

***Trigonella foenum-graecum* L.: A short review on folk medicine pharmacological effects, phytochemistry, and toxicology**

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Abstract:

Trigonella foenum-graecum L., commonly known as fenugreek, is largely used in folk medicine to its diverse pharmacological properties. This short review provides an overview of the medicinal uses, pharmacological properties, phytochemistry, and toxicological aspects of *Trigonella foenum-graecum* L. Throughout history, this plant have been employed for centuries to treat ailments. Nowadays, scientific investigations conducted in the field have indicated tha pharmacological properties including anti-inflammatory, antioxidant, hypoglycemic, and hypocholesterolemic properties, among others. Moreover, the plant was found to be of high richness with different bioactive compounds such as saponins, flavonoids, alkaloids, and fenugreek galactomannan. Despite its numerous pharmacological properties, this plant still demonstrates various side effects that need to be taken seriously to avoid potential risks or adverse reactions. This review summarizes the current state of knowledge on *Trigonella foenum-graecum* L., shedding light on its multiple applications, chemical constituents, and potential challenges in terms of toxicity. Further research are recommened to elucidate the mechanisms behind its pharmacological effects and to establish comprehensive safety profiles for its diverse applications in traditional and modern medicine.

Keywords: *Trigonella foenum-graecum* L.; Pharmacology; Phytochemistry; Folk medicine; Toxicology.

1. Introduction

Trigonella foenum-graecum also named fenugreek originated from the Mediterranean region and its surrounding territories (Al-Maamari et al., 2014). This plant belongs to the fabaceae family, papilionaceae subfamily, and *Trigonella* genus (Nathiya et al., 2014; Mehrafarin et al., 2011). *Trigonella foenum graecum* L. is called in French Fenugrec, while in Morocco this plant has several vernacular names including L-ḥalba (الْحَلْب), ḥalba (حَلْب), l-ḥolba (الْحَلْب), tīfīdās (تَفِيدَاس), r-ḥarḥorbat (رَحْرَحْرَبَت), and tafidast (تَفِيدَسْت) (Fakchich & Elachouri 2021). This annual herb is characterized by a height ranging from 20 to 130 cm, straight growth pattern, occasional ascension, and limited branching and it exhibits taproot development followed by an abundance of secondary roots that form root nodules. Its leaves are petiolate, alternate, trifoliate, and stipulate, while the stem stands erect, green, branched, smooth, and herbaceous. The inflorescence is racemose, and the flowers are bracteates, pedicellate, zygomorphic, bisexual, hypogynous, gamosepalous, valvate, polypetalous, papilionaceous with two wings. Additionally, it possesses 10 diadelphous stamens, with nine united to form a tube around the ovary, and one remaining free. The gynoecium is monocarpellary, with a superior ovary and a unilocular structure (Malhotra, 2011).

Back in time this plant was cultivated across the globe and was used by different civilization starting from ancient Egypt, Ethiopia, turkey and India (Bahmani et al., 2016; Malhotra, 2011; Mehrafarin et al., 2011). The plant's seeds, renowned for their numerous health benefits, are a staple in various cultures. Fenugreek is not only utilized as a spice in the India, North Africa, Mediterranean regions, and Yemen but is also recommended in Morocco as an appetite stimulant and for enhancing physical attractiveness. Furthermore, it finds application against stomach disorders, constipation, fever, anemia, and in the treatment of diabetes (Bellakhder, 1997).

The framework of the current review, is to critically summarize the phytochemistry, pharmacological properties, and safety of fenugreek and its derivatives. This comprehensive exploration aims to shed light on the diverse facets of fenugreek's properties and potential applications, contributing to a deeper understanding of its role in both traditional and modern medicine.

Origin and distribution:

Fenugreek native to eastern coasts of the Mediterranean and North Africa. The plant's name derives from Greek "trigonou" signifying triangle, owing to the triangular form of its leaflets. The term "foenum-graecum" translates to "Greek hay" or Greek grass, reflecting its widespread utilization in ancient Greece (Bahmani et al., 2016). According to experts, fenugreek was primarily indigenous to some regions of Iran to the north of India, before being introduced to other regions (Sun et al., 2021). It is now extensively cultivated in various countries, including India, China, Africa, Algeria,

Argentina, Saudi Arabia, Pakistan, Egypt, Turkey, Middle east, Ukraine, Spain, France, North Africa, and Italy (Ahmad et al., 2016; Bahmani et al., 2016). Notably, fenugreek is often exported from India, China, Turkey, and Morocco (Bahmani et al., 2016).

