



Fenugreek (*Trigonella foenum-graecum*) extract improves hyperglycemia and hyperlipidemia in high sugar diet fed mice

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ABSTRACT

Diabetes, obesity and other cardiovascular diseases are major public health problems that are increasing at an alarming rate. Diabetics and obesity are characterized by high blood glucose level caused by high sugar consumption. New treatment techniques are needed that can lower blood glucose levels without causing any negative effects. Fenugreek known as *Methi* in Bangla, has been well known to have medicinal properties, such as antidiabetic, anti-hyperlipidaemic, anti-inflammatory, anticancer, antioxidant, and neuroprotective activities. Thus, the supplementation of fenugreek could be an alternative diet that could mitigate the deleterious effect of high sugar consumption and prevent the development of metabolic diseases. Therefore, this experiment was designed to investigate the effect of Fenugreek extract (FE) supplementation on anti-hyperglycemic and anti-hyperlipidemic activities in high sugar diet (HSD) fed mice. Four diet paradigms were selected for this experiment- viz., normal diet (ND), normal diet with Fenugreek extract (ND+FE), 30% sucrose (HSD), and 30% sucrose with Fenugreek extract (HSD+FE). The supplementation of FE (300mg/kg BW) significantly ($*p<0.05$) hampers the increase in food intake due to high sugar diet consumption in mice. Additionally, mice fed with FE enriched diet significantly lowered body weight as compared with the HSD group. Also, FE supplementation significantly attenuated the increased blood glucose concentration caused by high sugar intake. The inclusion of FE had no effect on heart weight, kidney weight, white adipose tissue and brown adipose tissue but significantly decreased the increased weight of the liver in the HSD-fed group. In addition, FE supplementation also attenuated the HSD-induced elevation of serum total cholesterol (TC), triglycerides (TAG), and low-density lipoprotein C (LDL-C). Considering the above findings, FE could effectively tolerate a normoglycemic state and inhibit the development of diabetics and obesity caused by HSD. Therefore, FE could be beneficial for the management of metabolic disorders due to consumption of high sugar.

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Introduction

Diabetes, a metabolic disease which is characterized by high blood glucose level

(hyperglycemia) that involves abnormalities in either insulin secretion or action at peripheral tissues, resulting in reducing insulin sensitivity at

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skeletal muscle, adipose and liver tissues, which represents insulin resistance (Shaodong, 2014). The prevalence of diabetes mellitus (DM) represents a significant and growing global health problem. Both genetic (heredity) and environmental factors (obesity and sedentary lifestyle) play an important role in Type 2 Diabetes. Excess consumption of nutrients, inadequate physical activity, and other factors may speed up the accumulation of excess body fat which is known as obesity. Excess energy intake and low energy expenditure induce lipid accumulation in adipose tissue, liver, muscle, and other internal tissues, leading to the development of insulin resistance (IR) and metabolic disturbances. Ageing, unhealthy diets, obesity, a sedentary lifestyle, and malnutrition-related causes play a pivotal role to increase the incidence of diabetes and obesity in developing countries. Furthermore, the consumption of a high-sugar diet (HSD) accelerates the development of diabetes and obesity (Barrière *et al.*, 2018). It is also known that diet with high sugar promote the development of metabolic diseases both directly and indirectly (Barrière *et al.*, 2018). The fructose component in sugar directly causes dysregulation of lipid and carbohydrate metabolism. Sugar indirectly encourages a positive energy balance, which results in body weight and fat gain, which also leads to a dysregulation of the metabolism of lipid and carbohydrate. Dietary added sugar consumption increases body weight and fat, and also increases the risk of metabolic disease through both direct and indirect mechanisms. (Stanhope *et al.*, 2013). Consumption of various sugary foods containing refined carbs and simple sugars are preferred in South-Asian countries. Thus, supplementation of an alternative diet that could mitigate the deleterious effect of high sugar consumption is considerably needed. The major approach in the management of diabetes and obesity includes lifestyle modifications that involve exercise, diet modification, drug therapies, etc. The sedentary lifestyle in modern days has made it extremely difficult to overcome the occurrence of diabetes and obesity. Although several drugs are available in the market to treat metabolic disorders, their untoward side effects have made the treatment rather difficult. Nowadays, complementary and alternative medicines for the treatment of diabetes and obesity are chosen over synthetic drugs. Herbal medicines are used for the treatment of chronic metabolic diseases including diabetes and obesity. Therefore, there has been a

