Hypoglycaemic effect of aqueous extract of the leaves of *Trigonella foenum-graecum* in healthy volunteers

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نقص سكر الدم بفعل الخلاصة المائية لأوراق الحلبة في متطوعين أصحاء

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خلاصة: تم استقصاء مأمونية خلاصة الحلبة وفاعليتها، في عشرين متطوعاً من الذكور الذين تتراوح أعمارهم بين عشرين وثلاثين سنة. فقد عولجوا على نحو عشوائي إما بأربعين مليغرام/كيلوغرام من مسحوق الخلاصة المائية في عشرة مليلترات من الماء المقطر، أو بتناول عشرة مليلترات من الماء المقطر محتوياً على القهوة بدلاً من الخلاصة. ووجد أن الخلاصة قد خفضت، بدرجة يعتد بها، مستوى سكر الدم بنسبة 13.4 % بعد تناولها بأربع ساعات. كما لوحظ تغيُّر يعتد به إحصائياً بنسبة 14.1% في مستويات البوتاسيوم. و لم يحدث تغيُّر ملحوظ في مستويات كولستيرول المصل، والبروتين الكلي في المصل، ويوريا الدم. ولقد شعر حوالي ثلث الأفراد بالجوع أو تكرار التبول أو الدوار بعد تناول الخلاصة بأربع وعشرين ساعة. وخلاصة القول إن الخلاصة المائية قد خفضت سكر الدم بأمان في الأشخاص الأصحاء. أما تأثيرها الخافض للبوتاسيوم فيستحق مزيداً من الدراسة.

ABSTRACT The safety and efficacy of *Trigonella foenum-graecum* extract was investigated using 20 male volunteers aged 20–30 years. They were randomly treated with either 40 mg/kg aqueous extract powder in 10 mL distilled water or 10 mL distilled water in which coffee simulated the extract. The extract significantly lowered blood glucose level by 13.4% 4 hours after ingestion. A significant change of 14.1% was observed in potassium levels. No significant alteration in serum cholesterol, total serum protein and blood urea occurred. Approximately one-third experienced feelings of hunger, frequency of micturition or dizziness during the 24 hours after ingestion. The aqueous extract effectively reduced blood glucose in normal subjects safely. Its hypokalaemic effect merits further investigation.

L'effet hypoglycémique de l'extrait aqueux des feuilles de *Trigonella foenum-graecum* chez des volontaires en bonne santé

RESUME L'innocuité et l'efficacité de l'extrait de *Trigonella foenum-graecum* ou fenugrec ont fait l'objet d'une étude chez 20 volontaires de sexe masculin âgés de 20 à 30 ans. On leur a admi-nistré au hasard soit 40 mg/kg de poudre provenant de l'extrait aqueux diluée dans 10 ml d'eau distillée soit 10 ml d'eau distillée à laquelle on avait ajouté du café simulant l'extrait. L'extrait a fait diminuer de façon significative la glycémie de 13,4% quatre heures après l'ingestion. Un changement significatif de 14,1% a été observé dans le taux de potassium. Aucune modification significative du cholestérol sérique, des protéines sériques totales et de l'urée sanguine n'est survenue. Environ un tiers des volontaires ont eu une sensation de faim, une pollakiurie ou des vertiges 24 heures après ingestion. L'extrait aqueux a réduit efficacement et sans risque la glycémie chez les sujets normaux. Son effet hypokaliémique mérite d'être étudié plus à fond.

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Introduction

There is a growing global interest in herbal and other forms of traditional medicine [*1*]. Herbs have long been an important source of effective drugs. Among World Health Organization recommendations is the need for the investigation of local medicinal plants for their potential therapeutic efficacy [*2*].

Trigonella foenum-graecum is known locally as *helba* or in English as fenugreek [*2*]. It is known traditionally to induce hypoglycaemia. This activity has been previously demonstrated in its seeds [*3–5*].

The leaves of *T. foenum-graecum* have been investigated at our laboratories and have been found to exhibit a hypoglycaemic effect in animals [*6, 7*]. Acute toxicity and target organ studies of the aqueous and alcoholic extracts of the leaves have already been conducted [*6*] and their ability to lower blood glucose levels in normoglycaemic and alloxan-induced hyperglycaemic rats has been studied [*7*].

The present work was an extension of the previous studies of our team. We studied the safety and efficacy of the aqueous extract of *T. foenum-graecum* in healthy volunteers.

Subjects and methods

The leaves of *T. foenum-graecum* were collected from Basra region as described previously [*6*]. The 50 g of powdered leaves were mixed with 250 mL distilled water and were stirred magnetically overnight at 70 °C. The residue was removed by filtration and the extract was powdered by a freeze dryer. This procedure was repeated to obtain a sufficient amount to treat volunteers in the study group.

