

## *Trigonella Foenum Graecum* L. (Fenugreek) as an Alternative Herbal Remedy for Diabetes Mellitus

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### Abstract

**Background:** This minireview article analyzes the medicinal and remedial properties of *Trigonella foenum graecum* L. (fenugreek) as an alternative remedy for diabetes mellitus.

**Aim:** To understand fenugreek and the components of fenugreek seed extract (dysgenic, ethanol extract, hydro alcoholic extract, aqueous extract and methanol extract, IND01) as a remedial agent for diabetes mellitus in various *in vitro* and *in vivo* studies.

**Methods:** Contents for this minireview article was gathered searching for “fenugreek;” “Fenugreek and diabetes mellitus;” “fenugreek and type 2 diabetes;” “fenugreek extracts;” and “fenugreek and metabolism,” through electronic databases such as Pub Med, Science direct, Elsevier and Google Scholar. Journals included Phytomedicine, International Journal of Diabetes in Developing Countries, Journal of Diabetes Research, and Metabolic Syndrome and Related Disorders.

**Results:** Fenugreek seed and fenugreek seed extract successfully lowered blood sugar glucose and increasing glucose uptake in STZ and alloxan-induced animals. Studies comparing oral doses of fenugreek seed powder to insulin found that diosgenin, a steroid in fenugreek, to stabilize insulin and glucose in diabetic-induced animals. Ethanol extract helped reduce antioxidant enzymes SOD, catalase, and GSH-PX levels in STZ-induced diabetic control rats compared to normal rats and had similar results to ant diabetic drug glibenclamide. Fenugreek seed extract is also capable of triggering a response on cellular glucose absorption that increases GLUT4 movement to the cell surface.

**Conclusion:** Diabetes mellitus can be regulated through a healthy diet of carbohydrates, proteins, and lipids, and intake of prescription medication, including insulin. A curated diet regulates blood glucose level and hypoglycemia, and prescription medication assists chemical reaction of metabolism. The economic burden of a curated diet and prescription medication may be resolved with alternative herbal remedies, including fenugreek

**Key Words:** Fenugreek; Diabetes Mellitus; Type 2 Diabetes; Diosgenin; IND01; GII

**Abbreviations:** STZ: Streptozotocin

## Introduction

*Trigonella foenum graecum* L [Fabaceae] (fenugreek) is a self-pollinating plant that grows annually throughout regions of North and South America, Africa, Australia, Asia and Europe and is used as a daily ingredient in Africa, Asia, and the Mediterranean [1,2]. It is used as an ingredient in curry dishes, bread, and condiments, and tastes similar to maple syrup. Fenugreek can be consumed as a powder, dried seed, fried, or raw. Fenugreek seeds and leaves consist of vitamins, minerals, fibers, saponins, alkaloids, flavonoids, carbohydrates, proteins and lipids, iron, and calcium [2]. Fenugreek seeds also have a high volume of antioxidants. These phytochemical and chemical compounds serve as protective agents for diabetes mellitus and hypoglycemia, liver, and kidney disorders. Various studies have shown the positive effect of fenugreek seed extract in curbing symptoms of diabetes mellitus, including glucose absorption and insulin resistance. The focus of this minireview article is aimed to investigate the remedial properties of fenugreek seed in relation to diabetes mellitus and lowering blood sugar glucose and increasing glucose uptake.

Diabetes mellitus can be regulated through a healthy diet of carbohydrates, proteins, and lipids, and intake of prescription medication, including insulin. A curated diet regulates blood glucose level and hypoglycemia, and prescription medication assists chemical reaction of metabolism. The economic burden of a curated diet and prescription medication may be resolved with alternative herbal remedies, including fenugreek [2]. WHO reports the number of recorded deaths from diabetes mellitus and related disability as approximately 1.5 million, similar in number to the recorded number of deaths from HIV/AIDS [3-5]. In a study by *The Lancet*, diabetes mellitus has increased fourfold from 1980 to 2014: 108 million to 422 million. According to the 2014 National Diabetes Statistics Report, approximately 21.0 million individuals were diagnosed with diabetes and approximately 8.1 million people were undiagnosed [6]. The negative impact of long-term prescription use is a financial burden, accompanied with other negative side effects. Alternative solutions, including herbal remedies such as fenugreek, have proven as a possible pharmaceutical solution.

