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***Original Article***

# Antihyperglycemic and hepatoprotective effects of *Salvia tebesana* Bunge in diabetic rats

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***Abstract***

**Background and purpose:** Medicinal plants have been used to cure numerous diseases compared to orthodox medicines. The present study estimated the antidiabetic activity of ethanolic extract of *Salvia tebesana* Bunge in streptozotocin-induced diabetic rats.
**Experimental approach:** In this study type 2 diabetes was induced in male rats by streptozotocin (65 mg/kg, i.p.). After diabetes induction, normal control groups were treated with distilled water, the positive control group received metformin (500 mg/kg), and the other groups were orally treated with ethanolic extracts of *S. tebesana* (100, 200, and 400 mg/kg) for 4 weeks. Changes in body weight and some biochemical parameters were determined.
**Findings / Results:** The ethanolic extract of *S. tebesana* in all doses considerably declined serum glucose, total cholesterol, alanine aminotransferase, aspartate aminotransferase, and triglyceride compared with the diabetic control rats. Administration of ethanolic extract of *S. tebesana* reduced the serum of kidney and liver function factors and decreased the side effects on the function of these.
**Conclusion and implications:** These results revealed the potential of *S. tebesana* for the cure of diabetes and its problems.

***Keywords:*** Diabetic rat; Metformin; *Salvia tebesana* Bunge; Streptozotocin.

## INTRODUCTION

Type 2 diabetes mellitus is one of the most common chronic metabolic diseases described by insistent hyperglycemia resulting from a lack of insulin secretion or action. The occurrence of diabetes was estimated at 8.4% in 2017 and predicted to rise to 9.9% in 2045. Its incidence is increasing especially in middle and low-income countries. The persistent hyperglycemia may be the cause of difficulties such as microvascular, macrovascular, cardiovascular diseases, and neuropathic alterations (1,2).

The lifestyle alterations such as nutritional modifications, physical activity, insulin injections, and the use of diverse glucose-lowering drugs are the main approaches for the inhibition and management of diabetes type 2 (3). Moreover, due to some reasons including adverse effects, their low efficacy, and important risks of cardiovascular diseases, scientists have been encouraged to estimate new approaches to control the disease and its complications. Among the new methods, herbal medicine and nutraceuticals are used as a substitute for effective treatment, due to low toxicity and rare adverse side effects (4).

*Salvia tebesana* Bunge is one of the endemic plants of Iran that is locally named 'Maryamgoli Tabasi' present in the Tabas (5).

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The roots and leaves of this plant are traditionally used for the treatment of gout, chronic rheumatism, constipation, infection, cholera, cold, fever, liver disorders, epilepsy, and cancer (6,7). Previous studies have identified four bioactive compounds and reported that diterpenoids present in the roots of the plant were responsible for its antibacterial and cytotoxic activities (8). The studies conducted by Estakhr *et al*. and Zarei *et al*. displayed the antidiabetic effect of *S. hypoleuca* and *S. hydrangea* leaves in a streptozotocin-induced diabetes model (9,10). To our knowledge, no previous antihyperglycemic and antihyperlipidemic studies were accomplished with the roots of the *S. tebesana* in the streptozotocin-induced diabetes model. Thus, the present study assessed the antihyperglycemic, antihyperlipidemic, and liver-protective activity of *S. tebesana* in diabetic rats.

## MATERIALS AND METHODS

### *Plant material*

The roots of *S. tebesana* were obtained from Tabas, South Khorasan, Iran, during the flowering stage, in April 2020. The plant was characterized by M.R. Joharchi and a specimen of this plant was deposited in the Herbarium of the School of Pharmacy, Mashhad University of Medical Sciences, under Voucher No. 24864. The roots were dried in shade at room temperature and powdered using a grinder. The dried roots were extracted three times with EtOH 70% (each 24 h) at room temperature. After extraction, the solvent was filtered and removed by a rotatory flash evaporator. The obtained crude extract was stored at -20 °C.

### *Animals*

Sixty male Wistar rats initially weighing 200-250 g were used. Animals were housed in polyethylene cages at 21-25 °C, 12/12-h light/dark cycles, and relative air humidity of 40-45%. Rats had received standard commercial food and tap water. Research on animals was performed according to the guidelines of the Research Ethics Committee of Birjand University of Medical Sciences (Ethics No. IR.BUMS.REC.1399.130).

