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ANTIDIABETIC ACTIVITY OF PLANT EXTRACTS OF *TRIGONELLA FOENUM-GRAECUM* IN STREPTOZOTOCIN (STZ) - INDUCED DIABETIC RATS

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Keywords:

Albino rat, Diabetes mellitus, Streptozotocin, *Trigonella foenum-graecum*

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ABSTRACT: Introduction: The primary cause of type 2 diabetes is the body's inability to respond to insulin or produce adequate insulin. Diabetes mellitus (DM) is a metabolic disease that causes persistent hyperglycemia. It has been demonstrated that *Trigonella foenum-graecum* (TFG), often known as fenugreek, has anti-hyperglycemic effects on both humans and animals with type I and type II diabetes. Fenugreek improves peripheral glucose tolerance and utilization in diabetics who are not insulin-dependent. **Method:** Vacuum-dried TFG ethanolic extract was stored at -20°C until required. Streptozotocin (STZ, 70 mg/kg) dissolved in citrate buffer (pH 4.5) was injected intraperitoneally once into the abdomen of adult rats weighing 150–200 g in order to induce severe diabetes. The control rats received citrate buffer alone in proportion to their body weight. Oral (po) administration of TFG dry seed ethanolic extracts was started on the third day and continued for 21 days. **Results:** On day 21, (TFG) demonstrated a significant reduction in blood glucose levels, a significant difference in oxidative stress by raising SOD and GSH and lowering LPO and NO activity, and a significant reduction in blood TGA levels. However, there was no statistically significant reduction in cholesterol levels. **Conclusions:** Our findings indicate that TFG alcoholic extract significantly lowers blood TGA levels and has good long-term anti-hyperglycemic activity.

INTRODUCTION: Based on its therapeutic and nutraceutical qualities, herbal crops are still widely utilized for treating and preventing a wide range of diseases, even with the amazing advancements in medical research. Fenugreek, or *Trigonella foenum-graecum* L., is one of the plants that possess these characteristics. Also referred to as bird's foot, Greek hayseed, halba and methi [1], it is a self-pollinating annual herbaceous aromatic crop belonging to the Fabaceae family.

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Although it originated in India and Northern Africa, it is currently grown extensively in Europe, South Asia, Argentina, Australia, and Northern Africa. India is the primary producer of fenugreek, making almost 80% of global production [2]. Many nations utilize fenugreek seeds and leaves as a spice and ingredient in food preparation. It is utilized in nutraceuticals, physiological applications, and as a traditional and functional food.

Fenugreek has been used as an emulsifier and food stabilizer recently due to its high gum, protein, and fiber content. Fenugreek is one of the oldest known medicinal herbs in the world; its leaves and seeds are used to treat a variety of illnesses [3]. The leaves and seeds of TFG are widely used in several studies to create powder and extracts for medicinal

purposes. Numerous early studies on humans and animals have shown that fenugreek has hypoglycemic, hypolipidemic, and hypocholesterolemic properties. Moreover, anti-fertility, anti-cancer, anti-parasitic, and antibacterial properties of TFG have been documented [4]. Fenugreek is a member of the *Foenum-graecum* species, Trigonella genus, and Fabaceae family. The primary cause of type 2 diabetes is the body's tissues' inability to respond to insulin or produce enough of it [5, 6]. Diabetes mellitus (DM) is a metabolic disease characterized by persistently high blood sugar levels. It is a pathogenic illness that may involve abnormalities in the secretion or action of insulin [7, 8]. Worldwide, the use of medicinal plants or plant-based medicine has proven to be an affordable means of treating or preventing diabetes. T2DM, which makes up around 90% of DM cases, is the most prevalent kind of the disease.

MATERIALS AND METHODS:

Ethical Approval: The study protocol was approved by Central Animal Ethics Committee of Banaras Hindu University, Varanasi, via Letter No: Dean/2017/CAEC/248

Animals: Male or female inbred Charles-Foster (CF) albino rats weighing 150–200 g were obtained from Banaras Hindu University's Institute of Medical Sciences' central animal house in Varanasi. They were kept in the departmental animal house for a week before and during the trials, with day and dark cycles lasting 10 and 14 hours, respectively, and temperatures of 26 ± 20 C and 44-56% relative humidity. The mice were given a regular mouse pellet diet (Pashu aahar), but water was always available. The animals were not fed for eighteen to twenty-four hours before to the experiment. The principles outlined in "Principles of laboratory animal care" (NIH publication no. 82-23, amended 1985) guideline were followed [9]. Prior to beginning the experimental investigation, approval was obtained by the Institutional Animal Ethical Committee (Letter No: Dean/2017/CAEC/248).

