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Holistic approach of *Trigonella foenum-graecum* in Phytochemistry and Pharmacology- A Review

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***Abstract* — India is a country of herbs where a lot of varieties are cultivated, and their formulation developed and used for preventing, mitigating and curing of diseases and other health problems. *Trigonella foenum-graecum* (Fenugreek) is one of them. Its origin is in India and Northern Africa. The plant contains a variety of components *i.e.* alkaloids, glycoside, polyphenols, steroids, amino acids and volatile components etc. It is used as anti-diabetic, anti-fertility, anti-microbial, anti-parasitic and hypocholesterolaemic, antiepileptic, antibronchitis, carminative, aphrodisiac, analgesic, antipyretic, anticancer, antioxidant, immunomodulator, in phlegm disorders, and recently in balancing the blood sugar level. In India, fenugreek powder is also used as a lactation stimulant and protective against ethanol toxicity etc. Due to its versatile activities and holistic approach in pharmacology, it is a drug of choice for health related problems of the general person, patient and researchers also. Research is going on for developing various formulations for various activities of fenugreek. This review gives an account about the recent uses of the *T. foenum-graecum*.**

Keyword* - Anti-diabetic, Fenugreek, Immunomodulator, Pharmacology, Phytochemistry, *Trigonella foenum-graecum

INTRODUCTION

Trigonella foenum-graecum Linn. (Fenugreek) is an annual crop belonging to the family fabaceae. *Trigonella* means triangle shaped "pale yellow flower" and *foenum- greacum* means "Greek hay"[1]. It is about 30-60 cm tall and cultivated throughout the country. It has nearly smoothed erect, untoothed stipulate, and 2-2.5 cm long leaflets. There are 1-2 flowers, axillary, sessile, linear calyx-teeth, and corolla much exerted. Pods are 5-7.5 cm in a length with a long persistent beak often falcate and 10-29 seeds without transverse reticulations. Plant was first described around 1500 BC in Egyptian literature for various medicinal as well as dietary uses. In India, the first citation of fenugreek as Methi was found around 10th Century A.D. It is native to Western Asia where it has covered Europe, the Mediterranean region, and the rest of Asia. It is regarded as well as recommended a useful medicinal plant for the treatment of various dysfunctions and diseases in recorded history and in Ayurveda also. Due to versatile action of plant, widely use in Egypt, Greek, Italy and South Asia for treatment of health problems. It is used as anti-diabetic, anti-fertility, anti-microbial, anti-parasitic and hypocholesterolaemic, antileptic, antibronchitis, carminative, aphrodisiac, analgesic, antipyretic, anticancer [2], antioxidant, immunomodulator, in phlegm disorders, and recently reported in balancing the blood sugar level. In India, fenugreek powder is also used as a lactation stimulant and protective against ethanol toxicity [3].

Literature survey revealed that whole plant have a lot of activities for treatment of diseases e.g., fresh leaves are used for the treatment of indigestion, flatulence, and the dried leaves are used as a quality flavor for meat, fish, and vegetable dishes [4] while seeds are used as food preservative in pickles, chutneys and other similar food products. Seeds are very hard and difficult to grind so that seed extract is also used in vanilla, butterscotch and rum flavoring [5]. Gargle, made from the seeds, is used for recurrent ordinary sore throat and mouth ulcers. Main purpose of the use of this plant is to improve the health quality of person as well as prevention of the diseases [6], [7].

HISTORICAL USES OF *T. FOENUM-GRAECUM*

According to recorded data, people used different parts of plants like root, stem, seeds, leaves and fruits for curing diseases. Its origin was found in India and Northern Africa but its applications were found in ancient Egypt at first time and then in other countries [7]. It was used to embalm mummies and in incense. In ancient Rome, it was used to aid labor and delivery. In China, seeds were used as a tonic in treatment for weakness and edema of the legs. In modern era, it is still used as a supplement in wheat and maize flour for making bread in Egypt [8].

In India, it was used as a condiment and as medicine for lactic stimulation, treatments of indigestion and baldness. Recently it is also used as anti-diabetic, anti-cancer, immunomodulatory and anti-ulcer in different form such as aqueous extract, methanolic extract, powder and other forms also. Research is going on for determining the different activities of the various parts of plant [9].

PHYTOCHEMISTRY OF *T. FOENUM-GRAECUM*

Active Principles

Bioactive compounds isolated from fenugreek seeds include saponins (i.e: fenugreekine [10], diosgenin), alkaloids (i.e: trigonelline, gentianine, carpaine), amino acids (4-Hydroxyisoleucin, arginine), flavanoids. Seeds are rich source of protein (30%), starch (26%), natural detergent fibre (13%), gum (4%), lipids (6%) and ash (11%). It is also rich source of calcium, iron, β-carotene and other vitamins. In comparison to other legumes, fenugreek seeds contain higher proportions of minerals including Ca, P, Mg, Fe, Zn and Mn but there is no variation in the composition of other variety of fenugreek [11].

