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## REVIEW PAPER

# *Trigonella foenum-graecum* seeds in treatment of metabolic syndrome

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## Summary

Fenugreek has a long tradition of use as a medicine and also has been commonly used as food in many countries. This plant is well known, especially in Asia. In Europe, fenugreek seeds are regarded as a traditional herbal medicine consumed in case of loss of appetite and in confirmed skin inflammations. *Trigonella foenum-graecum* seeds contain wide spectrum of different biologically active constituents which affect the properties of preparations produced from this plant. Numerous preclinical studies confirm the use of fenugreek as a hypolipidemic and lowering blood glucose level drug. Unfortunately, there are not many clinical studies on fenugreek seeds in this area. Published studies often significantly differ in the amount and type of fenugreek seed preparation used. However, results of available scientific research are promising and suggest the possibility of using fenugreek seeds in metabolic syndrome therapy. Undoubtedly, further research is required to confirm such properties of *Trigonella foenum-graecum*.

**Key words:** *fenugreek (Trigonella foenum-graecum L.), metabolic syndrome, fenugreek seeds*

**Słowa kluczowe:** *kozieradka pospolita (Trigonella foenum-graecum L.), zespół metaboliczny, nasiona kozieradki*

## INTRODUCTION

Metabolic syndrome is a clustering of at least three of following five clinical conditions: abdominal obesity, hypertension, high blood glucose, high triglycerides

and low high-density lipoprotein cholesterol levels. Several definitions of metabolic syndrome have been proposed, with varied requirements [1].

Modified WHO definition includes hyperinsulinaemia (the upper fourth of the fasting insulin level among

non-diabetic subjects) or hyperglycaemia (fasting glucose  $\geq 110$  mg/dl) in addition to at least two of the following: waist girth  $\geq 94$  cm, dyslipidaemia (triglycerides  $\geq 150$  mg/dl or HDL  $< 40$  mg/dl), or blood pressure (BP  $\geq 140/90$  mmHg) or intake of BP medication [2].

Diagnosis of metabolic syndrome significantly increases a risk of cardiovascular disease and type 2 diabetes development over 5 to 10 years.

Currently, change of the lifestyle: diet and exercise leading to weight loss and pharmacological treatment of atherogenic dyslipidaemia, hypertension, and hyperglycaemia are the available options in handling metabolic syndrome [1].

However, it is also well known that several herbs may modulate at least some symptoms of metabolic syndrome. One of them is fenugreek (*Trigonella foenum-graecum* L.). Its seeds have been used in folk medicine for ages in the treatment of different disease symptoms. Moreover, according to traditional Chinese and Hindu medicine Fenugreek seeds may lower glucose level in blood [3, 4]. Therefore, fenugreek may be useful in modulation of metabolic syndrome.

## GENERAL DESCRIPTION

### Biologically active components of fenugreek seeds

Fenugreek (*Trigonella foenum-graecum* L.) belongs to *Fabaceae* family, formerly named *Papilionaceae*. The raw plant material is fenugreek seeds (*Foenugraeci semen*) containing 25–45% of mucous substances – galactomannan, proteins, 25–30% free amino acids (rich in tryptophan and lysine), alkaloids (trigonelline up to 0.37%), 0.1–0.3% steroidal saponins (diosgenin derivatives, yamogenins, tigenins, gitogenins, glycosidic combinations: trigofenosides, foenugraceina, greekine), 7–8% lipids (phospholipids, glycolipids), sterols, lecithin, choline (0.05%), flavonoids (isoorientin, isovitexin, orientin, saponarin, witextin 7-O-glucoside), 0.04% essential oil, vitamins and mineral salts. The following groups of mucous substances, steroidal saponins, alkaloids compounds are considered as antidiabetic and cholesterol-lowering factors.

### Uses of fenugreek

Fenugreek seeds have been used in traditional medicine for diarrhea, as an expectorant, appetite

stimulator as well as to shield and healing wounds. According to EMA, the traditional herbal medicinal product was used in the treatment of minor skin inflammations and in temporary loss of appetite.

