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Role of Fenugreek as Beneficial Anti-Diabetic Food Adjunct - A Review

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Abstract: ***Diabetes mellitus consider one of the major health problems all around the world today. Diabetes is characterized by hyperglycemia with an increase of glucose in blood. Studies on animals have shown that more than 400 plant species have hypoglycemic activity. Fenugreek (Trigonella foenum graecum) is one of the most common medicinal plants used for diabetes. After chemical profiling of Fenugreek's components, their biological activities including anti-diabetes were reported by many investigators. Fenugreek exhibits the beneficial effects due to presence the fiber and galactomannan rich fraction present in the seed. As a result, current studies have been performed mostly focusing on the bioactivity of fenugreek toward the recently generalized metabolic disorder involving diabetes. In this review article, we provide an overview of the recent literature describing Fenugreek 's potential for preventing the diabetes mellitus.***

Keywords: Fenugreek, Diabetes mellitus, Hyperglycemia, Insulin, Blood glucose

1. Introduction

Diabetes is a growing public health concern all over the world [1]. Conferring to the International Diabetes Federation Atlas guideline report, presently, there are 352 million adults with impaired glucose tolerance who are at high threat of developing diabetes in the future. In 2017, it was expected that 425 million people (20-79 years of age) suffered from Diabetes mellitus (DM), and the number is expected to rise to 629 million by 2045 [2].

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia either because the pancreas does not produce enough insulin or the peripheral target tissues are unable to respond to the normal concentration of insulin [3]. The common forms of diabetes mellitus are type 1 and type 2 diabetes, the latter being the more prevalent form and generally appearing later in life. Insulin resistance and impaired insulin secretion lead to type 2 diabetes, which has the features of chronic metabolic disorder and high levels of blood glucose. Regarding type 2 diabetes, because of the pancreatic β-cells' imperfection, damage or insulin resistance, the total secretion of insulin is insufficient, and as a result, the blood glucose of diabetics is much higher than the ordinary level[1]. In addition to death, diabetes also lead to many chronic conditions like neuropathy, nephropathy, and various vascular diseases associated with heart, kidney, brain, peripheral blood vessels and retinopathy [4].

Current oral anti-diabetic agents, which include insulin releasers, insulin sensitizers and α-glucosidase inhibitors, have modest efficacy and limited modes of action. In addition, current anti-diabetic drugs usually have adverse side effects, decreased efficacy over time, ineffectiveness against some long-term diabetic complications and low cost-effectiveness. Therefore, discovery and development of novel drugs for diabetes is still needed [5]. Many traditional plant treatments exist as a hidden wealth of potentially useful natural products for diabetes control [6]. Before the discovery of insulin in the 1920s and the development of oral hypoglycaemic agents, diabetes mellitus was treated mainly by a combination of fasting, diet control and plant therapeutics. The efficacy of plants in diabetes required confirmation and, therefore, the WHO (World Health Organization, 1980) recommended assessment of traditional plant treatments for diabetes mellitus. Currently, several hundred plants have been reported to have beneficial effects in the treatment of diabetes [7].

The global use of medicinal plants for the management of diseases like diabetes has promptly increased over the last decade. It is stated that up to 72.8% of people with diabetes used herbal medicine. Moreover, a large number of medicinal plants are believed to possess anti-diabetic activities and have been utilized to control diabetes [2]. One of the medicinal plants that is emerging as a possible therapeutic agent for the management of DM is Fenugreek.

Fenugreek (*Trigonella foenum-graecum* L.) belongs to the botanical family Papilionaceae. Its native geographic range is the area extending from Iran to northern India, but it is presently cultivated also in other regions of the world [8][9]. Fenugreek is grown mostly for its seeds, seldom for straw as cattle forage, and fresh fenugreek leaves are consumed in some cuisines, including Indian. This species has been mainly used in medicine for centuries. Fenugreek seeds contain chemical compounds with medicinal properties, and in the past, they were consumed by pregnant women [10]. Fenugreek seeds, leaf extractions, roots and stems have scientifically proven antidiabetic, anticarcinogenic, antimicrobial, and other health promoting properties [11] [12]. It is worth noting that fenugreek seed fibers, which are composed mostly of non-starch polysaccharides (saponins, tannin, pectin, and others), lower the rate of glucose absorption in the intestines and regulate blood sugar levels. On account of those properties, fenugreek seeds are recommended for diabetes diets[13]. Fenugreek seeds contain chemical compounds which are highly valued in the cosmetics industry. Akhtar *et al*. (2010)[14] reported that

cream bases and cream formulations containing fenugreek seed extract substantially improved skin elasticity, hydration and skin's ability to resist photo-aging [14].

