Multifarious Therapeutic Potential of Fenugreek: A Comprehensive Review

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Abstract
Fenugreek (Trigonella foenum-graecum) is used as a condiment and a medicinal plant. Various experimental and human studies have reported that fenugreek is a potential agent to treat diabetes mellitus. Fenugreek plays a key role to prevent the induction and progression of various disorders such as cancer, ulcer, obesity, etc. Moreover, the pleiotropic actions of fenugreek have been evaluated in hypertension, cataract, inflammation, thyroid dysfunction, malaria, endothelial dysfunction, etc. In this review, we have captured recent findings on fenugreek representing the distinct role of fenugreek in treating various disorders elaborating the mechanisms at molecular level.

Key words: Fenugreek, Diabetes, Cancer, Antioxidant, Therapeutic applications.

INTRODUCTION

Trigonella foenum-graecum L (Fenugreek) is an annual leguminous herb that belongs to the family Fabaceae. The common names of the plant are methi, Greek hayseed, and bird’s foot. It is grown extensively which is native to many Asian, Middle Eastern and European countries. It has a long history as both a culinary and medicinal herb. The seeds of fenugreek are commonly used as a spice in food preparations due to the strong flavour and aroma. Fenugreek seed contains 45-60% carbohydrates, mainly mucilaginous fiber (galactomannans); 20-30% proteins high in lysine and tryptophan; 5-10% fixed oils (lipids); pyridine-type alkaloids, mainly trigonelline (0.2-0.36%) choline (0.5%), gentianine and carpaine; flavonoids, such as apigenin, luteolin, orientin, quercetin, vitexin and isovitexin; free amino acids, such as 4-hydroxyisoleucine (0.09%); arginine, histidine and lysine; calcium and iron; saponins (0.6-1.7%); glycosides yielding steroidal sapogenins on hydrolysis (diosgenin, yamogenin, tigogenin, neotigogenin, gitongenin and trigogenin) cholesterol and sitosterol; vitamins A, B₁, C and nicotinic acid; coumarin compounds and 0.015% volatile oils (nalkanes and sesquiterpenes).[1-3] Smilagenin, sarsapogenin, and yuccagenin (minor steroidal sapogenins) have also been isolated from the seeds.[1, 4] Further, fenugreek seeds contain the saponin fenugrin B and the leaves contain at least 7 saponins, known as graecunins. [5] Moreover, the seeds are known to contain phosphates, lecithin and nucleoalbumin. Trigonelline degraded to nicotinic acid and related pyridines during roasting is responsible for the flavor of the seed. [6] The importance of diosgenin in the synthesis of oral contraceptives and sex hormones have been documented.[7] Numerous studies have been carried out to reveal the therapeutic potential of fenugreek in various pathological conditions such as diabetes mellitus, cancer, hypertension, cataract, gastric disorders and obesity.[8-13] This review critically discusses the mechanistic study of application of fenugreek in therapeutics.

1. Fenugreek and Diabetes Mellitus
The administration of fenugreek alkaloidal extract in streptozotocin (STZ)-induced hyperglycemic rats prevented the increased blood glucose level, reduced lipid profile to almost normal and showed antioxidant effect on the tissues of liver and kidney.[14] Further, fenugreek powder treatment in a dose of 25g, 50g, 75g and 100g/day in patients suffering from mild NIDDM (Non-insulin dependent diabetes mellitus) with dyslipidaemia produced marked reduction in blood sugar at a dose of 75 g/day and serum triglycerides up to a maximum dose of 100 g/day.[9] Moreover, the curative nature of fenugreek powder was observed in coronary artery disease patients with NIDDM,
produced significant decrease in the lipids levels of total cholesterol and triglycerides and blood sugar level.\textsuperscript{[15]} It has been documented from various studies that saponins and diosgenin present in fenugreek are responsible for hypolipidemic and anti-diabetic action on hypercholesterolaemic rats, alloxan-induced diabetic dogs and IDDM type 1 patients.\textsuperscript{[16-18]}

It has been observed that supplementation of diet with fenugreek leaves and seeds in STZ-induced and alloxan-induced hyperglycemic rats prevented the increased levels of glucose by stimulating the process of glycolysis and inhibiting gluconeogenesis via stimulating enzymes such as hexokinase and inhibiting enzymes such as glucose 6-phosphatase and fructose 1, 6-biphosphatase and subsequently increasing the secretion of insulin.\textsuperscript{[19, 20]}

The administration of defatted fraction of fenugreek in diabetic dogs for 8 days lowered the levels of basal blood glucose, plasma glucagon and somatostatin.\textsuperscript{[21]} It has been revealed in a study that administration of fenugreek seeds or its defatted fraction sensitizes the insulin receptor in mild type-2 diabetic patients and NIDDM.\textsuperscript{[22,23]}