Many reports have been published in the scientific literature on antidiabetic and hypolipidemic properties of preparations from *T. foenum-graecum*. The most important of them are described below.

## HYPOLIPIDEMIC ACTIVITY OF FENUGREEK SEEDS

### *In vivo* experiments

The studies concerned the use of fenugreek seeds supplementation at 15%, 30%, and 60% in the diet causing hypercholesterolaemia in rats. It was observed depending on the increase in biliary and cholesterol content in faeces. The cholesterol level in serum was also inhibited ( $p < 0.001$ ) [5]. Seed added in an amount of 30% higher in the rats dietary cholesterol for 4 weeks caused a significant reduction in serum cholesterol (210 mg/dl ( $p < 0.001$ ) in the control group (423 mg/dl).

Two fractions of degreased seeds – one polysaccharide fraction and second fraction of crude saponins given to rats in an amount corresponding to 30% of fenugreek seed content also reduced serum cholesterol level. Results obtained showed that the lipid fraction and isolated trigonelline do not reduce cholesterol. In these studies, there were no changes in triglyceride levels when fenugreek seeds or their individual fractions were administered ( $p < 0.001$ ) [6].

In other studies, the ethanol extract from defatted fenugreek seeds was added to the diet of hypercholesterolaemic rats at a dose of 30–50 g/kg and caused a reduction in the level of cholesterol in the blood plasma ( $p < 0.05$ ). This effect was attributed to the saponin present in the extract [7].

Seeds of *T. foenum-graecum* were extracted with ethanol and next the extract was fractionated with chloroform and n-butanol. The resulting aqueous fraction was subjected to silica gel column chromatography using ethyl acetate and methanol to obtain the amino acid 4-hydroxyisoleucine 5 (750 mg). The effect of oral administration of the amino acid in an amount of 50 mg/kg body weight of hamsters for 7 days on high-fat diet (HFD) was studied. It was observed a statistically significant decrease in plasma triglyceride levels by 33%, total cholesterol (TC) by 22% and free fatty acids 14% [8].

## Clinical studies

In a randomized, cross-sectional studies, the properties of hypolipidaemic fenugreek seeds were checked in 10 healthy volunteers with asymptomatic hyperlipidaemia (serum cholesterol >240 mg/dl). The volunteers used the isocaloric diet for two consecutive periods of 20 days, in second period of diet they were given 2 x 50 g of bitterness-free fenugreek seeds (no lipids and saponins). The use of fenugreek significantly reduced the level of total cholesterol by 24.4%, LDL and VLDL cholesterol by 31.7% and the level of triglycerides by 37.7% ( $p < 0.001$  for all parameters), while HDL cholesterol levels did not change [9].

Sprouting seeds of *T. foenum-graecum* clearly cause changes in the content of soluble fibre. The powdered preparation of these seeds was given to healthy volunteers (vegetarians) who consumed relatively low doses of cholesterol with food – 12.5 g (n=10) daily or 18 g for one month. In this experiment, a dose-dependent hypocholesterolaemic effect was observed with a significant reduction in blood plasma levels of total cholesterol and LDL-cholesterol in the group with 18 g of cholesterol in the diet. This effect was not observed in the group of a dose of 12.5 g of cholesterol. HDL- and VLDL-cholesterol as well as triglyceride levels did not change significantly in any of the groups [10].

The authors noticed, based on *in vivo* and clinical studies, that the hypocholesterolaemic effect is associated with an increase in cholesterol metabolism by accelerating its conversion to bile acids and their excretion in a complex with fibre. The compounds contained in fenugreek inhibit the activity of lipase, which also delays the absorption of fats [11].

## ANTIDIABETIC ACTIVITY OF FENUGREEK SEEDS

### *In vivo* experiments

Gastrointestinal preparation of defatted fenugreek seeds (rich in fibre: 79.4%) at a dose of 1.86 g/kg body weight per day for 8 days, reduced hyperglycaemia and hypercholesterolemic effect in dogs with alloxin diabetes ( $p < 0.05$ ) [12].

