

Review Article

A review on phytochemistry and pharmacological profile of fenugreek.

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Received 24 July 2015; received in revised form 21 August 2015; accepted 22 August 2015

Available online 04 October 2015

Abstract

Fenugreek is one of the most promising medicinal herbs, known from ancient period, having a versatile medicinal value. The plant seeds and leaves are having huge medical applications in daily life against a variety of ailments. The seeds are rich in fiber and 100 g of seeds provide more than 65% of dietary fiber. It is a complex reservoir of various pharmacologically active phytoconstituents as gum, alkaloid, fiber, saponin, flavonoids and volatile contents. Plant shows a variety of medicinal applications such as antidiabetic, anticancer, hypocholesterolemic, antioxidant, gastric stimulant, antibacterial agent, and anti-anorexic agent. The plant protein is found to be solubilized to 91.3% at alkaline pH of 11. This review article presents the phytochemistry and medicinal and other beneficial uses of fenugreek discovered from last 30 years of research in animal and human subjects as well as in other experiments.

Keywords: Fenugreek, Phytoconstituents, Flavonoids.

1. Introduction

Trigonella foenum - graecum (Linn.) belonging to the family *Fabaceae* commonly known as Fenugreek is a 30-60 cm tall, aromatic, annual herb, cultivated all over the country.^{1, 2} The plant is smooth erect annual. Stipules are not found toothed. Leaflets 2-2.5 cm long, oblanceolate-oblong and toothed. Flowers are 1-2, axillary, sessile. Corolla much exerted. Pod is 5-7.5 cm long, with a long persistent beak, often falcate, 10-29 seeded and devoid of transverse reticulations.^{1, 2}

Medicinal Uses

The seeds are hot, with a very sharp bitter taste. The seeds have the pharmacological activities as antipyretic, tonic, anthelmintic, appetizer, astringent, cures leprosy, antiemetic,

bronchitis, piles; removes bad and metallic taste from the mouth, useful in several heart disease (Ayurvedic).^{1,3} The plant and seeds are both shows potential pharmacological activities as suppurative, diuretic, useful in dropsy, chronic cough like symptoms, enlargement of the spleen and the liver. The leaves are useful in external and internal inflammations and burns; prevents the hair fall, so used in the hair shampoos.^{1, 3}



Fig: 1 Fenugreek plant.

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Fenugreek seeds are considered to be good carminative, aphrodisiac and tonic. The fenugreek preparations are recommended for use in dyspepsia with loss of appetite, in the diarrhea of puerperal women, and in rheumatoid arthritis.^{1,3} The infusion of seed are used by south Indians for treatment of dysentery, and as cooling drink in the conditions as small pox. In the konkan region, the leaves are used both internally as well as externally, owing to their cooling properties.

Phytochemistry

The seed contains galactomannan rich endosperm, fresh seeds usually contain carbohydrates and sugar in large amount. Mature seeds contain greatly amino acid, fatty acid, saponins and vitamins. The fenugreek seeds contain a large quantity of folic acid (84mg/100g). It also contains trigogenin, neogigogenin, disogenin, neogitogenin, gitogenin, homorientin and saponaretin.^{4,5} The core phytoconstituents of *T. foenum-graecum* are flavonoids, fibers, polysaccharides, saponins, flavonoids and polysaccharides fixed oils as well as some identified alkaloids viz., choline and trigonelline.^{6,7}

Pharmacological Profile

Urotoxicity Activity

Cyclophosphamide (CP), a commonly used anticancer drug, causes the toxicity by its reactive metabolites such as acrolein and phosphoramidate mustard. The study underlining modulation of toxicity caused by concomitant exposure to CP and L-buthionine-SR-sulfoximine (BSO) by fenugreek (*Trigonella foenum-graecum* L.) extract was evaluated by the measurement of lipid peroxidation value (LPO) and anti-oxidants in urinary bladder of mice. Fenugreek, a very common medicinal and dietary herb, showed protective effect not only on LPO but also on the enzymatic oxidation. CP-treated animals showed a significant decrease in the activities of enzymes such as glutathione S-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GP) and catalase (CAT) when compared to the controls animals. Pre-treatment with fenugreek extract restored activities of all above mentioned enzymes and thus showed an overall protective effect on additive effect of BSO and CP.⁸

