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Review Article

PHARMACOLOGICAL ACTIONS AND POTENTIAL USES OF *TRIGONELLA FOENUM-GRAECUM*: A REVIEW

*FEDELIC ASHISH TOPPO, RACHNA AKHAND, DR. A.K. PATHAK Department of Pharmacy, Barkatullah University, Bhopal-(M.P.) 462026 E-mail: ashish_two@yahoo.co.in

ABSTRACT

In ancient Egypt, fenugreek was used to ease childbirth and to increase milk flow. Today, it is still taken by Egyptian women for menstrual pain and as hilba tea to ease stomach problems of tourists. Introduced into the southern provinces of China, the beans were in use as a medicine since the time of the Tang dynasty. Usually parched or boiled, and given with aloes, anise-seed and other substances as a tonic. They contain mucilage, sugars, an alkaloid-trigonellin, which is not poisonous-cholin and a scented compound. A study in India involving insulin-dependent diabetics on low doses of insulin, pulverized fenugreek seeds were shown to reduce blood sugar and other harmful fats. Medicinal Action and Uses of Fenugreek like Allergies, Appetite/loss of, Catarrh/bronchial, Cholesterol/high, Diabetic Retinopathy, Gas, Gastric Disorders, Lung Infections, Mucus Excessive, Throat/sore, Abscesses, Anemia, Asthma, Boils, Body Odour, Bronchitis, cancer, Eyes/swollen, Fevers, Gallbladder Problems, Heartburn, Inflammation, Sinus Problems, Ulcers, Uterine Problems, Water Retention focused the investigator's attention on this plant.

KEYWORDS *Trigonella foenum-graecum;* Review; Potential uses; Pharmacology

INTRODUCTION

Trigonella foenum - graecum (Linn.) belonging to the family Papilionaceae commonly known as Fenugreek is a aromatic, 30-60 cm tall, annual herb, cultivated throughout the country.[1, 2]

A nearly smooth erect annual. Stipulets not toothed. Leaflets 2-2.5 cm long, oblanceolate-oblong, toothed. Flowers 1-2, axillary, sessile. Calyx-teeth linear. Corolla much exserted. Pod 5-7.5 cm long, with a long persistent beak, often falcate, 10-29 seeded, without transverse reticulations.[1, 2]

Medicinal uses

The seeds are hot, with a sharp bitter taste; tonic, antipyretic, anthelmentic, increase the apetite, astringent to the bowels, cure leprosy, " vata", vomiting, bronchitis, piles; remove bad taste from the mouth, useful in heart disease (Ayurvedic).[1, 3] The plant and seeds are hot and dry, suppurative, aperient, diuretic, emmenagogue, useful in dropsy, chronic cough, enlargement of the liver and the spleen. The leaves are useful in external and internal swellings and burns; prevent the hair falling off (yunani).[1, 3] Fenugreek seeds are considered carminative, tonic and aphrodisiac. Several confections made with this the article are recommended for use in dyspepsia with loss of appetite, in the diarrhea of puerperal women, and in rheumatism.[1, 3]

Other uses

The seeds being toasted and afterwards infused are used by native practitioners in southern India for dysentery. In the konkan, the leaves are used both externally and internally, on account of their cooling properties. An infusion of the seeds is given to small-pox patients as a cooling drink.[1]

PHYTOCHEMISTRY

The endosperm of the seed is rich in galactomannan, young seeds mainly contain

carbohydrates and sugar. Mature seeds content amino acid, fatty acid, vitamins, and saponins. The seeds of fenugreek contain a large quantity of folic acid (84mg/100g). It also contents disogenin, gitogenin, neogitogenin, homorientin saponaretin, neogigogenin, and trigogenin.[4, 5]

The main chemical constituents of *T. foenum-graecum* are fibers, flavonoids, polysaccharides, saponins, flavonoids and polysaccharides fixed oils and some identified alkaloids viz., trigonelline and choline.[6, 7]

