

A Variety of Bioactive Compounds can be Found in the Spice and Medicinal Herb *Trigonella foenum-graecum* Plant

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ABSTRACT

The annual plant fenugreek (*Trigonella foenum graecum*), which is indigenous to southern Europe and Asia, has white blossoms and hard, yellowish brown, angular seeds. It has long been valued for its nutritional content in addition to its therapeutic properties. The anti-inflammatory, hepatoprotective, cardioprotective, neuroprotective, immunomodulatory, nephroprotective and antimicrobial properties of fenugreek seeds, which are abundant in important chemicals, play a vital role in the treatment and management of disorders. *Foenum-graecum Trigonella*, fenugreek, Antioxidant and anti-inflammatory properties Health care and anti-cancer initiatives In Asia, fenugreek is a common herb used in cooking and as a traditional diabetic treatment. Acute reduction of postprandial glucose levels has been demonstrated, but the long-term impact on glycemia is still unknown. Clinical studies examining the impact of fenugreek consumption on glucose homeostasis indicators were thoroughly examined by us. The active ingredient in fenugreek, which also inhibits tumor necrosis factor, induces apoptosis and modulates the activation of several genes, including tumor suppressor genes. The identification of chemical components in this plant and its therapeutic benefits has been the subject of numerous investigations.

Keywords: Anti-inflammatory glycemia, Antioxidant, Fenugreek, *Trigonella foenum graecum*, Tumor and chemical components.

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INTRODUCTION

Growing customer demand for nutritious foods has pushed the food sector to create health-promoting food items. Industry acceptance of foods that are high in nutrients, provide health benefits, prevent disease and/or promote health has increased and these foods can be effective marketing tools. As a result, functional meals that contain a variety of ingredients such dietary fiber, vitamins, minerals, probiotics and prebiotics have become popular. Certain herbs have been taken into consideration in this regard due to their potential uses as food development, antimicrobials, antioxidants and health products. A plant belonging to the Leguminosae family, fenugreek (*Trigonella foenum-gracium*) is grown yearly and is often grown in Asia and the Mediterranean region, Due to the dried (Rafieian-Kopaei, 2012) seeds' antibacterial, anti-inflammatory, galactagogues, insulinotropic and restorative properties, they have long been used in Egypt, China, India and some regions of Europe Whole and crushed fenugreek seeds, which have a pleasant bitterness and a hint of sweetness, are used to flavor teas, curry powders and

spice blends. The seed's center hard, yellow embryo is surrounded by a horny, sizable coating of white, semi-transparent endosperm.

The chemical makeup of fenugreek is responsible for its amazing functional and therapeutic properties (20-25% proteins (Sewell and Rafieian-Kopaei, 2014), 45-50% dietary fiber, 20-25% mucilaginous soluble fiber, 6-8% fixed fatty acids and essential oils and 2-5% steroidal saponins). Furthermore, a few minor constituents have been identified and found to be the primary cause of its diverse biological effects, including free unnatural amino acids-hydroxyisoleucine), alkaloids (trigonelline, choline, gentianine, carpaine, etc.,) and distinct spirostanols and furastanols like diosgenin, gitogenin and yamogenin. Possessed the highest levels of protein (43.8 g/100 g) and saponin (4.63 g/100 g), while the husk had higher levels of total polyphenols (Karimi *et al.*, 2013) (103.8 mg of gallic acid equivalent/g) and Total Dietary Fiber (TDF) (77.1 g/100 g), which included Soluble Dietary Fiber (SDF) (45.2 g/100 g) and Insoluble Dietary Fiber (IDF) (31.9 g/100 g). Based on the free radical scavenging method (Nasri and Shirzad, 2013), extracts of husk, fenugreek seed and endosperm at 200 µg concentrations demonstrated 72%, 64% and 56% antioxidant activity, respectively (Rafieian-Kopaei and Nasri, 2014). Fenugreek's beneficial chemical compounds have demonstrated antidiabetic, anticancer, hypocholesterolemic, anti-inflammatory, antioxidant and chemo preventive properties.



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Fenugreek's nutraceutical qualities and possible culinary uses are covered in this review, which has never been examined before (Nasri and Rafeian-Kopaei, 2014).

