JOURNAL OF IRANIAN CLINICAL RESEARCH

ORIGINAL ARTICLE

Effect of Hydro-alcoholic *Teucrium Polium L.* Extract and Glibenclamide Administration on Blood Glucose and Lipid Profile Levels in Streptozotocin-induced Diabetic Rats

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ABSTRACT

Background: Hyperglycemia is the most important sign of diabetes. There are different herbal and chemical medications used for the treatment of diabetes. Some herbs can increase or decrease the therapeutic effects of chemical drugs. The aim of this study was to determine the effect of simultaneous administration of *Teucrium polium L.* (*T. polium L.*) extract along with glibenclamide on the improvement of the blood glucose and lipid profile levels in the diabetic rats.

Materials and Methods: This experimental study was conducted on 48 male Wistar rats. For the study, the rats were randomly divided into six groups (n=8) of control and sham control groups as well as four diabetic groups. The control groups received normal saline by gavage, whereas the diabetic groups were provided with a gavage of normal saline (diabetic control), glibenclamide (5 mg/kg), *T. polium L.* extract (200 mg/kg), and a combination of glibenclamide and *T. polium L.* extract. Diabetes was induced with intraperitoneal injection of 55 mg/kg streptozotocin. The rats were treated for six weeks. Blood samples were obtained at the beginning, middle, and end of the therapeutic course. The blood glucose, triglyceride, and cholesterol levels as well as body weight were measured. Finally, the obtained data were analyzed using the ANOVA.

Results: According to the results, the simultaneous administration of *T. polium L.* extract and glibenclamide significantly increased the body weight (P=0.01). However, the *T. polium L.* extract plus glibenclamide-treated group showed a significant reduction in the plasma glucose (P=0.001), triglyceride (P=0.001), and total cholesterol (P=0.001) levels as compared to the diabetic rats. Nevertheless, the simultaneous use of *T. polium L.* extract and glibenclamide was not more effective in the body weight as well as the plasma glucose, triglyceride, and total cholesterol levels than the separate administration of these drugs (P>0.05).

Conclusion: As the findings of the present study indicated, hydro-alcoholic *T. polium L.* extract and glibenclamide had similar effects on blood glucose and lipid profile levels in the streptozotocin-induced diabetic rats. However, the simultaneous administration of these two therapeutic agents resulted in no significant effect in this regard.

Key Words: Diabetes mellitus, Glibenclamide, Glucose, Lipid, Rat, *Teucrium polium L.* extract

➢ How to cite this paper:
Khoshdel Sarkarizi H, Sazegar G, Rajabzadeh A. Effect of Hydro-alcoholic *Teucrium Polium L.* Extract and Glibenclamide Administration on Blood Glucose and Lipid Profile Levels in Streptozotocin-induced Diabetic Rats. Journal of Iranian Clinical Research. 2015; 1(2): 38-45.

INTRODUCTION

Diabetes, which is a widespread metabolic disorder in the world, has a growing prevalence [1]. It is estimated that over 100 million people globally are afflicted with this illness [2]. Hyperglycemia is the most important sign of diabetes, which may be affected by fat destruction, gluconeogenesis, and lipid metabolism disorders. These conditions are considered as the evidence of atherosclerosis and cardiovascular disorders [3].

Diabetes is managed through both chemical and herbal drugs. The most important goals of diabetes treatment are the reduction of of blood sugar and suppression of secondary complications. Currently, glibenclamide, as the most popular sulfonylurea drug, is one of the most important chemical medications widely used in the treatment of diabetes [4]. This drug

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acts as an ATP-sensitive potassium channel inhibitor in the pancreatic beta-cells. This inhibition opens the voltage-dependent calcium channels, which result increasing if the intracellular calcium in beta cells, and finally stimulates insulin release [5, 6].

In the traditional medicine, different herbal drugs have been utilized for the treatment of diabetes [7]. *Teucrium polium L.* (*T. polium L.*), which is locally called Kalpooreh in the Persian language, is one of the most widely used anti-diabetic drugs. This plant extensively grows in the stony and dry regions of the deserts and hills of approximately all Mediterranean countries as well as Europe, South Western Asia, and North Africa. *T. polium L.* is in clusters and ranges from pink to white with small flowers and linear leaves of 3 cm length [8]. This herb has been used since Hippocrates and Galen [7].

