Elevated CRP levels not only reflect inflammatory responses in DM but also serve as indicators of macro- and microvascular complications. In the present study, CRP and pro-inflammatory cytokines were lowest in healthy controls and significantly increased in diabetic control rats (Gouliopoulos et al. 2018; Nnamudi et al. 2023). Administration of glycyrrhizin 100 mg/kg for 30 compared to days resulted in the greatest reduction of these inflammatory markers compared to licorice. Although consistent with our results, Akutagawa et al. (2019) reported that glycyrrhizin suppressed TNF-α, IL-6, and IL-1β levels in diabetic mice; however, their treatment was applied topically rather than systemically. Moreover, a review of ten studies indicated that glycyrrhizic acid significantly reduced CRP levels and improved hepatic function in patients with COVID-19 (Liu et al., 2022). These findings support glycyrrhizic acid anti-inflammatory and hepatoprotective effects (Hu et al., 2026). Numerous studies show that diabetes reduces GST, SOD, and GPX activity. Guanine is extremely prone to oxidation, and 8-OHdG is a sensitive biomarker of oxidative DNA damage (Verigos & Sagredou, 2020). Since reactive oxygen species (ROS) may overwhelm the antioxidant defense system, oxidative stress accelerates diabetes (An et al., 2023). In our study, GPX and SOD activities were significantly higher in healthy controls compared with diabetic controls. Treatment with glycyrrhizin 100 mg/kg for 30 days effectively prevented the reduction of these antioxidant enzymes. Conversely, MDA, a terminal product of lipid peroxidation (Mas-Bargues et al., 2021), was

significantly elevated in diabetic controls, while glycyrrhizin treatment produced the greatest reduction among treatment groups. Similarly, 8-OHdG levels were lowest in healthy rats and were significantly decreased by licorice and glycyrrhizin administration compared to diabetic controls. These results are consistent with previous reports. The increasing in MDA and decreased SOD was observed in the liver of diabetic rats due to superoxide overproduction (Aminzadeh et al. 2020). Comparable findings were reported by Giangrandi et al. 2024 and Abo-Samaha et al. 2022. Furthermore, a human trial demonstrated that licorice root powder administered for 12 weeks significantly improved oxidative stress parameters, including MDA, in women (Rostamizadeh et al., 2022). In animal models, licorice or glycyrrhizin intake has been studied little. The antioxidant, anti-inflammatory, and anti-apoptotic activities of licorice at 100 mg/g and glycyrrhizin at 100 mg/g seem interesting for future investigation.

Diethyl ether was used as the anesthetic in this study. However, ether has several limitations, including ethical concerns, irritant effects, and an unpredictable depth of anesthesia, which can restrict its use in certain surgical procedures, such as cardiac exposure. These factors may have influenced the reproducibility and precision of some procedures, and future studies could consider using more modern and ethically accepted anesthetic agents to improve animal welfare and procedural reliability. Although multiple treatment groups were included, not all possible pairwise comparisons between groups were performed. This makes it difficult to compare licorice extract with glycyrrhizic acid at different doses. Future studies should include comprehensive statistical comparisons among all groups to better clarify dose-dependent and treatment-specific effects.

The results of this study supported the effective role of licorice root hydroalcoholic extract and more specifically, glycyrrhizic acid as its active components, in the prevention of hepatic damage caused by DM. Comparing the effects of licorice extract and glycyrrhizic acid showed that glycyrrhizic acid at a dose of 50 mg/kg had the greatest effect in preventing liver damage in diabetic rats.

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Conflicts of interest

The authors had no competing interests.

Ethical Considerations

This study was conducted under the supervision of the Ethics Committee and the Clinical Trials Council of Islamic Azad University, Da.C., Damghan, Iran.

Code of Ethics

IR.IAU.DAMGHAN.REC.1398.002

Authors' Contributions

SJ: Literature search, Proposal writing, Data collection, Data Analysis, Data interpretation, Preparation Manuscript, Manuscript review. VH, GHV, RR: Data interpretation, Manuscript review.

Abbreviations

Licorice hydroalcoholic extract (Li); Glycyrrhizic acid (GA); Interleukin 1B (IL1B), Interleukin 6 (IL6), Tumor necrosis factor (TNF-α); C-Reactive Protein (CRP); Malondialdehyde (MDA); Superoxide dismutase (SOD); Glutathione peroxidase (GPX); 8-Hydroxy-2'-deoxyguanosine (8-OHdG); BCL2 associated X-protein (BAX); B-cell lymphoma 2 (BCL2); Standard deviation (SD).

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