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(RESEARCH ARTICLE)

A study to alleviate histological and physiological abnormalities Induced by Type 1 diabetes in male rats using ginseng components and metformin

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Abstract

Background and Objective: Type 1 diabetes is associated with alterations in urea, creatinine, and uric acid levels, as well as renal tissue lesions resulting from oxidative stress and inflammation. Therefore, this study aimed to evaluate the efficacy of ginseng root extract, ginsenoside Rg1, and metformin in alleviating these physiological and tissue abnormalities.

Experimental design: 35 male rats were used, divided into seven groups (5 rats per group): a control group, a diabetic group (induced by alloxan), and five groups that were treated with either metformin, ginseng extract, ginsenoside Rg1, (metformin + ginsenoside Rg1), or (ginseng extract + ginsenoside Rg1) for 5 weeks.

Results: The results showed a significant increase in urea, creatinine, and uric acid levels in the diabetic group, along with clear tissue damage such as necrosis, inflammation, congestion, hemosiderin deposits, and glomerulosclerosis in the kidneys. In contrast, treatment with ginseng, ginsenoside Rg1, and metformin led to a significant decrease in these indicators and a marked improvement in kidney tissue structure.

Conclusion: The study concluded that ginseng extract and ginsenoside Rg1 possess protective and therapeutic properties for the kidneys that are comparable to or sometimes even superior to metformin, and the combination of (ginseng extract and ginsenoside Rg1) was the most effective in improving biochemical and histological parameters.

Keywords: Diabetes; Kidneys; Metformin; Ginseng; Ginsenoside Rg1

1. Introduction

Type 1 diabetes is associated with changes in kidney function indicators such as uric acid, creatinine, and urea, which are important indicators of kidney health. Studies indicate that patients with type 1 diabetes often experience changes in blood uric acid levels, with some evidence suggesting that elevated uric acid levels increase the risk of diabetic nephropathy (Huang *et al*., 2025). Some therapeutic interventions can lower blood uric acid levels and improve kidney function by lowering creatinine and protein levels in the urine of diabetic patients (Luo *et al*., 2022). Type 1 diabetes leads to significant kidney tissue disorders, particularly diabetic nephropathy, which is characterized by glomerulonephritis, tubular damage, fibrosis, and inflammation. Hyperglycemia in type 1 diabetes triggers cellular dysfunction through mechanisms including oxidative stress and inflammatory cytokines, contributing to cell hyperplasia and renal fibrosis (Thomas and Ford Versypt, 2022; Thomas *et al*., 2023).

In adults with type 1 diabetes, metformin reduces body mass index, insulin requirements, glycated hemoglobin levels, and cholesterol levels (Wu *et al*., 2023; Snaith *et al*., 2025). Research also indicates that metformin improves insulin

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sensitivity markers and is associated with lower uric acid levels, which in turn is associated with improved insulin sensitivity (Ramaldes *et al*., 2024). Metformin also protects kidney structure by preventing pathological tissue damage and maintaining normal kidney structure in animal models with diabetes (Omolola *et al*., 2024).

Ginseng extract shows promising therapeutic effects on type 1 diabetes through multiple mechanisms. Studies conducted on animal models with type 1 diabetes indicate that ginseng and its components can lower blood glucose levels, improve lipid levels, and enhance antioxidant enzyme activity while reducing inflammation, partly by modulating cellular signaling pathways such as PI3K/AKT/mTOR (Xu *et al*., 2024). Ginseng has been found to lower blood uric acid levels by regulating urate transporters, reducing URAT1 levels and increasing OAT1 and OAT3 levels, and improving kidney function indicators such as creatinine and blood urea (Lee *et al*., 2024). The active components of ginseng exert antioxidant, anti-inflammatory, anti-fibrotic, and anti-apoptotic effects, improving kidney function by reducing protein in the urine, creatinine in the blood, and inflammatory cytokines in diabetic nephropathy (Chen *et al*., 2023a).