In addition to anti-diabetic feature [7, 9-11], this plant has been reported to have anti-inflammatory [12], anti-oxidant [13-17], anti-fever, anti-septic [18], anti-pain [19, 20], anti-ulceric [21], and anti-spasmodic [22-24] effects. Phytochemically, *T. polium L.* consists of tanen, trepnoid, saponin, esterol, flavonoid, and locoantosianin [25-29]. The extract of this herb can elevate the insulin secretion, and subsequently reduce the level of the plasma glucose level [7, 9-11, 30].

Some of the herbal drugs can increase or decrease the therapeutic effects of the chemical drugs [31, 32]. With this background in mind, the present study was conducted to investigate the anti-diabetic effects of glibenclamide and *T. polium L.* on the improvement of the blood glucose and lipid profile levels in the diabetic rats. It was hypothesized that the simultaneous administration of *T. polium L.* and glibenclamide at pharmacological doses can have positive impacts on the pancreatic islets of the diabetic rats.

MATERIALS AND METHODS

Animals

Male Wistar rats (Faculty of Medicine, Mashhad, Iran), weighting 200-220 g, were housed in an air-conditioned colony room at 22±2°C with 12:12 h light-dark cycle. The rats were supplied with standard pellet diet and tap water *ad libitum*. The procedures involving animals and their care were conducted in conformity with the National Institutes of Health guidelines for the care and use of laboratory animals. The present study was approved by the Local Research Ethics Committee.

Preparation of hydro-alcoholic Teucrium polium L. extract

The fresh leaves of *T. polium L.* were collected from South Khorasan, Iran, and dried at room temperature. Subsequently, 200 g of the air-dried leaves of the plant was milled into fine powder and soaked in 1 lit of 50% ethanol for 48 h in darkness. The obtained solution was filtered by ordinary filter paper, and then dried on a water bath (Memert, Germany) at 40°C for 36 h. The extract stock was kept at -20°C until being used. Based on the previous studies, a dose of 200 mg/kg was chosen for *T. polium L.*

Induction of experimental diabetes

After 12 h fasting, diabetes was induced by a single intraperitoneal (IP) injection of 55 mg/kg streptozotocin (STZ) in 0.9% sodium chloride (NaCl) [38, 39]. After 48 h of STZ injection, blood samples were collected from tail vein of the rats in fasting state. Afterwards, the blood glucose levels were measured by a portable glucometer (Easy GlucoTM, Infopia, Korea). The rats with a blood glucose value of > 250 mg/dL were considered as diabetic and included in the study.

Experimental design

The animals were randomly divided into six groups (n=8 in each group), including the control group (standard diet and tap water), sham control group (0.9% NaCl by gavage vehicle), diabetic control group (0.9% NaCl by oral gavage), hydro-alcoholic *T. polium L.* extract-treated group (200 mg/kg body weight), glibenclamide-treated group (5 mg/kg body weight), and hydro-alcoholic *T. polium L.* extract plus glibenclamide-treated group (simultaneous administration of 200 mg/kg and 5 mg/kg body weight of hydro-alcoholic *T. polium L.* extract and glibenclamide, respectively). The *T. polium L.* extract, glibenclamide, and normal saline were administered once a day by oral gavage. The treatment of the rats began 48 h after the STZ injection, which was considered as the first day of treatment. The animals received the treatment for six weeks.

Blood sampling

In order to investigate the biochemical factors, the plasma glucose, triglyceride, and total cholesterol levels were measured after the onset of the treatment, i.e., on the 1st, 7th, 21th, and 42th days of the intervention. A fasting blood sample was withdrawn from the retro-orbital venous plexus. The blood samples were centrifuged for 15 min with 3,500 rpm. The biochemical factors were measured using the enzymatic kit (Betagen, Iran) and photometer (Convergys®100, Germany).

Statistical analysis

The data were presented as mean and standard

deviation. The ANOVA was used to compare the differences between the experimental groups. In addition, multiple comparisons were accomplished using the Tukey's post hoc test. The statistical analysis was performed by the SPSS version 13.5 (Chicago, IL, USA).

RESULTS

Body weight

According to the results, there was no significant difference among the study groups in terms of the body weight at the first week and one week after the diabetes induction (P>0.05). Nevertheless, the study groups were comparable regarding the plasma glucose, triglyceride, and cholesterol levels were only at the beginning of the trial. Three weeks after the induction of diabetes, the body weight of the diabetic rats significantly reduced in comparison to that of the sham control group (P=0.01). However, this reduction was not significant in weeks 4-6.