Recent Therapeutic and Pharmacologic Investigations

Numerous studies on the various impacts of this plant have been carried out in order to confirm the use of beneficial chemicals and their mechanisms in the treatment of diseases, given the widespread usage of fenugreek and its significant therapeutic value (Baradaran *et al.*, 2014). According to recent research, this plant has a wide range of therapeutic benefits for various illnesses. Here is the most significant pharmacologic effects (Nasri *et al.*, 2014).

In vitro Studies

Fenugreek extract's hydroalcoholic extract has been shown to have up to 70% inhibitory effects on the proliferation of cancer cells, according to studies on the subject. Moreover, 200 mg/kg of the aforementioned extract administered intraperitoneally resulted in 62.3%+12.9% reduction in inflammation (Akbari *et al.*, 2013). Additionally, the number of peritoneal macrophages was considerably higher in this study at dosages of 100 and 200 mg/kg ($p < .01$) (Mirhoseini *et al.*, 2013).

Fenugreek seed has a dry ethanolic extract that is high in saponins (extract: plant ratio: 1:9). With a Minimum Inhibitory Concentration (MIC) of 1.25, this extract inhibits the growth of *Escherichia coli*, *Pseudomonas*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Candida* sp. Fungi (Asgary *et al.*, 2013). When compared to 1 mg/mL streptomycin, which produces an inhibitory zone of 19 to 32 mm, a dry extract made from fenugreek seeds at a concentration of 100 mg/kg demonstrated a mild antibacterial effect on *Bordetella bronchiseptica*, *Bacillus cereus*, *Bacillus pumilis*, *Micrococcus flavus*, *Sarcina lutea*, *E. coli* and *Proteus vulgare* with a 17-22 mm. Fenugreek's furostanolsaponins don't have antibacterial properties, but when they were converted to spirostanol, the resultant material showed a potent dose-dependent fungicidal action against *T. harzianum*, *Trichoderma viride* and *Rosellinia necatrix* (MIC₅₀ ¼ 50 mg/mL) (Asgary *et al.*, 2013). Additionally, *Candida albicans* (MIC₅₀ ¼ 25 mg/mL). At a dosage of 0.5 mg/mL, an aqueous fluid extract of fenugreek (1:1 ratio) exhibits a modest relaxing action on the smooth muscles of the isolated rabbit duodenum (Basch *et al.*, 2003).

Animal Studies

According to clinical and animal research, fenugreek seed lowers both acute and chronic blood sugar. In an animal study comparing fenugreek dry extract with insulin in rats, it was demonstrated that rats given alloxan-induced diabetes saw a 1.5 unit/kg drop in blood sugar, equivalent to that of insulin, when given a 15 mg/kg dose of fenugreek dry extract. After cellular variables were examined

(Rafeian-Kopaei *et al.*, 2014), it was shown that fenugreek extract was the cause of the drop in blood sugar and glucose tolerance via stimulating the synthesis of insulin in adipocytes and liver cells. When rats were fed fenugreek at 15%, 30% and 60% levels in a diet that caused hypercholesterolemia, the amount of cholesterol and bile acids in their feces rose dose-dependently and there was a significant rise in serum cholesterol at all three dosages ($p < 0.001$). In rats fed a hypercholesterolaemic diet for four weeks, adding 30% fenugreek to their food resulted in a significant reduction in cholesterol to 201 mg/dL, compared to 423 mg/dL in positive control animals ($p < 0.001$) (Khosravi-Boroujeni *et al.*, 2013). Fenugreek-containing diets had no effect on serum triglyceride levels. Another study found that adding 30 g/kg of dry ethanolic extract defatted from fenugreek to rats' hypercholesterolaemic diet significantly reduced plasma cholesterol ($p < 0.05$), which was attributed to fenugreek's saponins. Steroid saponins extracted from fenugreek (12.5 mg/dL, per 300 g body weight of animals for 2-4 weeks) had no effect on triglyceride levels but dramatically reduced plasma cholesterol levels in streptozotocin-diabetic rats and healthy rats ($p < 0.001$). After 600 and 80 mg loading doses of a soluble fenugreek gel (mostly composed of galactomannan) were given orally to rats, there was a 50% inhibition of bile salt uptake and starch digestion (Sadeghi *et al.*, 2014).

