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(RESEARCH ARTICLE)

Evaluation of the Protective Effects of Ginseng Root Extract and Ginsenoside Rg1 Against Liver Complications Induced by Type 1 Diabetes in Male Rats

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Abstract

Type 1 diabetes is an insidious disease and can cause many problems, most importantly high liver enzymes and liver damage caused by oxidative stress and inflammation. The goal of this study was to assess the protective and therapeutic properties of ginseng root extract, ginsenoside Rg1 alone and in combination against liver complications in male diabetic alloxan rats and to compare this effect with metformin. Thirty-five male rats were used and split into 7 groups, 1 normal and 6 diabetics. These groups consisted of metformin, metformin + Ginseng extract and metformin + ginsenoside Rg1 groups, as well as ginseng extract and ginsenoside Rg1 groups. Treatment was given for 5 weeks and liver enzymes such as AST, ALT and ALP were measured to assess the effect of treatment while liver histological changes were assessed. Both the diabetic group and non-diabetic group had significantly elevated liver enzymes with the diabetic group demonstrating marked changes in the liver histological sections, including fibrosis, inflammation and cellular swelling. Contrary to this, all the different treatments resulted in a decrease of such enzymes and an improvement of the histological structure of the liver. The most significant effect was observed in the groups treated with the ginseng extract + ginsenoside Rg1 combination, where the values approached normal. The study concludes that ginseng extract and Ginsenoside Rg1 have effective protective and therapeutic effects against liver damage associated with diabetes, especially when used together, suggesting the possibility of adopting them as an adjunctive treatment option in reducing liver complications associated with diabetes.

Keywords: Diabetes; Liver enzymes; Histological changes; Ginsenoside Rg1; Oxidative stress

1 Introduction

Type 1 diabetes (T1D) is a disease resulting from the destruction of insulin-producing beta cells in the pancreas, leading to lifelong insulin dependence and an increased risk of acute and chronic complications. Research conducted over the past decade has elucidated its causes, effects, and prevention and treatment strategies. Many adults develop the disease gradually and may not initially require insulin (Henriques *et al*., 2025). A study of a cohort of individuals with type 1 diabetes showed elevated levels of the enzymes ALT and GGT, suggesting a correlation between hepatitis and diabetic complications (Velayutham *et al*., 2025). Chronic hyperglycemia promotes fat accumulation in the liver, glycogen deposition, oxidative stress, and inflammation, leading to a slight increase in liver enzymes and non-alcoholic fatty liver disease associated with hepatic glycoprotein. Elevated liver enzymes in type 1 diabetes are associated with an increased risk of complications and may reflect a broader dysfunction in the vascular endothelium (Liu *et al*., 2025).

Metformin has shown an effect on type 1 diabetes in adolescents, with adjuvant metformin therapy leading to a decrease in glycated hemoglobin (HbA1c) levels, body mass index (BMI), and total daily insulin dose (Masouri *et al*., 2025). Metformin has also been shown to reduce liver enzyme levels, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in patients with metabolic dysregulation and non-alcoholic fatty liver disease

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(NAFLD) (Asghar *et al*., 2025). The mechanism of action of metformin in NAFLD involves blocking the production of reactive oxygen species by regulating important antioxidant pathways, which helps to safeguard liver cells from oxidative damage (Zhang et al., 2024). Ginseng extract has various therapeutic potential for type 1 diabetes. Through modulation of cellular signaling pathways like PI3K/AKT/mTOR and AMPK/mTOR, ginseng has been demonstrated to have the ability to lower blood glucose levels, enhance lipid profiles, and boost the activity of antioxidant enzymes while simultaneously depressing inflammation in animal models of type 1 diabetes (Han et al., 2025). Another anti-inflammatory property of ginseng is its ability to decrease pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta, and interleukin-6, which are associated with liver diseases, such as non-alcoholic fatty liver disease and alcoholic liver damage (Bian et al., 2023). Ginseng extract, particularly its active constituents, also demonstrate therapeutic activity to liver tissue disorders. Ginseng saponin extracts inhibit the activation of inflammasome, while stimulating liver cell mitochondrial autophagy, thereby inhibiting liver fat accumulation, fibrosis, and inflammation (Wang et al., 2021).