Preparation of Ethanolic Extract: The dried seed of TFG of 1000 grams was crushed into small pieces and prepared by adding sufficient amount of ethanol in a glass jar for 72 hours and then filtered off. The ethanolic extract of TFG was vacuum dried and stored at -20°C until further use. The yield of the extract was 22.86 grams.

Treatment Plan: Four groups of animals were randomly assigned, and 6 (six) animals in each group were chosen for the study.

Group I: Control rats (0.5% CMC)

Group II: STZ+CMC

Group III: Metformin+ STZ (7.4mg/kg)

Group IV: STZ+TFG (250mg/kg)

Treatment Protocol: The extracts and the standard anti diabetic drug metformin was suspended in 0.5% carboxy methyl cellulose (CMC) and given orally once daily. Control rats received 0.5% CMC only. The medication and extracts were administered orally to the animals via an oro-gastric tube at a rate of 10 milliliters per kilogram of body weight. The experiments were conducted after 21 days. When administered once daily, TFG was observed to have an impact on blood glucose, total cholesterol, and triglycerides, among other diabetic biochemical markers, in both normal and streptozotocin-induced severe diabetes rats. The course of treatment lasted for 21 days. In both normal and severe diabetic rats, TFG was also observed to have an impact on oxidative free radical lipid peroxidation (LPO), nitric oxide (NO) levels, antioxidants superoxide dismutase (SOD), and glutathione (GSH).

Methodology:

Induction of Severe Diabetes: A single intraperitoneal injection of streptozotocin (STZ, 70 mg/kg) dissolved in citrate buffer (pH 4.5) caused severe hyperglycemia in adult rats weighing 150–200 g [10]. Next, after that the rats received regular feedings. The control rats received only citrate buffer based on body weight. Following a 21-day course of STZ, blood glucose levels were assessed. The blood was extracted via the retro-orbital plexus. Rats having fasting mean blood glucose levels higher than 225 mg/dl were used in the study.

Blood Glucose Estimation:

Glucose concentration (mg/dl) = AT x 100 / AS AT = optical density (OD) of test

AS = OD of standard

Total Cholesterol Estimation:

Cholesterol concentration (mg/dl) = AT x 200 / AS

Triglycerides Estimation:

Triglycerides concentration (mg/dl) = AT x 200 / AS

Estimation of free Radical Generation: For 21 days, test and reference medications were given orally. On the day of the experiment, the animals were killed, and different parameters were measured in their serum and tissue. Muscle, pancreas, and liver tissue were homogenized (5% each) in 0.9 percent ice-cold saline for 30 seconds using a Potter-Elvehjem glass homogenizer.

The homogenate was centrifuged at 800 rpm for 10 min and then at 12,000 rpm for 15 min, yielding a supernatant that was used for the subsequent estimations [11]. The conventional approach was utilized to calculate the levels of lipid peroxidation (LPO), nitric oxide (NO), superoxide dismutase (SOD), and glutathione.

Statistical Analysis: Every outcome value is displayed as the mean ± standard error of the mean (SEM). Student's t-test was performed to assess the statistical analysis involving two groups, while Dunnett's multiple comparison posttest and one-way analysis of variance (ANOVA) were utilized to compare the control and different treatment groups statistically. At <0.05 values, statistical significance was deemed acceptable.

