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(RESEARCH ARTICLE)

Synergistic potential of ginseng root extract and ginsenoside Rg1 in Mitigating Type 1 Diabetes-Induced Oxidative Stress and Inflammatory Cytokines in Male Rats

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Abstract

Background & Objective: Type 1 diabetes mellitus (T1DM) has a close relationship with chronic oxidative stress and systemic immune dysfunction, which is usually accompanied by increased levels of lipid peroxidation parameters, for example malondialdehyde (MDA), and decreased levels of endogenous antioxidants, such as reduced glutathione (GSH) and catalase (CAT). It is also defined as having an imbalance of cytokines with high levels of the pro-inflammatory cytokine interleukin-6 (IL-6) and low levels of the anti-inflammatory cytokine interleukin-10 (IL-10). The purpose of this study was to investigate the synergic therapeutic effect of PGR and the main compound of PGR, Ginsenoside Rg1 for attenuating the diabetes-induced oxidative and inflammatory cascades as compared with the typical antidiabetic drug, Metformin. Experimental Design: Diabetic male rats were randomly divided into 7 experimental groups and they were treated with streptozotocin for 5 weeks: untreated diabetic control group, Metformin treated group, P. ginseng extract treated group, Ginsenoside Rg1 treated group, combined (Metformin + P. ginseng extract) group, combined (Metformin + Ginsenoside Rg1) group, and non-diabetic control group. Calorimetrically and immunologically, the serum levels of MDA, GSH, CAT, IL-6 and IL-10 were quantified before and after treatment. Results: An increase in the levels of MDA and IL-6 was seen to be significantly ($P<0.05$) high after the induction of T1DM and a decrease in GSH, CAT and IL-10 was seen to be significantly lower than healthy controls. The P. ginseng extract and Ginsenoside Rg1 significantly ($P < 0.05$) decreased the levels of MDA and IL-6, while increasing antioxidant enzyme activities and IL-10 levels when compared to the control group. Interestingly, P. ginseng extract with Ginsenoside Rg1 produced the greatest protective effect in each of the biomarker's profile compared to individual treatments and was evident of potentiation response. Conclusions: Panax ginseng extract and Ginsenoside Rg1 have strong antioxidant and immunomodulatory abilities. Their synergic effect in reduction of oxidative damage and restoration of cytokine balance highlights their potential usefulness as adjuvants in treatment of complications in T1DM.

Keywords: Diabetes; Oxidative Stress; Interleukins; Ginseng; Inflammatory Cytokines.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a disease where destruction of the insulin producing pancreatic beta-cells leads to increased blood sugar levels. In chronic hyperglycaemia, T1DM causes a chain of pathological mechanisms, mainly mediated via chronic oxidative stress and systemic inflammation. This is associated with significant decrease in the level of antioxidant defense systems including reduced glutathione (GSH) and catalase (CAT) which are important antioxidants in this system, accompanied by an increased level of malondialdehyde (MDA), one of the main markers of lipid peroxidation [1,2]. At the same time, immune dysregulation maintains pancreatic tissue damage, mainly under the control of the ratio of pro-inflammatory and anti-inflammatory cytokines. Remarkably, there is an increase in systemic interleukin-6 (IL-6) and a decrease in systemic interleukin-10 (IL-10) that positively correlate with disease severity, progressive pancreatic inflammation, and diabetic vascular complications [3,4].

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Metformin is a first line biguanide hypoglycemic drug that has been recognized to have a variety of effects beyond glucose regulation including antioxidant and immunomodulatory effects. In the pre-clinical phase, it has been proven that the use of metformin results in a significant decrease in the oxidative damage caused by the accumulation of MDA in diabetes models and an increase in the amount of GSH in cells and activity of CAT enzyme [5,6]. In addition, metformin has anti-inflammatory effects by reducing pro-inflammatory signal transduction, such as IL-6 signaling, and increasing the production of anti-inflammatory mediators, including IL-10, via pathways mostly dependent on the activation of AMP-activated protein kinase (AMPK) and inhibition of Nuclear Factor-kappa B (NF-κB) [7,8].

