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Research Article

Evaluation Of The Antidiabetic Potential Of Trigonella Foenum-Graecum L. Seed Extract In Streptozotocin-Induced Diabetic Rats.

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Abstract:
The current study's goal was to investigate the antidiabetic effects of *Trigonella foenum-graecum* seed extract using the streptozotocin-induced rat (STZ) model of diabetes mellitus (DM) in rats. Rats were given streptozotocin (STZ) intraperitoneally (I.P.) at a dose of 50 mg/kg. Use the serum glucose test to confirm that you have diabetes mellitus. The effects of oral *Trigonella foenum-graecum* seed extract (250 mg/kg b.w. and 500 mg/kg b.w.) and the standard drug Glibenclamide (0.5 mg/kg b.w. oral) were evaluated both acutely and subacutely in different sets of STZ-induced rats. Serum glucose levels were measured at 0, 1, 3, 5, and 7 hours in the acute hypoglycemia research, and at 0, 7, and 14 days in the subacute hypoglycemic phase; at 0, 1, 3, 5, and 7 days in the acute antidiabetic trial; and at 0, 1, 3, 5, and 7 days in the subacute antidiabetic research. The administration of glibenclamide (0.5 mg/kg b.w. oral) and *Trigonella foenum-graecum* (TFG) seed extracts (250 mg/kg b.w. and 500 mg/kg b.w. oral) resulted in a significant decrease in serum glucose levels, while the hydro-alcoholic extract of *Trigonella foenum-graecum* seeds extracts effectively reduced serum cholesterol, triglycerides, and LDL levels while increasing HDL levels after a 7-day treatment period.

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Introduction:
Diabetes mellitus (DM) is a metabolic disease that affects the body's ability to produce or use insulin, leading to persistently high blood sugar levels. Type 2 diabetes mellitus (T2DM) is 90% of all cases of DM, while type 1 diabetes mellitus (T1DM), which results in a total lack of insulin, is caused by the autoimmune death of pancreatic β-cells (1). Diabetes is currently the 16th leading cause of death worldwide and is rapidly on the rise, with an estimated 300 million or more people affected by 2025, up from the current 150 million (2). However, micro- and macrovascular issues associated with chronic diabetes lead to nephropathy, retinopathy, neuropathy, cardiovascular diseases, peripheral artery abnormalities, and stroke (3).

Meglitinides, thiazolidinediones, sulfonylureas, biguanides, D phenylalanine derivatives, and α-glucosidase inhibitors are used in addition to insulin to treat diabetes mellitus by lowering chronic hyperglycemia. However, due to unfavorable side effects, the efficacy of current drugs is in doubt, and new compounds are required to treat diabetes mellitus. Recently, there has been a growing interest in the utilization of natural substances as antidiabetic medications (4).
Trigonella foenum-graecum L. is one of the many medicinal plants that have demonstrated great promise in the treatment of type 2 diabetes and its related complications in recent years (5). Trigonella seeds and their main alkaloids, trigonilline, have been shown to have hypoglycemic activity when taken orally; Fournier

(1948) and Nadakarnis (1954) were the first to describe this effect. Fenugreek's pharmacological effects are attributed to a variety of bioactive compounds, including polyphenols, steroids, lipids, alkaloids, saponins, flavonoids, hydrocarbons, carbohydrates, galactomannan fiber, and amino acids.

According to one study, fenugreek enhanced the absorption of glucose in HepG2 cells by overexpressing the mRNA levels of the sterol regulatory element-binding protein (SREBP1C) and glucose transporter (GLUT-2) (6). The hypoglycemic effects of fenugreek have already been demonstrated in animal models and human clinical trials. A dose of 100 mg/kg body weight of fenugreek seed extract resulted in significant reductions in blood glucose levels and concurrent decreases in urea, creatinine, AST, ALT, and tri-glycerides in a study employing a streptazocin-induced diabetic mouse model (7). *Trigonella foenum-graecum*, also known as fenugreek, is a member of the Fabaceae family and possesses hypolipidemic and antioxidant qualities. In many non-industrialized nations, fenugreek seeds were also used to balance diabetes because they included the two primary molecular species, triacylglycerol and phosphatidylethanolamine, which are found in the neutral and polar lipid parts of the seeds, respectively (8).