Studies indicate that ginsenoside Rg1 modulates pathways associated with diabetes, including insulin signaling pathways and tumor necrosis factor (TNF) signaling, which supports its efficacy against diabetes (Li *et al*., 2023). In addition, Rg1 ginsenosides alleviate tissue lesions by activating the AMPK/mTOR pathway, thereby reducing apoptosis. These protective effects are partially reversed by autophagy inhibitors, indicating the pivotal role of autophagy (Chen *et al*., 2023b). The antioxidant and anti-inflammatory properties of ginsenoside Rg1 support its potential benefits in managing oxidative stress and inflammation associated with diabetes complications (Xie *et al*., 2023). Ginsenosides, including Rg1, exhibit antioxidant, anti-inflammatory, antifibrotic, and anti-apoptotic properties, contributing to kidney protection in diabetic nephropathy models. These findings support the therapeutic potential of ginsenoside Rg1 for diabetic kidney complications through multiple molecular pathways, including reducing oxidative stress and inhibiting fibrosis (Chen *et al*., 2023a). Therefore, the current study aimed to evaluate the effect of metformin, *Withania somnifera* leaf extract, and Ginsenoside Rg1 in normalizing serum urea, creatinine, and uric acid levels while alleviating kidney 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

In this study, thirty-five adult male albino rats were used 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 (Natural Control): Treated with a normal diet and given distilled water for five weeks.
- Group 2 (Diabetic): Treated with a normal diet and given distilled water for five weeks.
- Group 3 (Diabetic Control and Metformin): Treated with a normal diet and given metformin at a concentration of 200 mg/kg (Mahdizadeh *et al*., 2025) for five weeks.
- Group 4 (Diabetic Control and Ginseng Alcoholic Extract): 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 infected and 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 infected and 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.

- Group 7 (Control group infected and treated with ginseng alcoholic extract + 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.

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 kidneys were extracted for histological study.

2.5. Biochemical and Histological Examinations

The concentrations of urea, creatinine, and uric acid in blood serum were determined according to the instructions of the Biolabo kit (France) using the ELISA technique. The kidneys were then washed with physiological saline, and the samples were prepared for microscopic histological sections using hematoxylin and eosin staining. After preparation, the slides were examined under a light microscope, and images were taken.

2.6. Statistical Analysis

The 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

3.1. Serum Urea, Creatinine, and Uric Acid Concentrations

The results in (Figure-1) and Table (1) showed a significant increase in serum urea, creatinine, and uric acid concentrations 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), urea, creatinine, and uric acid concentrations 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.