A total of 20 men, 20–30 years of age, were selected for the study after giving written informed consent. They were non-smokers and apparently healthy on clinical examination. Their weights were within the normal range, their fasting blood sugar and haemoglobin percentages were within normal values, and they had no family history of diabetes mellitus and no drug had been taken in the past week. The participants were mainly selected from undergraduate and postgraduate students at the College of Science, University of Basra.

The study protocol was approved by the Ethics Committee of the College of Medicine, University of Basra. The volunteers were randomly allocated into one of two groups of 10 men each. Group 1, the study group, received 40 mg/kg of the aqueous extract powder dissolved in 10 mL distilled water in a dark-coloured plastic glass to mask the coffee-like colour of the extract. The dose was chosen according to our previous studies of the aqueous extract in animals and after testing in a pilot study of seven volunteers who gave consent to participate for this particular purpose. Group 2, the control group, received 10 mL distilled water in which a trace of diluted coffee was added to simulate the colour and taste of the extract, followed by 100 mL of distilled water.

The men were blind to the nature of the treatment they received (a single blind trial). In each of the two groups they were instructed to have breakfast at 06:30–07.00 of 1 cup (approximately 150 mL) of tea, 3 teaspoons sugar, no milk and one local bread. They were to be in attendance at 08.30 and to abstain from eating and drinking for 2 hours during the study.

The men had full clinical examinations with blood pressure and heart rate measured and subjective feelings recorded. A 5 mL venous blood sample was drawn through a sterile disposable syringe for

blood sugar, serum electrolytes (sodium, potassium and chloride), cholesterol, total protein and urea measurement. Then, 5 mL blood samples were taken at 2 and 4 hours after ingestion of the aqueous extract or placebo at which time a clinical examination was performed and any abnormal symptoms or signs were recorded. During the 4-hour duration of the study, the men were allowed to conduct their studies as usual but were restricted from physical exercise or exertion.

All the men were clinically re-examined 24 hours after ingestion of the extract and requested to report any signs or symptoms they may have had the day before.

Statistical analysis was performed using the Kruskal–Wallis one way analysis of variance by ranks. This was done to avoid assumptions of normality and homogeneity of variance between the two groups. Statistical significance between each two related or independent samples was performed using Wilcoxan matched pairs signed rank test or Mann–Whitney U test respectively.

Results

Subjects in both groups were matched for age, weight, height, haemoglobin level, fasting blood sugar, pulse rate and blood pressure (Table 1).

The aqueous extract reduced blood glucose by 8.7% and 13.4% at 2 and 4 hours after ingestion respectively. This reduction compared to blood glucose level before ingestion of the extract was statistically significant ($P < 0.005$) (Table 2).

Among the three electrolytes (sodium, potassium and chloride) measured in both groups, the only significant change was found in potassium. The extract resulted in a statistically significant reduction in serum potassium level of 14.1% ($P < 0.005$) 4 hours after ingestion (Table 3).

The extract did not affect the level of blood urea or total serum protein. There was a 9.2% reduction in serum cholesterol in the treatment group but this was not statistically significant (Table 4).

The men were requested to report any abnormal symptoms or signs they noticed

Table 1 **Characteristics of the men**

Characteristic	Study group ($n = 10$)	Control group ($n = 10$)
Age (years)	22.4 ± 2.2	24.7 ± 3.2
Weight (kg)	63.4 ± 9.8	72.3 ± 8.3
Height (cm)	171.0 ± 9.4	173.3 ± 6.9
Haemoglobin (g/100 mL)	14.9 ± 1.3	13.9 ± 1.6
FBS (mg/100 mL)	92.3 ± 6.4	87.9 ± 4.5
Serum electrolytes		
Potassium (mEq/L)	4.7 ± 0.3	4.4 ± 0.3
Sodium (mEq/L)	140.5 ± 2.4	139.4 ± 2.3
Chloride (mEq/L)	109.3 ± 7.7	108 ± 5.1
Serum cholesterol (mg/100 mL)	200.7 ± 26.2	202.2 ± 19.7
Total serum protein (g/100 mL)	7.2 ± 0.9	7.3 ± 0.6
Blood urea (mg/100 mL)	30 ± 6.5	30.4 ± 6.9
Pulse rate	78.6 ± 5.3	79.8 ± 3.7
Blood pressure (mmHg)		
Systolic	117 ± 6.7	122 ± 7.9
Diastolic	78.5 ± 7.8	83 ± 4.8

Difference between the study and control groups for all values shown in the table are not statistically significant.
Data are presented as mean ± standard deviation.
FBS = fasting blood sugar

Table 2 **Effect of the aqueous extract of the leaves of *Trigonella foenum-graecum* on blood glucose in normal subjects**

Group	Blood glucose (mg/100mL)		
	Pre-ingestion	2 hours after ingestion	4 hours after ingestion
Study (n = 10)	92.3 ± 6.4	84.3 ± 8.0[a]	79.9 ± 8.7[a]
Control (n = 10)	87.9 ± 4.5	89.9 ± 4.4	87.6 ± 5.7

[a]*Significant reduction with respect to pre-ingestion level ($P < 0.005$)*
Data are presented as mean ± standard deviation.

