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Fenugreek Uses, Therapeutic Applications, Safety and Toxicity:A Review

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ABSTRACT

Fenugreek (Trigonella foenum-graecum L.) is an annual leguminous crop, which is native to the Indian subcontinent and the Eastern Mediterranean region. Historically fenugreek leaves and seeds were used for many therapeutic purposes. Fenugreek has been used for treatment of mouth ulcers and chapped lips, cure of baldness, alleviation of abdominal abscesses and pain, alleviation of cardiovascular and hepatic disorders, treating arthritis, treatment of dropsy, heart disease, spleen and liver enlargement, and for kidney ailments. Various parts of fenugreek are used in different food products due to its diverse and rich constituents. Recent studies on animal models showed that fenugreek has a toxicity on acute large doses and on chronic low doses, despite this; fenugreek still stated as safe by food and drug administration (FDA).

1. Introduction

Fenugreek (Trigonella foenum-graecum L.) is an annual leguminous crop, which is native to the Indian subcontinent and the Eastern Mediterranean region (Petropoulos, 2002).

1.1 Botanical aspects of fenugreek

Fenugreek seeds germinate to form seedling, which in turn develops to into stems, flowers, pods, and seeds. Flowering of fenugreek usually starts 35 to 40 days from the date of sowing (Petropoulos 2002).

Fenugreek have long seed pods which are long, slender, sickle-shaped with pointed ends, they appear yellowish brown or brownish (Petropoulos, 2002).

Seeds of fenugreek have a rectangular shape with an oblique groove, the seeds are yellowish brown to golden yellow, and the weight of each thousand seeds is around 15-20 grams (A. et al., 2009).

1.2 Ancient use of fenugreek

Historically fenugreek leaves and seeds were used for many therapeutic purposes, such as treating mouth ulcers and chapped lips, cure of baldness, alleviation of abdominal abscesses and pain, alleviation of cardiovascular and hepatic disorders, treating arthritis, management of dropsy, heart disease, spleen and liver enlargement, and for kidney ailments, in the subcontinent of India, Greece, Arabic and China (Basch, Ulbricht, Kuo, Szapary, & Smith, 2003). In the tomb of the Egyptian Pharaoh, Tuthankhamun (1333 BC to 1324 BC), seeds of fenugreek were found, indicating the remote history of fenugreek.

The Egyptians also used the leaves of fenugreek as one of the components of holy smoke in fumigation and embalming rites .Fenugreek was used as an aid to induce labour during childbirth and delivery in ancient Rome (Bano, Tabassum, Ahmad, Mabood, & Ahmad, 2016).

1.3 Modern use of fenugreek

Fenugreek leaves and seeds have multiple uses throughout the world. For example, in India it is used as a part of traditional medicine (Basch et al., 2003).

In Yemen and Persia used as supplement to the wheat flower for daily bread making, while in many parts of the world fenugreek used for daily meal preparation and as herbal medicine (Bane et al., 2016).

1.4 Fenugreek in food and food products

Various parts of fenugreek are used in different food products due to its diverse and rich constituents. Fenugreek seed is a rich source of vitamins such as vitamin A, B1, B2, C, nicotinic acid, niacin, biotin, calcium pantothenate, pyridoxine, vitamin C and cyanocobalamin (Ahmad, Alghamdi, Mahmood, & Afzal, 2016). Because it is rich in fibers fenugreek is considered as a functional food. The soluble fibers of fenugreek (gum) have many characteristics such as ability to give textural, appeal, thickening, emulsifying, stabilizing, gelling, and encapsulating properties, and based on these properties fenugreek has multiple applications in food industry. The soluble fibers of fenugreek can be implemented to nutrition and used in dairy products. It has been used to fortify bakery flour for pizza, cake mix, bread, bagel, muffins, flat bread, tortilla and noodles, fried, baked corn chips (Im and Maliakel, 2008).

