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Mini-Review

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Anti-Diabetic Effects of Leaves of *Trigonella foenum-graecum* L. (Fenugreek): Leads from Preclinical Studies

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Abstract

Diabetes mellitus, a metabolic disorder of the endocrine system is one of the World's oldest diseases known to man. Since time immemorial plants have been used as anti-diabetic agents in the various traditional systems of medicine. *Trigonella foenum-graecum* commonly known as fenugreek in English and methi in various Indian languages is one such plant and has been an integral part in the treatment of diabetes in the Indian traditional system of medicine the Ayurveda. The seeds and leaves have been documented to be useful in reducing hyperglycemia and its complications. This review collates the traditional uses and validated anti-diabetic effects of the fenugreek leaves and on the mechanisms contributing to the therapeutic effects.

Keywords

Trigonella foenum-graecum, Fenugreek, Methi leaves, Diabetes

Introduction

Recent information from around the world has affirmatively confirmed that type II diabetes mellitus (DM), a metabolic disorder of the endocrine system is a major malady and that it is major health issue in India and China [1, 2]. From a medical perspective, the hyperglycemia resulting from the inadequate response of target cells to insulin causes glucotoxicity and consequentially causes long term side vascular and non-vascular complications [2, 3]. The most important vascular complications include retinopathy, nephropathy, neuropathy, coronary and peripheral artery and cerebrovascular ailments, while the most important non vascular complications includes gastroparesis, infections and skin changes [2, 3]. These secondary ailments merit regular and judicious medical attention inevitably affecting the individuals and their families at large [1]. From a mechanistic perspective, how hyperglycemia causes dysfunction of multiple organs is unknown. However, comparative molecular and biochemical studies are indicating the facts that activation of protein kinase C, formation of advanced glycosylation end products, increased sorbitol production, activation of hexosamine pathway and production of free radicals [reactive oxygen species (ROS) and reactive nitrogen species (RNS) cumulatively contribute towards the observed endothelial dysfunction and cellular damage [2, 3].

From a treatment perspective diabetes is usually treated with subcutaneous injections of insulin, oral hypoglycemic drugs like the insulin sensitizers (biguanides, thiazolidinediones), insulin secretagogues (sulfonylureas, meglitinides), α-glucosidase inhibitors, incretin agonists and dipeptidyl peptidase-4 inhibitors [4]. However, the use of these drugs is associated with untoward side effects

like hypoglycemia and localized lipoatrophy at the site of injection with insulin injection; acidosis and renal failure with metformin; fluid retention, weight gain and increased the risk of fracture with thiazolidinediones; abdominal discomfort, flatus, diarrhea, jaundice and cholestasis with alpha glucosidase inhibitors; nausea, pancreatitis and severe allergic reactions with glucagon like peptide (GLP 1) analogues; and nausea with amylin agonists [2, 4]. Despite being effective in reducing hyperglycemia, the presently available drugs are incapable of halting the progression of the disease and prevent complications. In lieu of these observations, discovering newer anti-diabetic agents especially from dietary sources and with medicinal properties is beneficial for these agents would be cheaper, orally administrable, possess fewer side effects and have easy acceptability [5, 6].

Trigonella foenum-graecum the all season plant

Among the various medicinal plants documented to be of use as a hypoglycemic agent, *Trigonella foenum-graecum* commonly known as fenugreek in English and methi in various Indian languages is important dietary and medicinal plants [7, 8]. The other names are enlisted in Table 1. The plant is annual and grows to an average height of two feet. Documents indicate that it is one of the oldest medicinal agents to be used in the treatment of diabetes in the various traditional and folk systems of medicine [8]. The plants were originally native to India and Northern Africa, but are today found growing in other parts of the world. The seeds, maturing in long pods and tender leaves are the plant parts used in various medicinal preparations as well as a spice in Indian curries [8]. The taxonomic classification of *Trigonella foenum-graecum* is as follows:

Kingdom: Plantae

Super division: Angiosperms

Division: Eudicots

Class: Rosids

Order: Fabales

Family: Fabaceae

Subfamily: Faboideae

Tribe: Trifolieae

Genus: Trigonella

Species: Foenum

Dietary and culinary use of fenugreek

Fenugreek and seeds have been an integral component of Indian, Pakistani, Bangladeshi and Sri Lankan cuisine and has wide use in variety of dishes like pickles and curry [7, 9]. The seeds are used as flavoring agent for various dishes and is also used a seasoning agents. The sprouted seeds are used as salads while the fresh stems and leaves are used to make pakodas, and curry with lentils [7, 9]. In Egypt and Ethiopia, fenugreek seeds are used in baking bread, while in Switzerland they are used as a flavoring agent in making of cheese [7, 9, 10]. Fenugreek has been used for centuries in European countries as a spice [7, 9]. However, its use in USA has been very recently and is principally used as a spice for soups and stews [7, 9]. The young plants and the leaves (Figure 1) are a very important source of vegetable and have been used in various cuisines [7, 9].

