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Ephedraceae as a Treatment for Hyperlipidemia and Hyperglycemia: An Experimental Study

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Abstract

The present study was carried out to evaluate the anti-diabetic and anti hyperlipidemic activity of *Ephedra* in streptozotocin induced diabetic rats. 40 male BALB/cArc Wistar rats aged eight to ten weeks (200 to 250 g) were randomly divided into 4 groups. No statistically significant difference was observed in body weight between the healthy group (A) and other groups before the trial. There was a significant differences between the diabetic and healthy groups. STZ injection was done in groups B and D, the mean blood glucose level increased notably in groups B and D on the 3rd day in comparison with other groups. The result shows that *Ephedra* extract can be used to control diabetes and absence of acute toxicity may offer a new hope to the diabetics in future.

Keywords: *Ephedra*; Streptozotocin; Serum glucose; Serum lipid

Introduction

Diabetes mellitus is characterized by hyperglycemia, together with biochemical alterations of glucose and lipid metabolism. The liver is an insulin dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected by diabetes. Diabetes mellitus is a chronic metabolic disease with life-threatening complications. Based on researches, the global estimation for diabetes in 2013 was 382 million people; this number is expected to rise to 592 million by 2035 [1]. Changes in human behavior and lifestyle over the last century have resulted in a dramatic increase in the incidence of diabetes worldwide. However, the main and effective treatment for diabetes mellitus is by administration of insulin and hypoglycemic agents. These compounds have numerous adverse effects such as an increase in fat reserves, shrinking fat tissue at the injection site and hypoglycemic shock. Plants that play a role in the treatment of diabetes are taken as food or medicines. Ephedraceac has been reported as one of the plants used traditionally to treat diabetes [2,3]. *Ephedra* is a genus of gymnosperm shrubs, the only genus in its family, Ephedraceae, and order, Ephedrales. Various species of *Ephedra* are widespread in many lands, native to southwestern North America, southern Europe, North Africa, as well as southwest and central Asia, northern China, and western South America [4]. *Ephedra strobilacea* is a species of *Ephedra* that is native to Iran and Central Asia (Afghanistan, Tajikistan, Turkmenistan, Uzbekistan) [5]. Plants of the genus *Ephedra*, including *E. sinica* have traditionally been used by indigenous people for a variety of medicinal purposes, including treatment of asthma, hay fever, and common cold [4]. The alkaloids ephedrine and pseudoephedrine are active constituents of *E. sinica* and other members of the genus. These compounds are sympathomimetics with stimulant and decongestant qualities and are chemically substituted amphetamines. *Ephedra* botanically belongs to the class, Chelamidosperm and family, Ephedraceae with more than 44 species in the world and 10 species in Iran. Diabetic patients traditionally used boiled *Ephedra* in the south of Fars province, Iran.

Today, there is a rising interest in the application of *Ephedra* in enhancing performance and appetite suppression [6]. Contrary to most of other herbal supplements, *Ephedra* products carry a remarkable health risk, which is aggravated by their misuse or abuse. According to the Food and Drug Administration (FDA) assessment in 2004, food supplements containing E-type alkaloids represent an unacceptable health risk, bearing in mind the conditions of use. Due to increasing knowledge about diabetes, there is the need to find effective compounds for the treatment of diabetes with fewer side effects. In recent decades, researchers have been attracted to use herbs for treatment in this area. Nowadays, the number of persons who tend to prefer traditional medicine has increased. Streptozotocin is the most well known diabetogenic chemicals in diabetes research and has been commonly used to induce diabetes in animal model. The aim of this study was to investigate the effect of *Ephedra* on the serum level of glucose and lipid in streptozotocin induced diabetic rat.

Materials and Methods

Study design: The study was initiated after obtaining approval from the Research and Ethics committee of Jahrom University of Medical Sciences. This experimental study was carried out on 40 male Wistar rats.