### *Induction of diabetes in rats*

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) freshly prepared in 0.1 M sodium chloride at 65 mg/kg body weight (10). Diabetes was revealed by the determination of fasting blood glucose by glucometer after 14 days of STZ administration. The animals having fasting blood glucose above 250-350 mg/dL were considered diabetic and used in experimental procedures.

### *Experimental design*

A total of 60 male rats were divided into 6 equal groups and treated as follows:

Groups 1-3: diabetic rats treated with 100, 200, and 400 mg/kg b.w. of *S. tebesana* extract

Group 4: diabetic rats treated with 500 mg/kg b.w. of metformin

Group 5: diabetic control rats treated with 1 mL/kg b.w. of normal saline

Group 6: normal control rats treated with 1 mL/kg b.w. of normal saline

At the end of the experiment, rats were anesthetized using xylazine 75 mg/kg, i.p., and ketamine 10 mg/kg, i.p. Blood was collected in anticoagulant tubes and centrifuged at 3000 g at 4 °C for 5 min. Plasma gained was used for the determination of biochemical parameters. After blood sample collection, the kidneys and liver were removed and rinsed in 0.9% NaCl solution.

### *Measurement of biochemical parameters*

Fasting blood glucose was examined by a portable glucometer (ACCU CHEK Active, Germany) before and after the treatment. Total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using standard kits (Pars Azmon, Iran) and an autoanalyzer method (Japan).

### *Histology*

Immediately after blood collection, the kidney and liver of the rats were rapidly analyzed and post-fixed in the equal fixative solution for 48 h at 4 °C. The tissues were embedded in paraffin blocks and processed by

routine histological approaches. The samples were sectioned (5-µm thickness) by sliding microtome (Leitz, Italy), mounted on poly-L-lysine coated slides, and stained with hematoxylin and eosin (H&E) dyes. For each rat, three random slides (8 sections) were examined under a light microscope (UPLAN FI, Japan) in a blinded manner. The morphometric parameters of the kidney and liver containing inflammation, fat changes, and presence of xenophagous cells in the sinusoidal spaces, and hyperemia were measured.

### *Statistical analysis*

All data were represented as mean ± SEM. The data were analyzed using one-way ANOVA followed by the Tukey post hoc test using SPSS Windows (SPSS, Chicago, IL, USA). The *P*-values < 0.05 were considered significant.

## RESULTS

### *Body weight and blood glucose level*

The effects of ethanolic extract of the roots of *S. tebesana* on body weight and blood glucose level of diabetic rats are displayed in Table 1. Treatment with metformin and different doses of the extract significantly increased the body weight in comparison with the diabetic control group.

The diabetic-control group considerably increased the blood glucose level compared to the normal groups. Ethanolic extract of *S. tebesana* at 200 and 400 mg/kg exhibited a significant reduction in blood sugar compared to the diabetic control group. In a similar way, metformin considerably decreased the blood glucose level compared to the diabetic control group.

At the end of the 28$^{th}$ day of cure, the ethanolic extracts of *S. tebesana* in all doses indicated important hypoglycemic activity in STZ-diabetic rats similar to metformin.

### *Effect of S. tebesana on plasma lipid profile*

Table 2 shows the effects of extract from the roots of *S. tebesana* on plasma lipid profile in diabetic animals. Metformin significantly reduced TG and LDL-c and significantly increased HDL-c compared to diabetic control animals. The ethanolic extract of *S. tebesana* at 100, 200, and 400 mg/kg decreased the concentrations of TG, total cholesterol, and LDL-c, and increased the plasma HDL level in treated animals compared to the diabetic-control animals.

