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Evaluating the effect of Ginseng root extract and Ginsenoside Rg1 in reducing Isoprostane-8, NF-κB, and TNFα levels induced by type 1 diabetes in male rats

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Abstract

Background: Type 1 diabetes is an autoimmune condition that leads to the destruction of beta cells in the pancreas, causing high blood sugar and a state of severe oxidative stress. This stress is associated with elevated levels of markers such as Isoprostane-8, SOD, and GPx, and activation of key inflammatory pathways including NF-κB and TNF-α, exacerbating tissue damage. Therefore, this study aimed to evaluate the effectiveness of ginseng root extract and ginsenoside Rg1, alone or in combination with metformin, in restoring Isoprostane-8, SOD, GPx, NF-κB, and TNF-α levels to normal in diabetic male rats.

Experimental design: 35 male rats were used, divided into 7 groups of (5) rats each. The control group and 6 groups in which diabetes was induced by Alloxan, namely the treatments with metformin (200 mg/kg), alcoholic ginseng extract (200 mg/kg), and ginsenoside Rg1 (20 mg/kg), in addition to the combination groups of (metformin + ginsenoside Rg1) and (ginseng extract + ginsenoside Rg1), and the trial lasted for five weeks.

Results: The results showed that diabetes led to a significant increase in Isoprostane-8, NF-κB and TNF-α, and a decrease in SOD and GPx. All treatments used led to a significant reduction in oxidation and inflammation markers and a significant increase in antioxidant enzyme levels compared to the diabetic group.

Conclusion: The study demonstrated that the combination of ginseng extract and ginsenoside Rg1 achieved the best effect in improving the studied biochemical parameters, indicating their effective role in reducing oxidative stress and inflammation associated with diabetes.

Keywords: Diabetes; Isoprostane-8; NF-κB; TNFα; Ginsenoside Rg1.

1. Introduction

Type 1 diabetes is an autoimmune disease in which insulin-producing beta cells in the pancreas are destroyed, resulting in high blood sugar levels. One of the hallmarks of type 1 diabetes physiology is severe oxidative stress, by which is meant an imbalance between the generation of reactive oxygen species (ROS) and antioxidants (AS). Diabetic patients exhibit impaired antioxidant defenses, as evidenced by reduced levels of enzymes that detoxify reactive oxygen species, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione (GSH) (Chen *et al*., 2025). Animal studies consistently show elevated levels of 8-isoprostane in diabetes, linking it to a risk of vascular and coronary heart disease, supporting its role as a key marker of oxidative stress in diabetes in general (Etchegaray-Armijo *et al*., 2025). In this process, tumor necrosis factor-alpha (TNF-α) is a major inflammatory cytokine that contributes to beta cell damage and to the development of long-term complications. TNF-α is produced by many immune cells and stimulates the release of other inflammatory mediators (such as IL-1β, IL-6) and adhesion molecules,

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leading to programmed cell death and cytotoxicity. In type 1 diabetes, TNF-α is secreted by activated $CD4^+$ helper T cells in the pancreas, leading to beta cell necrosis, lymphocyte infiltration, and increased local TNF-α production. TNF-α works with IL-1β and IFN-γ to activate NF-κB and other stress pathways in beta cells, leading to amplification of inflammation and autoimmunity (Conte *et al*., 2023; Xie *et al*., 2025).

The action of metformin on oxidative stress in T1D seems to be primarily through the upregulation of antioxidant enzyme activity (e.g. SOD, GPx) and a decrease in products of lipid peroxidation (e.g. isoprostanes). The results are from experiments on patients and animal models that reflect type 1 diabetes. Metformin-based treatment was found to decrease the blood isoprostanate level in adults with type 1 diabetes by up to 1.2 times, compared to baseline and control levels (Janić *et al*., 2022). Metformin has important anti-inflammatory effects. In type 1 diabetes models, it can modulate key immune pathways such as NF-κB and TNFα, which induce autoimmune beta cell damage and diabetes complications. Mechanistic studies show that metformin activates AMPK and inhibits NF-κB, thereby reducing pro-inflammatory cytokines, including TNFα (Ullah and Shen, 2025).

