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Antidiabetic Effects of Teucrium polium and Achillea millefolium aqueous extracts on Streptozotocin-Induced Diabetic Rats

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Introduction: Recently, the search for appropriate hypoglycemic agents has focused on plants. This study evaluated the antidiabetic Effects of Teucrium polium and Achillea millefolium aqueous extracts in diabetes.

Materials and Methods: Fifty adult male Wistar rats were randomly divided into fiveGroups: normal rats (A); Diabetic control (B); Diabetic rats were treated with Achillea millefolium extract (C); Diabetic rats were treated with Teucrium polium extract (D); Diabetic rats were treated with Teucrium polium and Achillea millefolium mixture extracts (E). Diabetes was induced by a single dose (55 mg/kg, ip) of streptozotocin. Rats in groups C, D and E received the Achillea millefolium, Teucrium polium and mixture extracts, respectively by gavages. The control diabetic rats (B) received the same volume of normal saline and the control healthy rats (A) received normal chow and tap water. Finally, animals were anesthetized, sacrificed and blood samples were collected from the cervical vein. The biochemical parameters were measured by ordinary methods.

Results: Our results showed that FBS, total cholesterol, triglyceride, and LDL, GGT, food and water intake decreased significantly in groups C, D and E while body weight and HDL increased significantly in these groups when compared to the diabetic control group. The activity of serum ALP decreased significantly in groups C and E while there were no significant diferences of ALT and AST between groups C, D and E compared to the diabetic control group ($P<0.05$).

Conclusions: The results demonstrated that extracts of Teucrium polium and Achillea millefolium have antidiabetic effects.

Keywords: Diabetes, Teucrium polium, Achillea millefolium, Fasting blood sugar, liver enzymes, Lipid profile

Introduction

Diabetes mellitus (DM (is known as a heterogeneous complex of metabolic disorders characterized by the common phenotype hyperglycemia due to disturbances in insulin secretion, action or both. Diabetes is clinically recognized by chronic elevation of the glucose level in the blood and is often accompanied by symptoms of the severe thirst, polyuria, polyphagia, and weight loss (Kuvandik et al., 2007). The world prevalence of diabetes mellitus among adults (aged 20-79 years) reached 6.4%, affecting 285 million in 2010 and will increase to 7.7% (439 million) by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with DM in developing countries and a 20% increase in developed countries. These predictions indicate a growing burden of DM, particularly in developing countries (Shaw et al., 2010). The goals of managing diabetes mellitus are to optimize the control of blood glucose level, reduce the oxidative stress effects, and normalize disturbances in lipid metabolism (Saravanan and Ponmurugan, 2012).

The main goal of treatment is to prevent the development or progression of chronic complications, such as microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary artery disease, stroke and peripheral arterial disease), while minimizing the risk for acute complications such as severe hypoglycemia (Harper et al., 2013). Currently, the most medications which used for diabetes are insulin and the oral hypoglycemic drugs (Lorenzati et al., 2010). Although early onset manifestations of diabetes can be controlled by current antidiabetic drugs, in many cases, late complications appear (Tzoulaki et al., 2009). In addition, the clinical uses of the current drugs are usually accompanied by some adverse effects including abdominal discomfort, severe hypoglycemia, lactic acidosis, and peripheral edema (Lorenzati et al., 2010).

Recent interests have focused on the use of medicinal plants with antidiabetic and antioxidant potential in lowering the ensuing complications in diabetic patient (Li et al., 2004). Antidiabetic effectse of several plants have been supported by results from animal models and clinical trials (Modak et al., 2007, Hui et al., 2009).

Achillea millefolium L (Asteraceae), commonly known as yarrow, has been used for centuries for treating spasms, digestive complaints, menstruation disorders, urinary infections, anti-inflammatory, spasmolytic, hemostatic, diarrhea, abdominal

pain, stomach, and other ailments (Jonsdottir et al., 2011). Achillea millefolium is also reported to have some pharmacological effects such as antispasmodic, antimicrobial, analgesic, antipyretic, choleretic, cytotoxic, and estrogenic (Potrich et al., 2010).

