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Experimental Research Article

Co-administration of hydro-alcoholic *Teucrium polium* l. extract and glibenclamide on pancreatic islets in streptozotocin-induced diabetic rats- a stereological analysis

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ABSTRACT

Introduction: As herbal drugs have the potential to influence the therapeutic outcomes of pharmaceutical drugs, we investigated the effects of co-administration of *Teucrium polium* L. extract (*TP*) and Glibenclamide (Glib) on pancreatic islets in diabetic rats.

Methods: Male Wistar rats were separated into six distinct groups (n=8). The control and sham control (normal saline), while four diabetic rats received different treatments (normal saline, Glib (5mg/kg), *TP* (200mg/kg), or co-administration of *TP* and Glib), via gavage, for 6 weeks. Induction of diabetes was performed with Streptozotocin injection, intraperitoneally at a dose of 55 mg/kg. The animals were anesthetized, and their dissected pancreases were fixed in 10% Formalin. Stereological assessments were done to determine pancreas volume, islet volume, volume density of islets relative to the pancreas, and the number of beta and apoptotic cells within the islets. Ultimately, the data analysis was conducted using SPSS and ANOVA.

Results: Histological examinations revealed that the administration of *TP*, Glib, and their co-administration did not non-significantly increase the islet volume and volume density of islets relative to the pancreas in diabetic rats. However, treatment with these drugs led to an increase in the number of beta-cells and a decrease in the number of apoptotic cells within the islet. Notably, co-administration of these drugs did not yield significant differences compared to individual treatments.

Conclusion: This study demonstrates that *TP* and Glib have similar impacts in streptozotocin-induced diabetic rats. Co-administration of the two agents did not lead to a statistically significant difference compared with either treatment alone.

Keywords:
Diabetes
Teucrium polium
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Pancreas
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Introduction

Type I diabetes stands as an autoimmune disorder characterized by the targeted destruction of beta-cells within the pancreatic islets. This immune-mediated assault on beta-cells leads to a disruption in insulin production, ultimately affecting the myriad functions associated with insulin. The result is hyperglycemia. Histological examinations of the pancreas in diabetic rats underscore the dramatic reduction in pancreatic islets. The remaining islets exhibit signs of atrophy, with smaller and irregularly shaped structures. Inflammatory cells infiltrate the islets and their immediate surroundings, further exacerbating the degenerative changes. These changes are marked by the loss of granules and cytoplasm in beta-cells, rendering them darker with the presence of vacuoles and compacted nuclei. Moreover, there is a significant decline in the number of beta-cells within each islet. The dearth of insulin production results in the inability of body cells to uptake glucose, promoting fat breakdown and gluconeogenesis (Ashrafihelan et al., 2010; Kasper et al., 2005). Given these profound metabolic disturbances, the foremost objective in diabetes treatment is the regeneration of islets and the restoration of beta-cells.

Diabetes treatment encompasses both chemical and herbal approaches. Presently, Glibenclamide represents one of the commonly utilized chemical drugs for diabetes management. Categorized as a Sulfonylurea drug, it is prescribed in 5 mg tablet form to diabetic patients. Glibenclamide operates by stimulating insulin release through exocytosis from pancreatic cells, resulting in blood glucose reduction (Eliasson et al., 1996; Flatt et al., 1994). Several studies have also indicated that Glibenclamide can improve diabetes-induced alterations in pancreatic islets (Akinlolu et al., 2015; Kumar et al., 2013).

Traditional medicine presents a rich source of diverse herbal remedies for diabetes management, with *Teucrium polium* L. (*TP*) being a notable example. *TP* belongs to the Labiatae family and is characterized by small clusters of pink to white flowers. It thrives in the deserts and hills of Mediterranean regions, Europe, North Africa, and South Western Asia, and has been used since the time of Hippocrates and Galen (Ardestani et al., 2008). *TP* can enhance insulin secretion, leading to a subsequent reduction in blood glucose concentrations (Asghari et al., 2020; Solati et al., 2013). In addition to anti-diabetic effects, *TP* also has another effect, including anti-inflammatory (Tariq et al., 1989), antioxidant and anti-ulceric (Loucif 2023), antipyretic and antiseptic (Alreshidi et al., 2020; Capasso et al., 1984), analgesic (Baluchnejadmojarad et al., 2005), and antispasmodic (Parsaee and Shafiee-Nick 2006).

The growing inclination toward herbal remedies has fostered their concomitant use with conventional chemical medications. However, it is important to recognize that certain herbal remedies may interact with and modify the therapeutic effects of chemical drugs (Lorenzati et al., 2010). *Teucrium polium* (*TP*) has been traditionally used for its anti-diabetic, antioxidant, and beta-cell regenerative properties. On the other hand, Glibenclamide is a commonly used chemical drug that stimulates insulin secretion from beta-cells. However, the combination of these two agents has been rarely investigated. In light of this context, we formulated a hypothesis that co-administration of *TP* extract and Glibenclamide would prove more efficacious in diabetes management than Glibenclamide alone. Consequently, the objective of the current study is to examine the impacts of *TP* when co-administered with Glibenclamide on islets of the pancreas using precise stereological methods in rats with STZ-induced diabetes.

Material and Methods

Animals

Procedures involving animals were in-accordance with the Guide for the Care. Forty-eight male Wistar rats, weighing between 200–250 grams and aged 6–8 weeks, were housed under controlled environmental conditions (22–24 degrees centigrade and 12-hour light/dark cycle with natural light). They had *ad libitum* access to a standard pellet diet and tap water.