PHARMACOLOGICAL PROFILE

Urotoxicity Activity

Cyclophosphamide (CP) is a commonly used anti-cancer drug which causes toxicity by its reactive metabolites such as acrolein and phosphoramide mustard. In the study 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 measuring lipid peroxidation (LPO) and anti-oxidants in urinary bladder in mice. Fenugreek, a common dietary and medicinal herb, showed protective effect not only on LPO but also on the enzymatic anti-oxidants. CP-treated animals exhibited a significant decrease in the activities of glutathione S-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GP) and catalase (CAT) when compared to the controls. Level of reduced glutathione (GSH) was also reduced with an increase in LPO in CP-treated animals. BSO treatment depicted an additive toxic effect in CP-treated animals. Pre-treatment of herbal extract restored activities of all the enzymes and thus showed an overall protective effect on additive effect of CP and BSO. Restoration of GSH by extract treatment may play an important role in reversing CP-induced apoptosis and free radical mediated LPO in urinary bladder.[8]

Immunomodulatory Effect

T. foenum-graecum extract has demonstrated immunomodulatory effect in mice.[9] A number of herbal extracts and their isolated constituents have also shown protective effect against CP-induced urotoxicity.[10, 11, 12] Thiols containing compounds such as mesna and cysteine have shown protective effects against CP-induced urotoxicity.[13] Its various pharmacological actions reported hitherto in ancient medicine literature have been scientifically validated later. These include its anti-inflammatory, antipyretic, hypoglycemic and immunomodulatory activities.[8, 14]

Modulatory effect of *Trigonella foenum-graecum* L. extract on deltamethrin-induced low dose immunosuppression in mice has shown to possess several medicinal properties. In clinical studies, it has shown hypoglycemic and anti-diabetic properties. Immunomodulatory effect of fenugreek extract has also been demonstrated in mice. Modulatory effect of *T. foenum-graecum* seed extract on the immunotoxic effects of deltamethrin in mice. Swiss albino male mice were treated per os with the aqueous extract (100 mg/kg, b.wt. daily for 15 days). Deltamethrin was administered orally in a single dose of 18 mg/kg b.wt. in corn oil. Body weight, relative organ weight, lymphoid organ cellularity, hemagglutination titre (HT), plaque forming cell (PFC) assay and quantitative hemolysis of SRBC (QHS) assay were studied in the treated animals. Deltamethrin showed significant suppressive effect on lymphoid organ weight and cellularity and humoral immune functions. Plant extract itself produced no immunotoxicity at the above dose whereas it resulted in restoration of humoral responses in deltamethrin-treated animals as shown by a significant ($p < 0.01$) increase in PFC response as well as QHS in

deltamethrin-treated animals. The results suggest that exposure to deltamethrin causes immunosuppression in mice and fenugreek extract has modulatory effects on these parameters. The antioxidant property of fenugreek seeds might be contributing to modulatory action resulting in its protective effect in immunosuppresed mice. [15]

Antioxidant Activity

Flavonoids of fenugreek extract have been observed to possess anti-oxidant activity.[16, 17 18] Quercetin has shown protective effect against CP-induced hemorrhagic cystitis.[18] Moreover, in a recent study fenugreek seed extract has been reported to prevent both LPO and hemolysis in RBC.[19] Fenugreek seeds have also been reported to raise the anti-oxidant levels and lower the LPO in liver of ethanol intoxicated [20] and diabetic rats.[21] The findings of the present investigation demonstrate that fenugreek extract pre-treatment prevented CP urotoxicity which is primarily mediated by LPO and depleted GSH by reversing these effects. This observation is strengthened by a number of clinical trials showing the efficacy of fenugreek as a hypoglycemic and anti-diabetic agent with limited toxic manifestations.[22, 23]