Immunomodulatory Effect

The fenugreek extract have shown immunomodulatory effect in mice.⁹ A variety of herbal extracts and their isolated phytoconstituents have also shown protective effect against CP-induced urotoxicity.^{10, 11, 12} *Trigonella foenum-graecum* L. extract have shown modulatory effect on deltamethrin induced low dose immunosuppression in mice. In clinical reports, the extract is known to possess hypoglycemic effect. Swiss albino male mice were treated with the aqueous extract (100 mg/kg, for 15 days) and deltamethrin was administered orally in a single dose of 18 mg/kg in corn oil. Body weight, relative organs weight, weight of lymphoid organs and cellularity, hemagglutination titre (HT). Deltamethrin significantly suppressed weight of lymphoid organ and cellularity and also humoral immune functions.¹³

Antioxidant Activity

Flavonoids present in fenugreek seed extract have been shown to possess anti-oxidant activity.^{14, 15 16} Quercetin, the phytoconstituents of plant has shown protective effect against hemorrhagic cystitis induced by CP.¹⁶ Moreover, in a recent study fenugreek seed extract is reported to prevent both LPO and hemolysis in RBC.¹⁷ Fenugreek seeds have also been reported to raise the level of anti-oxidants and lower the LPO value in liver of ethanol intoxication¹⁸ The findings demonstrate that pre-treatment with fenugreek extract prevents CP urotoxicity which is primarily mediated by LPO. The seed extract exhibited free radical scavenging activity. An aqueous methanolic extract of fenugreek seeds showed antiradical activity due to polyphenolic components present in the extract.

Chemo protective Activity

Cancer is the second leading cause of death all over the world. Conventional therapies extend the patient's lifespan by a few years at the cost of bearing serious side effects. Cancer control may therefore be benefited from alternative therapies. Fenugreek seeds showed potential protective effect against 7, 12-dimethylbenz (a) anthracene (DMBA)-induced breast cancer in rats at the dose of 200 mg/kg by inhibiting the mammary

hyperplasia and decreased its incidence significantly.¹⁹

Anticancer Activity

Apoptosis is a type of cellular death, and agents which have an ability to induce the apoptosis in tumors are known to be used for antitumor therapy. Flavonoids present in fenugreek produces several biological effects, and the apoptosis inducing property of flavonoids is identified in several previous reports.²⁰ Flavonoids and catechins were first proven to be apoptotic in human carcinoma cells.²¹ Similar observations have since been extended to lung tumor cell lines.²² The mechanism of action of fenugreek is Phagocytosis and killing of invading microorganisms by macrophages that constitute body's primary line of defense against infections.²³ Based on the published studies, flavonoids seem to be most likely candidates eliciting anti-tumorigenic effect of fenugreek.

Antidiabetic Activity

Treatment of vandate to diabetic rats has been reported to treat the altered carbohydrate metabolism and antioxidant status. However, vandate exerts these effects at high doses with several toxic effects are produced at the used higher doses. When low doses of vandate along with *Trigonella foenum-graecum* seed powder (TSP) are administered, enzymatic changes are produced in diabetic rats. Alloxan-induced diabetic rats were administered separately with insulin, vanadate (0.6 mg/ml), TSP and also a combined dose of Vanadate (0.2 mg/ml) and TSP for 21 days. At the end of the experiment, blood glucose levels and activities of phosphoenol pyruvate carboxykinase (PEPCK), pyruvate kinase (PK), glutathione reductase (GR), glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) were measured in cytosolic fraction in the liver and kidney. Blood glucose levels were found to be markedly increased in disease control group. Treatment with antidiabetic compounds resulted in the reduction of blood glucose levels. Rats administered with combined dose of vandate and trigonella had glucose levels comparable to control ones.²⁴ Fenugreek has been primarily described as an antihyperglycemic herb in humans as well as

in laboratory animals.^{25, 26} fenugreek also reduced cholesterol and the effect is well established.²⁷ The present study confirmed overall stimulatory effect of fenugreek on the specific as well as nonspecific immune functions in mice. From the seeds of *T. foenum-graecum* an unusual amino acid, 4-hydroxy isoleucine, has been isolated, which showed significant reduction in the plasma triglyceride levels by 33% ($P < 0.002$), total cholesterol level (TC) by 22% ($P < 0.02$), and free fatty acids level by 14%, accompanied by an increase in HDL/TC ratio by 39% in the dyslipidemic hamster model.

