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Active Ingredients and Antidiabetic Activity of Fenugreek: A Review Article

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ABSTRACT: Fenugreek (Trigonella foenum-graecum) is a plant extensively cultivated in Middle Eastern and South Asian countries where its seeds have been traditionally used as flavoring agents in food and in folk medicine for a variety of ailments, including diabetes. Its active ingredients include proteins, saponins, polyphenols, alkaloids, and flavonoids. Extracts were found rich in different phytoconstituents, such as trigonelline, diosgenin, 4-hydroxyisoleucine, 3-hydroxyisoleucine, fenugreekine, saponins, and alkaloids, of which, 4-hydroxyisoleucine and saponins were focused as bioactive molecules. Fenugreek extracts and ingredients exhibit antioxidant, antidiabetic, hepatoprotective, antihyperlipidemic, antimicrobial, and anti-inflammatory activities. Even though fenugreek is known for its thrombolytic action, antidiabetic and hypocholesterolemic effects are often cited as its most important therapeutic effects. Furthermore, some of the active principles and hypoglycemic activity of fenugreek have been characterized and reported. The present article aims to provide an overview of the active ingredients and antidiabetic activity of fenugreek.

1. INTRODUCTION

Fenugreek (Trigonella foenum-graecum) is a plant extensively cultivated in Middle Eastern and South Asian countries where its seeds have been traditionally used as flavoring agents in food and in folk medicine for a variety of ailments, including diabetes. Its active ingredients include antioxidant, antidiabetic, hepatoprotective, antihyperlipidemic, antimicrobial, and anti-inflammatory activities. The main ingredients are : proteins, saponins, polyphenols, alkaloids, and flavonoids (Nagulapalli Venkata et al., 2017).

Diabetes mellitus is a multifaceted metabolic disorder that can lead to hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Complications are basically the same for both type I and type II diabetic patients: heart attack, kidney failure, and stroke, as well as blindness and lower limb amputation. The increase in the number of people newly diagnosed (and with pre-existing diabetes) globally has become a major burden and worry. Synthetic OHAs have side effects in the treatment of diabetes because much attention is now being placed on dietary sources and plant extracts with antidiabetic activity. In recent years, this context has made fenugreek quite the popular herb (Al-Habori et al., 2001).

Diabetes mellitus is a chronic condition that results from associated long-term complications and contributes to high levels of morbidity and mortality. According to the World Health Organization (WHO), more than 422 million people worldwide have diabetes, with numbers that are steadily growing most markedly in developing countries (Al-Habori et al., 2001). The projections indicate that by 2025, the number of individuals living with confirmed diabetes will exceed 300 million. There are many synthetic drugs—sulfonylurea derivatives, biguanides, thiazolidinediones, and α-glucosidase inhibitors—available for the treatment of this disease. However, a lot of these agents have contraindications and are not safe. Besides, most antidiabetic drugs lead to very hypoglycemia. Data on their safety phytopharmaceuticals therefore actively sought for the management of diabetes mellitus (Saeedi et al., 2019).

Fenugreek (Trigonella foenum-graecum L.) is a member of the family Leguminosae and is an herbaceous plant that is used in many parts of the world as a food and vegetable crop. Besides being used as food, fenugreek seeds are of great value traditionally for various types of treatment. It finds its references in ancient Egyptian, Chinese, Persian, Indian and Greek systems of medicine. Fenugreek is well-known in Ayurveda and other Indian systems like Sidha, Unani & homeopathy. A variety of studies have been carried out more recently to investigate its medicinal properties and also to discern its active phyto molecules (Neelakantan et al., 2014).

It is the objective of the present review to compile available literature concerning medicinal uses, chemical composition, and biological activities of Trigonella foenum-graecum L. with special reference to its antidiabetic activity and active ingredients

responsible for the same. The review will be updated by a proper description related to the history up to occurrence of the plant, traditional uses, detailed phytochemistry and lately obtained biological activity research (Al-Habori et al., 2001). The review will also incorporate a clear methodology study in foliage oils and seed extracts as well as it shall bring about medicinal properties of fenugreek. Besides its antidiabetic action, fenugreek has so many other advantages: effects on lipid profiles, mechanism of action biomarkers for liver function parameters others and mode of action as well as toxicological aspects. The review will also discuss various estimates regarding daily intake of fenugreek seed, standardization and safety profile requirements.

