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Naveen Kumar
Assistant Professor, Arawali Veterinary College, Bajor, N.H- 52, Sikar, Rajasthan, India.

Mahesh Kumar
College of Veterinary and Animal Sciences, G. B. Pant University of Agriculture and Technology, Pantnagar, U. S. Nagar, Uttarakhand, India

Manish Kumar Verma
College of Veterinary and Animal Sciences, G. B. Pant University of Agriculture and Technology, Pantnagar, U. S. Nagar, Uttarakhand, India

Sivaraman Ramanarayanan
College of Veterinary and Animal Sciences, G. B. Pant University of Agriculture and Technology, Pantnagar, U. S. Nagar, Uttarakhand, India

Amita Ranjan
College of Veterinary and Animal Sciences, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

Rakesh Ranjan
ICAR-National Research Centre on Camel, Jorbeer, Bikaner, Rajasthan, India

Corresponding Author
Naveen Kumar
Assistant Professor, Arawali Veterinary College, Bajor, N.H- 52, Sikar, Rajasthan, India.

Bioactive effects and safety profiles of fenugreek (*Trigonella foenum-graecum* L.) for pharmaceutical and medicinal applications

Naveen Kumar, Mahesh Kumar, Manish Kumar Verma, Sivaraman Ramanarayanan, Amita Ranjan and Rakesh Ranjan

Abstract
The leaves and seeds of fenugreek (*Trigonella foenum-graecum* L), an annual herb, are common condiments used in India, Mediterranean and North African regions. Fenugreek has a long history of its use in traditional medicine. It is one of the oldest medicinal plants used in traditional medicine that contains many natural chemical compounds like trigonellin, diosgenin, quercetin, 4-hydroxyisoleucine, galactomannan, and scopoletin. Several studies on identification of different chemical compounds present in fenugreek and their therapeutic effects have revealed its hypocholesterolemic, antidepressant, galactagogues, antidiabetic, immunomodulatory, and hepatoprotective properties suggesting their potential use in prevention and treatment of many diseases in human and animals. This article summarizes recent research findings regarding the therapeutic potential and safety profile of fenugreek.

Keywords: fenugreek, safety, therapeutic properties, traditional-medicine, Trigonella

1. Introduction
Fenugreek (*Trigonella foenum-graecum* L.) is a leguminous herb belonging to the *Fabaceae* family and is grown as a spice crop in several countries of Asia, Africa, and Mediterranean Europe (Petropoulos, 2002; Srinivasan, 2006) [1, 2]. The plant grows 1-2 ft in height, seeds are present in sickle-shaped pods and are yellowish when ripened. Fenugreek, declared as safe for human consumption by United States Food and Drug Administration, have several medicinal applications (Sureshkumar *et al*., 2018) [3]. For centuries, it is being used for therapeutic purposes in Ayurvedic (Indian), Unani (Arabic) and Chinese traditional medicine (ElNour *et al*., 2015) [4]. In traditional medicine, it is being used for treatment of common cold, cough, bronchitis, sore throats, arthritis, menstrual pain and stimulate intestinal digestion (Herrera *et al*., 2019; Younesy *et al*., 2014) [5, 6]. Fenugreek seeds contain a high level of total polyphenols and flavonoids that provide beneficial physiological effects (Khlifi *et al*., 2016) [7]. Seeds have been identified as a commercial source of diosgenin, a chemical compound used for the production of steroids as drugs like sexual hormones, oral contraceptives and corticosteroids (Bahmani *et al*., 2016) [8]. Recently, standardized extracts are also available as capsules or tablets and are being used in the management of many diseases.