Ginsenoside Rg1 is able to exhibit therapeutic effects on type 1 diabetes mellitus by exerting regulatory effects on pancreatic islet injury, attenuating inflammatory response and inducing autophagy in diabetic mice. Rg1 lowers blood glucose levels, raises serum insulin levels, and inhibits inflammatory markers such as IL-1, TNF-α, and NF-κB in pancreatic and splenic tissues (Zong *et al*., 2023). Ginsenoside Rg1 also exhibits significant hepatoprotective effects by reducing levels of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are key indicators of liver injury. This compound protects against various liver injuries, including those caused by toxins such as paracetamol, alcohol, and ischemia-reperfusion, through mechanisms that include inhibiting cytochrome P450 enzymes and reducing oxidative stress, inflammation, and apoptosis (Li *et al*., 2022; Bi *et al*., 2021). Ginsenoside Rg1 has also demonstrated significant protective effects against liver tissue lesions across various models of liver injury and fibrosis. Rg1 mitigates chronic liver damage by activating the Nrf2 signaling pathway, enhancing antioxidant defenses and inhibiting inflammasomes such as NLRP3, NLRP1, and AIM2, thereby reducing inflammation, hepatocyte damage, apoptosis, and fibrosis (Dan *et al*., 2025; Zhou *et al*., 2024). Therefore, the current study aimed to evaluate the effect of metformin, *Withania somnifera* leaf extract, and Ginsenoside Rg1 in normalizing serum AST, ALT, and ALP enzyme levels while alleviating liver tissue lesions resulting from diabetes induction in male rats.

2 Materials and Methods

2.1 Materials

The root part of the Indian ginseng plant (*Withania somnifera*) was obtained from China. The root extract was prepared using 70% methanol. Ginsenoside Rg1 was obtained from the American company Sigma and metformin from the German company Merck Serono.

2.2 Animals

In this experiment, 16-week-old male Sprague Dawley rats weighing (190 ± 10) grams were used. The rats were placed in special cages and then subjected to laboratory conditions with a temperature of (22 ± 2)°C and equal lighting periods of 12 hours of light followed by 12 hours of darkness, with the cages being cleaned and disinfected. The animals were acclimatized for two weeks with free access to water and food.

2.3 Experimental Design:

Thirty-five adult male albino rats were used in this study and divided into seven groups of five rats each, with similar weights. Groups 2-7 were induced with type 1 diabetes by subcutaneous injection of alloxan at a dose of 150 mg/kg (Saleh and Abdullah, 2025). The groups were as follows:

- Group 1 (Normal Control): Treated with a normal diet and administered distilled water for five weeks.
- Group 2 (Diabetic): Treated with a normal diet and administered distilled water for five weeks.
- Group 3 (Control): Treated with a normal diet and administered metformin at a concentration of 200 mg/kg (Mahdizadeh *et al*., 2025) for five weeks.
- Group 4 (Control group treated with Ginseng Alcoholic Extract): This group was treated with a normal diet and given Ginseng Alcoholic Extract at a concentration of 200 mg/kg (Ahmed *et al*., 2023) for five weeks.
- Group 5 (Control group treated with Ginsenoside Rg1): This group was treated with a normal diet and given Ginsenosides at a concentration of 20 mg/kg (Abdi *et al*., 2025) for five weeks.

- Group 6 (Control group treated with Metformin + Ginsenosides): This group was treated with a normal diet and given Ginseng Alcoholic Extract at a concentration of 200 mg/kg and Ginsenoside Rg1 at a concentration of 20 mg/kg for five weeks.
- The seventh group (the infected control group and the group treated with Ginseng Alcoholic Extract + Ginsenosides): They were treated with the normal diet and were treated with Ginseng Alcoholic Extract at a concentration of (200 mg/kg) and Ginsenoside Rg1 at a concentration of (20 mg/kg) for five weeks.

2.4 Collection of blood serum:

After the end of the five-week experimental period, the animals were starved for 12 hours and then anesthetized with Ketamine at a dose of 5 mg/kg and Xylazine at a dose of 35 mg/kg of body weight by intramuscular injection. Blood serum was obtained after drawing blood from the heart, then the serum was stored at -20°C for the biochemical analyses of the study. After that, the rats were dissected and the liver was extracted for histological study.