The main chemical constituents of *T. Foenum-graecum* are fibers, flavonoids, polysaccharides, tannins, saponins, flavonoids, polysaccharides fixed oils, and some identified alkaloids viz., trigonelline and choline [6]. Fenugreek seed in powder or germinated form exhibitsanti-diabetic properties, hypocholesterolaemic effect and effect on thyroxine-induced hyperglycaemia. Fenugreek seeds have been used as an oral insulin substitute, and seed extracts have been reported to lower blood glucose levels. The antidiabetic and the blood cholesterol lowering activity are linked to the fibre and galactomannan rich fraction present in the seed[15]. In animal experiments, it has been shown that oral administration of plant extract decreased the blood glucose levels. Administration of fenugreek seeds improved glucose metabolism and reduced hepatic and renal glucose-6-phosphatase and fructose−1, 6- biphosphatase activity [16].

This review aimed to describe the therapeutic effect of Fenugreek seed extract in the diabetic animal models.

Chemical composition of Fenugreek

The main chemical components of fenugreek seeds include galactomanans, 4-hydroxyisoleucine, a pseudo alkaloid trigonelline, steroids like sitosterol, steroidal saponins like trigogenin and gitogenin.

Besides these linoleic and linolenic acid; g-lactone, sotolone (responsible for characteristic odor); diosgenin, trigocoumarin, trigomethylcoumarin, fibre and mucilage is also present [15]. The anti-diabetic and the blood cholesterol lowering activity are linked to the fibre and galactomannan rich fraction present in the seed [15]. Fenugreek seeds are rich source of soluble dietary fiber content revealed that the fiber substance of fenugreek extricate assumes a job in its capacity to direct digestion of glucose in the stomach related tract [17].

Fenugreek seed is a rich source of vitamins viz. vitamin A (3 ug/100g), B1 (0.43 mg/100g), B2 (0.36 mg/100g), C (12-43 Mg/100g), nicotinic acid (1.1 Mg/100g) and niacin (6 mg/100g). Its leaves also contain vitamins, but on boiling, steaming or frying, 7-11% of them may be lost. Fenugreek seeds contain of potassium (603.0 mg/100g), magnesium (42.0 mg/100g), calcium (75.0 mg/100g), Zinc (2.4 mg/100g) and iron (25.8 mg/100g) [17].

2. Review of effect of Fenugreek on Type-2 diabetes mellitus

This review investigates the hypoglycemic property of Fenugreek and its protective effects in diabetes mellitus disease. Several of animal studies support the effectiveness of Fenugreek in reducing blood glucose in streptozotocin-induced, as well as alloxan-induced diabetes mellitus in rats, rabbits and individuals.

Serairi Beji *et al*., (2016)[18] study was to investigate the antidiabetic, antihyperlipidemic and antioxidant activities of fenugreek in alloxan induced diabetic rats. Animal's standard diet was supplemented with fenugreek (5%) for 30 days. The results showed that fenugreek supplementation in diabetic rats significantly decreased the levels of glucose (342.2 ± 23.9 mg/dl vs 171.0 ± 18.7 mg/dl; $p< 0.05$) compared to diabetic control group. Fenugreek has the potential to be used as a dietary supplement for the management of diabetes [18].

Ramesh Babu K *et al*., (2010)[19] study was assessed to find out the effective anti-diabetic dose of the fenugreek extract in alloxan induced diabetic rats. The diabetic rats were orally given fenugreek extract in doses 200 and 400 mg/kg for 21 days. A total number of 24 rats (18 diabetic rats, 6 normal rats) were used. The rats were divided into four groups of six each. The results of this study clearly shows the hypoglycaemic activity of the extract. *Trigonella* have been shown to lower blood glucose levels and partially restore the activities of key enzymes of carbohydrate and lipid metabolism close to normal values in various animal model systems [19].