Furthermore, fenugreek was shown to alleviate diabetic hypertensive nephropathy by inhibiting oxidative stress in the kidney and decrease renal cell apoptosis and fibrosis in neonatal diabetic rats produced by streptozotocin (9). In rats with streptozotocin-induced diabetes, we investigated the effects of fenugreek seed ethanol extract on blood glucose levels, body weight, and antioxidant activity.

Material and Methods:

Fresh and nutritious seeds of *T.foenum-graecum* from a local market. Based on taxonomical features, the sample specimen was recognized. The seeds were allowed to air dry in the shade after being properly cleaned with distilled water to remove any remaining surface water. The seeds were ground into a powder and utilized for extraction after being dried for 48 hours at 400C in a hot air oven.

Preparation of solvent extract:

Trigonella foenum-graecum plant material was ground into a fine powder using a 20# and 40# sieve. Fifty grams of the powdered material was then loaded into a Soxhlet apparatus and extracted using a 50:50 ethanol-water solution until the extraction was finished. The solvent was then removed by distillation, and the individual extracts were dried using a rotary evaporator, with the residue being stored in a desiccator. The extract was then suspended by dissolving the weighed amount in a freshly made 2% acacia suspension solution.

Animals:

In the current study, adult, healthy Wistar Albino rats of either sex weighing 160–200 g and not having received any previous medication treatment were employed. Rats kept at 22 ±2 0C with a 12-hour light and dark cycle were given a regular diet and unlimited water. The animals were fasted for 16 hours before experimentation but allowed free access to water. The animal study was undertaken in Anuradha College of Pharmacy, Chikhli District Buldana. The Institutional Animal Ethical Committee of Anuradha College of Pharmacy, Chikhli Dist. Buldana, Maharashtra, India with necessary approval from Institutional Animal Ethics Committee.

Experimental design:

LD50 experiment:

T. foenum-graecum plant seed extracts were given orally in six animals (three females and three males) weighing around 150–180 g in a single dose of 875 mg/kg, 1.750 g/kg, 3.5 g/kg, and 5.250 g/kg. According to OECD Guidelines 421, (10), the animals were then continually monitored for gross autonomic, behavioral, neurologic, and toxic effects. Additionally, food consumption, feces, and urine were assessed every two hours, and subsequently every six hours for a total of twenty-four hours.

Selection of Doses:

For the purpose of evaluating antidiabetic activity, two dose levels were selected: one was roughly one-tenth of the maximum dose during acute toxicity studies, and the other high dose was half that of one-tenth dose (250 mg/kg, 500 mg/kg body weight) (11).

Oral Glucose tolerance test:

The V. Babu et al. approach was applied. For the investigation, five sets of six rats were employed. Animals in Group 1 received 2% acacia suspension as a normal control; animals in Group 2 received the standard medication glibenclamide (0.25 mg/kg b.w.); animals in Group 3 received an ayurvedic formulation; animals in Group 4 received an extract containing 250 mg/kg b.w.; and animals in Group 5 received a prepared extract containing 500 mg/kg b.w. Thirty minutes after the extract was administered, the rats in each group were given a 2 g/kg glucose solution intraperitoneally. Samples of blood were obtained from the tail before to medication administration and at 0, 30, 90 and 120 minutes following glucose loading. One Touch Glucometer was used to measure blood glucose levels (10).

Hypoglycemic effect in normal rats:

Following a 16-hour fast with water permitted, 30 rats were randomly assigned to five (5) groups and given oral treatment (n = 6/group) in the following ways: Group 1 received 1 ml of 2% acacia suspension; Group 2 received 0.5 mg/kg b.w. of glibenclamide; Group 3 received an Ayurvedic-marketed preparation that contained 500 mg/kg b.w.; Group 4 received 250 mg/kg of extract; and Group 5 received 500 mg/kg of extract. Blood samples were taken from tails 0, 1, 3, 5, and 7 hours for the acute hypoglycemia study, and from tails 0, 7, and 14 days after treatment for the sub-acute research using the tail prick method to measure serum glucose levels. Animals were decapitated to scarify them

on the fourteenth day, and serum and blood were extracted from the artery jugular (12).