2. Therapeutic properties and applications of fenugreek

Fenugreek seed mucilage found to improve the diabetic status by reducing blood glucose (Kumar et al., 2005). Seeds of Trigonella foenum-graecum are considered to be potentially useful for glucose control and for preventing hyperlipidaemia and atherosclerosis in diabetic subjects (Zia, Hasnain, & Hasan, 2001). Sindhu et al., (2012) reported the potential beneficial efficacy of fenugreek mucilage as anti-inflammatory in treatment of arthritis and attributed this to its anti-inflammatory and antioxidant properties (Sindhu et al.,2012). Fenugreek seeds approved to have an antioxidant activity and most likely due to its contents of flavonoids and polyphenols (Dixit et al., 2005). Fenugreek seeds examined for chemo protective property and found to be a chemo protective against breast cancer (Amin et al., 2005).

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Barathkumar, (2013) in his study showed that the diosgenin which is one of the active compounds of fenugreek seeds has benefits against renal failure-induced vascular calcification-associated oxidative stress, and he also found that this protective effect is dose dependent (Barathkumar, 2013). Different extract forms of fenugreek discovered to be as effective antibacterial and antifungal preparations because of their active phytochemicals (Dharajiya et al., 2016). Fenugreek seeds aqueous extract demonstrated more powerful antifertility effect in animal model when compared to the marketed combined oral contraceptive pills, which open the future for the safe use of fenugreek as a contraceptive herbal medicine (Hilles, Allow, & Mahmood, 2016). Fenugreek seed aqueous extract has an inhibitory property on fat accumulation and dyslipidaemia by inhibition of lipid digestion and absorption in addition to down regulation of lipogenic enzymes (P. Kumar, Bhandari, & Jamadagni, 2014). The hydro- alcoholic extract of fenugreek seeds showed a beneficial effects against peripheral neuropathy and facilitate healing (Moghadam, Vakili-zarch, & Shafiee, 2013). Morani et al., (2012) in their experiments demonstrated how fenugreek have an ameliorative effects on the painful peripheral neuropathy (Morani et al., 2012).

Fenugreek enhance breast milk production and facilitate infant birth weight gain in early postnatal days (Srinivas, Eagappan, & Sasikumar, 2014). Polyphenol seeds extract of fenugreek ameliorates the liver pathological changes and shown to be a hepatoprotective against alcohol-induced protein and lipid damage (Kaviarasan & Sundarapandiyan, 2008). Repeated administration of fenugreek seed extract to human causes a significant reduction in dietary fat consumption this was the result of clinical trial study has been done to demonstrate the metabolic effect of fenugreek as herbal remedy (Chevassus et al., 2009). The crude saponins extract from fenugreek seeds significantly reduces the deposition and formation of calcium oxalate stones in kidney, thus it has a renoprotective property against nephrolithiasis (Sabir, Adnan, & Private, 2015). Fenugreek aqueous extract exhibited antidiarrheal effect which may be attributed to its ability to inhibit prostaglandin biosynthesis (MLR & Kosanam, 2016).

Oligosaccharides based standardized fenugreek seed extract shown to have a prophylactic efficacy against insulin resistance associated with obesity (Kandhare et al., 2015). Fenugreek beside its glycaemic control in diabetes it showed a renoprotective function by reducing renal damage (Shetty & Salimath, 2009). Diosgenin is biologically active phytochemicals have been isolated from fenugreek found to have a role in the treatment of various types of disorder such as leukaemia, inflammation, hypercholesterolemia and cancer, in addition to that found to be able to prevent bone loss to the same extent as that of oestrogen (Atel et al., 2012).

3. Regions of cultivation of fenugreek

Fenugreek is widely grown in warm temperate and tropical regions in the Mediterranean, Europe, and Asia. Fenugreek is considered to have originated in the Mediterranean region of the "Old World" or in parts of Asia. Carbonized fenugreek seed recovered from Punjab (India) indicate its commercial use as far back as 2000 -1700 B.C. Even though it is native to Asia (an area extending from Iran to Northern India), but now it is widely cultivated in many parts of the world, including Canada, China, North and East Africa, Ukraine and Greece. The species name "foenum-graecum" means "Greek hay" which indicate its use as a forage crop in the past (Meena & Kumar, 2012).

