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ORIGINAL ARTICLE

The Effect of Hydro-Alcoholic *Teucrium polium* L. Extract with Glibenclamide Administration on Blood Glucose and Lipids in Streptozotocin-Induced Diabetic Rats

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

ABSTRACT

Introduction: The aim of this study was to determine the effect of simultaneous administration of Teucrium polium L. extract along with glibenclamide to improve the levels of blood glucose and lipids in diabetic rats.

Methods: Forty eight male Wistar rats were randomly divided to 6 groups (n=8): control and sham control rats received normal saline by gavage and 4 diabetic groups treated by gavage of normal saline (diabetic control), glibenclamide (5 mg/kg), T. polium L. (TP) extract (200 mg/kg) and glibenclamide- T. polium L. extract combination. Diabetes was induced with intraperitoneal injection of 55 mg/kg streptozotocin (STZ). Rats were treated at 6 weeks. At the first, middle and end of therapeutic course, blood samples were obtained. Blood glucose, triglyceride, cholesterol and body weight were measured. Finally, the obtained data were analyzed by SPSS 13.5 and ANOVA test.

Results: Administration of T. polium L. extract and glibenclamide significantly increased the body weight (P=0.01), decreased the plasma glucose (P=0.001), triglyceride (P=0.001) together with total cholesterol (P=0.001) in comparison to diabetic rats, but simultaneous treatment with T. polium L. extract and glibenclamide had not significant difference compared to administration of separate drugs on body weight, plasma glucose, triglyceride and total cholesterol (P>0.05).

Conclusion: Hydro-alcoholic T. polium L. extract and glibenclamide had similar effects on blood glucose and lipids in streptozotocin-induced diabetic rats; however simultaneous treatment had not significant difference in this regard. *JOURNAL OF IRANIAN CLINICAL RESEARCH* 2015;1(2):38-45

INTRODUCTION

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

Chemical and herbal drugs are used for the treatment of diabetes. The most important goals of diabetes treatment are decreasing of blood sugar and suppressing secondary complications. At present, glibenclamide, as a most popular sulfonylurea drug, is one of the most important chemical drugs used widely for diabetes treatment [4]. The drug acts as an ATP-sensitive potassium channels inhibitor in pancreatic beta cells. This inhibition opens the voltage-dependent calcium channels, which results increasing if the intracellular calcium in beta cells, and finally stimulates insulin release [5-6].

In traditional medicine, different herbal drugs are used for the treatment of diabetes [7]. Teucrium polium L. [TP] named Kalpooreh in Persian is one of the most widely used anti-

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diabetic drugs. TP is extensively grown in the stony and dry regions of the deserts and hills of approximately all of Mediterranean countries as well as Europe, South Western Asia and North Africa. TP has the linear leaves with a length of about 3 cm and small flowers, and is in clusters and ranges from pink to white [8]. TP were used since Hippocrates and Galen [7]. Besides anti-diabetic [7, 9-11], 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 have been reported for TP. Phytochemically, TP consists of Tanen, Trepnoid, Saponin, Esterol, Flavenoid and Locoantosianin [25-29]. TP extract can increase the insulin secretion and subsequently decrease the level of the plasma glucose [7, 9-11, 30].

Some of the herbal drugs can increase or decrease the therapeutic effects of chemical drugs [31-32]. According to the anti-diabetic effects of TP and glibenclamide, the aim of this study was to investigate the anti-diabetic effect of glibenclamide on TP administration alters. The hypothesis is that TP administration in combination to glibenclamide at pharmacological doses can have positive influences on the pancreatic islets of the diabetic rats.

MATERIALS AND METHODS

Animals

Male Wistar rats (Faculty of Medicine, Mashhad, Iran), weighting 200-220 gr, were housed in an air-conditioned colony room at 22±2 °C with 12 h light: 12 h dark cycle and supplied with standard pellet diet and tap water ad libitum.

Procedures involving animals and their care were conducted in conformity with NIH guidelines for the care and use of laboratory animals. The study was approved by local Ethics Committee.

Preparation of hydro-alcoholic Teucrium polium L. extract

Fresh leaves of TP were collected from southern Khorasan, and dried at room temperature. Two hundred gr of the air-dried leaves of the plant was milled into fine powder and soaked in 1 litter 50% ethanol for 48 h in darkness. The obtained solution was filtered by ordinary filter paper; then was dried on a Ban Mari (Memert, Germany) with 40 °C for 36 h. The extract stock was kept in -20 °C until used. A dose of 200 mg/kg of TP was chosen based on the previous studies.