El-Sadek *et al*., (2013) [20] study was performed to evaluate the glucose lowering effects of Olive leaves and Fenugreek leaves on diabetic rats. The diabetic rats were fed on basal diet containing different levels 2.5%, 5% and 7.5%Olive leaves and Fenugreek leaves, respectively. Results revealed that consuming diet containing 7.5% Olive leaves and 7.5% Fenugreek leaves lowers serum glucose level by 28.3% and 21.68% respectively and restoring all biochemical parameters to near normal levels as compared to positive control group [20].

Mowla *et al*.,(2009) [21] study was evaluated to the effects of ethanol extract of fenugreek seeds on the blood glucose levels in alloxan-induced diabetic rats at different doses (2g/kg, 1g/kg, 0.5g/kg and 0.1g/kg). The extract showed significant activity against the diabetic state induced by alloxan but the intensity of hypoglycemic effect varied from dose to dose. Comparative effect of different dose level of *T. foenum-graecum* on alloxan induced diabetic rats showed that 1gm/kg of extract has highest activity (39.32 %) which has decreased gradually for 2gm/kg (33.92 %), 0.5gm/kg (12.40 %), and 0.1 gm/kg (8.72 %), respectively [21].

Dizaye *et al*., (2016) [22] study was designed to evaluate the effect of *Trigonella foenum-graecum* seeds on blood glucose and insulin in diabetic rats. The whole seeds were delicately powdered. The plant powder was mixed at a concentration 0.75% (w/w) with a standard diet. The result of this study, showed that administration of *Trigonella foenum graecum* seeds (0.75%) to non diabetic rats did not exert any hypoglycemic or glucose lowering action and has no significant effect on the serum insulin. However, the same dose of *T. foenum graecum* seeds (0.75%) significantly reduced serum glucose of diabetic rats and induced a significant rise in serum insulin [22].

Prakash Sadashiv Ghadi *et al*., (2016)[23] study was evaluated the antidiabetic effects of *Trigonella foenum graecum* supplement in non- diabetic as well as in diabetic rats. The duration of the *Trigonella foenum graecum* supplement was 30 days with daily dose of supplement. The

results showed statistically significant reduction in the blood sugar levels of rats treated with Fenugreek in both diabetic and non-diabetic groups, in comparison to those without Fenugreek (p value < 0.0005). Fenugreek reveals significant anti-diabetic effect and anti-cholesterol effect through its insulin-like action on insulin receptors in hepatocytes and skeletal muscles [23].

Nadia Abdulkarim Salih, (2014) [24] study was conducted to investigate the effect of orally administered fenugreek in diabetic male rabbits experimentally induced by intra peritoneal injection of alloxan monohydrate 75 mg/kg. The diabetic rabbits treated with 2 and 3g/day single oral dose of fenugreek for 30 consecutive days respectively. Blood sample were taken at zero day, 2 weeks and 4 weeks for estimation of serum glucose. Oral administration of fenugreek showed a significant reduction in serum sugar in diabetic rabbits [24].

Kumar *et al.*,(2015) [25] study was evaluated the effect of fenugreek seeds taken orally in patients with type 2 diabetes mellitus (DM) with dyslipidemia after meeting inclusion and exclusion criteria. The 50 patients were divided into two groups (age matched). One group received 5g fenugreek seed powder four times a day before meal for 8 weeks and other group received drugs (oral hypoglycemic and hypolipidemic agents). Blood sugar (fasting) was recorded weekly. The results demonstrated after 8 weeks of treatment of fenugreek seeds in group 1 patients, there was a significant improvement in blood glucose Fasting level (178±72.4 to 104±28.2; $p < 0.0001$). This study concluded supports beneficial effects of fenugreek seeds on glycemia in patients with type 2 DM and can be used as an alternative in management of diabetes and its complications [25].

Subhani *et al.*,(2016) [26] study carried out to evaluate the effect of alcohol extract of fenugreek seeds on fasting blood glucose levels in alloxan induced diabetes in rabbits. The results demonstrated significant (P <0.001) reduction in the blood glucose levels in the alloxan induced diabetic rabbits in the 3 doses i.e. 0.5 gm/kg, 1 gm/kg and 1.5 gm/kg body weight after oral administration compared to the vehicle treated group (5ml of 2% gum acacia) orally over the period of 5 weeks[26].