The major seed producing countries are India, Ethiopia, Egypt and Turkey (A. et al., 2009). In recent years Ethiopia emerged as second largest producer of fenugreek, Indian subcontinent is the largest producer of fenugreek seeds in the world as 63 % of the world supply of fenugreek comes from India, Thus India continues to be the largest producer as well as largest exporter of fenugreek (Vidyashankar, 2014).

4. Chemical constituents of fenugreek

Various pharmacologically active compounds with different concentrations have been isolated from fenugreek seeds such as: Alkaloids, flavonoids, tannin like phenolic compounds, polyphenols, steroids, saponins, free amino acids, unusual amino acid 4- hydroxyisoleucine, lipids, phospholipids, mucilaginous fibers, vitamins, and minerals. Some functions of these active compounds are known, but many still unknown.

On the other hand, fenugreek seeds are well known to contain trypsin and chymotrypsin inhibitors as well as acetylcholinesterase inhibitor (Al-Ashban, Abou-Shaaban, & Shah, 2010). These active biochemical compounds can be classified into the following categories:

1) Steroidal saponins of which the diosgenin is medically and therapeutically important. 2) Fibers such as galactomannan which has its important as functional food, and it has medical application. 3) The amino acid 4-hydroxyisoleucine which is important as a nutrient and medicinal compound. 4) Phytochemicals and polyphenols which found to be a protective against oxidative stress and cellular damage caused by oxidative free radicals. 5) Alkaloids. 6) Fenugreek oils and oleoresin used as food additives and have other industrial applications (Lee et al., 2011). The fibre portion consists of both insoluble (30%) and soluble fraction (20%), which is mostly galactomannan. The 7.5% lipid present in the seed consists of mainly neutral lipids, such as, 6.3% triglycerides and 450 mg/100 g phospholipids (Srinivasan, 2006).

4.1 Bioactive compounds in fenugreek

Mature fenugreek seeds contain approximately 4-10% moisture, 6-8% lipids, 18-30% protein, and 48-55% fibers: 13-20% of which is galactomannan ((Lee et al., 2011; Srinivasan, 2006; & Sharma1986).

4.1.1 Galactomannan

Galactomannan is the predominant polysaccharide found in fenugreek seeds, it is found in high concentrated form around the seed coat (Bano et al., 2016). The chemical structure of the galactomannan of Trigonella Foenum-graecum, has been well documented, it has galactose and mannose residues in the ratios of 1:1 or in few cases of 1:2, it has been shown that different seeds species have different galactomannan structural ratio of galactose to mannose residues. Galactomannan is characterized by its high water-binding capacity and the formation of very viscous solution at relatively high dilutions (Garti et al., 1997). Presence of galactomannan in fenugreek seed is recognized as the principal source of soluble dietary fibers in the plant (Rathore et al., 2013).

Resembling other hydrocolloids, the galactomannan is insoluble in organic solvents, it can be precipitated from aqueous solution by addition of solvents like ethyl alcohol. The galactomannan is important viscosity builder and has many applications, some are related to food, and others are therapeutic. One of the important uses of galactomannan in the field of food, is its use as stabilizing agent, and as food emulsifier (Garti et al, 1997).

Therapeutically galactomannan shown to has an antidiabetic property and blood glucose lowering effect (Kumar et al., 2005).

Hannan et al. (2016) showed in their study on animal model that galactomannan which constitute the soluble part of fenugreek seeds fibers can significantly improve glucose homeostasis in type 1 and type 2 diabetes by delaying carbohydrate digestion and absorption. They also suggested that galactomannan fraction may enhance insulin action in type 2 diabetes as indicated by the improvement of oral glucose tolerance in the tested subjects (Hannan et al., 2007). The mucilaginous property of fenugreek is mainly attributed to the galactomannan content of fenugreek, and it is because of this character the fenugreek mucoadhesive extract has a potential use in nasal gel formulation (Kumar et al., 2014).

