Review Article

A Narrative Review on Evidence-based Antidiabetic Effect of Fenugreek (*Trigonella Foenum-Graecum*)

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Abstract

Diabetes mellitus is one of the most common endocrine metabolic disorders. Adverse effects of the conventional antidiabetic therapy are increasing. Many herbs have strong antidiabetic properties, and fenugreek is one among them. Although fenugreek is one of the most common herbs used for diabetes, its antidiabetic effects are not well-documented. The aim of this review was to report the evidence-based antidiabetic effects of fenugreek. We performed PubMed/Medline search to review relevant articles in English literature using keywords "*trigonella foenum graecum* for the management of diabetes." Out of 26 articles found, 18 articles were reported in this review. Based on the available literature, this review suggests that the fenugreek has the evidence-based antidiabetic effect, such as stimulating and/or regenerating effect on β cells along with the extrapancreatic effect, that is effective in reducing blood glucose levels in diabetic patients.

Keywords: Antidiabetic effect, diabetes, fenugreek, *Trigonella foenum-graecum*

Background

Diabetes mellitus (DM) is one of the most common endocrine metabolic disorders[1] characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both.[2] According to International Diabetes Federation, the prevalence of diabetes in 2011 crossed 366 million, with an estimated deaths about 4.6 million each year.[3] According to the World Health Organization, prevalence of DM in India was 31.7 million in 2000, and this would increase up to 79.4 million by 2030. Many side effects, such as hypoglycemia, lactic acid intoxication, and gastrointestinal upset, have been reported in patients with antidiabetic drug therapy.[4] There are many herbs having strong antidiabetic properties, and fenugreek is one among them.[1] Although fenugreek is one of the most common herbs used for DM, its antidiabetic effects are not well-documented. Hence, this review was performed to report the evidence-based antidiabetic effects of fenugreek.

Materials and Methods

We performed a PubMed/Medline electronic database search to review the relevant articles in English literature using the keywords "*Trigonella foenum graecum* for the management of diabetes." A total of 26 articles were available from the inception till March 16, 2017. All the relevant articles that fit into the following inclusion and exclusion criteria were reported in this review. ***Inclusion criteria:*** These are clinical trials, controlled trials, randomized controlled trials, systematic reviews, and meta-analysis that are dealing with fenugreek alone or in combination with other herbs. ***Exclusion criteria:*** Research protocols, comments, and articles that do not have either abstract or full text, articles with lack/similar information. Of 26 articles, 18 articles were reported in this review.

Fenugreek and the Methods of its Application

Fenugreek (*Trigonella foenum-graecum*)

Under the family of *Fabaceae*, which is found all over India, its seeds are frequently used as a constituent of spices[4] that possesses antidiabetic, antihyperlipidemic, and antioxidant properties.[5] The components such as saponins, 4-hydroxyleucine/4-hydroxyisoleucine, trigonelline, alkaloid,

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high fiber,[1,3] and diosgenin[6] are responsible for its therapeutic potential.

The various forms of fenugreek used in the studies

Powder and gum of the fenugreek seeds and leaves;[1] fenugreek seed soaked in water,[7] mucilage,[8] aqueous,[2] and hydroalcoholic extract;[9] fenugreek seed powder in hot water; fenugreek pills; mixed powder containing equal amount of raw fenugreek seed, bitter gourd, and Jambu seed powder in the form of capsules;[7] and fenugreek oil.[3,4]

The most common models used in the studies

Humans and relevant animal models like rats [Streptozotocin (STZ)-induced diabetic rat,[2,6] alloxanized rats],[3,9] diabetic obese KK-Ay mice,[10] and db/db mice model[4] were used for experiments.

Effects of fenugreek

Fenugreek is reported to have antidiabetic, antihyperlipidemic,[5,10] stimulating/regenerating effect on β cells,[11] antilithogenic potential,[4] antioxidant,[3,5] and neuroprotective effects.[12]

Various methods and doses of fenugreek used in the studies and its effects in DM

Fenugreek is one of the natural supplements that have been reported to reduce the risk, improve glycemic control, and to minimize the need for insulin therapy in DM.[13]

(1) An amount of 500 mg of fenugreek once/twice daily either alone or in combination with synthetic antidiabetic drugs, such as metformin and glipizide, controlled plasma glucose levels.

(2) Supplementation of 15-g fenugreek seed soaked in water significantly reduced the post prandial blood sugar (PPBS) levels.

(3) Dietary supplementation of 25 and 100 g of fenugreek seed powder daily for 15 and 10 days, respectively, significantly reduced fasting blood sugar (FBS) and improved the glucose tolerance test.