Induction of experimental diabetes

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

Experimental design

The animals were randomly divided into six groups (n=8). TP extract, glibenclamide and normal saline were administered once daily by oral gavage. The treatment of rats began on the 48 h after STZ injection and this was considered as the first day of treatment. The animals were treated for 6weeks as follows:

(I) Control group (C): Rats of this group received standard diet and top water. (II) Sham Control group (Sh): Rats of this group received gavage vehicle (0.9% NaCl). (III) Diabetic control group (D): in this group diabetes induced by i.p. injection of STZ. After induction of diabetes, rats of this group received 0.9% NaCl by oral gavage. (IV) Hydro-alcoholic TP extract-treated group (TP): Rats of this group received TP extract (200mg/kg body weight) 48 hours after the induction of diabetes. (V) Glibenclamide-treated group (G): Rats of this group received glibenclamide (5mg/kg body weight) after the induction of diabetes. (VI) Hydro-alcoholic TP extract with Glibenclamide-treated group (TP+G): Rats of this group received hydro-alcoholic TP extract (200mg/kg body weight) with glibenclamide (5 mg/kg body weight) simultaneously, after the induction of diabetes.

Blood sampling

For investigation of biochemical factors, after beginning of treatment course, plasma glucose, triglyceride and total cholesterol were measured at the first (D0), 7th (D7), 21th (D21) and 42th (D42) days. A fasting blood sample was withdrawn from the retro-orbital venous plexus. Blood samples were centrifuged for 15 min with 3500 rpm. The enzymatic kit (Betagen, Iran) and photometer (Convergys®100, Germany) were used for measuring of the biochemical factors from obtained samples.

Statistical analysis

Data are presented as the Mean±SEM. One-way analysis of variance (ANOVA) was used to compare differences between the experimental groups. Tukey's post hoc test was used for multiple comparisons. All statistical analyses were performed by SPSS 13.5 (Chicago, IL, USA).

RESULTS

Body weight

At the first and one week after diabetes induction, there was no significant difference in body weight between different groups (P>0.05), while plasma glucose, triglyceride and cholesterol levels were similar between different groups only at the beginning of trial. Three weeks after induction of diabetes, the body weight of the diabetic rats significantly reduced in comparison to sham control group (P=0.01), but there was no significant reduction at 4-6 weeks between them. Treatment with TP extract and glibenclamide significantly (P=0.01) improved the body weight of the diabetic rats compared to diabetic control rats especially at 3th week. However, the diabetic groups that received glibenclamide in combination with TP did not show significantly higher body weight than the diabetic rats that treated with TP or glibenclamide separately (Figure 1).

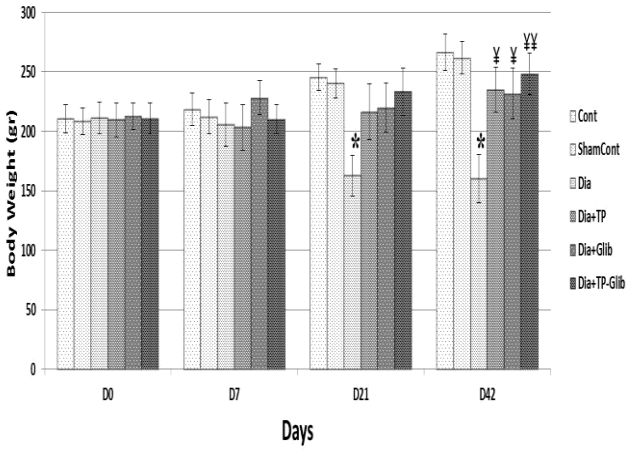

Figure 1. Comparisons of rat body weight indifferent groups (Mean ± SEM).
(C): control, (Sh): sham control treated with NaCl, (D): STZ-induced diabetic control rat, (G): STZ-induced diabetic treated with Glibenclamide, (TP): STZ-induced diabetic treated with hydro-alcoholic *Teucrium polium L.* extract, (TP+G): STZ-induced diabetic treated with hydro-alcoholic *T. polium L.* extract and Glibenclamide.
(D_0): first day of experience, (D_7): 7th day of treatment, (D_{21}): 21th day of treatment, (D_{42}): 42th day of 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.

Plasma glucose level

Firstly, the plasma glucose level in different groups of the rats was in normal range (D0). One week after diabetes induction, the plasma glucose level in
diabetic rats showed significantly increase compared to control group (P=0.01). After first week of treatment, the effect of TP extract, glibenclamide and their combination on plasma glucose level was no significant between experimental groups, whereas at 3rd week (P=0.01) and specially 6th week (P=0.001) had shown significant decrease compared to untreated diabetic rats (Figure 2). In contrast, there was no significant difference in diabetic rats that received TP in combination with glibenclamide compared to diabetic rats treated with TP or glibenclamide separately.