Phytochemical screenings revealed that chemical constituents of A. millefolium present several secondary metabolites, including sesquiterpenes, the alkaloid achilleine, steroids, triterpenes, and flavonoids, as presented by de Souza et al. (de Souza et al., 2011). Düsman et al. reported that the aqueous extracts of plants (Achillea millefolium and Bauhinia forficata), routinely used for the treatment of pain and diabetes, have considerable antioxidant activity, showing no cytotoxic activity, and may contribute to reducing the chromosomal damage induced by such chemotherapeutic agents as cyclophosphamide (Düsman et al., 2013). Zolghadri, et al. showed that diabetic rats treated with Achillea millefolium extract had higher insulin level associated with lower glucose level and lifting body weight compared to control diabetic group (Zolghadri et al., 2014).

Teucrium polium (Lamiaceae) is a perennial shrub, 20-50 cm in height, widely distributed in the dry and stony places of the hills and deserts of Mediterranean countries, South Western Asia, Europe, and North Africa. T. polium (locally called as Kalpooreh) is abundantly and widely found in Iran (Bahramikia and Yazdanparast, 2012). This plant has been used in folk medicine for various purposes such as anti-inflammatory, antibacterial, antipyretic, antispasmodic, antihypertensive, and antihyperlipedemia (Ardestani and Yazdanparast, 2007, Mousavi et al., 2012). Furthermore, the plant possesses hypoglycemic, insulinotropic, diuretic, diaphoretic, cholagogic and antioxidant properties (Couladis et al., 2003, Esmaeili and Yazdanparast, 2004a, Ljubuncic et al., 2006, Mousavi et al., 2012).

Vahidi et al. showed that 4% dose of Teucrium polium boiled extract can decrease serum glucose and triglyceride significantly, but cholesterol, ALT, and AST were not significant between the test and control groups after using Teucrium polium (Vahidi et al., 2010). Stevkov et al. reported that T. polium extract reduces blood glucose, but has no effect on plasma lipid levels; T. polium extracts contain flavonoids with insulin tropic and anti-hyperglycemic effects (Stefkov et al., 2011). Some data have revealed that traditional medicine can be hepatotoxic (Mirghazanfari et al., 2010).

Since, in traditional medicine, a high percentage of people with diabetes, combination of these two plants extracts are used to improving their blood sugar, this study evaluated the effect of Teucrium polium and Achillea millefolium aqueous extracts on serum glucose, serum lipids, and liver enzymes in streptozotocin-induced diabetic rats.

Materials and Methods

Preparation of extracts

Preparation of aqueous extracts was performed by Soxhlet method (Nadimi et al., 2013). Aerial parts of the plants were purchased from a local store in Zahedaan city, Iran and identified by the Department of Biology in Faculty of Science, Sistan and Baluchistan University, Zahedan, Iran. The air-dried leaves of the plants were milled into fine powder in a commercial blender. The dried and milled powdered plant material (120 g) was extracted with 1800 mL of distilled water by Suksyleh device in three steps at a temperature of 300°C. Then the aqueous extracts were filtered by filtration through a regular filter paper (Whatman No.2, Ashiess 40) and were dried by evaporation in temperature of 40°C (by oven-80). Finally, the extract was kept in 4°C freezer until being used. For preparation of mixture extract the air-dried leaves of the plants Teucrium polium and Achillea millefolium were powdered and mixed with ratio of 50%, 50%. Aliquot portions of the crude extract were weighed and dissolved in normal saline and used during each day of our experiment.

Animals

Male Wistar albino rats (n = 50), with a body weight of 200- 250 g were housed in cages (two rats in each cage) and had free access to food and water.

Experimental Groups

After acclimatization, animals were randomly divided into five groups: 1. normal rats (A); 2. Diabetic control (B); 3. Diabetic rats treated with Achillea millefolium extract (C); 4. Diabetic rats treated with Teucrium polium extract (D); 5. Diabetic rats treated with Teucrium polium and Achillea millefolium mixture extract (E). (n =10 in each group). Rats in groups C, D and E received the Achillea millefolium, Teucrium polium and mixture extract, respectively (100 mg/ kg)(Sabet et al., 2013, Zolghadri et al., 2014), by gavages, for 28 days. The control diabetic rats (B), received the same volume of normal saline and the control healthy rats (A), and received normal chow and tap water. The study protocol was care and use of laboratory animals in experimental studies complied with the ethical guidelines of the animal care of the Zahedan University of Medical Sciences, Zahedan, Iran.