Induction of Experimental Diabetes

To induce experimental type 1 diabetes, after a 12-hour fasting period, rats received a single intraperitoneal injection of streptozotocin (Sigma, 55 mg/Kg of body weight), dissolved in 0.9% NaCl. After a 72-hour period following streptozotocin (STZ) injection and while fasting, blood samples were collected from the tail vein, and blood glucose concentrations were measured using a glucometer (Easy Gluco^{TM}, Infopia, Korea). The criterion for classifying rats into the diabetic group is a blood glucose concentration exceeding 250 mg/dl (Sarkarizi et al., 2015).

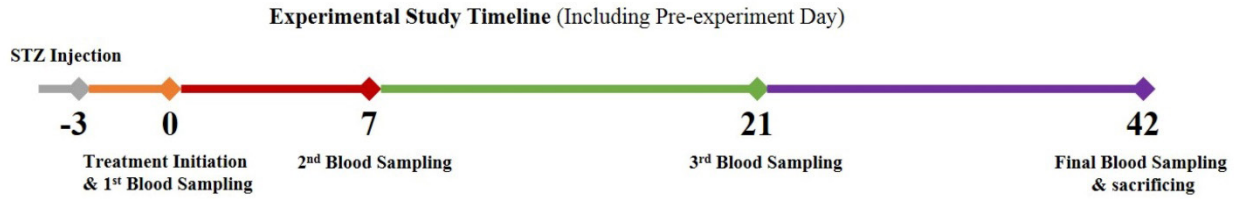

FIGURE 1. Timeline illustrating the experimental protocol, including the induction of diabetes, treatment periods, blood sampling days, and tissue collection.

Preparation of Hydro-Alcoholic Teucrium polium L. Extract

Fresh leaves of *TP* were collected from southern Khorasan, Iran. The plant was identified by an expert botanist from the division of pharmacognosy, Ferdowsi University, Mashhad, Iran (Herbarium No. 152-2016-4). Subsequently dried at room temperature. 200 grams of the dried leaves were milled into a fine powder, which was then soaked in 1 liter of 50% ethanol for 48 hours in the dark. The obtained solution was filtered by ordinary filter paper, and subsequently dried on a Bain Marie (Mamert, Germany) at 40 degrees centigrade for 36 hours. The *TP* extract was maintained at -20 degrees centigrade until it was required for further application, and the selected dosage for *TP* administration was 200 mg/kg (Sarkarizi et al., 2015).

Experimental Design

Rats were randomly divided into 6 groups (n=8). The groups received the following treatments:

1. Control (Cont): standard diet and tap water. 2. Sham control (ShamCont): 0.9% NaCl. 3. Diabetic control (Dia): 0.9% NaCl. 4. Diabetic treated with hydro-alcoholic *Teucrium polium* L. extract (Dia+*TP*): 200 mg/kg *TP* extract. 5. Diabetic treated with Glibenclamide (Dia+Glib): 5mg/kg Glibenclamide (Ebrahimi et al., 2020). 6. Diabetic co-treated with hydro-alcoholic *Teucrium polium* L. extract and Glibenclamide (Dia+*TP*-Glib): 200 mg/kg hydro-alcoholic *TP* extract with 5 mg/kg Glibenclamide.

The experimental protocol spanned 6 weeks (Ashrafihelan et al., 2010) (for diabetic groups, starting 72 hours after STZ injection). The NaCl, *TP,* and Glibenclamide were administered once daily by oral gavage.

Blood Sampling

Fasting blood samples were obtained at the first, and on days 7, 21, and 42 following the initiation of treatment from the retro-orbital venous plexus. Plasma glucose, triglyceride, and cholesterol concentrations were determined using enzymatic kits (Betagen, Iran) and a Photometer (Convergys®100, Germany). Furthermore, the body weight of the rats was measured on the same days (Fig. 1).

Tissue Preparation

Upon completion of the study, every rat was euthanized. After performing a laparotomy and dissecting the rat pancreas, tissue samples were placed in cold 0.9% NaCl, and their adipose tissues were removed. Fixation, tissue processing, and paraffin embedding were done. Each pancreas was exhaustively sectioned into 5µm thickness and stained with H & E to measure pancreas and islet volume (Rezagholizadeh et al., 2022), modified Gomori aldehyde fuchsin to detect beta-cells, and the TUNEL technique to detect apoptotic cells.

Quantification Analysis of Pancreas and Islet Volume

After H & E staining, section images were captured by a light microscope (BX51, Japan) connected to a camera (DP12, Japan). A fine grid of points was superposed. The points that made contact with the pancreas and islets were counted. The following formula was used to estimate the volume of the pancreas and volume of islets (Heidari et al., 2008):

$$\mathrm{estV} = \frac{\sum_{i=1}^{m} P \cdot a/p \cdot \bar{t}}{M^2}$$

estV: Estimation of the pancreas/Islets volume. $\sum_{i=1}^{m} \mathrm{p}$: Sum of the number of points landing within the pancreas/Islet's profiles. a/p: Area associated with each point. t: Distance between sections. M: Magnification. The objective lens was 10x. Volume density of islets relative to

TABLE 1: Rat Body Weight (gr)

Groups	At the first	Day 7	Day 21	Day 42
Cont	210.52±12.11	218.38±13.41	245.63±11.26	266.13±15.47
ShamCont	208.34±11.24	212.22±14.32	240.35±12.37	261.76±13.64
Dia	211.24±13.44	205.88±18.13	162.75±17.29 [a]	159.88±20.22 [a]
Dia+TP	209.55±14.21	203.25±19.17	216.38±23.48	235.13±18.73 [b]
Dia+Glib	212.47±10.99	228.25±14.28	219.88±20.44	231.75±21.43 [b]
Dia+TP-Glib	210.82±13.25	210.14±12.5	233.43±19.91	248.11±17.49 [c]

Values were expressed as Mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). a P= 0.01 compared to the sham control group. b P= 0.01 compared to the diabetic control group. c P= 0.001 compared to the diabetic control group.

the pancreas was also measured.