Natural bioactive phytoconstituents have been found to be potential complementary candidates in preserving the cellular integrity of islets while reducing the inflammatory damage, due to the multifactorial pathogenesis of T1DM. Ginseng bioactive compounds like ginsenosides have significant antioxidant and anti-inflammatory properties and interact with essential signaling pathways for example NF-κB, PI3K/Akt and JAK/STAT pathways [9,10]. Of these, Ginsenoside Rg1, a major monomeric saponin, has been shown to have potent cytoprotective activity against oxidative injury models by scavenging reactive oxygen species (ROS), decreasing level of MDA, and increasing antioxidant enzyme capacities (GSH and CAT) [11,12]. Cytokytotic cytokines, like IL-1β, TNF-α, and IL-6, which are released via activated immune cells, are one of the major hurdles in preserving the β-cells [13]. The synergism or additivity between ginseng extract with metformin in therapeutic effects on oxidative damage and cytokine imbalance associated with T1DM has not been fully understood; however, it is known that the individual pharmacological properties of both extracts and purified Ginsenoside Rg1 are established. Hence, the present study was planned to investigate the effect of Withania somnifera (Indian ginseng) root extract and its constituent Ginsenoside Rg1 both alone and with metformin on the normalization of oxidative stress parameters, viz., malondialdehyde, glutathione and catalase and restoration of cytokine balance (IL-6 and IL-10) in diabetic male rats induced by streptozotocin.

2. Materials and Methods

2.1. Materials

Dried roots of "Withania somnifera (Indian ginseng)" were purchased from a commercial vendor in China and a solvent of 70% aqueous methanol was used for preparation of crude extracts. Reference standards such as Ginsenoside Rg1 and Metformin were obtained from Sigma-Pacific (USA) and Merck Serono (Germany), respectively.

2.2. Animals

The adult male Sprague-Dawley rats (190±10 g, 16 weeks old) were maintained in polypropylene cages with access to standard laboratory food and water, and change the litter every day with the cages being sanitized and cleaned for hygiene.

2.3. Experimental Design

In the present study, thirty-five adult male albino rats of comparable body weight were randomly allocated into seven experimental groups (n=5 per group). Type 1 diabetes mellitus was experimentally induced in Groups 2 through 7 via a single subcutaneous injection of alloxan monohydrate (150 mg/kg body weight) [14]. The experimental groups were designated as follows:

- Group 1 (Natural Control): Fed on a normal diet and distilled water for 5 weeks
- Group 2 (Diabetic): Given a normal diet and distilled water for 5 weeks
- Group 3 (Diabetic Control and Metformin): After being fed a normal diet and then administered metformin (200 mg/kg) for five weeks [15].
- Group 4 (Diabetic Control and Ginseng Alcoholic Extract): The ginseng alcoholic extract (200 mg/kg) was administered to treated normal diet rats for 5-weeks [16].
- Group 5 (Control group infected and treated with Ginsenoside Rg1): This group received a normal diet and the ginsenosides at a dose of 20 mg/kg [17], for 5 weeks.
- Group 6 (Control group infected and treated with metformin + ginsenosides): This group was fed with a normal diet and treated with ginseng alcoholic extract (200 mg/kg) and ginsenoside Rg1 (20 mg/kg) for 5 weeks.
- Group 7 (Control group infected and treated with ginseng alcoholic extract + ginsenosides): This group received a normal diet and 200 mg/kg of ginseng alcoholic extract, and 20 mg/kg of ginsenoside Rg1 for 5 weeks.

2.4. Blood serum collection

Animals were allowed to eat for five weeks and then a 12-hour fast before being given intramuscular injections of ketamine (5 mg/kg) and xylazine (35 mg/kg) for anaesthetic. Blood serum was extracted from the heart and kept at -20°C for the study's biochemical tests.

2.5. Biochemical Tests

ELISA was used to measure the blood serum levels of MDA, GSH, CAT, IL-6 and IL-10 following the manufacturer's instructions from Biolabo (France).

2.6. Statistical Analysis

All data were statistically analyzed using the IBM "SPSS Statistics version 26.0 software" (Armonk, NY, USA) and the mean differences of the treatments were determined on the 0.05 level of significance by Duncan's Multiple Range Test (DMRT).

3. Results

3.1. Serum MDA, GSH, and CAT Concentrations

As shown in the results obtained in (Figure-1) and Table (1), there was significant increase in MDA concentration and significant decrease in the concentration of GSH and CAT in diabetic group as compared to normal control group. In diabetic groups treated with Ginseng Alcoholic Extract only, Ginsenoside Rg1 only, (metformin + Ginsenoside Rg1), and (Ginseng Alcoholic Extract + Ginsenoside Rg1) the concentration of MDA was reduced and GSH and CAT were increased compared to diabetic group. Ginseng Alcoholic Extract + Ginsenoside Rg1 group showed the greatest effect on the above parameters.

