Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

J P P Journal of Pharmacognosy and Phytochemistry

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2017; 6(3): 185-189
Received: 11-03-2017
Accepted: 12-04-2017

Sally Abd El-Monem El-Nawasany
Department of Tropical Medicine, Faculty of Medicine, Tanta University, Tanta, Gharbia Governorate, Egyp

Said Ibrahim Shalaby
Department of Complementary Medicine, Medical Division, National Research Center, Cairo, Egypt

Farid Abd El- Rahim Badria
Department of Pharmacogonsy, Faculty of Pharmacy, Mansoura University, Mansoura, Dakahlia Governorate, Egypt

Gamal Mohammad Magraby
Department of Pharmaceutics, Faculty of Pharmacy, Tanta University Tanta, Gharbia Governorate, Egypt

Neelima Gupta
Department of Animal Science, MJP Rohilkhand University, Bareilly 243006. UP. India

Correspondence
Neelima Gupta
Department of Animal Science, MJP Rohilkhand University, Bareilly 243006. UP. India

Diuretic effect of Fenugreek (*Trigonella foenum-graecum* Linn) in cirrhotic ascitic patients

Sally Abd El-Monem El-Nawasany, Said Ibrahim Shalaby, Farid Abd El-Rahim Badria, Gamal Mohammad Magraby and Neelima Gupta

Abstract
Herbs such as Fenugreek are known to have a diuretic effect in cirrhotic ascitic patients. The safety, tolerability and possible diuretic efficacy of Fenugreek were investigated. A study was carried out on 50 patients: Group I: Furosemide 40 mg tablet and Spironolactone 100 mg tablet once daily for 7 days, Group II: Fenugreek methanol extract 500 mg capsule twice daily for 7 days. Basal and final body weight, urine volume (24h), mean arterial blood pressure, Na and K in serum and 24h urine were estimated. In Group I, the mean loss of body weight was significantly greater. The mean of urine Na excretion in Group I significantly increased. Mean of serum Na decreased significantly in Group I, insignificantly increased in Group II. Values of K excretion were insignificant. No side effects were detected. This is the first human clinical trial indicating that Fenugreek is safe and tolerable.

Keywords: *Trigonella foenum-graecum*, fenugreek, cirrhosis, ascites, diuretic

1. Introduction
Ascites is considered to be the most common complication of cirrhosis (Lucena *et al*., 2002) [11] Portal hypertension and activation of vasoconstrictor and sodium-retaining systems (i.e., the sympathetic nervous system and the renin– angiotensin–aldosterone system) increase the extracellular fluid volume and lead to accumulation of ascites and edema (Moller and Henriksen, 2005; Ripoll *et al*., 2007) [13, 18] with subsequent diminution of sodium excretion in urine that results in a positive sodium balance (Schrier *et al*., 1988) [20]. Massive or refractory ascites are treated by paracentesis as the first-line therapy. However, diuretics are considered to be the main medical therapy for moderate ascites and are also required to prevent or delay further paracentesis in patients with massive peritoneal effusion (Bernardi, 2010) [5]. Several complications are associated with the use of diuretics such as renal failure, hepatic encephalopathy, electrolyte disturbance, gynaecomastia, and muscle cramps (Angeli *et al*., 2010; Bernardi, 2010) [3, 5].
Natural products are now becoming a major source of new drugs. *Trigonella foenum-graecum* Linn commonly known as Fenugreek is a medicinal plant that is used as a therapy in some diseases (Vuorelaa *et al*., 2000) [25]. It has been investigated in many animal and human toxicological studies. In an animal study, the acute oral LD50 was found to be >5 g/kg in rats, and the acute dermal LD50 was >2 g/ kg in rabbits (Opdyke, 1978) [15]. In another study, Fenugreek powder failed to induce any signs of toxicity or mortality in mice and rats who received acute and sub chronic regimens (Muralidhara *et al*., 1999) [14]. Moreover, there were no significant hematological, hepatic, or histopathological changes in weanling rats that were fed Fenugreek seeds for 90 days (Rao *et al*., 1996) [17]. Toxicological evaluation of 60 diabetic patients who took powdered Fenugreek seeds at a dose of 25 g per day for 24 weeks disclosed no clinical hepatic or renal toxicity and no hematological abnormalities (Sharma *et al*., 1996) [22]. Many clinical trials have investigated Fenugreek efficacy on human diseases. Fenugreek seed powder in the diet reduces blood and urine sugar with concomitant improvement in glucose tolerance and diabetic symptoms in type 2 diabetic patients (Analava and Debaprasad, 2004) [2]. