International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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The bioactive constituents and biological properties of *Trigonella Foenum-Graecum* (Fenugreek): A comprehensive review

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International Journal of Science and Research Archive, 2024, 13(01), 2140–2149

Publication history: Received on 31 July 2024; revised on 04 October 2024; accepted on 07 October 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.13.1.1679

Abstract

Fenugreek; the extremely nutritional plant of the *Fabaceae* family ranks amongst the oldest therapeutic plants used in traditional medicine. The plant has a broad –spectrum of pharmacological and biological activities which are traceable to its bioactive compounds and protective nutrients contained such as; flavonoids, diosgenin, saponins, galactomannans, trigonellin, essential oils, coumarins, 4-hydroxyisoleucine and scopoletin. These bioactive compounds elicit nutraceutical, immunomodultory, antioxidant, anti-atherogenic, anti-oxidative, anti-hyperlipidemic, hypoglycaemic, anticarcinogenic, antinociceptive, anti-inflammatory and anti-hypertensive effects via various mechanisms against common chronic diseases. Moreover, the plant also has protective effects on the digestive, cardiovascular, endocrine, and reproductive systems. This article considers the role of fenugreek contained bioactives on human milk production and lactation. The other biological activities are also discussed.

Keywords: Fenugreek; Galactagogue; Glycine; Plant; *Trigonella foenum-graecum*

1. Introduction

Trigonella foenum-graecum commonly known as fenugreek is a leguminous herb cultivated as a spice in many countries of Africa, Europe and Asia. Fenugreek been an herb, grows only to about 1-2 ft heights and produces yellowish seeds in sickle-shaped pods. The herb though a spice has been utilized through several centuries for medicinal purposes across the Chinese, Arabic (Unani) and Indian (Ayurvedic) traditional medicines to treat cough, common cold, sore throats, bronchitis, cramps, arthritis [1]. Furthermore, fenugreek seeds are a commercial resource of diosgenin; a compound used for the manufacture of steroids like drugs such as oral contraceptives, sexual hormones and corticosteroids. A mass spectrometry analysis conducted by Khalil et al (2015) listed fourteen bioactives be present in fenugreek including choline, quercetin, luteolin, trigonellin, steroidal spaonins, pyridine, lipids, coumarins, 4-hydroxyisoleucine and galactomannans. The pharmacological effects of the plant however are particularly linked to diosgenin, galactomannan, trigonelline, 4-hydroxyisoleucine, scopoletin and quercetin [2]. Moreover, the trigonelline alkaloid which is responsible for the flavour of the seeds gives off the flavour when degraded to pyridines and nicotinic acid upon roasting. Aside the biological compounds, fenugreek seed also contains nutrient macromolecules like proteins (25%) carbohydrates (51%), and lipids (8%) [3]. Amongst other multiple biological actions, fenugreek is a galactagogue and induces the production of breast milk. Its use for this purpose can be traced to centuries back. Galactagogues are frequently used by breastfeeding mothers in situations of insufficient breast milk and fenugreek is highly recommended in such cases of deficient or late lactogenesis to trigger the release of milk from the mammary glands and thus promote the production of milk in non-puerperal women. Furthermore, fenugreek was theorized to stimulate perspiration, which further stimulated milk production through increase of fluid flow to the tissues of the breast. Considering the extensive capacities of fenugreek, this review intends to give an overview of the biological constituents and activities of fenugreek placing emphasis on its ability to enhance the production of milk in breastfeeding mothers [4].

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2. Nutritional Constituents in Fenugreek

2.1. Fatty Acid and Lipid Profile of Fenugreek

The lipid profile of fenugreek seeds varies from 4.5 to 15g/100g of seeds and represent an exciting source of nutraceutical and functional ingredients being abundant in naturally occurring tocopherols, phytosterols and unsaturated fatty acids. Neutral lipids which make up 84% of the fenugreek seed lipid fraction consist of 6% diacylglycerols, 86% triacylglycerols and fewer quantities of phytosterols, monoacylglycerols and free fatty acids. Glycolipids and phospholipids constitute 5.5% and 10.5% of the crude lipids respectively [1]. A categorization of the fatty acid outline of nine fenugreek genotypes revealed that the lipids of fenugreek origin consisted mainly of di-unsaturated and tri-unsaturated triacylglycerols. Polyunsaturated fatty acids were the highest proportion of lipids (about 66%-71%) present, followed by monounsaturated and saturated fatty acids. Cycloartenol, campersterol and β-Sistosterol also account for 56-72% of the total sterol content and are among the key phytosterols lipids in fenugreek lipids [5].

2.2. Carbohydrates and Dietary Fibres

The carbohydrate content of fenugreek seeds is composed of a low amount of starch and total sugars and a high proportion of dietary fibre. Soluble and insoluble fibres which have appetite regulating effects are also present in amounts ranging from 0.6 -2.0 [11]. In addition, the soluble fibre contained in the seeds slow down the absorption of glucose in the bloodstream and decreases blood low density cholesterol levels [5]. It is important to note however that the fibre content of fenugreek seeds varies based on the processing it undergoes, while the raw seed contain 25% of fibre, the roasted seeds contain 23% and germinating seeds 21% [7]. The carbohydrate content of germinating fenugreek seeds also decreases from the 40%-30% but the protein content increases to about 30% [8].

2.3. Bioactive Peptides, Amino Acids and Proteins

Aspartic acid, glutamic acid and arginine are the principal ones in fenugreek seeds. Essential amino acids like lysine, leucine, threonine, isoleucine, valine, histidine and phenylalanine are also present in considerable amounts. Tryptophane and sulphur containing amino acids are however present only in small amounts. The amino acid 4-hydroxyisoleucine is proteogenic and accounts for about 80% of the free amino acids contained in fenugreek seeds. This amino acid has been lately recognized as a major bioactive component that mediates some physiological actions of fenugreek chiefly its antidiabetic and insulinotropic effects in humans [5]. The 4-hydroxyisoleucine amino acid is also thought to be the precursor of sotolone, the main volatile compound accountable for the distinctive seasoning-like essence of fenugreek [9]. *(S)*- canavanine is another proteogenic amino acid also present in fenugreek seeds which acts to inhibit nitric oxide synthase in mammalian cells [10]. Additionally, fenugreek seeds contain 13-39% of proteins with the endosperm containing 5.5 times more protein than the husk [6]. This is comparable to the high protein content of other legumes such as field pea, mung bean and cowpea. Although in vivo investigations of the quality of fenugreek protein in clinical applications are scanty; Allaoui et al. (2019) reported that protein hydrolysates of fenugreek reduced the growth of undifferentiated human colon adenocarcinoma cells, showing its probable usefulness as a nutraceutical in the treatment of colorectal cancer [11]. In addition to their nutraceutical and nutritional values, fenugreek proteins have outstanding technological characteristics, including high forming, stability, film-forming capacity, and solubility in comparison to the proteins of other legumes which are presently used in functional and regular foods [5].

2.4. Vitamins and Minerals

The outer layers of fenugreek seeds which are known to be fibre rich also contain the B- vitamins namely pyridoxine, niacin, thiamine, folate and riboflavin. This says that when seed coats are removed, the concentration of these vitamins gets reduced. Moreover, the seeds of fenugreek also contain vitamins A, E and C although in relatively low amounts. Vitamin E, the main lipid antioxidant present in fenugreek makes up about 84% of the total tocopherol in the lipid fraction [12]. Furthermore, the vitamins β-carotene and vitamin C are more copious in fresh fenugreek leaves than in the seeds but are easily lost upon cooking, blanching prolonged soaking and drying [13]. Considering its mineral content, it is worthy of note that the mineral profile of fenugreek seeds consists of significant amounts of phosphorus, potassium, calcium and magnesium alongside some important dietary trace minerals namely zinc, copper, zinc, iron, selenium and manganese. Roasting, soaking and germinating fenugreek seeds increases the content of phosphorus while the same processing procedures do not affect iron, zinc and calcium [7].

3. Bioactive Properties of Fenugreek

In all, four phytochemicals are responsible for the therapeutic effects of fenugreek; steroidal saponins, phenolic compounds, essential oil components and alkaloids. Numerous classes of phenolic compounds, mostly phenolic acids, flavonoids, stilbenoids, tyrosol and coumarins have been extracted from fenugreek seeds, stems, flowers and leaves where they are found bound to cell walls in both soluble and insoluble forms [14]. The total phenolic content of fenugreek seeds according to some reports are similar to those reported of other seeds of the same family of leguminous crops. The flavonoid content as reported from hyper pressure liquid chromatographic analysis also suggests that there are similarities of with other seeds [15]. There are also reports that soaking, roasting or germinating fenugreek seeds increases their phenolic content and consequent antioxidant activity [7]. Oleuropein, vanillic acid and pyrogallol were some major non-flavonoids among several flavonoid, non-flavonoid and phenolic compounds quantified from fenugreek leaves and seeds by Salem et al. (2023), apigenin-6-O-arabinose-8-O-galactose, hesperidin, catechin and quercitrin were the most copious flavonoids in the seeds according to the analysis while less abundant ones were naringin, quercetin, luteolin, rutin, vitexin, naringenin, vicenin-1, vicenin-2, tricin and isovitexin. Isoflavonoids such as genistein, diadzein and isoformononetin were also present [15]. It should be noted that most fenugreek contained flavonoids occur as flavonoid glycosides because of their conjugation with carbohydrates.

The fenugreek-contained class of saponins are thought to be the most abundant phytochemicals in the plant and range from 4-8% [16]. A total of 15 sapogenins and 50 saponins have been reported from fenugreek with dioscin and diosgenin been the most studied of these [17,18]. Moreover, diosgenin, yamogenin, yuccagenin and proto-diosgenin are sapogenin agylcones also present in fenugreek. Furthermore, Furostane saponins including trigoneosides, trigofoenosides A-G and protodioscin are also contained in the plant. These saponins occur as amphiphilic steroid glycosides in contrast to those in other crops of the same *Fabaceae* family. The compound diosgenin is presently the starting compound commercially used in the production of steroid drugs like progesterone and cortisone [19]. Growing research however indicates that the biological potentials of saponins and sapogenins could be more than currently known. Immunostimulant, hypoglycaemic, anti-inflammatory, proapoptotic, appetite regulation and cancer are some of these presumed biological activities [20]. The compound diosgenin is also attracting interest for its suggested efficiency against cardiovascular disease, diabetes, neurological disease, asthma, bone loss, arthritis etc. Saponins are however limited by their imperfect bioavailability [21].

Rich amounts of the alkaloid trigonelline are contained in fenugreek seeds alongside ecgonine, carpaine, glycine betaine, gentianine and kynurenic acid [22]. Trigonelline has protective functions against neurodegenerative disorders and type 2 diabetes. The compound is also a prime candidate for use against kidney and liver dysfunctions, hyperglycemia, migraine, viral and bacterial infections and tumor growth. Although the mechanisms by which alkaloids carry out their actions are unknown, it is known that the synergic actions of numerous alkaloid and non-alkaloid compounds may widen their spectrum of activities. For example, kynurenic acid was found in animal experiments to lower cholesterol, enhance glucose tolerance and elicit anti-atherosclerotic and antiobesity effects whereas glycine betaine acts against inflammation, neurodegenerative diseases and carcinogenesis [22]. Speaking from the sensory standpoint, alkaloids are responsible for the pungent and slightly bitter taste of fenugreek which can be removed by roasting, boiling and germination [23].

The reports of several investigations have named more than 50 volatile and aroma compounds including components of essential oil to be present in fenugreek seeds. Terpenoids, terpenes, apocarotenes, phenlpropanoids, non-terpenes derivatives and sulphur derivatives are among these aroma compounds. Aromatic notes of spicy, seasoning-like, roasty, pungent and buttery are often associated with these fenugreeks contained volatile compounds. Eugenol, acetic acid, butanoic acid, linalool, methoxypyrazines etc are other aroma compounds also present in fenugreek. Roasting, boiling and sprouting were seen to increase the amounts of the volatiles; aldehydes, alkanes, esters and alcohols in fenugreek [23]. Essential oils components of fenugreek are camphor, neryl acetate2,5-dimethylpyrazine, α-selinene, β-pinene, geranial and β- caryophyllene. These are known to be antiviral, antioxidant and analgesic in their activities [24]. Fig 1 gives the structures of some compounds contained in fenugreek.