growth in research focused on natural products and their active ingredients with therapeutic potential for diabetes and obesity. Plants have been reported as the rich sources of fibers, vitamins, minerals, and phytonutrients and have shown beneficial effects in management of diabetes, cardiovascular disorders, obesity, and some cancers (Craig, 2010). Medicinal plants contain anti-diabetic compounds such as flavonoids, alkaloids, phenolic, and tannins that improve the efficiency of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose (Wesam Kooti *et al.*, 2016).

Fenugreek (*Trigonella foenum-graecum* L), is a well-known leguminous annual herbaceous plant extensively cultivated in Asia, Africa, and Europe (Geetha *et al.*, 2011). Fenugreek, also known as *Methi* in Bengali, has been widely used as a condiment, edible vegetable, and medicinal plant for a long time. Fenugreek contains active constituents like alkaloids, steroids, flavonoids, and saponins (Ahirwar and Ahirwar, 2010). The medical benefits of fenugreek, including its anti-diabetic, anti-hyperlipidemic, anti-inflammatory, anti-cancer, antioxidant, and neuroprotective qualities, are well known (Venkata *et al.*, 2017; Anjaneyulu *et al.*, 2018). Fenugreek seeds are used as a general tonic to improve metabolism and health, to treat weakness and edema of legs, to stimulate lactation (Basch *et al.*, 2003). The mechanism of hypoglycemia induced by fenugreek seed extract was suggested to be mediated through stimulation of an insulin signaling pathway (Vijayakumar *et al.*, 2005).

However, no study has yet been done to evaluate the beneficial effects of fenugreek extract in high-sugar diet-fed mice. Therefore, we have undertaken the present study to examine whether the oral administration of fenugreek extract could prevent the development of metabolic disorders caused by a high sugar diet (HSD).

Materials and Methods

Animal Ethics

The Mice were handled in accordance with the guidelines of Animal Welfare and Experimentation Ethics Committee at Bangladesh Agricultural University, Mymensingh, Bangladesh [AWEEC/BAU/2021 (15)].

Preparation of Fenugreek seed extract

Fenugreek seeds were collected from the local market of Mymensingh, Bangladesh. After collection, fenugreek seeds were dried under sunlight and later in the oven. After proper drying, the fenugreek seeds (1kg) were coarsely powdered and refluxed (three times) at 85°C with 70% ethanol to prepare the fenugreek seed extract. After filtration, the hydro-alcoholic extract was vacuum-concentrated. A freeze dryer was used to dry the final extract (121g).

Formulation of diet

Normal food formulation (NFF) includes Wheat, wheat bran, rice polish, fish meal, oil cake, gram, pulses, milk, soybean oil, molasses, salt and Embavit (vitamin) at different proportions (Table 1).

Table 1: Composition of control diet (for 100 g)

Ingredients	Unit (g)
Wheat	45
Wheat bran	20
Rice Polishing	5.5
Fish meal	10.0
Oil cake	6.0
Gram	4.5
Pulses	4.0
Milk	1.5
Soybean Oil	1.5
Molasses	0.95
Salt	0.95
Embavit (vitamin)	0.1

Two different types of diets were formulated with the addition of sucrose and/or Fenugreek seed extract. Types of food were - 100% Normal food formulation (control group) and 70% Normal food formulation + 30% Sucrose (HSD).

