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Possible Antidiabetic Effect of peganum Harmala on Streptozocine-Induced Mouse

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Abstract: Peganum harmala is a Mediterranean plant with pharmaceutical and toxical properties. To investigate the antidiabetic activity of this plant, hydroalcoholic extract were used. 30 mice separated in 6 groups, 1 group used as control and 5 groups induced by streptozotocin. The blank group has been received normal saline and the other groups treated by IP injection, oral and rectal prescription of P.h. The used doses for IP injection were 6, 15 and 30 mg/Kg, for oral administration were 90, 180 and 270 mg/Kg and for rectal application were 15 and 30 mg/Kg. 6 mg/Kg of IP injection and 30 mg/Kg of rectal application were completely significant, in addition, 15 mg/Kg of IP injection, 270 mg/Kg of oral administration and 15 mg/Kg of rectal application were clinically effective. According to the results Pegnaum harmala has anti diabetic activity but a lot of studies should be conducted in order to find the optimum dose and best way of prescription and minimize the possible pathological effects.

Key words: Diabet · Peganum harmala · Glucose · Hypoglycemic

INTRODUCTION

Diabet is one of the oldest known disease which 1552 BC it is described as a high urinary sickness by an Egyptian doctor. Eritios, a Greek doctor described it by permanent thirsty and weight loss beside high urinate 30 - 90 AC and he named this disease Diabet. Diabet is a disability of glucose metabolism which is the result of disorderly in insulin production or/and response to it and consequently increase in the blood glucose rate. The high level of blood glucose harms the body organs like eye, kidney, skin and vessels. There are two types of diabet: 1) type one which is an autoimmune disease that immune system attacks the ß cells of longerhans islets which produce insulin, so insulin levels drops and it cause high blood glucose level. This types inclusions 5 to 10 percent of USA diabetics' people. 2) type two, in this type, there is enough insulin in the blood but body is unable to pick them up (target cells) this condition called insulin resistance and it inclusions 90 to 95 percent of diabetic people in the USA. The first type mostly is seen in the young people but the second one is seen in the olders. There is another type of diabet which occurs in the pregnancy period.

Peganum Harmala has been classified in Zygophylaceae family, this plant originates from middle East and north Africa [1]. P.h has been used as a traditional herb in these regions. There are a lot of usages mentioned: antibacterial, antiviral, antioxidant, hypothermic, anticancer and etc, even it has been recognized as a toxic herb which has emmenagogue and abortifacient agent [1, 2]. One of main pharmaceutical substances in this plant is Alkaloids which inclusions at least 4% of it; harmine, harmaline, peganine and harmalol are the main alkaloids in this plant [3].

In this study, we tried to prove the anti diabetic activity of this plant by its extract in three different ways; IP injection, Oral and Rectal prescription in 6 various dosages. The study performed on Streptozocine induced mice in order to turning them into diabetic form.

MATERIALS AND METHODS

Extract Preparation: Peganum harmala were collected from West Azerbaijan province, Iran and then they identified by Agricultural department of Urmia University. The powdered seeds placed in plates with Ethanol and they left in room temperature (25°c) for

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24 hours (1 kg/4 lit). This process repeated four times. Then the ethanol evaporated by rotavaporator in vacuum under 50°c to concentrate the extract, then the Hydroalcoholic extract collected.

Animal: In this study, 30 mice from Albino strain were used, male mice were chosen. The weights of mice were between 13.22 and 29.8 gr and the average weight was 24±2 gr. The mice separated in 6 groups and each group contained 5 mice. There were one group as a control group and one blank group and 4 treatment groups (A, B, C and D).

First, all the groups were kept in animal lab of veterinary college of Urmia university in standard condition – 12 hours light cycle, 20°c temperature, enough food and water – for 24 hours.

Making Diabetic: In second stage, they were kept in the same condition but without any food for 24 hours (water was served). Then blood glucose level was measured by glucometer set. Then they were injected intraperitonealy by 50 mg/kg body weight of Streptozocine. 6 hours after injection glucose level was measured and the measurement repeated every 6 hours for 3 days, after 3 days the mice were diabetic. The glucometer set was German made from *Converjent* (*Elegance* brand) factory.

Treatment: Every 6 hours the blood glucose level of all groups were measured and it continued for three days. Control group did not received any thing, but 3 mice in the blank group were received 6, 15 and 30 mg/Kg normal saline respectively and the other two mice were received 90 and180 mg/ Kg orally.