Synonyms:

According to World Flora Online, *Trigonella foenum-graecum* has many synonyms, including *Buceras foenum-graecum* (L.) All., *Buceras odoratissima* Medik., *Fenugraecum officinale* Czechov, *Foenum-graecum officinale*, Moench *Foenum-graecum officinale* var. *cultum* Alef., *Foenum-graecum officinale* var. *gladiatum* Alef., *Foenum-graecum officinale* var. *prostratum* Alef., *Foenum-graecum officinale* var. *rhodanthum* Alef., *Foenum-graecum officinale* var. *tibetanum* Alef., *Foenum-graecum sativum* Medik., *Folliculigera graveolens* Pasq., *Medicago foenugraeca* (L.) E.H.L.Krause, *Telis foenumgraecum* (L.), Kuntze *Trigonella ensifera* Trautv., *Trigonella foenum-graecum* subsp. *culta* Gams, *Trigonella foenum-graecum* subsp. *indica* Sinskaya ex Soskov & Bairamov, *Trigonella foenum-graecum* subsp. *jemenensis* Serp., *Trigonella foenum-graecum* var. *haussknechtii* Širj., *Trigonella graeca* St.-Lag., *Trigonella haussknechtii* (Širj.) Vassilcz., *Trigonella jemenensis* (Serp.) Sinskaya, *Trigonella rhodantha* (Alef.) Vassilcz., *Trigonella tibetana* (Alef.) Vassilcz., *Xiphostylis erectus* Gasp (WFO (2023)

Fenugreek traditional uses

Fenugreek boasts have rich history of traditional uses across different cultures. In Iran, the seeds are applied as a cataplasm to address local inflammation, serving as a local emollient and demulcent to alleviate joint pain. While, the leaves are employed to ease cold-related coughs, backaches, hepatitis, splenomegaly, and bladder-cooling reflex. Additionally, there are reports of fenugreek being used to manage diabetes and combat mouth odor. A blend of fenugreek infusion with honey is recommended for addressing internal oedema and asthma (Basch et al., 2003; Salman & Qadeer, 2021). In Egypt, the plant is utilized as a facilitating childbirth agent, lactagogue, and emmenagogue (Morcos et al., 1981). In China, fenugreek has historical use in treating gout and asthenia. In India, it serves as a spice, tonic, and a stimulant for breast milk flow (Bahmani et al., 2016). However, in Morocco, *Trigonella foenum-graecum* L. seeds are recommended as an appetite stimulant and for enhancing physical performance. Furthermore, it is utilized to manage diabetes, accelerate bone fracture healing, ease childbirth, address stomach disorders, combat constipation, alleviate fever and anemia, and fortify hair. Moreover, fenugreek is regarded as an aphrodisiac, anti-inflammatory, and galactogenic agent (Bellakhder, 1997; Daoudi et al., 2023).

Pharmacological effects

Fenugreek is endowed with numerous pharmacological effects such as antidiabetic effect (Mowla et al., 2009). The solution derived from fenugreek seed powder has exhibited marked effects

in improving lipid metabolism in patients with type 2 diabetes. This is manifested by a significant elevation in fecal bile acid and cholesterol excretion, which may contribute to its antidiabetic effect (Geberemeskel et al., 2019). Moreover, in a Streptozocin-induced diabetic model, the oral and intraperitoneal administration of the seed extract at 100 mg/kg, demonstrated significant enhancements in blood glucose levels, and improvements in renal and hepatic functions (Baset et al., 2020). According to Anwar et al. (2011), fenugreek seeds contain key constituents, including galactomannan, known for their hypoglycemic properties. Fenugreek galactomannan exhibits promising antidiabetic effects and has been recognized as a potential agent for reducing blood glucose levels. Recent observations highlight galactomannans as highly effective dietary fibers in patients with type 2 diabetes. These fibers contribute to the reduction of hemoglobin glycation (HbA1c) levels, fasting blood glucose, triglycerides, and LDL cholesterol (Juhász et al., 2023). Furthermore, *Trigonella foenum-graecum* L. leaves extract has been found to have inhibitory effects on both diabetes key enzymes α -amylase and α -glucosidase enzymes (Ganeshpurkar et al., 2013). Then it has ability to reduce the carbohydrate digestion and then the intestinal glucose absorption. Following (El-Abhar & Schaalan, 2014; Neelakantan et al., 2014), fenugreek has been shown to improve insulin sensitivity and increase insulin secretion from the pancreas.