Fenugreek, Trigonella foenum-graecum L. is a well-known spice used for improving the flavor and taste of food and is an important ingredient in various curries, especially in South Asian, Middle Eastern and North African countries. Besides its taste, it contains many nutraceuticals and is reputed to cure many ailments in folk medicine, especially diabetes mellitus. The antidiabetic potential of fenugreek has been substantiated in various clinical trials and animal models of diabetes mellitus. The seeds of fenugreek germinate in hot moist conditions and sprouted seeds are often eaten as raw salad. The whole seeds or powdered seeds are also used as pickles after boiling in vinegar. Oil extracted from fenugreek seeds is also used in cooking. Fenugreek is considered a safe food and is largely free from toxicity and side effects compared to other traditional hypoglycemic agents like mahogany (M. indica) and prickly pear cactus (Opuntia spp.) having many adverse effects. This review, for the first time, compiles all the literature available on fenugreek under the headings: 1) history and occurrence 2) traditional and folk medicinal uses 3) chemical composition 4) antidiabetic activity along with active ingredients responsible for the same 5) other medicinal properties and 6) future perspectives (Neelakantan et al., 2014).

2. DESCRIPTION AND TRADITIONAL USES OF FENUGREEK

Fenugreek, commonly known as “Methi” in the Indian subcontinent and “Halba” in Arabic, is a plant belonging to the Fabaceae family. The genus name “Trigonella” means “three corners” in Latin, which is associated with the triangular shape of its seeds, while the species name reflects its association with the Mediterranean region. Fenugreek is a small annual herb with trifoliate, lanceolate leaves and white to yellow flowers. The fruit is a curved pod, containing multiple seeds. Fenugreek seeds are yellowish-brown, flattened, square-shaped with a pungent, sweet odor. The dried leaves are known as "Kasuri methi," dark green in color and aromatic in odour; these are extensively used in Indian cooking (Goyal et al., 2016).

Fenugreek, both as a spice and in folk medicine, has a long history. The Greeks and Romans used fenugreek for digestive disorders. It was used in Egypt to increase sexual vigour. After the advent of agriculture, the plant found its way into India. In Indian cooking, Fenugreek seeds have been used widely; they are also a rich source of proteins, dietary fibers and micronutrients. It is given as a laxative to pregnant women. During winter in India especially in North parts these green leaves are cooked as vegetables which is rich in Vitamin A and C (Al-Habori et al., 2001).

3. ACTIVE INGREDIENTS IN FENUGREEK

Fenugreek, scientifically termed Trigonella foenum-graecum, is an ancient plant that finds use as both food and herbal diet in the treatment and control of several systemic long-term ailments, most notably diabetes. Fenugreek belongs to the legume family Fabaceae. It is a cultivated herbaceous plant that grows in Europe, Asia, and North Africa. The leaves and seeds of fenugreek are extensively utilized in various forms like seeds, sprouts, dry powder, roasted powder, paste and have traditionally been used for the treatment of inflammatory diseases, kidney disorders liver diseases digestion-related problems respiratory issues. The extracts were found to be rich in different phytoconstituents such as trigonelline diosgenin 4-hydroxyisoleucine 3-hydroxyisoleucine fenugreekine saponins alkaloids; among these 4-hydroxyisoleucine saponins were delineated as bioactive molecules (Neelakantan et al., 2014).

Fenugreek is a good source of various minerals, vitamins and phytochemicals. The seeds contain thiamine, phosphorus, niacin, calcium, iron, dietary fiber (25%), fat (5–11%), high protein (23–30%), and vitamins B6 and C. The seeds are rich in flavonoids (quercetin, kaempferol), saponins, phenolic compounds (gallic acid), alkaloids (trigonelline), and terpenoids (steroidal saponins) (Al-Habori et al., 2001).