Streptozotocin induced hyperglycemia (13) **:**
Streptozotocin was injected intraperitoneally (i.p.) at a dose of 55 mg/kg to induce diabetes. After being observed for 48 hours, the animals were examined using a glucometer to check for hyperglycemia. Based on their fasting blood glucose levels (FBG), the animals exhibiting hyperglycemia were split into two groups: moderate diabetic rats (FBG 120–250 mg/dl) and severe diabetic rats (FBG >250 mg/dl). then divided into five (5) groups, each consisting of six (6) animals. As a normal control, six more normal animals were used.
Group 1 was given a 2% acacia suspension in conjunction with the vehicle. (Normal rats)
Group 2 acted as the negative control for diabetes, remaining untreated.
Group 3 received glibenclamide at a dosage of 0.25 mg/kg in a 2% acacia suspension.
Group 4 was given a commercially available herbal antidiabetic formulation.
Group 5 was treated with an extract at 250 mg/kg body weight.
Group 6 was treated with an extract at 500 mg/kg body weight.

Blood samples were taken from tails after 0, 1, 3, and 5 hours for the acute antidiabetic investigation. In order to determine the serum sugar levels for the sub-acute study, blood samples were taken from the tails on days 0, 1, 3, 5, and 7 after treatment using the tail prick method. For seven days, the animals received treatment and unrestricted access to food and water. Animals were decapitated to scarify them on the seventh day, and serum and blood were extracted from the artery jugular.

Biochemical parameters:
Using a spectrophotometer, serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides were determined in accordance with manufacturer guidelines (14).

Statistical analysis:
One Way ANOVA was used to calculate the statistical significance, which was then followed by Dunnet's multiple comparison test. The results were compared with the diabetic untreated control group using standard medication, an antidiabetic formulation marketed by Ayurveda, and various extracts in varying dosages. Each group consisted of six animals. The threshold for statistical significance was set at $P<0.05$. Graph Pad Prism 8.0, a statistical software application, was used to do statistical analysis using One Way ANOVA and Dunnet's multiple comparison test. The data are shown as Mean ± Standard Error Mean (S.E.M.).

Result:
Trigonella foenum-graecum hydro-alcoholic seed extract was administered orally at doses ranging from 1000 to 5000 mg/kg/day in acute toxicity trials. No neurological consequences were seen, and the animal's behavior was all normal. According to observations, *Trigonella foenum-graecum* seed hydro-alcoholic extract is non-toxic in the observed circumstances. In the glucose tolerance test (GTT), a significant drop in blood glucose levels was seen within 90 minutes (29.61%) following the injection of 500 mg/kg b.w. of *Trigonella foenum-graecum* hydro-alcoholic seed extract. In rats given glucose, the maximum impact was seen at a dosage of 500 mg/kg b.w. Ayurvedic-marketed preparations and the standard medication glibenclamide (0.25 mg/kg b.w.) both shown a decrease in blood glucose levels after 90 minutes (5.39%) and 19.88%, respectively.

Table No. 1: *Trigonella foenum-graecum* hydro-alcoholic seed extract glucose tolerance test in normal rats.

Group	Treatment	Concentration of blood glucose (mg/dl)				
		0 min	30 min	60 min	90 min	120 min
I	Control	84.2±2.40	114.6±8.20	102.4±4.50	92.8±6.20	89.6±2.40
II	TFG (HA) 250 mg/kg b.w.	78.6±3.10	106.4±4.30	88.8±2.30	80.6±1.30	83.4±1.60
III	TFG (HA) 500 mg/kg b.w.	82.4±1.20	120.2±2.50	94.3±2.10	84.6±4.20	85.2±1.20
IV	Marketed Ayurvedic Antidiabetic Formulation	74.6±2.30	81.6±3.20	102.4±1.20	77.2±3.50	78.3±2.30
V	Std. Glibenclamide Drug (0.25 mg/kg b.w.)	82.4±3.20	105.6±2.20	96.2±1.50	84.6±3.20	89.3±2.10

Every value corresponds to mean ±S.E., n=6.