RESULTS:

Study Site: The study was conducted in the Department of Pharmacology, IMS BHU Varanasi. Rat (Charles-Foster) was procured from animal house of IMS BHU. They were then feeded with appropriate food under standard condition till they gain weight of 150g to 200g. Diabetes mellitus was induced in adult rats (150-200 g) by injecting streptozotocin (STZ; 70 mg/kg, 14.0 mg/ml, 1 ml/200g body weight in citrate buffer, pH 4.5) intra-peritoneally (ip) and the blood glucose levels were estimated at 0 day, 3rd days, 7th day and 21st day of STZ injection. The blood glucose level at 0 day was 95.16 ± 13.24 mg% which increased to a level of 285.16 ± 82.27% at day 3 of STZ administration. Thus, the adult Charles-Foster strain rats showed diabetes (mean fasting blood glucose level >200 mg%) with STZ (70 mg/kg, ip). For future study therefore, rats showing blood glucose level greater than 200 mg% at 3rd day of STZ administration were selected for respective studies. TFG showed a decrease in blood glucose level of 5.4% at day 7 and 59.61% at day 21 and metformin showed a decrease in blood glucose level of 50.27 at day 21.

TABLE 1: EFFECT ON BLOOD GLUCOSE LEVEL

Day	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG
0 days	96.5±18.97	104.66±12.83	93.33±16.23	93.5±7.23
3rd days	99.66±17.66	274±11.93	277.83±9.08	312±129.60
7th days	97.66±6.74	279.83±12.62	202.5±3.78	295.5±127.72
21st days	97.16±6.73	285.66±11.20	138.16±6.31	126.16±7.35

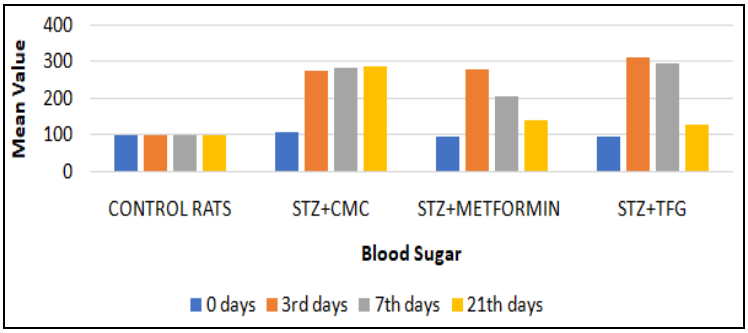

FIG. 1: COMPARISON OF RANDOM BLOOD SUGAR BETWEEN VARIOUS GROUPS

Table 1 TFG showed statically significant reduction in blood glucose level at day 21 (p - 0.012). At day 7 TFG were showing slight decrease in blood glucose level which was not statistically significant. It is concluded that TFG are effective on long term administration while we observe no beneficial effect on short term use.

TABLE 2: EFFECT ON BLOOD TRIGLYCERIDES AND CHOLESTEROLS LEVEL

Parameters	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG
Blood Cholesterols	108±6.72	142.66±10.63	117.5±8.96	137.66±39.79
Blood TGA	74.33±1.87	97.5±4.92	81.83±5.7	86.33±5.03

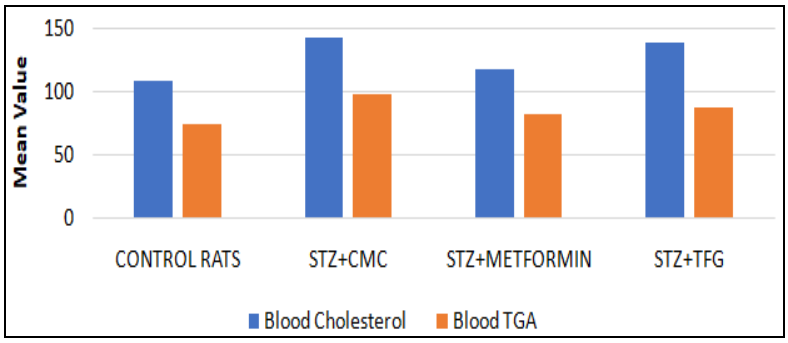

FIG. 2: COMPARISON OF TG AND TC BETWEEN VARIOUS GROUPS

Table 2 shows effect of plant extract on blood TGA and Cholesterol level at day 21. Plant TGF did not show any statistically significant reduction in Cholesterol level but there was significant reduction in blood TGA level ($p < 0.005$).