Khosla *et al.*, (1995) [27] study was undertaken to study the effect of Fenugreek seeds on blood glucose levels in normal and alloxan induced diabetic rats. Thirty Wistar rats of either sex maintained on standard diet were administered unroasted Fenugreek seed powder mixed with the diet daily in a low dose of 2 g/kg and high dose of 8 g/kg body weight. Blood glucose level decreased significantly both in normal and diabetic rats following unroastecl Fenugreek seed powder administration. The hypoglycemic effect was more pronounced with higher dose. The percentage fall was 23.09% with high dose and 15.59% with the low dose in normal rats and 21.33% and l3.2% in diabetic rats respectively [27].

Sajad Arshadi *et al.*, (2015) [28] study was to investigate the hypoglycemic effect of fenugreek seed extract and its effects in combination with swimming exercise compared to glibenclamide consumption on type 2 diabetic rats. Eighty Wistar Kyoto male streptozotocin-induced diabetic rats were divided randomly into eight groups: diabetic control (C); fenugreek seed extract 0.8 g/kg (F1); fenugreek extract 1.6 g/kg (F2); swimming training (S); swimming training plus fenugreek extract 0.8 g/kg (SF1); swimming training plus fenugreek extract 1.6 g/kg (SF2); glibenclamide (G) and swimming training plus glibenclamide (SG). The rats were orally administrated with the treatments once a day with the respective treatment, and the training groups were subjected to swimming training every day for 60 min. The plasma glucose concentration levels in the F1, F2, S,SF1, SF2, G, and SG groups were significantly decreased compared to the C group ($p<0.05$), and among the groups, SF1 and SF2 groups exhibited the most reduction [28].

Sheikh *et al.*, (2019) [29] study was conducted to evaluate the antidiabetic effect of aqueous extract of fenugreek seed on normal and streptozotocin-Nicotinamide (STZ-NT) induced diabetic rats. The aqueous extracts were administered to STZ-NT induced diabetic rats at the dose of 500 mg/kg BW P.O. per day for 60 days. The results indicated that the aqueous extract of fenugreek posses beneficial effects for producing hypoglycemic effect in diabetic rats [29].

Koukhdan *et al.*, (2015) [30] study investigated the antidiabetic effect of *Trigonella foenum-graecum* L ethanolic extract on embryo of Streptozotocin STZ- (50 mg/kg) induced female diabetic rats. Diabetic mothers were given Fenugreek seed extract at a dose of 1000 mg/kg daily for 21 days. The result shown that administration of Fenugreek seed extract(1000mg/kg) reduced the blood glucose significantly so that it reached 123.5 ± 4.342 mg/dl and 121.2 ± 4.258 mg/dl at the end of 18 and 20 days ($p<0.05$)[30].

Roja Rani *et al.*, (2017) [31] study aimed to find a dose of aqueous extract of *Trigonella foenum-graecum* seed powder effective to reduce hyperglycemia. Male albino Wistar rats were procured and diabetes was induced by a single dose intraperitoneal injection of120 mg/kg b.w Alloxan monohydrate. The anti-diabetic effect of two different doses (400 and 800 mg/kg b.w) of the fenugreek seed extract. The results of the study showed that fenugreek given in a dose of 800 mg/kg is a good effective method of controlling diabetes [31].

Abor M.M. Abd El Rahman., (2014) [32] study was investigated the hypoglycemic and hypolipidemic effects of fenugreek on forty-two Sprague Dawley adult male rats. Seven rats kept as Negative control (-ve) and 35 Streptozotocin induced diabetic rats. The diabetic rats were classified into positive control (+ve) and four treated groups which were fenugreek powder (5% in diet), aqueous extract, methanolic extract (3mg/kg body weight) and oil (5% in diet). The experiment period was 60 days. Compared with control (+ve) group, the four treated groups showed significant decrease in glucose, glucosalated heamoglobin (HbAIC %) and fructose amine (FA) values, but significant increased in insulin [32].

Saadh MJ., (2020) [33] study aimed to evaluate the hypoglycemic effects of oral administration of 2 g/kg

fenugreek seeds per day for 4 weeks in alloxan-induce diabetic albino rats. Oral administration of fenugreek seeds for 2 weeks resulted in significant improvement in body weight, blood glucose levels, glycosylated hemoglobin (HbA1c) in diabetic rats. After 4 weeks, this ameliorative effect was significantly elevated with respect to blood glucose (155.00±9.70 mg/dL vs. 427.50±5.70 mg/dL; $p<0.001$), HbA1c (5.5±0.19% vs. 13.65±1.77%; $p<0.001$), as compared with non-treated diabetic rats. This study concluded that fenugreek seeds possess hypoglycemic properties and could be used as natural compounds that are suitable as parent compounds for the development of new anti- diabetic drugs [33].