Animals: All the experiments were carried out with 40 male BALB/cArc Wistar rats aged eight to ten weeks (200 to 250 g), purchased from the Central Animal House, Jahrom University of Medical Sciences (Jahrom, Iran). They were approved by the ethical committee, Jahrom University of Medical Sciences. The animals were acclimatized in polypropylene cages and provided with water and standard pellet diet. All the animals were placed at a temperature of 24°C to 22°C, 12 h of darkness and 12 h of light photoperiod in groups of 3 to 4 animals per cage. A total of 40 rats were randomly divided into 4 groups: A, B, C and D. Diabetes mellitus was induced in rats of groups B and D by single intraperitoneal injection of streptozotocin (STZ). A standard diet of saline was administered to the rats by gavage.

Group A: Rats in the healthy control group were fed a standard diet within 30 days of the experiment.

Group B: Rats in the diabetic control group were fed a standard diet.

Group C: Herbal extracts were administered to rats in the healthy group, 5 ml per kg *Ephedra* every morning.

Group D: Diabetic rats treated with herbal extract, received 5 ml per kg *Ephedra* every morning.

Plant material: The basic plant material of *Ephedra* sample (batch NO 12396; Fars Research Center for Agriculture and Natural Resources). Hundred gram of *Ephedra* were extracted with 1,500 ml of water by the method of continuous hot extraction at 60°C for six hours and evaporated. The residual extract was dissolved in water and used in the study.

Induction of experimental diabetes: A freshly prepared solution of streptozotocin (50 mg/kg i.p) in 0.5 M citrate buffer, pH 4.5 was injected intraperitoneally in a volume of 1 ml/kg. In cases of severe lethargy due to low blood sugar, glucose solution (5%) was administered to animals through a gavage tube in the first 12 h. After 12 h, glucose injection decreased as a result of the diminishing effect of streptozotocin on the beta cells of the pancreas.

After 96 h of streptozotocin administration, rats with moderate diabetes having glycosuria and hyperglycemia (that is, with a blood glucose of 200 to 300 mg/dl) were taken for the experiment.

Experimental procedure: Fasting blood glucose was estimated by the O-toluidine method [2] Plasma insulin level was assayed by Enzyme Linked Immunosorbent Assay (ELISA) kit, using human insulin as standard. For each sample: TC, TG, HDL, and LDL were directly measured in duplicate using Technicon® Technicon RA-XT, USA).

Statistical analysis: All values were expressed as the mean obtained from a number of experiments (n). Data from all the tables of normal animals, diabetic control animals, reference drug treated and untreated animals were compared by ANOVA followed by Duncan's Multiple Range Test (DMRT). All statistical tests were performed using SPSS 16.0 software. $P<0.05$ was considered significant.

Results

Mean weight:

A comparison of the effects of plant extracts on the mean weight during the study is shown in **Table 1**. No statistically significant difference was observed in body weight between the healthy group (A) and other groups before the trial (p value>0.05). There was a significant differences between the diabetic and healthy groups (p value<0.05).

In groups C and D, the mean weight was significantly lower after 30 days of trial (p value<0.05).

Table 1: Comparison of the mean weight (gr) (Mean ± Sd) (g) in different days of the trial period.

Weight after 30 days	Initial weight	Days of trial
		Group
246/60 ± 17/49	250/90 ± 18/46	A
240/30 ± 25/31	249/90 ± 21/06	B
236/10 ± 13/13	251/03 ± 13/25	C
241/30 ± 9/97	255/80 ± 10/39	D

Glucose level:

Table 2 shows the comparison of glucose level in different days of trial. There was no significant difference between the mean blood glucose levels in diabetic and healthy rats before the testing began in the different groups (p-value>0.05). STZ injection was done in groups B and D, the mean blood glucose level increased notably in groups B and D on the 3rd day in comparison with other groups (p-value<0.05).

There was significant difference in mean blood glucose level between group A and other groups on the fifteenth day after the treatment (p-value<0.05). In addition, the same change was observed in groups C and D which received *Ephedra*. On the 30th day, the mean blood glucose in the *Ephedra* extract-treated diabetic group (D) was markedly reduced in comparison with other groups (p-value<0.05).

Table 2: comparison of mean blood glucose level in different days of trial period.

