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The Effects of Methanolic Extract of Prosopis Farcta Seed on Blood Glucose in Streptozocin Induced Diabetic Rats

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Abstract

Background: Previous studies have shown the beneficial effects of Prosopis species in the treatment of diabetes in traditional medicine. This study was performed to evaluate the antihyperglycemic effects of Prosopis farcta (P.farcta) in streptozocin- induced diabetic rats.

Methods: Diabetes was induced by intraperitoneal injection of streptozocin (55mg/kg). Male Wistar rats were treated with either P. farcta (100, 150, and 300 mg/kg.) or glibenclamide (10mg/kg) orally once a day for a period of 28 days. Control rats received saline. Changes in body weight and blood glucose were measured at the end of each week for 4 weeks.

Results: The results of this study showed a significant increase in blood glucose, and decrease of body weight in streptozocin-induced diabetic rats. P. farcta administration for 28 days in streptozocin-induced diabetic rats suppressed the weight reduction significantly in a dose dependent manner ($P<0.001$). Also, P. farcta, like glibenclamide, showed significant antihyperglycemic effects and reversed the above parameters significantly in a dose dependent manner when compared to diabetic control rats ($P<0.001$, $P<0.05$, respectively).

Conclusions: The results of the present study showed that P. farcta possesses antidiabetic activity in hyperglycemic rat models. The underlying mechanism(s) has not been known yet and needs further investigation.

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Introduction

According to the World Health Organization estimation, there are annually almost 3 million deaths due to diabetes and that there will be 366 million cases of diabetes by the year 2030 (1). In short, diabetes mellitus designates a group of metabolic diseases characterized by hyperglycemia, which results from defects in insulin secretion and/or increased cellular resistance to insulin. This chronic hyperglycemia results in long-term tissue and organ damage and an increase in the risk of coronary artery disease (2-5).

Patients suffering from type 1 diabetes mellitus require lifelong insulin therapy for survival as there is no cure for this

immune-mediated disease and the management of type 2 diabetes has always been a challenge due to several limitations of currently available drugs, including their limited efficacy, limited tolerability and significant side effects (6).

Previous researches showed that diabetes is associated with impairment of endothelium function as a result of reduction in nitric oxide (NO) bioavailability which represent an important triggering event in the initiation and progression of diabetes disease (7, 8). Dysfunction Of vascular endothelium is regarded as an important factor in the pathogenesis of diabetic micro-and macro-angiopathy (8, 9). Chronic hyperglycemia exhibits enhanced oxidative stress and an increased generation of reactive oxygen species (ROS) in pancreatic islets, with a consequent reduced bioavailability of NO (7, 8).

In recent years, plant-based medicines have gained importance in the management of diabetes mellitus (10-12). Several of these plant-based bioactive components have shown significant antidiabetic activity and decreased insulin resistance (13-16). Numerous of them have been found to be more effective than oral hypoglycaemic agents used clinically (14).

The genus Prosopis includes 44 species, distributed in south-western Asia, Africa and predominantly in America and only few species are native to Southwest Asia and Africa (17). According to the previous studies, Prosopis glandulosa treatment moderately lowers glucose levels in different animal models of diabetes, stimulates insulin secretion, leads to the formation of small cells and improves insulin sensitivity of isolated cardiomyocytes (18). Also, other Prosopis species showed antihyperglycemic activity in animal diabetic models (19, 20).

It has been reported that P. farcta plant extract has a dose dependent as well as an endothelium dependent relaxing effect on thoracic aorta in rats and the effect is mediated through the release of NO from the endothelium (21). Aaqueous extracts of P. farcta beans exhibit hepatoprotective activity against acetaminophen- induced hepatic failure by attenuation of biochemical indices of hepatotoxicity (22).

To our knowledge, very few studies have been conducted on the Prosopis farcta (P. farcta) plant. Silver nanoparticles (Ag-NPs) synthesized from extract of Prosopis farcta showed significant antibacterial activity against multi drug resistant clinical isolates (23). Also, P. farcta plant extract showed a dose dependent, as well as, an endothelium dependent relaxing effect on thoracic aorta in rats (21); however, its effects on carbohydrate metabolism has not been determined yet. So, the main aim of the present study was to investigate the blood glucose lowering capacity of methanolic extract of P. farcta seed in streptozocin (STZ) induced diabetic rats.

Material and methods

Preparation of P. farcta extract

Seeds of P. farcta were collected from the plants available locally at Herbal plant stores of Kerman, Iran. Kerman is the largest province of Iran with more than 15 cities, located 1000 km south of Tehran. The plant was identified and confirmed by the Pharmacognosy Department of School of Pharmacy, Kerman, Iran as P. farcta. Dried seeds were grinded to powder form and then extracted with 50% aqueous methanol by percolation method for 72 h at room temperature. The solvents were removed in a rotary evaporator and, after filtering, the extracts were concentrated until a semisolid mass was obtained. The yield of extract was 5% w/w (with respect to

crude material). The suspension of extract of the seed was prepared in 20% tween 20 in normal saline and was used in the experiment (24).