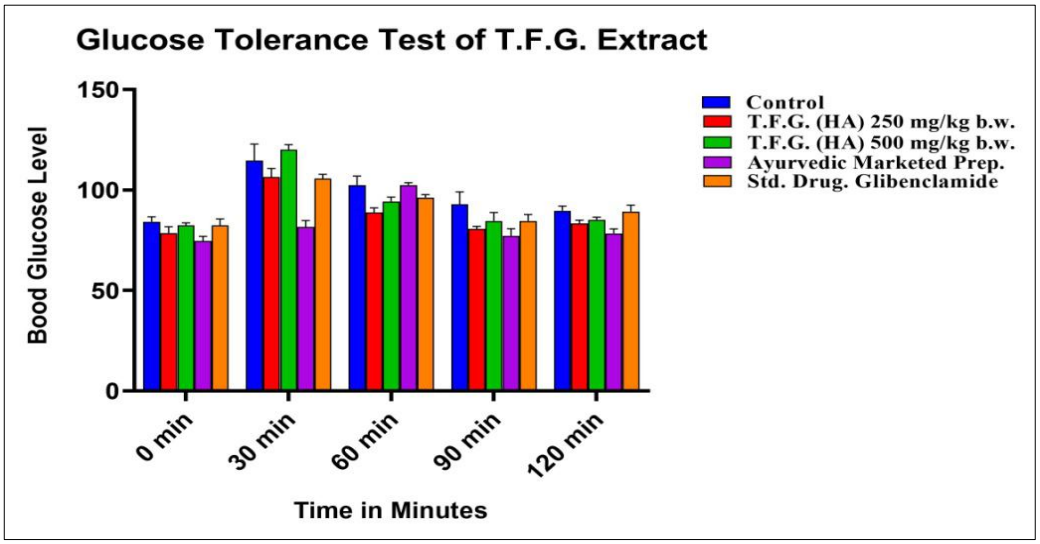


Figure No. 1 shows the glucose tolerance test of THF hydroalcoholic extract in normal rats graphically.

In an acute hypoglycemic study, a single 500 mg/kg dose of Trigonella foenum-graceum seed hydro-alcoholic extract significantly decreased blood glucose levels after one hour (20.94%), but only after three hours did a single 250 mg/kg dose of the same seed extract significantly lower blood glucose levels. In contrast, the ayurvedic-marketed antidiabetic mixture shown a reduction in blood sugar levels after 7 hours (11.97%), while the conventional medication glibenclamide demonstrated a drop in blood sugar levels after 1 hour (17.96%).

Table No. 2: *Trigonella foenum-graceum* hydro-alcoholic seed extract acute hyperglycemic experiments in normal rats:

Group	Treatment	Concentration of blood glucose (mg/dl)				
		0 Hour	1 Hour	3 Hour	5 Hour	7 Hour
I	Control	74.2±2.40	71.4±4.60	69.3±3.20	67.7±4.40	65.42±1.60
II	TFG (HA) 250 mg/kg b.w.	73.5±1.80	62.7±3.40	46.2±1.80	48.4±2.60	56.68±3.20
III	TFG (HA) 500 mg/kg b.w.	76.4±3.20	60.4±3.20	46.2±4.20	51.6±2.40	58.14±2.20
IV	Marketed Ayurvedic Antidiabetic Formulation	77.5±5.30	69.2±1.80	64.4±2.30	66.3±2.40	68.22±1.70
V	Std. Glibenclamide Drug (0.25 mg/kg b.w.)	74.6±1.50	61.2±1.60	48.4±2.50	51.2±2.40	53.12±1.20

Every value corresponds to mean ±S.E., n=6.