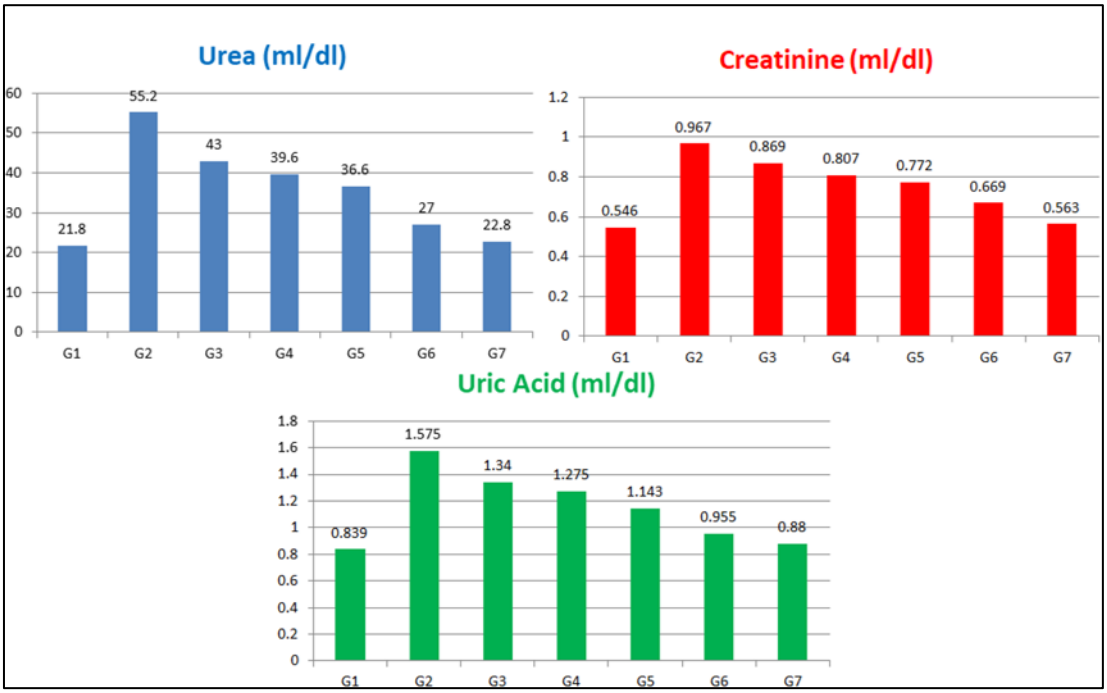

Figure 1 Serum concentrations of urea, creatinine, and uric acid

Table 1 Effect of ginseng alcoholic extract and ginsenoside Rg1 on serum concentrations of urea, creatinine, and uric acid in male albino rat experimental groups

Parameters / Groups	Urea (ml/dl)	Creatinine (ml/dl)	Uric Acid (ml/dl)
Control	21.80±4.66e	0.546±0.021f	0.839±0.024g
Diabetic	55.20±4.15a	0.967±0.022a	1.575±0.019a
Metformin	43.00±3.16b	0.869±0.021b	1.340± 0.027b
Diabetic + Ginseng Alcoholic Extract	39.60±3.65bc	0.807±0.023c	1.275±0.026c
Diabetic + Ginsenosides	36.60±3.05c	0.772±0.016d	1.143±0.016d
Diabetic + metformin + Ginsenosides	27.00±3.16d	0.669±0.019e	0.955±0.019e
Diabetic + Ginseng + Ginsenosides	22.80±2.86de	0.563±0.017f	0.880±0.024f
F	**57.40**	**303.96**	**727.14**
P-Value	**<.0001*** **	**<.0001*** **	**<.0001*** **

The values represent the arithmetic mean ± 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 Kidney

The results of the current study for the normal control group dosed with distilled water showed the normal shape of the kidney cross-section, as the nephrocarcinoma showed the glomerular (G) and Bowman's space (BS). Proximal convoluted tubules (PCT) and Distal convoluted tubules (DCT) were also observed intact, as in (Figure 2a).

In the diabetic group injected with alloxan, several histological changes were observed, including vascular congestion (VC) due to a large interlobular blood vessel filled with a dense accumulation of blood cells, dilation of the intertubulal space indicating interstitial edema (IE), hemosiderin deposits (DH), which are small, dark-colored granular deposits within the blood vessel and in some surrounding areas, tubular necrosis (TN) due to loss of brush margins or the appearance of nuclear shadows, endothelial damage (ED) of the blood vessels, and an inflammatory response (IR) due to the presence of inflammatory cells in the interstitial tissue, as shown in (Figure 2b). Hyaline arteriolosclerosis (HA) results from inflammation of the renal artery wall and glomerulosclerosis (Gs) due to proliferation of cells and increased thickness of the basement membrane. Necrosis (N) and atrophy (A) were observed as in (Figure 2c).