Animals

Male Wistar rats, weighing 200-250g were purchased from Kerman Neuroscience Research Center (Kerman, Iran). They were housed under standard laboratory conditions of light (12:12 h L: D cycle) and temperature (23 ± 2°C). The animals were provided standard laboratory pellet diet and had free access to tap water. Maintenance and treatment of all animals were conducted in accordance with the Guiding Principles for the Care and Use of Research Animals and were approved by the Animal Ethics Committee at Kerman University of Medical Sciences, Kerman, Iran (EC/KNRC/94-14).

Induction of experimental diabetes & antidiabetic evaluation in rats

After fasting for 18 hours, rats were administered 0.1 M cold citrate buffer (pH 4.5) of freshly prepared STZ (55 mg/kg) by intra-peritoneal route (25). After 6 h of STZ administration the rats had free access to food and water and were provided with 50% glucose solution to drink overnight to counter drug induced hypoglycemic shock due to spontaneous massive pancreatic insulin release after STZ administration (26). Induction of diabetes was verified after 72 h by measurement of blood glucose level using glucometer (Accu-Check, Germany) by glucose oxidase – peroxidase method using strips (25). Rats with a fasting blood level greater than 300mg/dl were considered diabetic (25). Fasting blood glucose (FBG) concentration of all the six experimental groups was determined at the end of each week during 28 days of intervention period by withdrawing blood from the tail vein. All rats were weighed weekly and the body weight was recorded for 4 weeks of intervention period.

Experimental Design

Rats were randomly divided into 6 groups of 10 rats each described as follows:

Group I: Normal control (N group): normal rats received saline normal

Group II: Diabetic control (D group): diabetic rats received saline normal

Group III: Glibenclamide group (D+ GLI group): diabetic rats received glibenclamide (10mg/kg) (27, 28).

Groups IV to VI: D+ PF groups, Diabetic rats received P. farcta extract (100, 150 and 300 mg/kg, respectively) (22, 29).

Glibenclamide and P. farcta extract were administered orally, once in a day and for 28 days (18). Control rats received saline with the same protocol as experimental groups.

Statistical analysis

Statistical analysis of data was performed using SPSS version 17 software. All the quantitative data expressed as mean ± SEM were evaluated by one-way analysis of variance (ANOVA), followed by tukey's test for multiple comparisons and $p < 0.05$ was considered as statistically significant. Comparison of changes in blood glucose among different groups was performed by repeated measure ANOVA.

Results

Confirmation of STZ- induced diabetes

Blood glucose levels in the STZ- induced diabetic rats was significantly higher compared with the normal group which

confirmed the development of hyperglycemia as a result of STZ injection (P<.0001). The mortality rate in STZ- induced diabetic rats was 40%, while mortality rates in rats treated with glibenclamide and P. farcta seed extract were 10% and 20%respectively.

The effect of P. farcta on body weight

Table 1 shows the changes of body weight in experimental groups during the intervention period. As shown in Table 1, body weights of rats in diabetic group were significantly lower than those in other groups during the 28 days of intervention period (P<0.001). Mean body weight of diabetic rats in the 28th day (162.5± 4.2g) was significantly lower in comparison to the control group (262 ± 7.3 g, P<.0001), glibenclamide group (235.7± 6.6 g, P<.0001), and P. farcta (300 mg/kg) treated rats (232.1 ± 2.8, P<.0001). STZ-induced diabetic rats showed a significant weight loss compared to the control group, while treatment with P. farcta (100, 150 & 300 mg/kg) or glibenclamide significantly suppressed body weight reduction in STZ- induced diabetic rats (P<.0001). However, the body weight in P. farcta and glibenclamide treated rats were significantly lower than that in the normal control group; i.e, , 28 days after the administration of P. farcta dozes of 100, 150 &300 mg/kg, mean body weights were respectively 185.9 ± 6.4g, 217.2 ± 5.1g, and 232.1 ± 2.8 g compared to the normal control (262 ± 7.3 g, P<.0001).