Figure 1: Fenugreek leaves.

Phytochemistry of fenugreek

Fenugreek is one of the most well investigated plants and studies have it to possess alkaloids like trimethylamine, neurin, trigonelline, choline, gentianine, carpaine and betaine; the amino acids isoleucine, 4-hydroxyisoleucine, histidine, leucine, lysine, l-tryptophan, arginine; saponins like graecunins, fenugrin b, fenugreekine, trigofoenosides a–g; the steroidal sapinogens yamogenin, diosgenin, smilagenin, sarsasapogenin, tigogenin, neotigogenin, gitogenin, neogitogenin, yuccagenin, saponaretin; flavonoids like quercetin, rutin, vitexin, isovitexin; the lipids triacylglycerols, diacylglycerols, monoacylglycerols, phosphatidylcholinephosphatidyl ethanolamine, phosphatidylinositol, free fatty acids and lipids, vitamins, minerals. 28% mucilage; 22% proteins; 5% of strong smelling, bitter fixed oil [7, 9, 11-13]. Reports also suggest that fresh fenugreek leaves contain ascorbic acid (220.97 mg/100 g) and β-carotene (19 mg/100 g) [14] and are a rich source of calcium, iron and zinc content [8].

Traditional and validated medicinal uses

Fenugreek has been an important medicinal agent in the Indian, Chinese, Arabic, Greek and Latin pharmacopoeia [9]. Historical reports indicate that fenugreek was used in ancient Egypt to incense and to embalm mummies [8]. They were also used to relieve menstrual cramps, reduce abdominal pain, ease childbirth and as a lactagogue to increase milk flow in the mother [9]. The ancient Romans fenugreek seeds to facilitate labor and delivery; while in the traditional Chinese medicine it has been used as a tonic and to mitigate weakness and edema of the legs [8].

Fenugreek finds wide use in the Indian traditional systems of medicine the Ayurveda, Siddha and Unani and also in various folk medicines as an aphrodisiac agent, to mitigate digestive and respiratory problems [8, 15]. Fenugreek has been used in the folk medicines for treating cellulitis, boils,

Table 1: Colloquial name of Fenugreek in various languages.

Language	Fenugreek
Albanian	Kopër Greqie, Trëndetina yzerlike,
Amharic	Bish
Arabic	Hulba, Hilbeh
Aramaic	Pila, Qart, Shebbelila
Armenian	Chaiman
Assamese	Methi, Mithi, Mithi guti
Basque	Allibre, Allorbe
Bengali	Methi
Bodo	Mithi
Bulgarian	Sminduh, Sminduh grutski, Tilchets, Chimen
Burmese	Penantazi
Catalan	Fenigrec
Chinese (Cantonese)	Wuhlouhba
Chinese (Mandarin)	Hu luba
Coptic	Ali, Jofi, Tili
Croatian	Grčka djetlina, Grčko sijeno, Piskavica
Czech	Pískavice řecké seno, Senenka
Danish	Bukkehornskløver, Bukkehorns-frø
Dhivehi	Oabaiy, Oabath
Dogri	Methi
Dutch	Fenegriek
Esperanto	Fenugreko
Estonian	Kreeka lambalääts, Põld-lambalääts
Farsi	Shanbalile
Finnish	Sarviapila
French	Fenugrec, Sénegré, Trigonelle
Galician	Fenogreco, Alforfa
German	Bockshornklee, Griechisch Heu
Georgian	olinji, Chaman
Greek	Trigonella, Moschositaro
Greek (Old)	Telis, Boukeros
Gujarati	Methi
Hebrew	Hilbeh
Hindi	Methi
Hungarian	Görögszéna
Indonesian	Kelabet, Klabat, Kelabat
Italian	Fieno greco
Japanese	Koruha, Fenu-guriku
Kannada	Mente, Mentya
Kashmiri	Meth
Korean	Horopa, Penigurik
Latin	Fænum Græcum
Latvian	Sierāboliņš
Lithuanian	Vaistinė ožragė
Macedonian	Grčko seme
Maithili	Methi
Malay	Halba, Kelabet
Malayalam	Uluva, Venthayam
Manipuri	Methi
Marathi	Methi
Mongolian	Grek Chireg
Nepali	Methi
Newari	Mi
Norwegian	Bukkehornkløver
Oriya	Methi
Pahlavi	Shabaliidag
Polish	Kozieradka pospolita; Nasiona kozieradki
Portuguese	Feno-grego, Alfarva, Alforba, Fenacho
Provençal	Senigré
Punjabi	Methi
Romanian	Molotru, Molotru comun, Schinduf
Russian	Pazhitnik grecheski, Shambala, Pazhitnik cennoj
Sanskrit	Methika
Serbian	Piskavica, Grčko seme
Sinhala	Uluhal
Slovak	Pískavica, Senovka grécka
Slovenian	Grško seno, Sabljasti triplat
Spanish	Alholva, Fenogreco
Swahili	Uwatu
Swedish	Bockhornsklöver
Tamil	Meti, Vendayam, Vetani
Telugu	Mentikura, Mentulu
Thai	Luk sat
Tibetan	Mi ti
Tigrinya	Abaka
Tulu	Mente, Mette
Turkish	Çemen, Poy baharatı, Çimen, Boy tohumu, Hulbe, Kokulu yonca
Ukrainian	Hunba sinna
Urdu	Methi, Shanbalid
Yiddish	Khilbe, Fenigrekum