When fenugreek (50-200 g/kg) was given to rats, the production of bile acids rose significantly ($p < 0.05$), which may have been due to its ability to promote the conversion of cholesterol to bile salts. For 2 weeks, adding 2 or 8 g/kg of powdered fenugreek to the diet of both healthy and alloxan-diabetic rats significantly and dose-dependently reduced the levels of total blood cholesterol, triglycerides, low- and very low-density lipoprotein and cholesterol ($p < 0.05$ and $p < 0.001$). Additionally (Shirzad *et al.*, 2009), it raised high-density lipoprotein cholesterol in rats with alloxan-induced diabetes ($p < 0.05$). Rabbits that had been fed a high-fat diet for nine weeks showed improvements in their plasma fat profile when they were given powdered fenugreek at 20%, 30% and 60% of their diet for two weeks, along with three fenugreek-based fractions (defatted, saponin-free and crude saponin added at levels equivalent to fenugreek powder at 30% of diet). All of the aforementioned diets had no effect on high-density lipoprotein cholesterol, but they did lower the ratio of plasma total cholesterol to high-density lipoprotein cholesterol ($p < 0.01$) and fenugreek powder and each fraction decreased cholesterol and triglyceride levels ($p < 0.01$) (Shirzad *et al.*, 2011). A portion of crude Compared to other fractions and fenugreek powder, saponin was more effective. In the glucose tolerance test, streptozotocin-induced diabetic rats were given an oral suspension of fenugreek powder (0.25 g in 5 mL of water), which resulted in a drop in blood sugar levels following a meal and defatted When given orally for eight days at a dose of 1.89 g/kg body weight (Ghaed *et al.*, 2012), fenugreek reduced blood sugar in dogs with alloxan-induced diabetes ($p < 0.05$). This product dose reduced the basal glucagon ($p < 0.02$) and reaction to oral

glucose ($p<0.05$) in healthy dogs. Blood sugar ($p<0.01$) and blood cholesterol in dogs with diabetes caused by alloxan. When given orally to rats with alloxan-induced diabetes, triphenelline, which is derived from fenugreek, dramatically reduced blood sugar levels. This effect persisted for 24 hr (Nasri *et al.*, 2013).

Fenugreek aqueous decoction could reduce blood sugar in both healthy and alloxan-induced diabetic rats in a dose-dependent manner, with the greatest effect occurring over 6 hr ($p<0.05$). In rats with alloxan-induced diabetes, the oral administration of a dry ethanolic extract of fenugreek (1:21 ratio) at a dose of 200 mg/kg body weight exhibited a blood sugar-lowering effect comparable to that of tolbutamide at the same dosage. In a glucose tolerance test (Heidarian *et al.*, 2013), fenugreek decoction (40 g in 300 mL water) dramatically reduced fasting blood sugar (17.7%) when given orally to rabbits at a dose of 4 mL/kg body weight. When 20% fenugreek was added to the rats' food for two weeks, their blood glucose levels dropped 95% in the starch tolerance test (1 g/kg body weight), but there was no discernible difference in the glucose tolerance test. For two weeks, adding 2 or 8 g of fenugreek powder per kilogram of body weight to the diet reduced blood glucose levels in both healthy rats ($p<0.05$) and alloxan-induced diabetic rats ($p<0.01$) as compared to the control group. For 14 days, 300 g rats given a 10 mg dose of dry hydroalcoholic fenugreek extract (containing 12.5% steroid saponin and 4.8% free amino acids) orally showed a substantial increase in plasma insulin levels ($p<0.01$) when compared to the control group (Heidarian *et al.*, 2013).

When rats were given a 10-mg oral dose of a dry hydroalcoholic extract of fenugreek seed (12.5% saponin and 4.8% free amino acid) for two weeks, their food intake and attention to eating increased by 20% ($p<0.01$ on day 14), while their drinking water intake remained unchanged. The same diet has been shown to raise plasma insulin ($p<0.01$) and decrease total cholesterol ($p<0.05$) as well as low- and very low-density lipoprotein cholesterol ($p<0.05$). When compared to the control group, rats' digestive wounds caused by phenylbutazone and azepein improved more quickly after receiving an oral aqueous extract (1:1) at a rate of 1 mL/100 g body weight for five days. ($p<0.05$) (SalehiSurmaghi, 2008). Fenugreek extract's modest cholinergic action and tissue surface structure were linked to this effect. Fenugreek seed given daily at a rate of 500 mg/kg for four weeks dramatically ($p<0.01$) reduced the amount of oxalate renal stones that formed in rats. By supplementing their diet with 3% glycolic acid, these rats developed renal stones (Basch *et al.*, 2003).