Quantification Analysis of the Number of Beta-Cells and Apoptotic Cells within the Islets

The number of beta-cells (Nβ) and TUNEL-positive cells per unit area (N_A) was measured according to standard morphometric procedures. The sections were digitally photographed using a ×40 objective lens. The number of these cells was counted using a counting frame and the following formula (Sarkarizi et al., 2020):

$$N_\beta / N_A = \frac{\Sigma Q}{a/f.\Sigma p}$$

Nβ or N_A: Beta or apoptotic cells number per unit area. ΣQ: total of calculated particles in islets. a/f: area corresponding to each frame. ΣP: total of calculated frames in sections.

Statistical Analysis

Data were presented as the mean±S.E.M. Statistical evaluations were carried out using SPSS 13.5. One-way ANOVA was used to compare differences between groups. For analysis of time-dependent differences (body weight and plasma glucose, triglyceride, and cholesterol levels measured over time), a repeated measures ANOVA was performed. In this analysis, the independent factor was group, and the repeated factor was time. Post hoc comparisons were performed using Tukey's test. A significance threshold of P<0.05 was used.

In this study, the sham control group was included to account for the potential effects of oral gavage. Therefore, comparisons were made between the diabetic control and sham control groups to evaluate the effects of STZ injection independently of the oral gavage procedure. Additionally, treatment groups were compared with the diabetic control to assess the effects of the administered drugs using oral gavage.

Result

Rat Body Weight

Induction of diabetes significantly decreased the rat body weights on days 21 and 42 in comparison to the sham control group (P=0.01). Treatment with *TP* extract, Glibenclamide, and co-administration of them effectively prevented the loss of body weight in diabetic rats on day 42 (P=0.01, P=0.01, P=0.001, respectively) in comparison to the diabetic control group. Notably, co-administration of *TP* and Glibenclamide did not exhibit a significant difference in body weight improvement compared to diabetic rats treated with *TP* or Glibenclamide alone (P>0.05, Table 1).

Plasma Glucose, Triglyceride, and Cholesterol Concentrations

Initially, the plasma glucose, Triglyceride, and Cholesterol concentrations in different groups were within the normal range. Induction of diabetes significantly increased all of them on days 7, 21, and 42 in comparison to the sham control group (P=0.01, P=0.001, and P=0.001, respectively, for each day). Treatment of diabetic rats with *TP* extract, Glibenclamide, and co-admin-

TABLE 2: Plasma Glucose Concentration (mg/dl)

Groups	At first	Day 7	Day 21	Day 42
Cont	105.42±6.24	107.57±8.45	107.31±4.38	106.57±6.75
ShamCont	102.24±4.15	105.41±8.3	108.63±6.78	104.28±4.99
Dia	103.5±8.2	331.5±12.1[a]	389.36±14.24[b]	495.08±14.49[b]
Dia+TP	104.44±4.6	306.35±6.76	268.73±16.74[c]	137.84±14.68[d]
Dia+Glib	105.1±6.8	311.75±10.55	226.5±12.32[c]	122.3±6.91[d]
Dia+TP-Glib	101.66±8.95	301.4±8.18	230.4±14.12[c]	109.85±10.87[d]

Values were expressed as Mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). a P = 0.01 compared to the sham control group. b P= 0.001 compared to the sham control group. c P= 0.01 compared to the diabetic control group. d P= 0.001 compared to the diabetic control group.

TABLE 3: Plasma Triglyceride Concentration (mg/dl)

Groups	At first	Day 7	Day 21	Day 42
Cont	75.36±4.5	74.2±5.3	79.25±3.8	76.98±4.7
ShamCont	74.86±5.1	78.24±4.9	77.34±5.4	79.74±6.2
Dia	78.41±4.7	177.98±11.3[a]	225.82±23.33[b]	260.21±28.12[b]
Dia+TP	74.12±5.5	176.69±13.2	111.27±10.4[d]	90.31±8.7[d]
Dia+Glib	77.36±4.2	138.09±11.5[c]	112.75±9.4[d]	93.52±7.9[d]
Dia+TP-Glib	79.66±4.5	127.64±12.4[c]	102.71±10.4[d]	83.57±8.8[d]

Values were expressed as Mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). a P = 0.01 compared to the sham control group. b P= 0.001 compared to the sham control group. c P= 0.01 compared to the diabetic control group. d P= 0.001 compared to the diabetic control group.

istration of them effectively prevented the increase in plasma glucose, Triglyceride, and Cholesterol concentrations when compared to the diabetic control group, especially on days 21 (P=0.01, P=0.001, and P=0.001, respectively, for each concentration) and 42 (P=0.001, for each concentration). Notably, co-administration of *TP* and Glibenclamide did not show a significant difference in these concentrations compared to diabetic rats treated with *TP* or Glibenclamide alone (P>0.05, Table 2, 3, and 4).

Pancreas and Islet Volume, and Volume Density of Islets Relative to the Pancreas

Comparing the mean pancreas volume between different groups did not show any significant difference (P>0.05, Fig. 2 and 3A). This study demonstrated that induction of diabetes significantly decreased the islet volume and volume density of islets relative to the pancreas in comparison to the sham control group (P<0.05). Yet, no significant differences were found in them after treatment with *TP*, Glibenclamide, or co-administration of *TP* and Glibenclamide when compared to the diabetic control group (Fig. 2 and 3B and C).