A study conducted by Murugesan, Revathi, et Manju (2011) demonstrated that fenugreek has cardioprotective effect by playing an inhibiting role of lipid peroxidative damage. This effect is essentially due to its ability to remove free radicals. Indeed, the beneficial effects are generally due to its potent antioxidant activity. It was noted that fenugreek seeds have shown antiradical scavenging activities based on two basic techniques (DDPH \bullet) and (ABTS \cdot^-) (Kaviarasan et al., 2007). In addition, Sharma et al. (2015) confirmed the necessity of seed powder of fenugreek to restore the impaired activity of cellular antioxidant enzymes, including superoxide dismutase, glutathione reductase, catalase, and glutathione peroxidase, in tissues such as muscles, including heart and brain during diabetes. Likewise, it may help in improving lipid profiles in diabetic patients (Geberemeskel et al., 2019). Other studies indicated the antihyperlipidemic and hypocholesterolaemia effects of fenugreek (Sowmya & Rajyalakshmi, 1999; Vijayakumar et al., 2010; Zameer et al., 2018). A conducted study on rats showed that fenugreek seeds extract had nephroprotective effect against sodium nitrite-induced kidney damages by reducing pro-inflammatory cytokine levels, and hepatoprotective effect against ethanol-induced cell death in human liver cells (Farshori, 2022; Uslu et al., 2019). Meanwhile, other studies have highlighted the anti-inflammatory and the immunomodulatory effect of *Trigonella foenum-graecum*. It was found that seed extract displayed protective effects against inflammation and oxidative stress and the total aqueous extract may exert immunomodulatory effects in mice (Abedinzade et al., 2015; Bin-Hafeez et al., 2003).

Fenugreek possess also anticancer effect by inducing apoptosis in cancer cells with no harm on normal cells (Alsemari et al., 2014), gastroprotective (Pandian et al., 2002), laxative, chemopreventive, anti-atherogenic, appetite stimulation (Nathiya et al., 2014), galactagogue, and anorexia activities (Yadav & Baquer 2014), and anti-cataract effect (Vats et al., 2004). Hadi et Mariod (2022), have reported that fenugreek oil has both antibacterial and antifungal properties. However, methanolic and aqueous extracts leaves have been found to have a potent antibacterial effect and the ethanolic extract showed potent effects against gram-negative bacteria and *Sacromysis fungi* (Al-Hussainy, 2015; Dharajiya et al., 2016). Additionally, the seeds extract has been found to possess antibacterial activity against six pathological bacteria strains, including *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, and *Vibrio parahaemolyticus*.

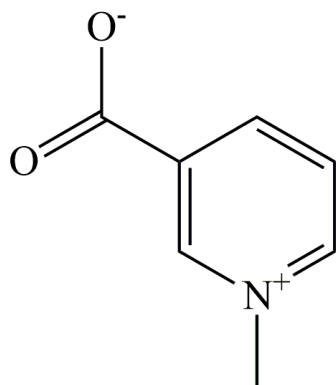
Alternative applications

Fenugreek serves various purposes beyond its traditional uses. It is incorporated with vitamins and essential nutrients to create tablets or capsules (Wani & Kumar 2018). Additionally, fenugreek oil finds application in cosmetics for strengthening and enhancing the beauty of hair, as well as addressing issues like black spots, mouth diseases, and unpleasant body odor (Bahmani et al., 2016). Moreover, fenugreek is uses as a spice, enhancing the sensory appeal of various foods (Srinivasan, 2006). Its rich content of natural dietary fibers has led to its inclusion in the preparation of diverse food products. Fenugreek is utilized to fortify bakery flour used in items such as pizza, bread, noodles, tortillas, baked corn chips, fried goods, cake mixes, and muffins. Furthermore, it plays a role in the preparation of soups, milkshakes, candies, and sweets sweets (Wani & Kumar 2018).