2. Chemical constituents and bioactive compounds
Major bioactive compounds present in fenugreek include alkaloids (pyridine, trigonellin), polyphenols (choline, luteolin, quercetin), steroidal saponins (diosgenin, protodioscin, yamogenin), coumarin, lipids, a non-proteinogenic amino acid (4-hydroxyisoleucine), vitamins, galactomannans and minerals (Sureshkumar *et al*., 2018; Kiss *et al*., 2018) [3, 9]. The fenugreek seeds contain 51.5% carbohydrates, 25.0% protein, and 6-8% lipids, while leaves contain 20-30% protein, 22-30% starch, 12.5% neutral detergent fiber, 4.0% gum 10.6% ash, and 4-6% lipids (Basu and Srichamroen, 2010) [10]. Trigonelline is the primary alkaloid present in fenugreek that is degraded to nicotinic acid and pyridines during roasting and provide typical flavor to the seeds (Ouzir *et al*., 2016) [11]. Fenugreek contains trigonelline that has high therapeutic potential and low toxicity. About 80% of the total content of free amino acid present in seeds is 4-hydroxyisoleucine (Fuller and Stephens, 2015) [12]. Fenugreek seeds also constitute dietary fiber (both insoluble and soluble), mainly galactomannan (Srinivasan, 2019) [13]. Presence of fourteen bioactive compounds was evident in fenugreek seeds in a

Chromatography-Mass Spectrometry (GCMS) analysis (Khalil *et al*., 2015) [14]. Fenugreek leaves contain highest amount of phenolic compounds and flavonoids (Premanath *et al*., 2011) [15]. The major active components responsible forvarious pharmaceutical properties of fenugreek have been described as diosgenin, trigonelline, galactomannan, 4-hydroxyisoleucine quercetin and scopoletin. The chemical structure of these components is mentioned in Figure 1 (Belaid-Nouira *et al*., 2012; Bairi *et al*., 2017) [16, 17].

3. Fenugreek on health promotion and disease prevention

Multiple biological effects have been reported in fenugreek and its derivatives, on both health promotion and disease prevention (Figure 2). The pre-clinical and clinical data related to fenugreek bioactive effects is briefly discussed with respective mode of action in following sections.

3.1 Anti-inflammatory activity

Nowadays, most anti-inflammatory treatments decrease the levels of cytokines associated with inflammatory diseases. Joints of rheumatoid arthritis patient contain more pro-inflammatory cytokines such as interleukin (IL-6) and tumor necrosis factor alpha (TNF-alpha) than the normal joints, and are associated with the pathogenesis of rheumatoid arthritis (Szollosi *et al*., 2018; Kawabata *et al*., 2011) [18, 19]. Both, cytokines and myeloperoxidase are important pro-inflammatory mediators for inflammatory reactions (Sindhu *et al*., 2012) [20]. Blocking cytokines and myeloperoxidase could produce a relief of symptoms in rheumatoid arthritis. Fenugreek seeds extract inhibit the production of inflammatory cytokines in cultured THP-1 cells (Sindhu *et al*., 2018) [21]. Mucilage from fenugreek markedly decreases the level of cytokines (TNF-alpha and IL-6) and myeloperoxidase activity in experimentally induced arthritis (Yacoubi *et al*., 2011; Suresh *et al*., 2012) [22, 23]. In another study, ethanolic extract of fenugreek significantly decreased the level of cytokines, TNF-alpha and IL-6 in arthritic albino rats. These findings suggested anti-inflammatory activities of fenugreek (Goto *et al*., 2004) [24].

3.2 Antinociceptive activity

Antinociceptive activity of fenugreek seed, leaves and stem extracts were investigated by several workers. Fenugreek extracts have proven antinociceptive and antipyretic effects in animal model similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) (Ahmadiani *et al*., 2001; Abbas *et al*., 2016) [25, 26]. Serotonergic system involves in the antinociceptive action of NSAIDs (Miranda *et al*., 2003) [27]. The alkaloid content of fenugreek seeds might be responsible for antinociceptive effect (Kaviarasan *et al*., 2008) [28]. In an experimental study on rats, ethanolic extract of fenugreek seeds showed antinociceptive effects, perhaps due to presence of some endogenous opoids (Biswal *et al*., 2003) [29]. Methanolic extract of fenugreek leaves were found to have greater inhibitory effect than paracetamol on writhing in rats induced by acetic acid (Bhalke *et al*., 2009) [30]. Likewise, in a double-blind placebo controlled clinical trial, transdermal patch containing 10% ethanolic extracts of fenugreek seeds were found to decrease pain score and demand for morphine in postherniotomy patients (Ansari *et al*., 2019) [31].