As for the diabetic group that was treated with metformin only, hemosiderin accumulation (HA) was observed, as the stored iron appeared as small yellowish-brown granules within some tubular cells and the interstitial space, and degeneration (D) was observed in the interstitial tissue, while the glomerular (G), Bowman's space (BS), proximal convoluted tubules (PCT), and distal convoluted tubules (DCT) were observed intact, as in (Figure 2d). As for the diabetic group that was injected with Ginseng Alcoholic Extract only, it showed Interstitial Expansion (IE) within and Congestion (Con) within the glomerulus in Bowman's capsule and Hydropic Degeneration (HD) as a result of swelling of the urinary tubule cells, while the Glomerular (G), Bowman's space (BS), Proximal convoluted tubules (PCT) and Distal convoluted tubules (DCT) were observed intact as in (Figure 2e). For the diabetic group that was injected with Ginsenoside Rg1 only, the glomerular (G), Bowman's space (BS), proximal convoluted tubules (PCT) and distal convoluted tubules (DCT) were found to be intact, as shown in (Figure 2f).

For the diabetic group that was treated with (metformin + Ginsenoside Rg1) and (Ginseng Alcoholic Extract + Ginsenoside Rg1), the glomerular (G), Bowman's space (BS), proximal convoluted tubules (PCT) and distal convoluted tubules (DCT) were observed to be intact, as shown in (Figure 2g and Figure 2h) respectively.