Number of Beta (Nβ) *and Apoptotic* (N_A) *Cells within the Islet*

Results obtained from modified Gomori Aldehyde Fuchsin staining and TUNEL technique revealed that induction of diabetes significantly decreased Nβ and increased N_A within the islets in comparison to the sham control group (P<0.05). Treatment of diabetic rats with *TP*, Glibenclamide, and their co-administration signifi-

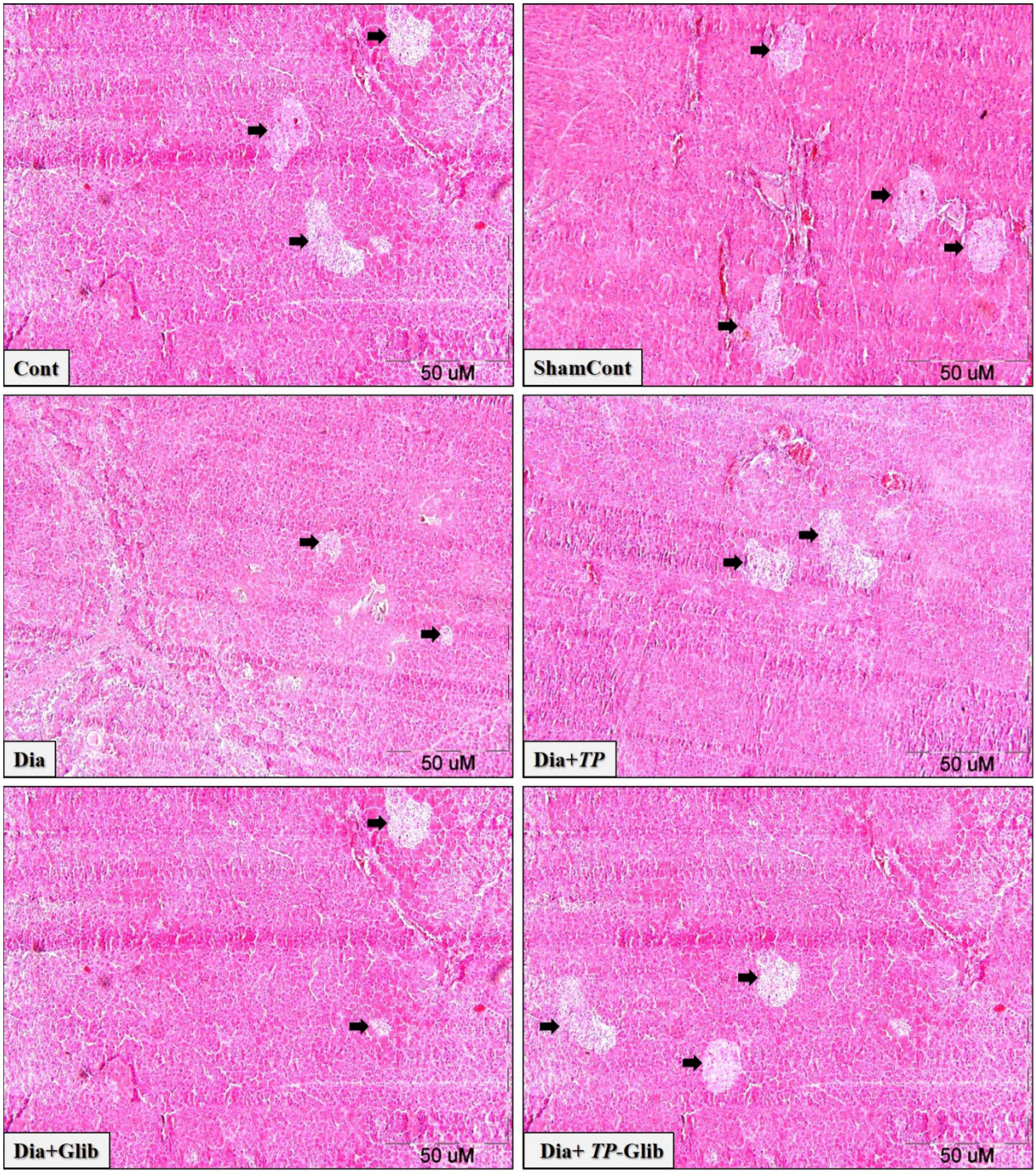

FIGURE 2. Photomicrographs illustrating the rat pancreas in different groups. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide. Arrows show pancreatic islets. (H & E ×10).

cantly increased Nβ and decreased N_A when compared to the diabetic control group (P<0.05). However, co-administration of *TP* and Glibenclamide did not show a significant difference in Nβ and N_A compared to diabetic rats treated with *TP* or Glibenclamide alone (Fig. 4-6).

Discussion

In this research, we evaluated the impacts of *Teucrium Polium* (*TP*), Glibenclamide, and their co-administration on various parameters, including body weight, plas-

TABLE 4: Plasma Cholesterol Concentration (mg/dl)

Groups	At first	Day 7	Day 21	Day 42
Cont	76.25±3.5	73.23±7.4	79.57±5.2	78.85±8.3
ShamCont	74.62±5.5	77.19±7.7	75.88±4.8	79.42±6.7
Dia	78.42±6.4	118.15±11.4[a]	165.46±14.3[b]	199.53±17.1[b]
Dia+TP	69.23±4.9	120.23±10.2	101.16±12.2[c]	84.63±9.3[c]
Dia+Glib	74.18±5.7	116.11±11.7	99.5±10.6[c]	90.75±8.5[c]
Dia+TP-Glib	70.83±8.1	102.36±9.9	93.48±10.4[c]	77.94±8.8[c]

Values were expressed as Mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). a P= 0.01 compared to the sham control group. b P= 0.001 compared to the sham control group. c P= 0.001 compared to the diabetic control group.