Experimental animals

Healthy adult Swiss Albino male mice were obtained from the Animal Resources Facility of International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) and acclimated for 10 days so that they would become accustomed to the new environment. Animals were housed in a well-ventilated room at 28± 2°C and a relative humidity of 70-80% with natural day and light. Normal food and water were

available *ad libitum* before the starting of feeding experiments. Animals were divided into four groups and each group contained at least 4 mice. To reduce the possibility of stress reactions during the experiment, animals were also used to daily handling during the rearing period.

Diet paradigms

In this study, four different diet paradigms were used: the normal diet (ND), the normal diet with fenugreek extract, 30% (w/w) high-sugar diet (HSD), and the high-sugar diet combined with fenugreek extract. Table 2 displays the dietary makeup for each paradigm. The animals were given access to *ad libitum* food and changed regularly to maintain its quality. For four weeks, the diet paradigms-based treatment was administered continuously.

Measurement of Food intake and body weight

Food intake by the individual mouse was measured weekly at 10:00 am for 4 weeks as Food intake = Initial food weight- remaining food weight. The body weight of each mice was measured with the help of an electric balance (eki300-2n electronic scale, A&D company Ltd., Korea) at 7 days interval up to the end of the experiment.

Blood glucose measurement

Using a standardized automated blood glucose test meter, the fasting blood glucose level was determined (Glucoleader™ Enhance Blood Glucose Meter, HMD Biomedical Inc., Hsinchu County, Taiwan). The measurement was carried out in accordance with the suggested protocol (Maejima et al., 2014). Mice were fasted overnight for approximately 4 hours by transferring mice to clean cages with no food or feces in hopper or bottom of cage. At all times, there was guaranteed access to drinking water. The tip of the tail was scored using a fresh or sterilized scalpel blade. First small drop of blood was discarded. A small drop of blood (<5µl) was placed on the test strip of the blood glucose meter. The concentration of blood glucose was recorded for each mouse at 15, 30, 60, and 120 min after glucose administration. After administering glucose, the blood glucose levels were used to determine the area under the curve (AUC) data.

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Blood Samples Collection and Preparation of Serum

At the end of 4 weeks, after 18 hours fasting, blood samples were collected from the Posterior Vena Cava by the method described previously (Hoff *et al.*, 2000). The mice were placed inside the air tight container one by one containing cotton soaked with chloroform. The abdominal cavity of anesthetized mouse was opened by making a V-cut through the skin and abdominal wall 1 cm caudal to the rib cage. The intestines were shifted over to the left and the liver was pushed forward. The widest part of the posterior

vena cava (between the kidneys) was located. A 26 gauge needle and a 1 ml syringe were used. The needle was carefully inserted into the vein and blood was drawn slowly until the vessel wall collapses. The blood was collected in a 1.5 ml eppendorf tube containing EDTA which acts as anticoagulant. Then the blood containing tubes were centrifuged at 4000 rpm for 10 min at 4°C (Gyrozen 1580R Multi-Purpose High-Speed Refrigerated Centrifuge, Gangnam-gu, Seoul, KOREA). After centrifugation, the supernatant serum without unwanted blood cells was collected in a new tube. Serum samples were stored at -20°C until lipid profile assay.

Table 2. Composition of diets in different treatment.

Diets	Proportion (%)		Fenugreek seed extract
	Normal composition	Sucrose supplementation	
Normal diet (ND, Control)	100	0	0
Normal diet + Fenugreek (ND+FE)	100	0	300mg/kg/day (oral)
Normal diet + Sucrose (HSD)	70	30	0
Normal diet + Sucrose + Fenugreek (HSD+FE)	70	30	300mg/kg/day (oral)

Measurement of organ weight

After collecting the blood samples, the internal organs like liver, heart and kidney were harvested and trimmed to remove additional tissues. The organs were cleansed in a saline solution, and then the saline on the surface was removed by placing them on filter paper. Then the organ weights were measured using a digital balance (eki300-2n electronic scale, A&D company Ltd., Korea).