**Table. 1.** The effect of ethanolic extract of *Salvia tebesana* on body weight and blood glucose level. Data are presented as mean ± SEM, n = 7.

| Groups | Body weight (g) | | Blood glucose level (mg/dL) | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Normal group | 255 ± 2.33 | 281.6 ± 3.85 | 180.02 ± 2.33 | 179.18 ± 0.85 |
| Diabetic control | 188 ± 10.04*** | 162.57 ± 0.95*** | 263.4 ± 8.93*** | 512.23 ± 4.04*** |
| Diabetic + metformin at 500 mg/kg | 206.85 ± 2.5 | 208.42 ± 1.56### | 298.8 ± 8.65*** | 285.2 ± 0.5### *** |
| Diabetic + extract at 100 mg/kg | 230.4 ± 1.86 | 237.4 ± 8.37### | 415 ± 0.79*** | 341.4 ± 6.35## *** |
| Diabetic + extract at 200 mg/kg | 159.6 ± 1.79 | 185.3 ± 1.7### | 365.2 ± 7.86*** | 259.4 ± 7.08### *** |
| Diabetic + extract at 400 mg/kg | 167.5 ± 1.92 | 231.33 ± 5.91### | 357 ± 6.92*** | 241.8 ± 5.25### *** |

***$P < 0.001$ Indicates significant differences in comparison with the normal control group and ## $P < 0.05$, ###$P < 0.001$ against the diabetic control.

**Table. 2.** The effect of ethanolic extract of *Salvia tebesana* on lipid profile concentration. Data are presented as mean ± SEM, n = 7.

| Groups | Triglyceride | Cholesterol | Low-density lipoprotein | High-density lipoprotein |
|---|---|---|---|---|
| Normal group | 88.40 ± 6.51 | 112.40 ± 9.76 | 30.00 ± 8.56 | 37.82 ± 4.68 |
| Diabetic control | 122.82 ± 2.07 | 98.20 ± 1.38 | 31.71 ± 5.46 | 30.06 ± 5.15 |
| Diabetic + metformin at 500 mg/kg | 116.50 ± 0.71** | 109.00 ± 5.07 | 27.87 ± 7.55** | 32.25 ± 1.39* |
| Diabetic + extract at 100 mg/kg | 110.40 ± 8.69** | 94.20 ± 4.79** | 22.71 ± 6.39** | 36.71 ± 2.75** |
| Diabetic + extract at 200 mg/kg | 108.40 ± 9.96** | 91.85 ± 7.55** | 20.71 ± 4.34** | 39.2 ± 2.76** |
| Diabetic + extract at 400 mg/kg | 87.80 ± 7.60** | 85.16 ± 5.28** | 20.66 ± 6.91** | 46.8 ± 3.74** |

**$P < 0.01$ Indicates significant differences in comparison with the diabetic control.

### *Effect of S. tebesana on serum liver function markers*

The level of AST, ALT and alkaline phosphatase (ALP) of normal and diabetic animals are shown in Table 3. The consumption of *S. tebesana* (100, 200, and 400 mg/kg body weight) markedly reduced the serum activities of ALP, ALT, and AST compared to the diabetic control. The level of creatinine and blood urea in diabetic groups preserved with ethanolic extract of *S. tebesana* and metformin significantly decrease compared to the diabetic control group, while ethanolic extract of *S. tebesana* at 200 and 400 mg/kg) increased the level of total protein in the urine compared to the diabetic control group.

### *Kidney histology*

Figure 1 shows the kidney sections of the calculated groups. Figure 1A exhibits a normal kidney with a normal appearance. However, in untreated diabetic groups marked increase in the mesenchymal matrix, dilatation of urinary space, adhesion of visceral and wall membranes of Bowmann capsule, hyperemia in the glomeruli, and hemorrhage in the interstitial space of the tubules were seen (Fig. 1B). Treatment with *S. tebesana* and metformin exhibited a slight improvement in coagulation necrosis and hyperemia in the glomeruli (Fig. 1C and D). The ethanolic extract of *S. tebesana* dose-dependently improved kidney histology and decreased coagulation necrosis and hyperemia in the glomeruli.

### *Liver histology*

Figure 2 shows the liver sections of the studied groups. In the diabetic group compared with the control decreased acidophilia of peripheral cells in hepatic lobules and increased acidophilia of central cells of lobules were seen (Fig. 2A and B). Also, the increase of inflammatory cells, the appearance of degenerative variations, and necrosis in the liver lobules were observed in diabetic groups. In diabetic control samples, in addition to the findings of hepatocyte cell compression, sinusoid dilation and loss of hepatic cord order were also observed.

In the diabetic group treated with metformin and the extract of *S. tebesana*, the vascular destruction of liver cells was observed but it is very small compared to the diabetic control group (Fig. 2C and D).