Research links ginseng to a reduction in oxidative stress, which is critical in diabetes complications, and has found that taking ginseng supplements significantly increases SOD levels, total antioxidant capacity, and GPx levels (Ren *et al*., 2023). Many ginseng preparations inhibit the activation of the nuclear transcription factor NF-κB, thereby reducing the phosphorylation of nuclear IκBα and p65, and consequently reducing inflammatory signaling in phagocytic cells, microglia, kidney cells, and nerve cells. In diabetic patient models, ginseng extract (Panax ginseng) inhibited RAGE/NF-κB activation in Schwann cells and neurons under elevated glucose levels, restoring pathway balance (Jang *et al*., 2023; Liu *et al*., 2025).

Studies have shown that ginsenoside Rg1 significantly increases (SOD) enzyme activity and reduces the malondialdehyde (MDA) oxidative damage index in diabetes models. Rb1 ginsenosides in streptozotocin-induced diabetic rats (STZ) also showed an increase in SOD and GPx enzyme activity and a decrease in MDA levels in lung and heart tissues, indicating a general antioxidant pattern within this class of compounds (Su *et al*., 2022; Xie *et al*., 2023). Ginsenoside Rg1 is a major active compound in ginseng and has anti-inflammatory and anti-type 1 diabetes effects in animal models. This compound modulates major inflammatory pathways, including NF-κB and cytokines such as TNF-α, which were studied mainly in streptozotocin-induced type 1 diabetes (STZ) mice. Rg1 (at a dose of 20 mg/kg) reduced the mRNA level of TNF-α in the pancreas and spleen and significantly inhibited the protein expression of NF-κB, as well as other inflammatory markers (IL-1β, NOS2, CXCL16, and TF). Rg1 also reduces the level of NF-κB and iNOS in beta cells, indicating inhibition of the NF-κB–iNOS–NO inflammatory axis in the pancreas of patients with type 1 diabetes (Zong *et al*., 2023).

Therefore, the current study aimed to evaluate the effect of metformin, *Withania somnifera* leaf extract, and Ginsenoside Rg1 in normalizing Isoprostane-8, SOD, and GPx levels with serum NF-κB and TNFα levels resulting from the induction of diabetes in male rats.

2. Material and methods

2.1. Materials

Indian Ginseng (Withania somnifera) was sourced from the root part of the plant from China. 70% methanol was used to extract root extract. 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 (normal 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 treated with 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 treated with 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. Blood serum collection

After the five-week trial period, the animals were fasted 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 via intramuscular injection. Blood serum was obtained by drawing blood from the heart and then stored at -20°C for the biochemical analyses of the study.

2.5. Biochemical Tests

The concentrations of Isoprostane-8, SOD, and GPx, as well as NF-κB and TNFα in serum, were determined according to the instructions of the Biolabo kit using ELISA.

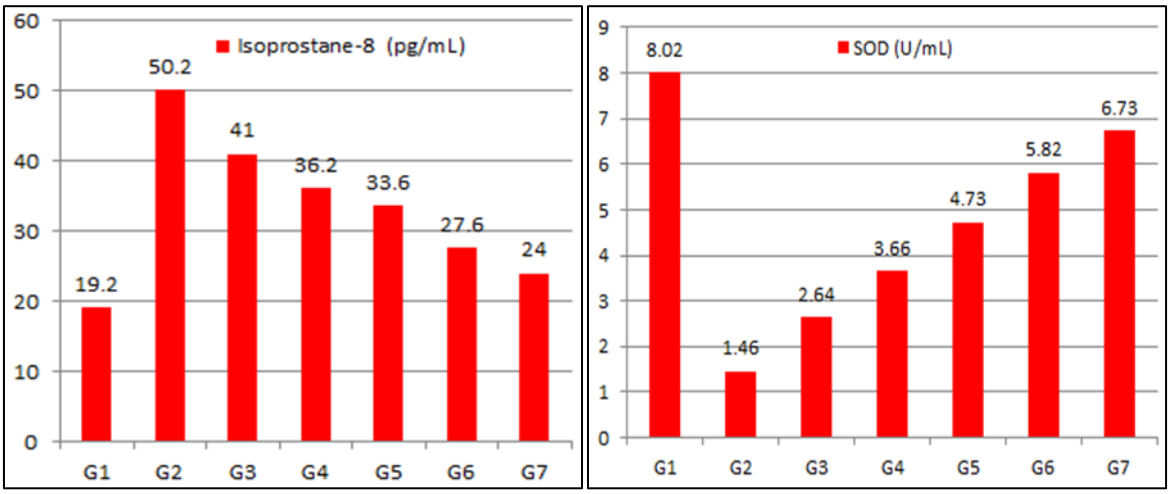
2.6. Statistical Analysis

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 Isoprostane-8, SOD, and GPx Concentrations