Table 1. The effects of P. farcta administration on body weight (g) during 28 days of intervention period

Groups	1st week	2nd week	3rd week	4th week
Normal Control	208.3 ± 5.6	219± 7.2	232± 4.9	262 ± 7.3
Diabetic Control	174.1 ± 6.9[a]	170.2 ± 5.2[a]	165.7 ± 3.4[a]	162.5± 4.2[a]
D+PF (100mg/kg)	179.9 ± 5.8[a]	180.3 ± 4.7[a]	182.8 ± 3.8[a]	185.9 ± 6.4[a]
D+PF (150mg/kg)	188.3±4.6[a]	202.3 ± 8.3[b]	209.6±7.4[b]	217.2 ± 5.1[a]
D+PF (300mg/kg)	189.3 ± 5.7[a]	208.9± 6.1[b]	221.7 ±3.8[b]	232.1 ± 2.8[b]
D + GLI (10mg/kg)	203.2 ± 6.3	212.4± 4.2[c]	219.8 ± 5.1[c]	235.7±6.6[c]

Diabetes was induced by 55 mg/kg/i.p. STZ in citrate buffer (pH 4.5). Rats received P. farcta (100, 150 & 300 mg/kg/d) and glibenclamide (10 mg/kg) by intragastric gavage for 4 weeks after the induction of diabetes. Control rats received saline. All data are expressed as mean ± SEM (n=10).
D + PF group: diabetes plus P. farcta treatment, D + GLI: diabetes plus glibenclamide
a: P<0.0001 diabetic control and diabetic P. farcta treated compared with normal control group.
b: P<0.05 P. farcta (150 and 300 mg/kg) compared with diabetic control group.
c: P<0.05 Glibenclamide (10 mg/kg) compared with diabetic control group.

The effects of P. farcta on blood glucose in STZ- induced diabetic rats

Table 1 shows the blood glucose concentration in STZ-induced diabetic rats. One way ANOVA showed a significant increase in blood glucose concentration in STZ- diabetic rats during the 28 days of intervention period in comparison to the control group (P<.001). P. farcta administration caused a significant reduction in blood glucose level in STZ- induced diabetic rats in a dose dependent manner (table 1).The blood glucose levels after 28 days treatment with 100, 150 & 300 mg/kg of P. farcta extract were 379.1± 36.4, 313.4± 35.7 and 216.5 ± 26.9 mg/dL respectively as compared to normal diabetics (588± 4.3 mg/dL, P<.0001). P. farcta reduced the blood glucose of STZ- induced diabetic rats in a dose

dependent manner, i.e. blood glucose levels at 28th days of treatment with 100mg/kg, 150mg/kg and 300 mg/kg of P. farcta treatment were 379.1±36.4 mg/dL, 313.4± 35.7 mg/dL and216.5± 26.9 mg/dL, respectively (Table 2). Overall, P. farcta treatment indicated almost 35% - 65% reduction in blood glucose compared to control STZ- induced diabetic rats (Table 2).

The blood glucose in P. farcta treated rats was significantly higher than that in normal control (92.7± 1.9 mg/dL) and glibenclamide treated rats (93± 7.3mg/dL) during the 28 days of study period which indicate that P. farcta seed extract reversed partially, but not completely, the blood glucose of STZ- induced diabetic rats (P<.0001, Table 2).

Table 2. The effects of P. farcta administration on blood glucose level (mg/dL) during 28 days of intervention period

Groups	1st week	2nd week	3rd week	4th week
Normal Control	94.5± 2.2	94.5± 1.9	90 ± 1.1	92.7± 1.9
Diabetic Control	567± 20.7[a]	592± 1.7[a]	598± 3.2[a]	588± 4.3[a]
D+PF (100mg/kg)	473.2±32.5[a,c]	455.4 ± 41.5[a,c]	387.3± 42.1[a,c]	379.1±36.4 [a, c]
D+PF (150mg/kg)	358.7 ± 20.7[a,c]	326.1 ± 32.1[a,c]	321.2 ± 18.6[a,c]	313.4± 35.7[a,c]
D+PF (300mg/kg)	288.7± 37.4 [a,c]	290.5 ± 59.3[a,c]	286.5± 36.9 [a,c]	216.5± 26.9[a,c]
D + GLI (10mg/kg)	129.8 ± 11.9[b,c]	112.2 ± 12.5[b,c]	104 ± 9.5[b,c]	93± 7.3[b,c]

Blood glucose level (mg/dL) was estimated by glucometer. Diabetes was induced by 55 mg/kg/i.p. STZ in citrate buffer (pH 4.5). Rats received P. farcta (100, 150 & 300 mg/kg/d) and glibenclamide (10 mg/kg) by intragastric gavage for 4 weeks after the induction of diabetes. Control rats received saline. All data have been expressed as mean ± SEM (n=10). D + PF group: diabetes plus P. farcta treatment, D + GLI: diabetes plus glibenclamide treatment.
a: P<0.0001 diabetic control and diabetic P. farcta treated compared with normal control group; b: P<0.05 glibenclamide 10 mg/kg compared to normal control group
c: P<0.001 P. farcta (100, 150 and 300 mg/kg) and glibenclamide (10 mg/kg) compared with diabetic control group

Glibenclamide , a standard oral antidiabetic drug , too, showed significant antihyperglycemic effect in STZ- induced diabetic rats; i.e. the administration of glibenclamide caused a significant decrease in blood glucose levels (93±7.3 mg/dL in 28th day) when compared with diabetic group (588± 4.3 mg/dL, P<.0001).