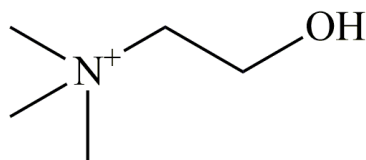
Phytochemistry

The remarkable array of beneficial effects exhibited by fenugreek can be attributed to its rich phytochemical composition. numerous active ingredients contribute to these effects, including alkaloids such as trigonelline, choline, carpaine and gentianine (Visuvanathan et al., 2022). Saponins, such as Fenugrin, foenugracin, glycoside, yamogenin, trigonoesides, smilagenin, gitogenin, sarsasapogenin, yuccagenin, hederagin, diosgenin, tigonenin, and neotigogenin, play a significant role (Gupta, Gupta, et al 2001). Furthermore, fenugreek contains flavonoids like naringenin, lilyn, kaempferol, vecenin-1, tricin 7-O-D glucopyranoside, saponaretin, isoorientin, orientin, vitexin, luteolin, and quercetin (Ahmad et al., 2016). It also contains a major class of phenolics like gallic acid, protocatechuic acid, catechin, gentisic acid, chlorogenic acid, vanillic acid, and syringic acid (Rababah et al., 2011). Coumarin compounds such as methyl coumarin, trigocoumarin, and trimethyl coumarin contribute to its phytochemical profile (Raju et al., 2004). Additionally, essential vitamins

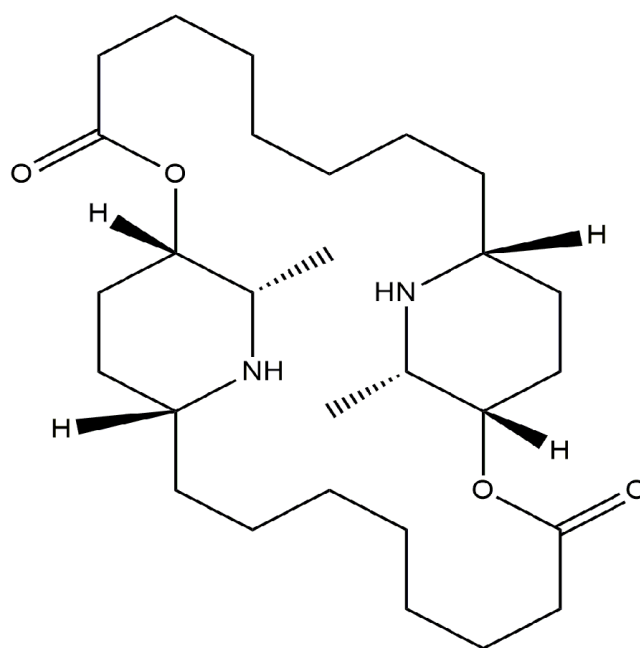
including Vitamin A, folic acid, ascorbic acid, thiamin, riboflavin, biotin, and nicotinic acid also enrich the phytochemistry of fenugreek (Ahmad et al., 2016; hamden et al., 2010).



Trigonelline. PubChem CID 5570



Choline. PubChem CID 305



Carpaine. PubChem CID 442630

Figure 1. Major alkaloids of *Trigonella foenum-graecum* (drawn with ChemDraw software 18.1)