(4) An amount of 1-g mixed powder containing equal amount of raw fenugreek seed, bitter gourd, and Jambu seed powder in the form of capsules and in the form of salty biscuits daily for 1.5 months, followed by 2-g mixed powder for another 1.5 months, showed a significant reduction in FBS and PPBS.[7]

(5) Daily oral administration of diosgenin (an active compound of fenugreek) at different doses (15, 30, and 60 mg/kg body weight) to diabetic rats for 45 days has shown to produce a significant decline in blood glucose level and a significant increase in plasma insulin level along with significant reversal of the altered activities of carbohydrate metabolic key enzymes in muscle and kidneys of diabetic rats to near normal level. Moreover, these results were comparable with Glibenclamide (a standard oral hypoglycemia drug).[6]

(6) Hydroalcoholic extract of fenugreek seeds at different doses (500, 1000, and 2000 mg/kg) was shown to produce increased body weight and glucose uptake, reduced plasma glucose, glycosylated hemoglobin (HbA1c), liver glucose transport, proinflammatory cytokines, pancreatic enzymes, and restored depleted glycogen (muscle and liver) and total protein significantly and dose dependently. It has also shown to produce prevention of lipid peroxidation and restoration of glutathione and superoxide dismutase (liver and pancreas). Moreover, the histoarchitecture of liver and pancreas was shown to have marked improvement in alloxan-induced DM rat.[9]

Effect of fenugreek when mixed with hot water and yogurt

An amount of 10-g fenugreek seed powder in hot water daily for 8 weeks significantly decreased the FBS, triglycerides, and very low-density lipoprotein (VLDL) cholesterol, unlike the fenugreek seeds mixed with yoghurt.[7,14]

Fenugreek with Sulfonylureas

In uncontrolled type-2 DM, 18 pills of fenugreek daily along with oral sulfonylureas have shown to significantly decrease FBS, PPBS, and HbA1c levels and the associated clinical symptoms. It suggests that the supplementation of fenugreek along with sulfonylureas was an effective therapy to manage diabetic patients with uncontrolled blood glucose level.[7]

Hydroalcoholic extract of fenugreek seeds with Glimepiride: It has been reported to potentiate the hypoglycemic activity of Glimepiride.[9]

Antidiabetic Effects of Fenugreek with Possible Mechanisms

Fenugreek seed extracts have been reported to exhibit antidiabetic potentials by producing delay in gastric emptying time and glucose absorption rate; reducing the glucose uptake in the small intestine by its high-fiber content that slows carbohydrate metabolism and lowered blood glucose; restoring the function of pancreatic tissues;[1,5] protecting β cells; elevating serum insulin level possibly through β-cell regeneration or stimulation of insulin release from existing β cells of islets; stimulating the activity of glycogen synthetase and promote the formation of liver and muscle glycogen;[2] reducing the proinflammatory cytokines and pancreatic enzymes, and promote the restoration of depleted glycogen (muscle and liver);[9] correcting the insulin-sensitive carbohydrate metabolic enzymes activities; correcting serum lipid profiles;[2] preventing lipid peroxidation and restoring glutathione and superoxide dismutase (liver and pancreas);[9] promoting insulin sensitivity; improving insulin action at cellular level;[1,5] and recovering the level of HbA1c by utilization of glucose in peripheral tissues where by maintain the blood glucose level.[2]

Many studies have reported the role of free radicals in the pathogenesis of DM where oxidative stress coexists along with decrease in antioxidant status.[4] Fenugreek has been proven to have antioxidant activity[3,5] that might prevent the pathogenesis of diabetes. In a previous study, solid-state bioconversion of the fenugreek substrate by *Rhizopus oligosporus* has shown to significantly increase the natural α-amylase inhibitors associated with high phenolic antioxidants, which potentially reduces the glycemic index and hence, reported to be useful in the management of carbohydrate metabolism disorders linked to DM.[15] 4-Hydroxyleucine, a novel amino acid from fenugreek seed, was reported to increase glucose-stimulated insulin release by isolated islet cells in rats, mice, and humans. A specific amino acid called 4-hydroxyisoleucine, which represents 80% of the free amino acid in fenugreek seeds, was reported to possess insulin-stimulating properties,[1] and enhance insulin sensitivity and glucose uptake in peripheral tissues.[3] In a study, 4-hydroxyisoleucine has reported to suppress the progression of type-2 diabetes in mice model.[4]

In another study, fenugreek oil has been reported to produce antidiabetic effect due to its immunomodulatory- and insulin-stimulating action in alloxanized rats.[4] Daily oral treatment of fenugreek steroids has shown to produce significant reduction in blood glucose level and a substantial enhancement in the area of insulin-immunoreactive β cells along with considerable reduction in sperm-shape abnormality and improved sperm counts in diabetic rats.[4]

Role of Fenugreek in the Pathogenesis and Complications of DM

DM indicates a condition with disturbed carbohydrate and fat metabolism.[4] Important carbohydrate metabolic enzymes, such as hexokinase, glucose-6-phosphatase, and glucose-6-phosphate dehydrogenase, were altered in STZ-induced diabetic rat. But, aqueous-extract seeds of *T. foenum-graecum* L. and *Psoralea corylifolia* in composite manner (1:1) have shown to produce a significant recovery in the activities of these enzymes in hepatic tissue[2] and thus, reported to correct the abnormal metabolism.