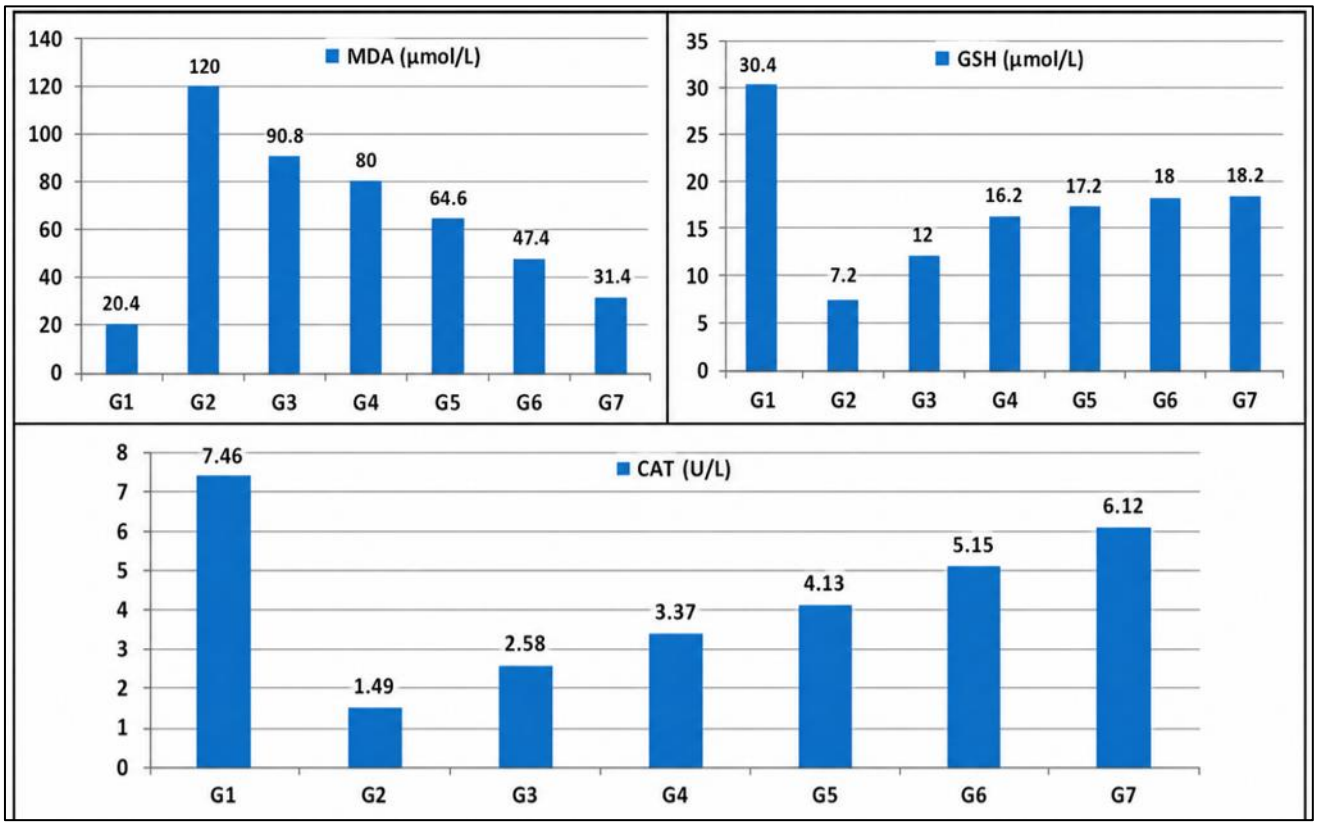

Figure 1 Concentration of MDA, GSH and CAT in blood serum.

Figure 1. Concentrations of the oxidative stress and antioxidant biomarkers in serum from experimental groups (G1 to G7). The concentration of malondialdehyde (MDA) was significantly higher in G2 than in G1 and then slightly decreased in the following groups. Conversely, the activities of reduced glutathione (GSH) and catalase (CAT) were significantly decreased in G2 and gradually increased from G3 to G7. These results suggest a significant relationship between oxidative stress and antioxidant defense mechanism, where a partial recovery was seen in treated groups.

Table 1 The results showed that there were no changes in the serum level of MDA, GSH and CAT in the experimental groups (Male Albino rats).