The body weight was significantly (P=0.01) improved in the hydro-alcoholic *T. polium L.* extract plus glibenclamide-treated group, compared to that in the diabetic control group, especially at the third week of the intervention. However, this group did not show significantly higher body weight than the hydro-alcoholic *T. polium L.* extract-treated and glibenclamide-treated groups (Figure 1).

Plasma glucose level

On the first day of the treatment, the plasma glucose level was within the normal range in all of the groups. One week after the diabetes induction, the plasma glucose level showed a significant increase in the diabetic rats, compared to that in the control group (P=0.01). After the first week of the treatment, the effect of *T. polium L.* extract, glibenclamide, and their combination on the plasma glucose level was not significant between the experimental groups. Nonetheless, at the third (P=0.01) and especially sixth weeks (P=0.001), the experimental groups showed a significant decrease in this regard, compared to the untreated diabetic rats (Figure 2). On the other hand, the *T. polium L.* plus glibenclamide-treated group had a significant difference with the glibenclamide-treated and *T. polium L.*-treated groups in terms of the plasma glucose level.

Plasma triglyceride level

Figure 3 presents the changes of plasma triglyceride levels in the study groups from the first day of the treatment until the sixth week. There was no significant difference among the study groups in terms of the plasma triglyceride concentration at the beginning of the intervention. However, one, three, and six weeks after the induction of diabetes, the plasma triglyceride level significantly increased in the diabetic rats as compared to that in the sham control group (P=0.01, P=0.001, and P=0.001, respectively). However, the *T. polium L.* extract had no significant effect on the plasma triglyceride level at the first week of the

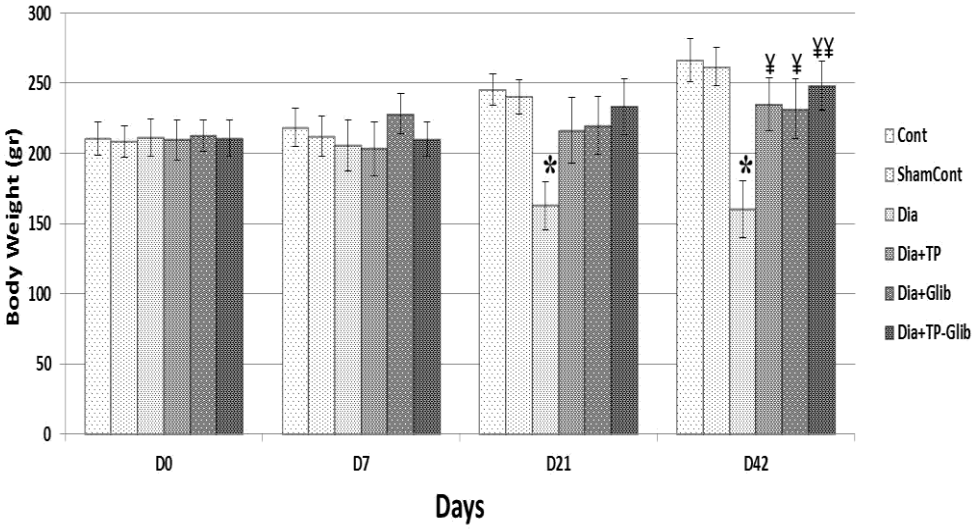

Figure 1. Comparison of body weight among the study groups (C): control, (Sh): sham control treated with sodium chloride, (D): streptozotocin-induced diabetic control rat, (G): streptozotocin-induced diabetics treated with glibenclamide, (TP): streptozotocin-induced diabetics treated with hydro-alcoholic Teucrium polium L. extract, (TP+G): streptozotocin-induced diabetics treated with hydro-alcoholic *T. polium L.* extract plus glibenclamide; (D_0): first day of the treatment, (D_7): 7th day of the treatment, (D_{21}): 21th day of the treatment, (D_{42}): 42th day of the treatment
*P=0.01 (compared to sham control group), ¥ P=0.01 (compared to diabetic control group), ¥¥ P=0.001 (compared to diabetic control group)