tuberculosis, dysmenorrhea, postmenopausal symptoms, as lactagogue, to relieve colds, bronchial complaints, influenza, asthma, catarrh, constipation, sinusitis, pleurisy, pneumonia, sore throat, laryngitis, hay fever tuberculosis and emphysema [9]. A cross-sectional survey conducted in Sri Lanka has also shown that patients with diabetes use fenugreek indicating that their use is prevalent [8].

Scientific studies carried out in accordance to the tenets of modern medicine have shown fenugreek to possess anti-diabetic, antifertility, anticancer, antimicrobial, antiparasitic, lactation stimulant, galactagogue, hypocholesterolemic, immunomodulatory, anti-carcinogenic, anthelmintic, anti-nociceptive, antioxidant, anti-microbial, anti-ulcer, gastro-

and hepatoprotective, anti-obesity, anti-hyperglycemic, anti-diabetic and hypocholesterolemic effects [9, 16]. Of these the anti-diabetic properties of the seeds have been investigated the most and reports are suggestive to the fact that the protective effects are seen in both laboratory animal and humans [3, 15]. From a phytochemical perspective the anti-diabetic effects are attributed to the presence of galactomannan, 4-hydroxyisoleucin (4-OH-Ile), diosgenin and trigonelline and detailed mechanistic studies have also shown that 4-hydroxyisoleucin increases insulin secretion, galactomannan to decrease insulin resistance and glucose resorption from the GIT and trigonelline to improve β-cells regeneration [15].

Methi leaves possess anti-diabetic effects

Inducing hyperglycemia and evaluating the hypoglycemic effects in laboratory animals has been one of the principal endpoints in ascertain a medicinal agent's effectiveness. With respect to methi leaves, seminal studies by Abdel-Barry and co-workers (1997) [17] showed that the aqueous and alcoholic extracts of the leaf were effective in inducing hypoglycemic activity in both the non-diabetic (normal) and diabetic (alloxan-induced) rats [17]. The investigators tested graded doses of aqueous extract of the leaf by both i.p. (0.06, 0.2, 0.5, 1 g/kg) and P.O (1, 2, 8 g/kg) in both normal and alloxan-diabetic rats [17]. A significant reduction of blood glucose concentration was noticed also in subsequent studies with the aqueous extracts indicating its usefulness [18].

On a comparative note, the ethanolic extract was observed to be effective only through the i.p. route indicating that the hypoglycemic compound/s were present in the aqueous fraction. The LD50 for i.p. and oral administration were 1.9 and 10 g/kg respectively and the liver was the affected part after i.p. administration [17]. Together these data clearly suggest that the aqueous extract of leaves when given both orally and intraperitoneally possesses a hypoglycemic effect in normoglycaemic and alloxan induced hyperglycemic rats and also that the oral route was safe and devoid of any systemic toxic effects [17].

Studies with streptozotocin-induced diabetic rats have also shown that feeding methi leaves improved the body weight, reduced hyperglycemia and the levels of glycosylated hemoglobin [19]. Feeding methi leaves increased the levels of insulin and liver glycogen contents [19]. The anti-diabetic effects of the leaves were similar to that of glibenclamide and that the insulin levels were restored to near normal levels [19]. Feeding methi leaves corrected the diabetes-induced altered levels of the key carbohydrate metabolic enzymes [19] and lipids in serum, liver, heart, and kidney [20].

In addition to the metabolic effects diabetes-induced oxidative stress is a major health issue and fastens the glycotoxic effects on the vital organs. Studies with streptozotocin-induced diabetes rats have shown that feeding methi leaves caused a marked reduction in the levels of oxidative stress as affirmed by a decrease in the levels of thiobarbituric acid-reactive substances and concomitant increase in levels of reduced glutathione and in activities of catalase and superoxide dismutase in liver, heart, and kidney [21]. Subsequent studies have also confirmed that the aqueous extract of the leaf also caused a concentration dependent decrease in MDA and increase in the levels of GPx and SOD in liver, and WBC [18].

Conclusion

Scientific studies carried out in the past two decades have shown that methi leaves possess anti-diabetic effects in alloxan and streptozotocin induced diabetic rats. These reports validate believes and use of methi leaves as anti-diabetic agents in various traditional and folk systems of medicine. However clinical data are lacking and is the need of the time. Scientifically designed clinical trial with sufficient sample size and statistical power are required to validate the acclaimed benefits of methi as a natural nutritional treatment for diabetes mellitus. The outcomes of such studies may be useful for the clinical applications of methi in humans and may open up a new therapeutic avenue.

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