## Pharmacology

Fenugreek seed has a unique pharmacological profile

that assists with anti-inflammation, curbs the side effects of chemotherapy, reduces fever, stimulates appetite, lowers high cholesterol and also acts as a laxative [7]. Fenugreek seed makeup includes flavonoids, alkaloids, salicylates, and nicotinic acid [7]. Approximately (45-60%) of seeds consist of carbohydrates, predominately galactomannan [8], (20-30%) of seeds consist of proteins, one of the most predominate to be amino acid 4-hydroxyisoleucine [8], (6-10%) of seeds consist of lipid, predominately polyunsaturated fatty acids [8], (2-3%) of seeds consist of alkaloids, and (5-6%) of seeds consist of saponins [8]. Fenugreek seed also consists of amino acid 4-OH-Ile. As observed by Mandegary et al., it is important to understand the pharmacology of a plant and its active ingredients when considering plants as medicinal alternatives [9].

## Diosgenin

Diosgenin is a steroid living in fenugreek that alleviates symptoms related to diabetes mellitus, inflammation, oxidative stress, cardiovascular disease and cancer [10]. Experimental studies have found diosgenin in fenugreek to stabilize insulin and glucose in diabetic-induced animals. A study by Kalailingam et al. found diosgenin to decrease glycolytic enzyme glucokinase concentrations in Streptozotocin (STZ)-induced diabetic rats ( $p < 0.05$ ) and stabilize to a normal level ( $p < 0.05$ ) after 30 days of diosgenin treatment [11]. Controlled doses of diosgenin were administered at 10mg/kg, daily [11]. Kalailingam et al. observed an increase in the number of insulin granules and beta cells in STZ-induced diabetic rats following 30 days of diosgenin treatment [11]. Additionally, antioxidant enzyme concentrations, glucose-6-phosphatase, pancreatic  $\beta$ -cell number, serum HDL, alanine transaminase, glycated hemoglobin, serum LDL, and total cholesterol, were stabilized following 30 days of controlled dosage of diosgenin [11].

A similar study by Saravanan et al. tested diosgenin on STZ-induced diabetic rats and found oral doses of diosgenin at various amounts reduced blood glucose level and increased plasma insulin concentrations [12]. Controlled doses of diosgenin ranged from 15, 30 and 60mg/kg based on body weight, and were administered for a period of 45 days. STZ-induced rats had high blood glucose levels ( $p < 0.05$ ) and low insulin levels before diosgenin dosage. Following diosgenin treatment, blood glucose level and plasma insulin levels increased [12]. Diosgenin doses also stabilized the changed muscle and kidney carbohydrate metabolic key enzymes of the diabetic rats ( $p < 0.05$ ) [12].

This active compound may be a successful component to medications that curb the negative impact of diabetes.

### Ethanol Extract

Premanath et al. tested the effect of ethanol leaves extract of fenugreek seeds on levels of blood glucose, creatinine and urea, antioxidant enzymes, and islets cells of pancreas of STZ-diabetic rats and non-diabetic rats and found that ethanol leaf extract had similar results to Antidiabetic drug glibenclamide [13].

Rats were organized into the following treatment groups:

- **Group A:** saline control; saline was given orally via mouth gauge.
- **Group B:** normal control; supervised with leaf extracts of 250 and 500mg/kg based on body weight and observed for toxic impact on kidney and liver. Leaf extract given orally via mouth gauge.
- **Group C:** normal control; supervised with leaf extracts of 250 and 500mg/kg based on body weight and observed for toxic impact on kidney and liver. Leaf extract given orally via mouth gauge.
- **Group D:** diabetic control
- **Group E:** glibenclamide group; supervised under a dose of 0.5mg/kg based on body weight. Glibenclamide was given orally via mouth gauge.
- **Group F:** diabetic control group administered with 250 and 500mg/kg of leaf extract based on body weight. Leaf extract given orally via mouth gauge.
- **Group G:** diabetic control group administered with 250 and 500mg/kg of leaf extract based on body weight. Leaf extract given orally via mouth gauge.