Discussion

Our study showed that blood glucose levels in the STZ-induced diabetic rats was significantly higher compared with the normal group. The methanolic extract of P. farcta seed caused a significant reduction in blood glucose in STZ-induced diabetic rats in a dose dependent manner as compared to control diabetic rats. However, our results showed that blood glucose in STZ- induced diabetic rats was significantly higher than glibenclamide treated rats. The body weight of STZ- induced diabetic rats progressively reduced and was significantly lower than that in all other experimental groups. Treatment of diabetic rats with P. farcta and glibenclamide improved body weight significantly, which indicates the prevention of muscle tissue damage due to hyperglycemic condition. The body weight reduction in STZ- induced diabetic rats was reversed partially, but not completely, following P. farcta treatment.

The blood glucose in STZ-induced diabetic rats decreased almost by 36% following the administration of 100 mg/kg P. Farcta seed extract and the highest decrease (about 65%) was observed for 300 mg/kg of P. farcta seed extract at 28th day. Although P. farcta seed extract did not reverse the blood glucose elevation in STZ- induced diabetic rats completely, its efficacy was almost similar to some approved antihyperglycemic agents such as acarbose which lowers postprandial glucose levels in diabetic patients by 30–50% (30-31).

Other studies reported the reversal of weight reduction in STZ- induced diabetic rats following glibenclamide or other antihyperglycemic agents which is in complete agreement with our results (32, 33).

The blood glucose levels following 28 days of treatment with P. farcta extract significantly reduced (35% - 65%) compared to diabetic rats ($P < 0.001$). Our results are in complete agreement with some previous reports about the antihyperglycemic properties of other Prosopis species in STZ- diabetic rats (18, 20, 34). Also, Campuzano-Bublitz et al (2016) showed that acute and chronic oral treatment of Prosopis ruscifolia hydroalcoholic extract was effective to reduce fasted blood glucose level, and the body weight gain was less after 28 days in alloxan- induced diabetic rats (19).

Sharma et al (2010) reported that treatment with crude ethanolic extract of bark of Prosopis cineraria (P. cineraria) for 45 days was associated with a significant reduction in blood glucose level, hepatic glycogen content elevation, maintenance of body weight and also the beneficial effects on lipid-profile parameters and reduction of the oxidative damage in the tissues of diabetic animals (20).

Antidiabetic drugs lower blood glucose through different mechanisms including increase of insulin release by binding to the sulfonyl urea receptors, their actions on the liver, muscle and adipose tissue, or through the inhibition of glucose absorption (31, 35).

The mechanism(s) underlying the beneficial effects of Prosopis species on blood glucose has not been determined yet, however, it could be mediated via the significant increased insulin levels, increased small beta-cells in the pancreata and improvement in insulin sensitivity, decrease of glucose absorption, or effects on insulin target organs such as liver, muscle and adipose tissues. (18,34). We suggest further investigation for determination of possible antidiabetic mechanism(s) of P. farcta extract. Also, it is necessary to evaluate the effects of its co-administration with other oral antihyperglycemic agents for possible drug interactions.

The chemical composition of Prosopis farcta has not been determined yet, but Lamarque et al (1994) reported that Prosopis species seeds contain a relatively large proportion of unsaturated fatty acids with linoleic and oleic acids as well as β-Stitosterol which could mediate the possible beneficial antihyperglycemic effects of P. farcta seed extract (36). Also, Astudillo et al (2000) reported that catchin, as the main phenolics consitutent of P alba, showed a strong free radical scavenging effects (37).

In summary, our results showed the antihyperglycemic activity of P. farcta; even though the exact mechanism(s) of the beneficial effects of P. farcta was not determined, it might be mediated via several different mechanisms including increase in insulin sensitivity, increase in number of beta-cells, decrease in insulin resistance and decrease in reactive oxygen species (ROS) production in pancreatic islets and the

consequent increase in the bioavailability of NO (18, 21, 34, 38).

Conclusion

In summary, our results showed that P. farcta seed extract has a significant dose dependent antihyperglycemic activity as well as a suppressive effect on weight reduction in STZ-induced diabetic rats. The underlying mechanism(s) was not determined and further researches are required to determine the chemical components of P. farcta and their effects on blood glucose in diabetic animals..

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Ethics approval

Ethnic's approval was obtained from the Animal Ethics Committee at Kerman University of Medical Sciences, Kerman, Iran (EC/KNRC/94-14).

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