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CLINICAL TRIAL

A fenugreek seed extract selectively reduces spontaneous fat intake in overweight subjects

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Abstract
Purpose Fenugreek seeds (*Trigonella foenum-graecum* L.) have long been used as a herbal medicine for treating metabolic and nutritive dysfunctions. They have been shown to modulate feeding behaviour in animals. We have recently observed a selective decrease in fat consumption in healthy normal weight volunteers treated with a hydro-alcoholic seed extract. However, strong clinical data on the effects of fenugreek seeds on energy intake are lacking, especially in overweight individuals. The aim of our study was to investigate the effects of a repeated administration of a fenugreek seed extract on the eating behaviour of overweight subjects.
Methods Thirty-nine healthy overweight male volunteers completed a 6-week double-blind randomized placebo-controlled parallel trial of a fixed dose of a fenugreek seed extract. Main endpoints were energy intake (dietary records and meal test), weight, fasting and post-absorptive glucose and insulin, appetite/satiety scores and oxidative parameters.
Results Daily fat consumption, expressed as the ratio fat reported energy intake/total energy expenditure (fat-REI/TEE), was significantly decreased in our overweight subjects administered the fenugreek seed extract relative to those receiving the placebo (fat-REI/TEE 0.26±0.02 vs. 0.30±0.01, respectively; P=0.032). We also observed a significant decrease in the insulin/glucose ratio in subjects treated with fenugreek seed extract relative to the placebo group (0.89±0.09 vs. 1.06±0.10 mUI mmol^{-1}, respectively; P=0.044). No significant effect was observed on weight, appetite/satiety scores or oxidative parameters.
Conclusion The repeated administration of a fenugreek seed extract slightly but significantly decreased dietary fat consumption in healthy overweight subjects in this short-term study.

Keywords Eating behaviour · Energy intake · Fat · Fenugreek seed · Overweight subjects · Human

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Introduction

Fenugreek (*Trigonella foenum-graecum* L.) is an herbaceous annual plant belonging to the Leguminosae family that is cultivated in Mediterranean countries and India. Its seeds have been long been used as a herbal medicine to

treat various pathological conditions. A number of pharmacological and clinical studies have shown that the seed itself, its extracts or its purified components have glucose- and lipid-lowering properties (see [1] for review). In addition, antioxidant properties have been observed in animal studies [2, 3].

Fenugreek-based preparations are used in humans to stimulate appetite and promote weight gain [4]. However, these properties are supported only by animal data, and there are some inconsistencies. In an earlier study on rats, we demonstrated that the repeated administration of a hydro-alcoholic extract of fenugreek seed enhanced the motivation to eat and consume food, resulting in a slight weight increase [5]. Appetite and food intake were also increased by a subchronic treatment with a steroid saponin fraction purified from the fenugreek seed, with a modified circadian rhythm of feeding behaviour [6]. In contrast, in a safety study using a dietary supplement of fenugreek seeds in animals [7], no effect was observed on food consumption. In a more recent study, treatment with a fenugreek seed extract was found to reduce the body weight gain induced by a high-fat diet in obese mice [8]. However, no clinical data on body weight and food intake have become available since the publication of our recent study showing reduced fat consumption in healthy normal weight volunteers under free-living conditions who had received 14 days of treatment with a fenugreek seed extract [9].

Should fenugreek seed indeed have the property of reducing fat consumption, it would be of great interest to overweight subjects. Consequently, the aim of the study reported here was to investigate the effects of our fenugreek seed extract on fat intake in overweight patients. Our secondary objectives were to determine the effects of fenugreek seeds on weight, glycaemia, plasma insulin, lipid profile and oxidative stress and antioxidant capacities. Studies using animal models have demonstrated that fenugreek seeds improve these properties in animals, but these effects have never been shown in humans.

Materials and methods

Study design

The study was designed as a 6-week double-blind randomized placebo-controlled parallel trial.