Hypertension, hyperlipidemia, and atherosclerosis are often associated with diabetes.[4] In a study, fenugreek diet has shown to produce a significant reduction in FBS, 24-h urinary glucose excretion, and improvement in glucose tolerance test, along with significant reduction in serum total cholesterol, low-density lipoprotein (LDL) cholesterol, VLDL cholesterol, and triglycerides.[16] In another study, a polyherbal formulation consisting *T. foenum-graecum*, *Allium sativum*, *Aloe vera*, *Nigella sativa*, *Plantago psyllium*, and *Silybum marianum* has shown to be safe and efficacious in lowering the levels of FBS, HbA1c, triglycerides, and LDL cholesterol levels in patients with advanced stage of type-2 diabetes.[17] It suggests that fenugreek might have hypolipidemic and antilithogenic potential due to its effect on cholesterol metabolism. This will help in reducing the risk of development of hypertension, hyperlipidemia, and atherosclerosis.[4]

Although the pathophysiology of diabetes is not entirely understood, many studies have reported the role of free radicals in the pathogenesis of diabetes and its complications.[4] Oxidative stress may play an important role in the onset and progression of diabetic vascular complications, and it can be prevented and treated with antioxidants.[5] Fenugreek has been reported to have antioxidant activity,[3,5] and its substrates were shown to significantly increase phenolic antioxidants[15] that might be useful for the prevention of diabetes pathogenesis and its complications. Reactive oxygen species (ROS) are being reported to be formed in different tissues in diabetes which are also involved in the progression of insulin resistance as well as pancreatic β-cell dysfunction.[4] The presence of amino acid 4-hydroxyisoleucine in fenugreek seed has reported to enhance insulin sensitivity and stimulating/regenerating β cells of pancrease[11] that might be useful for the prevention of insulin resistance as well as pancreatic β-cell dysfunction by ROS.

Liver- and insulin-dependent tissues play a vital role in glucose and lipid homeostasis. These are severely affected during diabetes.[2] In a study, fenugreek has reported to ameliorate hepatic steatosis and hyperlipidemia by suppressing the messenger ribonucleic acid (mRNA) expression of lipogenic genes. Diosgenin (an active component of fenugreek) has reported to have a liver-X-receptor-α antagonist-like effect that suppresses lipid accumulation in HepG2 cells. Hence, it plays an important role in the therapeutic effect of fenugreek on lipid metabolism disorders in the liver of diabetic obese KK-Ay mice.[10] In other studies, its seed powder has been shown to normalize the activity of creatinine kinase in liver, skeletal muscles, and heart. Intake of fenugreek oil has reported to produce a notable reduction in renal toxicity and improvement in hematological status of alloxanized rats.[3,4] Specific activities of intestinal disaccharidases were shown to be increased significantly during diabetes. Whereas intake of fenugreek seed mucilage has reported to ameliorate, these activities indicate their beneficial role in the management of diabetes and its complication.[8]

Diabetic retinopathy and neuropathy are the common complications of DM. In a study, fenugreek seed has shown to be effective in the prevention of retinopathy and other diabetic complications when used alone or in combination with sodium orthovandate.[4] In another study, fenugreek seed powder exerts have been reported to have neuroprotective effects that probably mediate through a decrease in hyperglycemia and oxidative stress, thereby ameliorating the control and management of diabetic-complications.[12]

Role of Fenugreek in Type-1 DM

Insulin-dependent diabetes (IDDM) is categorized as autoimmune (immune-mediated) diabetes or idiopathic diabetes.[4] In patient with IDDM, intake of 100 g of defatted fenugreek seed powder during lunch and dinner has shown to significantly reduce the FBS, triglycerides, serum total cholesterol, LDL, and VLDL cholesterol and improved the glucose tolerance test. The high density lipoprotein (HDL) cholesterol fraction remained unchanged.[16] This improvement in IDDM could be possibly through elevation in serum insulin level, β-cell regeneration, and/or increased pancreatic insulin from existing β cells of islets,[2] as IDDM is characterized with β-cell destruction and causes severe damage to the pancreatic β cells.[4]

Other Factors to be Considered for the Use of Fenugreek in DM

Medicinal plants like fenugreek provide better alternatives as they are generally less toxic, affordable, nongenotoxic, and have a wide safety margin.[4] There is good scientific evidence (Level B2) suggesting that fenugreek is effective in reducing blood glucose levels in diabetic patients,[7] and it has been experimentally documented to possess antidiabetic potential.[18]

Conclusion

Based on the available literature, this review suggests that fenugreek has evidence-based antidiabetic effect, such as stimulating and/or regenerating effect on β cells along with extrapancreatic effects that are effective in reducing blood glucose levels in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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