Rats were injected with STZ dissolved in saline (45mg/kg based on body weight) following 16 hours of blood glucose fasting. Rats that were able to maintain a constant level of hypoglycemia (fasting blood glucose >200mg/dl) were included in the study [13]. The test lasted 28 days, after which blood was extracted from the tail, under anesthesia. Leaf extract helped stabilize blood glucose level for almost 4 weeks. Blood glucose level of diabetic control rats increased (68.7%) [13].

Controlled doses of ethanol extract of fenugreek leaves

decreased dose dependent blood glucose concentrations by approximately (23.5%) ( $P=0.000$ ) and (31.2%) ( $P=0.000$ ), respectively [13]. When comparing results of 500mg/kg based on body weight of extract compared to commercial drug glibenclamide, Premanath et al. found that the dose dependent impact lasted approximately 25 days of the experiment and remained consisted for 4-5 days following the treatment. Premanath et al. report consistent levels of glucose fasting in both normal control rats and normal control rats administered with ethanol extract.

After STZ was induced, ethanol extract of fenugreek leaves lowered the weight of rats in Group D (diabetic control), Group E (glibenclamide), Group F (diabetic control administered with leaf extract) and Group G (diabetic control group administered with leaf extract). Weight loss was observed for 4 weeks in diabetic control animal groups, although Group F and Group G saw an increase of (42%) ( $P=0.000$ ) and (44.9%) ( $P=0.000$ ), respectively, in weight with controlled doses of 250 and 500mg/kg ethanol extract based on body weight. Group A, Group B, and Group C also experienced weight gain during the experiment. There was also a comparable difference in the weight of Group F and Group G compared to Group D [13]. In the kidney, ethanol extracts increased serum creatinine, urinary creatinine and blood urea concentrations in diabetic control rats compared to normal rats. By the 28th day of administered ethanol extract and glibenclamide, creatinine and urea concentrations were much lower. Doses of 500mg/kg per body weight dropped serum creatinine concentration to 73.6%; urinary creatinine concentration to (62.7%) and serum urea concentration to (50.6%), respectively [13]. Premanath et al. report that ethanol extract treated rats saw greater reduction in serum creatinine concentration, urinary creatinine concentration, and serum urea concentration, compared to rats treated with glibenclamide. Group B and Group C did not experience any reduction or increase in urea or creatinine concentrations [13].

Ethanol extract helped reduce antioxidant enzymes SOD, catalase, and GSH-Px levels in STZ- induced diabetic control rats compared to normal rats. SOD was lowered to 3.23U/mg proteins; catalase was recorded at a level of 6.37U/min/mg protein; and GSH-Px was at a level of 3.45U/mg protein, respectively [13]. It took 28 days of ethanol extract and glibenclamide doses to reduce creatinine and urea concentrations. Diabetic rats administered with 500mg/kg of ethanol extract based on body weight experienced a higher level of SOD activity than rats administered with

glibenclamide [13]. Group B and Group C also experienced more enzyme activity. Islets were reduced in the pancreas and there was a significant difference in islets located in the  $\beta$  cell area when rats were treated with either 250mg/kg based on body weight, or 500mg/kg based on body weight. At a dose of 250mg/kg, cells were stabilized to a normal number in the  $\beta$  Cell. The 500mg/kg dose of the extract raised the number and heightened the size of the islets. These findings were measurable to results from glibenclamide [13].

### Hydroalcoholic Extract

STZ is a necrosis agent for  $\beta$ -cells. GLUT2, a glucose transporter, allows STZ to infiltrate  $\beta$ - cells. When STZ infiltrates  $\beta$ -cells, GLUT2 becomes an agent for alkylation of DNA, an advanced ATP dephosphorylation of superoxide radicals. STZ also rids nitric oxide that is toxic to aconites movement and DNA damage [14,15].

Studies have shown that specific doses of fenugreek seed extract create a triggering response on cellular glucose absorption that increases GLUT4 movement to the cell surface. Kulkarni et al. used neonatal STZ-induced rats to test the effect of fenugreek seed extract and its ability to trigger a cellular response that activates GLUT4 cells to the cell surface, and the impact on diabetic symptoms [14,15].