Subjects

Thirty-nine healthy overweight male volunteers, aged 18-59 years (mean 38 years) completed this study. All were of stable weight (mean weight 85.4 kg, range 75.2–105.5; mean body mass index 27.3 kg m^{-2}; range 24.9–29.4). One subject among the 40 initially enrolled was withdrawn from the study before the first administration of the drug due to partaking in a non-authorized treatment.

Ethical aspects

This study was approved by the Ethics Committee "Comité de Protection des Personnes Montpellier-Saint-Eloi" and conducted in accordance with the Helsinki declaration and the ICH guideline for Good Clinical Practice. All subjects gave written informed consent to participate.

Test compound

The test compound was a marketed dry hydro-alcoholic fenugreek seed extract administered three times daily as oral coated tablets. The tablets originated from the batch used in our previous study on healthy normal weight volunteers [9]. The total daily dose of 1176 mg (approximately 14 mg kg^{-1}) is double the daily dose of the extract commonly prescribed for human consumption. It was selected because it appeared to be the active dose in healthy volunteers [9]. This dose is also in accordance with the two active doses used in an earlier animal study that tested the same extract [5], corresponding to 5 and 53 mg kg^{-1} human equivalent doses, respectively. The extract contains diosgenine, steroid saponins, 1.38% trigonelline and 1.50% 4-hydroxyisoleucine, as characterized by thin-layer chromatography and high-performance liquid chromatography (HPLC). Placebo tablets were manufactured using the same excipients, the same process and the same packaging as for active tablets, making them indistinguishable. The similarity between the seed extract and the placebo tablets was verified on five criteria (aspect, size, weight, colour and smell).

Investigations

The diet and physical activity of the patients were assessed under free-living conditions before and at the end of the ambulatory treatment period, using a 7-day record that was reviewed by a trained dietician and a physician for its accuracy. Reported energy intake (REI) was determined with Enkal-Pro software (Loging Software, Lille, France), and total energy expenditure (TEE) was calculated as basal metabolic rate (BMR) multiplied by physical activity level (PAL) according to Black et al. [10]. Energy intake was expressed as the ratio REI/TEE. Underreporting was defined as a ratio REI/BMR < 1.1 [11].

The day following the completion of the first 7-day record, subjects attended the study centre for a baseline visit in the fasting condition. Body weight was recorded while the subjects were dressed in their underwear and after they

had urinated, using the same balance for all subjects (Seca 861; Seca, Hamburg, Germany), with an accuracy of ±0.1 g. Body composition was measured by a multi-frequency bioelectrical impedance analysis. Blood was drawn, and urine was collected for the determination of plasma glucose, serum insulin and lipid profiles, oxidative stress and antioxidant capacities. The subjects were then discharged, and treatment was taken ambulatory. During the last week of treatment, subjects completed a second 7-day record and then attended the study centre after an overnight fast for their final visit, which included evaluation of all of the baseline parameters. The subjects also had to completely consume, within a maximum of 30 min, a standardized breakfast (13% protein, 35% fat, 52% carbohydrate) that provided 20% of their daily energy requirements. In addition, they were asked to describe their appetite, satiety and palatability feelings on visual analogue scales [12, 13] at different time points: before starting to eat the breakfast and at 30-min intervals after starting to eat the breakfast for a total of 270 min. At 12:30A. M, the subjects were served an ad libitum mixed meal consisting of 13% protein, 35 % fat, 52 % carbohydrate, and the amount of food ingested was weighed with an accuracy of ±0.1 g.

Analytical methods

Plasma glucose was assayed by the glucose oxidase method. Serum insulin was measured by a radioimmunoassay (BI-INSULIN IRMA; CIS Bio-international, Gif-sur-Yvette, France). Serum triglycerides, total cholesterol and high-density lipoprotein (HDL)-cholesterol were assayed using an enzymatic method (lipase/glycerokinase, cholesterol oxidase and cholesterol oxidase after separation, respectively).

