

Therapeutic Applications of Fenugreek

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Abstract

Fenugreek has a long history of medical uses in Ayurvedic and Chinese medicine, and has been used for numerous indications, including labor induction, aiding digestion, and as a general tonic to improve metabolism and health. Preliminary animal and human trials suggest possible hypoglycemic and antihyperlipidemic properties of oral fenugreek seed powder.

(*Altern Med Rev* 2003;8(1):20-27)

Historical Uses of Fenugreek

Fenugreek (*Trigonella foenum-graecum* L. *Leguminosae*) is one of the oldest medicinal plants, originating in India and Northern Africa. An annual plant, fenugreek grows to an average height of two feet. The leaves and seeds, which mature in long pods, are used to prepare extracts or powders for medicinal use. Applications of fenugreek were documented in ancient Egypt, where it was used in incense and to embalm mummies. In modern Egypt, fenugreek is still used as a supplement in wheat and maize flour for bread-making.¹ In ancient Rome, fenugreek was purportedly used to aid labor and delivery. In traditional Chinese medicine, fenugreek seeds are used as a tonic, as well as a treatment for weakness and edema of the legs.² In India, fenugreek is commonly consumed as a condiment² and used medicinally as a lactation stimulant.³ There are numerous other folkloric uses of fenugreek, including the treatment of indigestion and baldness. The possible hypoglycemic and antihyperlipidemic properties of oral fenugreek seed powder have been suggested by the results of preliminary animal and human trials.

Active Constituents

The fraction of fenugreek that contains the testa (i.e., the portion of the fenugreek seed with the peculiar smell and bitter taste) and the endosperm of the defatted seeds (i.e., the “A” subfraction) are thought to be associated with the hypoglycemic effects of fenugreek. These effects have not been observed in studies of lipid extracts.^{4,5} It is possible fenugreek lowers lipids because it contains saponins that are transformed in the gastrointestinal tract into saponinins. Fenugreek seeds contain 50-percent fiber (30-percent soluble fiber and 20-percent insoluble fiber) that can slow the rate of postprandial glucose absorption. This may be a secondary mechanism for its hypoglycemic effect.

Mechanisms of Action

The hypoglycemic effects of fenugreek have been attributed to several mechanisms. Sauvaire et al demonstrated *in vitro* the amino acid 4-hydroxyisoleucine in fenugreek seeds increased

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glucose-induced insulin release in human and rat pancreatic islet cells.⁶ This amino acid appeared to act only on pancreatic beta cells, since the levels of somatostatin and glucagon were not altered. In human studies, fenugreek reduced the area under the plasma glucose curve and increased the number of insulin receptors, although the mechanism for this effect is unclear.⁷ In humans, fenugreek seeds exert hypoglycemic effects by stimulating glucose-dependent insulin secretion from pancreatic beta cells,⁸ as well as by inhibiting the activities of alpha-amylase and sucrase,⁹ two intestinal enzymes involved in carbohydrate metabolism.

Fenugreek seeds also lower serum triglycerides, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C).¹⁰⁻¹⁴ These effects may be due to saponins, which increase biliary cholesterol excretion, in turn leading to lowered serum cholesterol levels.^{10,15-17} The lipid-lowering effect of fenugreek might also be attributed to its estrogenic constituent, indirectly increasing thyroid hormone T₄.

Fenugreek in the Treatment of Diabetes

Type 2 Diabetes

In animal and several small, human trials, fenugreek seeds have been found to lower fasting serum glucose levels, both acutely and chronically.

Gupta et al reported the results of a small randomized, controlled, double-blind trial to evaluate the effects of fenugreek seeds on glycemic control.¹⁸ Twenty-five patients with newly diagnosed type 2 diabetes received either 1 g daily of a hydroalcoholic extract of fenugreek seeds or “usual care” (dietary discretion and exercise). After two months, mean fasting blood glucose levels were reduced in both groups without significant differences between groups (148.3 mg/dL to 119.9 mg/dL in the fenugreek group versus 137.5 mg/dL to 113.0 mg/dL in the “usual care” group). There were no significant differences between groups in mean glucose tolerance test values at the study’s end. The authors did note differences between groups in the area under the curve for

blood glucose and insulin levels. This study suggests that fenugreek seed extract and diet/exercise may be equally effective strategies for attaining glycemic control in type 2 diabetes. However, the trial may have been too small or brief to detect significant mean differences between groups. In addition, it is not clear if mean glucose values would have normalized without intervention, and design and methods were not well described, which limits the clinical relevance of these results.