Induction of Diabetes

The rats were not fed for 16 h before injection (Tatar et al., 2012). Type I diabetes was induced by intraperitoneal (i.p.) injection of streptozotocin (STZ; Sigma, USA; 55 mg/kg body weight). Three days after STZ administration, diabetes was confirmed by the presence of hyperglycemia, polyphagia, polydipsia, polyuria and animals with fasting blood glucose levels of 250 mg/ dL or more were considered as the diabetic rat.

Measurement of biochemical parameters

At the end of treatment) 28th day), the rats were fasted at least 12 h, and the body weights of all the rats were measured (final weight), all animals were anesthetized under high dose of ether (Shahraki et al., 2013) anesthesia and sacrificed by cervical decapitation and blood samples were collected from cervical vein for the determination of serum liver enzymes, plasma glucose, and other parameters and were immediately kept in -70°C until usage. Blood glucose was measured using glucose oxidase reagent (Pars Azmun, Iran). Serum triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), were evaluated with standard enzymatic colorimetric kits from Pars Azmun (Iran). Serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) activities were calorimetrically measured by commercially available kits (Pars Azmun, Iran). Serum gamma glutamyl transferase (GGT) concentrations were photometrically measured by commercially available kits (Pars Azmun, Iran). The parameters like food and water consumption were determined and recorded during the study period.

Statistical analysis

Data were presented as mean ± SD. Data analysis was carried out by using one- way ANOVA and Tukey's multiple comparison test as the post hoc (SPSS version 16.0.) and P-value of less than 0.05 ($P< 0.05$) was considered statistically significant.

Results

Effect of Extracts of Achillea millefolium (AM) and Teucrium polium (TP) on Blood Glucose

As shown in Table 1, prior to diabetes induction, the level of FBS was not significantly different between all the groups. Three days after the administration of streptozotocin, the diabetic rats in groups B, C, D and E showed a significant increase in FBS level compared to the normal controls. The diabetic control rats showed further increase in FBS level after 28 days ($P<0.05$). However, administration of extracts to diabetic rats in groups C, D and E blocked the increase of blood glucose and caused a significant decrease in the serum glucose level at 4th week ($p<0.005$) compared to the diabetic control group.

Table 1- Effect of Achillea millefolium (AM) and Teucrium polium (TP) Extracts on Blood Glucose and Body Weight in diabetic and normal groups

Parameters / Groups	FBS(mg/dl)			Body Weight (g)	
	Baseline	3th day	28th day	Initial weight	final weight
Control(A)	97±2	102±4	108±4	213±12	255±14
Control diabetic(B)	96±4	465±126*	575±64*	218±10.05	162±18*
Diabetic + AM(C)	98±4	605±147	373±179#	219±10	193±25#
Diabetic + TP(D)	99±5	383±136	271±125#	220±14	201±17#
Diabetic + Mixture extract(E)	100±4	670±75#	363±188#	218±9	193±15#

Data are represented as means ± standard deviation and analyzed by one way ANOVA fallowed by Tukey's posttest. ∗P<0.05 as compared to diabetic control vs normal group, # P<0.05 as compared extract treated groups vs diabetic control.

Effect of extracts of Achillea millefolium (AM) and Teucrium polium (TP) on the levels of serum lipid

Figure 1 shows the level of serum lipids in studied groups. There was a significant elevation in the level of triglyceride, Low density lipoprotein (LDL) and total cholesterol ($P< 0.05$) in diabetic control rats as compared to normal group. However, administration of extracts to diabetic rats in groups C, D and E caused a significant decrease in the levels of triglyceride, LDL and total cholesterol ($p<0.05$) compared to the diabetic control group. Diabetic rats in group B showed significant decrease in the level of high-density lipoprotein (HDL) compared to the normal controls while it was found to be significantly elevated in the extracts treated diabetic rats with the same value of normal controls ($P< 0.05$).