Trigonelline is a major and important alkaloid component of the seeds, which also contain some aromatic constituents such as n-alkenes, sesquiterpenes and nonalactone. It has been found that it also rich in saponins, including diosgenin, gitogenin and tigogenin [12].

Fenugreek contains some chemical constituents which have great medicinal value; i.e. steroidal sapogenins; isoleucine and galactomannans. These constituents provide specific place to fenugreek among the most commonly recognized "nutraceutical" or health food products [13]-[15]. First fenugreek cultivar "Tristar" was developed by the Lethbridge Research Centre (LRC) in close collaboration with researchers from Alberta Agriculture, Food and Rural Development by genetic variability and modification of genotype. It is very high quality forage because it contains the steroidal compound diosgenin which require for the animals [16]-[18].

Environmental factors such as light, temperature, pH, salinity [19] and soil moisture affects the germination of seeds and due to this, chemical composition of plant changed from one species to another species. Therefore, the germination process for particular crops requires specific environmental factors but another research also conclude that alkaloid contents are mainly controlled by genotypic characteristics rather than ecological ones [20]-[22].

Alkaloids

Seeds have been reported to contain pyridine (trigonelline and gentianine), piperidine (carpaine) and steroidal (choline) group of alkaloids in smaller quantities [23], [24].

Trigonelline- ($C_7H_7NO_2$, mol.wt- 137.14g/mol) [25] (N-methyl-nicotinate). It is also known as Coffearin, Coffearine and Gynesine. It is derived from vitamin B_6 and produced by nicotinic acid (pyridinium-3-carboxylic acid) methylation using methionine, a kind of amino acid containing sulfur, in green coffee beans [26]. It has bitter taste in comparison to caffeine but 100% water solubility. It is found in pure crystalline form at 424 °F and melted at 218° c. This compound exerts mild hypoglycemic and anti-pellagra effect. It is the first chemically identified hormone that controls the cell cycle at G2 phase in plants and animals. This is most effective in aseptic media because at that time its activity is sufficient to promote cell arrest in G2 [27]. It has highly toxic effect on neuromuscular preparations [28].

Gentianine- It is widely distributed in plants like *Gentiana crassicaulis, G. kirilowii, G. macrophylla, G. marginata, Swertia caroliniensis, S. chirayita, S. japonica* and *T. foenum graecum* etc. belonging to the family *Gentianaceae*. It is bitter in taste and crystalline monoterpene alkaloid. It has many activities like antiamoebic, anti-bacterial, anti-convulsant, diuretic, anti-histaminic, hypotensive, anti-inflammatory, antimalarial, antipsychotic and sedative [16], [23].

Carpaine- ($C_{28}H_{50}N_2O_4$, mol.wt- 478.70 g/mol). It is one of the minor alkaloid components of plant but the major component of papaya leaves. It has cardiovascular effect dominantly but other effects are also studied. These effects may be related to its macrocyclic dilactone structure, which is a possible cation chelating structure [29].

Glycosides

Steroidal Saponin- Plant contains steroidal saponins at which Diosgenin is a major component and used for manufacturing of oral contraceptives and sex hormones by the pharmaceutical company as a raw material. Bitter taste of seed is due to presence of saponins. Yamogenin is (25S) - epimer of diosgenin and present in the ratio of 2:3 with diosgenin in the seed [30].

Trigofoenoside A, B [31], C, D [32], E, F, G [33], trigonelloside C, yamogenin tetroside B, C, tenugrin B, tigogenin [34], neotigogenin, yamogenin [10], gitogenin, neogitogenin, yuccagenin, lilagenin, sarsapogenin and smilagenin are glycosides of *T. foenum-graecum*. Glycosides of diosgenin are graecunins A, B, C, H, I, J, K, L, M and N [35]-[39].

Polyphenolic Compounds

Polyphenolic compounds have anti-oxidative effect that remove free radicals and protect against oxidation, hence used to prevent some chronic diseases. Fenugreek seeds are rich source of polyphenols (100mg/g). It contains various classes of flavonoids such as flavones, flavonones, flavonols, flavanols (flavan-3-ols), isoflavones, proanthocyanidins and anthocyanins. Some reported flavonoids are quercetin, luteolin, vitexin, isovitexin, saponaretin, homoerietin, vicenin-1 and vicenin-2 [40].

Some phenolic compounds are isolated from *T. foenum-graecum* i.e. coumarin, scopoletin, chlorogenic, caffeic and P-coumaric acid.

Coumarin- ($C_9H_6O_2$, mol.wt-146.14 g/mol) It is oxygen containing heterocyclic compound, present in either free or combined form with the sugar glucose (coumarin glycoside), having vanilla like flavor. It has blood-thinning, anti-fungicidal and anti-tumor activities. Particularly their physiological, bacteriostatic and anti-tumor activities make these compounds attractive. Its metabolite i.e. 7-hydroxycoumarin has antitumor activity against several human tumor cell lines. It shows potential inhibition of cellular proliferation in various carcinoma cell lines. It is toxic at high doses when used for long period [41].