The results in (Figure-1) and Table (1) showed a significant increase in Isoprostane-8 concentration and a significant decrease in SOD and GPx concentrations compared to the normal control group. As for the diabetic groups treated with metformin only, Ginseng Alcoholic Extract only, Ginsenoside Rg1 only, (metformin + Ginsenoside Rg1), and (Ginseng Alcoholic Extract + Ginsenoside Rg1), Isoprostane-8 concentration decreased and SOD and GPx concentrations increased compared to the diabetic group. The group treated with Ginseng Alcoholic Extract + Ginsenoside Rg1 together had the best effect on improving the above parameters.



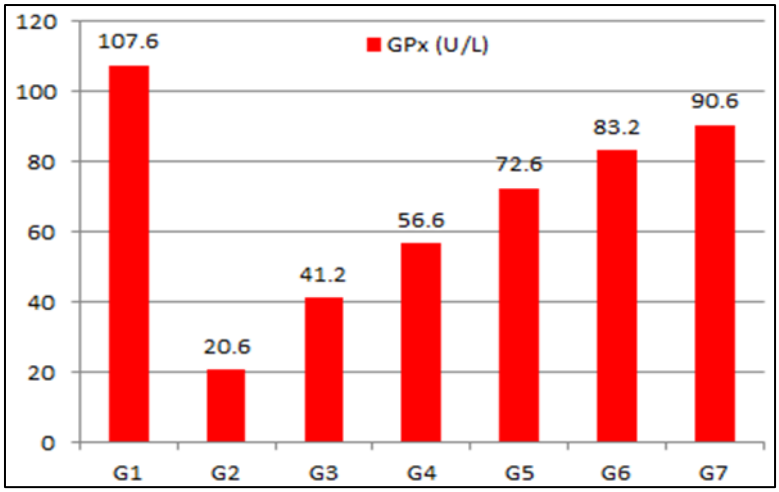


Figure 1 Serum concentrations of Isoprostane-8, SOD and GPx.

Table 1 Effect of Ginseng Alcoholic Extract and Ginsenoside Rg1 on the concentration of Isoprostane-8, SOD and GPx in the serum of male albino rat experimental groups.

Parameters / Groups	Isoprostane-8 (pg/mL)	SOD (U/mL)	GPx (U/L)
Control	19.20±3.42 e	8.02±0.29a	107.60±8.47a
Diabetic	50.20±4.15a	1.46±0.20g	20.60±3.65g
metformin	41.00±3.16b	2.64±0.20f	41.20±5.40f
Diabetic + Ginseng Alcoholic Extract	36.20±3.96c	3.66±0.32e	56.60±3.58e
Diabetic + Ginsenoside Rg1	33.60±2.41c	4.73±0.38d	72.60±3.85d
Diabetic + metformin + Ginsenoside Rg1	27.60±2.41d	5.82±0.21c	83.20±3.49c
Diabetic + Ginseng + Ginsenoside Rg1	24.00±2.24d	6.73±0.23b	90.60±3.65b
F	54.97	369.23	189.02
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. Serum NF-κB and TNFα Concentrations.

The results in Figure 1 and Table 1 showed a significant increase in NF-κB and TNFα concentrations compared to the normal control group. However, for the diabetic groups treated with metformin alone, ginseng alcohol extract alone, ginsenoside Rg1 alone, metformin + ginsenoside Rg1, and ginseng alcohol extract + ginsenoside Rg1, NF-κB and TNFα concentrations decreased compared to the diabetic group. The group treated with ginseng alcohol extract + ginsenoside Rg1 combined had the greatest effect on improving the aforementioned parameters.