The antioxidant parameters investigated were total plasma antioxidant capacity (quantitative colorimetric

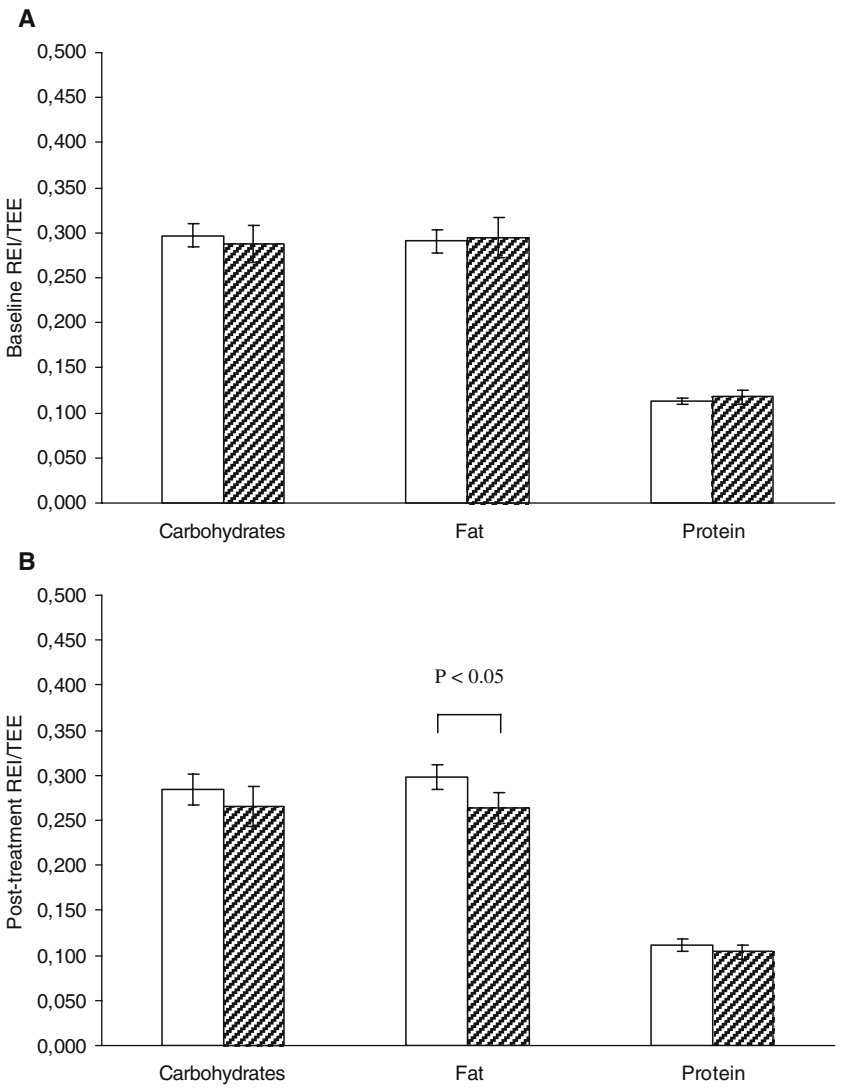

Fig. 1 Ratio energy intake/energy expenditure (*REI/TEE*) recorded by healthy overweight subjects under free-living conditions, before treatment (baseline data, **a**) and during the last 7 days of the 6-week treatment period (post-treatment data, **b**) for the placebo group (*white bars*) and for the group receiving the fenugreek seed extract at 1176 mg/day (*striped bars*)

technique), susceptibility of low-density lipoproteins (LDL) to oxidation, serum and LDL vitamin E levels (by HPLC) and plasma vitamin C level (HPLC). LDL levels were obtained by plasma sequential ultracentrifugation with a potassium bromide-adjusted density of 1.063. LDL oxidation was initiated with copper [Cu (II), 5 μM] and continuously monitored for 6 h by measuring the increase in absorbance at 234 nm due to conjugated diene formation. LDL susceptibility to oxidation was expressed by the reaction lag phase time, the maximal propagation rate, the time of half oxidation and the slope of the propagation phase. Oxidative stress was assessed by plasma malonyldialdehyde [14], plasma advanced oxidation protein products [15], plasma advanced glycation end products (fluorescence spectroscopy) and the urinary ratio of free 8-iso PGF_2/creatinine (liquid chromatography–tandem mass spectroscopy).