Scopoletin- ($C_{10}H_8O_4$, mol.wt-192.16 g/mol) It belongs to the group of coumarins. Pure scopoletin is a yellow to beige (a pale pinkish- yellow) crystalline powder. It regulates the blood pressure: when the blood pressure is high, it helps to lower it and when BP is too low, it helps to raise it. It has bacteriostatic activity against various species of bacteria, including *Escherichia coli, Staphylococcus aureus, Streptococcus* sp., *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [42]. It is used to treat bronchial illnesses and asthma also because of its anti-inflammatory activity. It regulates the serotonin hormone, which helps to reduce anxiety and depression [41].

Chlorogenic acid- ($C_{16}H_{18}O_9$, mol.wt- 354.31g/mol) It is obtained from a family of esters of hydroxycinnamic acids (caffeic acid, ferulic acid and *p*-coumaric acid) with quinic acid. It is an important intermediate in biosynthesis of lignin and one of the major phenolic compound, identified in peach, prunes and coffee. It also slows the release of glucose into the bloodstream after a meal. It is reported as chemical sensitizer so that it is responsible for human respiratory allergy as a type of plant material. It also has the laxative effect and observed in prunes [43].

Caffeic acid- ($C_9H_8O_4$, mol.wt-180.16 g/mol) It is found in many plants and foods but coffee is the primary source of caffeic acid in the human diet. It produces many effects e.g. antioxidant, anti-inflammatory and immunomodulatory in the body. Researchers have reported that it might decrease the growth of cancer cells and viruses also. It also has a mild stimulant effect, and reduces fatigue related to exercise. However it is used as supplements for boosting athletic performance, weight loss, cancer, HIV/AIDS, herpes and other conditions [43].

Amino Acids

T. foenum graecum is rich source of amino acids such as 4-OH Ile, alanine, aspartate, arginine, cysteine, glycine, isoleucine, leucine, lysine, histidine, serine, tryptophan and valine [44].

4-OH Ile - It is extracted from seeds and its absolute stereo configuration is determined as (2S, 3R, 4S) [45], [46]. It is a natural nonproteinogenic amino acid possessing insulinotropic biological activity and responsible for antidiabetic activity of plant [47]. It increases glucose-induced release of insulin so that it is strictly dependent on the glucose concentration. This unique property allows us to avoid undesirable side-effects such as hypoglycemia in the therapy of type II diabetes. Thus, 4-OH Ile seems a promising dietary supplement in the treatment and prevention of chronic diseases.

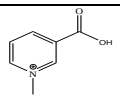
Essential Oil

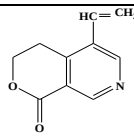
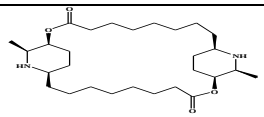
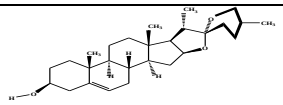
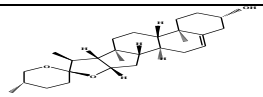
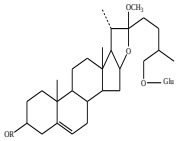
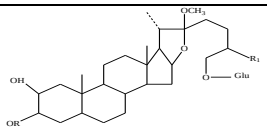
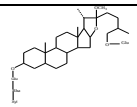
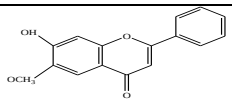
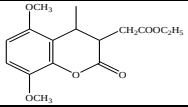
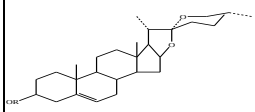
Seed contains approximately 6-8% oil components while oil is rich in unsaturated fatty acids (nearly 70 % of the total fatty acids), and polyunsaturated fatty acids (61.42 % mass percentage) of the total amount [48]. Approximately 175 volatile components are identified, which are carbonyls, sesquiterpene hydrocarbons, alcohols, heterocyclic and furan etc. Volatile components are responsible for the aroma and flavor of plant. Sotolone (3-hydroxy-4, 5-dimethyl-2(5H)-furanone) has been identified as the principal component, contributing to the flavor of plant [49]. Sotolone and anethol together impart the flavor of burnt sugar, curry or maple syrup, which is the characteristic of the plant [41], [50]-[54].

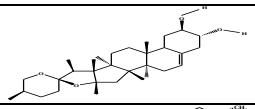
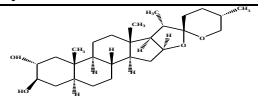
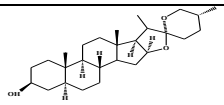
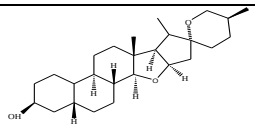
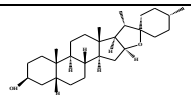
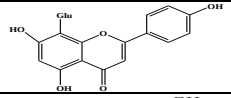
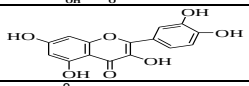
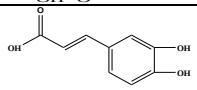
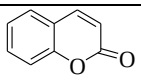
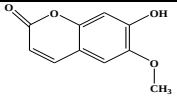
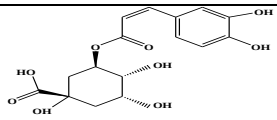
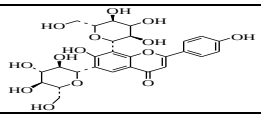
Lipid components