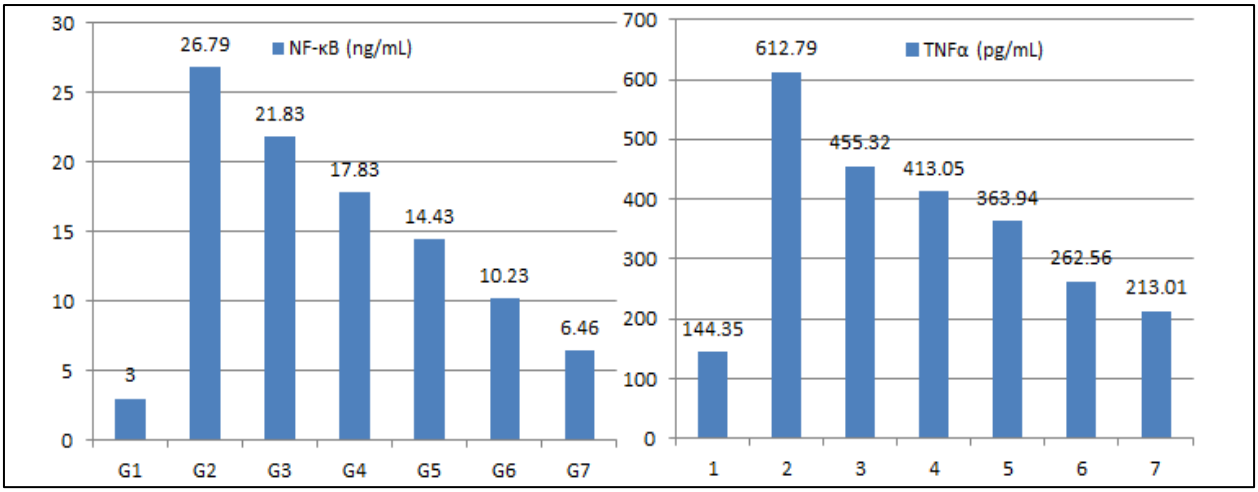


Figure 2 NF-κB and TNFα concentrations in blood serum.

Table 2 Effect of Ginseng Alcoholic Extract and Ginsenoside Rg1 on the concentration of NF-κB and TNFα in the serum of male albino rat experimental groups.

Parameters / Groups	NF-κB (ng/mL)	TNFα (pg/mL)
Control	3.00±0.30g	144.35±29.43g
Diabetic	26.79±0.92a	612.79±21.61a
metformin	21.83±0.72b	455.32±34.36b
Diabetic + Ginseng Alcoholic Extract	17.83±0.72c	413.05±18.23c
Diabetic + Ginsenoside Rg1	14.43±0.74d	363.94±24.55d
Diabetic + metformin + Ginsenoside Rg1	10.23±1.02e	262.56±25.43e
Diabetic + Ginseng + Ginsenoside Rg1	6.46±1.19f	213.01±19.64f
F	507.83	199.16
P-Value	<.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 ($P \geq 0.05$).

4. Discussion

Elevated blood glucose levels in diabetic patients lead to increased production of reactive oxygen species (ROS) via multiple pathways. Isoprostane-8, SOD, and GPx are among the most important clinical biomarkers of oxidative stress, and these markers are associated with an increased risk of complications. High levels of SOD and GPx enzyme activity generally indicate chronic oxidative stress with compensatory overactivity, while low levels (as seen in type 1 diabetes) suggest impaired antioxidant defense (Pinzaru *et al*., 2025). Type 1 diabetes is closely associated with oxidative stress, which can be tracked using lipid peroxidation products (such as 8-isoprostane) and antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). Numerous studies demonstrate that type 1 diabetes alters this balance, leading to increased oxidative damage and adaptive changes in antioxidant defenses. F2-isoprostanes (including 8-isoprostane) are established markers of lipid peroxidation and are strongly associated with diabetes and its complications (Sabitha *et al*., 2024; Nuñez-Selles *et al*., 2025). Insulin deficiency is not the only factor with type 1 diabetes—it's also a chronic inflammatory condition. Tumor necrosis factor-alpha (TNF-α) is a key pro-

inflammatory cytokine that plays a role in beta cell damage, type 1 diabetes systemic inflammation and complications. The macrophage, dendritic cells, T cells and other immune cells produce TNF-α, which induces IL-1 beta (IL-1β), IL-6, adhesion molecules, and apoptosis pathways. In type 1 diabetes, TNF-α secreted by helper T cells (CD4+) and macrophages infiltrating the islets of Langerhans directly contributes to beta cell death and islet inflammation (Fogarasi *et al*., 2024; Haber *et al*., 2023). Activation of the transcription factor NF-κB contributes to beta cell damage, tissue inflammation, and diabetic complications, and several studies have explored how inhibiting this pathway may be protective. In type 1 diabetes, immune cytokines such as IL-1β, TNF, and CD40L activate the transcription factor NF-κB in pancreatic beta cells via classical and non-classical pathways, generally promoting beta cell death and disease progression (Xiao *et al*., 2022; Guo *et al*., 2024).