Data analysis and statistics

The sample size (40 subjects to be enrolled in two groups of 20) was determined using data obtained in our previous study [9], with an expected mean difference for energy consumption (main outcome) between the fenugreek seed extract and placebo of 216 kcal per day, a common standard deviation (SD) of 238 kcal par day, a two-sided alpha of 0.05 and a statistical power of 80%.

Results are expressed as the mean ± standard error of the mean (SEM), and 95% confidence intervals for the differences (95% CI) are given where necessary.

Means were compared using an analysis of covariance (ANCOVA) with baseline data as the covariate. The means were subjected to logarithmic transformation if necessary. Nonparametric data were compared using the Mann–Whitney test.

Calculations and statistical analysis were performed using the Systat ver. 10.0 software for Windows (SPSS, Chicago, IL). The level of significance was set at $P<0.05$.

Results

Underreporting was similar between the fenugreek and placebo groups [38.9% (7/18) vs. 40% (8/20), respectively; nonsignificant). As a result, total-REI was lower than daily TEE in both groups [basal ratio total-REI/TEE 0.74±0.05 (n=18) and 0.73±0.03 (n=20), respectively; nonsignificant]. At baseline, macronutrient intake was similar between the fenugreek and placebo groups (Fig. 1a). After 6 weeks of treatment with the fenugreek seed extract, a significant decrease in TEE-adjusted reported fat intake was observed [post-treatment fat-REI/TEE 0.26±0.02 (n=18) vs. 0.30±0.01 (n=20); P=0.032], while protein and carbohydrate intakes were not significantly modified (Fig. 1b). Total-REI was not significantly modified by the treatment [post-treatment total-REI/TEE 0.68±0.05 (fenugreek, n=18) vs .0.73±0.03 (placebo, n=20); nonsignificant]. Spontaneous food intake during the ad libitum meal test, weight, body composition, appetite and satiety scores did not differ between fenugreek and placebo groups.

The main biological parameters are described in Tables 1 and 2. The ratio of fasting serum insulin/plasma glucose was significantly decreased in subjects treated with fenugreek seed extract relative to the placebo group [0.89±0.09 (n=19) vs. 1.06±0.10 (n=19) mUI $mmol^{-1}$, respectively; P=0.044) (Table 1). No effect on plasma lipid profile (Table 1), antioxidant parameters and oxidative stress markers (Table 2) were observed.

No serious adverse events occurred. Among the 35 non-serious adverse events reported (17 with fenugreek, 18 with placebo), only five may be related to the experimental treatment. In total, there were four cases of mild gastrointestinal symptoms and one case of specific urine and sweat smell.

Discussion

We demonstrate here for the first time that a treatment with a fenugreek seed extract selectively reduces spontaneous fat

Table 1 Comparison of fasting data of plasma glucose, serum insulin and lipid profile between healthy overweight subjects receiving fenugreek seed extract 1176 mg/day and those receiving placebo