Parameters / **Groups**	**MDA (µmol/L)**	**GSH (µmol/L)**	**CAT (U/L)**
Control	20.40±3.65g	30.40±3.98a	7.46±0.39a
Diabetic	120.00±6.78a	7.20±1.92d	1.49±0.22g
metformin	90.80±3.19b	12.00±1.58c	2.58±0.36f
Diabetic + Ginseng Alcoholic Extract	80.00±4.47c	16.20±1.43b	3.37±0.34e
Diabetic + Ginsenoside Rg1	64.60±6.19d	17.20±2.86b	4.13±0.22d
Diabetic + metformin + Ginsenoside Rg1	47.40±3.50e	18.00±1.58b	5.15±0.22c
Diabetic + Ginseng + Ginsenoside Rg1	31.40±3.65f	18.20±1.92b	6.12±0.18b
F	274.78	44.18	264.37
P-Value	<.0001***	<.0001***	<.0001***

All values are means ± SDs.; Statistically significant difference (P ≥ 0.05) is indicated by numbers followed by different letters vertically.

3.2. Serum IL-6 and IL-10 Concentrations

As seen in Figure 1 and Table 1, the diabetic groups presented a significant increase in serum IL-6 concentrations with a significant decrease in IL-10 concentrations, when compared with the healthy control group ($P < 0.05$). On the contrary, each group of treated diabetic animals presented a significant decrease in the concentration of IL-6 and an increase in the concentration of IL-10 when compared with the untreated diabetic group ($P < 0.05$). Interestingly, the combination of Panax ginseng alcoholic extract and Ginsenoside Rg1 showed a more pronounced IL-6 suppressing effect and IL-10 elevating effect than all other groups, bringing the cytokines into homeostasis.

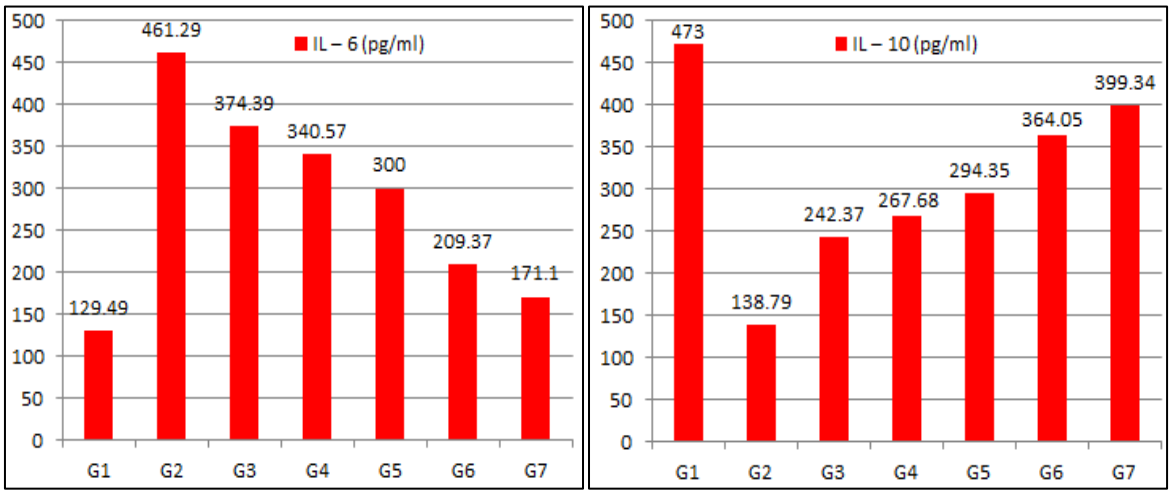

Figure 2 Pro-inflammatory cytokine levels (IL-6) and anti-inflammatory cytokine levels (IL-10) in the serum of the different experimental groups (G1–G7). The level of IL-6 was significantly higher in G2 than in the control (G1) and continued to drop in all the subsequent groups. IL-10 levels, on the other hand, were significantly decreased in G2 and increased in a similar manner as G3 to G7, suggesting improvement of the anti-inflammatory response in treated groups. The results indicate inflammatory balance modulation under experimental conditions.

Table 2 The blood serum levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 in the experimental groups of male albino rats after the treatments with Ginseng Alcoholic Extract and Ginsenoside Rg1.

