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OBM Integrative and Complementary Medicine

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Research Article

Preclinical Investigation of the Acute Effects of *Trigonella foenum-graecum* Seed Powder on Blood Glucose in Normal and Alloxan-Induced Diabetic Rabbits

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Academic Editor: Gerhard Litscher

Special Issue: Herbal Medicines for the Treatment of Metabolic Syndrome

OBM Integrative and Complementary Medicine
2020, volume 5, issue 3
doi:10.21926/obm.icm.2003036

Received: May 03, 2020
Accepted: August 3, 2020
Published: August 6, 2020

Abstract

To investigate the blood glucose lowering effect of the seed powder of *T. foenum-graecum* Linn (Papilionaceae) in normal and alloxan-induced diabetic rabbits. The blood glucose lowering effect of the seed powder was determined in normal and alloxan-induced (100 mg/kg, i.v.) diabetic rabbits, after oral administration of doses of 50, 100 and 150 mg/kg body weight. Blood samples were collected from the marginal ear vein before and also at 4, 6, 8, 10, 12, 16, 18, 20 and 24 h after drug administration and blood glucose was analysed by Nelson-Somogyi's method using a visible spectrophotometer. The data was compared statistically by using Student's t-test. The seed powder of *T. foenum-graecum* produced a

dose-dependent reduction in blood glucose of both normal and diabetic rabbits and comparable with that of standard drug, glibenclamide. The results indicate a prolonged action in reduction of blood glucose by *T. foenum-graecum* and the mode of action of the active compound (s) of *T. foenum-graecum* is probably mediated through enhanced secretion of insulin from the β-cells of Langerhans or through extrapancreatic mechanism. The present study clearly indicated a significant anti-diabetic activity with the seed powder of *T. foenum-graecum* and supported the traditional usage of the seed powder by Ayurvedic physicians for the control of diabetes.

Keywords
Diabetes; alloxan; beta-cells; rabbit; Trigonella foenum-graecum

1. Introduction

Diabetes mellitus is a metabolic disease that emerges as one of the leading diseases all over the World. Global statistics on diabetes indicate that approximately 50% of diabetic population live in Asia. Recent estimates indicate that approximately 366 million people are affected with diabetes, with 90% suffering from *T2D* and by the year 2030, this number is expected to increase to 552 million [1]. Increased consumption of high-calorie fatty food associated with decreased physical activity also contributes to the pandemic of *T2D* [2]. The current therapeutic options such as diet modification, oral hypoglycaemic agents (OHA) and insulin treatment have their own limitations in treating *T2D*. Ayurveda, the indigenous Indian system of medicine, has offered many herbal medicines for the treatment of diabetes or 'madhumeha'. Although, some of these traditional herbal medicines have been experimentally evaluated, search for new anti-diabetic drugs continues. [3-9].

Trigonella foenum-graecum Linn (Papilionaceae) commonly referred as fenugreek is a herb that belongs to the family, *Papilionaceae* and indigenous to the Indian sub-continent and Eastern Mediterranean [10]. In Ayurveda, the seeds and leaves of *T. foenum-graecum* have been regarded as carminative, tonic, aphrodisiac and used to treat diabetes and cardiovascular disorders [11-13]. Its dried ripe seeds are known as Trigonella seeds or fenugreek seeds. The seeds possess pungent aromatic properties [14] and often used as a spice in food preparations to enhance its flavor [15], while the leaves are widely consumed as a leafy vegetable in India [16]. A converging point of evidence from earlier investigations on the seed extract and leaf extracts of *T. foenum-graecum* revealed significant anti-diabetic effects in both animals [17-22] and humans [16, 23-25]. The pharmacological effects of *T. foenum-graecum* are attributed to a range of bioactive compounds such as polyphenols, steroids, lipids, alkaloids, saponins, flavonoids, hydrocarbons, carbohydrates, galactomannan fiber, and amino acids. More recently, Sharma and colleagues have reported that the chronic administration of fenugreek seed extract showed protective effect against diabetes induced oxidative DNA damage in alloxan-induced diabetic rats [26]. Furthermore, it has also been demonstrated that fenugreek seed extract, protects brain tissue by mitigating oxidative stress induced by alloxan-exposed diabetic rats [27]. Diosgenin saponin is considered the most bioactive

substance of *T. foenum-graecum* seeds and found to have anti-oxidative effects and plays a pivotal role in improving the diabetic condition in several *in vivo* and *in vitro* models [28].