Main metabolic parameters	Fenugreek	Placebo	P
Fasting plasma glucose (mmol l^{-1})			
- Baseline	4.61±0.21	4.87±0.19	0.355
- Post-treatment	5.38±0.10	5.26±0.16	0.545
Fasting serum insulin (mU l^{-1})			
- Baseline	5.10±0.41	5.02±0.31	0.887
- Post-treatment	4.73±0.43	5.38±0.36	0.057
Fasting insulin/glucose ratio (mU $mmol^{-1}$)			
- Baseline	1.17±0.13	1.07±0.08	0.708
- Post-treatment	0.89±0.09	1.06±0.10	0.044
Total cholesterol (mmol l^{-1})			
- Baseline	4.82±0.26	5.19±0.19	0.254
- Post-treatment	4.88±0.25	5.06±0.20	0.207
HDL-cholesterol (mmol l^{-1})			
- Baseline	1.27±0.05	1.22±0.08	0.555
- Post-treatment	1.30±0.05	1.17±0.07	0.067
Triglycerides (mmol l^{-1})			
- Baseline	1.25±0.15	1.15±0.11	0.732
- Post-treatment	1.27±0.16	1.41±0.14	0.148

Values are given at the mean ± standard error of the mean (SEM)

Table 2 Comparison of antioxidant status between healthy overweight subjects receiving fenugreek seed extract 1176 mg/day and those receiving placebo

Antioxidant status	Fenugreek	Placebo	*P*
Total plasma antioxidant capacity (mmol l^{-1})			
- Baseline	1.48±0.03	1.51±0.03	0.572
- Post-treatment	1.51±0.04	1.49±0.04	0.138
LDL susceptibility to oxidation:lag phase time (min)			
- Baseline	16.2±1.7	15.5±0.8	0.826
- Post-treatment	15.3±0.6	14.8±0.7	0.546
LDL susceptibility to oxidation:slope of the propagation phase (OD min^{-1})			
- Baseline	0.017±0.001	0.018±0.001	0.419
- Post-treatment	0.018±0.001	0.020±0.001	0.264
LDL susceptibility to oxidation : maximal propagation rate (OD min^{-1})			
- Baseline	0.019±0.001	0.020±0.001	0.339
- Post-treatment	0.020±0.001	0.021±0.001	0.647
LDL susceptibility to oxidation : half-time of maximum diene formation (min)			
- Baseline	35.4±2.6	34.9±1.2	0.788
- Post-treatment	33.9±1.0	34.1±1.4	0.877
Serum vitamin E (μmol l^{-1})			
- Baseline	27.9±1.6	27.3±0.9	0.752
- Post-treatment	28.1±1.8	27.7±1.2	0.870
LDL vitamin E (mg l^{-1} of LDL)			
- Baseline	10.9±0.9	12.3±0.6	0.210
- Post-treatment	12.4±1.1	11.8±0.77	0.220
Plasma vitamin C (μmol l^{-1})			
- Baseline	42.2±4.0	52.7±4.1	0.071
- Post-treatment	43.9±4.0	52.1±4.3	0.762
Plasma malonyldialdehyde (μmol l^{-1})			
- Baseline	0.89±0.07	0.85±0.05	0.758
- Post-treatment	0.85±0.06	0.82±0.05	0.841
Urine F2-isoprostanes/creatinine (pmol $mmol^{-1}$)			
- Baseline	307±31	478±55	0.004
- Post-treatment	357±54	510±82	0.704
Plasma advanced glycation end products			
- Baseline	13887±982	12302±445	0.261
- Post-treatment	12737±697	12204±478	0.804
Plasma advanced oxidation protein products(μmol l^{-1})			
- Baseline	57.9±5.5	61.4±3.4	0.592
- Post-treatment	54.0±6.9	61.6±5.3	0.504

LDL, Low-density lipoprotein; OD, optical density

Values are given at the mean ± SEM

consumption in overweight male subjects. We also show that the fenugreek seed extract does not increase food consumption. This latter result differs from the traditional use of fenugreek-based preparations for appetite stimulation and weight gain [4]. It also contrasts with our previous observations of enhanced food consumption in animals administered a hydro-alcoholic crude extract or a purified steroid saponin fraction of fenugreek seed [5, 6]. However, our results are in agreement with those of our earlier investigation in healthy normal weight subjects [9].