Parameters / Groups	IL – 6 (pg/ml)	IL – 10 (pg/ml)
Control	129.49±8.24g	473.00±14.55a
Diabetic	461.29±8.27a	138.79±12.68g
metformin	374.39±20.15b	242.37±19.79f
Diabetic + Ginseng Alcoholic Extract	340.57±22.60c	267.68±7.40e
Diabetic + Ginsenoside Rg1	300.00±19.25d	294.35±11.84d
Diabetic + metformin + Ginsenoside Rg1	209.37±12.13e	364.05±13.00c
Diabetic + Ginseng + Ginsenoside Rg1	171.10±12.30f	399.34±10.38b
F	288.78	346.30
P-Value	<.0001***	<.0001***

Values are given as mean ± SD.; Statistically significant difference between numbers (P ≥ 0.05) vertically indicated by different letters.

4. Discussion

Individuals with type 1 diabetes show elevated levels of MDA and decreased levels of GSH and CAT in the liver, pancreas, or blood [18,19]. The level of the enzyme catalase (CAT) is significantly reduced in patients with type 1 diabetes, indicating a deficiency of a key intracellular antioxidant compared to healthy individuals. According to one study, the lowest levels of catalase were found in patients with type 1 diabetes, moderate levels in those with type 2 diabetes and the highest levels in healthy individuals [19]. High blood levels of the cytokine interleukin-6 (IL-6) are linked to poorer glycemic control (hyperglycemia, high fasting blood glucose, HbA1c) and be a very powerful predictor for type 1 diabetes. In the context of poor glycemic control, Type 1 diabetes is linked with increased IL-6 and decreased IL-10 levels, indicating a shift towards inflammation [20,21].

Evidence supports the role of metformin in restoring redox balance in type 1 diabetes. Studies have shown that metformin significantly reduces elevated MDA levels resulting from hyperglycemia in type 1 diabetes models. Metformin also consistently increases GSH and catalase levels, which are typically reduced due to the oxidative stress associated with diabetes [22,23]. Effect of metformin specifically on IL-6 and IL-10 in patients with T1DM is scarce and indirect. From the available evidences based on animal models, laboratory studies, and related autoimmune diseases, metformin seems to decrease the level of IL-6 and may modulate the signaling of IL-10 [24,25].

Ginseng supplementation has been found to lower the level of MDA while raising the level of GSH, total antioxidant capacity, SOD enzyme, glutathione reductase enzyme and CAT. Likewise, animal and cell models utilizing ginseng extracts or ginsenosides demonstrate reductions in MDA and elevations in GSH, CAT and other enzyme levels in various disease models [26,27]. In animal and human models of diabetes, ginseng derivatives reduce interleukin-6 (IL-6) and other pro-inflammatory cytokines while increasing interleukin-10 (IL-10) levels, suggesting a shift toward an anti-inflammatory profile relevant to autoimmune processes in type 1 diabetes. Type 1 diabetes models treated with ginseng components (such as panaxadiol and ginseng flower saponins) demonstrate improved glycemic control and organ protection through inhibition of inflammatory signaling [26,28].

Ginsenoside Rg1 and related ginsenosides increase glutathione (GSH) levels and catalase (CAT) activity, thereby enhancing the body's endogenous antioxidant defense system. Ginsenoside Rg1 has been found to significantly reduce MDA and improve antioxidant status (such as SOD) while simultaneously lowering glucose levels in diabetic animals. Furthermore, ginsenoside Rg1 has been shown to reduce MDA and improve GSH levels and other antioxidant markers across multiple models of oxidative stress [29,30]. Ginsenoside Rg1 has demonstrated well-documented effects by reducing markers of oxidative stress and pro-inflammatory cytokines, and limiting tissue damage. Specifically, Rg1 significantly reduces interleukin-6 as part of its anti-inflammatory mechanism of action. Other ginsenosides (particularly Rb1) can reduce interleukin-6 and increase interleukin-10 in diabetic complications, demonstrating a shift toward anti-inflammatory properties [28, 31].

5. Conclusions

The study concludes that type 1 diabetes leads to severe physiological dysfunction characterized by increased oxidative stress and inflammation. Diabetes causes elevated levels of MDA (a lipid peroxidation index) and IL-6 (an inflammatory mediator), while significantly decreasing levels of the antioxidants GSH and CAT, and IL-10 (an anti-inflammatory mediator). The results demonstrate that metformin, ginseng extract, and ginsenoside Rg1 play a crucial role in mitigating these effects by restoring biochemical balance. They contribute to reducing harmful markers (MDA and IL-6) and enhancing the effectiveness of the body's defenses (GSH, CAT, and IL-10). The study confirms that the synergistic effect of ginseng extract and ginsenoside Rg1 resulted in the best therapeutic response in normalizing these levels and reducing disease-induced tissue damage.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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