3.3 Antimicrobial activity

Aqueous and ethanolic fenugreek seed extract was found to have potent antibacterial activity (ElNour *et al*., 2015; Al-Hussainy, 2015; Dharajiya *et al*., 2016) [4, 32, 33] against many pathogenic bacterial strains including *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Al-Timimi *et al*., 2019) [34]. In another study, ethanolic extract of fenugreek leaf was found to have potent antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Premanath *et al*., 2011) [15]. Likewise, methanolic extract of leaves of stem was found to have good antibacterial activity against *Staphylococcus aureus* and *E. coli* (Sharma *et al*., 2017) [35]. Aqueous extract and essential oil derived from fenugreek seeds failed to inhibit the growth of some common food borne pathogens including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. coli*, *Bacillus cereus* and *Enterococcus feacalis* (Bhatia and Sharma, 2012) [36]. However, in other study, silver nanoparticles (AgNPs) engineered fenugreek seed extract has been found excellent antibacterial efficacy against Gram positive, Gram negative, and even multidrug resistant bacteria (Guardiola *et al*., 2018) [37].

3.4 Anticarcinogenic activity

Targeting the cell proliferation or inducing apoptosis is a critical point in the cancer therapy. Apoptosis, the programmed cell death, is characterized by the morphological changes including DNA fragmentation (Kitai *et al*., 2017) [38]. Apoptotic pathways can be classified into extrinsic and intrinsic that occurs inside the cell for the DNA fragmentation. The activation of caspase-3 is common in both, extrinsic and intrinsic pathways (Thakur and Ahirwar, 2019) [39]. Epithelial cells adaptation to persistent oxidative stress is an important step in carcinogenesis. Activation of Nrf2 (nuclear factor erythroid 2-related factor 2), through proteasome, pathway results into carcinogenesis (Khan and Khosla, 2018) [40]. Therefore, inhibiting Nrf2 is an important target in anticancer therapy. Ethyl iso-allocholate, a steroidal derivative from fenugreek seeds, is a potent anticancer agent that produces apoptosis by activation of caspase signaling pathway (Sebens *et al*., 2011) [41]. Alkaloid trigonelline isolated from fenugreek also has potential use in cancer therapy (Basu and Srichamroen, 2010) [10]. Trigonelline promote programmed cell death in cancer cells by blocking Nrf2-dependent proteasome activity (Cersosimo *et al*., 2018) [42].

3.5 Antidiabetic effect

Diabetes may lead to multiple organ complications due to long term progression before treatment. The pathogenesis of type 2 diabetes mellitus (T2DM) involves aberrant alteration in levels and function of many hormones including insulin (Cersosimo *et al*., 2018) [42]. The glucose homeostasis in the body is maintained by both insulin secretion and tissue sensitivity to insulin. Cellular glucose uptake is dependent on stimulation of insulin, which causes the translocation of glucose transporter-4 (GLUT-4) to the plasma membrane. Insulin resistance impairs glucose disposal by inhibiting cellular glucose uptake in muscle and adipose tissue (Avalos-Soriano *et al*., 2016) [43]. In T2DM patients, insulin stimulate cellular glucose uptake by inducing GLUT-4 from an intracellular compartment to the plasma membrane (Jaiswal *et al*., 2012) [44]. Peroxisome proliferators activate receptor (PPAR), a nuclear receptor that has supreme roles in lipid metabolism, particularly PPARgamma is critical for adipogenesis (Wafer *et al*., 2017) [45]. Variant in PPARgamma reduce the adipocyte differentiation and is associated with a substantial risk of T2DM. Fenugreek seeds contain large