This effect was observed with a reliable evaluation of energy intake under free-living conditions, i.e. baseline and post-treatment 7-day records, adjustment of physical activity, systematic review by a dietician. While self-reported dietary records may underreport energy intake, they remain an important tool for nutrition researchers, and a record of 7 consecutive days is considered to be a reliable approach for quantifying the diets of outpatients [16]. As expected in an overweight population [17], underreporting of energy intake was frequent (approx. 40%), but this underreporting was similar in the treatment and control groups, which were initially comparable.

The effect of fenugreek on fat consumption could not be assessed under standardized conditions because the meal test used was composed of a single course that did not allow any dietary choice.

This specific effect of fenugreek, in the absence of any significant change in the intake of other nutrients and without any alteration of appetite or palatability, has already been observed in pharmacological studies undertaken in rats activated through the hypothalamic serotonin pathway [18] and in human studies after a methylphenidate challenge activating the brain dopamine pathway by blocking its re-uptake [19].

The moderate magnitude of this effect (−10%) made it unlikely that a decrease in weight would be induced over a short period of time, and indeed we did not observe any modifications in body weight or body composition. It is also noteworthy that Sharma et al. [20] also did not observed any significant change in body weight in a clinical study evaluating the safety of fenugreek seeds consumed by diabetic patients, although their study was not designed to assess eating behaviour or weight modifications. Nevertheless, it can be hypothesized that fenugreek seed extract may favour a weight reduction in the long term, particularly in overweight or obese patients for whom a low-fat diet is recommended. As such, it may improve the metabolic status of these subjects.

The lower ratio of fasting serum insulin/plasma glucose may reflect an improved insulin sensitivity, as previously described in patients with type 2 diabetes who received fenugreek seed preparations [21]. This effect may be related to 4-hydroxyisoleucine, an amino acid present in fenugreek seeds, which is known for its insulin-sensitizing effect [22]. However, even if this biological mechanism would support the hypothesis of an improved insulin sensitivity in our sample, fasting glucose and insulin values (and related calculated indexes) are an insufficient basis for drawing such a conclusion, and specific investigations, such as clamp studies, would be required. As fenugreek is traditionally used to treat type 2 diabetic patients in Mediterranean and Asian countries, our results provide a rationale for conducting further research on the potential usefulness of fenugreek in disorders of carbohydrate metabolism.

Despite an extensive investigation, we were unable to determine any significant effect of fenugreek seed extract on plasma antioxidant capacity or oxidative stress, which were ancillary biological objectives. This result is in contrast with previously reported data in rats [2] and mice [3] and may be related to our experimental conditions. First, our study population was characterized by a normal baseline oxidative/antioxidant profile, and antioxidant properties are easier to detect in conditions of increased oxidative stress. Second, our sample size may have been too small to reveal a significant difference for these parameters. Alternatively, it is possible that the antioxidant properties shown in animal studies are simply not present in humans.

Finally, it has to be noted that the treatment with the fenugreek seed extract did not modify the subjects' lipid profile, which also may be explained by the healthy status of the subjects.

Although fenugreek seed extract is coloured and displays a specific smell, active and placebo tablets could not be identified by the investigators and the subjects, thanks to the coating process making them indistinguishable. Nevertheless, one subject detected an unusual smell in his urine and sweat during the treatment period without having expressly been interpreted as treatment-related. This unique case of a subject possibly identifying the treatment did not lead to any de-blinding of the study for the rest of the volunteers. However, in light of this occurrence,, the possibility of de-blinding has to be systematically tested for in clinical studies investigating fenugreek seed preparations.

Conclusion

The repeated administration of a fenugreek seed extract slightly—but significantly—decreased dietary fat consumption in human volunteers in this short-term study. This novel property of fenugreek seeds, together with a potential favourable effect on insulin sensitivity, may be helpful in subjects who need to decrease their fat intake. It may also improve the metabolic status of overweight subjects. The component(s) involved and the mechanism(s) of this effect remain to be elucidated for fenugreek seed.

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