**Table. 3.** The effect of ethanolic extract of *Salvia tebesana* on serum liver function markers. Data are presented as mean ± SEM, n = 7.

| Groups | Aspartate aminotransferase | Alanine aminotransferase | Alkaline phosphatase | Creatinine | Urea | Total urinary protein |
|---|---|---|---|---|---|---|
| Normal group | 141.7 ± 2.33 | 110.4 ± 3.85 | 246 ± 3.12 | 0.73 ± 0.41 | 51.2 ± 8.47 | 124.7 ± 6.31 |
| Diabetic control | 154.4 ± 10.0 | 152.3 ± 8.95 | 1131.6 ± 7.89 | 0.78 ± 0.04 | 124.3 ± 6.2 | 88 ± 7.54 |
| Diabetic + metformin at 500 mg/kg | 125.7 ± 14.5** | 110.8 ± 12.56 | 890.5 ± 9.54** | 0.69 ± 0.052** | 43.75 ± 1.74** | 51.75 ± 5.63 |
| Diabetic + extract at 100 mg/kg | 119.7 ± 10.86** | 90.98 ± 8.37** | 626 ± 8.74** | 0.64 ± 0.086** | 78 ± 2.37** | 46.5 ± 7.54 |
| Diabetic + extract at 200 mg/kg | 95.6 ± 1.79** | 85.8 ± 2.70** | 502.2 ± 8.74** | 0.62 ± 0.079** | 61.8 ± 9.62** | 99.6 ± 7.84** |
| Diabetic + extract at 400 mg/kg | 89.5 ± 5.22** | 73.3 ± 5.63** | 488.4 ± 6.56** | 0.61 ± 0.022** | 62.3 ± 6.53** | 101.4 ± 2.35** |

**$P < 0.01$ Indicates significant differences in comparison with the diabetic control.

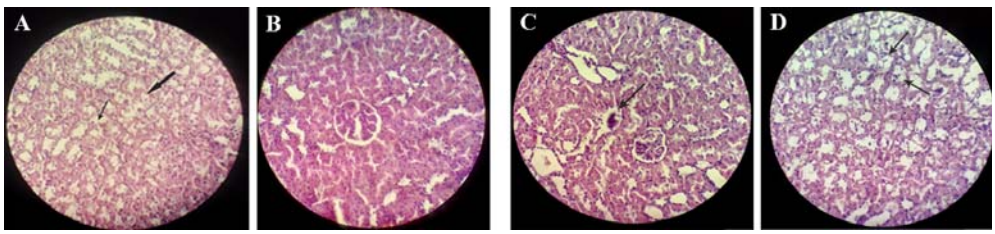


**Fig. 1.** Microscopic image of rat kidney tissue. (A) Normal control rats, (B) diabetic rats, (C) diabetic rats treated with metformin, and (D) diabetic rats treated with 400 mg/kg of *Salvia tebesana* ethanolic extract.

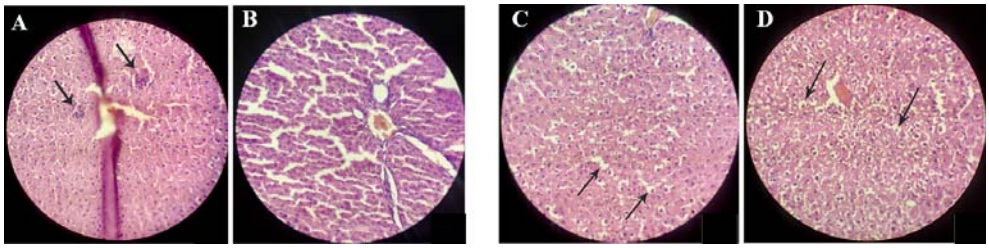


**Fig. 2.** Microscopic image of rat liver tissue. (A) Normal control rats, (B) diabetic rats, (C) diabetic rats treated with metformin, and (D) diabetic rats treated with 400 mg/kg of ethanol extract of *Salvia tebesana*.

## DISCUSSION

Induction of diabetes mellitus by STZ caused rises in the blood glucose, destruction of the β cells, rise in hepatic glycogenogenesis and glycogenolysis, and a decrease in the use of glucose in tissues (11-14). This work examined the antihyperglycemic, antihyperlipidemic, and hepaprotective effects of *S. tebesana* in diabetic rats.