2.5 Biochemical and Histological Examinations:

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels in serum were determined using the ELISA kit provided by BT Lab Korea. The liver was then washed with physiological saline, and the samples were prepared for microscopic histological sections using hematoxylin and eosin staining. After preparation, the sections were examined under a light microscope, and images were taken.

2.6 Statistical Analysis

Statistical analysis of the results was performed at a significant level ($P \geq 0.05$) using Duncan's multiple range test with SPSS software.

3 Results and Discussion

3.1 Serum AST, ALT, and ALP Concentrations

The results in (Figure-1) and Table (1) showed a significant increase in the concentration of AST, ALT, and ALP compared to the normal control group. However, for the diabetic groups treated with metformin only, ginseng alcoholic extract only, ginsenoside Rg1 only, (metformin + ginsenoside Rg1), and (ginseng alcoholic extract + ginsenoside Rg1), the concentration of AST, ALT, and ALP decreased compared to the diabetic group. The group treated with ginseng alcoholic extract + ginsenoside Rg1 together had the best effect on improving the above parameters.

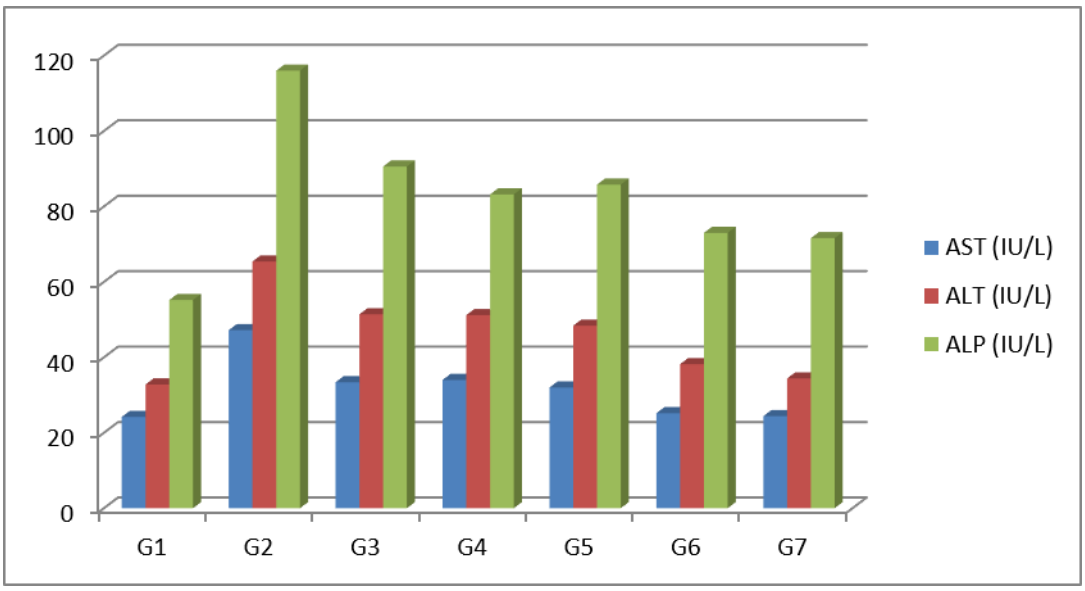

Figure 1 Concentration of AST, ALT and ALP in blood serum

Table 1 Effect of Ginseng Alcoholic Extract and Ginsenoside Rg1 on the concentration of AST, ALT and ALP in the blood serum of male albino rat experimental groups

Parameters / Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Control	24.20±2.77c	32.80±2.86d	55.20±3.49e
Diabetic	47.20±5.12a	65.40±4.28a	116.00± 6.93a
metformin	33.40±2.07b	51.40±3.36b	90.60±3.51b
Diabetic + Ginseng Alcoholic Extract	34.00±1.58b	51.20±4.32b	83.20±2.86c
Diabetic + Ginsenoside Rg1	32.00±1.58b	48.40±3.65b	85.80±2.39bc
Diabetic + metformin + Ginsenoside Rg1	25.20±1.92c	38.20±2.86c	73.0±3.16d
Diabetic + Ginseng + Ginsenoside Rg1	24.40±2.07c	34.40±2.41cd	71.60±1.95d
F	45.57	56.24	125.34
P-Value	<.0001***	<.0001***	<.0001***

The values represent the arithmetic mean ± the standard deviation.