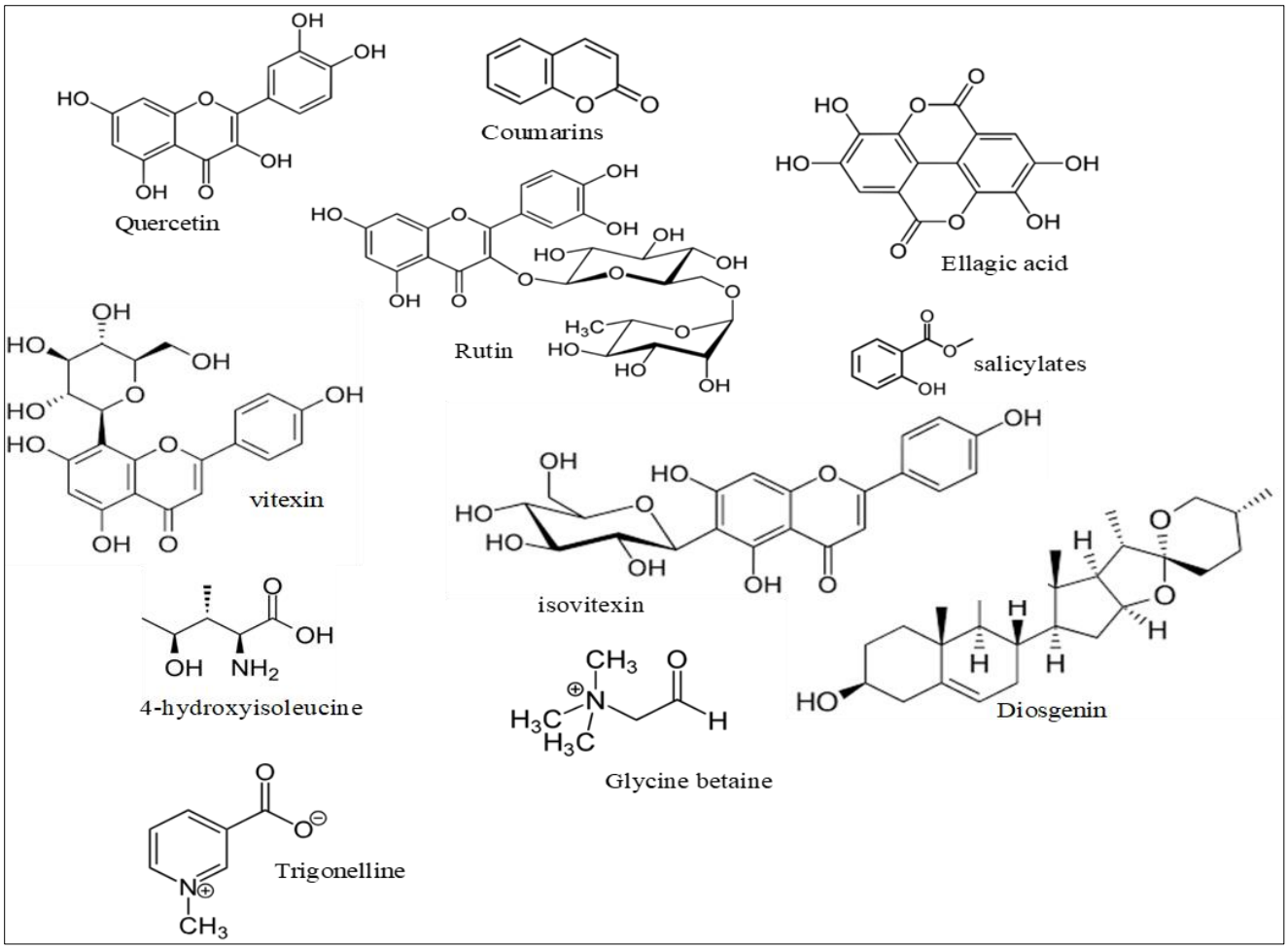

Figure 1 The structures of bioactive compounds contained in fenugreek

4. Biological Activities of Fenugreek

Several health promoting and disease barring biological activities have been observed with the use of fenugreek and its by-products. Clinical and preclinical data reported on the use of and effects of fenugreek are discussed below

4.1. Anti-Nociceptive Activity

The pain relieving or antinociceptive properties of the extracts of fenugreek leaves, seed and stem have been reported by several investigations. The plant exhibited similar antipyretic and antinociceptive effects to non-steroidal anti-inflammatory drugs in animal models according to an investigation by [25]. These antinociceptive properties of the plant are thought to be linkable to its alkaloid content. Another experiment that involved the use of the ethanolic extracts of fenugreek seeds against acetic acid-induced pain in rats. The relief of pain was by endogenous opioids. The methanolic extracts of the leaves also when investigated were seen to exhibit greater pain suppressing effects on the rats than paracetamol [26]. Additionally, a 10% fenugreek seed extracts–contained transdermal patch used in a double-blind placebo clinical trial was seen to reduce the demand for morphine following a reduction in the pain of postherniotomy patients [27]. These confirm the pain-relieving properties of fenugreek.