Fenugreek seed also contains about 5.5–7.5% lipid constituents mainly of neutral lipids (85%) followed by phospholipids (10%) and glycolipids (5%). Qualitative and quantitative estimation of the major free fatty acids have done by GC/MS and results obtained that linoleic acid is the major fatty acid (36% of the total fatty acids) followed by linolenic (18%), oleic (13%) and palmitic acid (9%). Two minor membrane lipid components are also implicated in lipid signalling pathway i.e N-acylethanolamines (NAEs) and their precursor, N-acyl phosphatidylethanolamines (NAPEs). They were identified as phospholipid constituents as well as fatty acid amides with a physiological role in mammalian nervous system. Oleamide, recently reported in some plants, is a member of that class [55].

Table 1: Phytochemical Constituents of *T. foenum-graecum*

S.	Name	Structure	Activities
1.	**Alkaloids**		
(a)	Trigonelline [56]		Mild hypoglycemic, anti-pellagra and controling the cell cycle at G2 phase

(b)	Gentianine [41]		Antiamoebic, anti-bacterial, anti-convulsant, diuretic, anti-histaminic, hypotensive, anti-inflammatory, antimalarial, antipsychotic and sedative
(c)	Carpaine [58]		Cardiovascular effect
2.	**Glycosides**		
(a)	Diosgenin [39]		Raw material for oral contraceptives and sex hormones
(b)	Yamogenin [59]		-
(c)	Trigofoenoside A_1: R= -Glu-Rha Trigofoenoside D_1: R= -Glu-Rha-Glu Trigofoenoside F_1: R= -Glu-Glu-Rha Trigofoenoside G_1: R= -Glu-Glu-Rha-Xyl[60]		-
(d)	Trigofoenoside B_1: R= -Glu-Rha R_1= α- Me Trigofoenoside C_1: R= -Glu-Rha-Rha R_1= β- Me [60]		-
(e)	Trigofoenoside E_1 [60]		-
(f)	Trigraecum [60]		-
(g)	Trigocoumarin [60]		-
(h)	Graecunin E: R= -Glu-Rha-Glu-Glu Graecunin G: R= -Glu-Rha-Glu [60]		-

(i)	Yuccagenin [60]		-
(j)	Neogitogenin [61]		-
(k)	Tigogenin [62]		-
(l)	Sarsapogenin [63]		-
(m	Smilagenin [64]		-
3.	**Polyphenolic Compounds**		
(a)	Vitexin [60]		Anti-aging effects, free radical scavenging activity
(b)	Quercetin [60]		Anti-cancer, anti-inflammatory and antihistamine activity
(c)	Caffeic acid [60]		Antioxidant, anti-inflammatory, immunomodulatory, a mild stimulant, reduces fatigue, as supplements for boosting athletic performance, weight loss, anti- cancer, anti-HIV/AIDS, anti- herpes
(d)	Coumarin [60]		Flavoring, blood-thinning, anti-fungal, anti-tumor, bacteriostatic and anti-tumor activity
(e)	Scopoletin [65]		Regulation of blood pressure, bacteriostatic, anti asthmatic, anti-inflammatory and regulation of serotonin hormone
(f)	Chlorogenic acid [66]		Anti allergic, laxative
(g)	Vicenin-2 [67]		Anti-cancer and antispasmodic activity
4.	**Amino Acids**		

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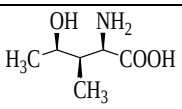
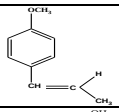
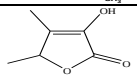
(a)	4-Hydroxyisoleucin [56]		Insulinotropic and antidiabetic activity
5.	**Essential Oils**		
(a)	Anethol [65]		Flavor of plant
(b)	Sotolone [68]		Flavor of burnt sugar, curry or maple syrup

PHARMACOLOGICAL ACTIVITIES

T. foenum-graecum is a mixture of bioactive compounds include alkaloids, saponins, amino acids (act as insulin secretogogues i.e. 4-OH Ile, arginine), flavonoids, coumarins, mucilaginous fibers (galactomannan), nicotinic acid and other vitamins and minerals (Fe, Mn, Mg, Zn etc.). Flavonoids show remarkable biological activities i.e. inhibitory effects on enzymes, modulatory effect on some cell types, antioxidant, anticarcinogenic property, anti-allergic, antibacterial, antifungal, antiviral, anti-malarial and anti-inflammatory properties. Flavonoids, in the class of benzo-gamma pyrone derivatives, have high pharmacological potency and show the antioxidant activity of these polyphenolic compounds. Much of the hypoglycemic effect of fenugreek seeds in clinical studies is likely due to the inhibitory effects of mucilaginous fibers on glucose absorption. Some therapeutic activities include [23]:

Anti-Diabetic Activity

In humans, seeds exert hypoglycemic effects [69] by stimulating glucose-dependent insulin secretion [70]-[72]. The hypoglycemic effect of plant has been attributed to different mechanisms. Plant extract act directly on pancreatic cells and stimulate insulin secretion by beta cells and/or inhibit α-cells and release of hyperglycemic factor. By this way, the effect of insulin and adrenalin is enhanced and assist in inhibition of the synthesis of glucose-6-phosphate phosphatase, fructose diphosphatase, pyruvate carboxylase or phosphoenol pyruvate carboxykinase, and stimulate the synthesis of glucokinase [73].