Extract of fenugreek (*Trigonella foenum-graecum*) seeds was isolated and evaluated for antioxidant activity using various in vitro assay systems. The seed extract exhibited scavenging of hydroxyl radicals (OH) and inhibition of hydrogen peroxide-induced lipid peroxidation in rat liver mitochondria. The OH scavenging activity of the extract was evaluated by pulse radiolysis and the deoxyribose system. The antimutagenic activity of the extract was recorded by following the inhibition of c-radiation induced strand break formation in plasmid pBR322 DNA. The extract at high concentrations acted as a scavenger of 2, 20 - diphenyl-1- picryl hydrazyl hydrate (DPPH) and 2, 20 - azinobis 3-ethylbenzothiazoline – 6 - sulfonate (ABTS) radicals. The total phenolic content in the extract was determined pectrophotometrically according to the Folin–Ciocalteau procedure and expressed as mg or mM gallic acid equivalents. The results indicate that the extract of fenugreek seeds contains antioxidants and protects cellular structures from oxidative damage. These findings provide evidence for the in vivo beneficial effects of the seeds reported in the literature. An aqueous methanolic extract of fenugreek seeds was examined for its antiradical and in vitro antioxidant activity in different model systems. The antiradical activity could be correlated with the polyphenolic components present in the extract. The results gained by these methods provide some important factors responsible for the antioxidant potential of fenugreek seeds and offer evidence for the large number of in vivo beneficial effects of the seeds reported in the literature. [24]

Chemopreventive Activity

Cancer is the second leading cause of death worldwide. Conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Cancer control may therefore benefit from the potential that resides in alternative therapies. There is thus an increasing demand to utilize alternative concepts or approaches to the prevention of cancer. It showed potential protective effect of Fenugreek seeds against 7, 12-dimethylbenz (a) anthracene (DMBA)-induced breast cancer in rats at 200 mg/kg b.wt. Fenugreek seeds extract significantly inhibited the DMBA-induced mammary hyperplasia and decreased its incidence. Epidemiological studies also implicate apoptosis as a mechanism that might mediate the Fenugreek's antibreast cancer protective effects. [25]

Anticancer Activity

Apoptosis is a type of cell death, and agents with the ability to induce apoptosis in tumors have the potential to be used for anti-tumor therapy. Flavonoids produce several biological effects, and the apoptosis inducing activities of flavonoids have been identified in several previous studies.[26] Flavonoids and catechins were first shown to be apoptotic in human carcinoma cells.[27] Similar observation has since been extended to lung tumor cell lines[28] colon cancer cells, breast cancer cells, prostate cancer cells[29] stomach cancer cells[30] brain tumor cells, head and neck squamous carcinoma[31] and cervical cancer cells[32] quercetin, rutin, and other food flavonoids have been shown to inhibit carcinogenesis in animal models. They all induce apoptosis in tumor cells. [33, 34, 35, 36] It appears that these flavonoids can also differentially induce apoptosis in cancer cells, but not in their normal counterparts. The ultrastructure of mammary acini from protected rats showed dying cells with large numbers of cytoplasmic vacuoles; some of these vacuoles appear autophagic. Recently, alternative cell death processes have been recognized in epithelial cells, including autophagy and para-apoptosis. [37, 38, 39] These pathways can be activated in parallel with apoptosis, and significant crosstalk between apoptotic and alternative death pathways may exist.[40] Thus, herbal induced autophagic or ‘‘type II’’ cell death may also contribute to the cell death and hence inhibiting the DMBA-induced tumor progression. *T. foenum- graecum* has also been shown to have stimulatory effects on macrophages. Phagocytosis and killing of invading microorganisms by macrophages constitute body’s primary line of defense against infections.[41] The present study establishes that *T. foenum-graecum* has appreciable anti-cancer activity. It is not possible to identify the most effective anti-cancer constituent of *T. foenum- graecum* at this point. However, based on the published studies, flavonoids seem to be most likely candidates eliciting anti-tumorigenic effect.