4.2. Antioxidant Activity

Oxidants and other free radicals all come either from endogenous or exogenous sources. These compounds affect the integrity of vital biological molecules like proteins, lipids and nucleic acids thus interfering with the normal redox status and causing several disease conditions like diabetes mellitus, cancers, cardiovascular diseases, liver damage and aging [28]. Antioxidants work either to prevent the excessive production of oxidants or to accelerate their removal from the cells mitigating damage to vital cell components. Fenugreek seeds have high antioxidant capacity as reported by an experiment that used the aqueous extracts of fenugreek. Antioxidant enzymes were activated and hepatic lipid peroxidation was lowered in the rats which received the fenugreek extracts [29]. Moreover, a functional assay showed

that a fenugreek seeds diet could significantly restore high fat and high sugar caused-arterial non-response to acetylcholine; a typical vasodilatory signal molecule [30]. The antioxidant properties of fenugreek have also been seen to protect erythrocytes against oxidative damage [31].

4.3. Antihypertensive Properties

Statistics say that hypertension a condition caused by high blood pressure is among the most prevalent but preventable global causes of death. The condition is usually controlled by drugs like beta blockers, diuretics, angiotensin converting enzymes, aldosterone antagonists and calcium channel blockers which medications are not without some adverse effects [32]. A preclinical investigation that investigated the antihypertensive properties of fenugreek on rats showed that the named seeds exhibit antihypertensive properties via the serotonergic receptors. The essential oil rich content of fenugreek seeds mimics the actions of angiotensin converting enzyme antihypertensive medications. When investigated on diabetic animals, onions and fenugreek seeds were seen to act synergistically in reducing angiotensin converting enzyme levels [33]. Mimicking the actions of thiazide diuretics, aqueous extracts of fenugreek seeds were also in another experiment seen to increase the excretion of potassium and sodium ions [34], thus the varied antihypertensive mechanisms of actions of fenugreek.

4.4. Anti-Carcinogenic Activity

Inducing the apoptosis of cancerous cells and or reducing their proliferation are critical points in cancer therapy. Morphological changes like DNA fragmentation characterize apoptosis which occurs via intrinsic and extrinsic pathways resulting in the activation of caspase-3. A steroidal derivative of fenugreek seeds has potent anticancer properties that cause apoptosis by the activation of caspase signalling pathway [35]. Additionally, the fenugreek contained trigonelline alkaloid also exhibits anticancer properties as it blocks the activity of Nrf2-dependent proteasome thus promoting programmed cell death in cancerous cell [36]. A fenugreek seed extract containing zingerone, eugenol, gingerol, vanillin and cedrene acted to trigger cellular death in human T lymphoma cells through autophagy showing a possible anticancer mechanism of fenugreek [36].

4.5. Effects on Reproductive System

Painful uterine contraction during menstruation also called dysmenorrhea is often experienced by many women. The decrease of oestrogen production at menopause also gives rise to reduction in bone density, cardiovascular diseases and cognitive instability. The phytoestrogen contents of fenugreek seeds show estrogenic actions following their binding to oestrogen receptors. The symptoms of polycystic ovarian syndrome were seen to be ameliorated; decreased size and number of ovarian cysts present and considerable increase in follicle stimulating hormone and luteinizing hormone [37]. In addition, vulval itching and vaginal discharge were reported to be significantly decreased in patients after a perineal wash with the decoction of fenugreek seeds. In male's libido support and a general balancing of hormones are named as potentials of fenugreek seeds. Extracts of fenugreek seeds also improves the total level of serum testosterone and sexual functions in elderly men [38].