TABLE 3: EFFECT ON BLOOD GLUTATHIONE LEVEL

Groups &Tissue Homogenate	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG	*p* – Value
Liver	217.5± 27.02	196 ±20.89	218.66 ±28.73	209 ±23.95	0.137
Kidney	196 ± 11.11	158.66 ± 26.25	187.5 ± 12.38	172 ±12.40	0.049*
Pancreas	216.5 ± 16.63	179.16 ± 16.63	220.16 ± 19.27	193.33 ±12.59	0.130
Muscle	187.33 ± 9.77	132.33 ± 21.33	190 ± 12.21	165.83 ± 6.68	0.010*

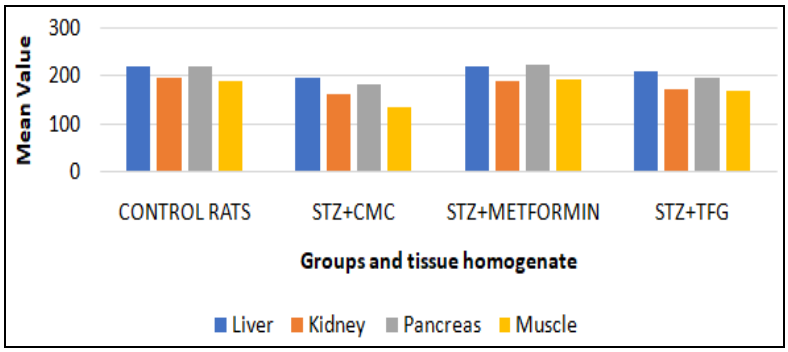

FIG. 3: COMPARISON OF GSH BETWEEN VARIOUS GROUPS

Table 3 shows after 21 days of treatment; the value of GSH was decreased in streptozotocin treated group in liver, kidney, muscle and Pancreas homogenate compared to Control group. (TGF) group showed significantly increased value of GSH in muscle (p – 0.01) and Kidney (p-0.049). This indicates anti-oxidant activity of TGF.

TABLE 4: EFFECT ON BLOOD SOD LEVEL

Groups &Tissue Homogenate	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG	*p* – Value
Liver	232±6.75	197.5±7.23	216.5±4.08	205.33±5.60	0.064
Kidney	202.83±5.84	167.5±7.44	184.66±9.09	180.33±7.99	0.017*
Pancreas	199.33±7.04	157.33±14.06	190.16±9.19	181.5±5.85	0.025*
Muscle	198.33±8.21	164±8.69	187.5±9.37	173.33±7.23	0.073

Table 4 shows after 21 days of treatment; the value of SOD was decreased in streptozotocin treated group in liver, kidney, muscle and Pancreas homogenate compared to Control groups. TGF group showed significantly increased value of SOD in kidney (p – 0.01) and pancreas (p -0.02) and homogenate. This indicates anti-oxidant activity of TGF.

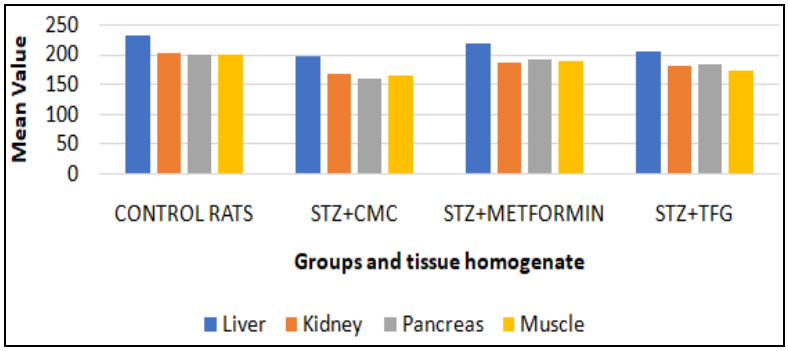

FIG. 4: COMPARISON OF SOD BETWEEN VARIOUS GROUPS

TABLE 5: EFFECT ON BLOOD NO LEVEL

Groups &Tissue Homogenate	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG	*p* – Value
Liver	42.16±7.6	54.66±6.9	39.66±3.32	38.66±3.26	0.046*
Kidney	54.7±1.31	58.08±1.31	56.78±2.79	55.71±1.42	0.014*
Pancreas	49.41±4.51	54.91±3.05	50.33±3.10	50.16±2.80	0.019*
Muscle	45.33±2.92	49.66±3.54	46.91±2.99	47.08±3.2	0.244