In other research with significant blood glucose ( $p < 0.02$ ), serum glucagon ( $p < 0.01$ ) and plasma cholesterol after the addition of a defatted fenugreek

seed formulation to the diet (53.9% fibrin), 4.8% saponin steroids at a dose of 1.86 g/kg/day for 8 days. Administration of defatted seeds at this level in the diet of dogs with diabetes and hypercholesterolemia at lowering cholesterol ( $p < 0.02$ ) and lowering hyperglycaemia ( $p < 0.05$ ) [13].

Isolated trigonellin administered after alimentary rats with alloxane-induced diabetes at a dose of 50 mg/kg body weight had a significant hypoglycaemic effect lasting 24 hours [14].

Coumarin, a secondary component of fenugreek seed at a dose of 250 mg/kg and 1 g/kg, caused a hypoglycaemic effect for a minimum of 24 hours in rats with alloxan diabetes as well as in healthy animals, however, at this dose level it caused toxicity [15].

A single dose of 0.5 ml decoctions (1:7.5 or 1:15) from fenugreek seeds administered alimentary to mice with alloxin diabetes, as well as to healthy animals induced with a dose-dependent hypoglycaemic effect reached a maximum after 6 hours from administration ( $p < 0.0005$ ). The occurrence of dose-dependent hypoglycaemia was also observed after ingestion of dry, ethanolic fenugreek seed extract (21:1) in mice with alloxan diabetes in a dose of 200–400 mg/kg. The 200 mg/kg extracts produced a similar effect as tolbutamide at the same dose [16].

The dry, water-ethanol extract of fenugreek seed (12.5% steroid saponins, 4.8% free amino acids) given with rats at a dose of 10 mg per 300 g body weight per day for 14 days caused a significant increase in the level of insulin in the blood plasma ( $p < 0.01$ ), as compared to control group [17].

The effect of ethanolic extract of *T. foenum-graecum* seeds (fenugreek) on the level of glucose in blood of rats with alloxane-induced diabetes at doses of 2 g/kg, 1 g/kg, 0.5 g/kg and 0.1 g/kg was investigated. Hypoglycaemic effects of the extract was compared with a single dose of a standard antidiabetic drug – glimepiride administered in an amount of 4 mg/kg. The extract showed significant anti-diabetic activity. The most effective dose was 1 g/kg, but less effective than the standard antidiabetic medication. No acute toxicity was observed for the ethanol extract from *T. foenum-graecum* seeds when given orally at high dose levels (3 g/kg body weight). The fenugreek seed extract was a rich source of mainly steroid alkaloids and carbohydrates [18].

The next study determined the antihyperglycaemic activity of *T. foenum-graecum* L. (fenugreek) seed and the effect on GLUT-2 protein expression in pancreatic  $\beta$  cells in rats with streptozotocin-induced diabetes. Tested rats were divided into groups. Group 1 was the control group, groups

2–5 consisted of animals with STZ-NA-induced diabetes: group 2 was the negative control group (CMC Na 1%) and group 3 was the positive control group (glibenclamide); groups 4 and 5 were administered the ethanol extract from fenugreek seeds (in an amount of 100 mg/kg body weight and 200 mg/kg body weight). The formulation was administered orally for 14 days. Results obtained showed that extract from fenugreek seeds at a dose of 200 mg/kg of decreased the blood glucose level and increased the density of the GLUT-2 protein in pancreatic  $\beta$  cells [19].