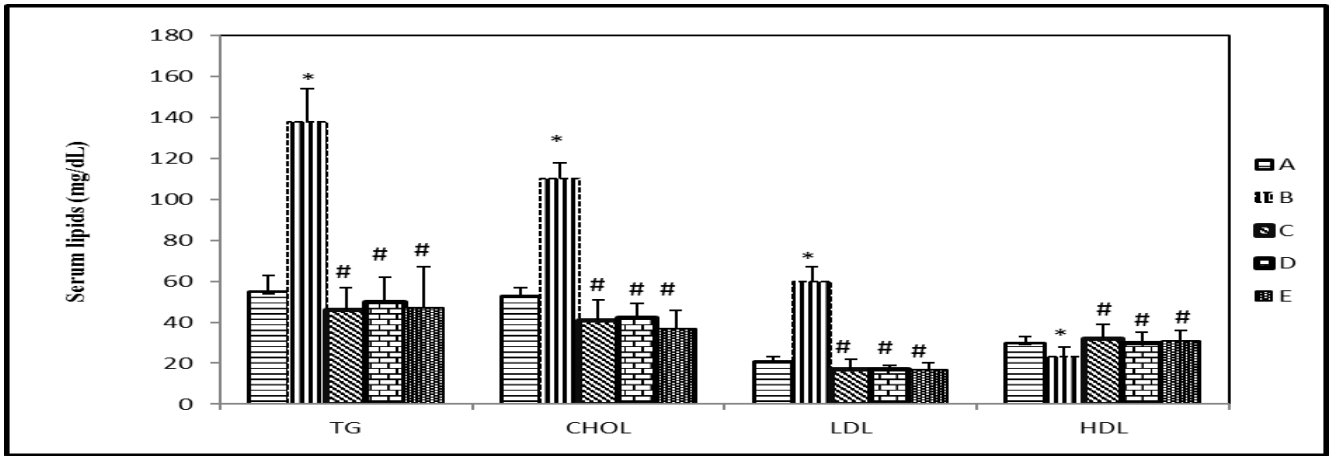

Figure 1: Effect of extracts ofAchillea millefolium (AM) and Teucrium polium (TP) on lipid profile in diabetic and normal groups. Normal rats (A); diabetic control (B); diabetic rats treated with Achillea millefolium. Extract(C); diabetic rats treated with Teucrium polium extract (D); diabetic rats treated with Teucrium polium and Achillea millefolium mixture extract (E) (n=10 in each group). Data are represented as means ± standard deviation and analyzed by one way ANOVA followed by Tukey'sposttest .∗P<0.05 as compared to diabetic control vs.normal group, # P<0.05 as compared to extract treated groups vs. diabetic control.

Effect of extracts of Achillea millefolium (AM) and Teucrium polium (TP) on hepatic enzymes

In diabetic control rats (Group B), the activities of ALT, AST, ALP and GGT increased significantly ($P< 0.05$) when compared to normal controls. After 28 days of administration of extracts ,diabetic rats in groups C and E showed significant decrease in the activity of serum ALP ($p<0.05$) compared to the diabetic control group; while there was no significant difference between the groups B and D in the activity of serum ALP. The extracts were also significantly lowered the level of GGT in extracts treated rats ($p<0.05$) when compared to non-treated diabetic rats. On the other hand, there was no significant difference between groups C, D, and E in the activities of ALT and AST after administration of extracts compared to the diabetic control group (Figure. 2).