Antidiabetic Activity

Vanadate treatment to diabetic rats has been reported to correct the altered carbohydrate metabolism and antioxidant status. However, vanadate exerts these effects at relatively high doses and several toxic effects are produced. Low doses of vanadate in combination with *Trigonella foenum- graecum* seed powder (TSP) effect on the enzyme changes in diabetic rats. Alloxan-diabetic rats were treated separately with insulin, vanadate (0.6 mg/ml), TSP and a combined dose of Vanadate (0.2 mg/ml) and TSP for 21 days. At the end of the experimental period, blood glucose levels and activities of pyruvate kinase (PK), phosphoenolpyruvate carboxykinase (PEPCK), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT) were measured in cytosolic fraction in the liver and kidney. Blood glucose levels increased markedly in diabetic rats. Treatment with antidiabetic compounds resulted in the reduction of glucose levels. Rats treated with combined dose of vanadate and *trigonella* had glucose levels comparable to control ones. Similar results were obtained with the activities of PK, PEPCK, SOD, GPx, GR, and CAT in liver and kidney of diabetic rats. Combined dose of vanadate and *Trigonella* was found to be most effective in correcting these alterations.[42]

Fenugreek has primarily been described as an antihyperglycemic herb in humans as well as in laboratory animals.[43, 44] Its cholesterol-reducing effect is also well established.[45] In the present study, fenugreek showed an overall stimulatory effect on the specific as well as nonspecific immune functions in mice. Stimulatory effects were observed at 100 mg/kg body weight dose and in some cases at 250 mg/kg. Though there was an increase in liver weight,

estimation of the LFT enzymes did not reflect any toxicity. Similarly, fenugreek powder did not alter GOT, GPT and alkaline phosphates (ACP) levels either in serum or liver in rats maintained on 1%, 5% and 10% debitterized fenugreek powder up to 90 days. However, in contrast to our observation, they did not report any significant increase in the liver weight of treated animals.[46]

The soluble dietary fibre (SDF) fraction of *Trigonella foenum-graecum* (Tf-sdf) has shown to reduce postprandial elevation in blood glucose level of Type 2 model diabetic rats by delaying the digestion of sucrose. The Tf-sdf has now been investigated for its chronic effect on serum fructosamine, insulin and lipid levels, and on platelet aggregation in Type 2 diabetic rats. Tf-sdf was administered orally twice daily at a dose of 0.5 g/kg for 28 days. It lowered the serum fructosamine level ($P < 0.05$) with no significant change in the insulin level as compared with the control. Atherogenic lipids, i.e. triglycerides, cholesterol and LDL-cholesterol were found to decrease significantly in Tf-sdf fed rats ($P < 0.01$). HDL-cholesterol showed an opposite trend ($P < 0.024$), but serum non-esterified fatty acid (NEFA) values paralleled the atherogenic lipids ($P < 0.001$). No significant effect on platelet aggregation (%) was found although there was a tendency to lower the aggregation ($P < 0.069$). It is concluded that Tf-sdf has a beneficial effect on dyslipidemia and has a tendency to inhibit platelet aggregation in Type 2 model diabetic rats.[47] The hypoglycemic effect of the aqueous (Aq) extract of the bark of *Pterocarpus arsupium* (PM) and alcoholic (Alc) extract of seeds of *Trigonella foenum-graecum* (FG) and leaves of *Ocimum sanctum* (OS) was investigated in both normal and alloxan-induced diabetic rats. The Aq extract of PM (1 g/kg PO) significantly ($P<0.001$) reduced the blood sugar levels from 72.32 ± 5.62 to 61.35 ± 1.2 mg% 2 h after oral administration of the extract and also significantly lowered the blood glucose in alloxan diabetic rats from 202.91 ± 5.44 to 85.22 ± 11.28 mg% 21 days after daily oral administration of the extract ($P<0.001$). Similarly, reduction was seen with Alc extract of FG (74.33 ± 4.77 to 60.56 ± 1.9 in normal rats and 201.25 ± 7.69 to 121.25 ± 6.25 in diabetic rats) ($P<0.001$) and OS (204.48 ± 11.0 to 131.43 ± 7.86 in normal rats and 73.54 ± 3.7 to 61.44 ± 2.3 in diabetic rats) ($P<0.001$). In addition, the extract also showed a favorable effect on glucose disposition in glucose fed hyperglycemic rats.[48]