Fenugreek (*Trigonella foenum graecum* L.) was tested on alloxan induced diabetic mice, Alloxan induced group received s.c. injection of alloxan 150 mg/ kg to induce diabetes and recovery group received s.c. injection of fenugreek seed extract 15 mg/kg per day for 15 days. At the end of study, histological and ultrathin sections of pancreas were prepared, where disturbances in pancreatic arrangement was observed. Fenugreek seed extract could normalize the diabetes and provides protection to pancreatic tissues from damaging effect of diabetes.²⁸

Gastroprotective Effect

The antiulcer effect of fenugreek seeds (*Trigonella foenum-graecum*) in ethanol-induced gastric ulcer was studied. Both the aqueous extract and a gel fraction isolated from the seeds showed significant ulcer protective effects. The antiulcer effect of fenugreek was not only due to cytoprotective effect but also due to the effects on mucosal glycoproteins. The fenugreek seeds also prevented the gastric mucosal injury due to ethanol consumption thereby providing gastroprotective effect.²⁹

Anti-inflammatory and Antipyretic Effect

Anti - inflammatory and antipyretic effects of the fenugreek leaves extract were examined. In anti-inflammatory activity, the formalin-induced edema model was used for study. The induction of hyperthermia was carried out by intraperitoneal injection of 20% (w/v) aqueous suspension of brewer's yeast. Sodium salicylate (SS) was used as a treatment in positive control group. Both TFG and SS significantly reduced inflammation as well as hyperthermia in single dose (TFG 1000 and

2000 mg/kg, SS 300 mg/kg) and chronic administration (TFG 1000 mg/kg and SS 300 mg/kg). The existence of all three anti-inflammatory, analgesic and antipyretic effects in this extract suggest a NSAID-like mechanism, its analgesic effect on tail-flick test that usually is not produced by NSAIDs, suggest another mechanism for the extract.³⁰

Antidepressant activity

The methanolic extract of *Trigonella foenum graecum* Linn. Seeds (METFGS) was investigated for its antidepressant activity in mice. Forced swim test (FST) and Tail suspension test (TST) were used for the screening. The results showed treatment with METFGS (250 and 500 mg/kg, i.p.), daily for 7 days significantly reduced the immobility duration in FST and TST dose dependently. The effects produced by extract were found comparable to the standard antidepressant imipramine. Flavonoids and Saponin glycosides present in fenugreek seeds may be responsible for antidepressant activity mediated through serotonergic, dopaminergic, adrenergic and GABAergic system.³¹

Insulin resistance

The efficacy and possible mechanism of oligosaccharides based standardized fenugreek seed extract (SFSE-OS) was studied on high-fat diet (HFD)-induced insulin resistance in male C57BL/6 mice. SFSE-OS after oral administration (30, 60 and 100 mg/kg, twice daily) was evaluated on HFD fed mice for anthropomorphic, gene expression related, glycemic, and histopathological parameters. Administration of HFD showed significant prophylactic effects on insulin resistance in terms of plasma glucose and insulin levels, body weight, insulin resistance (IR), glycated hemoglobin, area under the curve of plasma during intraperitoneal insulin tolerance and oral glucose tolerance and. SFSE-OS showed potential effect in prevention of insulin resistance through modulation of Glut-2, Glut-4, IRS-2 and SREBP-1c expression.³²

Anabolic and androgenic effect

Glycoside fraction of fenugreek (*Trigonella foenum-graecum*) seeds (Fenu-FG) was evaluated for efficacy and safety on physiological parameters related to androgenic hormones, muscle anabolism and body fat in

healthy male subjects during 8-week resistance training program using a prospective, randomized, double-blind, placebo controlled design. Supplementation of Fenu-FG demonstrated significant anabolic and androgenic activity in comparison with the placebo. Fenu-FG treated subjects have shown significant improvements in body fat without reduction in muscular strength and repetitions to failure. The supplement was found to be safe, effective and well tolerated.³³