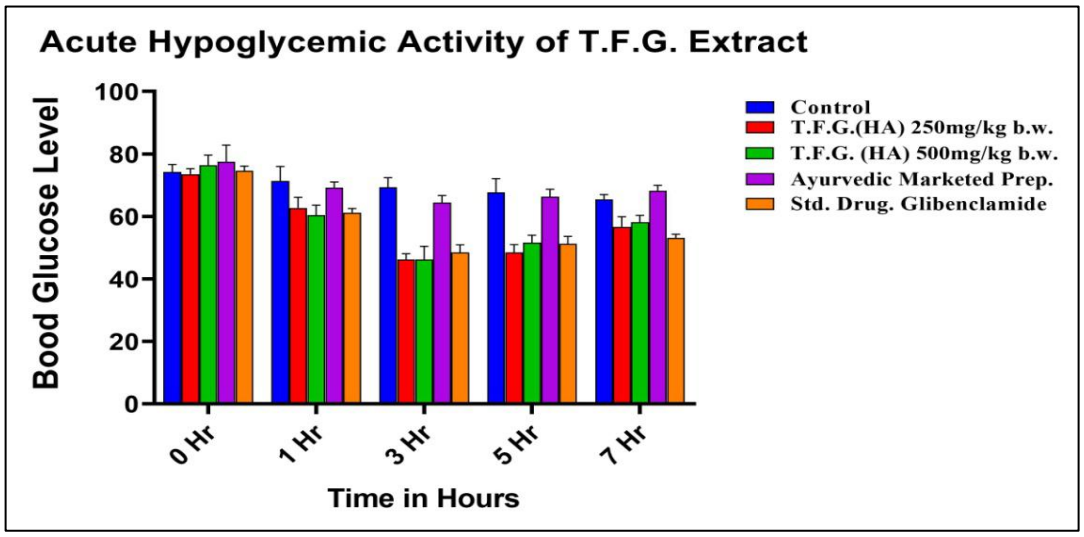


Figure No. 2 shows the Acute Hypoglycemic Studies of THF hydroalcoholic extract in normal rats graphically.

On the fourteenth day of the subacute hypoglycemic research, a hydro-alcoholic extract of *Trigonella foenum-graecum* seeds at a dosage of 500 mg/kg b.w. shown a substantial (21.16%) decrease in blood glucose levels as compared to the group treated with glibenclamide (0.25 mg/kg).

Table No. 3: *Trigonella foenum-graecum* hydro-alcoholic seed extract sub-acute hypoglycemia experiments in normal rats

Group	Treatment	Concentration of blood glucose (mg/dl)		
		Day 0	Day 7	Day 14
I	Control	72.4±4.10	70.6±2.40	71.2±1.40
II	T.F.G. (HA) 250 mg/kg	72.6±2.40	66.8±4.20	62.4±2.30
III	T.F.G. (HA) 500 mg/kg	75.6±2.60	67.2±2.30	59.6±3.20
IV	Ayurvedic Marketed Antidiabetic Preparation	78.4±3.20	71.5±3.40	64.5±1.80
V	Std. Glibenclamide Drug (0.25 mg/kg)	76.4±2.40	66.5±2.40	52.4±2.40

Every value corresponds to mean ±S.E., n=6.

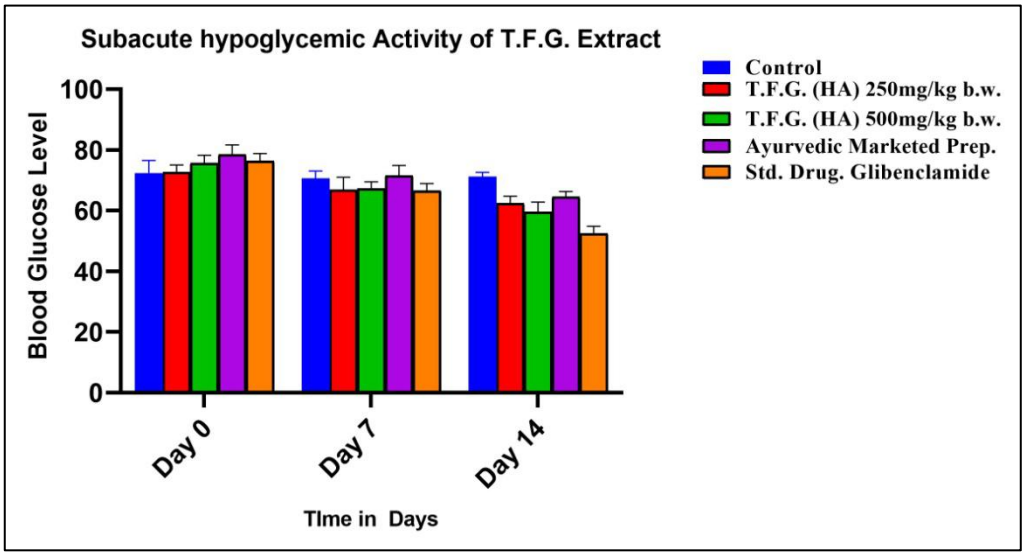


Figure No. 3 shows the Sub-acute hypoglycemic studies of THF hydro-alcoholic extract in normal rats graphically.