The antidiabetic activity of standardized *T. foenum-graecum* seed extract (IND01) has been determined. Diabetes (DM) was induced in neonatal rats with streptozotocin (n-STZ 50 mg/kg *i.p.*). After 8 weeks, diabetes was confirmed by checking the level of fasting serum glucose. The effect of fenugreek extract (IND01 100 mg/kg, orally) was compared to standard drug – glyburide (10 mg/kg, *per os*). Rat body weights and serum glucose levels were evaluated every day after 0, 2, 4, 6 and 24 hours (group 1) and after 7, 14, 21 and 28 days (group 2). Glycosylated hemoglobin (HbA1c) levels and serum insulin levels were measured on day 28 (group 2). Administration of streptozotocin resulted in an increase of serum glucose, weight gain and HbA1c levels in 28 days. Treatment with IND01 fenugreek extract (100 mg/kg, *per os*) and glyburide (10 mg/kg, *per os*) resulted in the reduction of changes induced by n-STZ. Histopathological examination of the pancreas of the group treated with IND01 (but not with glyburide) showed an increase in the number and size of  $\beta$ -cell pancreatic islets. IND01 has the potential to alleviate DM symptoms and improve glycaemic function in diabetic rats with induced n-STZ [20].

The study performed by Kumar *et al.* consisted of administration of 21 IU insulin per day plus diet with 5% powdered seeds of *T. foenum-graecum* (TSP) to rats with alloxane-induced diabetes (15 mg/100 g body weight). Next, blood glucose oxidase levels, monoamine (MAO), membrane fluidity, neurolipofuscin content, DNA degradation and glucose-4 transporter accumulation (GLUT4) were checked. Increase has been reported in diabetic rats both in MAO activity and the degradation of the genomic DNA in brain. These observations support the hypothesis that oxidative stress is associated with catecholamine oxidation and loss of membrane fluidity and a rise in neurolipofuscin as well as reduced expression of GLUT4 in the brain. It was found that consumption of fenugreek seeds leads to antidiabetic and neuroprotective effects [21].

In another study, rats with streptozotocin-induced diabetes were given fenugreek seeds in an amount of 0.5 g and 1 g/500 ml of water. Animal blood glucose, total cholesterol, triacylglycerol and insulin levels were analysed, and the activity of 6-phosphofructo-1-kinase (PFK-1) in liver and intestinal mucosa was examined. It was noted that in diabetic rats, PFK-1 activity in liver and intestinal mucosa was significantly lower, as compared to control rats. It was also observed that in diabetic rats treated with 1.0 g fenugreek seeds, PFK-1 activity in the liver and intestinal mucosa increased by 54% and 75%, respectively. In this group of rats, total cholesterol and triacylglycerol levels decreased by 57% and 42%, respectively. In addition, plasma glucose in rats treated with 0.5 g and 1.0 g fenugreek seeds decreased by 32% and 43%, respectively [22].

### Clinical studies

In randomized crossover study, 8 healthy volunteers were tested for glucose tolerance to 100 g glucose in 250 ml of fluid. After a week, glucose was re-administered in the same manner, but 25 g of fenugreek seed powder was additionally added. Compared to the results of studies after the administration of glucose alone, the results of the administration of fenugreek seed showed a significant reduction in plasma glucose after 30 and 60 minutes ( $p < 0.05$ ) and glucose AUC (glucose dependence in time) by 42.2% ( $p < 0.001$ ) [23].

There are also available research data, in which fenugreek seed formulation administered orally to 30 healthy volunteers at a dose of 2.5 g two times daily for 3 months did not cause changes in blood lipid profile or glucose level (fasting or postprandial) [24].

In the next study carried out in 21 patients with type II diabetes, the same type of diet was used for 4 to 7 days. Powdered fenugreek seed preparation at a dose of 15 g of was added to the meals. At the end of the experiment, a significant reduction in postprandial glucose was observed 2 hours after a meal ( $p < 0.05$ ). However, there were no changes in the level of cholesterol or triglycerides. The level of insulin in the blood plasma decreased. However, these data were not statistically significant [25].

In a randomized, cross-sectional clinical study on 10 patients with non-insulin-dependent diabetes, hypoglycaemic effects was analysed. They received an isocaloric diet enriched with fenugreek seed: 12.5 g twice a day, for 15 days. The test included glucose tolerance. Significant reduction in mean plasma



glucose level after oral administration ( $p < 0.05$  after 40 minutes,  $p < 0.02$  after 60 minutes) and a decrease in glucose AUC was observed. In addition, the use of the preparation significantly shortened the plasma half-life of glucose ( $p < 0.02$ ). A significant increase in the number of insulin receptors on erythrocytes ( $p < 0.02$ ) was also observed. The results suggest that preparations from *T. foenum-graecum* seeds may improve peripheral glucose utilization and showed hypoglycaemic effects [26].