In *In-vitro* study, result found that 4-OH Ile, in seeds have property to increase the amount of insulin which is glucose induced in human and also release insulin in rat pancreatic islet cells and act as insulinotropic agent by insulin signalling pathway [74]-[76].

Moorthy have reported that GII compound, extracted from aqueous extract of *T. foenum graecum*, is responsible for hypoglycemic effects in the plant [77].

The levels of somatostatin and glucagon do not alter because amino acid acts only on pancreatic beta cells. Bioavailability studies show that, *T. foenum-graecum* increases the number of insulin receptors and reduce the area under the plasma glucose curve. Seeds also contain sapogenins which increase biliary cholesterol excretion, might be attributed to increase thyroid hormone T4 by estrogenic constituent [78]. This plant is also used in treatment of diabetes induced cataract as anticataractic agent [5], [79], [80].

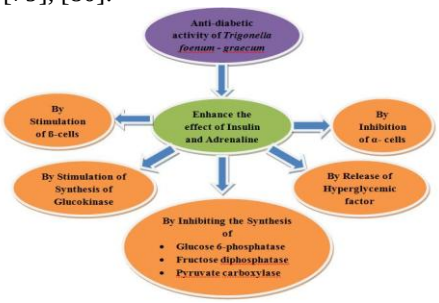


Fig.1. Mechanism of Anti-diabetic Activity of *T. foenum-graecum*

Antioxidant Activity

Biological oxidation occurs when free radicals or reactive oxygen species (ROS) are formed in our body but the over production of free radicals such as hydroxyl radical, hydrogen peroxide, superoxide anion radical can cause oxidative stress then damage to the body organs. Oxidative damage of proteins, DNA and lipid can cause chronic degenerative diseases including cancer, hypertension, coronary artery disease, diabetes etc. Most of the reactive oxygen species are scavenged by endogenous defense systems such as super oxide, dismutase -glutathione peroxides system and catalase [18].

Numerous crude extracts and pure natural compounds have been found to have beneficial effects against free radicals in biological systems as anti-oxidants. Kaur have evaluated antioxidant activity by b-carotene and linoleic acid model system and found that high phenolics may provide a source of dietary anti-oxidants [81], [82]. In case of *T. foenum-graecum*, the antioxidant property of the plant material is due to the presence of many active phytochemicals including vitamins, flavonoids, terpenoids, carotenoids, cumarins, lignin, saponin, and plant sterol etc [83]. Ethanolic extract of fenugreek seeds and its major alkaloid, trigonelline both are promising natural antioxidants, act by lowering plasma MDA or increasing the plasma GSH

markers and may be used in the treatment of many diseases especially diabetes mellitus [84].

Seeds also lower the LPO in liver of ethanol intoxicated and diabetic rats by scavenging of hydroxyl radicals (-OH) and inhibition of hydrogen peroxide induced lipid peroxidation in rat liver mitrochondria [85]. The (-OH) scavenging activity of the extract is evaluated by pulse radiolysis and deoxyribosome system. Quercetin, a type of flavonoid, has shown protective effect against CP-induced hemorrhagic cystitis [86].

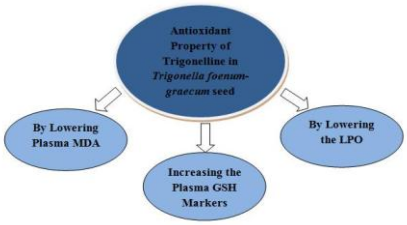


Fig.2. Mechanism of Antioxidant Property of Trigonelline

Phytoestrogenic Activity

In a dose response study, results obtain that trigonelline stimulate MCF-7 cell proliferation. Cell growth is significantly increased even in dose as low as 100pM. Furthermore, co treatment of estradiol with trigonelline stimulates MCF-7 cell growth to a greater extent than estradiol alone. Estrogen response element reporter assays establish that trigonelline promotes MCF-7 cell growth via the estrogen receptor and is estrogenic by nature. ICI, an estrogen receptor antagonist, inhibited trigonelline stimulated cellular proliferation in MCF-7 cells. Estrogen dependent breast cancer (MCF-7) cells are used for cell proliferation assays to examine whether the compound is indeed estrogenic. Therefore, trigonelline is found to be a novel Phytoestrogen [87], [88].