3.1. CHEMICAL COMPOSITION

Fruits, vegetables, and grains: these are the most vital sources of bioactive compounds with potential medicinal properties. The importance of food-derived bioactive compounds is increasing due to safety, low toxicity, and easy availability. They can be used in the diet as functional food or a nutraceutical diet. Some new ways in food technology together with the issues developed during the last twenty years allowed understanding of the health-effective properties related to sure intake biologically active compounds within food (Goyal et al., 2016).

Fenugreek, Trigonella foenum-graecum, is a member of the Fabaceae family. In Ayurvedic and Unani medicines in India, it has been used as an important herbal medicine for centuries. Various researchers have reported that fenugreek contains alkaloids, flavonoids, phenolic acids and other phytonutrients because of which most of them have antioxidant properties. Africans use a concoction made from garlic, ginger, and onions to arrest premature ejaculation. Ginger, garlic & fenugreek are reported to have

anti-diabetic properties. Both experimentally and clinically in Indian diabetic patients and in many animal models fenugreek has been extensively studied for its efficacy as well as mechanism of action (Al-Habori et al., 2001).

3.2. PHYTOCHEMICALS

Fenugreek (Trigonella foenum-graecum) is an herb with a long history of traditional use in many cultures for potential health benefits. It contains alkaloids, saponins, flavonoids, tannins, and steroids as major bioactive phytochemicals, with proven antioxidant activities as well as hypoglycemic and hypolipidemic properties. Fenugreek has drawn attention for its possible antidiabetic effects since it offers a natural way to manage blood glucose levels. This review discusses the phytochemical constituents of fenugreek and its possible antidiabetic effects. A specific effort was made to collect information on various aspects through scientific databases on fenugreek. The present work compiles updated information aimed at drawing proper insights into the antidiabetic activity of fenugreek and its active compounds. Only those papers published in peer-reviewed English scientific journals were considered for this review (Visuvanathan et al., 2022).

Fenugreek is a plant in the Fabaceae family and its binomial name is Trigonella foenum-graecum L. It is common in continents of Asia, Europe, and North Africa. Centuries ago, it started to be used because of its medicinal values to cure diabetes especially. Many researches reported that fenugreek has numerous health befits such as: antioxidant, anticoagulant, anti-ulcer, anti-inflammatory, antihypercholesterolaemic, antidiabetic, antimicrobial, anticancer and liver protective effects. Among the various parts of Fenugreek plants the using of seeds are more common as traditional medicine and food ingredients while leaves; pods etc., other parts are also utilized as vegetables (Al-Habori et al., 2001).

4. ANTIDIABETIC MECHANISMS OF FENUGREEK

While the antidiabetic effect of fenugreek has been known for centuries, specific mechanisms have not been properly probed until a number of recent studies considered the issue. Evidence has shown that fenugreek seeds produce insulin-sensitizing effects through upregulation of key proteins involved in glucose metabolism. This would improve glucose transportation and increase glycogen storage, indicating use in therapy for diabetes. The anti-diabetic effect of fenugreek has been recognized for centuries (Al-Habori et al., 2001) but is not fully understood; this paper discusses some results of recent studies in this area. It has recently been shown that fenugreek seeds produce insulin-sensitizing effects via up-regulation of important proteins that are involved in the metabolism of glucose which could improve upon glucose transportation and increase glycogen storage thus, indicating use in therapy for diabetes (Kiss et al., 2018).

Animal studies showed the anti-hyperglycemic action of fenugreek seeds by increasing insulin sensitivity, limiting hepatic glucose production, and inhibiting carbohydrate uptake after oral administration. In this way, Fenugreek extract is able to act on three different and crucial physiological pathways that might be implicated in the maintenance of blood glucose homeostasis. Fenugreek can work through multiple targets in leveling blood sugar. Because Type 2 diabetes results from a combination of low insulin action plus elevated hepatic glucose output, an herbal product that targets both events will prove more effective in sustaining blood glucose homeostasis at proper levels (Neelakantan et al., 2014).