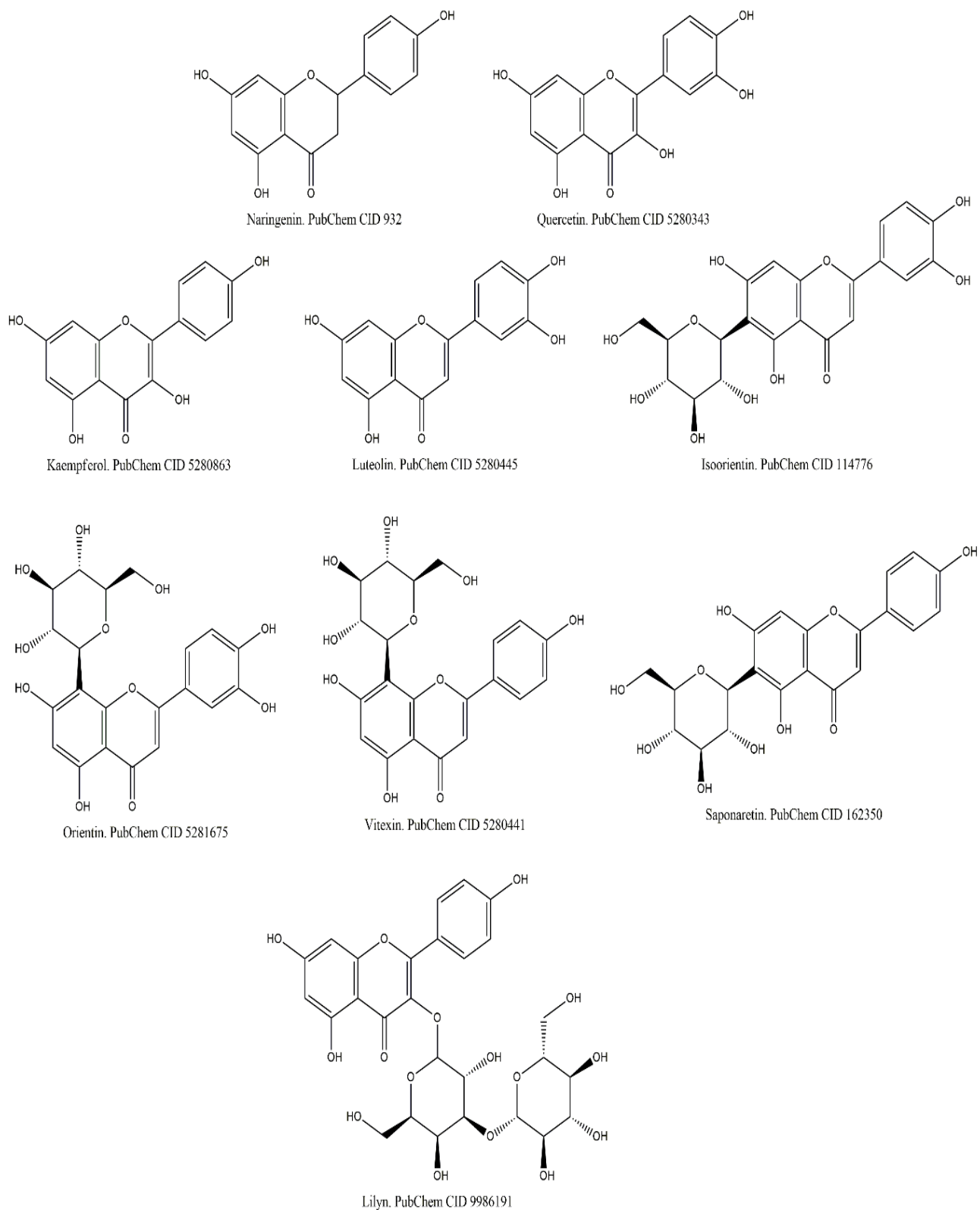
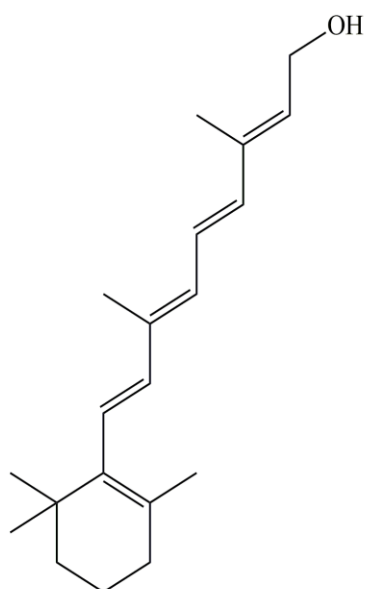
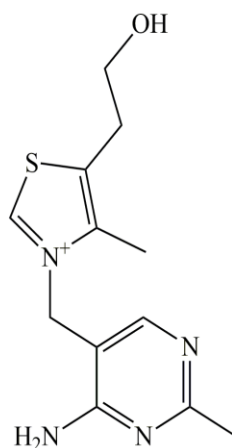


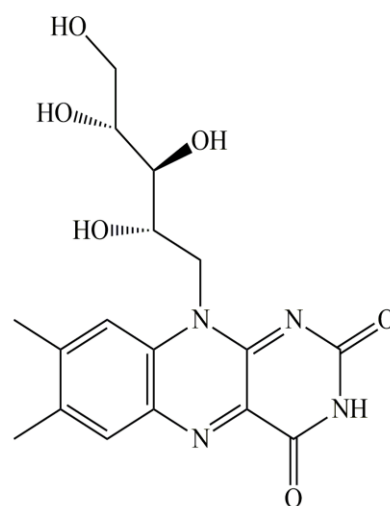
Figure 2. Major flavonoids of *Trigonella foenum-graecum* (drawn with ChemDraw software 18.1)