After five hours of treatment with a hydro-alcoholic extract of *Trigonella foenum-graecum* seeds at a dosage of 500 mg/kg b.w., a substantial drop in blood sugar levels was seen in an acute antidiabetic research in diabetics produced by streptozotocin.

Table No. 4: *Trigonella foenum-graecum* hydro-alcoholic seed extract acute antidiabetic experiments in streptozotocin-induced diabetic rats:

Group	Treatment	Concentration of blood glucose (mg/dl)			
		0 Hour	1 Hour	3 Hour	5 Hour
I	Control	74.2±2.40	73.6±2.20	72.6±2.40	73.6±2.35
II	Diabetic Control	195.2±2.20	198.2±2.10	199.4±1.50	202.30±1.28
III	TFG (HA) 250 mg/kg b.w.	192.4±2.40	192.4±2.20	189.4±2.40	186.30±3.42
IV	TFG (HA) 500 mg/kg b.w.	194.6±2.20	191.2±2.40	188.4±3.40	185.40±2.42
V	Ayurvedic Marketed Ayurvedic Formulation	187.4±3.20	184.6±2.40	181.4±1.30	176.20±3.63
VI	Std. Glibenclamide Drug (0.25 mg/kg b.w.)	191.4±2.42	189.6±2.42	182.60±3.12	173.40±1.22

Every value corresponds to mean ±S.E., n=6.

Figure No. 4 shows the acute antidiabetic studies of THF hydro-alcoholic extract in streptozotocin induced diabetic rats graphically.

Dose-dependent fall in blood sugar levels observed in sub-acute antidiabetic study after seven days of daily treatment of hydro-alcoholic extract of seeds of *Trigonella foenum-graceum* (500mg/kg b.w.) and lead by 12-39% blood glucose level reduction after treatment with hydro-alcoholic extract.

Table No. 5: *Trigonella foenum-graecum* hydro-alcoholic seed extract sub-acute antidiabetic experiments in streptozotocin-induced diabetic rats:

Group	Treatment	Concentration of blood glucose (mg/dl)				
		0 Days	1 Days	3 Days	5 Days	7 Days
I	Control	84.2±2.40	83.6±3.10	82.6±3.20	83.6±2.30	84.52±3.40
II	Diabetic Control	198.4±4.40	210.4±9.40	222.5±13.30	237.4±12.20	249.36±6.40
III	TFG (HA) 250 mg/kg	195.4±6.40	185.4±3.30	178.4±6.40	171.6±6.40	161.4±8.50
IV	TFG (HA) 500 mg/kg	194.7±4.20	171.4±4.80	161.4±7.30	142.2±2.42	119.4±6.50
V	Marketed Ayurvedic Antidiabetic Formulation	196.4±4.20	191.4±7.50	187.2±8.30	181.4±7.60	177.4±5.50
VI	Std. Glibenclamide Drug (0.25 mg/kg)	191.6±6.20	171.5±7.40	153.4±6.30	132.4±3.60	112.4±4.20

Every value corresponds to mean ±S.E., n=6.