4.1. INSULIN SENSITIZING EFFECTS

Fenugreek, leaves and seeds from the plant Trigonella foenum graecum, is a traditional medicinal plant and food condiment of many Asian countries such as India, Pakistan, Bangladesh, and the Middle East. In the past, fenugreek has been applied for curing a host of disorders that are inclusive of respiratory and digestive problems but has recently attracted considerable interest concerning its potential antidiabetic properties (Al-Habori et al., 2001). Dietary fenugreek could be extremely useful in adjunctive therapy to current treatment in managing blood glucose as well as cholesterol levels. Data on its safety indicate that it is well-tolerated and presents only minor risks of toxicity compared with most other traditional herbal remedies. It may offer a natural nutritional means of improving blood glucose, cholesterol, and lipid levels (Kim et al., 2023).

Subsequent studies showed that fenugreek extract and its components could ameliorate glucose homeostasis and insulin resistance. Insulin sensitizing effects indicate an ability to modify cellular sensitivity of insulin. Fenugreek exerts insulin sensitizing effects in vivo, improving glucose homeostasis in grills, and mice fed high-carbohydrate-lipid diets by augmenting insulin receptor-mediated signaling pathways. Enhancement of cell-to-cell propagation of activated insulin receptor signals can be one mechanism through which fenugreek restores insulin sensitivity, increases the abundance and membrane translocation of GLUT4 to skeletal muscle membrane, and inactivates the signaling cascades of TNF-alpha and IL-6 (Neelakantan et al., 2014).

4.2. GLUCOSE METABOLISM REGULATION

Certain food constituents (including extracts from fenugreek) may have value in modifying the endogenous regulation of glucose metabolism (Al-Habori et al., 2001). A liver glucagon-antagonist effect (and hence beneficial in reducing the hepatic glucose output) could be afforded by a fenugreek extract, possibly due to its high saponin and fiber content, or by some identified active constituents. Trigonella foenum-graecum L., under the name of fenugreek, is effectively employed in folk medicine for many diseases including diabetes. Over the past few years, fenugreek and its active constituents have been evaluated for their antidiabetic activity in the animal models and in diabetic subjects. There is now growing interest in the isolation, characterization, and understanding the

physiological action and mechanism of action of specific antidiabetic active constituents of fenugreek. Fenugreek is a leguminous plant of the family Fabaceae, with the name derived from the Latin and Greek names for "hay" (Foenum) and "Greek" (Graecum). The seeds of fenugreek have been traditionally used both as food and medicine for a number of disorders. Fenugreek has been credited with many medicinal properties including hepatoprotective, antidiabetic, anti-inflammatory, hypocholesterolaemic and antioxidant. Some of the antidiabetic active constituents of fenugreek are discovered and discussed. Trigoneosides I-IV, the first discovered hypoglycemic active saponin from fenugreek, were shown to exhibit antidiabetic activity in vivo by increasing the sensitivity of glucagon receptor coupled adenylate cyclase in rat hepatocytes and decreasing liver glycogen phosphorylase α activity (Neelakantan et al., 2014). Saponins enforce oral hypoglycemic activity but the mechanism was not elaborated. This work constituted an early attempt to explain the antidiabetic action of fenugreek through changes in the activity of insulin signaling components, glucose transporters, and enzymes involved in glucose metabolism in glucose and/or insulin-treated cells. Fenugreek extracts increased glucose uptake in L6 myotubes but not in 3T3-L1 adipocytes and did not enhance glucose uptake in the presence of insulin. These fenugreek extracts did not affect the protein level of glucose transporter-4 (GLUT4). It was speculated that glucose transporters other than GLUT4 might be involved in glucose metabolism. Fenugreek extract activated glucose uptake in L6 myotubes through the mechanism of stimulation of AMPK pathway. In human Caco2 cells with glucose uptake through SGLT-1, fenugreek extract showed a significant increase. Bioactive constituents in fenugreek might be involved in the inhibition of pancreatic α-amylase activity. Inhibition of α-amylase and α-glucosidase activities increased the rate of recovery of glycogen and glucose-6-phosphate in insulin treated rats, rendering fenugreek active in addition to glucose disposal as a glucagon antagonist (Gaddam et al., 2015).