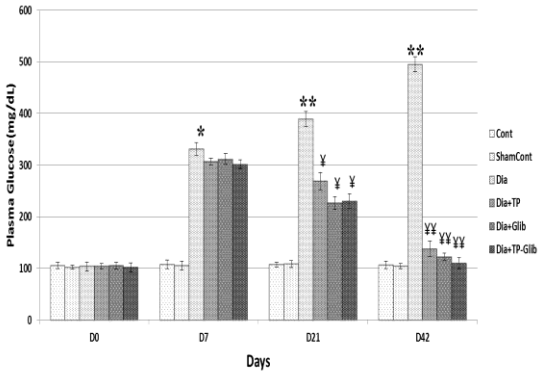

Figure 2. Comparisons of plasma glucose level in different groups (Mean ± SEM).
(C): control, (Sh): sham control treated with NaCl, (D): STZ-induced diabetic control rat, (G): STZ-induced diabetic treated with Glibenclamide, (TP): STZ-induced diabetic treated with hydro-alcoholic *Teucrium polium L.* extract, (TP+G): STZ-induced diabetic treated with hydro-alcoholic *T. polium L.* extract and Glibenclamide.
(D_0): first day of experience, (D_7): 7th day of treatment, (D_{21}): 21th day of treatment, (D_{42}): 42th day of 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.

Plasma triglyceride level

Figure 3 shows changes the plasma triglyceride levels in different groups from beginning day of experience until 6th week. Plasma triglyceride concentration at beginning of experience had not significant difference between study groups, while one, three and six weeks after induction of diabetes, plasma triglyceride level in diabetic rats significantly increased in comparison to sham control group (P=0.01, P=0.001 and P=0.001 respectively). However, TP extract had no significant effect on the plasma triglyceride level at the first week after diabetes induction, treatment of rats with TP extract in 3rd and 6th week significantly decrease the level of the plasma triglyceride in diabetic rats. Administration of glibenclamide or its combination with TP extract caused significant decreasing in the plasma triglyceride level compared to diabetic group (P=0.001) (Figure 3) at the 1st, 3rd and 6th weeks after induction of diabetes.

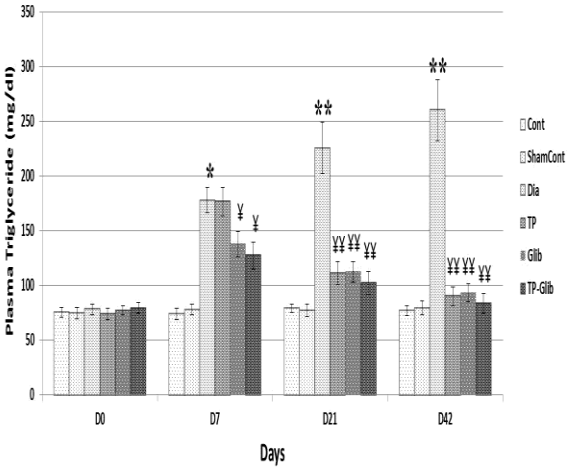

Figure 3. Comparisons of plasma triglyceride level in different groups (Mean ± SEM).
(C): control, (Sh): sham control treated with NaCl, (D): STZ-induced diabetic control rat, (G): STZ-induced diabetic treated with Glibenclamide, (TP): STZ-induced diabetic treated with hydro-alcoholic *Teucrium polium L.* extract, (TP+G): STZ-induced diabetic treated with hydro-alcoholic *Teucrium polium L.* extract and Glibenclamide.

(D_0): first day of experience, (D_7): 7th day of treatment, (D_{21}): 21th day of treatment, (D_{42}): 42th day of 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.

Plasma cholesterol level

The plasma cholesterol level was measured in different groups. First, third and especially sixth weeks after induction of diabetes, the cholesterol level of diabetic rats had significantly increased in comparison to sham control group (P=0.01, P=0.001 and P=0.001 respectively). Administration of TP extract and glibenclamide had no significant effects on the plasma cholesterol level at the first week, whilst, after 3 and 6 weeks of treatment, TP extract and glibenclamide could significantly decrease the plasma cholesterol level in comparison to untreated diabetic rats (P=0.001) (Figure 4).

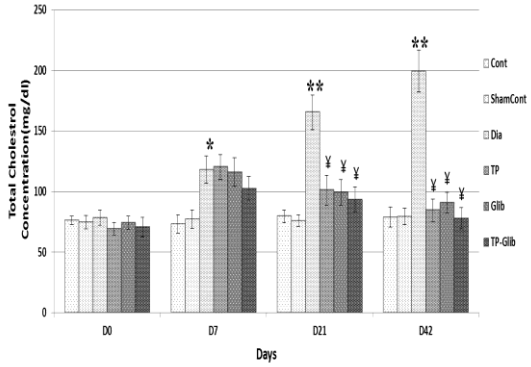

Figure 4. Comparisons of plasma cholesterol Level in different groups (Mean ± SEM).
(C): control, (Sh): sham control treated with NaCl, (D): STZ-induced diabetic control rat, (G): STZ-induced diabetic treated with Glibenclamide, (TP): STZ-induced diabetic treated with hydro-alcoholic *Teucrium polium L.* extract, (TP+G): STZ-induced diabetic treated with hydro-alcoholic *T. polium L.* extract and Glibenclamide.
(D_0): first day of experience, (D_7): 7th day of treatment, (D_{21}): 21th day of treatment, (D_{42}): 42th day of treatment.
* P = 0.01 compared to sham control group, ** P = 0.001 compared to sham control group.
¥ P = 0.001 compared to diabetic control group.

