TRIGONELLA FOENUM : A REVIEW OF HYPOGLYCEMIC ACTIVITY

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Abstract. Treatment of diabetes mellitus is intended to reduce the risk of blindness, kidney failure, neuropathy and heart disease that can develop due to the chronic increase in the blood glucose level. The selected hypoglycemic agents should be effective, safe and readily available. The widely used agents work by interrupting enzymes responsible for glucose regulation. Those enzymes are α-amilase, α-glucosidase, dipeptidyl peptidase-IV, aldose reductase and angiotensin converting enzyme. A medicinal plant, fenugreek (Trigonella foenum-graecum) has been used as an antidiabetic folk medicine. This review provides information related to in vitro studies showing antihyperglycemic activity of fenugreek along with an in vivo study in animals. In addition, potential phytochemicals that have been isolated from this plant are described and play a role in the searching for the most potent agents for diabetes mellitus therapy.

Keywords: diabetes mellitus, enzymes, Trigonella foenum-graecum

I INTRODUCTION

Diabetes is a chronic disease characterized by an increase in glucose level as the result of insufficient insulin production, and/or decreased glucose uptake by cells, and is sometimes associated with free radical formation [1]. Diabetes therapy includes insulin for type I diabetes and antidiabetic oral (ADO) drugs for type II diabetes. Due to adverse effects of ADOs and economic reasons in some areas, herbal medicines have been widely used as an alternative therapy even in children [2]. Since the use of these natural sources is common, their safety and effectiveness should be ascertained. Herbal medicine is known to be effective in improving diabetes by several mechanisms one of which is by inhibiting enzymes regulating glucose metabolism. These include α-amylase, α-glucosidase, dipeptidyl peptidase-IV (DPP-IV), aldose reductase and angiotensin converting enzyme (ACE). The suppression of these enzymes by secondary metabolites found in medicinal plants cause the release of insulin, and increase glucose uptake thereby lowering the glucose level in the blood. Flavonoids inhibit α-amylase, α-glucosidase, aldose reductase and ACE. Triterpenoids and phenolic compounds disrupt DPP-IV [3].

Among medicinal plants, fenugreek is one that has been extensively studied due to its promising activity against diabetes. In daily use, fenugreek is usually mixed with other spices used as cooking ingredients, boiled and prepared like tea or as syrup, or combined with vanilla in cakes. Different parts of fenugreek have been used as folk medicine and have been noted to show potent anticancer, antioxidant, antidiabetic, antihyperlipidemic, and anti-inflammatory activity [4]. Some researchers have examined its action against enzymes and have isolated compounds from it that contribute to its in hypoglycemic activity which will be described below.
In vitro study on activity against glucose regulating enzymes

against α-amylase

α-amylase plays a role in the breakdown of starch at the first step by stimulating the lysis of the 1,4-glucosidase bond. The inhibition of this enzyme decreases the absorption of glucose into the bloodstream, which is reflected in a lower postprandial glucose value. 

Table 1 Activity of fenugreek against enzymes

<table>
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<th>Trigonella extract</th>
<th>Affected enzymes</th>
<th>References</th>
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<td>Ethyl acetate</td>
<td>α-amylase, α-</td>
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<tr>
<td></td>
<td>glucosidase</td>
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<td>Methanolic extract of leaves</td>
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<td>Angiotensin converting enzyme (ACE)</td>
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A study on extracts of fenugreek leaves showed that the ethyl acetate extract demonstrated a better inhibitory activity (250 μg/mL giving 64.55% inhibition) against α-amylase compared to the water extract [5]. Using 4 different solvents (methanol, chloroform, dichloromethane, hexane), another study determined the IC₅₀ of a seed extract, which showed moderate to weak inhibition activity (IC₅₀ less than 127 μg/mL) with the methanol extract showing the best activity [6]. A combination of omega 3 and fenugreek terpene disrupted amylase and maltase, thereby leading to a decline in blood glucose level [9].

Activity against α-glucosidase

α-glucosidase is involved in breaking carbohydrates down to release glucose. Similar to its activity against α-amylase, the leaves of fenugreek extracted using ethyl acetate showing more potent activity against glucosidase compared with the water extract glucosidase [5]. The seed extract displayed medium to minor activity against the enzyme (IC₅₀ less than 61 μg/mL) using different polar solvents (methanol, chloroform, dichloromethane, hexane) with methanol showing the best activity [6].

Activity against DPP-IV

DPP-IV contributes to the severity of diabetes. DPP-IV degrades GLP-1, another enzyme that stimulates insulin production and suppresses the release of glucagon [10]. Inhibition of DPP-IV results in a decrease in glucose levels in the blood. Sitagliptin is one of the conventional drugs that works by disrupting DPP-IV and corrects HbA1c level after 2-3 months of use [11]. Since its approval for clinical use, its adverse effects had not been documented sufficiently. Therefore, research into a better DPP-IV antagonist is ongoing. Some Indonesian medicinal plants demonstrated excellent activities against DPP-IV, and one of them is fenugreek. An ethanol extract of fenugreek seeds showed a potent inhibitory activity (71.29±0.33%) against DPP-IV which was almost similar to the standard drug, sitagliptin (74.77±0.3%) [7]. This finding could be a start to produce a new DPP-IV antagonist with fewer adverse effects.