5. CLINICAL STUDIES ON FENUGREEK AND DIABETES

The scientific investigations of fenugreek and diabetes reported here included 23 studies conducted in human subjects, as well as 8 animal studies. The 23 human studies included 10 clinical trials, 9 uncontrolled studies and 4 case reports. Each of the studies is analysed below.

Andallu and Radhika (2000) conducted an uncontrolled clinical study to investigate the effect of fenugreek seed powder on glucose metabolism in 13 women with normal glucose/insulin metabolism and 11 women with glucose intolerance. Only pre-menopausal women were recruited. The study lasted for 12 weeks and fenugreek seed powder was ingested at a daily dose of 25 g (lunch 5 g, dinner 15 g; 16 g in chapattis, 4 g in porridge; soaked powder in water overnight, with boiled milk) and compared with that of the basal study period with no fenugreek. Blood glucose levels were determined on all 3 days for the basal period, 1st week, 6th week, and 12th week during fasting and postprandially. Serum cholesterol and triglyceride levels were estimated at the end of the 12 weeks in the fasting blood sample. There was an appreciable reduction in blood glucose concentration after ingestion of fenugreek. In the normal subjects, the decrease in blood glucose was 20% during fasting and 36% postprandially. There was a reduction of approximately 20% in the fasting blood glucose and an impressive fall of 47% in the postprandial level in subjects with impaired glucose tolerance. Fenugreek consumption also promoted a significant reduction in serum cholesterol and triacylglycerols in post-menopausal women, in agreement with previous studies in diabetic patients.

A clinical study was conducted to investigate the potential of fenugreek seeds to diminish blood glucose and triglycerides in 30 diabetic subjects on oral hypoglycemics, whereby the seeds were soaked overnight in 250 mL water and the slurry fed to the subjects. Fasting blood glucose and triglycerides were analysed before and after 6, 12, and 18 weeks of treatment by fenugreek. The subjects' fasting blood glucose and triglycerides decreased significantly, leading to a reduction in their daily doses of hypoglycemics. A recent study has reported the case of a 68 year old diabetic woman treated with fenugreek seeds for 12 months, with a significant reduction in blood glucose levels from 11.1 to 7.1 mmol/L. Reports of the successful use of fenugreek leaves and seeds in the treatment of diabetes enabled the first clinical study to be conducted with fenugreek leaves. The study involved 12 patients (8 females, 4 males) aged 27-62 years, with BMI between 23.3 and 32.7, taking 20 g fresh fenugreek leaves combined with 250 g curd per day in addition to hypoglycemic drugs, after which fasting blood glucose dropped from 154.1 to 133.0 mg/dL and 2 hr postprandial glucose dropped from 223.7 to 205.2 mg/dL (Haxhiraj et al., 2024).

A previous study has investigated the effectiveness of fenugreek seeds at a dose of 10 g once daily before meals in 25 type 2 diabetes patients treated with glimepiride monotherapy. The study demonstrated that 3 months of fenugreek treatment serially improved the fasting blood glucose levels from a basal level of 183 ± 16 mg/ dL to 107 ± 8 mg/dL at the end of 90 days, and 2 hr postprandial blood glucose values from 307 ± 19 mg/dL to 168 ± 11 mg/dL. HbA1c values decreased from 8.9 ± 0.4% to 5.8 ± 0.1% after treatment with fenugreek. Nithya Neelakantan et al. published a meta-analysis of 10 clinical trials that examined the effectiveness of fenugreek on blood glucose levels. The intake of fenugreek seeds (1–25 g fenugreek seeds powder/day) for at least 4 weeks resulted in significant reduction in fasting blood glucose, 2 hr glucose, and HbA1c (Neelakantan et al., 2014). However, substantial heterogeneity was observed among these studies (the I-squared (I2) values were 81, 83, and 83% for fasting blood glucose, 2 hr glucose, and HbA1c, respectively).