4.1.2 Diosgenins

Diosgenins are steroidal sapogenins found in a considerable percentage in fenugreek seeds, from each 100 grams of fenugreek seeds, 2 grams of sapogenins can be extracted (Srinivasan, 2006). Diosgenin is a biologically active phytochemical, it has a very important medical and therapeutic applications, such as treatment of hypercholesterolemia, leukaemia, and colon cancer. It is also used in the synthesis of many steroid hormones, oral contraceptives, and other steroidal compounds because it is an excellent initial intermediate for their synthesis (Atel et al., 2012).

Pharmacological activity of diosgenin has been investigated by many researchers and authors found diosgenin has a significant effect in reducing the viral load of hepatitis C virus (HCV) (Ashfaq & Idrees, 2014). But appeared to be weak antimicrobial against *Candida albicans* (Sautour et al., 2004).

Diosgenin has multiple effects on different body systems in animal models, haematologically found to be antithrombotic because it inhibits platelets aggregation, prolong the prothrombin time (PT), the activated partial thromboplastin time (APTT), bleeding time, and the clotting time (Gong et al., 2011). Neurologically, diosgenin can elevate the intracellular calcium (Ca2+) in human cortical neurons-1A (HCN-1A), and in other experiment it showed a significant Acetylcholinesterase (AchE) inhibitory effect (Atel et al., 2012). On bone metabolism and calcium homeostasis, a studies on animal models showed diosgenin supplementation reduces osteoporosis, and enhance bone formation (Zhang et al., 2014). Diosgenin in animal model studies found to be a vasodilator and associated with increased nitric oxide (NO) levels, and it has hypocholesterolaemic effect because it found to reduce the total cholesterol (TC), low density lipoprotein (LDL), and increase the high density lipoprotein (HDL) level (Atel et al., 2012). Diosgenin has a hypoglycaemic property through its inhibitory effect on the intestinal disaccharidases (Lavle, Shukla, & Panchal, 2016).

Barathkumar et al., (2013) in their study provide clear evidence of the renal protective role of diosgenin through its antioxidant activity and hence renal vascular protection against calcification (Barathkumar et al., 2013).

4.1.3 4-hydroxyisoleucine

The amino acid 4-hydroxyisoleucine is an unusual amino acid, and represents the most abundant amino acid found in fenugreek seeds despite different percentages given by studies of determination and quantification in previous researches. In a study on Iranian fenugreek done by H & Givi E, (2010), showed that the major acidic amino acid in fenugreek seeds is 4-hydroxyisoleucine with a percentage of 0.4% (H & Givi E, 2010). The anti-hyperglycaemic property of fenugreek and the hypocholesterolemic effect are attributed in part to 4- hydroxyisoleucine (Goyal, Gupta, & Chatterjee, 2016). The antihyperglycaemic effect of 4-hydroxyisoleucine shown to be due to stimulation of beta-cells of pancreas (E. E. L. Lee, 2006).

4.1.4 Polyphenols and flavonoids

Many studies shown fenugreek seeds are good source of polyphenols and flavonoids (Kenny et al., 2013). Fenugreek seeds reported to contain 100 mg of polyphenols per 100 grams of dried seeds (Nair, Nagar, & Gupta, 1998). Recent years showed increased areas of research on phenolic compounds and flavonoids and their importance for human protection and health from nutritional point of view. Among flavonoids there is a class of isoflavonoids which exist in a precursor form in the plant, then metabolized by intestinal flora to more active form, and they have estrogenic activity due to their capability to bind oestrogen receptors, and due to this property they have the potential to be used in the treatment of cardiovascular diseases, osteoporosis, age-related diseases, and hormone-dependent cancers such as breast, prostate, and lung cancer (Sharma & Ramawat, 2013). Polyphenols are very protective against oxidative stress as demonstrated by many studies. Kaviarasan et al., (2004) in their study showed the protective effect of polyphenol-rich fenugreek seed extract on erythrocytes oxidative damage (Kaviarasan et al., 2004). Kenny.et al. (2013) in their study showed the antioxidant property of phenolic compounds extracted from fenugreek seeds and their ability of scavenging the free radicals (Kenny et al., 2013). The highest antioxidant activity of fenugreek seeds is exhibited more by aqueous fraction which contains the highest content of phenolic and flavonoid compounds (Ashish, Sancheti & Puja, 2014).