4.6. Anti-Diabetic Effects

Alterations in the levels and functions of several hormones such as insulin are implicated in the pathogenesis of type 2 diabetes mellitus. This is so because insulin maintains the glucose homeostasis in the body. Thus, the insensitivity of cellular receptors to insulin brings about altered balance of glucose between cells and plasma [39]. The 4-hydroxyisoleucine content of fenugreek stimulates the secretion of insulin as well as enhances the uptake of glucose by translocating GLUT4 to the plasma membrane. Furthermore, the stilbenes, rhaponticin and polyphenol compounds in fenugreek also increase the sensitivity of cells to insulin. Diosgenin also exhibits anti hyperglycaemic effects. Zhang et al. (2020) isolated some 33 sapogenins and saponins from fenugreek. Amongst these, two saponins and three sapogenins showed better inhibition of the α-glucosidase enzyme [17]. The team also reported that saponins are less bioavailable than sapogenins which are both bioavailable and metabolically active. Furthermore, the report from a meta-analysis of 46 randomized controlled trials (2685 participants), the galactomannans fibres were found to have highest effectiveness against type 2 diabetes [40]. The mechanisms of action by which galactomannans lower glucose in vivo is are by the repression of carbohydrate-digesting enzymes, increased bowel movement and delayed gastric emptying. Type 2 diabetes patients who were newly supplemented with galactomannans for a 12-week period recorded a considerably reduced HbA1c and fasting blood glucose. Their blood lipid profile was also reduced. Another investigated also reported a decline in the usual rise of postprandial hyperglycaemia after a meal of fenugreek-enriched whole wheat chapatti or boiled rice [1].

4.7. Neuroprotective Effect

There are several mechanisms implicated in disorders of the CNS that result in changes in the functions and general integrity of the brain including oxidative stress, inflammation, diabetes and high cholesterol [41]. The neuroprotective ability of fenugreek was seen in its ability to oppose 6-hydroxy dopamine and restore the activity of neurons in Parkinson's disease [42]. furthermore, fenugreek extracts were reported to repress the activity of acetylcholinesterase enzyme which is vital for the regulation of cognitive functions in neurodegenerative disorders. Fenugreek seeds were seen to attenuate memory loss, tau and amyloid pathology in Alzheimer's disease in rat models. Being an antiamnesic agent, the methanolic extract of fenugreek seeds also improved learning and memory processes in mice according to another investigation [43].

4.8. Anti-Obesogenic Action

The anti-obesogenic properties of fenugreek are thought to be mediated by its multiple bioactive compounds via various interrelated mechanisms like decreased lipid digestion, improved satiety and enhanced regulation of fat metabolism, the dietary fibres contained in the seeds of this plant form a viscous gel in the intestine thereby decreasing the absorption of sugars and lipids. The aqueous extracts of fenugreek seeds in an experiment were administered to rats for 28 days, hyperlipidaemia and white adipose tissue were reduced due to improved fat metabolism, impaired lipid digestion, down regulation of lipogenic enzymes and improved sensitivity to insulin. Furthermore, diosgenin was seen to enhance adipocyte differentiation and to decrease inflammation in adipose tissues in vitro while trigonelline reduced lipid accumulation and adipocyte differentiation in 3T3-L1 cells [44].

4.9. Galactagogue Activity

Galactagogues are foods, herbal supplements or pharmaceutical substances that induce and sustain milk production in females at levels that meets their infant's need. Antagonists of the dopamine receptor are common galactagogues utilized in clinical practice. These dopamine receptor antagonists increase the production of milk by increasing prolactin levels since the production of milk is controlled by the prolactin hormone. Fenugreek is an herbal dopamine receptor antagonist [4]. Although dopamine receptor antagonists are some medicinal products that enhance the supply of breast milk, the use of medications for this purpose is not advised when the causing problem is known. The galactagogue effect of fenugreek has been investigated and the plant has been reported to enhance the secretion of milk via stimulating the production of sweat since the breast is a special apocrine sweat gland. This sweat production in turn enhances the secretion of breast milk. The scientific claims and folklore published in favour of fenugreek led to its commercialization as part of milk promoting supplements in the markets [1]. Lactation consultants and midwives often recommend the plant to lactating mothers for the purpose of increasing the breast milk production. Milk production is reported to increase within 24-72 hours after taking fenugreek [45]. Moreover, a randomized, placebo-controlled, double-blind trial conducted in a Turkey maternal hospital reported that 66 women received a fenugreek contained herbal tea. The women were separated into three groups; The first group received 3 cups of fenugreek contained herbal tea each day; the second group which was the placebo group received three cups of herbal tea and apples each day and the third group which was the control group had no tea. Maternal milk volume was measured on the third postpartum day after electrical pumping for 15 minutes. The results revealed that the first group that received fenugreek infused tea had up to double the mean volume of pumped milk (73ml) as compared to the control (31ml) and the placebo (39ml) groups [46]. **Table 1** and **Fig 2** both give an overview of the biological activities of fenugreek.