amounts of 4-hydroxyisoleucine that stimulates insulin secretion and enhances the glucose uptake by translocation of GLUT4 to the plasma membrane (Szabo *et al*., 2018) [46]. Polyphenol, stilbenes and rhaponticin present in fenugreek seeds can increase insulin sensitivity (Li *et al*., 2018) [47]. PPARγ is one of the major molecular targets in T2DM. Diosgenin showed antihyperglycemic effect mediated selectively by the PPARgamma (Sangeetha *et al*., 2013) [48]. Glycated hemoglobin is the most commonly used marker for long term glycemic control (Sirsikar *et al*., 2016) [49]. Ingestion of fenugreek seeds significantly reduced fasting blood glucose levels and glycosylated hemoglobin levels in patients of T2DM (Khan and Khosla, 2018; Ranade and Mudgalkar, 2017) [40, 50].

3.6 Antihypertensive effect

High blood pressure (*i.e.*, hypertension) is one of the most common preventable causes of death, worldwide. Hypertension can be controlled using medicines like diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers, calcium channel blockers and aldosterone antagonist (Thomopoulos *et al*., 2018) [51]. Chronic administration of a mineralocorticoid, deoxycorticosterone acetate (DOCA) salt, induces hypertension due to salt and water retention. It is assumed that 5-HT_2B receptor is up-regulated by DOCA, resulting into continued elevated blood pressure (Banes and Watts, 2003) [52]. Administration of methanolic extract of fenugreek seeds to rats showed antihypertensive action mediated through serotonergic antagonistic property (via 5-HT_2 receptor) (Balaraman *et al*., 2006) [53]. Seeds of fenugreek are rich in essential oil (*i.e.*, terpenenes and omega-3 fatty acid), exhibit antihypertensive effect by decreasing the activity of ACE (Hamden *et al*., 2011) [54] in diabetic rats. In addition, combination of dietary fenugreek seeds and onion synergistically reduce the level of ACE in diabetic animals (Pradeep and Srinivasan, 2017) [55]. The aqueous extract of fenugreek showed diuretic activity, hence is helpful in management of hypertension (Rohini *et al*., 2008) [56]. In another study, fenugreek extracts increased excretion of sodium and potassium ions with a hypocalciuric effect (Al-Atwi, 2010) [57] like thiazide diuretic. Thiazide diuretics are often used as the first choice drug in hypertension.

3.7 Immunomodulation

Natural immunomodulators produce strong activity with negligible side effects. The natural immunostimulators synthesis or/and secrete several cytokines including IL-1, IL-2, IFN-gamma and TNF alpha (Vetvicka and Vetvickova, 2014) [58]. Bioactive compounds isolated from fenugreek can inhibit the cytokines like IL-1, IL-6 and TNF-α (Goyal *et al*., 2018) [59]. Fenugreek is widely known for its immunostimulatory properties (Guardiola *et al*., 2018) [37]. Dietary administration of seed stimulates the innate and adaptive immune parameters in *Sparus aurata* L (gilthead seabream). Different extracts of fenugreek showed immunomodulatory effect on immune functions in rats (Anarthe *et al*., 2014) [60], and Swiss albino mice (Bin-Hafeez *et al*., 2003) [61] through stimulating specific and non-specific immune mechanism.

3.8 Hypocholesterolemic activity

Excessively high plasma cholesterol level is a strong risk factor for cardiovascular diseases, particularly for development of peripheral vascular and coronary artery diseases (Stapleton *et al*., 2010) [62]. 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis is clinically used to treat cardiovascular disease (Jiang *et al*., 2018) [63]. Galactomannan from fenugreek seeds exerts hypolipidemic effect due to increased HMGA-CoA reductase activity with additional bile acids and neutral sterols excretion in faeces (Ramulu *et al*., 2011) [64]. Diosgenin, a furostanol saponin, in fenugreek inhibits the absorption of cholesterol and thereby lower hepatic cholesterol concentration and increases biliary cholesterol excretion, ultimately lowering the serum cholesterol concentration (Sfar *et al*., 2018) [65]. Fenugreek seeds powder improve atherogenic index (El-Masry *et al*., 2018) [66], a novel index associated with triglycerides and high-density lipoprotein cholesterol (Zhu *et al*., 2018) [67].