Determination of lipid profile parameters

Lipid profile studies involved analysis of parameters such as total cholesterol (TC) level determined by CHOD-PAP method (Richmond, 1973); triglyceride (TG) level determined by GPO-PAP method (Cole *et al.*, 1997); HDL cholesterol level determined by CHOD-PAP method (Henry *et al.*, 1974). HumaTex febrile antigen test kit

(Human Diagnostic, Wiesbaden, Germany) was used and the absorbance of all the tests was determined using Humalyzer, Model No-3000 (Human GmbH, Wiesbaden, Germany). Serum LDL cholesterol concentrations were calculated using the Friedewald equation - LDL cholesterol (mg/dl) = Total cholesterol - HDL cholesterol - (Triglyceride ÷ 5) (Friedewald *et al.*, 1972).

Statistical analysis

All statistical analyses were performed using Prism 5 (GraphPad Software, CA). All data were presented as mean ± SE. To justify the significant differences among groups of treatment an analysis of variance (ANOVA) followed by Tukey's post-hoc test was used. For all analyses, $p < 0.05$ was used as a significant value.

Results

Food Intake

We carried out food intake measurement throughout the experimental period of 4 weeks. There was no significant difference in daily food intake among the groups at the beginning of the experiment which was continued until the 2nd week of the feeding treatment. High sugar diet (HSD) supplementation showed an increase in food intake than the normal diet (control) which was reversed by the administration of Fenugreek seed extract (FE).

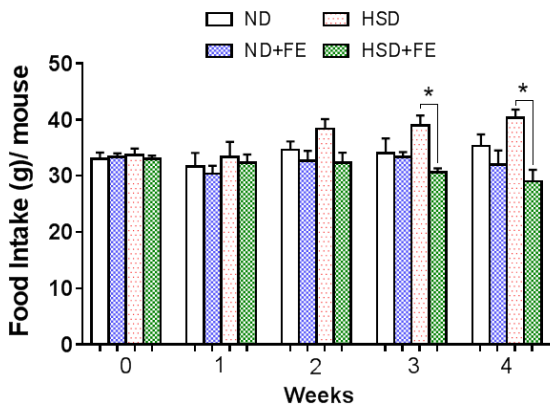


Figure 1: Effect of fenugreek seed extract on feed intake of mice. Average daily food intake was measured for 4 weeks. ND: control, HSD: High sugar diet, FE: Fenugreek seed extract. * $p < 0.05$ by ANOVA followed by Tukey's post-hoc test. Bars represent mean \pm SE. $n \geq 4$ for each group

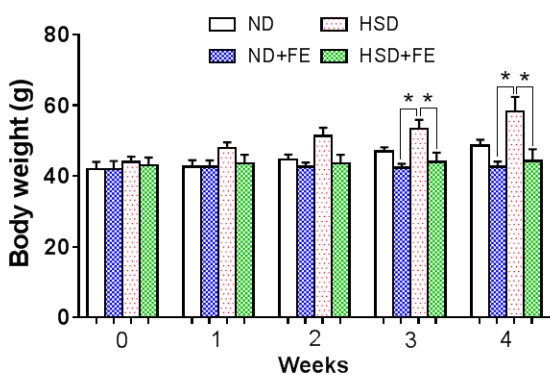


Figure 2: Effect of fenugreek seed extract on body weight in HSD fed mice. Body weight was measured weekly for 4 weeks. ND: control, HSD: High sugar diet, FE: Fenugreek seed extract. * $p < 0.05$ by ANOVA followed by Tukey's post-hoc test. Bars represent mean \pm SE. $n \geq 4$ for each group

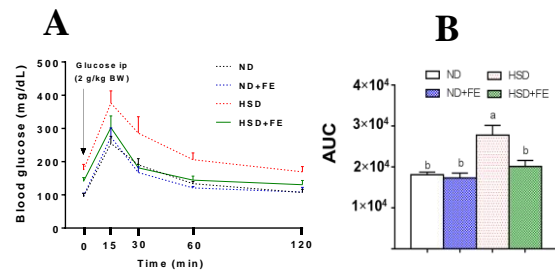


Figure 3: Effect of FE on glucose tolerance in HSD-fed mice. (A) Glucose tolerance test (GTT) was performed after an intraperitoneal injection of glucose 2 g/kg BW at 28 days of experiment. (B) The corresponding area under the curve (AUC) of glucose tolerance test was calculated. ND: control, HSD: High sugar diet, FE: Fenugreek seed extract. * $p < 0.05$ by ANOVA followed by Tukey's post-hoc test. Bars represent mean \pm SE. $n \geq 4$ for each group.