Numbers followed by different letters vertically indicate a statistically significant difference at a probability level of ($P \geq 0.05$).

3.2 Histological Study of the Liver

The results of the current study for the normal control group dosed with distilled water showed a normal liver cross-section, with the central vein (CV), hepatocytes (HC), sinusoids (S), and Kupffer cells (KC) appearing intact, as shown in (Figure 2a).

In the diabetic group injected with alloxan, several histological changes were observed, including fibrosis (F) of the portal zone, cytoplasmic changes such as vacuoles and cloudy swelling (CS) within hepatocytes (which may indicate metabolic stress), sinusoidal dilation (SD) between hepatocyte cords within normal limits, congestion (Con) within the central vein, and a granular appearance of the cytoplasm with normal glycogen storage (indicating the onset of hydropic degeneration, as shown in (Figure 2b). An immune response was also present, characterized by inflammatory infiltrate (II) and clusters of dark purple nuclei extending into the liver tissue (interstitial hepatitis). Hepatocyte swelling (HS) was observed in areas where cells appeared larger or paler, which may indicate ballooning degeneration. Congestion (Con) indicates that the presence of blood cells within the vessels indicates a certain level of vascular congestion, as shown in (Figure 2c).

In the diabetic group treated with metformin alone, inflammatory infiltrate (II) and congestion (Con) were observed in the central venous system, while the majority of hepatocytes (HC), sinusoids (S), and Kupffer cells (KC) remained normal, as shown in (Figure 2d). In the diabetic group treated with ginseng alcohol extract alone, congestion (Con) was observed, while the majority of hepatocytes (HC), sinusoids (S), and Kupffer cells (KC) remained normal, as shown in (Figure 2e). For the diabetic group that was injected with Ginsenoside Rg1 only, the Central Vein (CV), most Hepatocytes (HC), Sinusoids (S), and Kupffer Cells (KC) were found to be in their normal form, as shown in (Figure 2f).

For the diabetic group that was treated with (metformin + Ginsenoside Rg1) and (Ginseng Alcoholic Extract + Ginsenoside Rg1), the Central Vein (CV), most hepatocytes (HC), sinusoids (S), and Kupffer Cells (KC) were found to be in their normal form, as shown in (Figure 2g and Figure 2h) respectively.