Anticarcinogenic Activity

In rats, fenugreek seeds inhibit colon carcinogenesis. Diosgenin present in seeds, suppress total colonic aberrant crypt foci formation by inhibiting bcl-2 and induced caspase-3 protein expression, thereby inducing apoptosis and inhibit cell growth. Fenugreek extract significantly inhibits the growth of MCF-7 human breast cancer cells in vitro. Due to the wide distribution of sterols and steroidal sapogenins, extract induced apoptosis is mediated by the increased levels of caspases -3, 8, 9 expressions by the death receptor and mitochondrial apoptotic pathways. It also activates the extrinsic death pathway (Fas and FADD-mediated apoptosis) by increased expression levels of caspase-8. p53 is the most commonly mutated gene associated with cancer, helps to regulate the cell cycle and plays a key role to ensure that damaged cells are destroyed by apoptosis. Extract exhibits anticancer effects by blocking the proliferation of MCF-7 cells and induced apoptosis is affected by its ability to regulate the expression of pro-apoptotic genes such as caspase-3, 8, 9, p53, Fas, FADD, Bax and Bak. Some plant constituents also modulate beta-glucuronidase and mucinase activities. Trigonelline, an alkaloid of fenugreek, is also revealed for using in cancer therapy [89]. Therefore, the literature survey shows that fenugreek extract have anticancer activity, and it is conducted through the regulation of gene expressions [90], [91].

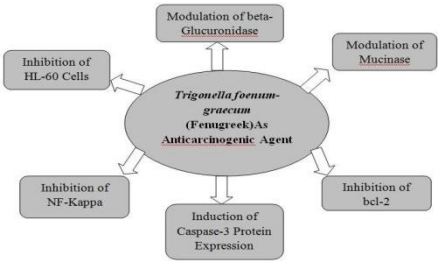


Fig.3. Anticarcinogenic Activity of *T. foenum-graecum*

Antiulcer Activity

The present study demonstrates that the antiulcer activity of plant is due to the presence of various phytochemical constituents such as alkaloids and flavonoids [92]. The gastric mucosal damage is induced by various factors such as stress. Stress inactivates mucosal prostaglandin synthesis by accumulation of hydrogen peroxide, a prostaglandin biosynthesis inhibition which causes ROS generation.

Different therapeutic agents including plants extract are used to inhibit the secretion of gastric acid or to increase the mucosal production on surface epithelial cells or interfere with the synthesis of PG [93]. Various mechanisms have been reported for antiulcer activity such as production of acidic environment, by altering the urease activity of the *Helicobacter pylori* bacteria, disruption of membrane proton motive force [94]. According to various data, antiulcer activity of plant is due to the presence of alkaloids and flavonoids; which protect the mucosa and thus prevent the formation of lesions induced by various necrotic agents [95]. It also protects ulcer formation by decreasing gastric volume, ulcer index value, total acidity, lesion formation and curative ratio by increasing the level of mucus secretion and glutathione. Scopoletin, a coumarin derivative, inhibits electron transport chain in prokaryotes and act as anti-ulcerogenic agent [96].

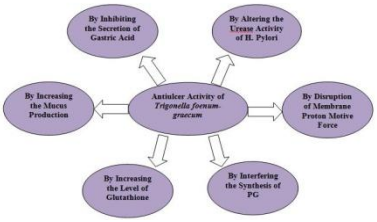


Fig.4. Mode of Action of Antiulcer Activity of *T. foenum-graecum*

Immunomodulatory Effect

T. foenum graecum shows stimulatory effects on macrophages. Macrophages are an integral part of the immune system; act as primary line of defense against infections by phagocytosis and killing of invading microorganisms as phagocytic, microbicidal and tumoricidal effector cells. Macrophages interact with lymphocytes and regulate immune response. There are many plants reported but they show nonspecific immunity, i.e. macrophages functions. Fenugreek shows immunomodulatory effects on the specific as well as non-specific immune functions [97].

Fenugreek seeds are rich source of dietary fiber as well as mucilage (about 28%). Both of these induce macrophages. Fenugreek also contains small quantity of iron in an organic form, which may be readily absorbed and facilitate haematopoietic stimulation in bone marrow. Thus by specific as well as non-specific way, fenugreek shows immunomodulatory effects [98].

Anti-obesity and Hypolipaedemic Activity

T. foenum-graecum seeds reduce serum lipids by excretion of bile acids and neutral sterols in feces, so depletion of the cholesterol occurs in the body. The effect of fenugreek is shown in hyper-cholesterolemic diabetic patients not in control group.

For anti-obesity, the probable mechanism of fenugreek may be that seeds contain (40%) soluble fiber which suppresses appetite due to its gelatinous nature (similar to gaurgum) and may slow the digestion and absorption of food. thus promotes weight loss. It also flushes out the carbohydrates before entering in to the blood stream so weight loss occurs due to deficiency of glucose in blood. In case of lipid profile, fenugreek reduces the level of serum total cholesterol, serum triacylglyceride and serum LDL-cholesterol in hyperlipidemic type 2 diabetic patients and the level of the serum HDL-cholesterol level increases. Fenugreek does not show any effect on the weight of solid organs like liver, spleen and kidney [99], [100].