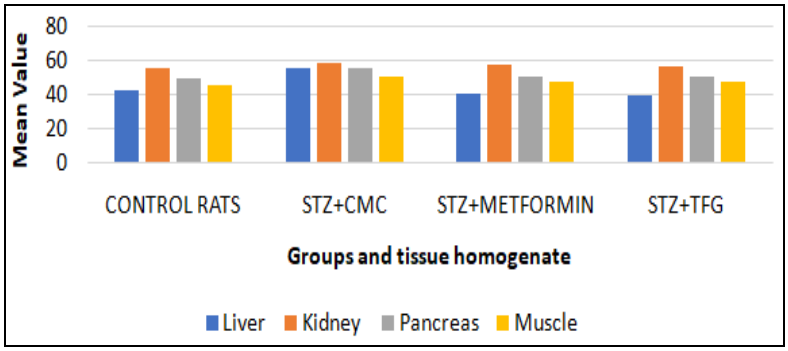

FIG. 5: COMPARISON OF NO BETWEEN VARIOUS GROUPS

Table 5 shows after 21 days of treatment; the value of NO was increased in streptozotocin treated group in liver, kidney, muscle and Pancreas homogenate compared to Control group. TGF group showed significantly decrease value of NO in Liver (-0.046), kidney (p – 0.01) and pancreas (p – 0.01) homogenate. This indicates anti-oxidant activity of TGF.

TABLE 6: EFFECT ON BLOOD LPO LEVEL

Groups &Tissue Homogenate	Control Rats	STZ+CMC	STZ+Metformin	STZ+TFG	*p* – Value
Liver	5.7±0.91	7.5±0.53	6.4±0.73	6.6±0.43	0.010*
Kidney	7±0.50	10.4±0.72	8.33±0.56	11.06±0.82	0.070
Pancreas	7.15±0.70	8.71±.94	7.5±0.89	7.7±0.802	0.073
Muscle	7.61±.66	9.65±1.02	8.41±1.22	8.21±0.80	0.024*

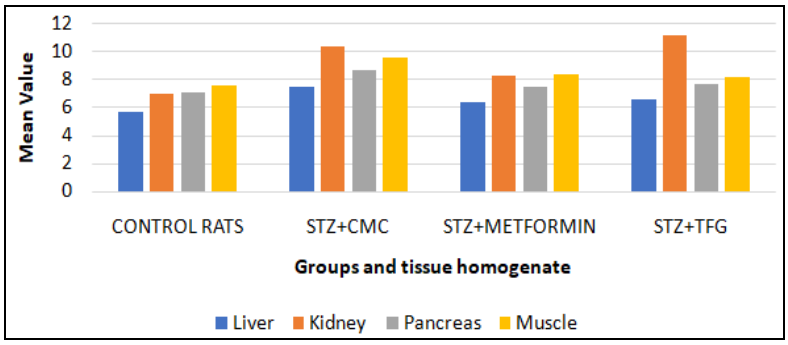

FIG. 6: COMPARISON OF LPO BETWEEN VARIOUS GROUPS

Table 6 showed After 21 days of treatment, the value of LPO was increased in streptozotocin treated group in liver, kidney, muscle and Pancreas homogenate compared to Control group. TGF

group showed significantly decrease value of LPO in liver (0.01) and muscle (p – 0.02) homogenate. This indicates anti-oxidant activity of TGF.

DISCUSSION: The prevalence of diabetes in adults increased to 8.8% of the global population in 2017, and by 2045, it is predicted to reach 9.9% of the population. According to estimates, there were 424.9 million diabetics globally in 2017; by 2045, that number is expected to rise by 48% to 628.6 million [12]. Numerous natural treatments have been advocated for the treatment of diabetes mellitus, and several of them have shown promise in both clinical and experimental settings. The oral glucose tolerance test, streptozotocin and alloxan-induced diabetic mice or rat models were the most widely used models for screening antidiabetic medications in various investigations. There are theories on how they increase insulin sensitivity, how they modify the activity of beta cells in the pancreas, and how plant extracts resemble insulin. Other possible pathways could be decreased glutathione effect, decreased intestinal glucose absorption, decreased glycaemic index of carbohydrates, improved peripheral glucose consumption, increased hepatic glycogen synthesis or decreased glycogenolysis, and so on [13].