Raghuram et al reported the results of a randomized, controlled, crossover trial of fenugreek seeds in 10 patients with type 2 diabetes.⁷ The doses of these patients’ antidiabetic drug, glibenclamide, ranged from 2.5-7.5 mg per day; both medication dose and dietary intake were stabilized prior to the actual study periods. The patients were given either 25 g powdered fenugreek seeds in two equal doses with meals or meals without fenugreek supplementation for 15 days. The fenugreek powder was added to the experimental diet in the form of dietary fiber, resulting in higher fiber content in the experimental diet than in the control diet. Five diabetic patients were randomized to receive fenugreek during the first 15-day period; the other five received it during the second period. Subjects were then crossed over an additional 15 days with no washout period. In the fenugreek-treated patients, statistically significant mean improvements were reported for glucose-tolerance test scores and serum-clearance rates of glucose (control group, 153 ± 11.92 mg/mL/min; fenugreek group, 136.4 ± 6.36 mg/mL/min). The absolute difference in glucose between the two groups was not mentioned. Larger studies with washout periods are needed to confirm these results.

Sharma and Raghuram conducted two randomized, controlled, crossover studies in patients with type 2 diabetes.¹⁹ The doses of 15 patients’ antidiabetic drug, glibenclamide/glipizide/metformin, were reduced by 20 percent and both medication dose and dietary intake were stabilized for one week prior to the actual study periods. In the first study, subjects ate meals with or without 100 g of defatted fenugreek seed powder, divided into two equal doses, for 10 days. Patients were

Table 1. Summary of Fenugreek Studies for Diabetes

Condition Treated (Primary or Secondary Outcome)	Evidence/ Study Type	Author, Year	N	Statistically Significant Results?	Quality of Study 0- 2=poor 3-4=good 5=excellent	Magnitude of Benefit (how strong is the effect?)	Absolute Risk Reduction	Number of Patients Needed to Treat for One Outcome	Comments
Type 2 diabetes, hyperlipidemia	Randomized, controlled, double-blind study	Gupta, 2001	25	Yes	3	None	NA	NA	Improved fasting glucose and GTT with fenugreek seeds or diet/exercise, without differences between groups. Altered AUC and insulin resistance with fenugreek.
Type 2 diabetes	Randomized, crossover study	Raghuram, 1994	10	Yes	1	Large	NA	NA	Improved peripheral glucose utilization with fenugreek seed supplementation.
Type 2 diabetes	Randomized, crossover study	Sharma, 1990	15	Yes	1	Small	NA	NA	Improvement in reported diabetic symptoms.
Type 2 diabetes	Case series with matched controls	Neeraja, 1996	12	Yes	1	Medium	NA	NA	Improvement of acute glycemic response, most notable with raw fenugreek seed powder.
Type 1 diabetes, hyperlipidemia	Randomized, crossover study	Sharma, 1990	10	Yes	1	Large	NA	NA	Fasting blood glucose levels and GGT improved; serum insulin levels unchanged.

then crossed over an additional 10 days. Seven of the 15 patients received the fenugreek diet first; there was no washout period.

The second study had a similar study design, except the duration of the study was 20 days and the total subject number was five (three patients received the fenugreek diet first).¹⁹

Table 2. Jadad Score Explanation

Item	Score*
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1

*Points are added, and a score ≥ 4 is considered high quality methodologically. Based on Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

Significant mean improvements in fasting blood-glucose levels and glucose-tolerance test results were described in the fenugreek-treated patients. The reduction in fasting blood glucose ranged from 179 ± 24 mg/dL to 137 ± 20.2 mg/dL ($p < 0.05$) in the first study and from 157 ± 22.2 mg/dL to 116 ± 17.1 mg/dL ($p < 0.05$) in the second study. The 24-hour urinary glucose excretion in both studies was statistically significant. The fenugreek-treated patient group also reported subjective improvements in polydipsia and polyuria.