Groups	Initial	After 3 days	After 15 days	After 30 days
A	89.7 ± 9.79	88.9 ± 8.99	87.8 ± 8.77	86.5 ± 8.57
B	92.5 ± 8.98	272.6 ± 8.44	280.7 ± 6.99	285.7 ± 8.99
C	91.6 ± 9.43	92.2 ± 11.23	82.4 ± 11.38	80.8 ± 9.88

D	90.00 ± 8.49	259.8 ± 12.12	159.3 ± 19.88	100.6 ± 14.17

Serum lipids level:

Table 3 shows the levels of total cholesterol, triglycerides, LDL-c, and HDL-c as compared with the normal range of serum lipids in 8 to 10 week-old rats.

The administration of *Ephedra* resulted in a significant decrease in the level of TG (p-value<0.05), LDL (p-value<0.05) and total cholesterol (p-value<0.05) and increase in the level of HDL (p-value<0.05) when compared with groups A and B without *Ephedra* administration.

Table 3: Total cholesterol, triglycerides, LDL-c, HDL-c level in all groups at the end of trial compared with normal range.

	Triglyceride (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Normal range	50-100	80-160	50-70	11-80
A before	64.4 ± 6.77	110.7 ± 7.99	51.6 ± 6.71	33.5 ± 7.6
A after	60.7 ± 14.72	107.8 ± 11.43	58.5 ± 4.67	31.8 ± 6.8
B before	67.7 ± 13.7	71.8 ± 13.9	52.4 ± 8.3	38.9 ± 5.9
B after	110.6 ± 13.6	113.8 ± 15.7	49.7 ± 3.9	40.3 ± 5.9
C before	68.9 ± 8.9	100.9 ± 8.9	54.9 ± 9.8	35.9 ± 7.8
C after	50.4 ± 7.8	75.9 ± 9.8	63.9 ± 8.7	23.9 ± 3.9
D before	66.9 ± 8.7	110.1 ± 9.0	53.9 ± 8.4	33.8 ± 8.9
D after	59.9 ± 9.8	90.9 ± 9.8	68.9 ± 8.2	21.9 ± 8.8

Discussion

In an effort to elucidate the effect of *Ephedra* on blood glucose, a case-control experimental study was performed on 40 rats, which were randomly divided into 4 groups, A, B, C and D. In addition, lipid peroxidation is one of the characteristic features of chronic diabetes. We also decided to investigate cholesterol and triglyceride level in diabetic rats. Currently, there are various hypoglycemic drugs available like sulfonylureas and metformin; however, each has numerous side effects. Therefore, it is necessary to develop a natural hypoglycemic agent and also antihyperlipidemic agent.

In the present study, blood glucose level increased three days after injecting rats with streptozotocin. The administration of *Ephedra* extract to treated diabetic rats, reduced blood glucose and serum lipid on the fifteenth day of trial. *Ephedra* is beneficial and effective, since it lowers TG level, LDL-c level and blood glucose in the diabetic group as compared to healthy groups with standard diet. Similar effect of another plant types in induced diabetic rats were reported [7-9]. As a result of the side effects of hypoglycemic agent, the demand for natural products has increased, due to the high cost and poor access to conventional medical therapy for most rural populations, especially in developing countries. Traditional herbal medicine is used to improve diabetic complications [10].

Although many studies have been conducted on the anti-diabetic effects of various plants in the world, rare study has been done in this case. Recently, a study was done on the effect of *Ephedra* on serum lipid levels in rats with the same result as the present study [11]. The results showed that the use of *Ephedra* extract had hypoglycemic effects at the end of the treatment. Also, this extract could reduce cholesterol levels, triglycerides, LDL-c, and increase HDL-C levels at the end of the 30th day.

Conclusion

The *Ephedra* extracts did not show a consistent effect on normal blood sugar levels but it effectively changed the blood sugar level and serum lipid level in STZ induced diabetic rats. These extracts also showed improvement in parameters like body weight and lipid profile as well as its anti-hyperglycemic effect. The result shows that *Ephedra* extract can be used to control diabetes and hyperlipidemia and absence of acute toxicity may offer a new hope to the diabetics in future. Further investigation is necessary to determine the exact phytoconstituents (s) responsible for anti-hyperglycemic and anti-hyperlipidemic effect.

Conflict of Interests

The authors declare that they have no competing interests.

Author's contribution: MS supervisor, participated in the design of the study. MH wrote the paper, revised manuscript. GJ conceived and designed the experiment. HT performed the experiment. All authors read and approved the final manuscript.

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