Metformin use increased blood levels of SOD and GPx enzymes, as well as improved overall antioxidant status; this antioxidant effect was accompanied by improved arterial function. Diabetes in type 1 diabetic rats resulted in decreased SOD and GPx enzyme levels; metformin treatment restored the activity of these enzymes and reduced redox markers (TOS, MDA) and apoptosis-related gene expression, suggesting cardiac protection through reduced oxidative stress. Other animal models of diabetes (liver, brain, and blood vessels) have also consistently shown that metformin enhances or maintains SOD and GPx enzyme levels and reduces oxidative damage products (Naghdi *et al*., 2022; Dagsuyu *et al*., 2023). In retinal endothelial cells exposed to high glucose levels, metformin directly inhibited the transcription factor NF-κB p65 and reduced TNFα and other cytokine levels, partially independently of AMPK. Metformin also reduced NF-κB levels in multiple tissues (lung, kidney, heart, brain, and vascular endothelium), leading to decreased TNFα and IL-1β levels (Li *et al*., 2022).

Ginseng extract reduced oxidative stress and improved mitochondrial function via Nrf2-related pathways in diabetic rats with peripheral neuropathy, suggesting enhanced antioxidant defenses (Liu *et al*., 2025). Animal models of diabetes use streptozotocin-induced hyperglycemia, which is similar to type 1 in its mechanism of action, but the focus is on complications (retinopathy, neuropathy), and not on systemic indicators such as Isoprostane-8 in type 1 patients (Li *et al*., 2024). Ginseng extract (Panax ginseng) also alleviated diabetic peripheral neuropathy in streptozotocin-induced diabetic rats (STZ) by inhibiting RAGE/NF-κB, reducing TNFα and IL-6 levels, and mitigating oxidative stress. Ginseng saponins (Panax notoginseng) also improved diabetic retinopathy and atherosclerosis by inhibiting NF-κB and reducing TNFα, IL-6, and adhesion molecules. Reviews on diabetes and inflammatory cell death (pyroptosis) highlight the role of ginseng in regulating IκB/NF-κB/NLRP3 and related inflammatory pathways in diabetic complications (Wang *et al*., 2024; Li *et al*., 2025).

Ginsenoside Rg1 reduces reactive oxygen species (ROS) and improves endothelial function by inhibiting the calpine-1/ROS/PKC-β axis, mechanistically linking this to reduced oxidative stress in models of endothelial dysfunction in type 1 diabetes. This supports the notion that Rg1's effects on SOD reflect broader ROS control. Increases in GPx have been observed with ginsenoside Rb1 in the diabetic heart and with ginsenoside Re in brain aging models (Nguyen *et al*., 2022; Feng *et al*., 2024). Another study in mice with type 1 diabetes showed that Rg1 improved pancreatic injury and beta cell apoptosis via AMPK/mTOR-associated autophagy, but it did not directly quantify NF-κB or TNF-α. Its effects were primarily anti-apoptotic and metabolic. Studies have found that Rg1 consistently reduces TNF-α levels, likely by inhibiting NF-κB signaling, which contributes to lower blood glucose and oxidative stress (Chen *et al*., 2023; Xie *et al*., 2023).

5. Conclusion

Type 1 diabetes leads to a severe oxidative imbalance, characterized by a significant increase in Isoprostane-8 levels and activation of the inflammatory pathways NF-κB and TNFα, counteracted by a depletion of the antioxidant defenses SOD and GPx. Metformin, ginseng extract, and ginsenoside Rg1 all possess the ability to effectively alleviate these effects by reducing lipid peroxidation products and inhibiting inflammatory cytokines. The combination of ginseng extract and ginsenoside Rg1 achieved the best effect in restoring physiological balance and normalizing biochemical indicators in blood serum.

Compliance with ethical standards

Statement of ethical approval

All the experiments in this study were performed in compliance with the ethical and official regulations for animal experimentation and appropriate approvals were obtained from the local animal care and use committee.

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