However, some clinical trials did not show any benefit from fenugreek [29, 30]. The seeds of *T. foenum-graecum* are also known to possess antiulcer [31], hepatoprotective [32] and hypocholesterolaemic effects [33, 34]. Nevertheless, the seed powder of *T. foenum-graecum* is being prescribed by Ayurvedic physicians for the treatment of diabetes [35]. However, there are only meager reports on the direct usage of the seed powder. Therefore, the present study was aimed to study the influence of the seed powder of *T. foenum-graecum* on the fasting blood glucose in normal and alloxan diabetic rabbits.

2. Materials and Methods

2.1 Plant Material

The seeds of *T. foenum-graecum* were bought at the local market, botanically authenticated and a voucher specimen was preserved for future reference. Seeds were cleaned, dried for 4 hours and then grounded to fine powder.

2.2 Chemicals Used

Glibenclamide was a generous gift sample by Hoechst Pharmaceuticals, Mumbai whereas alloxan was purchased from Sigma-Aldrich, St. Louis, MO, USA. All other reagents used were of analytical grade and purchased from Loba-Chemie, Mumbai, India.

2.3 Animals

A total of fifty (50) adult albino rabbits (B.N. Ghosh & Co., Kolkata, India) weighing 1.5-2 kg of both sexes were chosen for investigation. The rabbits were maintained in a well-ventilated animal house with an ambient temperature (24 ± 2 ºC) and relative humidity (50-60%) with 12-h light and dark cycle. The rabbits were acclimatized to the laboratory environment for 1 week before the start of the experiments and fed with standard diet and water *ad libitum*. They were fasted for overnight, allowing only access to water, and deprived of both food and water during the 24-hour monitoring cycle of the experiment after treatment with either the drug or distilled water (control) to reduce plasma volume changes. For each treatment the same procedure has been followed. The local Institutional Animal Ethics Committee has approved the use and handling of the animals in the experimental protocol (Regd. No. 516/01/A/CPCSEA) following the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

2.4 Experimental Design and Treatments

The rabbits were matched in weight and split into 10 groups, each consisting of five rabbits. Groups I, II and III were respectively given the seed powder of *T. foenum-graecum* (suspended in distilled water) by oral gavage at doses of 50, 100 and 150 mg/kg body weight. Glibenclamide was given by oral gavage in Group IV (positive control) at a dose of 40 µg/kg body weight in a total volume of 3 mL for each rabbit. Group V used as normal control and administered with 3 mL of

distilled water. Diabetes was induced in Groups VI to X by injecting 100 mg/kg of alloxan into the marginal ear vein after determining the baseline blood glucose levels. Two weeks post-alloxan treatment when stable diabetes was achieved, rabbits with blood glucose levels above 300 mg/dl were selected for the experiments. Animals in groups VI, VII & VIII, received by oral gavage, the seed powder of *T. foenum-graecum* at doses of 50, 100 and 150 mg/kg respectively. Group IX (positive control) received glibenclamide by oral gavage at a dose of 40 μg/kg while group X served as diabetic control.

2.5 Blood Collection and Analytical Procedure

Approximately 0.3 mL of blood samples were drawn from the marginal ear vein of rabbits before and also at 4, 6, 8, 10, 12, 16, 18, 20 & 24 h after treatment. The samples were collected in glass vials that contained a small amount of an anti-coagulant mixture of potassium oxalate and sodium fluoride. Separation of plasma was done by centrifuging at 2000 rpm and stored at -20°C until analysis for glucose by Nelson-Somogyi's method [36, 37] using a visible spectrophotometer.

2.6 Data and Statistical Analysis

Data was presented as a means ± SEM. To examine the quantitative differences among the experimental groups, the respective data were subjected to analysis of variance (ANOVA) using GraphPad Prism-7.03 (GraphPad Software Inc., California, CA) statistical programme. Post hoc comparisons were made using Student's unpaired *t*-test. In all tests, $p<0.05$ value was used as the criterion for statistical significance.