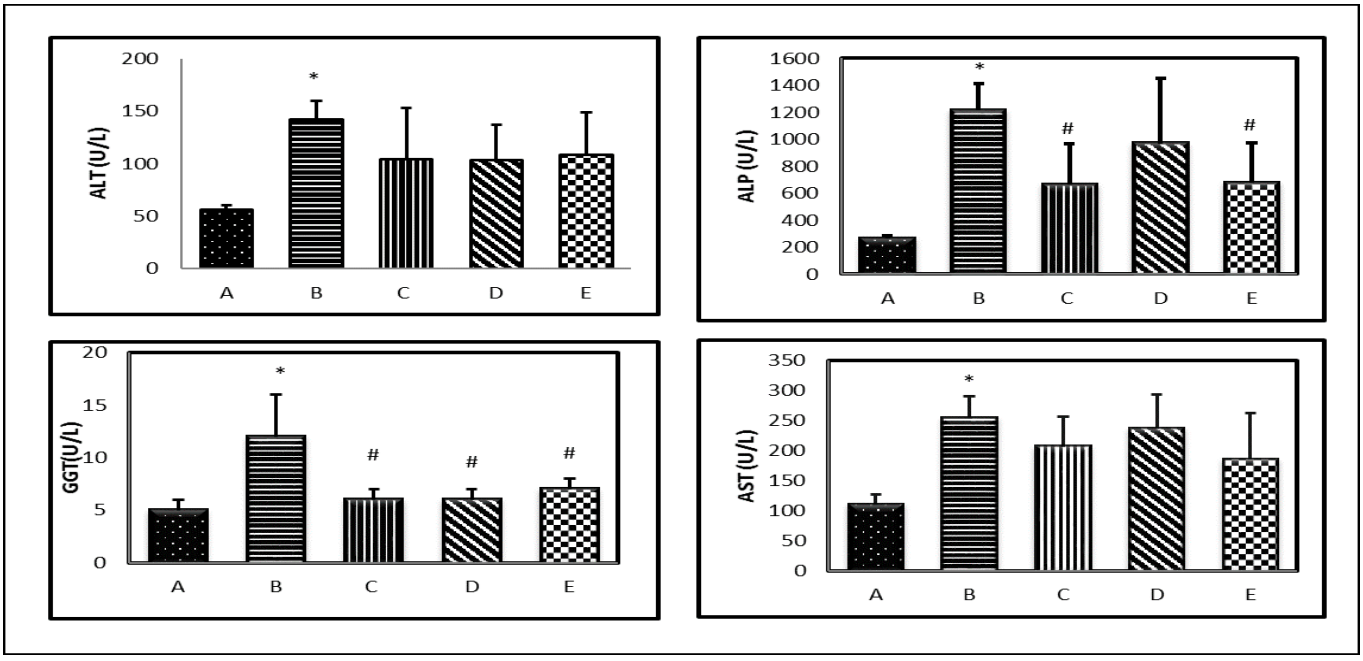

Figure2: Effect of extracts of Achillea millefolium (AM) and Teucrium polium (TP) on Hepatic Enzymesin diabetic and normal groups. normal rats(A) ; diabetic control (B) ; diabetic rats treated with Achillea millefolium L. extract (C); diabetic rats treated with Teucrium polium extract (D); diabetic rats treated with Teucriumpolium and Achillea millefoliummixture extract(E) (n=10 in each group). Data are represented as means ± standard deviation and analyzed by one way ANOVA followed by Tukey'sposttest.∗P<0.05 as compared to diabetic control vs. normal group, # P<0.05 as compared to extract treated groups vs.diabetic control.

Effect of extracts of Achillea millefolium(AM) and Teucrium polium(TP) on food and water consumption

In all groups prior to diabetes induction, the levels of food and water consumption were not significantly different. However, there was a significant increase in the levels of food and water intake in all groups of diabetic rats after STZ administration (fig3). Although the polydipsia and polyphagia conditions were evident from the first week to the end of the experiment period, the level of water intake in the extracts- treated rats in groups C, D and E was significantly lower than that of control diabetic group at weeks 3 and 4 ($P<0.05$) (fig3-a). The extracts-treated rats in groups C, D and E were also shown to significantly lower in the amount of food consumption when compared to non-treated diabetic rats at 4th week ($P<0.05$). (Fig3-b).