Fenugreek seeds contain hydroxyisoleucine, a crucial amino acid. In a single investigation on animals. When insulin-resistant and streptozotocin-induced diabetic rats were fed fructose, the liver damage indicator, aspartate transaminase, rose dramatically (84% and 93%, respectively; $p<0.001$) in comparison to the control group, which returned to normal after 8 weeks of treatment with 4-hydroxyisoleucine (50 mg/kg) in both groups ($p<0.01$).

4-hydroxyisoleucine reduced blood glucose levels in diabetic rats fed fructose by 36%. In rats with streptozotocin-induced diabetes, 4-hydroxyisoleucine treatment resulted in a 31% decrease in high-density lipoprotein cholesterol ($p<0.05$) but no change in blood glucose or liver variables (Dini *et al.*, 2006). The study's researchers came to the conclusion that 4-hydroxyisoleucine could regulate factors linked to liver damage in streptozotocin-induced and insulin-resistant diabetes. It also caused blood glucose levels to drop in the first group and high-density lipoprotein cholesterol levels to rise. In a study on rats, fenugreek seed extract was added to the food along with glucose. After the sport test, muscle tissue was biopsied and the results showed that the extract enhanced the production of muscle tissue glycogen by 63% when compared to the control group. The rats in this study, who were streptozotocin-induced diabetic rats, were fed 0.5 and 0.1 g/kg body weight of fenugreek leaf every day, whereas the control group received 600 mg/kg of the antidiabetic medication glibenclamide (Anis *et al.*, 1985). Blood sugar levels, glycated hemoglobin, plasma insulin and liver enzymes (glucose 6-phosphatase and hexokinase) were assessed after 45 days. When fenugreek leaf (1 g/kg body weight) was administered, blood sugar levels dropped while plasma insulin and hexokinase enzyme activity-a crucial enzyme in boosting glucose metabolism (Mirzaei *et al.*, 2012).

Clinical Studies

Effectiveness in Decreasing or Controlling Blood Glucose: Effectiveness in regulating blood glucose was noted in double-blind clinical research conducted by Gupta *et al.* To regulate blood sugar, 25 patients with type 2 diabetes were split into two groups. One group took 1 g of dry hydroalcoholic extract of fenugreek seeds per day, while the other group followed a diet and exercise regimen (Varshney and Sharma, 1996). Both groups' blood sugar levels dropped after two months (from 148.3 to 119.9 mg/dL in the fenugreek group and from 137.5 to 113 mg/dL in the diet group and sport), but there was no discernible difference between them. Researchers came to the conclusion that fenugreek, along with diet and exercise, may help patients with type 2 diabetes control and lower their blood sugar levels. Patients with type 2 diabetes participated in a randomized, controlled, crossover study by Sharma *et al.* The study found that eating a diet high in fenugreek dramatically reduced blood glucose levels from 179+24 to 137+20.2 mg/dL. Both groups showed improvements in glucose tolerance as well as in hyperphagia and polyuria symptoms (Bu Ali Sina, 1988). Other case studies have demonstrated that fenugreek seeds help people with type 2 diabetes control and improve their blood sugar levels.

Treating Body Weakness and Anorexia: This plant works well for treating children's skeletal TB and osteomyelitis. This plant contains iron, phosphorus, carbohydrates, diastases and other nitrogenous elements that can be used to cure several diseases caused by anorexia and myasthenia disorders (Sweetman,

2009). This plant is also useful in a variety of situations when phosphorous and iron supplements are required.

Toxicology Studies

One study examined the effects of fenugreek seed consumption on 60 type 2 diabetic patients over a 24-week period, looking at changes in weight, clinical signs and serum variables of toxicity such as serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase, alkaline phosphatase, creatinine, bilirubin and blood urea (Morcos *et al.*, 1981). Both the control and treatment groups were given 300 g of carbs per day for 7 days at the start of the trial. Following this time, blood samples were obtained to calculate the base size of the variables. The diabetic patients' regular diet was supplemented with 25 g of powdered fenugreek seed on day 7. Fenugreek seed recipients had a nonsignificant weight change of 1+1.6 kg. After taking fenugreek leaf for three to four days (Yoshikawa *et al.*, 1997), several people who had digestive issues including diarrhea and cramps went away. There was no discernible change in blood factors and there were no adverse effects on the liver or kidneys.

Side Effects

For fenugreek, no unique adverse effects have been documented. There was one instance of a 5-week-old baby's consciousness level dropping after consuming herbal tea containing fenugreek. The issue was linked to a metabolic disease and the sotolon content of fenugreek seeds, which are used to make herbal tea (Sur *et al.*, 2001).