Kulkarni et al. found that hydro alcoholic fenugreek seed extract decreased serum glucose concentration, body weight, and HBA1c concentrations in STZ-induced rats [15]. Rats were administered with fenugreek seed for 28 days, during which  $\beta$ -cell activity and alteration, glucose levels and glycemia, were observed in relation to type 2 diabetes mellitus. Neonatal rats were injected with STZ develop symptoms similar to humans with type 2 diabetes mellitus, making it easier to pinpoint symptoms specific to diabetic patients, including abnormal glucose tolerance, insulin resistance, hyperglycemia, polyphagia, polydipsia, and ptyuria [15]. Kulkarni et al. used IND01, hydro alcoholic extract of fenugreek seed with galactomannan, 4-HI, and trigonelline, which help reduce diabetic mellitus symptoms in diabetic-induced animals [15]. 4-HI has been linked to  $\beta$ -cell mass reproduction in the pancreas, although the relationship between IND01 and the development of diabetes mellitus, specifically on  $\beta$ -cell mass in the pancreas, are not well defined.

### Aqueous Extract and Methanolic Extract

In a separate study analyzing the hypoglycemic function

of water extract and methanolic extract of fenugreek seed on mice, Zia et al. found methanolic extract to have a dose-dependent effect on reducing hypoglycemia in normal mice [16]. Aqueous extract was administered at a dose of 0.5 and 1g/kg and methanolic extract was administered at a dose of 1g/kg [16]. Blood glucose levels lowered at the administered aqueous dose of 0.5g and 1g/kg, respectively, based on body weight in mice with normal blood glucose levels in mice with oral doses of water extract [16]. Blood glucose amounts were lowered at methanolic extract amounts of 1g/kg, respectively, based on body weight, although no difference was seen at a dose of 0.5g/kg, respectively, based on body weight [16]. Zia et al. propose the reason for this difference to be in the nature of the seed, as the seed may be more soluble in water compared to methanol [16]. The chemical components and activity of fenugreek seed in relation to hypoglycemic function is under investigation by Zia et al. discuss that the small doses may have played a role in negatively affecting the outcome of the results, as the small administered amount did not yield a strong decrease in blood glucose amount between 1 and 4 hours of the experiment time.

### IND01

IND01, a component of fenugreek seed extract, successfully weakened hyperglycemia, elevated glucose homeostasis, including lowering HBA1c levels and raising  $\beta$ -cell activity in the pancreas and boosting serum insulin levels in neonatal STZ-induced rodents [15]. Neonatal STZ-induced rats served as the control group. STZ achieved a consistent level of basal hyperglycemia and glucose intolerance, lowered insulin concentration, and increased HbA1c, also found in previous studies of neonatal STZ-induced rats [15]. When IND01 (100mg/kg), a component of fenugreek seed extract, and glyburide was tested on neonatal STZ-induced rats, serum glucose levels were reduced after 6 hours of administration [15]. It took 7 of the 28 experiment days for blood serum glucose level to show stabilized antihyperglycemic activity in neonatal STZ-induced rodents [15].

## Results and Discussion

Review article by Neelakantan et al. conducted a comprehensive literature analysis by analyzing 10 clinical trials using fenugreek to assist postprandial glucose levels [17]. Neelakantan et al. included clinical trials looking at both single herb use of fenugreek and a control. The control was either a placebo or sans treatment. Clinical trials included

analysis of glycemia, which included blood glucose 2 hours after mealtime, the percentage of HbA1c (glycosylated hemoglobin), and/or serum insulin concentration, respectively [17]. Fenugreek seed successfully lowered blood glucose levels as to control agents, depending on symptoms of diabetic patients and the effect of dosage on fasting [17]. Successful postprandial glucose levels were achieved with 25g of cooked seeds, whole fenugreek raw seeds, 5g of gum isolate of seeds, and extracted seed powder. Degummed seeds, approximately 25g, did not have a significant impact in trial studies. Neelakantan et al. propose that these findings help establish gum fraction as most significant for lowering blood glucose [17]. Neelakantan et al. report the most significant form of fenugreek on lowering blood glucose was powdered, although the selection of analyzed trials was not a comprehensive meta-analysis [17].