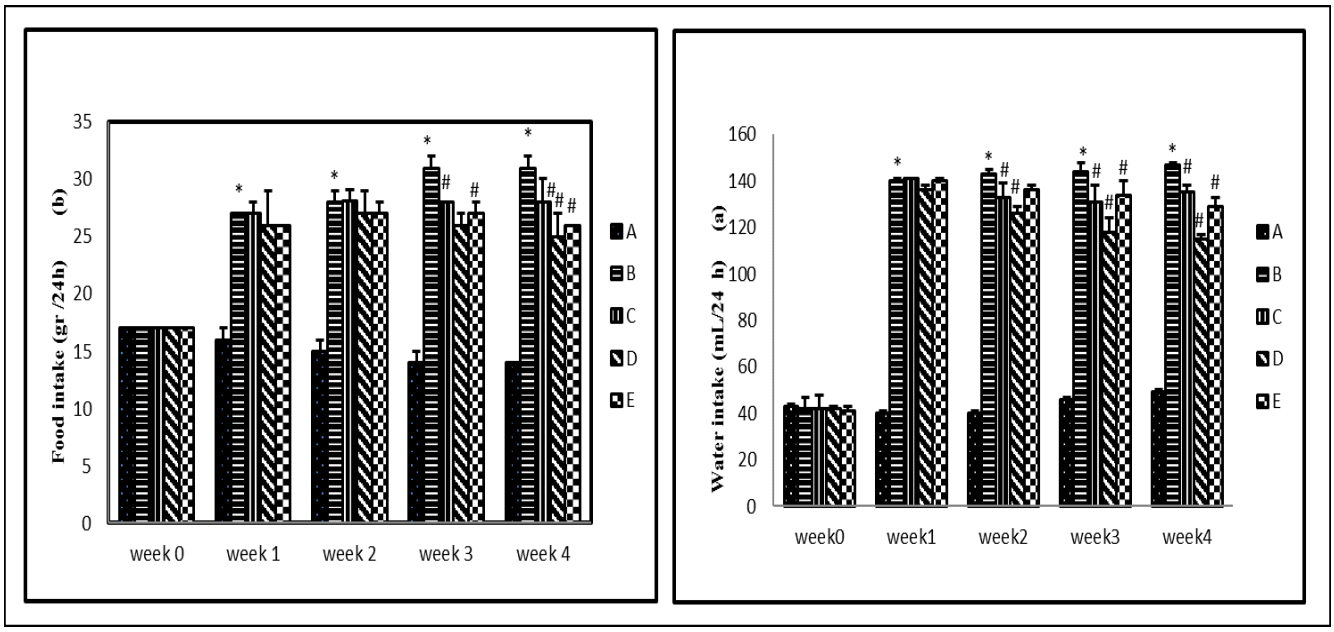

Figure 3: Effect ofextracts of Achillea mille folium (AM) and Teucrium polium (TP) on Food (a) and Water (b) Consumption in diabetic and normal groups. Normal rats (A); diabetic control (B); diabetic rats treated with Achillea millefolium. Extract(C); diabetic rats treated with Teucrium polium extract (D); diabetic rats treated with Teucrium polium and Achillea millefolium mixture extract (E) (n=10 in each group). Data are represented as means ± standard deviation and analyzed by one way ANOVA fallowed by Tukey'spost test .*P<0.05 as compared to diabetic control vs.normal group, # P<0.05 as compared to extract treated groups vs.diabetic control.

Effect of extracts of Achillea millefolium (AM) and Teucrium polium (TP) on Body Weight

As shown in Table 1, prior to the onset of this experiment, animals were selected in a narrow weight range 200- 250 g, so there was no significant difference between the animals weight in different groups. Following the induction of diabetes, the diabetic rats showed a significant reduction in body weight compared to the normal controls ($P < 0.05$). However, after 4 weeks administration of extracts, extracts- treated rats showed a significant recovery in body weight when compared to non-treated diabetic rats ($P<0.05$).