3.9 Neuroprotective effect

Several mechanisms are involved in different CNS disorders including inflammation, oxidative stress, high cholesterol level, and diabetes thus resulting into changes in brain integrity and functions (Zameer *et al*., 2018) [68]. Neuroprotective effect of fenugreek has been observed due to its efficacy in opposing 6-hydroxy dopamine (6-OHDA) induced Parkinson's disease and restoration of neurons (Mirzaie *et al*., 2016) [69]. Extract of fenugreek is reported to inhibit the acetylcholinesterase enzyme (Satheeshkumar *et al*., 2010) [70] which is crucial for the modulation of cognitive functions in neurodegenerative disorders. Dementia is the most common phenotype in Alzheimer's disease which is a chronic neurodegenerative disorder (Fahanik-Babaei *et al*., 2019) [71]. Fenugreek seeds attenuated the memory deficits, amyloid and tau pathology against Alzheimer's disease in rats (Prema *et al*., 2017) [72]. Methanolic extract of fenugreek seeds, as an antiamnesic agent, improved learning and memory processin mice (Assad *et al*., 2018) [73]. Fenugreek extract also exhibited neuroprotective effect in persons suffering from Parkinson's disease (Nathan *et al*., 2014) [74].

3.10 Antioxidant activity

Free radicals and other oxidants are derived from both endogenous sources and exogenous sources. Free radicals adversely affect the integrity of important biological molecules including nucleic acids, proteins, and lipids, thereby altering the normal redox status leading to several disease conditions such as cancer, aging, neurodegenerative diseases, cardiovascular diseases, diabetes mellitus, liver damage, etc (Phaniendra *et al*., 2015) [75]. Antioxidants either prevent excess generation of reactive oxygen species, or speeds up their removal (Kunwar and Priyadarsini, 2011) [76] so that damage to vital components of the cell can be minimized. Fenugreek seeds exhibited a high antioxidant potential (Kumar *et al*., 2021) [77] and restored the altered activity of cellular antioxidant enzymes in tissue (Yashin *et al*., 2017) [78]. The aqueous extract of fenugreek ameliorated the oxidative stress in rats (Al-Sultan and El-Bahr, 2015) [79] by activation of antioxidant enzymes and lowering hepatic lipid peroxidation. Fenugreek seeds have also been reported to provide protection to erythrocytes against oxidative damage (Fatima *et al*., 2018) [80]. A functional assay indicated that dietary fenugreek seed significantly restored the high-fat, high-sugar diet-damaged arterial response to acetylcholine (Szabo *et al*., 2018) [46], a classic vasodilatory signal

molecule.

3.11 Effects on reproductive system

Women with dysmenorrhea suffer from increased painful uterine contractions during menstruation. At menopause, there is decrease in estrogen production leading to life altering symptoms like cognitive instability, bone density reduction, cardiovascular disease, etc (Harlow and Signorello, 2000) [81]. Fenugreek has been used for the treatment of dysmenorrhea (Younesy *et al*., 2014; Yassin, 2018) [6, 82]. Fenugreek seeds contain phytoestrogen compounds, exhibit estrogenic effects, bind to estrogen receptors and induce expression of estrogen responsive genes (El-Masry *et al*., 2018) [66]. The seed extract ameliorated the symptoms of polycystic ovarian syndrome associated with decrease in both size and number of ovarian cysts, significant increase in LH and FSH level (Srinivasan and Sharma, 2018) [83]. It is also reported that perineal wash with seeds decoction significantly reduced vaginal discharge and vulval itching (Thilagavathy, 2016) [84]. Fenugreek seed has potential in balancing hormones to support libido in male (Steels *et al*., 2011) [85]. Seeds extract improves the level of total serum testosterone and sexual function in aging men (El-Masry *et al*., 2018; Rao *et al*., 2016) [66, 86].