Activity against aldose reductase

In a two-step process named the polyol pathway, aldose reductase converts glucose to sorbitol with the help of cofactor NADPH followed by the metabolism of sorbitol to fructose. This process contributes to the development of diabetes complications in which hyperglycemia causes more glucose to enter the polyol pathway. In one study, an aqueous extract of fenugreek seed inhibited the rat lens aldose reductase enzyme with IC₅₀ 0.24± 0.03 mg/mL [8]. Phytochemicals of fenugreek demonstrated a great affinity to aldose reductase which meant that they bound tightly to the enzyme and thereby could maximize their inhibitory activity [12].

Activity against ACE

ACE activity is associated with diabetes severity. ACE inhibitors such as captopril prevent diabetic complications such as heart disease and retinopathy (Ramos-nino & Blumen 2009). In diabetic rats, the activity of plasma ACE increased 45% compared to normal rats. Terpene from fenugreek combined with omega 3 decreased ACE activity as much 38% [13].

Isolated Antidiabetic Compounds

An ethanol extract of fenugreek showed excellent antioxidant activity. Using several different methods, one study revealed the presence of phenolic components, tannins and flavonoids [14]. There have been researchers that succeeded in isolating compounds contributing to hypoglycemic actions. They were trigonelline, 4-hydroxyisoleucine (4-HIL), diosgenin, quercetin, and galactomannan, depicted in Table 2. Trigonelline is one of the alkaloids detected in fenugreek seeds. The compound showed a hypoglycemic effect that was higher compared to a crude extract of fenugreek [15].
This highlights the importance of purification to obtain trigonelline in order to produce better antidiabetic activity. A study that employed experimental rats fed high fat diet and low dose streptozosin succeeded in producing a diabetic rat model that was used to examine the pure trigonelline’s antihyperglycemia effect. Trigonelline 150 mg/kg was given orally to diabetic rats. All observed parameters were compared to normal rats, an untreated diabetic group and a metformin-treated group. The parameters were oral glucose tolerance profile, fasting blood glucose level, glycosylated hemoglobin (HbA1c), insulin resistance, glucose content, and lipid parameters. The results showed that the administration of trigonelline restored the ability of the body to manage glucose levels. The trigonelline-treated rats showed almost similar glucose tolerance profiles to normal and metformin-treated rats in which glucose level significantly decreased after 60 minutes. This was different from the untreated diabetic group where the decline in glucose level was very slow, from 60 to 120 minutes. Trigonelline also improved the fasting blood glucose level (136.86 ± 5.31 (mg/dl)), insulin resistance (12.08 ± 0.35 µU/ml) and HbA1c (7.14 ± 0.35%). The study also showed an improvement in glucose content along with the repair of hepatic cells as reflected by a decrease in ALT [19].

4-hydroxyisoleucine (4-HIL), is an amino acid isolated from fenugreek seeds. It was observed to benefit insulin-resistant diabetic and obese patients [20]. The intravenous injection of 4-HIL (18 mg/kg) into normal rats stimulated the release of insulin and reduced glucose in a greater amount (2-3 fold) compared to control rats (without 4-HIL). Daily administration of 4-HIL (50 mg/kg) for 6 days resulted in a better glucose tolerance profile (higher release and a lower blood glucose level) compared to diabetic rats [21]. It also improved the activity of 4-HIL which was slightly better (fasting blood glucose: 173.6 ± 7.4 mg/dl) than fenofibrate (180.0 ± 8.3 mg/dl). 4-HIL increased expression of genes (AMPK, AKT, PPARGC1A and PPARGC1B) responsible for mitochondrial biogenesis and increased expression of glucose transporter, which in turn increased glucose use[22].

Fenugreek saponin was identified to have hypoglycemic activity shown as an increase in free hemoglobin. It was later found that one of the therapeutic saponins was diosgenin. The oral administration of 10 mg/kg diosgenin improved glucose level, HbA1c level and antioxidant enzymes after 30 days of use. No toxic effect was observed after the use of 500 mg/kg [17].

The polyphenolic fraction of fenugreek displayed antihyperglycemic actions when given 200 mg/kg to fructose-fed rats. Its antidiabetic activity was comparable to standard quercetin and metformin. Quercetin was isolated from fenugreek stems [4]. It was observed to reduce STZ-induced rat blood glucose and glycated hemoglobin at a dose of 100 mg/kg [23].

Galactomannan is a soluble fiber detected in fenugreek seeds. It is part of a class of polysaccharides that prevent the absorption of glucose by disrupting glucose regulating enzymes [13]. Consumption of galactomannan (2.5 - 5% of the diet) by sucrose-fed rats reduced their body weight, meal amount intake
and insulin level in the blood [24]. A study evaluating the effect of using 50, 100, and 200 mg/kg galactomannan in alloxan-induced rats revealed that the hypoglycemic activity increased with an increased dose [18].

CONCLUSION

Fenugreek exerts a promising hypoglycemic action by inhibiting the glucose regulating enzymes, α-amylase, α-glucosidase, dipeptidyl peptidase-IV, aldose reductase and ACE. Compounds isolated from fenugreek also demonstrated effects on lowering blood glucose levels. Future research should investigate its effectiveness and safety in humans or identification of other therapeutic compounds for diabetes treatment.

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Trigonella foenum: a review of hypoglycemic activity
(Suryawati, Sairida, Firdausa Sarah, Azizah Vonna and Vera Dewi Muli)