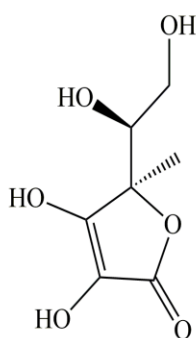
Vitamin A. PubChem CID 445354



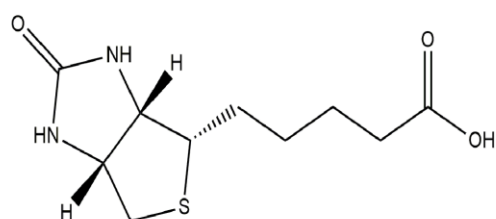
Thiamin. PubChem CID 1130



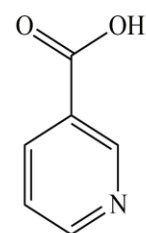
Riboflavin. PubChem CID 493570



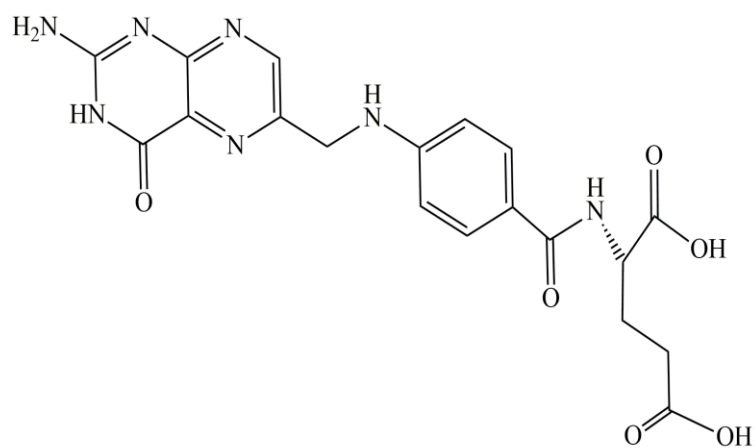
Ascorbic acid. PubChem CID 54670067



Biotin. PubChem CID 171548



Nicotinic acid. PubChem CID 938



Folic acid. Pubchem CID135398658

Figure 3. Other chemical compounds of *Trigonella foenum-graecum* (drawn with ChemDraw softwear18.1)

Safety of usage:

Multiple investigations have explored the toxicological impact of *Trigonella foenum-graecum* L. findings revealed that the oral administration of trigonelline, a principal compound in fenugreek, resulted in an LD₅₀ value of 5 g/Kg body weight (Ouzir et al., 2016). Notably, the administration of de-bittered fenugreek powder to rats and mice at doses of up to 2 g/Kg and 5 g/Kg, respectively, did not elicit toxicological symptoms or mortality (Muralidhara et al., 1999). Additionally, the safety of the plant was affirmed through oral administration of water-soluble fenugreek seeds extract enriched with furostanolic saponins in female rats (LD₅₀ of 5 g/Kg) and aqueous fenugreek leaf extract in mice (LD₅₀ of 10 g/Kg) (Ouzir et al., 2016; Swaroop et al., 2014). Intraperitoneal injection of aqueous and ethanolic fenugreek extracts in rats demonstrated LD₅₀ values of 4.1 and 5 g/Kg (Ouzir et al., 2016; M. L. Sharma et al., 1978). Clinical toxicity trials, assessing the safety of fenugreek consumption, underscored its efficacy in diabetic patients. However, adverse effects were noted, including diarrhea, abdominal pain, dizziness, flatulence, dyspepsia, the risk of hypoglycemia, and potential allergic reactions (Ouzir et al., 2016).

Conclusion:

Despite the various pharmacological properties this plant has, a cautious approach is demanded in order to avoid in adverse effect that could be caused by its misuse. Hence, further investigations required in order to refine dosage recommendations and implementation of new guidelines for judicious use of this potent botanical resource. However, despite acknowledging *Trigonella foenum-graecum*'s pharmacological effectiveness, it is often necessary to carefully weigh the dangers and advantages when integrating it into healthcare procedures.

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