Anti-lipidaemic effect

Inhibitory effect of aqueous extract of *Trigonella foenum-graecum* seeds (AqE-TFG) was studied on fat accumulation and dyslipidemia in high fat diet- (HFD-) induced obese rats. Female Wistar rats were fed with HFD, and the rats on HFD were treated as AqE-TFG or orlistat (HFD for 28 days + AqE-TFG (0.5 and 1.0 g/kg) or orlistat (10mg/kg) from day 8 to 28, orally). Treatment with AqE-TFG have shown significant decline in body mass index (BMI), body weight gain, blood glucose, serum insulin, white adipose tissue (WAT) weights, leptin, lipase, lipids, and apolipoprotein-B levels along with elevation in adiponectin levels. Also, AqE-TFG improved serum aspartate amino transferase (AST), lactate dehydrogenase (LDH) levels, alanine amino transferase (ALT), reduced the hepatic and cardiac thiobarbituric acid reactive substances (TBARS) and elevated the antioxidant enzyme (glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT)) levels. In addition, liver and uterine WAT lipogenic enzyme (fatty acid synthetase (FAS) and glucose-6-phosphate dehydrogenase (G6PD)) activities were restored towards normal levels.³⁴

Anticataract

The anti-cataract potential of *Trigonella foenum-graecum* L seeds [fenugreek] in selenite-induced both *in vitro* and *in vivo* cataract were evaluated. *In vitro* rat lenses were maintained in culture containing Dulbecco's modified Eagles medium [DMEM] alone or in combination with 100 µM selenite and served as standard and control groups, respectively. In the test group, the medium was supplemented with selenite and aqueous extract of *Trigonella foenum graecum*.

Thereafter lenses were incubated for 24 h at 37°C. Then, the lenses were processed for the estimation of reduced glutathione [GSH], lipid peroxidation product [malondialdehyde] value, and the antioxidant enzymes. Reduction in GSH and an increase in malondialdehyde levels were seen in control as compared to standard lenses. *Trigonella foenum-graecum* drastically restored glutathione and decreased malondialdehyde levels.³⁵

Anti-plasmodium

In vitro anti-plasmodial assay of the extracted fractions of fenugreek leaves was carried out using *Plasmodium falciparum* isolates. Schizont maturation inhibition assay was carried out for analyzing the potential of the extracts. Ethanolic extract (50%) seemed to possess profound anti-plasmodial activity with IC(50) value of 8.75 +/- 0.35 micro g ml(-1) and 10.25 +/- 0.35 micro g ml(-1) against chloroquine sensitive and resistant *P. falciparum* isolates, respectively.³⁶

Effect on Sexual function

Trigonella foenum-graecum (fenugreek) seed extract was evaluated on sex hormones and sexual function in healthy menstruating women who have reported low sexual drive. Short term, single site, double blind, randomised, placebo-controlled study was conducted on 80 women, aged 20 to 49 years. Participants were randomized to oral dose of a standardized *T. foenum-graecum* seed extract at a dose of 600 mg/day or placebo treatment over two menstrual cycles. Dehydroepiandrosterone sulfate, progesterone, androstenedione, total and free testosterone, estradiol (E2), luteinizing hormone, follicle stimulating hormone, sex hormone binding globulin and cholesterol were measured at baseline and 8 weeks. The individual aspects of sexual function were measured. There was a significant increase in free testosterone and E2 in the active group as well as sexual desire and arousal compared with the placebo group. The results indicate that this extract of *T. foenum-graecum* may be a useful treatment for increasing sexual arousal and desire in women.³⁷

Effect on dysmenorrhoea

Effects of fenugreek seeds on the severity of primary dysmenorrhoea was evaluated among students. Unmarried Students were randomly

assigned to two groups who received fenugreek (n=51) or placebo (n=50). For the first 3 days of menstruation, 2–3 capsules containing fenugreek seed powder (900 mg) were given to the subjects three times daily for two consecutive menstrual cycles. Pain severity was evaluated using a visual analog scale and systemic symptoms were assessed using a multidimensional verbal scale. Pain severity was significantly reduced in both groups after the intervention; however, the fenugreek group experienced significantly larger pain reduction (p<0.001). With respect to the duration of pain, there was no meaningful difference between the two cycles in the placebo group (p=0.07) but in the fenugreek group, the duration of pain decreased between the two cycles (p<0.001). Systemic symptoms of dysmenorrhoea (fatigue, headache, nausea, vomiting, lack of energy, syncope) decreased in the fenugreek seed group (p<0.05). No side effects were reported in the fenugreek group. These data suggest that prescription of fenugreek seed powder during menstruation can reduce the severity of dysmenorrhoea.³⁸