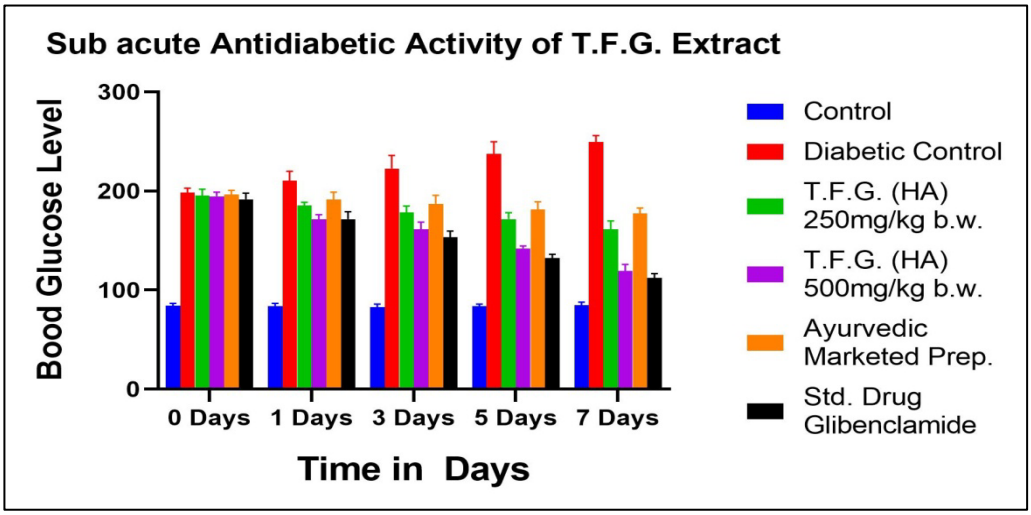


Figure No.5 shows the sub-acute antidiabetic studies in THF hydro-alcoholic seed extract in streptozotocin-induced diabetic rats graphically.

After seven days of therapy, glibenclamide and hydro-alcoholic extracts of *Trigonella foenum-graecum* seed significantly lowered serum cholesterol, triglycerides, and LDL levels. HDL levels are raised by the common medication Glibenclamide and by hydro-alcoholic extracts of *Trigonella foenum-graecum* seeds.

Table No. 6: *Trigonella foenum-graecum* hydro-alcoholic seed extract's impact on the blood lipid profile in diabetic rats

Group	Treatment	Triglyceride (mg/dl)	Total Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)	VLDL Cholesterol (mg/dl)
I	**Control**	94.2±1.40	58.4±1.20	51.4±0.40	50.2±1.10	13.52±1.10
II	**Diabetic Control**	177.7±3.00	126.6±2.30	36.5±1.30	44.8±0.50	18.21±0.42
III	**Std. Glibenclamide Drug (0.25 mg/kg)**	56.3±1.20	64.7±1.30	19.5±0.20	35.2±0.40	14.32±0.64
IV	**Marketed Ayurvedic Formulation**	84.3±070	67.6±0.80	19.4±0.40	34.6±0.70	16.54±0.24
V	**TFG (HA) 250 mg/kg b.w.**	84.3±0.20	66.4±0.60	18.3±1.20	33.6±0.50	16.35±0.35
VI	**TFG (HA) 500 mg/kg b.w.**	80.6±1.30	54.3±2.10	52.4±0.60	32.3±0.50	17.62±0.25

Every value corresponds to mean ±S.E., n=6.

***Trigonella foenum-graecum* hydro-alcoholic extract's impact on body weight in rats with diabetes caused by streptozotocin.**

The impact of a hydroalcoholic extract of *T. foenum-graecum* on body weight in rats with diabetes caused by streptozotocin. On days 0, 7, 14, and 28 of the research period, the rats were weighed. Weights of the bodies were recorded. Mean body weight (g) was used to express the data. Table No. 7 presents the findings.

Table No. 7: *Trigonella foenum-graecum* hydro-alcoholic extract's impact on experimental animals' weight

Group	Treatment	Body Weight in gm			
		0 Day	**7 Day**	**14 Day**	**28 Day**
I	**Control (Untreated)**	158.87±6.75	161.25±7.32	171.47±8.43	167.92±7.24
II	**Diabetic Control**	153.24±6.72	134.52±9.52	122.98±10.64	112.22±12.57ns
III	**TFG (HA) 250 mg/kg b.w.**	151.32±7.34	154.30±5.34	158.51±8.51	161.76±13.16^{ns}
IV	**TFG (HA)- 500 mg/kg b.w.**	135.20±5.35	136.52±7.50	142.42±12.20	138.40±9.52*

V	**Marketed Ayurvedic Formulation**	142.48±6.55	146.35±4.62	150.72±8.50	153.82±8.65*
VI	**Std. Glibenclamide Drug (0.25mg/kg b.w.)**	153.70±7.51	151.65±5.20	148.56±6.59	143.94±8.14ns