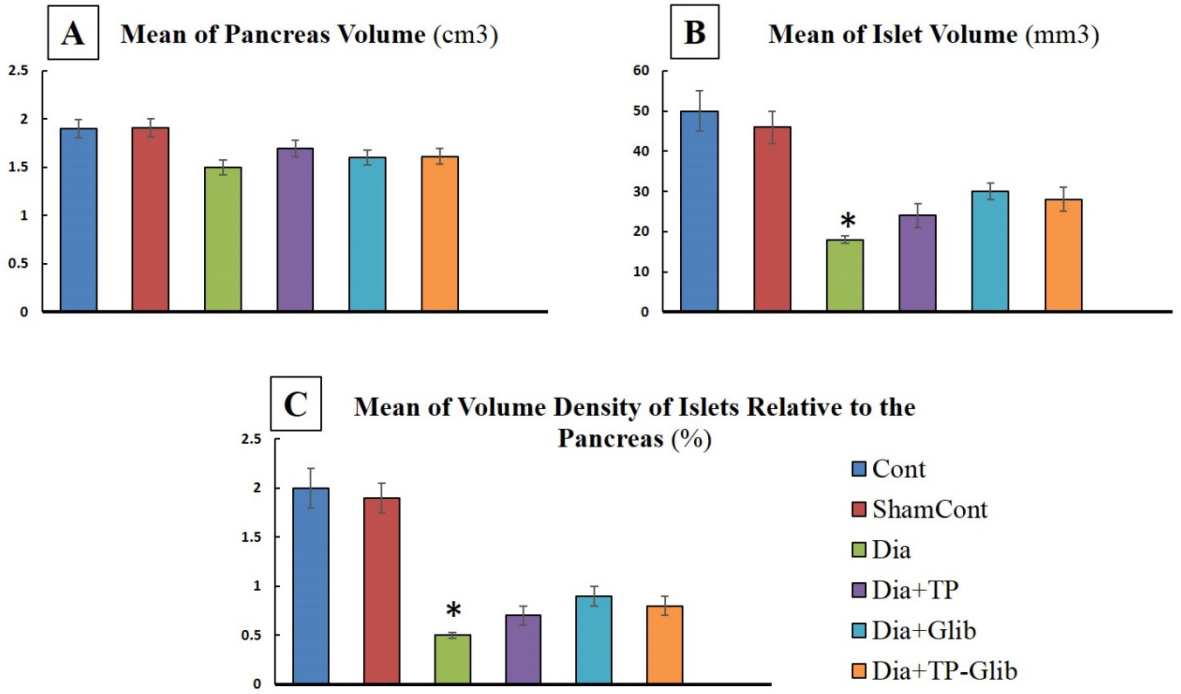

FIGURE 3. Pancreas volume (A), Islet volume (B), and Volume density of islets relative to the pancreas (C) in different groups. Values were expressed as mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). * P< 0.05 compared to the sham control group.

ma glucose, triglyceride and cholesterol concentrations, pancreas volume, islet volume, volume density of islets relative to the pancreas, the number of beta-cells, and apoptotic cells in diabetic rats. The results of our investigation indicate that the effects of *TP* extract are similar to the effects of Glibenclamide, and co-administration of these substances did not lead to any remarkable differences compared to separate administration.

Previous studies have indicated that diabetes induces degenerative changes within the pancreatic islets, characterized by the darkening and shrinkage of cell nuclei, followed by a reduction in the number of beta-cells and a subsequent decrease in islet volume (Ashrafihelan et al., 2010). Similarly, in the present study, administration