In the current study, STZ-induced diabetic rats were treated with the ethanolic extract of *S. tebesana* at three doses (100, 200, and 400 mg/kg) for 28 consecutive days. The ability of the plant to decrease lipid concentration and blood sugar in diabetic rats is related to its main compounds. *S. tebesana* roots have been reported to be rich in terpenoids, especially diterpenoids (5) which have strong antioxidant activity that is responsible for the hypoglycemic effects. In another study, *S. hydrangea* and *S. hypoleuca* significantly decreased blood sugar and increased serum insulin levels in diabetic rats associated with the presence of flavonoid and terpenoid composites in these plants (9,10).

Diabetes mellitus induced weight loss and muscle protein degradation caused by carbohydrate metabolism in diabetic rats. The administration of the ethanolic extract of *S. tebesana* at 100, 200, and 400 mg/kg protected rats from a drastic drop in body weight but the dose of 100 mg/kg was more effective. This result might be due to an increase in insulin sensitivity and secretion, increases renal excretion of lipoproteins, enhancement of the activity of lipoprotein lipase, and the absorption of fats into the cell (9).

Diabetes is associated with a change in the lipid profile which can be responsible for cardiovascular diseases. The administration of metformin and *S. tebesana* extracts for 4 weeks significantly reduced the levels of LDL, TG, and TC, and significantly increased HDL-c. These findings confirmed that *S. tebesana* probably acts through the inhibition of enzymes responsible for cholesterol biosynthesis, stimulation of cholesterol hydroxylase, and inhibition of intestinal absorption of triglycerides. The repair of the lipid profile may be attributed to the action of bioactive terpenoids and flavonoids compounds present in the ethanolic extract of *S. tebesana* (8).

In diabetic patients, an increase in the concentration of uric acid, urea, and creatinine may indicate renal dysfunction (15). The administration of metformin and different doses of *S. tebesana* extract caused a major decrease in urea and creatinine. Previous studies have shown that the consumption of antioxidants in diabetic rats reduces kidney damage (16,17). Furthermore, the antioxidant properties of *S. tebesana* increase the antioxidant capacity and inhibit oxidative stress that caused a reduction in kidney damage.

The plant extract considerably decreased the activity of ALT, AST, and ALP caused hepatoprotection. This hepatoprotective influence may be due to hypoglycemic effects and the presence of flavonoid and terpenoid compounds as well as the antioxidant properties of *S. tebesana*.

The results of histopathological analysis of the liver displayed that the plant extract efficiently recovers damage. However, administration of *S. tebesana* in a dose-dependent manner efficiently improved liver alterations. Cellular changes, as well as extracellular matrix in STZ-induced diabetes, reflected cellular degenerative changes. In this study, the ethanolic extract of *S. tebesana* due to the presence of antioxidant compounds reduced the activity of liver enzymes, exerted a

positive effect on the liver, and prevented degenerative cellular changes. Similar to our outcomes, some evidence indicated that phytochemicals can regenerate β cells in STZ-induced diabetic rats. The consumption of garlic and onion extract modulates liver enzymes and prevents liver damage (18). In another study, treating the diabetic rats with *Strychnos henningsii* extract led to increasing albumin biosynthesis and reducing the activity of liver enzymes significantly, which indicates plasma membrane stability and protection of liver cells (19). The ethanolic extract of *S. tebesana* mitigated the destructive effects of diabetes on kidney tissue including acute tubular necrosis, interstitial tubular nephrosis, and vacuolar nephrosis. The consumption of *S. tebesana* decreased the occurrence of tubular necrosis and interstitial hyperemia in the diabetic due to the presence of antioxidant compounds in the plant.

## CONCLUSION

The present study demonstrated the extract of *S. tebesana* caused antihyperglycemic and anti-hyperlipidemia activities and treated the liver and kidneys from hyperglycemia. Our study indicated *S. tebesana* extract as a potential treatment for diabetes and its problems.

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***Conflicts of interest statement***

The authors declared no conflict of interest in this study.

***Authors' contributions***

S. Eghbali participated in the study design, data interpretation, and manuscript development (draft, revision and final editing); H. Aramjoo contributed to doing experiments, data analysis, and article writing; Z. Kiani contributed to manuscript development (draft revision and final editing). All the authors studied and approved the final version of the manuscript.

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