Furthermore, it has been reported that the administration of active principle of water extract of seeds of \textit{Trigonella foenum graecum} (fenugreek) in alloxan-induced subdiabetic and overtly diabetic rabbits stimulated insulin synthesis and/or secretion from the beta pancreatic cells of Langerhans and increased the sensitivity of tissues to available insulin.\textsuperscript{[24]}

It has been documented in an \textit{in vivo} experiment that alloxan-induced diabetic mice have shown hypoglycaemic activity by the administration of fenugreek seed extract via stimulating insulin signalling pathway leading to equipotent effect as that of insulin. This was further demonstrated by an \textit{in vitro} study that the treatment of fenugreek on CHO-HIRc-mycGLUT4eGFP and 3T3-L1-mycGLUT4 cells models showed dose-dependent stimulatory effect on cellular glucose uptake, causing GLUT4 translocation to the cell surface and phosphorylation of tyrosine proteins such as insulin receptor, insulin receptor substrate 1 and p85 subunit of PI3-K, in adipocytes and human hepatoma cells.\textsuperscript{[25]}

It is well known that diabetes mellitus induces lowering of cortical thickness of thymus gland and a recent study showed that fenugreek plays a vital role in improving the lowering of cortical thickness of thymus gland by inhibiting death of cortical thymocytes induced by diabetes mellitus in streptozotocin model of rat.\textsuperscript{[26]}

Taken together, further studies are warranted to elucidate the mechanism involved in improving the diabetes mellitus by the use of fenugreek. The mechanism associated with fenugreek induced improvement of diabetes mellitus have been depicted in Fig. 1.

2. \textbf{Fenugreek and Cancer}

The effect of fenugreek seeds observed in 7,12-dimethylbenz(a)anthracene (DMBA)-induced breast cancer in rats halted the DMBA-induced mammary hyperplasia which may be mediated through apoptosis.\textsuperscript{[27]} Further, the ethanolic extract of fenugreek showed antineoplastic effect on the growth of MCF-7 cells (an estrogen receptor positive breast cancer cell line) by reducing cell viability, inducing early apoptotic changes via flipping of phosphatidylserine, declining the mitochondrial membrane potential and degrading cellular DNA into fragments.\textsuperscript{[10]} Moreover, an \textit{in vitro} study revealed that diosgenin inhibited cell growth and induced apoptosis in the HT-29 human colon cancer cell line in a dose-dependent manner mediated through inhibition of bcl-2 and upregulation of expression of caspase-3.\textsuperscript{[28]}

The chemoprotective potential of diosgenin and fenugreek seeds have been delineated in aoxymethane-induced rat colon carcinogenesis reporting cytotoxicity at higher concentrations and inhibition of cell proliferation at lower concentration and reducing the number of multicyclic foci in a dose dependent manner respectively.\textsuperscript{[29]}

Other possible mechanisms of diosgenin and fenugreek-induced chemoprotection in HT-29 cells, osteosarcoma cells and DMBA-induced cancer in AKR/J H-2\textsuperscript{a} mice involve downregulation of cyclooxygenase-2 and subsequent inhibition of arachidonic acid metabolism; increased the mRNA expression of p53 and p21 and activated nuclear factor kappa B (NFκB) leading to apoptosis.\textsuperscript{[29, 30]}

Further, reducing the levels of cholesterol and decreasing the expression of phospholipase A and C are responsible for prevention of tumor formation and improving the histological features including adenocarcinoma, dysplasia and cellular pleomorphism in fenugreek seeds treated 1,2-dimethylhydrazine-provoked colon cancer in male Wistar rats.\textsuperscript{[31]} Cell lines expressing arachidonate lipooxygenase are known to play a hallmark in promoting carcinogenesis.\textsuperscript{[32]} It has been observed experimentally that fenugreek diet downregulated the expression of DMBA-induced increase in ALOX12 mRNA in AKR/H-2 super(k) mice.\textsuperscript{[13]}

The cytostatic effects of DMBA-induced increase in ALOX12 mRNA in AKR/H-2 super(k) mice.\textsuperscript{[13]}

It has been reported in a recent study that fenugreek stimulates the proliferation of MCF-7 cells, downregulates estrogen responsive elements; increases the expression of estrogen responsive gene pS2 in MCF-7 cells; are some of the possible mechanisms
responsible for its estrogenic property. Therefore, its estrogenic property can be employed as anticancer and in hormone replacement therapy in which further studies are warranted. However, the further studies are mandatory to observe the implications of these proposed mechanisms involved in the fenugreek-induced attenuation of carcinogenesis-provoked by various experimental models. The possible mechanisms involved in fenugreek-induced prevention of cancer have been shown in Fig. 2.