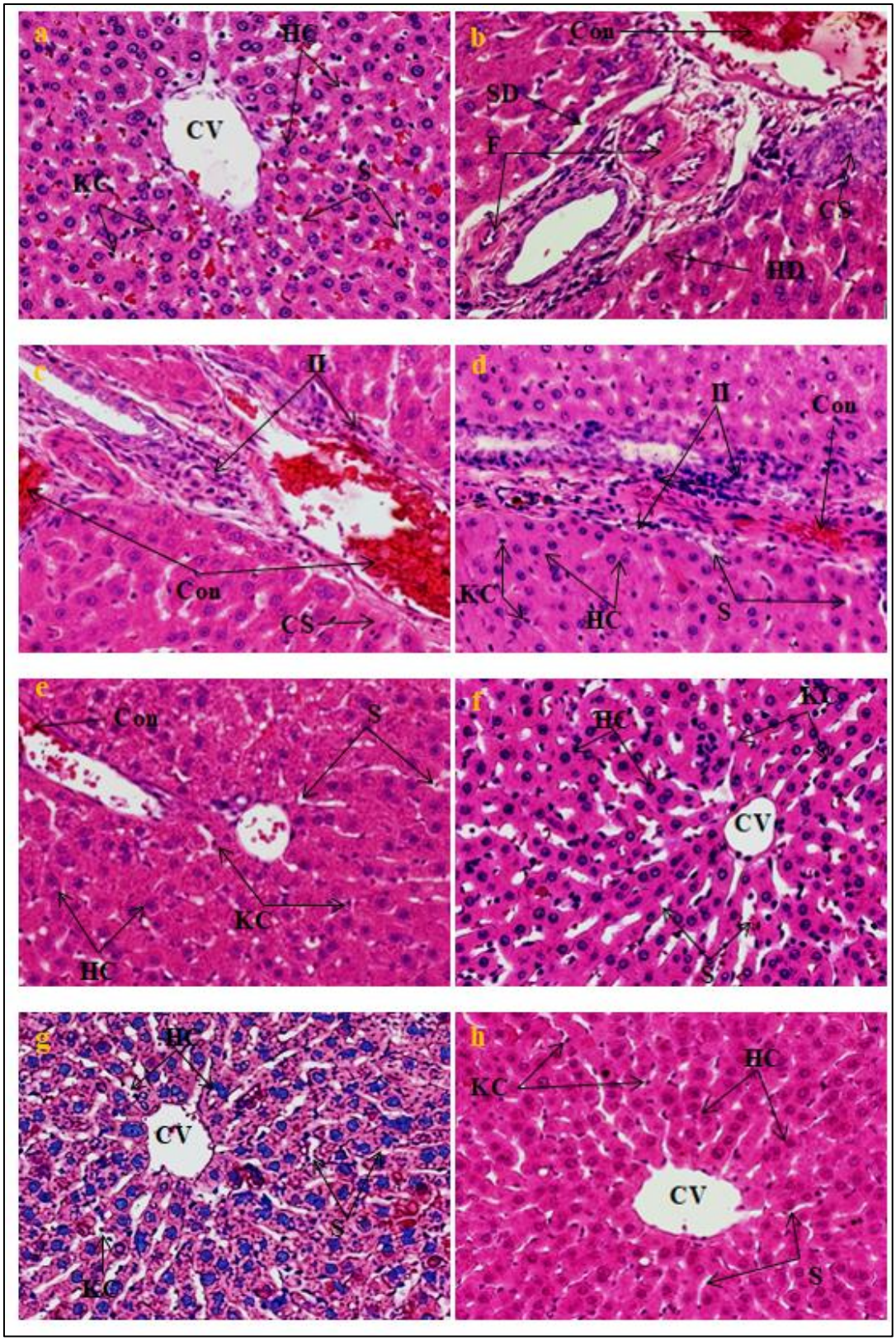

Figure 2(a) Liver section of the normal control group. Figures (b, c) Liver sections of the diabetic group. Figure (d) Liver section of the diabetic group treated with metformin only. Figure (e) Liver section of the diabetic group treated with ginseng alcoholic extract only. Figure (f) Liver section of the diabetic group treated with ginsenoside Rg1 only. Figure (g) Liver section of the diabetic group treated with metformin + ginsenoside Rg1. Figure (h) Liver section of the diabetic group treated with ginseng alcoholic extract + ginsenoside Rg1, H&E 40X.

4 Discussion

Our results in the livers of the diabetic group showed elevated liver enzymes and histological abnormalities. Liver changes that are significant, with liver enzyme levels also being elevated, and the presence of inflammatory liver diseases are associated with Type 1 Diabetes. Research shows increased ALT and AST blood levels may be a sign of inflammation or damage of the liver, which may be caused by type 1 diabetes. Other liver markers like bilirubin, ammonia and immunoglobulins can also be affected in type 1 diabetes, as a result of liver inflammation and metabolic stress, and due to liver complications, such as ketoacidosis (Betlejewska et al., 2025). Diabetic liver damage (diabetic sclerosis), hepatopathy due to glycogen accumulation, fatty liver accumulation, and fibrosis are more prevalent than previously thought in type 1 diabetes. These disorders are related to reduced insulin production, as well as blood sugar swings. Liver damage is characterized by endoplasmic reticulum stress, programmed cell death, and changes in lipid metabolism gene expression (Taufani et al., 2025).

The role of metformin in normalizing liver enzyme levels and tissue disorders is attributed to its ability to inhibit the progression of type 1 diabetes by modulating immune cell signaling pathways. Metformin has also demonstrated efficacy as an adjunctive therapy for adolescents with type 1 diabetes, improving glycemic control and reducing insulin requirements (Suzuki *et al*., 2025). Studies have shown that metformin reduces fat accumulation in the liver. Furthermore, metformin alleviates inflammation and liver damage associated with sepsis by modulating inflammatory pathways. Overall, the beneficial effects of metformin on liver enzymes appear to be linked to improved insulin sensitivity, reduced inflammation, and modulated hepatic glucose metabolism (Hakkak *et al*., 2021). Metformin has also shown multiple benefits in treating various liver tissue disorders, including cirrhosis, metabolic disorders, inflammation, and injury. It improves liver fibrosis by inhibiting the activation of hepatic stellate cells and markers of fibrosis in models of congestive liver disease (Yang *et al*., 2023).