Antimicrobial activity

Antimicrobial activities and phytochemical screening of methanolic and petroleum ether extracts of seeds and callus derived from hypocotyls and cotyledons explants of fenugreek (*Trigonella foenum-graecum*) was studied. Antimicrobial activities were tested against standard microorganisms, *Bacillus subtilis* (NCTC 8236 G+Ve), *Staphylococcus aureus* (ATCC 25923 G+v), *Escherichia coli* (ATCC 25922 G-V), *Pseudomonas aeruginosa* (ATCC 27853 G-V), *Aspergillus niger* (ATCC 9763) and *Candida albicans* (ATCC7596) using paper disc diffusion method. The petroleum ether extract of *T.foenum- graecum* seeds showed highest antimicrobial activity compared to methanolic extracts. Antibacterial activity of petroleum ether extract of *T.foenum-graecum* seeds were recorded (17±0.33mm) and (15±0.57mm) of inhibition zone against *Escherichia coli* and *Staphylococcus aureus* respectively by concentration 250 mg/ml.³⁹

Miscellaneous Effects

Regulation of Hyperthyroidism

The combined effects of *T. foenum graecum* and *Allium sativum* extracts were evaluated for

their ameliorative potential in the L-thyroxine-induced hyperthyroidism rat model to understand the interaction between the two extracts. Propylthiouracil (PTU), an antithyroid drug, was used as a reference compound. Alterations in serum levels of triiodothyronine (T3), tetraiodothyroxine (T4), hepatic glucose-6-phosphatase (G-6-Pase), and glucose and oxygen consumption were studied as parameters. Superoxide dismutase (SOD), lipid peroxidation (LPO), catalase (CAT) activities and reduced glutathione (GSH) levels were examined to reveal any toxic effects of the drugs. The combined effects of *Trigonella* and *Allium* at 200 and 500 mg/kg body wt. respectively, were equipotent as compared to the individual extracts in lowering the serum concentrations of T3 and T4 in hyperthyroidic rats.⁴⁰

Toxicity

Administration of fenugreek to rats at levels equivalent to two and four times the therapeutic dose recommended for humans (25 g/day) produced non toxic effects as evidenced by normal liver function tests, lack of any adverse histopathological changes in the liver and no adverse effects on hematological parameters.⁴¹ Moreover, chronic (24 weeks) administration of fenugreek seeds at a dose of 25 g/day, exhibited no clinical hepatic or renal toxicity or hematological abnormalities in diabetic subjects.⁴² Two cases of severe reactions to fenugreek seed powder administration were reported in patients suffering from food allergies.⁴³ The first subject developed rhinorrhoea, wheezing and fainting followed by inhalation of the powder. The second subject developed numbness of the head and facial angioedema after application of fenugreek paste to the scalp as a dandruff treatment.⁴⁴ The LD50 of fenugreek aqueous extract in male and female mice was found to be about 10 g/kg body weight for oral administration and 2 g/kg for intraperitoneal administration. Central nervous system stimulation, increased rate of respiration and tremors were observed following high doses of the aqueous extract^{45, 46} The LD50 in mice of a similar extract was found to be 4 g/kg by the same route.

Use of aluminium as phosphate binders among patients with renal failure continued

despite of the reports on safety concerns regarding the relationship between aluminum salts and some of the neurological and bone diseases. In search for a diet supplement which could reduce aluminum toxicity related to renal failure, the animal study was carried out in which the fenugreek seeds were assessed for their effects on rats nephrotoxicity induced by aluminum chloride (AlCl₃). Oral AlCl₃ administration for 5 months (500 mg/kg bw i.g for one month then 1600 ppm via drinking water) led to lipid peroxidation (LPO) in the blood and brain, in addition to kidney atrophy and morphological alterations at the level of Bowman's capsule. However, the maintenance of a diet supplemented with fenugreek seeds could offer protection for the kidney, bone and brain, at the same time.⁴⁷

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Source of Support: Nil.

Conflict of Interest: None declared