3.12. Gastroprotective effect

Various experimental trials have shown that fenugreek can combat several pathologiccal conditions associated with gastrointestinal disorders. Fenugreek seed extract significantly decreased the volume of gastric juice, total acidity and gastric ulcer index (Singaravelu *et al*., 2018) [87]. In rats, aqueous extract of seeds exhibited ulcer protective effects by its antisecretory action (Pandian *et al*., 2002) [88]. Dietary fenugreek attenuates lithogenicity of bile thereby prevents pathogenesis of gallstones formation (Reddy and Srinivasan, 2011) [89]. Authors also reported the gastroprotective effect of fenugreek by increasing mucin secretion (Ghosal *et al*., 2016) [90]. The H^+/K^+-ATPase pump is a crucial target for gastroprotective effect. Fenugreek seeds produced gastroprotective effect by antagonizing this pump (Figer *et al*., 2017) [91].

3.13 Galactagogue activity

Galactagogues are a group of substances used to induce and maintain milk production in female (Sim *et al*., 2015) [92]. Dopamine (D_2 receptor) antagonists are conventional galactagogues, commonly used in clinical practice. Dopamine receptor antagonists increase milk production by increasing the levels of prolactin (Sim *et al*., 2015) [92]. Fenugreek is a safe and effective galactagogue (Forinash *et al*., 2012; Yadav and Baquer, 2014) [93, 94]. The chemical compounds present in fenugreek like diosgenin, luteolin and apigenin stimulate anterior pituitary to enhance milk production (Bumrungpert *et al*., 2018) [95]. Fenugreek increases breast milk volume and prolactin levels in mother (Reeder *et al*., 2013) [96]. Stimulating sweat production may be another possible way by which it increases milk production (Gabay, 2002) [97].

4. Safety and toxicity profile

Several *in vitro* and *in vivo* studies have established that fenugreek seeds and other parts of the plant are quite safe in animals and humans. Nevertheless, some reports have highlighted certain deleterious side effects of fenugreek seeds that are descried briefly in following sections.

4.1 Single dose effect

The acute oral median lethal dose (LD_{50}) of fenugreek seed extract was recorded to be greater than 2500 mg/kg body weight/day in Wistar rats (Sureshkumar *et al*., 2018) [3]. In another study, the oral LD_{50} of fenugreek seed powder was found 2 and 5 g/kg or more in mice and rats, respectively (Sharma *et al*., 1996) [98]. As per the guidelines of Organization for Economic Corporation and Development (OECD),value of LD_{50} < 2 gm/kg body weight is relatively safe, hence fenugreek may be considered as non-toxic (Sureshkumar *et al*., 2018) [3].

4.2 Repeated dose effect

In sub-chronic (90 days) toxicity study, debitterized fenugreek seeds powder was found safe even at a dose of up to 20% in the diet of weaning rats (Sharma *et al*., 1996) [98]. In a clinical study in 60 diabetic patients, daily single intake of 25 gram fenugreek seed powder for 24 weeks did not produce any sign of adverse or toxic effect (Khalki *et al*., 2012) [99]. Saponin-rich standardized seed extract is reported to be safe in rats even after repeated intake for 90 days, with no observed-adverse-effect level (NOAEL) of 1000 mg/kg body weight per day (Sureshkumar *et al*., 2018) [3].

Alteration in neurobehavioral performance in mice was recorded during the post-weaning period after prenatal exposure to high dose of fenugreek seeds (Posadzki *et al*., 2013) [100]. The consumption of fenugreek during pregnancy is not recommended assaponincompound is reported to have anti-fertility, anti-implantation and abortifacient activity (Ouzir *et al*., 2016) [11]. In addition, fenugreek may increase chances of morphological abnormalities and fetal death rate (Khalki *et al*., 2010) [101].