Discussion

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by a selective destruction of the insulin producing β-cell (Eizirik et al., 2009). During the inflammatory process known as insulitis , Pro-inflammatory cytokines such as Interleukin-1β (IL-1β), tumor necrosis factor (TNFα) and interferon -Y are secreted by immune cells invading the contribute for β-cell dysfunction and apoptosis(Eizirik et al., 2009). The cytokines IL-1β and TNFα induce β-cell death in Type 1 diabetes via nuclear factor-kappa beta (NF-κβ) activation (Ortis et al., 2012). Also, diabetes is associated with disturbances in carbohydrate, protein and fat metabolism which occur secondarily to an absolute or relative lack of insulin (hypoinsulinemia) (Schmatz et al., 2012).

The enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) which serve as biomarkers of hepatocyte damage are involved invarious in the liver. Plasma levels of AST and ALT increased following hepatocyte injury while ALP, and gamma glutamyltransferase (GGT), total bilirubin levels were elevated in biliary tree obstruction (Lee et al., 2012). These findings were consistent with others who reported the rise in serum ALT (Xourafas et al., 2012), AST (Masjedi et al., 2013), GGT, and AST (Mnafgui et al., 2013) in diabetic rodents and humans.

So, in the present study, we tested the possible beneficial effects of two plants Achillea millefolium and Teucrium polium extracts on biochemical parameters of diabetic rats.

our findings showed that rats treated with Teucrium polium and Achillea millefolium mixture extract had a significant decrease in blood glucose level, serum lipids (total cholesterol (TCho), triglyceride (TG) and LDL), GGT, and ALP in diabetic rats but ALT and AST did not show any significant difference in the groups E and B. In addition, there was a significant elevation in the level of HDL in the extracts treated diabetic rats in groups C, D and E compared to the diabetic control group. In our study, a significant weight loss was observed in the diabetic group while Teucrium polium and Achillea millefolium mixture extract treated, rats exhibited significant increase in the body weight in comparison with diabetic control group but was lower than in the normal controls. The levels of food and water intake also decreased compared to group B. Some reports indicated that Teucrium polium and Achillea millefolium include variety of

Flavonoids, which have antioxidant properties (Candan et al., 2003, Trumbeckaite et al., 2011, Sabet et al., 2013). In addition, some flavonoids of the plants could have anti-diabetic and hypoglycemic potential (Shahraki et al., 2007). In the present study, we showed that administration of the Achillea millefolium extract causes significant decrease in blood glucose level, serum lipids (total cholesterol (TCho), triglyceride (TG) and LDL in diabetic rats compared to the diabetic control group. Our findings also showed that administration of Achillea millefolium extract to diabetic rats in groups C caused the significant increase in body weight, but food and water intake decreased compared to group B. It has been reported that Achillea millefolium extract showed significant decrease in blood glucose level, serum lipids and liver enzymes in diabetic rats and prevented the β-cells of pancreas from the cytotoxic effects of alloxan (Mustafa et al., 2012).

Zolghadri et al. have reported that beneficial effect of Achillea millefolium on STZ- induced diabetes is at least partly due to amelioration of IL- 1β and iNOS gene over expression which can have a β-cell protective effect (Zolghadri et al., 2014). Some reports indicated that Achillea millefolium includes variety of flavonoids, which mainly occurs as mono and diglycosides of apigenin, luteolin and quercetin and phenolic compounds, which have antioxidant properties (Candan et al., 2003, Trumbeckaite et al., 2011). Most of the flavonoids have been found to possess the antidiabetic potential (Hussain and Marouf, 2013). Furthermore, several flavonoids have been shown to inhibit the expression of NF-κB-dependent cytokines, iNOS, and cyclooxygenase-2 genes (Moussaieff et al., 2007). In addition, flavonoid may help improve the activity of carbohydrate metabolizing enzymes in the liver (Sundaram et al., 2013). Considering the results obtained, it appears that the observed antioxidant activity is directly correlated with the total content of phenolic compounds and flavonoids in the plants. In addition, Our findings showed that, in a 4-week treatment period, aqueous extract of Achillea millefolium caused decreased significantly in the activity of ALP and GGT compared to the diabetic control ($p < 0.05$) but ALT and AST did not show any significant difference between groups C and B. The present finding also showed that the aqueous extract of Teucrium polium caused significant decrease in the level of GGT compared to the diabetic control group ($p < 0.05$). Sanz et al. have reported that natural flavonoids present in medicinal plants have the ability to decrease serum transaminase activity in animals (Sanz et al., 1994). The presence of flavonoids may be responsible for these beneficial effects.