DISCUSSION

Irreversible destruction of the pancreatic beta cells in streptozotocin-induced diabetic rats causes decrease of insulin secretion and increase in blood glucose level [35]. The results of this study showed that glibenclamide and TP significantly reduced diabetes-induced hyperglycemia. In addition, present study showed that TP along with glibenclamide could have similar effects in diabetic patients [36]. However, our findings indicated that simultaneous administration of TP and glibenclamide in comparison to each one alone had no significant difference on the body weight, plasma glucose, triglyceride and cholesterol levels in diabetic rats.

Our results illustrated that STZ-induced diabetes caused the loss of body weight especially after three weeks of induction compared to sham control group. In addition, administration of TP extract and glibenclamide simultaneously preventes the reduction of diabetic rats body weight. Similarly, there was a significant decrease of body weight in diabetic rats, which received TP or glibenclamide alone. Although mechanism or mechanisms that explain the effect of TP or glibenclamide on body weight is unknown, but previous studies demonstrated anabolic effects of insulin on proteins
metabolism by stimulation of protein production and reduction of proteins destruction [37]. Both of TP extract and glibenclamide can increase insulin secretion in the rest pancreatic beta cells [10, 30, 38].

The results of present study showed that TP administration in combination to glibenclamide could decrease the plasma glucose concentration in diabetic rats after six weeks of treatment. However, TP or glibenclamide treatment did not significantly effect on the plasma glucose level.

Glibenclamide has insulin-like effects on the glucose metabolism. On the other hand, the drug decreases glycogenolysis and glucogenesis in the body cells and then it reduces the level of blood glucose [39]. In addition, glibenclamide inhibits ATP-sensitive potassium channels in the membrane of pancreatic beta cells. Following the inhibition, voltage dependent calcium channels are activated and then calcium ion import into beta cells. Finally, the increased cytoplasmic calcium stimulates insulin secretion [40-41].

In this study, the blood glucose level was decreased in diabetic rats under TP treatment. Probable mechanism or mechanisms that explain the hypoglycemic effects of TP are often dependent on its pharmacologic agent's especially flavonoids [8, 29, 42-43].

Vessal et al, demonstrated the effects of flavonoids [especially cuirestin existing in TP] on pancreatic islets as a regeneration factor in the beta cells of STZ-induced diabetic rats [44]. Ashrafihelan et al., showed that the flavonoids increased insulin secretion by Ca^{2+} metabolism changes [30]. TP increased hepatic glucokinase activity in the hepatocytes. The enzyme altered glucose to glucose-6-phosphate within the cells and then it prevented the entrance of glucose into blood. Thus, TP has hypoglycemia effects [45].

The present study showed that the triglyceride and total cholesterol levels increased in STZ-induced diabetic rats. The reduction of insulin secretion could increase fat destruction and free fatty acids in hepatocytes. Subsequently the elevation in triglyceride synthesis may also cause hyperlipidemia [46-47].

The present study showed that administration of TP extract or glibenclamide during 6 weeks could significantly decrease triglyceride and total cholesterol in STZ-induced diabetic rats. However, simultaneous administration did not significantly effect on the total cholesterol level.

Glibenclamide decreases the triglyceride and cholesterol levels in diabetic rats [46]. The results of our study is in agreement with previous studies findings improved the effects of glibenclamide on diabetic dyslipidemia [48-51]. Biochemical results of our study clearly support earlier reports that TP extensively decreases blood lipids level in diabetic rats [36, 52-53]. However, this is in disagreement with Stefkov et al. who did not find any difference in cholesterol and triglyceride levels following administration of TP in diabetic mice [54].

Results of experimental and population studies explained that the flavonoids could decrease the plasma cholesterol level in diabetes-induced hyperlipidemia [55]. However, many studies have reported a little or no change in plasma lipid and lipoproteins levels following increased flavonoid intake [56-57]. Additional studies are needed to confirm the therapeutic efficacy of TP in combination with glebenclamide in diabetic patients.

Combination treatment with *T. polium* and glibenclamide is not more effective than each of these drugs alone in improving hyperglycemia and hyperlipidemia in STZ-induced diabetic rats. It seems that a similar mechanism probably exists for insulin secretion between *T. polium* and glibenclamide in pancreatic beta cells.

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