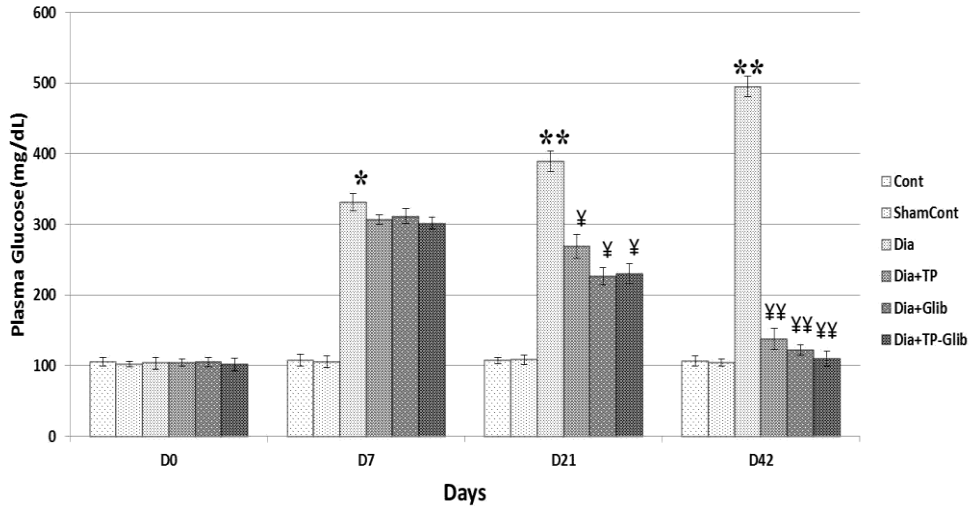

Figure 2. Comparison of plasma glucose level among the study groups (C): control, (Sh): sham control treated with sodium chloride, (D): streptozotocin-induced diabetic control rat, (G): streptozotocin-induced diabetics treated with glibenclamide, (TP): streptozotocin-induced diabetics treated with hydro-alcoholic Teucrium polium L. extract, (TP+G): streptozotocin-induced diabetics treated with hydro-alcoholic *T. polium L.* extract plus glibenclamide; (D_0): first day of the treatment, (D_7): 7th day of the treatment, (D_{21}): 21th day of the treatment, (D_{42}): 42th day of the treatment
*P=0.01 (compared to sham control group), **P=0.001 (compared to sham control group)
¥ P=0.01 (compared to diabetic control group), ¥¥ P=0.001 (compared to diabetic control group)

diabetes induction. The *T. polium L.* extract led to a significant reduction in the level of the plasma triglyceride in the diabetic rats in the third and sixth weeks of the treatment. Furthermore, the glibenclamide-treated and the *T. polium L.* extract plus glibenclamide-treated groups demonstrated a significant decrease in the plasma triglyceride level, compared to the diabetic group (P=0.001) (Figure 3) at the first, third, and sixth weeks of the diabetes induction.

Plasma cholesterol level

As the results indicated, the cholesterol level of the diabetic rats significantly increased as compared to that of the sham control group at the first, third, and especially sixth weeks of the diabetes induction (P=0.01, P=0.001, and P=0.001, respectively). Furthermore, the administration of *T. polium L.* extract and glibenclamide had no significant effects on the plasma cholesterol level at the first week of the treatment. Nevertheless, after three and six