Table 1 The Biological activities of fenugreek

Bioactive compounds	Category of compounds	Biological activities
Ellagic acid, quercetin, coumarin, rutin, salicylates, isovitexin and vitexin	Flavonoids and phenolic compounds	Anti-inflammation, antihypertension, antidiabetic, antioxidant, antiobesity
4-hydroxyisoleucine	Non proteogenic amino acids	Antidiabetic, antidyslipidemia, antiobesity
Diosgenin and dioscin	Sapogenins and steroidal saponins	Antioxidant, anti-inflammatory, antiobesity, anticancer, cardioprotective
Glycine betaine and Trigonelline	Alkaloids	Anti-inflammatiory, antidyslipidemia, antinociceptive, neuroprotective, anti-migrane

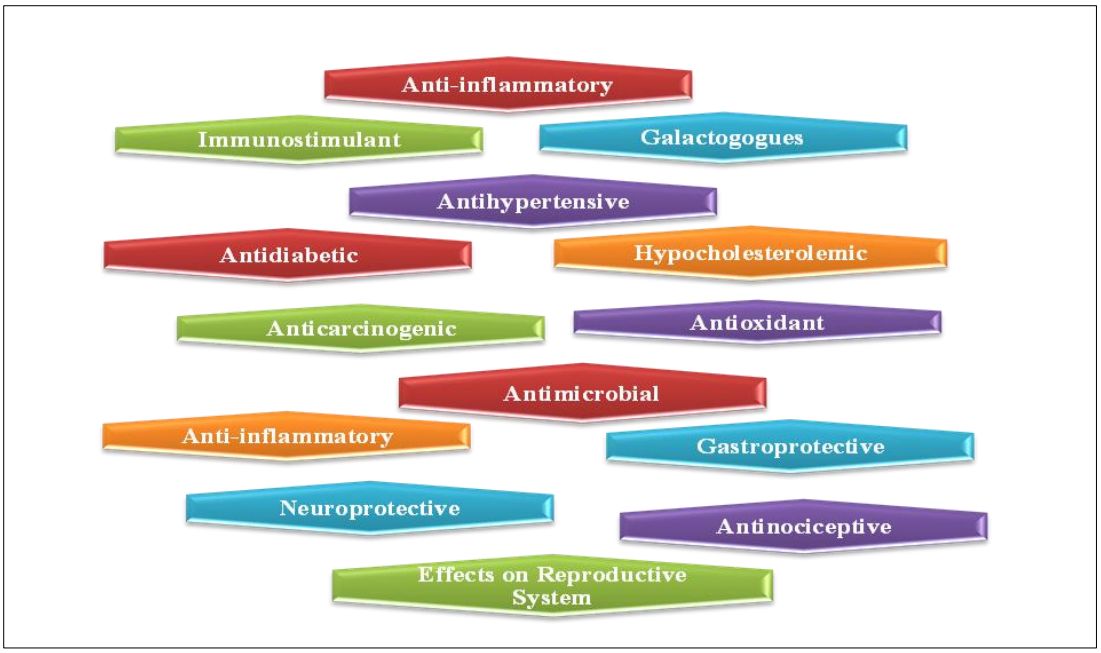

Figure 2 A summarized illustration of the biological activities of fenugreek Kumar et al. (2021)

5. Conclusion

In addendum to being one of the most nutrient dense plants, fenugreek has a strong record of safe usages in diverse pharmacopeia. The bioactive profile and outstanding nutritional value of this plant can be used in adjuvant therapy as dietary adjuncts in improving or out rightly preventing metabolic disorders like lipid and glucose dysregulation. These effects of fenugreek have strong support clinical evidence although this is not the case with the other biological activities of the plant. More research is thus necessary to establish the existing claims concerning other effects of fenugreek.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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