A study by Vijayakumar et al. investigated the impact of fenugreek seed aqueous extract on hypoglycemia in alloxan-injected diabetic mice. Vijayakumar et al. looked at a water extract of fenugreek seeds in vivo and the ways the extract impacted insulin activity and movement in liver cells and adipocytes. Seeds were washed and rinsed with distilled water, after being sterilized with sodium hypochlorite (soaked in 0.1%) and nonidenti P-40 (soaked in 0.05%). Vijayakumar et al. state that fenugreek seed extract was commensurable to insulin in alloxan-injected diabetic mice. Seed extract also positively impacted intraperitoneal glucose absorption in normal mice [18]. This was conducted in vivo and insulin was measured at 1.5U kg<sup>-1</sup> [18].

In a separate study testing GII, a purified water soluble compound of fenugreek seed on alloxan-induced rabbits, it was found that GII treatment: lowered elevated lipids caused by diabetes; lowered the increased liver and heart total lipids; raised the low levels of hexokinase, lucokinase, pyruvate kinas, glucokinase, aldose reeducates', malice enzyme, superoxide dismutase, glutathione peroxides, glucose-6-phosphatase dehydrogenises; and lowered the raised levels of glucose-6-phosphatase, aldose reeducates', and sorbitol dehydrogenises, according to Puri et al. These results were achieved after rabbits were given controlled doses of GII for 15 days, orally. Rabbits were injected with alloxan and sub diabetic and moderately diabetic rabbits were fed 50 mg/kg based on body weight, every morning for 15 days [19]. Extremely diabetic rabbits were given the same dose, once every morning, for 30 days [19].

Baquer et al. set to test the function of fenugreek seed in reducing blood glucose levels and found that oral doses

of fenugreek seed powder was comparable to insulin. Baquer et al. administered tests investigating the function of manganese and vanadate, plant-based supplements used for treating diabetes mellitus, and fenugreek seed, and the similarity in function as compared to insulin. Fenugreek seed is a strong candidate for restoring normal levels of blood glucose because of its ability to trigger GLUT4. When insulin exists at levels below normal, GLUT4 transporters are unable to function properly and remain staged in the cell. Glucose is unable to move and is absorbed inefficiently, increasing blood glucose levels. GLUT4 must be properly activated in order to stabilize glucose levels. Baquer et al. report that vanadate, a plant-based supplement suggested to heighten insulin sensitivity for diabetic patients, was combined with fenugreek seed to restore GLUT4 transportation to stable levels [20]. Baquer et al. also tested the impact of manganese, an additional supplement used to monitor protein phosphates and activity in relation to insulin mimetic function of manganese, according to Baquer et al. Baquer et al. investigated the impact of manganese to find that manganese helps stabilize the functional component of insulin mimetic activity of manganese, meaning the metal ions on lipolysis in rat adipocytes works positively with manganese [20-22]. Baquer et al. propose that the manganese-dependent enzymes are more functional when manganese is available. A study by Gong et al. found that fenugreek lactone plays a positive role in reversing the erratic function of insulin secretion in pancreatic NIT-1  $\beta$ -cells by triggering oxidative stress. Additional research may find the link between oxidative stress and fenugreek lactone, further advancing the field of diabetic research and alternative remedies [23].

### Conclusion

Directing research attention on fenugreek seed and fenugreek seed extract could help develop a new drug diabetes mellitus. Advanced research in alternative remedies could provide an innovative solution for recovering  $\beta$ -cell activity and mass caused by adult pancreas plasticity. Healthier eating habits, maximizing healthy eating and exercise habits in early life and during pregnancy, fiber intake [13,15,24-28], increasing exercise, and maintaining a healthy weight can help stabilize long-term effects of type 2 diabetes mellitus, as stated by the American Diabetes Association, additional research will help stop the progression of diabetes [29,30].

### Conflict of Interest

Authors declare no conflict of interest.

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