Table 3 **Effect of the aqueous extract of leaves of *Trigonella foenum-graecum* on serum electrolytes**

Electrolyte	Electrolyte level (mEq/L)		
	Pre-ingestion	2 hours after ingestion	4 hours after ingestion
Potassium			
Study (n = 10)	4.7 ± 0.28	4.3 ± 0.25[a]	4.0 ± 0.13[a]
Control (n = 10)	4.4 ± 0.32	4.4 ± 0.18	4.4 ± 0.16
Sodium			
Study (n = 10)	140.5 ± 2.4	139.4 ± 2.0	138.2 ± 2.8
Control (n = 10)	139.4 ± 2.3	139.2 ± 3.3	140.0 ± 2.5
Chloride			
Study (n = 10)	109.3 ±7.7	105.7 ± 5.8	102.3 ± 2.2
Control (n = 10)	108.9 ± 5.1	107.4 ± 5.2	107.0 ± 5.0

[a]*Significant reduction with respect to pre-ingestion level ($P < 0.005$)*
Data are expressed as mean ± standard deviation.

during the 4 and 24 hours after ingestion of the extract or placebo. All the men were then questioned according to a checklist that included the following: nausea, vomiting, dyspepsia, epigastric pain, anorexia, diarrhoea, feeling of hunger, frequency of micturition, skin rash, palpitation, chest pain, headache, dizziness, vertigo and sweating. No significant findings were reported in the control group, whereas a feeling of hunger, frequency of micturition or dizziness were reported by an average of four subjects in the treatment group.

Discussion

The aqueous extract of *T. foenum-graecum* leaves was found in our previous study to be significantly more effective than its alcoholic extract at reducing the glucose level in the blood of rats [7]. Moreover, in local medical folklore, *T. foenum-graecum* is traditionally used after boiling with water. For these reasons the aqueous extract rather than alcoholic extract was used to test its safety and efficacy in normal subjects.

The aqueous extract of *T. foenum-graecum* leaves was found to be effective at

Table 4 **Effect of the aqueous extract of leaves of *Trigonella foenum-graecum* on serum cholesterol, total serum protein and blood urea**

Measurand	Pre-ingestion	2 hours after ingestion	4 hours after ingestion
Cholesterol (mg/100 mL)			
Study (n = 10)	200.7 ± 26.2	186.9 ± 29.2	182.2 ± 34.3
Control (n = 10)	202.2 ± 19.7	198.6 ± 28.9	196.4 ± 25.0
Total protein (g/100 mL)			
Study (n = 10)	7.2 ± 0.9	6.5 ± 0.6	7.1 ± 0.8
Control (n = 10)	7.3 ± 0.6	7.1 ± 0.8	6.9 ± 0.4
Urea (mg/100 mL)			
Study (n = 10)	30.0 ± 6.5	29.7 ± 5.7	31.1 ± 5.0
Control (n = 10)	30.4 ± 6.9	29.6 ± 6.1	29.0 ± 5.3

Data are expressed as mean ± standard deviation.

reducing blood sugar within 4 hours after ingestion with minimal adverse effects (feeling of hunger, frequency of micturition and dizziness). The frequency of micturition experienced by the treatment group is consistent with that reported in several historical Arabic medical books. Paradoxically, Shani et al., experimenting with the two major componenets of *Trigonella* seeds, coumarin and sparteine, found that both had antidiuretic activity [5]. Sparteine had the stronger effect. However, this activity was observed in rats after administering the pure chemical (5 mg sparteine sulfate) not after the seed extract. Thus, it is possible that *Trigonella* extracts can exhibit a mild diuretic effect at low doses while at higher doses, the antidiuretic effect predominates.

An important finding of our study which could be related to the above-cited effects on the kidney is the ability of the aqueous extract to significantly lower the potassium level in the blood. The extract may, however, act in a way similar to insulin to facilitate potassium uptake by the cells through activation of sodium, potassium-ATPase. These speculations require further investigation.

The 4-hour period was chosen according to our earlier observations [7] and that of Shani et al. [5] that the hypoglycaemic effect lasts around 4 5 hours after administering to animals. However, the 4-hour study period and the use of a single oral dose may not be enough to detect or to cause changes in serum cholestrol, total serum protein and blood urea. A longer period of follow-up and frequent administration of the extract are thus necessary.

The study demonstrates that a single dose of the aqueous extract of *T. foenum-graecum* leaves is relatively safe for use in humans and can significantly reduce blood glucose in normal subjects. It has a hypokalaemic effect which is worth investigating.

Acknowledegements

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