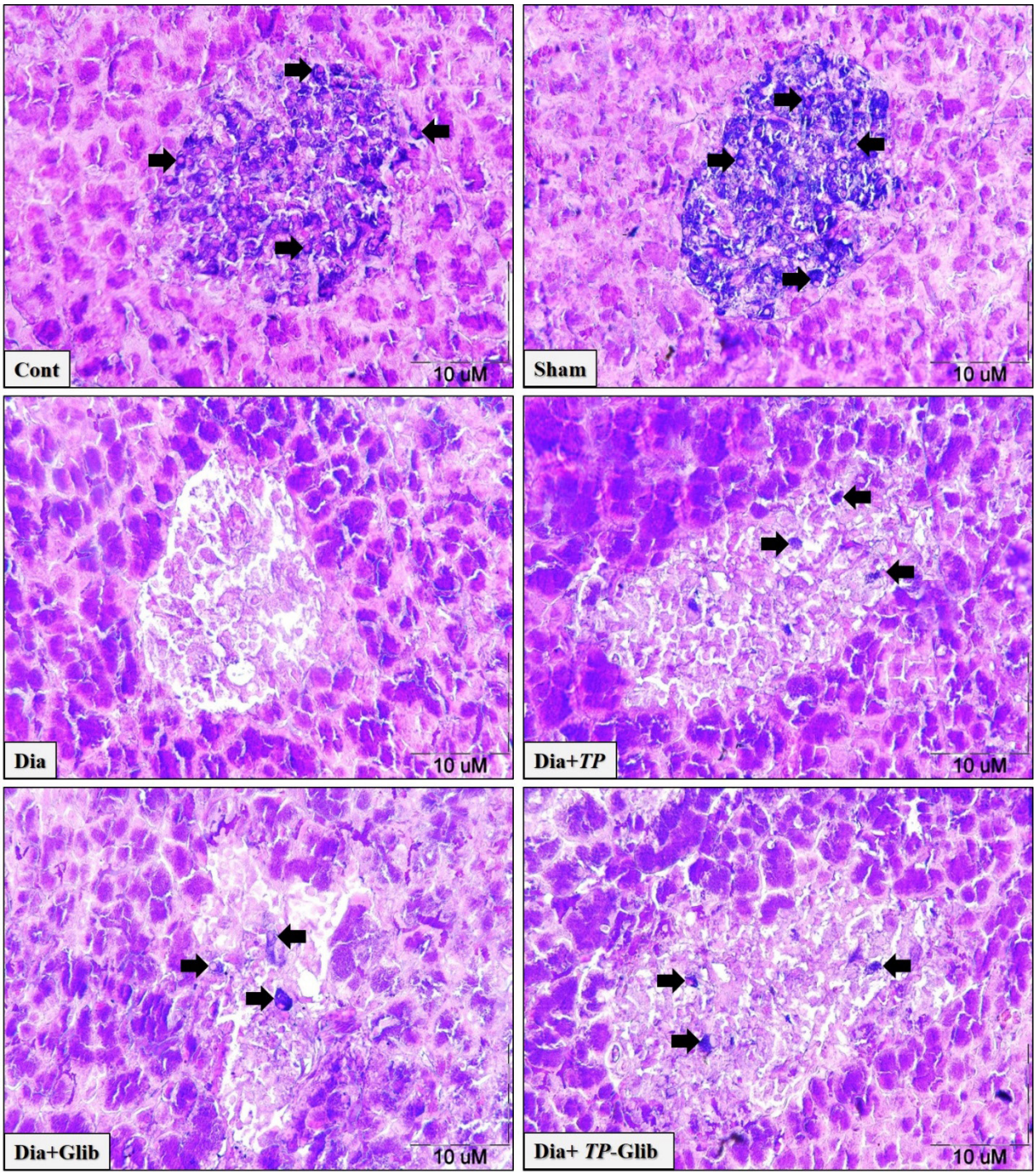

FIGURE 4. Photomicrographs illustrating the rat pancreatic islets in different groups. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide. Arrows show beta-cells within the islet. (Modified Gomori Aldehyde Fuchsin ×40).

of STZ led to an increase in apoptosis and a reduction in beta-cell number, resulting in a decrease in islet volume and volume density of islets relative to the pancreas. Furthermore, consistent with previous studies, the reduction in the number of Beta cells leads to decreased insulin levels, resulting in impaired glucose uptake by body cells. Consequently, plasma glucose concentration rises, which is accompanied by an increase in triglyceride and cholesterol concentrations (Kasper et al., 2005). These elevated concentrations were associated with de-

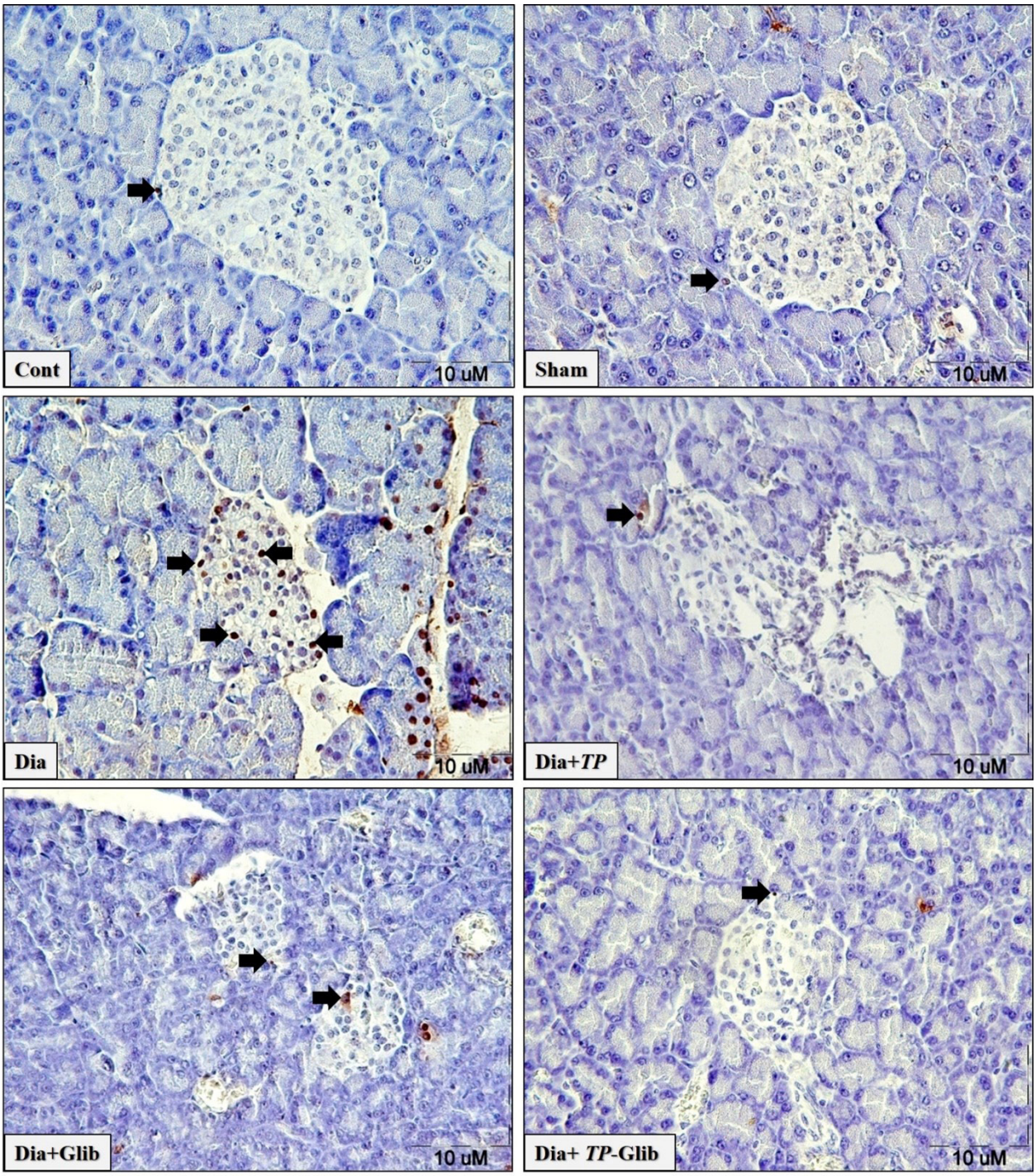

FIGURE 5. Photomicrographs illustrating the rat pancreatic islets in different groups. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide. Arrows show TUNEL-positive cell nuclei within the islet. (TUNEL ×40).

creased body weight in diabetic rats.