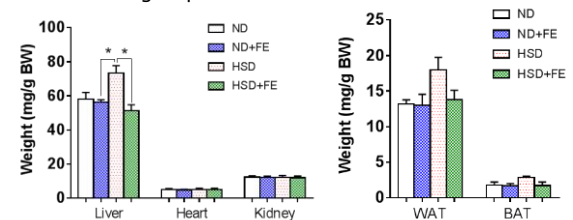


Figure 4: Effect of FE supplementation on organ weight and adipose tissue weight. After the feeding experiment, animals were sacrificed and organs such as Liver, Heart and Kidney were isolated and weighed. White adipose tissue (WAT) and Brown adipose tissue (BAT) were also measured after feeding experiment. ND: control, HSD: High sugar diet, FE: Fenugreek seed extract. * $p < 0.05$ by ANOVA followed by Tukey's post-hoc test. Bars represent mean \pm SE. $n \geq 4$ for each group.

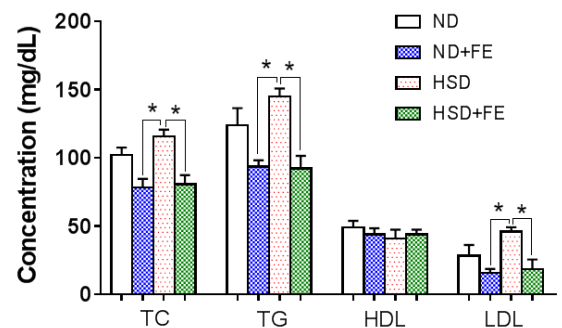


Figure 5: Effect of Fenugreek Seed Extract (FE) on blood lipid profile of mice. Blood lipid profile including Total cholesterol (TC), Triglycerides (TG), HDL and LDL. ND: control, HSD: High Sugar Diet, FE: Fenugreek seed extract. * $p < 0.05$ by ANOVA followed by Tukey's post-hoc test. Bars represent mean \pm SE. $n \geq 4$ for each group

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Fenugreek seed extract (FE) supplementation significantly ($p < 0.05$) reduced food intake in comparison to high sugar diet group (30% sucrose) at 3rd and 4th week of the experiment (Fig. 1).

Body Weight

The effectiveness of Fenugreek seed extract (FE) in preventing the development of HSD-induced obesity was also determined by weighing the body weight of each mouse. The result showed that no significant difference was found in body weight of mice until 2nd weeks of the experiment (Fig. 4). The body weight observed in FE supplemented group was significantly lower compare to HSD group at 3rd and 4th weeks of experiment (Fig. 2).

Blood Glucose

Estimation of blood glucose concentration in control and experimental mice are mentioned in Figure 3. There was an elevation in blood glucose concentration in HSD diet fed mice compared to the other groups (Fig. 3A). Fenugreek seed extract (FE) supplementation in HSD diet fed mice significantly attenuates the elevated blood glucose concentration in blood plasma (Fig. 3A). Furthermore, the GTT graph's area under the curve (AUC) data (Fig. 3B) showed that the FE-treated group's AUC was considerably ($p < 0.05$) lower than that of the HSD group.

Organ Weight

HSD group showed significantly ($p < 0.05$) higher liver weight compared to FE group (Fig. 4A). No differences observed in case of heart and kidney weight among the different groups (Fig. 4A). No significant differences were occurred in case of White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT) (Fig. 4B).