Marzouk *et al.*, (2013) [34] study was conducted to investigate the anti- diabetic and antioxidative effects of water suspension of Fenugreek seeds powder (1 g/kg b.wt.) for 30 days in Streptozotocin (STZ)(50 mg/kg, i.p.) induced diabetic rats. Fenugreek seeds supplementation significantly decreased STZ-induced hyperglycemia and the percentage reduction was 53.66% in comparison with the diabetic control. This study suggests that fenugreek seeds powder supplementation may be beneficial for preventing diabetic complications in this animal model [27].

D. V. Joshi *et al.*, (2015) [35] study evaluated the effect of hydroalcoholic extract of *Trigonella foenum-graecum* seeds (HEF) on alloxan-induced type-II diabetic rat model in different doses (500, 1000, and 2000 mg/kg), glimepiride (4 mg/kg), and combination of HEF (500 mg/kg) + glimepiride (2 mg/kg), on alloxan-induced diabetic rats. The results demonstrated that the treatment with HEF (at different doses), glimepiride, and HEF + glimepiride increased body weight and glucose uptake, reduced plasma glucose, glycosylated hemoglobin, liver glucose transport. The study suggests that HEF may be useful as an adjuvant with clinically effective anti-diabetic drugs in the management of type-II diabetes [35].

From the results of previous studies with diabetic rats and rabbits support the notion that fenugreek supplements have hypoglycemic effects.

Possible Mechanism of action of Fenugreek in diabetes mellitus

Fenugreek seed extracts have been reported to exhibit anti-diabetic potential by delaying both gastric emptying time and rate of glucose absorption. It reduced uptake of glucose in the small intestine mainly due to its high fiber content that slows the metabolism of carbohydrates and lowered blood glucose. It also restores the function of pancreatic tissues, protecting β-cells, evaluating serum insulin level possibly through the regeneration of β-cells or stimulation of insulin release by the existing β- islet cells. Besides it corrects the insulin-sensitive carbohydrate metabolic enzymes activities, serum lipid profiles, prevents lipid peroxidation, restores glutathione and superoxide dismutase (liver and pancreas), enhances insulin sensitivity, improving insulin action at cellular level, and recovers the level of HbA1c by utilization of glucose in peripheral tissues where by maintain the blood glucose level [17].

Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renalglucose-6-phosphatase and fructose –1, 6-biphosphataseactivity [36].

Insulin stimulates cellular glucose uptake in muscle and adipose tissues by inducing the translocation of glucosetransporter-4 (Glut-4) from an intracellular pool to the plasma membrane. In the diabetic state, because of deficiency of insulin, Glut-4 translocation does not take place efficiently and Glut-4 transporters remain inside, where they are not functional. This results in decreased uptake of glucose by muscle cells, which contribute significantly to the elevated blood glucose levels. Therefore, restoration of Glut-4 will achieve normoglycaemia. The effectiveness of the antidiabetic compounds vanadate and Trigonella have been successfully used to reverse the diabetes effect on the Glut-4 transporter to normal levels in experimental diabetes [37].

The seeds contain up to 50% mucilaginous fibre. Other seed constituents include 4-hydroxyisoleucine, an amino acid, and fenugreekine. Fenugreek is thought to delay gastric emptying, slow carbohydrate absorption, and inhibit glucose transport. It has been shown to increase erythrocyte insulin receptors and improve peripheral glucose utilization, thus showing potential pancreatic as well as extrapancreatic effects. Various components of the seeds have varying activities. For example, the component called fenugreekine, a steroidal sapogenin peptide ester, may have hypoglycaemic properties [16].

3. Conclusion

The above studies confirm that fenugreek possesses potent hypoglycemic properties in diabetic rats and rabbits; therefore, we believe fenugreek to be a significant therapeutic tool for attenuating and inhibiting diabetic complications. However, further investigations are required to confirm the specific mechanisms to identify the active ingredients of fenugreek and to test its efficacy in improving and prolonging a patient's life.

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