The main aroma component of fenugreek seed is sotolon, a lactone derivative and potent aromatic molecule that has a curry or fenugreek-like scent. In addition, it can be found in aged sake and white wine, roasted tobacco and dried mushroom fruiting bodies. Foods high in sotolon, such fenugreek, can give one's sweat and urine a maple syrup scent. Sotolon can also travel through the body largely unaltered (Abbasoglu and Turkoz, 1995). Some people with genetic disorders generate it on their own and expel it in their urine, which results in the disease's distinctive odor (Bhatti *et al.*, 1996).

Use in the Lactation Period: The production of breast milk can be improved by fenugreek. However, based on research, it is advised that nursing mothers take into account the following when ingesting fenugreek seeds.

1. Fenugreek should be consumed carefully by women who have signs of asthma or digestive disorders.
2. Minimum amount of consumption that provides effect should be considered.
3. It should be avoided in women with blood pressure and patients with cardiovascular diseases.

4. Women who have sensitive skin should check sensitivity to fenugreek.
5. Women who use warfarin plus aspirin should use fenugreek with caution.
6. Women who use fenugreek for their milk supply increase should avoid long-term use of it. It is recommended to check coagulation time and blood glucose test during the consumption period.

CONCLUSION

Since ancient times, fenugreek has been used extensively to treat and prevent illnesses. Numerous traditional applications have been validated by the conducted investigations, which also clearly demonstrate the plants medicinal worth and the capabilities of traditional medicine. Nevertheless, there is insufficient scientific data to determine this plant's mode of action. There is a significant antidiabetic benefit of fenugreek. It can reduce blood sugar in diabetic patients by slowing down the gastrointestinal tract's absorption of sugar and stimulating the release of insulin. Fenugreek is also used to treat several other conditions, including hypertension, atherosclerosis, gastritis, inflammation, upset stomach and loss of appetite. Sometimes, nursing mothers use fenugreek to encourage the flow of milk. Nevertheless, the mechanisms of action under these circumstances remain undefined. Because of its high iron content, fenugreek can help people who are iron deficient. Kidney problems and other toxicities are treated with it. It has antioxidant activity, and it appears that this plant's antioxidant capacity is one of the primary elements that contributes to fenugreek's beneficial effects. Flavonoids, plant sterols, vitamins, cumarins, terpenoids, carotenoids, curcumins, lignin and saponin are among the numerous active phytochemicals that have been linked to the plant's antioxidant qualities. But the chemicals that have contributed most to this effect are phenolic ones. Thus, there is a strong relationship between the extract's antioxidant activity and the polyphenolic components it contains.

Therefore, fenugreek, which has antioxidant properties and phenolic components, should be able to counteract these situations and could be a promising herbal medication candidate.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

TB: Tuberculosis; **MIC:** Minimum Inhibitory Concentration; **CV:** Cardiovascular; **ROS:** Reactive Oxygen Species; **HbA1c:** Glycated Hemoglobin; **SGOT:** Serum Glutamic Oxaloacetic Transaminase; **SGPT:** Serum Glutamic Pyruvic Transaminase; **ALP:** Alkaline Phosphatase; **BUN:** Blood Urea Nitrogen; **TDF:** Total Dietary Fiber; **SDF:** Soluble Dietary Fiber; **IDF:** Insoluble Dietary Fiber; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **H₂O₂:** Hydrogen Peroxide; **mg/kg:** Milligram per Kilogram; **mL:** Milliliter; **µg/mL:** Microgram per Milliliter; **nm:** Nanometer; **M:** Molar; **pH:** Potential of Hydrogen; **v/v:** Volume/Volume; **RT:** Retention Time; **SD:** Standard Deviation; **SEM:** Standard Error of the Mean; **LOD:** Limit of Detection; **LOQ:** Limit of Quantification; **RSD:** Relative Standard Deviation; **ICH:** International Council for Harmonisation; **AR:** Adrenoreceptor; **β₃-AR:** Beta-3 Adrenoreceptor; **USP:** United States Pharmacopeia; **HPTLC:** High-Performance Thin Layer Chromatography; **LC-MS/MS:** Liquid Chromatography-Tandem Mass Spectrometry; **ESI-MS:** Electrospray Ionization-Mass Spectrometry; **UHPLC:** Ultra-High Performance Liquid Chromatography.

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