Given the growing interest in herbal medicines, there is a common practice of combining them with prescribed chemical drugs. Some herbal drugs may amplify or reduce the therapeutic impacts of chemical drugs. In our study, we evaluated the effects of *TP*, a traditional herb with a long history of consumption, and Glibenclamide, a prescribed Sulfonylurea drug, on streptozotocin (STZ)-induced diabetic rats.

Consistent with previous research, our findings

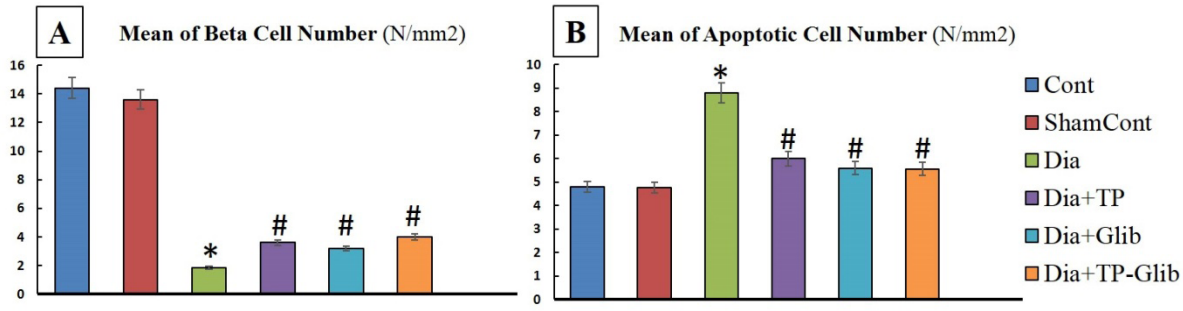

FIGURE 6. Beta (A) and Apoptotic cells Number (B) within the Islets in different groups. Values were expressed as mean±S.E.M. Cont: Control, ShamCont: Sham control, Dia: Diabetic control, Dia+*TP*: Diabetic treated with *TP* extract, Dia+Glib: Diabetic treated with Glibenclamide, Dia+*TP*-Glib: Diabetic treated with *TP* extract and Glibenclamide (n=8). * compared to the sham control group. # compared to the diabetic control group. P< 0.05.

demonstrate that both *TP* and Glibenclamide significantly reduced hyperglycemia and hyperlipidemia in diabetic rats, and these effects were associated with increased body weight. Numerous studies suggest that *TP,* by improving beta-cell sensitivity and Glibenclamide by blocking potassium channels, can enhance and stimulate insulin secretion from the remaining pancreatic beta-cells, thereby preventing hyperlipidemia and promoting anabolic processes that lead to increased body weight (Asghari et al., 2020; Eliasson et al., 1996). Our study implies that *TP* and Glibenclamide may have similar effects on these parameters, with no significant differences observed between the simultaneous administration of these two substances compared to their individual use.

Histologically, Vesal et al. reported that flavonoids (especially cuirestin present in *TP*) can reconstruct beta-cells in STZ-induced diabetic rats (Vesal et al., 2003). Our investigations also revealed that *TP* administration was able to decrease the number of apoptotic cells and promote the reconstruction of islets, ultimately increasing the number of beta-cells.

Akinlolu et al. have suggested that Glibenclamide can enhance pancreatic islets and potentially promote beta-cell regeneration (Akinlolu et al., 2015). Furthermore, Kumar et al. reported that Glibenclamide can repair the necrotic and fibrotic changes in the islets and increase the number of beta-cells (Kumar et al., 2013). Our data support these findings, as Glibenclamide administration could decrease apoptotic cells and increase beta-cells in the diabetic rat model. Although some in vitro investigations have reported that Glibenclamide may increase beta-cell apoptosis, these studies were not conducted in vivo and had different objectives, focusing on non-diabetic pancreases (Maedler et al., 2005; Sawada et al., 2008).

Importantly, our investigations demonstrated that co-administration of *TP* extract with Glibenclamide for six weeks did not lead to significant differences compared to separate administrations. This lack of difference could be attributed to the limitations imposed by remaining progenitor cells or the restricted regenerative capacity of beta-cells within diabetic islets of the pancreas.

Conclusion

The results of this study indicate that the effects of *Teucrium Polium* L. extract are similar to the effects of Glibenclamide, and the simultaneous usage of these substances did not yield any remarkable differences compared to separate administrations. This can be due to the decrease in the regeneration capacity of beta-cells following diabetes.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

This study was approved by the ethics committee of deputy research of Mashhad university of medical sciences.

References

Akinlolu A A, Salau B A, Ekor M, Otulana J. Musa sapientum with exercises attenuates hyperglycemia and pancreatic islet cells degeneration in alloxan-diabetic rats. Journal of Intercultural Ethnopharmacology 2015; 4: 202. https://doi.org/10.5455/jice.20150525030003

Alreshidi M, Noumi E, Bouslama L, Ceylan O, Veettil V N, Adnan M, et al. Phytochemical screening, antibacterial, antifungal, antiviral, cytotoxic, and anti-quorum-sensing properties of Teucrium polium L. aerial parts methanolic extract. Plants 2020; 9: 1418. https://doi.org/10.3390/plants9111418

Ardestani A, Yazdanparast R, Jamshidi S. Therapeutic effects of Teucrium polium extract on oxidative stress in pancreas of streptozotocin-induced diabetic rats. Journal of Medicinal Food 2008; 11: 525-532. https://doi.org/10.1089/jmf.2006.0230

Asghari A A, Mokhtari-Zaer A, Niazmand S, Mc Entee K, Mahmoudabady M. Anti-diabetic properties and bioactive compounds of Teucrium polium L. Asian Pacific. Journal of Tropical Biomedicine 2020; 10: 433-441. https://doi.org/10.4103/2221-1691.290868

Ashrafihelan J, Yazdanparast R, Esmaeili M, Nowrozi M. A pathologic study on changes of pancreas, liver and kidney due to Teucrium polium extract in streptozotocin induced-diabetic rats. Pharmaceutical Sciences 2010; 16: 11-20.