The aqueous and alcoholic extracts of *Trigonella foenum-graecum* leaf were tested for hypoglycaemic activity in normal and alloxan-diabetic rats. Graded amounts (0.06, 0.2, 0.5, 1 g/kg, i.p. and 1, 2, 8 g/kg, p.o.) of the aqueous extract of *Trigonella foenum- graecum* leaf when given to both normal and alloxan-diabetic rats, a significant reduction of blood glucose concentration was noticed. On the other hand ethanolic extract of *Tigonella foenum-graecum* leaf produced no reduction in blood glucose concentration in normal rats but intra-peritoneal administration of 0.8 g/kg of the ethanolic leaf extract to diabetic rats produced a significant reduction of blood glucose concentration ($p < 0.02$) at 2 and 24 h only. Intraperitoneal and oral acute toxicity (LD_{50}) and target organ effects were studied for the aqueous extract of *Trigonella* leaf in mice. LD_{50} of i.p. and oral administration were 1.9 and 10 g/kg respectively. The main organ affected after i.p. administration of the aqueous extract was the liver while oral administration of the aqueous extract of *Trigonella* did not produce any sign of organ damage. These results suggest that the aqueous extract of *Trigonella foenum-graecum* leaves given both orally and intraperitoneally possesses a hypoglycaemic effect in normoglycaemic and alloxan induced hyperglycaemic rats.[49]

Trigonella foenum-graecum, commonly known as fenugreek, is an annual herbaceous plant. From the seeds of *T. foenum-graecum* an unusual amino acid, 4-hydroxyisoleucine 5, has been isolated, which significantly decreased the plasma triglyceride levels by 33% ($P < 0.002$), total cholesterol (TC) by 22% ($P < 0.02$), and free fatty acids by 14%, accompanied by an increase in HDL–C/TC ratio by 39% in the dyslipidemic hamster model.[50]

Gastroprotective Effect

The effect of fenugreek seeds (*Trigonella foenum-graecum*) compared to omeprazole was studied on ethanol-induced gastric ulcer. The aqueous extract and a gel fraction isolated from the seeds showed significant ulcer protective effects. The cytoprotective effect of the seeds seemed to be not only due to the anti-secretory action but also to the effects on mucosal glycoproteins. The fenugreek seeds also prevented the rise in lipid peroxidation induced by ethanol presumably by enhancing antioxidant potential of the gastric mucosa thereby lowering mucosal injury. Studies revealed that the soluble gel fraction derived from the seeds was more effective than omeprazole in preventing lesion formation. These observations show that fenugreek seeds possess antiulcer potential.[51]

Anti-inflammatory and Antipyretic Effect

Anti - inflammatory and antipyretic effects of the *Trigonella foenum-graecum* (TFG) leaves extract, an Iranian medicinal plant, were examined. For anti-inflammatory activity, the formalin-induced edema model was used. Hyperthermia was induced by intraperitoneal injection of 20% (w/v) aqueous suspension of brewer's yeast. Sodium salicylate (SS) was used as a positive control. Both TFG and SS significantly reduced formalin-induced edema 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). TFG and SS also significantly reduced hyperthermia induced by brewer's yeast in 1 and 2 h after their administration. Phytochemical studies indicate that alkaloids, cardiac glycosides, and phenols are the major component in the extract. Although existence of three anti-inflammatory, analgesic and antipyretic effects in this extract suggest a NSAID-like mechanism for it, but the presence of alkaloids, the absence of other effective compounds such as flavonoids, saponins, steroids, etc., and also its analgesic effect on tail-flick test that usually is not produced by NSAIDs, suggest another mechanism for the extract. So the possibility of alkaloids as effective compounds, in this extracts increases.[52]