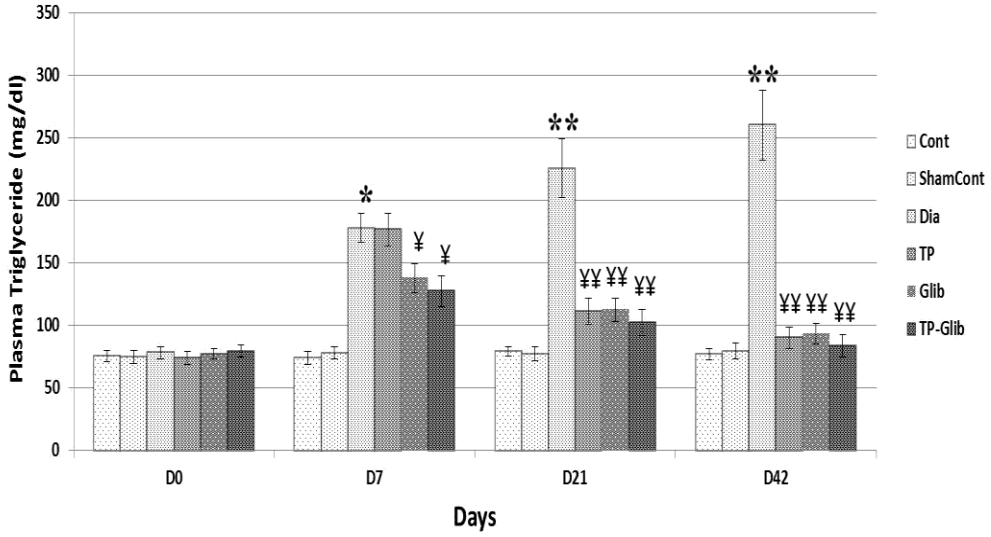

Figure 3. Comparison of plasma triglyceride level among the study groups (C): control, (Sh): sham control treated with sodium chloride, (D): streptozotocin-induced diabetic control rat, (G): streptozotocin-induced diabetics treated with glibenclamide, (TP): streptozotocin-induced diabetics treated with hydro-alcoholic Teucrium polium L. extract, (TP+G): streptozotocin-induced diabetics treated with hydro-alcoholic *T. polium L.* extract plus glibenclamide; (D_0): first day of the treatment, (D_7): 7th day of the treatment, (D_{21}): 21th day of the treatment, (D_{42}): 42th day of the treatment
*P=0.01 (compared to sham control group), **P=0.001 (compared to sham control group)
¥ P=0.01 (compared to diabetic control group), ¥¥ P=0.001 (compared to diabetic control group)

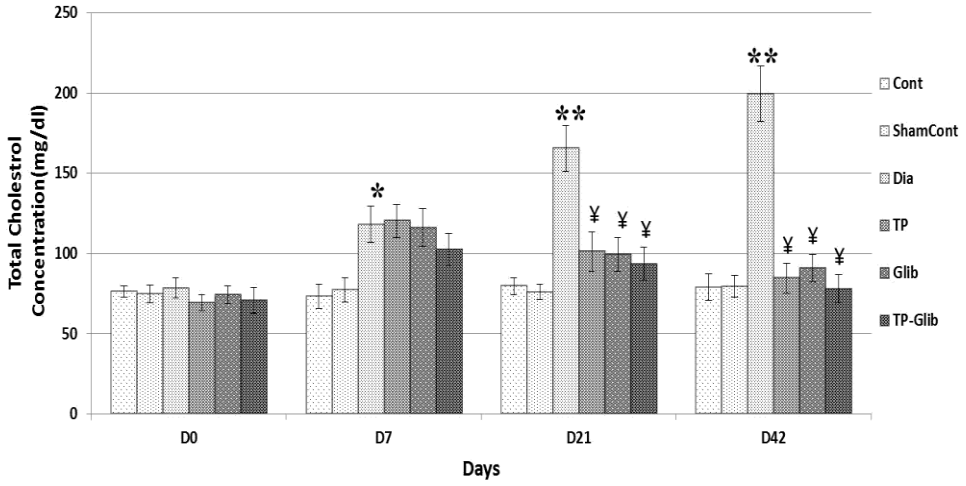

Figure 4. Comparison of plasma cholesterol Level among the study groups (C): control, (Sh): sham control treated with sodium chloride, (D): streptozotocin-induced diabetic control rat, (G): streptozotocin-induced diabetics treated with glibenclamide, (TP): streptozotocin-induced diabetics treated with hydro-alcoholic Teucrium polium L. extract, (TP+G): streptozotocin-induced diabetics treated with hydro-alcoholic *T. polium L.* extract plus glibenclamide; (D_0): first day of the treatment, (D_7): 7th day of the treatment, (D_{21}): 21th day of the treatment, (D_{42}): 42th day of the treatment
**P*=0.01 (compared to sham control group), ***P*=0.001 (compared to sham control group)
¥ *P*=0.01 (compared to diabetic control group)

weeks, *T. polium L.* extract and glibenclamide could significantly decrease the plasma cholesterol level as compared to that in the untreated diabetic rats (P=0.001) (Figure 4).

DISCUSSION

The irreversible destruction of the pancreatic beta-cells in the STZ-induced diabetic rats leads to the reduction of insulin secretion and elevation of blood glucose level [33]. The results of this study showed that glibenclamide and *T. polium L.* significantly reduced the diabetes-induced hyperglycemia. Karimi et al. reported that the *T. polium L.* and glibenclamide had similar effects on blood glucose level. Likewise, in the present study, the simultaneous administration of *T. polium L.* and glibenclamide could have a comparable impact on the diabetic patients [34]. However, the *T. polium L.* and glibenclamide combination had no significant effect on the body weight as well as plasma glucose, triglyceride, and cholesterol levels in the diabetic rats as compared to the separate administration of these agents.