Baluchnejadmojarad T, Roghani M, Roghani-Dehkordi F. Antinociceptive effect of Teucrium polium leaf extract in the diabetic rat formalin test. Journal of Ethnopharmacology 2005; 97: 207-210. https://doi.org/10.1016/j.jep.2004.10.030

Capasso F, De Fusco R, Fasulo M, Lembo M, Mascolo N, Menghini A. Antipyretic and antibacterial actions of Teucrium polium (L.). Pharmacological Research Communications 1984; 16: 21-29. https://doi.org/10.1016/S0031-6989(84)80101-0

Ebrahimi B, Azizi H, Sarkarizi H K, Bahrami-Taghanaki H, Rajabzadeh A. Comparing the effect of electroacupuncture and glibenclamide on blood glucose level and histological markers of pancreas in streptozotocin-induced diabetic rats. Alternative Therapies in Health and Medicine 2020; 26: 12-19.

Eliasson L, Renström E, Ämmälä C, Berggren P-O, Bertorello A M, Bokvist K, et al. PKC-dependent stimulation of exocytosis by sulfonylureas in pancreatic β cells. Science 1996; 271: 813-815. https://doi.org/10.1126/science.271.5250.813

Flatt P, Shibier O, Szecowka J, Berggren P-O. New perspectives on the actions of sulphonylureas and hyperglycaemic sulphonamides on the pancreatic beta-cell. Diabete & Metabolisme 1994; 20: 157-162.

Heidari Z, Mahmoudzadeh-Sagheb H, Moudi B. A quantitative study of sodium tungstate protective effect on pancreatic beta cells in streptozotocin-induced diabetic rats. Micron 2008; 39: 1300-1305. https://doi.org/10.1016/j.micron.2008.02.014

Kasper D L, Braunwald E, Fauci A, Hauser S, Longo D, Jameson J, et al. Principles of internal medicine. New York. McGrow-Hill 2005.

Kumar V, Ahmed D, Anwar F, Ali M, Mujeeb M. Enhanced glycemic control, pancreas protective, antioxidant and hepatoprotective effects by umbelliferon-α-D-glucopyranosyl-(2 I→ 1 II)-α-D-glucopyranoside in streptozotocin induced diabetic rats. Springerplus 2013; 2: 1-20. https://doi.org/10.1186/2193-1801-2-639

Lorenzati B, Zucco C, Miglietta S, Lamberti F, Bruno G. Oral hypoglycemic drugs: pathophysiological basis of their mechanism of action. Pharmaceuticals 2010; 3: 3005-3020. https://doi.org/10.3390/ph3093005

Loucif K. Antioxidant and anti-ulcer activities of teucrium polium aqueous extract. Tobacco Regulatory Science (TRS) 2023: 3141-3158.

Maedler K, Carr R D, Bosco D, Zuellig R A, Berney T, Donath M Y. Sulfonylurea induced β-cell apoptosis in cultured human islets. The Journal of Clinical Endocrinology & Metabolism 2005; 90: 501-506. https://doi.org/10.1210/jc.2004-0699

Parsaee H, Shafiee-Nick R. Anti-spasmodic and anti-nociceptive effects of Teucrium polium aqueous extract. Iranian Biomedical Journal 2006; 10: 145-149.

Rezagholizadeh L, Ojarudi M, Moradi A, Salimnejad R, Khonakdar-Tarsi A, Matin S, et al. Protective effects of Cinnamomum zeylanicum and Zingiber officinale extract against CCl4-induced acute kidney injury in rats. Physiology and Pharmacology 2022; 26: 158-167.

Sarkarizi H K, Salimnejad R, Jafarian A H, Fani M, Khajavian N, Nourmohamadi E, et al. Effects of electrocauterization smoke on nasal mucosa in rats. Crescent Journal of Medical

& Biological Sciences 2020; 7: 34-39.

Sarkarizi H K, Sazegar G, Rajabzadeh A. The effect of hydro-alcoholic Teucrium polium L. extract with glibenclamide administration on blood glucose and lipids in streptozotocin-induced diabetic rats. Journal Of Iranian Clinical Research 2015; 1: 38-45.

Sawada F, Inoguchi T, Tsubouchi H, Sasaki S, Fujii M, Maeda Y, et al. Differential effect of sulfonylureas on production of reactive oxygen species and apoptosis in cultured pancreatic β-cell line, MIN6. Metabolism 2008; 57: 1038-1045. https://doi.org/10.1016/j.metabol.2008.01.038

Solati M, Farshidfar G, Vakil M K, Saberi P, Kamalinejad M, Soltani N. Effect of administration of Teucrium polium on blood glucose and lipid levels in. Physiology and Pharmacology 2013; 16: 423-434.

Tariq M, Ageel A, Al-Yahya M, Mossa J, Al-Said M. Anti-inflammatory activity of Teucrium polium. International Journal of Tissue Reactions 1989; 11: 185-188.

Vesal M, Zal F, Vaseei M. Effects of Teucrium polium on oral glucose tolerance test, regeneration of pancreatic islets and activity of hepatic glucokinase in diabetic rats. Archives of Iranian Medicine 2003; 6: 35-39.