In another placebo-controlled clinical trial, 30 patients with type 2 diabetes and coronary heart disease received a fenugreek seed powder formulation at a dose of 2.5 g twice a day, for 3 months. Compared to 30 patients with placebo-treated disease, patients administered with a fenugreek seeds formulation achieved a reduction in serum cholesterol as well as triglycerol levels (for both  $p < 0.01$  in 3 months, related to baseline). The level of HDL-cholesterol has not changed significantly [24].

In the same study, a group of patients with moderate ( $n = 20$ ) or advanced ( $n = 20$ ) type 2 diabetes, but without coronary heart disease received fenugreek at identical doses for one month. Postprandial, as well as fasting glucose, were significantly lowered in subjects with moderate diabetes ( $p < 0.01$ ). This effect was not observed in the advanced stage of diabetes. Surprisingly, the same dose administered to 30 healthy volunteers for 3 months did not cause the effects observed earlier [24].

Oral administration of 500 mg trigonellines induced a transient hypoglycaemic effect within 2 hours in 5 of 10 patients with diabetes. In others, the effect was weak or not observed at all. A two or four fold increase in the dose did not increase the hypoglycaemic effect. Administration of 500–1000 mg trigonelline 3 times a day for 5 days did not cause a decrease in daily blood glucose level [14].

A single randomized trial was performed, in which 10 patients with type 1 diabetes received a fenugreek seed formulation without any bitterness (saponins and lipids), twice a day, 50 g each with an isocaloric diet for 10 days. At the end of the study, patients were tested for glucose tolerance. The diet enriched with fenugreek caused a significant decrease in mean fasting blood glucose ( $p < 0.01$ ). Glucose levels were also reduced after 30, 60 and 90 minutes, decreasing the AUC for glucose ( $p < 0.05$ ). A significant decrease in total cholesterol, VLDL cholesterol, LDL cholesterol and triglycerides was also observed. This effect was not observed in HDL and insulin levels [27].

Inclusion of bitterness-free (saponin-lipid-free) fenugreek seed preparation to meals of 5 patients

with type 2 diabetes mellitus at a dose of 12.5 g per day for 21 days caused significant progress of glucose tolerance. These tests showed a decrease in plasma glucose level over 30, 60, 120 and 150 minutes ( $p < 0.05$ ) as well as AUC glucose ( $p < 0.05$ ). Reduction of glucose level in urine during its daily collection was also observed ( $p < 0.05$ ), along with decrease of serum cholesterol level [23].

In other randomized, cross-sectional clinical study 15 patients with type 2 diabetes had the same type of diet. In some patients 50 g free from bitterness (free from saponins and lipids) fenugreek seeds preparation two times daily were used, for 10 days. The use of the test preparation caused a decrease in fasting glucose level ( $p < 0.01$ ), progress in glucose tolerance test ( $p < 0.01$  in 30–120 minutes) and a 64% reduction in urinary glucose excretion (daily collection,  $p < 0.05$ ). Serum insulin levels were also reduced in patients who received a fenugreek seed ( $p < 0.05$ ). Significant changes were observed in the level of serum lipids. The LDL- and VLDL-cholesterol fraction as well as triglyceride level was reduced ( $p < 0.001$ ). The level of HDL-cholesterol has not changed. To extend the study, the same type of therapy was used for next 20 days in 5 patients with type 2 diabetes. At the end of the study, changes in patients were observed that had not occurred before, but with a greater severity for the parameters tested [28].

In a further crossover study, 6 patients with type 2 diabetes were given 12.5 g of powdered fenugreek seed in 7 consecutive days of diet. Then, after a 7-day break, this diet was used for the control group. On the basis of postprandial glucose level and AUC glucose it was concluded that fenugreek significantly reduces response related to the amount of glucose in blood ( $p < 0.05$ ) in both groups of patients [29].