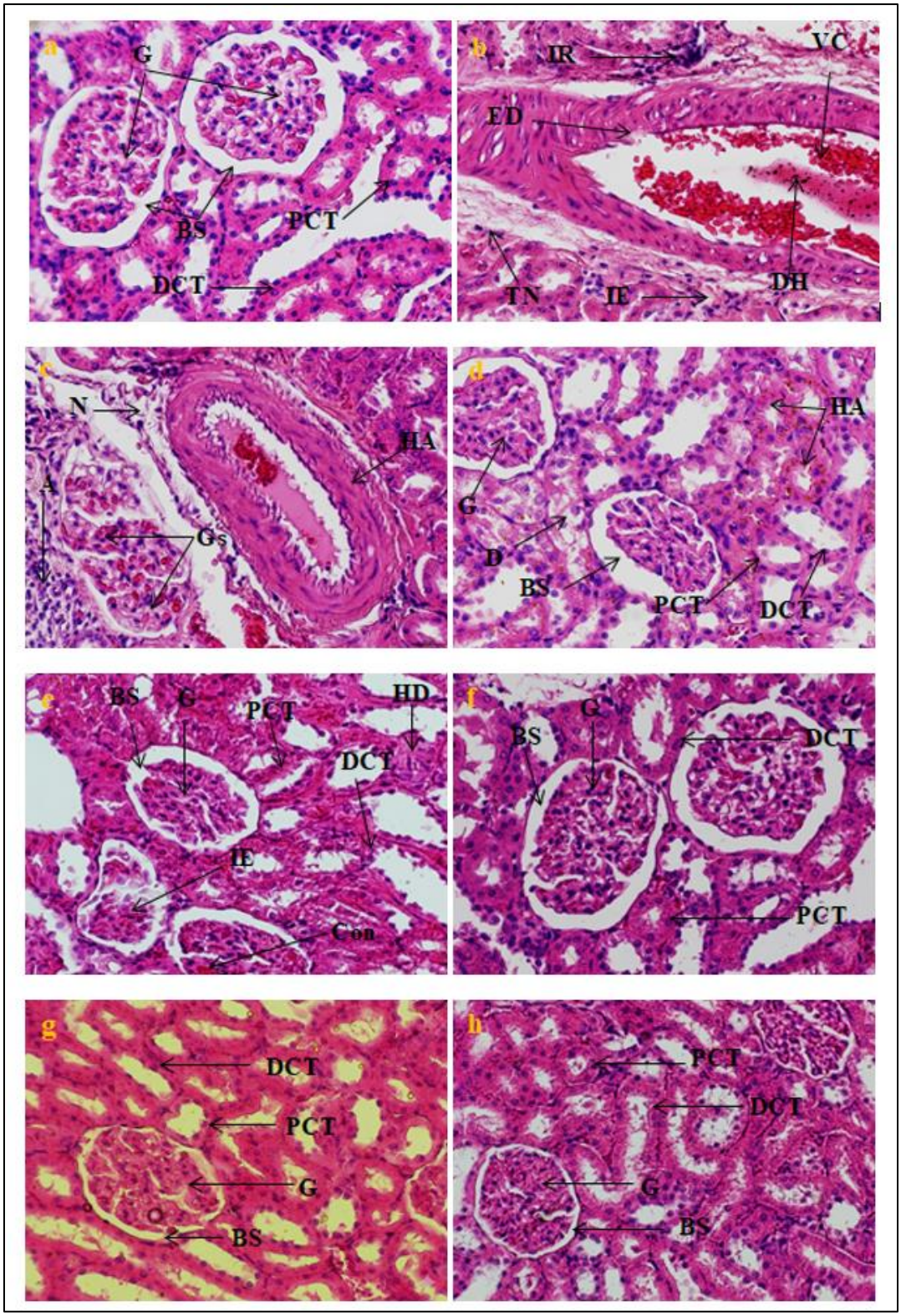

Figure 2(a) Kidney section from the normal control group. Figures (b, c) show kidney sections from the diabetic group. Figure (d) shows a kidney section from the diabetic group treated with metformin only. Figure (e) shows a kidney section from the diabetic group treated with ginseng alcoholic extract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

4. Discussion

Creatinine and urea levels are usually elevated in diabetic patients, reflecting impaired kidney function; and blood creatinine shows a positive correlation with fasting blood glucose and blood pressure (Akpotaire and Seriki, 2023). Blood uric acid levels are positively correlated with the urinary albumin-to-creatinine ratio and diabetic nephropathy, suggesting that uric acid may contribute to the onset of diabetic nephropathy in patients with type 1 diabetes (Jiang *et al*., 2023). Studies conducted on animal models have also shown that type 1 diabetes causes pathological histological changes, such as vacuole formation and disruption of the kidney tissue structure, which can be mitigated by interventions such as calorie restriction or the use of anti-inflammatories (Jafari-Khataylou *et al*., 2023; Taufani *et al*., 2025). The accumulation of fat accelerates the damage to the renal tubules in the kidneys of diabetic patients, indicating that metabolic disturbance plays a role in tissue damage (Hu *et al*., 2024).

Metformin is shown to be an adjunctive therapy in type 1 diabetes. In adolescents with this type of diabetes, metformin has been found to significantly reduce glycated hemoglobin levels, body mass index, and total daily insulin dose (Masouri, *et al*., 2025; Li *et al*., 2025a). Metformin also shows potential immunomodulatory effects that may inhibit the development of autoimmune diseases in animal models of type 1 diabetes, by affecting immune cell signaling pathways (Suzuki *et al*., 2025). In general, metformin can improve metabolic parameters and reduce insulin requirements in patients with type 1 diabetes (Mondkar *et al*., 2024). When added to insulin therapy in type 1 diabetes, metformin has shown beneficial effects on metabolic parameters, including reductions in glycated hemoglobin, insulin dose, and weight, with some studies indicating improvements in renal biomarkers and reductions in uric acid and protein levels in patients with type 1 diabetes (Janić *et al*., 2024). Metformin also demonstrates protective effects on the kidneys in diabetic kidney disease, including type 1 diabetes models, by improving glycemic control. Metformin reduces renal fibrosis, inflammation, oxidative stress, and cellular aging in kidney tissue, partly by inhibiting factors such as E2F1 and suppressing pro-inflammatory cytokines via inhibition of the NF-κB pathway (Corremans *et al*., 2023; Xie *et al*., 2025).