4.1.5 Alkaloids

Several pyridine alkaloids found in fenugreek, among which trigonelline is the most abundant alkaloid (Zandi et al., 2014). From each 100 grams of dried fenugreek seeds, 380 mg of trigonelline can be extracted (Srinivasan, 2006). Other alkaloids found in fenugreek include choline and carpaine, in fact one of the major causes of bitter taste and odour of fenugreek is its content of alkaloids (Ahmad et al., 2016). Trigonelline is considered to be a cardio protective against myocardial injuries due to its antioxidant property and prevent lipid peroxidation (Panda, Biswas & Kar, 2013). Trigonelline will have beneficial future applications in the treatment of many medical disorders as it found to have hypoglycaemic ,hypolipidemic, neuroprotective, antimigraine, sedative, memory-improving, antibacterial, antiviral, and anti-tumour activities, and it has been shown to reduce diabetic auditory neuropathy and platelet aggregation (Zhou, Chan & Zhou, 2012).

5. Safety and toxicity

Although fenugreek is stated as "Generally recognized as safe" (GRAS) status by the U.S. Food and Drug Administration (FDA)-SP/ESO, GRAS - 182.10, 182.20 (U.S. Food and Drug Administration, 2006), and it has been used as medicinal plant since thousands of years, new studies on animal models in the recent years showed that fenugreek has a toxicity on acute large doses and on chronic low doses.

5.1 Findings of previous fenugreek toxicity studies

In one study conducted on fenugreek leaves aqueous extract, the LD_{50} of oral dose found 10 g/kg, with mild central nervous system excitation, but administration of 12 and 15 g/kg was significantly associated with rapid respiration, excitation, tremor, and twitches, administration of doses more

than 15 g/kg causes convulsion and death of majority of animals, same study showed no liver damage at oral dose of 8 g/kg (Abdel-Barry et al., 1997). Kandhare et al. (2015) in their mice animal model study used glycoside based fenugreek seeds extract, reported a mortality rate of 40% at acute dose of 5g/kg body weight, with neural excitation, and liver toxicity with raised enzymes and hepatic histopathological changes on chronic toxicity (Kandhare et al., 2015). Al-Ashban et al., (2010) in their study show low blood glucose at a maximum tested dose which was 3g/kg body weight (Al-Ashban et al., 2010).

On the other hand, acute administration of debitterized fenugreek powder to albino mice at a dose of 2 g/kg body weight showed no alteration in liver function test and no histopathological changes (Muralidhara et al., 1999). Acute administration of fenugreek seeds aqueous extract to male mice at doses of 3, 6, and 9g/kg body weight, in our previous study showed mild hepatic portal inflammation, and mild mononuclear cell infiltration in liver parenchyma (Hamad, Allow, Hamdan, & Mohamed, 2017). Daily oral administration of fenugreek aqueous extract to mice at doses of 153mg/kg, 305mg/kg, and 610mg/kg for 90 days showed reproductive toxicity in the form of teratogenic, foetotoxic, reproductive changes and abnormal sperm shapes (Al-Yahya, 2013). In other study, female mice received fenugreek seeds aqueous extract at doses of 0.5g/kg and 1g/kg once daily during gestational period, no death or physical signs of toxicity recorded, but developmental abnormalities in the offspring reported in the form of increased foetal death rate, and decreased in the foetal body weight, with increased incidence of morphological abnormalities (Khalki et al., 2010).

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