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 hyperthyroidic rat model to contribute to an understanding of interaction between the two extracts. The investigation was carried out using two different doses. A comparison was made with the response of individual plant extracts at the previously studied effective dose in adult Wistar rats rendered hyperthyroidic by daily injections of L-thyroxine (300 µg/kg body wt., *s.c.*). Propylthiouracil (PTU), an antithyroid drug, was used as a reference compound. Alterations in serum triiodothyronine (T3), thyroxine (T4), glucose, hepatic glucose-6-phosphatase (G-6-Pase) and oxygen consumption were studied as end parameters. Superoxide dismutase (SOD), catalase (CAT) activities, lipid peroxidation (LPO) and reduced glutathione (GSH) 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. Our findings reveal that some plant extracts in combination may not always prove to be synergistic. It is therefore suggested that *T. foenum-graecum* and *Allium sativum* extracts may be used individually and not together in the regulation of hyperthyroidism.[53]

Glycosidic Extract and Toxicity

Study was carried out to determine the acute toxicity of the leaf glycosidic extract of *T. foenum-graecum* by estimation of its medium lethal dose (LD_{50}) after oral and intraperitoneal administration to mice and also to identify the target organs for its possible toxic effects. The main target organ affected among the four organs studied (liver, kidney, stomach, small and large intestine) was the liver, where early degeneration with infiltration of mononuclear and mild hepatitis was found in some animals treated with toxic doses of glycosidic extract. It is concluded that the glycosidic extract of *T. foenum-graecum* leaves is considered to be safe and have minimal adverse effect.[54]

Toxicity

Short-term (90 days) feeding of fenugreek seeds to rats at levels equivalent to two and four times the therapeutic dose recommended for humans (25 g/day) produced no toxic effects as evidenced by normal liver function tests, lack of any histopathological changes in the liver and no changes in haematological parameters.[55] Moreover, long-term (24 weeks) administration of fenugreek seeds at 25 g/day, exhibited no clinical hepatic or renal toxicity or haematological abnormalities in diabetic subjects.[56] This dose was sufficient to improve glucose tolerance [57, 58] and lipid profile [59] in NIDDM humans. Two cases of severe reactions to fenugreek seed powder were reported in patients known to suffer from food allergies.[60] The first developed rhinorrhoea, wheezing and fainting following inhalation of the powder. The second developed numbness of the head, facial angioedema and wheezing after applying fenugreek paste to the scalp as a dandruff treatment. Immunoglobulins capable of binding to proteins in fenugreek seeds were found in the sera of some patients. Fenugreek seed extract did not produce any effect on the mean arterial blood pressure of anaesthetized rabbit in a dose of 20 mg i.v. nor on the isolated heart at a dose of 2.5 mg added to the perfusion fluid.[61] The LD_{50} of fenugreek leaf aqueous extract in male and female mice was reported to be about 10 g/kg body weight for oral administration and 2 g/kg for intraperitoneal administration. Mild central nervous stimulation, rapid respiration and tremors were observed following high doses of the aqueous extract [62, 63] estimates the LD_{50} in mice of a similar extract as 4 g/kg by the same route.

CONCLUSION

Fenugreek is one of the primary supplements used to support type II diabetics or noninsulin-dependent diabetes mellitus (NIDDM). Most NIDDM patients typically have enough insulin but it is not used effectively. Research as to the cause seems to indicate high levels of body fat; too many calories consumed from refined foods, lack of polyunsaturated fats and chromium deficiencies. Fenugreek Seed helps by not only reducing blood sugar levels with its high concentrations of phytochemicals, but it has also helped reduce low density cholesterol's and triacylglycerols.

T. foenum-graecum was found to possesses different activities such as Anticancer, Anti-Inflammatory, Antiseptic, Aphrodisiac, Astringent, Bitter, Demulcent,

Emollient, Expectorant, Anthelmintic, Wound healing and Gastro protective. Fenugreek seeds are a rich source of the polysaccharide galactomannan. They are also a source of saponins such as diosgenin, yamogenin, gitogenin, tigogenin, and neotigogens. Other bioactive constituents of fenugreek include mucilage, volatile oils, and alkaloids such as choline and trigonelline.

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