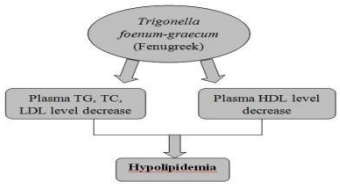


Fig.5. Basic Principle of Hypolipidemia

Hepatoprotective activity

Fenugreek seeds are reported to possess hepatoprotective activity. In one experimental report, it was determined that 1%, 5% and 10% debitterized fenugreek powder consumption up to 90 days, does not increase the level of GPT, GOT and alkaline phosphate, and weight of liver does not increase significantly [101]. When fenugreek seed polyphenol extract (FPEt) is administed to alcohol-fed rats, significantly improved lipid profile and reduced collagen content, crosslinking, aldehyde content and peroxidation have been found [102]. The hepatoprotective properties of fenugreek seed flour is used for preventing/improving the condition of ethanol intoxicated liver [103]. It may occur due to the presence of different flavonoids in it [104]. Fenugreek oil is also enhanced the efficiency of liver and ovarian tissue [98], [105]-[108].

Antifertility Effect

T. foenum-graecum is also used as antifertile natural agent. In the case of male, it reduces the weight of testis, plasma concentration of the androgen hormone and sperm concentrations. In females, the circulating plasma progesterone concentrations is significantly increased at 10 and 20 days of gestation and pre-breeding estrogen concentrations does not show any significant effect. In Research, it was found that for antifertile activity of fenugreek, female rabbits are more susceptible than male rabbits, but male rabbits are more prone toward toxic effect than female rabbits [109].

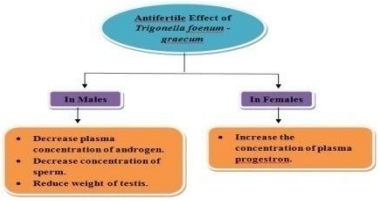


Fig.6. Antifertile effect of *T. foenum-greacum* in reproductive system

Skin Soothening Activity

Research has shown that it is an effective topical treatment for skin problems such as abscesses, boil, burns, eczema and gout. Therefore, it is used as a simple skin inflammation remedy. For this, spoonful of seeds is taken and grinded then mixes it into warm water. Simple piece of clean cloth is taken and soaked into the mixture, then this soaked cloth is directly applied on to the affected skin as a poultice. It provides relief to the affected area.

Fenugreek seeds are primarily composed of galactomannans which is natural effective ingredient and through a humectants mechanism, improve the mechanical property of the skin. Seeds extract improve the mechanical parameters like skin elasticity, ageing, hydration and Fatigue [110].

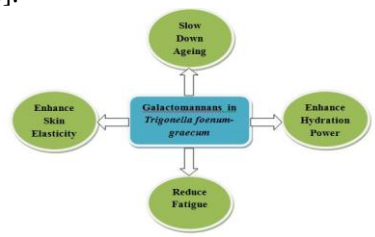


Fig.7. Skin Soothening Property of *T. foenum-graecum*

Anti-Inflammatory, Analgesic and Antipyretic Activity

Existence of anti-inflammatory, analgesic and antipyretic effects in *T. foenum-graecum* extract suggest a NSAID-like mechanism, but the absence of effective compounds such as flavonoids, saponins, steroids etc. does not show.

Methanol extract of fenugreek seed contains glycoside and steroidal moieties that may be responsible for the pharmacological activities. Its polar nature and potential analgesic and anti-inflammatory activity are due to its aqueous solubility. It inhibit production of inflammatory cytokines such as TNF-α in a monocytic cell line and inhibit melanin synthesis in melanoma cells but recently reported that in obese rat, oral supplementation of fenugreek upregulated TNF-α protein levels in the liver and plasma, and this may occur due to the difference in the study patterns (in vitro and in vivo systems) [111]. Further investigations are needed for determining its anti-inflammatory activity as well as its influence on various pain and inflammatory mediators. This analgesic effect of plant extract is produced via the spinal 5-HT system or purinoceptors [112], [113].

Breast Enlargement, Ease Child Birth for Pregnant Woman and Galactagogue Activity

Consumption of seeds enhances the secretion of sex hormones. It helps to balance woman's hormones and also enlarge the breasts. Daily consumption of seeds is used as home remedy for breast enlargement. It also stimulates the contraction of uterus so used for induction of childbirth but pregnant woman should consult with their doctor before using it as home remedy during their pregnancy [9].

Seeds are often used to increase the milk production in lactating mother but milk will come out slightly darker than normal and with different taste due to the contents but no other side effect is produced. Mechanism of this galactagogue activity is not known but researchers speculate that oil contents of seeds are responsible for this action. Thus regular use of the seeds is beneficial for lactating mother [9].

Antibacterial Activity

The aqueous extract of *T. foenum-graecum* seeds shows various degrees of bacteriostatic activity against gram positive and gram negative bacteria. Seeds are found to be effective against bacteria like *Escherichia coli, Salmonella typhi* and *Staphylococcus aureus.* Seeds show variation in activity due to variation in plant components that's gets from different area [114]-[116].