3. Results

3.1 T. foenum-graecum Lowered Blood Glucose in Normal Rabbits

In normal rabbits the seed powder of *T. foenum-graecum* produced dose-dependent hypoglycemia. A maximum reduction in blood glucose of 9.4% (105.8 *vs* 95.4; 6 h), 26.9% (106.4 *vs* 77.8; 8 h, $p<0.01$), and 39.2% (108.2 *vs* 65.8; 10 h, $p<0.001$) with doses of 50, 100 and 150 mg/kg body weight respectively (Table 1) and the glucose reduction tendency continued up to 24 hours with 100 and 150 mg/kg doses. Glibenclamide (40 μg/kg) produced a significant ($p<0.01$) reduction of blood glucose relative with control (31.9%, 8 h).

Table 1 Effect of *T. foenum-graecum* seed powder on blood glucose levels after oral administration in normal rabbits.

Group (n=5)	Dose	Blood glucose levels (mg/dL)								
		4	**6**	**8**	**10**	**12**	**16**	**18**	**20**	**24 (h)**
Control	---	107.2 ± 5.3	105.8 ± 6.5	106.4 ± 6.2	108.2 ± 5.1	103.5 ± 6.3	106.1 ± 4.3	105.4 ± 9.9	100.9 ± 5.5	104.8± 4.7
T. foenum-graecum	50 mg/kg	100.3 ± 3.5	95.4 ± 4.5	98.0 ± 5.7	101.6 ± 4.8	103.8 ± 4.6	105.1 ± 3.3	101.6 ± 4.4	98.1 ± 6.3	101.0 ± 6.7
T. foenum-graecum	100 mg/kg	90.2 ± 5.8**	82.3 ± 6.4**	77.8 ± 5.9**	83.4± 6.1**	79.0 ± 6.8**	84.7 ± 5.8***	84.8 ± 6.5	82.2 ± 7.6*	88.9 ± 5.9**
T. foenum-graecum	150 mg/kg	76.5 ± 6.9***	67.6± 6.9***	67.5 ± 6.5***	65.8 ± 5.7***	73.4 ± 4.1**	75.2± 6.1***	88.2 ± 6.4	87.2 ± 8.7*	92.9 ± 6.6*
Glibenclamide	40 μg/kg	79.9 ± 4.1**	74.4 ± 4.9**	72.5 ± 4.8**	76.0 ± 5.2**	74.2 ± 4.7**	81.6 ± 3.6**	82.3 ± 3.6	80.8 ± 7.4	86.8 ± 4.7

Values are the mean blood glucose (± S.E.M.) of five animals.
Significant difference from control at corresponding intervals: *p<0.05, **p<0.01, ***p<0.001

Table 2 Effect of *T. foenum-graecum* seed powder on blood glucose levels after oral administration in alloxan-induced diabetic rabbits.

Group (n=5)	Dose	Blood glucose levels (mg/dL)								
		4	**6**	**8**	**10**	**12**	**16**	**18**	**20**	**24 (h)**
Control	---	324.7 ± 9.3	316.5 ± 11.2	312.8 ± 10.4	315.9 ± 10.9	310.1 ± 12.2	310.6 ± 10.5	305.4 ± 11.9	307.5 ± 10.1	312.5 ± 10.3
T. foenum-graecum	50 mg/kg	293.8 ± 8.3***	277.2 ± 10.7***	277.9 ± 12.7***	292.5 ± 9.8***	291.3 ± 9.9***	297.6 ± 10.3**	273.5 ± 11.4**	300.1 ± 10.7**	308.0 ± 11.3
T. foenum-graecum	100 mg/kg	265.5 ± 9.6**	235.5 ± 12.2***	211.0 ± 11.8***	232.3 ± 12.7***	247.5 ± 8.4***	262.8 ± 12.8***	268.5 ± 12.2**	278.6 ± 11.9*	295.5 ± 12.3
T. foenum-graecum	150 mg/kg	258.1 ± 10.8**	226.3 ± 9.6***	173.5 ± 12.2***	206.6 ± 14.9***	223.0 ± 13.2***	248.3 ± 15.6**	270.1 ± 13.2**	284.4 ± 12.4**	297.3 ± 13.2
Glibenclamide	40 µg/kg	253.0 ± 10.6***	226.5 ± 10.5***	205.8 ± 14.6***	225.2 ± 16.5**	233.3 ± 15.7**	234.5 ± 14.1***	240.9 ± 15.6**	254.0 ± 19.8*	266.9 ± 15.9*

Values are the mean blood glucose (± S.E.M.) of five animals.