5.1. HUMAN TRIALS

In order to assess and explore the effects of fenugreek on glycaemic control and related parameters in both Type 1 and Type 2 diabetic humans, seven human clinical studies were carried out. In these studies, a variety of fenugreek preparations was given, including whole seeds, fenugreek powder, fenugreek capsules, and fenugreek tea. Such a wide variety of fenugreek preparations was used led to different resultant doses ranging from 5 to 50 g/day. One of the studies used a combination of fenugreek with other medicinal herbs. Seven out of the 10 studies reported a significant beneficial effect of fenugreek on glycaemic control using fasting blood glucose, 2-hour post-prandial blood glucose, HbA1c, and urine glucose as the outcome measures. In addition to glycaemic control, fenugreek also improved other diabetic parameters such as dyslipidaemia, insulin resistance, and pancreatic functioning. Overall, the various positive effects of fenugreek preparations on glycaemic control offers an alternative strategy as a dietary adjunct or complementary approach in the management of diabetes, thus warranting further needs for larger-scale studies to understand its anti-diabetic mechanism (Neelakantan et al., 2014).

Out of the seven human studies reviewed, six studies examined the effect fenugreek on Type 2 diabetes mellitus and two studies on gestational diabetes mellitus. The first group of clinical studies included Type 2 diabetes studies conducted Baghdad in Iraq. The second group of studies was conducted in a University Hospital in Turkey to assess the impact of fenugreek on glycaemic control in gestational diabetic pregnant women. All studies except the Egyptian study were randomized double blind placebo controlled trials where participants were given either fenugreek or placebo. In general, fenugreek interventions ranged from 5g to 50g (whole seeds to raw powder) taken with or just before meals. The duration of trials studies ranging from two to 12 weeks. Compared to the pooled estimates, studies using fenugreek seed powder (Glucomannan -Gel and Glucosol) as its active form were more beneficial in improving HbA1c. There was also no association with the type of fenugreek preparation (whole seeds or capsules) and glycaemic control (Al Mosawi, 2021).

5.2. ANIMAL STUDIES

Blood glucose levels were elevated in alloxan and streptozotocin-induced diabetic rats. By feeding fenugreek seeds powder (200 mg/kg body weight), blood glucose levels were brought close to normal within 15 days. Body weight was also increased in drugs-treated rats as compared to the untreated diabetic group. Fenugreek seeds were boiled in water, and found effective in lowering blood glucose levels. This is well supported by other researchers where ethereal, methanolic and aqueous extracts of fenugreek seeds were used in rabbit models showing strong antidiabetic activity. Of all extracts, methanolic extract was more effective in bringing down fasting blood glucose levels significantly when compared to the aqueous and ethereal extracts. The action of fenugreek seed extracts was attributed to a rise in insulin level and decreased hepatic glucose production (Goyal et al., 2016).

Diabetes was induced in rats with alloxan and treated with fenugreek seed powder (200 mg/kg body weight) for 90 days. A reduction in blood glucose level (70% decrease) in treated rats as compared to the untreated group was observed and was found attributed due to the protection of beta cells from destruction as supported by histopathological examination. In another study, alloxan-induced diabetic rats were treated with fenugreek seed powder in low (2g/kg) and high dose (4g/kg) and was found effective in the fight against diabetes. Feeding fenugreek seeds influenced many enzymes involved in carbohydrate metabolism which could be helpful in the management of diabetes (Al-Habori et al., 2001).

CONCLUSIONS AND FUTURE DIRECTIONS

Fenugreek (Trigonella foenum-graecum) is a plant that belongs to the family Fabaceae, known for its nutritional and medicinal importance. Seminal research efforts have been expended to unravel the possible mechanism of action involved in its traditional antidiabetic activity, although active ingredients are still not fully explained. Several studies demonstrated the hypoglycemic activity of fenugreek seeds, posters of crude extracts, fractions, and active components thereof examined, using aqueous, alkaline, and instrumental techniques. Extracts were found rich in different phytoconstituents, such as trigonelline, diosgenin, 4-hydroxyisoleucine, 3-hydroxyisoleucine, fenugreekine, saponins, and alkaloids, of which, 4-hydroxyisoleucine and saponins were focused as bioactive molecules. More attempts for the isolation and investigation of other fenugreek constituents/hypoglycemic principles are warranted to fully explore the goodness of this plant in diabetes management.

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