Results from the clinical study are also available, in which 60 patients with mild, moderate and severe non-insulin-dependent diabetes, as well as 10 healthy volunteers in the control group, were administered 12.5 g of fenugreek seed powder 2 times a day for 24 weeks. The entire study was proceeded by a 7-day initial period, which, like the basic study, was characterized by a similar, isocaloric diet. A decrease in the fasting blood glucose level, reduction of urinary glucose excretion in daily collection ( $p < 0.001$ ) and also progress in the glucose tolerance test was observed in the study group. The level of insulin also decreased. The level of glycosylated hemoglobin measured after 8 days of fenugreek seed was also significantly reduced ( $p < 0.001$ ) [30].

In patients with diabetes, a decrease in the level of lipids, in particular total cholesterol, LDL-, VLDL-cholesterol and serum triglycerides (for all listed

$p < 0.001$  after 24 months) was also observed [31].

In the next study, 60 patients were divided into two groups, each of 30 individuals. First group received daily 10 g fenugreek seeds soaked in water, while the second group was treated with *placebo*. Statistical analysis showed the decrease in glucose level in blood in the 5th month ( $p = 0.0421$ ), however, concentration of HbA1C was not statistically significant ( $p = 0.52$ ). After the 6th month, there was statistically significant difference in fasting blood glucose values ( $p = 0.0351$ ) and HbA1C values ( $p = 0.0201$ ) [32].

In a clinical trial on 60 patients with newly diagnosed type 2 diabetes, fenugreek seeds were administered in an amount of 2.5 and 5 g for 4 weeks. Phytochemical analysis of fenugreek seeds showed a high level of total polyphenols and flavonoids, and antioxidant potential in the DPPH and ABTS tests. The examined patients showed an improvement in blood glucose after 4 weeks and a decrease in the total cholesterol and triglyceride levels [33].

A group of researchers observed that the administration of an alcoholic extract from seeds of fenugreek (588 and 1176 mg) resulted in a decrease of fat consumption in 12 healthy volunteers of normal weight [34].

At a later stage, researchers checked whether a similar effect can be obtained in overweight people and 39 healthy overweight men took part in a 6-week, randomized, double-blind, *placebo*-controlled study. They were given fenugreek seed extract. The daily dose of seed extract was 1176 mg ( $14 \text{ mg/kg}^{-1}$ , approximately) and was chosen because was active in healthy volunteers [34].

Diet and physical activity was evaluated in non-ambulatory conditions before and after the outpatient treatment period. Energy consumption (REI) and total energy consumption (TEE) was determined using Enkal-Pro® software (Logging Software, Lille, France). Daily fat intake was expressed as a ratio of energy intake to total energy consumption (fat-REI/TEE). A decrease in fat intake was observed when fenugreek extract was administered after 6 weeks of therapy. There was also a statistically significant decrease in insulin/glucose ratio in patients treated with fenugreek seed extract compared to the *placebo* group. No statistically significant effect on body weight, appetite/satiety or oxidative consumption of fenugreek was observed [35].

## CONCLUSIONS

Nowadays, diseases such as obesity, atherosclerosis and diabetes are more common. The coexistence

of these diseases is associated with metabolic syndrome. People suffering from these diseases are looking for opportunities to improve their health by changing diet and also with implementing of phytotherapy as an alternative treatment. Several animal studies and the clinical data show that the use of fenugreek seeds can be useful in lowering cholesterol and blood glucose level. It has been found that the addition of fenugreek seeds, germinated seeds and powdered water-alcohol extracts to the diet increases bile secretion and a reduction in blood cholesterol. Administration of both seeds and extracts from fenugreek seeds and also trigonelline itself has a beneficial effect on blood glucose level as it was confirmed by many studies performed in animals and in humans. It seems that such activity of compounds contained in fenugreek seeds may be particularly beneficial for people struggling with concomitant diseases in the metabolic syndrome.

*Ethical approval: The conducted research is not related to either human or animal use.*

*Conflict of interest: Authors declare no conflict of interest.*

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