Significant difference from control at corresponding intervals: *p<0.05, **p<0.01, ***p<0.001

3.2 T. foenum-graecum Lowered Blood Glucose in Diabetic Rabbits

The diabetic rabbits treated with *T. foenum-graecum* also displayed a dose-dependent decrease in blood glucose. However, a higher reduction of blood glucose was seen in the diabetic rabbits compared with the normal rabbits. A significant reduction ($p<0.001$) of blood glucose of 12.4% (316.5 *vs* 277.2; 6 h), 32.5% (312.8 *vs* 211.0; 8 h) and 44.6% (312.8 *vs* 173.5; 8 h) respectively was seen with *T. foenum-graecum* at doses of 50, 100 and 150 mg/kg body weight (Table 2). Although less significant, the glucose lowering tendency continued up to 20 hours with all the doses of *T. foenum-graecum*. Glibenclamide (40 μg/kg) resulted in a significant reduction ($p<0.001$) in blood glucose at 8 h (34.1%) compared to diabetic control.

4. Discussion

Diabetes mellitus is probably the biggest rising metabolic condition in the world, and as understanding of this complex condition is advanced, there is an increasing need for more effective treatment [9, 36]. Traditional plant medicinal products are used for a variety of diabetic complications around the world. Studying such medicines could give a natural key for opening the potential pharmacy of a diabetologist. The seeds of *T. foenum-graecum* are commonly used for managing diabetes in India. For this reason, the seed powder of *T. foenum-graecum* was tested, and the results verified the conventional indications as well. The findings of our experiments on rabbits are also substantiated by earlier investigations [20, 22, 37, 38]. In addition, our findings also suggest a prolonged period of antidiabetic activity that could be attributed to several sites of activity possessed by the active principles of T. foenum-graecum.

Earlier, it was reported that the seed powder of *T. foenum-graecum* lowered blood glucose in normal and streptozotocin-induced diabetic rats [37]. Our present study in rabbit model also substantiates the previous results observed in rats. Herefele and colleagues isolated galactomannan and 4-hydroxy isoleusine, an insulin releasing substance from the seeds that appears to be responsible for the hypoglycaemic effect of *T. foenum-graecum* [39]. Additionally, another potential action mechanism of *T. foenum-graecum* is an effect on the digestion of intestinal carbohydrate, as shown by the strong inhibitory effect on the digestive enzymes [40, 41].

Alloxan, a beta-cytotoxin induces significant death of pancreatic β-cells leading to decreased synthesis and release of insulin [42-44]. Sulphonylureas are well known to cause hypoglycaemia by increasing insulin secretion from the pancreas [45, 46] and these compounds are active in mild diabetes induced by alloxan while they are inactive in intense alloxan diabetes (nearly all β-cells were destroyed). Since our findings have shown that glibenclamide has decreased blood glucose levels in hyperglycemic animals, diabetes status is not severe. Alloxan-treated animals receiving the seed powder of *T. foenum-graecum* showed rapid normalisation of blood glucose levels relative to control and this may be due to the fact that certain β-cells still survive to function on *T. foenum-graecum* to exert its insulin releasing effect. In addition, hypoglycaemia was produced in normal animals by oral administration of *T. foenum-graecum* in the same way as sulphonylureas. This indicates that the mode of action of the active ingredients of *T. foenum-graecum* is possibly mediated by an increased insulin secretion, like sulphonylureas. Nevertheless, the likelihood increased tissue glucose utilization by *T. foenum-graecum* cannot be ruled out. It is speculated

that one or more of the previously isolated bioactive compounds of *T. foenum-graecum* could be responsible for the observed acute lowering of blood glucose. Further work on fractionation, purification, identification of active principle(s) and detailed mechanistic evaluation is obviously required on the seeds of *T. foenum-graecum*.

5. Conclusion

Our research clearly showed a major anti-diabetic activity with *T. foenum-graecum* seed powder, and supports the traditional use of seed powder for diabetes control. This can also help to avoid diabetic complications and act as a strong adjuvant in the new anti-diabetic medication armamentarium.

Author Contributions

SN, RA, HG and VI made substantial contributions to conception design and conduction of research. SN and RA designed the study and executed the project. Data collection, analysis, graphical representation and interpretation were done by HG and SN. Article was written by HG and VI. Critical revision of the article was done by SN and RA. Critical statistical analysis was done by HG and VI. All Authors read and approved the final manuscripts.

Funding

The financial assistance provided by University Grants Commission, New Delhi, India to SN is greatly acknowledged.

Competing Interests

The authors declare that they have no conflicts of interest concerning this article.

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