Neeraja and Rajyalakshmi presented a poorly designed, complex case series including six men with type 2 diabetes and six without diabetes.²⁰ The cases suggest fenugreek reduced post-prandial hyperglycemia primarily in subjects with diabetes, but less so in subjects without diabetes. This effect might be more pronounced if raw seeds rather than boiled seeds had been used.

Results from several additional case series²¹⁻²⁴ also suggest fenugreek seeds may improve glycemic control in type 2 diabetes. As with all

case series, however, the lack of controls increases the possibility the results obtained were due to confounding from other interventions. Although the results of some of these case series are promising, the conclusions drawn from them are preliminary. The studies conducted to date have been methodologically weak, lacking adequate descriptions of blinding, randomization, baseline patient characteristics, statistical analysis, and standardization data for the therapy used. Demonstrating the efficacy of fenugreek has also been confounded by inconsistencies in the preparations, dosing regimens, and outcome measures used in the trials. Moreover, none of the investigations have been conducted over the long term. Additional study of fenugreek is warranted in this area before firm conclusions can be drawn.

Type 1 Diabetes

Sharma et al conducted a randomized, controlled, crossover trial in 10 patients with type 1 diabetes.²⁵ Over a 10-day period, the subjects were served meals that contained 100 g fenugreek seed powder in two divided doses each day (lunch and dinner) or meals without fenugreek. At the study's end, significant improvement was noted in the fenugreek group in several parameters, including a 54-percent reduction in 24-hour urine glucose levels and mean reductions in glucose-tolerance test values and fasting serum-glucose levels (from 15.1 ± 2.4 mMol/L to 10.9 ± 2.75 mMol/L; $p < 0.01$). Although these data are intriguing, they cannot be considered definitive. This study suggests fenugreek may aid with insulin secretion, as suggested by animal studies, since typically these patients have little or no endogenous insulin production. More studies in people with type 1 diabetes are warranted.

Table 1 summarizes the fenugreek studies for diabetes, while Table 2 describes the scoring procedure for these studies.

Effects on Lipid Lowering

In the Sharma et al trial on type 1 diabetes cited above,²⁵ small but statistically significant reductions were noted in TC (approximately 1.3 mMol/L; $p < 0.001$) and in LDL-C levels (approximately 1.0 mMol/L; $p < 0.01$), but the level of high-density lipoprotein cholesterol (HDL-C) remained unchanged. Without an adequate description of blinding and randomization, the results of this study can only be considered preliminary.

Several case series have also found hypocholesterolemic effects associated with oral fenugreek. Sharma et al investigated 15 nonobese, asymptomatic, hyperlipidemic adults.²⁶ After the subjects had ingested 100 g defatted fenugreek powder per day for three weeks, their triglyceride (TG) and LDL-C levels were lower than baseline values. Slight decreases in HDL levels were also noted.

In a later study, normalization of lipid profiles was observed in 60 patients with type 2 diabetes whose diets were supplemented with 25 g powdered fenugreek seeds per day for 24

weeks.^{27,28} While mean TC, LDL-C, and TG levels decreased by 14-16 percent during the study period, mean HDL-C levels increased by 10 percent. Similarly, Sowmya and Rajyalakshmi observed significant reductions in TC and LDL-C levels in 20 adults with hypercholesterolemia who received 12.5-18.0 g powdered, germinated fenugreek seeds for one month, although no changes in HDL-C, very-low-density lipoprotein (VLDL), or TG levels were observed.²⁹

In another study, Sharma also reported a decrease in total cholesterol levels in five diabetic patients treated with fenugreek seed powder (25 g orally per day) for 21 days.³⁰ Bordia et al studied the effects of fenugreek seed powder (2.5 g administered twice daily for three months) in a subgroup of 40 subjects.²² In the subjects who had coronary artery disease and type 2 diabetes, significant decreases in the TC and TG levels were observed, with no change in HDL-C level. The methodology for this study was not clearly documented.

Most available studies are case series lacking proper controls, randomization, or blinding. Further, double-blind research is warranted.