Lipid Profile parameters

FE supplementation did not affect HDL concentration but FE supplementation significantly ($p < 0.05$) decreased the HSD-induced elevation of serum concentration of total cholesterol (TC), triglycerides (TAG), and Low-density lipoprotein C (LDL-C) (Fig. 5).

Discussion

Our research showed that fenugreek seed extract (FE) administration could successfully prevent the

excessive body weight increase brought on by HSD. Importantly, the supplementation of FE also exerted a remarkable effect to hamper the increase in food intake due to high sugar diet consumption in mice. FE supplementation in diet also prevents the increase in blood glucose concentration caused by high sugar intake for a period of 4 weeks. Hormonal and neural mechanism that regulates hunger and satiety is linked to reduced food consumption (Santoso *et al.*, 2015, Benton and Young, 2017). Reduced food intake simply reduces energy intake which eventually lowers blood sugar and fat mass (Benton and Young, 2017). A substance's potential to prevent the onset of diabetes and obesity may simply be accomplished by reducing food intake. In support of the above statement, our results demonstrated that the oral delivery of FE changed the amount of meals consumed. Therefore, it seemed probable that FE's ability to avoid the signs of diabetes and obesity would coincide with a decrease in food intake

Consuming high-sugar diets may cause excessive weight gain, which quickens the development of obesity in rodents (Torres-Villalobos *et al.*, 2015). Previous studies reported that frequent use of fast food and drinks high in sugar could greatly raise the risk of obesity and diabetes in people (Oo *et al.*, 2017, El-Wakkad *et al.*, 2012). Our current research showed that after two weeks of supplementation, the mice fed HSD gained more body weight, and it was significantly ($p < 0.05$) hampered by the oral administration of FE.

Consuming a high-sugar diet is linked to the emergence of metabolic dysregulations like diabetes and obesity (Torres-Villalobos *et al.*, 2015; Lean and Morenga, 2016, Barrière *et al.*, 2018). In this study, mice fed with HSD exhibited statistically significant ($p < 0.05$) fasting blood glucose than other groups as expected. This finding may point to a dysfunctional blood glucose balance that could lead to the development of diabetes (Andriopoulos *et al.*, 2008). However, supplementation of FE in HSD significantly ($p < 0.05$) reduced fasting blood glucose in mice.

Maintaining healthy levels of lipids circulating in blood stream is important to prevent cardiovascular diseases. In this study, the blood lipid profile parameters such as total cholesterol, triglycerides, and LDL-C in FE treated group are statistically comparable with other groups. The essential fatty acid rich oil seeds have been reported to have the beneficial effect on maintaining blood lipid parameters. According to Biswas *et al.* (2010) Dietary sesame protein lowers plasma total cholesterol, triacylglycerol, and LDL cholesterol, and LDL-C reduces lipid peroxidation in both hypercholesterolemia and normocholesterolemic diet groups, raises HDL-C, and increases LDL-C..

However, reports on the effect FE on blood lipid parameters are lacking. Furthermore, we did not find any significant difference in heart, and kidney weight of the mice. In case of Liver weight the result showed significantly ($p < 0.05$) higher in HSD group and FE administration reverse the HSD induced Liver weight. The decreasing Liver weight of FE administered mice were likely to be corresponded with the changes in body weight. Further molecular investigation is needed to clarify the complete mechanisms and the physiological effect of FE.

Conclusion

Fenugreek seed extract helped to attenuate the increased food intake and blood glucose concentration caused by high sugar diet consumption. It also plays an important role to ameliorate the high sugar diet induced serum total cholesterol, triglycerides and low density lipoprotein. In conclusion, the fenugreek seed extract prevented the development of diabetes and obesity by maintaining a normoglycemic state, body weight, and food intake in high sugar diet fed mice.

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Conflict of interest: The authors declare that there is no conflict of interests regarding the publication of this article.

Author's contribution:

RC and CG were involved in the conception and design of the experiment, executed the trail, data collection and analysis. RC, CG, KHK and TA contributed to writing the manuscript. All authors read the article and endorsed the final draft for publication.

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