3. Fenugreek and Antioxidant

It has been documented in various studies that fenugreek bears potential of a powerful antioxidant in which the presence of flavonoids and polyphenols have been found to be responsible for the same. This study has further been evaluated in normal and diabetic human erythrocytes by the exposure of polyphenol-rich extract of fenugreek seeds which showed protective effects against hydrogen peroxide-induced oxidation by protecting the erythrocytes from haemolysis and lipid peroxidation in a dose dependent manner. Further, fenugreek administration to diabetic animals showed a reversal of the disturbed antioxidant levels of enzymes such as catalase, superoxide dismutase and glutathione peroxidase and peroxidative damage in the tissues of heart and kidney. Moreover, it has been documented that the supplementation of fenugreek seed powder for 30 days to alloxan-induced diabetic rats normalized the alterations in lipid peroxidation and oxidative stress-induced by alloxan. In addition, the antioxidant property of fenugreek has been studied in vivo and in vitro in ethanol-induced toxic rats which reduced lipid peroxidation and prevented enzyme leakage. The in vitro activity showed equipotent effect as that exhibited by reduced glutathione and alpha-tocopherol. Furthermore, a recent in vitro study has reported that the fenugreek extract has shown antioxidant and anti mutagenic property by acting as scavanging DPPH and ABTS free radicals and by inhibiting the \( \gamma \)-radiation-induced strand break formation in plasmid pBR322 DNA.

4. Fenugreek and Ulcer

The administration of fenugreek seeds aqueous extract and gel fraction in ethanol-induced gastric ulcer in rats elaborated its cytoprotective actions by its anti-secretory activity and its effect on mucosal glycoproteins exerted by its antioxidant action via inhibiting lipid peroxidation thereby preventing gastric mucosa and reducing gastric lesions. However, the gel fraction of fenugreek has been reported to be more potent in preventing lesion formation in ethanol-induced gastric ulcerated rats. It is worth noting that fenugreek protects ulcer formation in aspirin-induced rats via decreasing gastric volume, ulcer index value, total acidity, lesion formation and curative ratio by markedly increasing the level of mucus secretion and glutathione. It may be suggested that the cytoprotective action of fenugreek can be attributed to the presence of flavonoids; which exert their anti-ulcer effect by protecting the mucosa and thus preventing the formation of lesions induced by various necrotic agents. It is important to note that fenugreek extract derived via solid state bioconversion using \( \text{Rhizopus oligosporus} \) has shown its defensive effect on gastric mucosa by its antimicrobial activity on \( \text{Helicobacter pylori} \). The possible mechanisms responsible for gastroprotective action may include the production of acidic environment by altering the urease activity of the bacteria, disruption of membrane proton motive force; attributed to phenolic extract due to which bacterial cell lysis may occur; presence of scopolin, a coumarin derivative reported to inhibit electron transport chain in prokaryotes. Thus, the abovementioned studies put insights into the fine pharmacological profile of fenugreek in protecting ulcer but the applications of these studies in clinical trials are missing.

5. Fenugreek and Inflammation

Fenugreek at a dose of 100 and 200 mg/kg reduced carrageenan-induced paw edema in rats. Further, the presence of alkaloids in extract of fenugreek has been reported to produce anti-inflammatory property by reducing formalin-induced edema in rat and antipyretic property by significantly reducing hyperthermia induced by Brewer’s Yeast. Moreover, the topical preparation containing 3% and 5% fenugreek showed its anti-inflammatory property probably due to the presence of saponins and flavonoids because flavonoids act as antioxidant and potential inhibitors of cyclooxygenase, lipooxygenase, and nitric oxide synthase. It has been demonstrated in a recent study that fenugreek administration to diabetes obese KK ay mice inhibits macrophage infiltration into adipose tissues and decreased the mRNA expression levels of inflammatory genes, which is responsible for its anti-inflammatory action. Fenugreek has been reported to accelerate the process of wound healing via its antioxidant potential in rats injured in the posterior neck area. It may be suggested that the presence of diosgenin in fenugreek plays a key role in producing anti inflammatory action probably by acting the precursor of various steroid hormones such as progesterone and cortisone; which have set a benchmark for preventing inflammation in various pathological conditions; but the relevant data in this regard is missing and thus further studies are needed to be evaluated in this thirst area of research.
6. Fenugreek and Obesity

The beneficial effects of fenugreek fiber was studied in healthy obese subjects which demonstrated that fenugreek administration showed marked increase in satiety and fullness and marked fall in hunger and prospective food consumption with reduced energy intake using visual analog scale which may act supportive for treating acute obesity patients. Galactomannan and unpalatability of the fenugreek fiber is assumed to be responsible for promoting satiety by decreasing the rates of gastric emptying and decreased energy intake respectively. It has been reported in a recent study that treatment of fenugreek to diabetes obese KK ay mice ameliorated diabetes-induced obesity by promoting adipocyte differentiation via increasing the mRNA expression levels of differentiation related genes in adipose tissues mediated by diosgenin.