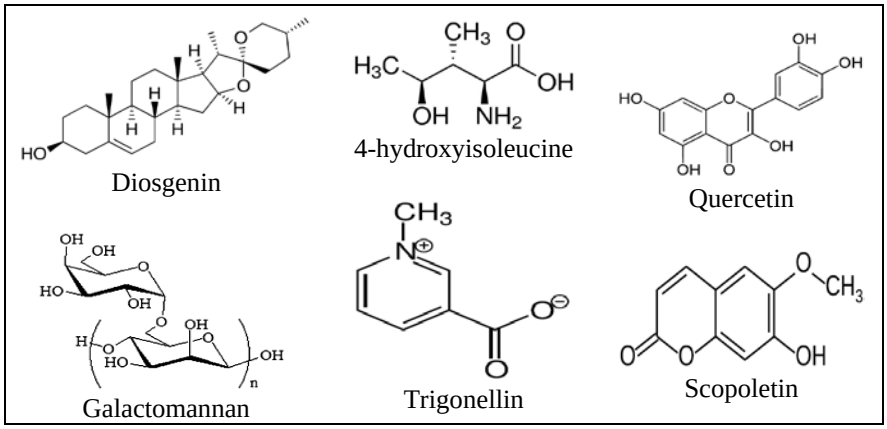

Fig 1: Chemical structures of Fenugreek bioactive compounds

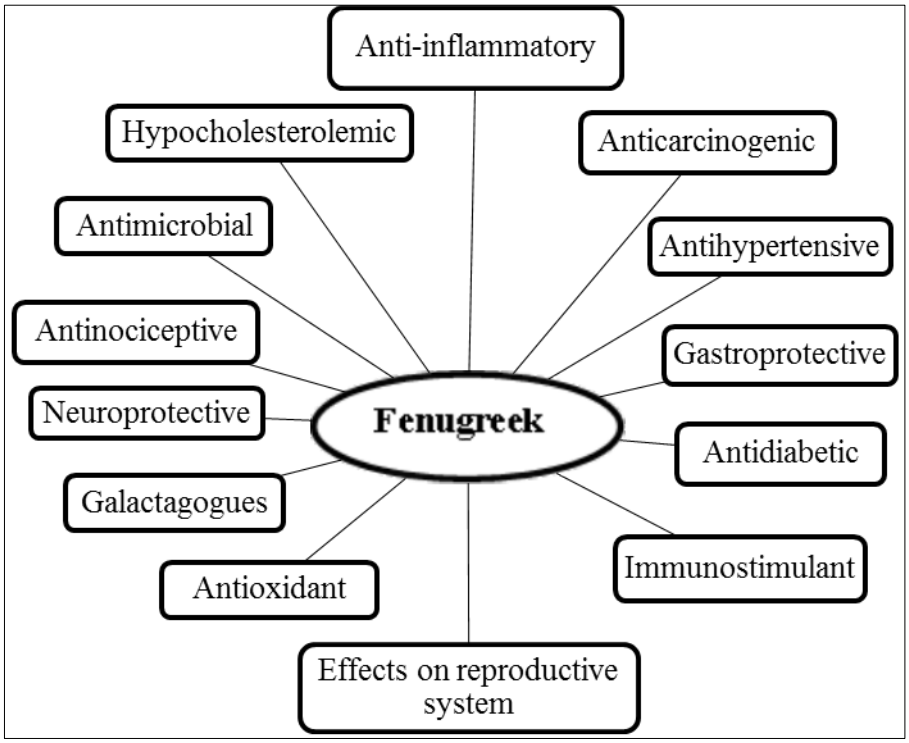

Fig 2: Schematic illustration of fenugreek biological activities

5. Conclusion

Based on available scientific information, fenugreek appears to have unique pharmacotherapeutic properties. Though it is a part of our dietary constituents, it may also be recommended as a therapeutic agent in several human and animal ailments. However, the unusual high human equivalent dose to achieve desired therapeutic effect is the major limiting factor in use of fenugreek crude extracts in various human ailments. The crude extract of any plant product is a complex mixture of several compounds, hence pointing a specific action of a particular component is often difficult. The process of drug development from herbs or any plant product includes multiple steps. Different active constituents extracted from fenugreek can also be studied for their therapeutic potential and subjected to drug designing and development. The research for new drugs with minimal toxicity is of interest in phytochemistry as occurrence of adverse drug effects is frequently reported after prolonged use of several drugs.

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7. Conflicts of interest

All authors read and approved the final manuscript and declare that they have no conflict of interests.

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