Regarding the role of Ginseng Alcoholic Extract in improving liver enzyme levels and tissue lesions, this is attributed to the protective effect of ginseng alcoholic extract against diabetic complications, such as premature kidney failure and liver damage, by restoring metabolic balance and tissue integrity (Wang *et al*., 2022). Ginseng also affects inflammatory cell death pathways, which contribute to the development of diabetes and its complications, although most of the evidence is derived from preclinical studies that require further clinical validation (Li *et al*., 2025). Ginseng extract and its components have been shown to be highly protective for the liver and decrease serum levels of liver enzymes like ALT and AST, markers of liver damage. Ginseng extracts have been shown to decrease the markers of oxidative stress and enhance the antioxidant enzymes in animal models, which helps to prevent liver damage from toxins, alcohol or high-fat diets. Moreover, ginseng has been shown to have protective effects against toxic metabolites in the event of alcoholic liver damage (Elblehi et al., 2023; Wang et al., 2025). Some studies suggest that ginseng regulates the molecular pathways involved in oxidative stress, inflammation, apoptosis and endoplasmic reticulum stress that may benefit the liver. Ginseng extract also exhibits antioxidant and anti-inflammatory effects via the endoplasmic reticulum stress pathway, reducing reactive oxygen species and markers of inflammation in models of non-alcoholic fatty liver disease (NAFLD) (An *et al*., 2021). Ginseng extract mitigates the progression of NAFLD by inhibiting inflammatory adhesion molecules in hepatic sinusoidal endothelial cells (Lee *et al*., 2022).

The role of ginsenoside Rg1 in reducing enzyme levels and histological abnormalities in the liver is attributed to Rg1's role in modulating key pathways associated with diabetes, including insulin signaling pathways and TNF signaling, thus contributing to its anti-diabetic effects (Li *et al*., 2023). Furthermore, Rg1 inhibits diabetic complications, such as diabetic retinopathy, by suppressing the formation of abnormal blood vessels. Overall, Rg1 exhibits multi-targeted effects that improve pancreatic function and reduce inflammation and oxidative stress in T1D models, suggesting its potential as a therapeutic agent for type 1 diabetes (Xue *et al*., 2025). In addition, Rg1 improves liver function markers (ALT, AST) and reduces markers of oxidative stress (ROS), inflammatory cytokines (IL-1β, IL-6, TNF-α), and fibrosis markers (α-SMA, collagen IV) in cases of liver damage caused by aging or chemicals (Li *et al*., 2021). In summary, Rg1 ginsenoside has potential as a therapeutic agent to preserve liver function by reducing elevated liver enzymes and reducing underlying liver pathological processes in different liver injury models (Bian et al., 2023). Based on molecular studies, Rg1 ginsenoside can regulate hepatocyte metabolism through several pathways including PI3K-AKT while also affecting the gene expression involved in autophagy, inflammatory cell death, and maturation of immune cells (Chen et al., 2023).

5 Conclusions

Based on the results of this study, it may be concluded that the type 1 diabetes significantly increased the serum ALT, AST and ALP enzymes and cellular changes such as fibrosis, inflammatory infiltration, hydronephrosis and enlargement

of hepatic sinusoids have been seen in the liver. This suggests that hepatocytes are under oxidative stress and that there is a definite metabolic dysfunction. Conversely, biochemical and histological markers were significantly improved in treated affected animals that received metformin, ginseng extract or ginsenoside Rg1. The liver enzyme levels decreased with each treatment and the pathological changes in liver tissue were reduced in severity, and the cells (hepatocytes) and the sinusoids in the liver improved their normal structure.

The findings also indicated that the therapeutic benefits were more effective with the combination of drugs, particularly ginseng extract with ginsenoside Rg1 that showed the best liver enzyme normalization values and histological improvement of liver tissue, suggesting that there is a synergic effect between ginsenoside Rg1 and ginseng extract. Therefore, it can be concluded that ginseng and Rg1 have hepatoprotective activity in type 1 diabetes, by reducing oxidative stress, inflammation and metabolic dysfunction, and this makes ginseng a good candidate for the treatment of liver complications resulting from type 1 diabetes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

All institutional and national guidelines for the care and use of laboratory animals were followed during the conduct of this research work.

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