Ginseng extract also contributes to the prevention of diabetes complications, such as premature kidney failure and liver damage, by restoring metabolic balance and tissue integrity (Xin-Sen *et al*., 2022). In addition, ginseng regulates inflammatory cell death pathways associated with oxidative stress and inflammation, two key factors in the development of diabetes and its complications. These findings suggest that ginseng extract has potential as an adjunctive therapy for type 1 diabetes and its complications (Li *et al*., 2025b). Ginseng extract, particularly its active components called ginsenosides, has demonstrated beneficial effects on kidney function in diabetes, including type 1 diabetes, by reducing blood levels of creatinine, urea, and uric acid. Preclinical animal studies suggest that ginsenosides improve diabetic nephropathy through anti-inflammatory and antioxidant mechanisms, thus helping to protect kidney function (Chen *et al*., 2023a). In addition, ginseng extract alleviated renal fibrosis and inflammation in obese mice with hyperuricemia by improving uric acid, creatinine, and urea levels and modifying proteins involved in kidney injury. Overall, these findings support the idea that ginseng extract can positively affect uric acid, creatinine, and urea levels in patients with type 1 diabetes through multiple nephroprotective mechanisms (Zhang *et al*., 2024). In mouse models of type 1 diabetes, ginseng extract, and especially its bioactive components such as ginsenosides, show promising protective effects against kidney tissue disorders in type 1 diabetes and diabetic nephropathy. Ginseng extract improves metabolic markers, rebuilds biomarkers of kidney damage, maintains kidney tissue integrity, and alleviates early kidney dysfunction (Xin-Sen *et al*., 2022).

Ginsenoside Rg1 shows promising therapeutic effects in type 1 diabetes, primarily by reducing inflammation, improving tissue lesions, and promoting autophagy. In mouse models of type 1 diabetes, administration of ginsenoside Rg1 reduced blood glucose levels, increased serum insulin levels, and inhibited inflammatory markers such as IL-1 and TNF-α, while enhancing proteins associated with autophagy (Zong *et al*., 2023). Studies have shown that ginsenoside Rg1 improves indicators of kidney function associated with diabetes, including lowering creatinine, urea, and uric acid levels in animal models of diabetic nephropathy, suggesting protective effects on kidney function in type 1 diabetes (Chen *et al*., 2023a). In addition, Rg1 ginsenoside can inhibit iron cell death (a form of cell death associated with oxidative damage) in renal tubular cells, which may help protect kidney function by lowering blood creatinine and urea levels (Guo *et al*., 2022). Ginsenoside Rg1 has also demonstrated protective effects against kidney tissue disorders, and these effects have been studied primarily in type 2 diabetes models, suggesting potential mechanisms that may also be relevant to type 1 diabetes. In type 2 diabetic mice, Rg1 mitigates kidney fibrosis and damage by inhibiting pathways that reduce oxidative stress, lipid accumulation, inflammation, and fibrosis in the kidney (Ji *et al*., 2023).

5. Conclusions

Type 1 diabetes mellitus (alloxan-induced) leads to a marked decline in kidney function, causing significant increases in serum urea, creatinine, and uric acid levels. This elevation is attributed to impaired glomerular filtration associated with hyperglycemia. At the histological level, diabetes has led to clear degenerative changes in kidney tissues, including necrosis of the cells lining the renal tubules, glomerulonephritis, dilation of the urinary spaces, hemosiderin deposits, inflammatory response, and glomerulosclerosis.

In contrast, treatment with Metformin, alcoholic ginseng extract, and Ginsenoside Rg1 showed an effective role in lowering biochemical parameters, reducing kidney tissue damage, and decreasing the severity of inflammation and tissue necrosis. The study proved that ginseng extract and ginsenoside Rg1 have a strong protective and therapeutic ability against diabetic nephropathy, and the therapeutic combination between them was superior in restoring kidney efficiency and protecting it from structural damage caused by the disease.

Compliance with ethical standards

Statement of ethical approval

All institutional and national guidelines for the care and use of laboratory animals were adhered to in the course of this research work.

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