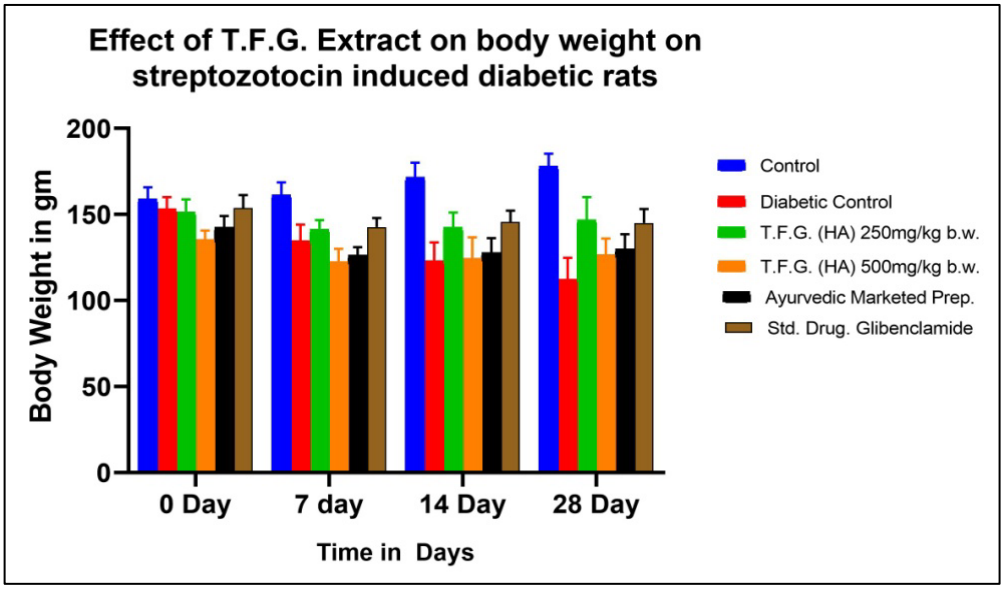


Figure No. 6: Impact of T.F.G. hydro-alcoholic extract on body weight (gms) in rats with diabetes caused by streptozotocin.

Discussion:

N-[methylnitrocarbamoyl]-D-glucosamine, another name for streptozotocin, is a potent DNA methylator that also provides pancreatic cells with nitric oxide. Beta cells are particularly susceptible to nitric oxide and free radical damage because they lack enzymes that scavenge free radicals. (15). For the study of antihyperglycemic medications, streptozotocin-induced hyperglycemia in rats is thought to be an appropriate first screening model (16).

Blood glucose levels significantly increased as a result of streptozotocin-induced diabetes. Blood sugar levels were considerably lowered by the ethanol extract of *T. foenum graecum* seeds, coming close to the glibenclamide-treated control group. It was discovered that 500 mg/kg b.w. of extract had a dose-dependent effect on blood glucose reduction. Blood glucose levels promptly reverted to normal when glibenclamide releases insulin. Antidiabetic plant extracts may include one or more blood glucose-lowering compounds, suggesting that natural components may work together to provide a hypoglycemic effect (17).

Weight loss, most likely due to muscle atrophy, is a common adverse effect of streptozotocin-induced diabetes (18). A typical reduction of body weight is linked to streptozotocin-induced diabetes, most likely as a result of muscle atrophy. Diabetic rats in our study saw a substantial decrease in body weight, while diabetic rats treated with the hydro-alcoholic extract of *T. foenum-graecum* seeds at both dosages exhibited an improvement in body weight ($p<0.05$). Its ability to prevent muscular atrophy is the likely mechanism (19). Finally, as *T. foenum-graecum* hydroalcoholic seed extract lowers blood glucose levels in diabetic rats, our results suggest that it has potent antidiabetic effects. It has been demonstrated that the extract encourages the pancreatic islets to regenerate and return to their typical shape.

The current study suggests that *T. foenum-graecum* seeds might be utilized to treat diabetes; however, further investigation is needed to identify the type of active ingredients and their mechanisms of action.

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Conflicting interest: None

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