Glycogenesis results from the activation of glycogen synthase by synthase phosphatase. This activation appears to be compromised in STZ-diabetic mice [14, 15]. After one to two weeks, the inhibition of synthase phosphatase is almost complete in patients with STZ-insulin-dependent diabetes. Diabetes tends to change the ratio of cholesterol to phospholipids, non-enzymatic glycation, and higher levels of lipid peroxidation in cell membranes [16].

In STZ diabetic rats, there were increases in plasma levels of phospholipids, free fatty acids (FFA), total cholesterol (TCH), and triglycerides (TC). Glycaemic control has improved in people with mild type II diabetes mellitus, according to a clinical study. They believe that the galactomannan-rich soluble fraction of fenugreek is responsible for the hypoglycaemic activity because the fibre slows stomach emptying, delaying the uptake of glucose in the small intestine [2]. A study on alloxan-induced diabetic rats [17] found that fenugreek seed extract that had been dialyzed showed hypoglycemic activity similar to insulin. In newly diagnosed type II diabetes mellitus patients, a double-blind placebo research found that fenugreek seed consumption reduces insulin resistance and enhances glucose control [18].

Recently, the pharmacokinetics of metformin with and without concurrent fenugreek extract administration was examined in a rat animal model. The results showed that concurrently ingesting fenugreek and metformin increased the drug's bioavailability and decreased its distribution volume by 70% [19]. Another study shows that the pectin component of fenugreek, which absorbs bile salt [20], is responsible for the reductions in triglyceride (TG) and LDL in people receiving the herb. Dyslipidemia and type II diabetes are frequently associated. TC, TG, and LDL were significantly reduced ($p > 0.001$) in the newly diagnosed patient after receiving a 25 mg dose of fenugreek seed powder solution for 30 days [21]. Reactive oxygen species excess leads to oxidative destruction of lipids and proteins. Chronic degenerative disorders are linked to these damages. Numerous researches have been conducted that indicate fenugreek may have antioxidant properties. Alcoholic fenugreek extract also has a radical scavenging activity [22].

In addition, a different study that assessed lipid peroxidation and antioxidants in the mice urinary bladder [23] showed the protective impact of fenugreek on enzymatic antioxidant and lipid peroxidation in cyclophosphamide-treated mice. According to our research, TFG ethanolic extracts exhibit potent anti-diabetic properties. In rats with streptozocin-induced hyperglycemia, alcoholic extract of TFG demonstrated notable anti-hyperglycemic effects.

Numerous animal models have been used to study the cellular regeneration associated with diabetes. The balance between these cells' renewal and loss is reflected in the total mass of cells. Moreover, it was proposed that the primary reason that streptozocin-injected rats recovered from the drug's effects might be the regeneration of islet ß cells after they were destroyed by the medication. TFG alcoholic extracts may function through cellular renewal [24].

CONCLUSION: Our research provided scientific validation for the widely reported usage of TFG as an ethnomedicinal herb for diabetic management. TFG's significant phytochemical content increased its utility as a therapeutic herb. Rats with streptozocin induced diabetes show a hypoglycemic response to alcoholic TFG extracts. Treatment with the reference medication, metformin, showed a similar result. In order to manage diabetes mellitus, there is currently an increasing interest in assessing herbal medicines, which are said to be less toxic and have insignificant side effects. This is especially true in nations where access to traditional diabetes treatment is limited. Therefore, as TFG seems to be usually safe, its usage is advised. Our research indicates that TFG alcoholic extract has good long-term anti-hyperglycemic efficacy with a significant reduction in blood TGA level, based on the current data. Our investigation revealed a significant difference in anti-oxidant parameters, i.e., increased GSH & SOD while decreased NO, LPO in multiple tissue homogenates (muscle, kidney, liver, and pancreas), after 21 days of treatment of an alcoholic extract of TFG, indicating its anti-oxidant qualities. Thus we can conclude that alcoholic extract of TGF might be a good candidate/ cost effective/ rational /anti-oxidant treatment in cases of type 2 DM.

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CONFLICT OF INTEREST: None declared

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