Safety/Adverse Effects

A review of the literature on fenugreek reveals no reports of clinically significant harmful adverse effects. Although fenugreek has traditionally been considered safe and well tolerated, some side effects have been associated with its use. Caution in using fenugreek is warranted in patients known to be allergic to it or who are allergic to chickpeas because of possible cross-reactivity.³ Fenugreek contained in curry powder was found to be an allergen in a patient who reported severe bronchospasm, wheezing, and diarrhea.³¹

Other reported side effects include transient diarrhea and flatulence,^{23,27,30} and dizziness.³² Hypoglycemia is an expected effect; therefore, care should be taken to monitor blood glucose levels when beginning supplementation.^{19,21-25,32-34} Decreased body weight has also been reported and attributed to decreases in T_3 .³⁵ Because fenugreek preparations can contain coumarin derivatives,

there is a theoretical risk prothrombin time (PT) or the international normalized ratio (INR) might be increased, which, in turn, increases the risk of bleeding.³⁶ Fenugreek should not be used during pregnancy because of its potential uterine stimulating properties observed in early animal studies.³⁷

Potential Drug Interactions

Products rich in fiber (such as fenugreek fiber) can interfere with the absorption of oral medications because its fiber is mucilaginous and has high viscosity in the gut. Prescription medications, therefore, should be taken separately from fenugreek-containing products. Because concomitant use of fenugreek with other hypoglycemic agents might lower serum glucose levels more than expected, the level should be monitored closely.^{19,21-25,32,33} An aqueous extract of fenugreek reduced potassium levels in a small group of healthy subjects 14 percent.¹⁵ Consequently, fenugreek may precipitate hypokalemia when used in combination with some diuretics, laxatives, mineralocorticoids, or other hypokalemic agents.³² Fenugreek is also purported to contain an estrogenic constituent. Decreases in the serum level of T_3 and in the T_3/T_4 ratio, as well as an increase in the serum level of T_4 , have been observed in mice and rats given fenugreek.³⁵

Toxicology

Toxicological evaluation of 60 diabetic patients who took powdered fenugreek seeds at a dose of 25 g per day for 24 weeks disclosed no clinical hepatic or renal toxicity and no hematological abnormalities.²⁷ In an animal study, the acute oral LD_{50} was found to be >5 g/kg in rats, and the acute dermal LD_{50} was found to be >2 g/kg in rabbits.³⁸ In another animal study, fenugreek powder failed to induce any signs of toxicity or mortality in mice and rats who received acute and subchronic regimens.³⁹ Moreover, there were no significant hematological, hepatic, or histopathological changes in weanling rats fed fenugreek seeds for 90 days.⁴⁰

Dosage

Defatted powdered fenugreek seeds (100 g), divided in two equal doses,²⁵ have been used to treat type 1 diabetes. Fenugreek seed powder in capsule form (2.5 g twice daily for three months)²² and in seed powder (25 g divided into two equal doses)^{7,27,28} have been used to treat type 2 diabetes. Fenugreek has also been used to treated hyperlipidemia, both as seed powder in capsule form (2.5 g twice daily for three months)²² and as defatted powdered seeds (100 g divided in two equal doses).²⁵ Commercially, fenugreek is available in seed powder capsules, teas, and pulverized seeds that can be mixed in water.

Conclusions and Future Direction

The incidence of type 2 diabetes is increasing dramatically worldwide, resulting in large measure from the increasing prevalence of obesity.⁴¹ In addition, research is uncovering the importance of the “pre-diabetic” state or metabolic syndrome, when insulin resistance gives rise to impairment of glucose metabolism.^{41,42} Unfortunately, patients who have metabolic syndrome or diabetes are at greatly increased risk of cardiovascular morbidity and mortality.^{42,43} Thus, dietary supplements that can modulate glucose homeostasis and potentially improve lipid parameters would be desirable. This is especially true for diabetes prevention in patients with metabolic syndrome. These patients already manifest abnormalities of glucose handling and could benefit from a low-risk, inexpensive, food-based intervention aimed at normalizing their metabolic milieu. Fenugreek is a dietary supplement that may hold promise in this regard. The data generated to date are sparse but will hopefully lead to the development of well-designed, adequately powered, randomized, clinical trials evaluating the effect of fenugreek seed powder on measures of insulin resistance, insulin secretion, and cholesterol metabolism.

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