3 mice in A group received 6 mg/Kg of hydroalcoholic extract of Peganum Harmala intraperitonealy and the other two received 90 mg/Kg of P.h orally. In the B group, 3 mice received 15 mg/Kg by IP injection and the 2 rest received 180 mg/Kg orally of P.h. 30 mg/Kg were injected to 3 mice in the C group and 270 mg/Kg were prescribed orally to the 2 others. D group received 15, 15, 30, 30 and 30 mg/Kg P.h by rectal prescription.

Statistical Analysis: After the blood level of all groups were collected, they were compared and analyzed by Statistical Package for Social Sciences (SPSS software, 18th version). *Tukey, Dunnett* and *Benferroni* tests were used for statistical comparison. The comparison made between groups and between different types of prescriptions. $P < 0.05$ were considered as significant difference.

RESULTS

For IP administrations, the 6 mg/Kg of P.h were completely significant in contrast of IP administrated of blank group, the 15 mg/Kg of P.h was not significant but it was clinically effective and surprisingly the highest dose of IP administration (30 mg/Kg) was not significant at all.

Statistically, none of orally administrated groups were significant, but only the 270 mg/Kg was clinically effective.

In rectal application, the dose 15 mg/Kg of P.h was clinically effective but it was not significant, the dose 30 mg/Kg statistically was completely significant (Table 1).

DISCUSSION

In present study, we tried to find if the Peganum Harmala has Anti diabetic activity or not. According to the results, it seems this plant can lower the blood glucose level in streptozocin-induced mice. But in this study, the oral administration were the most ineffective prescription, which only 270 mg/Kg showed clinical effect that was not statistically significant. This is in contrast of *Chaturvedi et al* work in 2008 [4]. Their study shows that P.h can lower the blood glucose level in both diabetic rats and normoglycemic ones by oral administration. They used 150 and 250 mg/Kg in their studies and both the doses showed significant effect which the 250 mg/Kg was even more effective. Although in our study we used three

Table 1: Peganum harmala effect on blood glucose level in streptozotocin-induced mice

Group	Blood Glucose Level
Control	132.80±5.96
Blank (IP)	298.44±19.61
Blank (O)	296.37±17.34
A (IP)	191.30±17.34**
A (O)	337.04±19.65
B (IP)	208.85±13.02*
B (O)	307.04±16.82
C (IP)	290.27±18.41
C (O)	211.04±15.91*
D (R / 15 mg/Kg)	214.33±18.03*
D (R / 30 mg/Kg)	197.02±14.26**

The data are mean of 12 blood glucose levels (per 6 h for 3 d).
Values are Mean ± SEM, ** $P < 0.05$, * clinically effective, n = 5. O = Oral, R = Rectal.

different doses and one of them was higher than 250 mg/Kg, there was no significant anti diabetic activity in oral prescription. If we assume the functional substance or substances of P.h is/are proteinic, it is sensible that it may have broken through the digestive system and it lose its functional activity.

In IP injection the 6 mg/Kg was significant and effective. As the main alkaloid in P.h is Harmine, this can be expected. *Sharifi et al* proved the blood pressure reduction activity of harmine in 2010 [5]. They studied the harmine effect on NO production and the activity of ACE enzyme by IP injection. The ACE enzyme activity increases in the diabetic person and it lessens the vessels diameter so blood pressure increases in diabetic person and it has been shown that in diabetic person the NO blood level falls so this is another cause for blood pressure increase. *Sharifi et al* found that Harmin lowers the ACE activity and increase the NO blood level. But the weird thing which has been seen in our study is that by increasing the dose of P.h extract it lost its hypoglymic activity instead of intensifying, which it only showed clinical activity in 15 mg/Kg and in 30 mg/Kg it lost both its clinical and statistical efficiency.

Zakir Hussain et al reported [6] that Peganum harmala has no insulin secretion activity in 2004, so the possible hypoglycemic activity is not related to pancreas and maybe it effects by using or/and absorption of glucose. Studies should be conducted to find out the mechanism of action.

Also, as there are a lot of mentioned toxicological activities for P.h, it should be examined carefully to lessen the possible pathological effects. *Hamid reza Monsef et al* reported [7] P.h as an strong antinociceptive in 2007 while, *Zuhair Muhi-eldeen et al* showed [3] that P.h is responsible for a great inflammatory reaction in the site of IM injection, also they proved the convulsion and tremors activity in P.h. *Mohamed Bnouham et al* mentioned a few toxic and pharmacological properties for P.h: hallucinogenic, nervous diseases, asthenia, bowels diseases, emmenagogue, antirheumatic, antidiarrheal, antihelmintic, antispasmodic, antimicrobial, cicatrizing.

There should be a lot of investigations on P.h to find the optimum doses and best prescription for this plant, also the pathological activities should be considered and studied.

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