This finding is consistent with the report by Dröge which stated that the phenolic compounds present in most plants inhibit the formation of free radicals (Dröge, 2002). Our findings also indicate that, Teucrium polium extract-treated rats had a significant decrease in blood glucose level and serum lipids (total cholesterol (TCho), triglyceride (TG) and LDL) in diabetic rats compared to the diabetic control. Previous studies reported that the aqueous extract of Teucrium polium reduced the serum levels of lipids in rats (Sharififar et al., 2009). Many investigators have shown that Teucrium polium extract reduces blood glucose via mechanisms such as enhancement of peripheral metabolism of glucose rather than an increase in insulin release (Rasekh et al., 2001). The Teucrium polium extract also modulates the serum, liver and muscle triglyceride content and improves the insulin resistance in the experimental animal (Mousavi et al., 2012). Tatar et al. showed that Teucrium polium aerial parts extract stimulate pancreas repair and may be clinically beneficial as an agent to restore or maintain pancreas tissue after injury (Tatar et al., 2012). The results of the previous studies have shown that Teucrium polium administration to diabetic rats could protect and in part restore secretory function of beta cells in pancreatic tissue, and thereby applied its antihyperglycemic and antidiabetic effect (Esmaeili et al., 2009). Such compounds have been suggested to inhibit hepatic gluconeogenesis through a ROS-dependent pathway (Ardestani et al., 2008). In addition, these flavonoids could exert an insulinomimetic effect and produce the cellular effects of insulin such as reducing gene expression of rate-limiting gluconeogenic enzymes (Esmaeili and Yazdanparast, 2004b). Furthermore, these flavonoids like the hormone insulin could increase tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 and it reduces phosphoenolpyruvate carboxykinase gene expression in a phosphoinositide 3-kinase- dependent manner (Esmaeili and Yazdanparast, 2004b). Some data have revealed that Teucrium polium compounds could possibly suppress TNF-α elevation which also might have either direct or indirect beneficial reciprocal effect on other markers (Movahedi et al., 2014). Since oxidative stress, due to an increased production of ROS, plays an important role in pathophysiology of diabetes, Teucrium polium extract has the ability to attenuate oxidative stress and lipid peroxidation(Ardestani et al., 2008), and in this way may have affected carbohydrate metabolism in this study.

In addition, this report showed that , in rats treated with aqueous extract of Teucrium polium, there were no significant difference in the activities of ALP, ALT , and AST compared to the diabetic control ($p < 0.05$). This part of the results is the same as that of Vahidi et al. who reported that extract of Teucrium polium has hypoglycemic activity in diabetic rats but did not affect the activities of ALP, ALT, and AST (Vahidi et al., 2010). Some data have revealed that hepaticenzymes values increased after Teucrium polium administration (Mazokopakis et al., 2004, Shahraki et al., 2007, Mirghazanfari et al., 2010). Also, some data revealed that oral administration of Teucrium polium did not cause any adverse effect on liver (Shtukmaster et al., 2010). Beneficial effect of Teucrium polium on liver enzymes, including AST and ALT, has been previously reported (Amini et al., 2009, Forouzandeh et al., 2013, Movahedi et al., 2014). Our results also showed that, in rats treated with Teucrium polium extract, body weight increased significantly after 4 weeks when compared to non-treated diabetic rats but food and water intake

decreased which is in accordance with those of Sabet et al. who reported that Teucrium polium extract-treated rats had a significantly higher weight versus diabetic rats at 4th week (Sabet et al., 2013).

Conclusion

We observed that the aqueous extracts of two plants Achillea millefolium and Teucrium polium, which are routinely used for the treatment of diabetes, have considerable antidiabetic and anti hyperlipedia activities that the confirmation of these effects, more researches are also needed to analyze the effective compounds and to introduce new hypoglycemic drugs.

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Conflict of Interest

The authors declared no conflicts of interest

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