Other uses/application of *T. foenum-graecum*

1. Seeds are rich source of vitamin E and used as preservative.
2. Fresh leaves are beneficial in the treatment of indigestion, flatulence and a sluggish liver.
3. The dried leaves have flavor so used as a quality flavor for meat, fish and vegetable dishes.
4. An infusion of the leaves and gargle made from the seeds, both are used for recurrent mouth ulcers and for ordinary sore throat.
5. If fresh leaves paste applied over the scalp regularly, it helps to grow hair, preserves natural color, keeps hair silky and also cures dandruff.
6. Topically, the gelatinous texture of seed sooths skin that is irritated by eczema or other conditions. It has also been applied as a warm poultice to relieve muscle aches and gout pain.
7. Seeds reduce the amounts of calcium oxalate in the kidneys which is one of the causes of kidney stones.
8. In animal studies, *T. foenum-graecum* appears to lessen the chance of developing colon cancer by blocking the action of certain enzymes.
9. *T. foenum-graecum* is currently used as a source of the steroid diosgenin from which other steroids, sex hormones and contraceptives can be prepared [42].
10. Leaf powder decrease the level of acetyl cholinesterase, malondialdehyde on brain and increase the reduced glutathione level, and used for management of mental disorders like Alzheimer's disease [117].
11. Fenugreek seed extract is neuroregenerative and use for the control of peripheral neuropathy [118], [119].
12. Fenugreek increases activity of renal enzymes which involved in the synthesis/degradation of glycosaminoglycans (L-glutamine fructose-6-phosphate aminotransferase, N-acetyl glucosaminidase and b-glucuronidase) and act as reno-protective.
13. Fenugreek also overcomes the diabetis induced complications like polydypsia, polyuria, urine sugar, hyperglycaemia, renal hypertrophy and glomerular filtration rate [120].

SIDE EFFECTS

Direct seed and extract of seeds, both are safe but some time because of variable factors i.e. age, sex, body weight, dose, rate of metabolism, elimination, enzyme level and drug interaction etc. it cause side effects. These are listed below:

- It may increase bleeding in some cases.
- It may reduce potassium levels in the blood. Numbness, facial swelling, breathing difficulty and fainting are produced as a result of an allergic reaction.
- Dizziness, diarrhea and gas may occur after the recommended dose of the drug.
- It may cause loose stools in some women, produce uterine contractions, hypoglycemia in some mothers during pregnancy [121].

POSSIBLE INTERACTIONS [122]

- The adrenocortical or corticosteroidal action of plant may be antagonized by heparin.
- Its anti-inflammatory activity can be seriously inhibited by phenobarbital and certain other sedatives and hypnotics, such as chloral hydrate, meprobamate

and by beta-adrenergic blocking agents, such as propranolol.

- Coumarin constituents of plant contribute to anticoagulant effects so care should be taken at the time of any coagulating agent.
- Fenugreek also shows synergistic effect with glibenclamide in streptozotocin induced diabetic rats [123].

TOXICITY

In teratogenic dosages, fenugreek can decrease the severity of bone marrow cell proliferation and increase fetal mortality rate [124] but its high dosage may adversely influence the bone marrow cell proliferation [125].

CONCLUSION

Natural products play a valuable and prestigious role in the health of the human being without or minimally producing any unwanted effects likes side effects and adverse effects. They are generally the mixture of the primary and secondary plant metabolites like alkaloid, glycoside, flavonoids, saponine etc., and provide the health protective and disease curing action. *T. foenum-graecum* is one of the natural gifts for us, and because of their constituents, takes part in different health related activities. It contains some important alkaloids like trigonelline, gentianine; saponins like diosgenin, fenugreekine; amino acids like 4-OH Ile; and flavonoids like quercetin, luteolin, vitexin, isovitexin, saponaretin, homoerietin, vicenin-1 and vicenin-2. *T. foenum-graecum* is used for various health related problems like diabetes, cancer, ulcer, oxidative stress, allergy, bacterial, fungal, viral infection, malaria and inflammation etc. It is also used as antioxidant, immunomodulator, hypolipaedemic agent, hepatoprotective agent, antifertility agent, breast enlarging agent, anti-inflammatory, analgesic and antipyretic agent. Its uterus relaxing effect and galactagogue principle is also beneficial in delivery and lactating mother. Clinical application of fenugreek is beneficial for present as well as for future but due to lack of focusing on research and clinical trial, all of actions are not reported for human problems. *T. foenum-graecum* is widely used in various diseases like cancer, ulcer, diabetes, obesity and liver dysfunction. Research is going to explain its use in other types of cancer and other disease/ disorder. This review reveals that the plant possesses the potential for its use in diseases and as immunomodulatory, galactagogue and also as skin smoothening agent. Therefore more and more research, models and clinical trials are required for getting the maximum benefits, and understanding the mode of action of it in human being.

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