7. Fenugreek and Hypertension

Endothelial dysfunction is a devastating condition which is associated to induce various disorders such as atherosclerosis, hypertension, diabetes mellitus, etc. The administration of fenugreek to old N Mari rats was found to be equipotent as that of lovastatin in normalizing the lipid profile and improving the function of vascular endothelium exhibited by reducing the thickness of aortic intimal layer and lipid deposits. It has been elucidated that the administration of fenugreek methanol extract and methanol fraction to rats administered deoxycorticosterone acetate-salt and fructose were found to show antihypertensive action mediated through serotonergic antagonistic property via 5 HT2 receptor. The essential oil obtained from fenugreek in combination with other essential oils has been employed to reduce systolic blood pressure in spontaneously hypertensive rat. The aqueous and benzene extract of fenugreek has been found to show diuretic action in a dose dependent manner by increasing the volume of urine and natriuretic activity by increasing the levels of Na+/K+ ions ratio in Wistar rats; which can be employed to treat hypertension. There have been very few reports on the studies of fenugreek to exploit its therapeutic potential to combat with hypertension.

8. Fenugreek and Other Disorders

Administration of fenugreek seed extract to both mice and rats revealed its effect on thyroid hormone that fenugreek inhibits the synthesis of triiodothyronine concentration estimated by decrease in serum triiodothyronine concentration and T3/T4 ratio and consequently increased thyroxine levels which can be mediated through fenugreek-induced hypoglycaemia. It has been reported that oral treatment with fenugreek reduced the quantity of calcium oxalate deposited in the kidneys induced by 3% glycolic acid in rats; which further supports its use in Saudi folk medicine. Fenugreek showed anticataract property in sodium selenite-induced cataract in rats by restoring the levels of glutathione, and other antioxidant enzymes such as superoxide dismutase, catalase, etc. in the lens and inhibiting the lipid peroxidation. Further, the exposure of fenugreek in vitro protected the lens morphology and clarity in selenite-induced cataract. Moreover, fenugreek is known to cure alloxan-induced diabetic cataract by decreasing the opacity index.

The fenugreek seed treatment in a dose of 60 g/day for 7 weeks in Saudi goat from Zumri breed reported to increase the milk production via stimulating the release of growth hormone. The alkaloidal, ethanol and butanol extract of fenugreek has been documented to possess antiplasmodial activity against in vitro culture of chloroquine sensitive and resistant Plasmodium falciparum. Fenugreek extract in a dose of 50, 100 and 250 mg/kg in albino swiss mice showed immunomodulatory property through various mechanisms such as increase in relative organ weight of thymus, delayed type of hypersensitivity response, humoral immunity, increase in phagocytic index and phagocytic capacity of macrophages.

Conclusion

Fenugreek has an extensive variety of actions which are likely to protect the human body against a variety of insults. Fenugreek has the potential to ameliorate diabetes mellitus exhibited by stimulating glycolytic enzymes, inhibiting gluconeogenesis, translocating GLUT 4, sensitizing insulin receptors, and inducing hypolipidemia. Further, the exaggerated action of fenugreek in treating cancer has been demonstrated through various mechanisms such as induction of apoptosis, inhibition of cell proliferation and arachidonic acid pathway. But, the clinical data in this regard is lacking. Increasing body of evidences suggests that oxidative stress plays a vital role in the induction and progression of various disorders such as atherosclerosis, Parkinson’s disease, heart failure, myocardial infarction and Alzheimer’s disease. But the promising antioxidant effect of fenugreek needs to be explored in these diseases. In spite of various pleiotropic actions of fenugreek on chronic disorders such as obesity, inflammation, hypertension and ulcers, the relevant clinical applications of fenugreek is still in the queue of thirst area of research. Therefore, more focused research on specific experimental models, human trials and an understanding the mechanism of action is necessary.
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Abbreviations
STZ  Streptozotocin
NIDDM  Non-insulin dependent diabetes mellitus
DMBA  7,12-dimethylbenz(α)anthracene
NFκB  Nuclear factor kappa B

Fig. 1 The mechanisms associated with fenugreek-induced improvement of diabetes mellitus

GLUT 4 indicates glucose transporter 4; TG indicates triglycerides; TC indicates total cholesterol; LDL indicates low density lipoprotein; HDL indicates high density lipoprotein.
Fig. 2 The possible mechanisms involved in fenugreek-induced prevention of cancer

DNA indicates deoxyribo nucleic acid; PLA indicates phospholipase A; PLC indicates phospholipase C; NF-κB indicates nuclear factor kappaB; COX-2 indicates cyclooxygenase 2; ALOX indicates arachidonate lipoxygenas.

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