In the present study, the STZ-induced diabetes group had the loss of body weight, especially after three weeks of induction, compared to the sham control group. In addition, the simultaneous administration of *T. polium L.* extract and glibenclamide prevented the reduction of body weight in the diabetic rats. Similarly, the diabetic rats that separately received *T. polium L.* or glibenclamide showed a significant decrease in their body weight. Although the mechanism(s) that explain the effect of *T. polium L.* or glibenclamide on body weight is unknown, the previous studies demonstrated the anabolic effects of insulin on protein metabolism by the stimulation of protein production and reduction of protein destruction [35]. Both *T. polium L.* extract and glibenclamide can increase the insulin secretion in the pancreatic beta-cells [10, 30, 36].

Based on the results of the present study, the combined administration of *T. polium L.* and glibenclamide could decrease the plasma glucose concentration in the diabetic rats after six weeks of treatment. Nevertheless, *T. polium L.* or glibenclamide treatment did not significantly affect the plasma glucose level.

Glibenclamide has insulin-like effects on the glucose metabolism. On the other hand, this drug decreases glycogenolysis and glucogenesis in the body cells, which in turn reduces the level of blood glucose [37]. In addition, glibenclamide inhibits the *T. polium L.*-sensitive potassium channels in the membrane of pancreatic beta-cells. Following the inhibition, the voltage-dependent calcium channels are activated, and then calcium ion is imported into the beta cells. Finally, the increased cytoplasmic calcium stimulates the insulin secretion [38, 39].

In this study, the blood glucose level was decreased in the diabetic rats under *T. polium L.* treatment. Probable mechanism(s) that explain the hypoglycemic effects of *T. polium L.* are often dependent on its pharmacologic agents, especially flavonoids [8, 29, 40, 41].

Vessal et al. demonstrated the effects of flavonoids (especially cuirestin existing in *T. polium L.)* on the pancreatic islets as a

regeneration factor in the beta cells of the STZ-induced diabetic rats [42]. Ashrafihelan et al. showed that the flavonoids elevated the insulin secretion by changing the calcium ions metabolism [30]. The *T. polium L.* increases the hepatic glucokinase activity in the hepatocytes. The enzyme alters glucose to glucose-6-phosphate within the cells; as a result, it prevents the entrance of glucose into the blood. Therefore, *T. polium L.* can be concluded to have hypoglycemia effects [43].

According to the findings of the present study, the triglyceride and total cholesterol levels increased in the STZ-induced diabetic rats. The reduction of the insulin secretion could enhance fat destruction and free the fatty acids in hepatocytes. Subsequently, the elevation of triglyceride synthesis may also cause hyperlipidemia [44, 45]. The present study showed that the administration of *T. polium L.* extract or glibenclamide during six weeks could significantly decrease the triglyceride and total cholesterol levels in the STZ-induced diabetic rats. However, the simultaneous administration of these two drugs did not significantly affect the total cholesterol level.

Glibenclamide decreases the triglyceride and cholesterol levels in the diabetic rats [44]. The results of our study are in line with those reported by the previous studies investigating the effects of glibenclamide on diabetic dyslipidemia [46]. The biochemical results of our study clearly supported the earlier reports indicating that *T. polium L.* extensively decreased the blood lipids level in the diabetic rats [34, 47, 48]. However, this is inconsistent with the results obtained by Stefkov et al., who did not find any difference in the cholesterol and triglyceride levels following the administration of *T. polium L.* in the diabetic mice [49].

The results of the experimental and population studies revealed that flavonoids could decrease the plasma cholesterol level in the diabetes-induced hyperlipidemia [50]. However, many studies have reported a little or no change in the plasma lipid and lipoproteins levels following the increased flavonoid intake [51, 52]. Further studies are needed to confirm the therapeutic efficacy of *T. polium L.* plus glebenclamide in the diabetic patients.

As our findings demonstrated, the combined administration of *T. polium L.* and glibenclamide was not more effective in the improvement of hyperglycemia and hyperlipidemia in the STZ-induced diabetic rats than the separate use of these drugs. It seems that *T. polium* and glibenclamide have a similar mechanism in the pancreatic beta-cells for the insulin secretion.

CONCLUSION

Based on the current results, hydro-alcoholic *T. polium L.* extract and glibenclamide had similar effects on blood glucose and lipid profile levels in the streptozotocin-induced diabetic rats. However, the simultaneous administration of these two therapeutic agents resulted in no significant effect in this regard.

ACKNOWLEDGEMENTS

This study was financially supported by a grant (No. 911275) from the Research Deputy of the Mashhad University of Medical Sciences, Mashhad, Iran. The data provided in this paper were derived from the results of an MSc thesis. In this regard, we would like to express our sincere thanks to the Research Deputy for their financial support. The authors also gratefully thank Mr. Hosseinzadeh for his helpful comments.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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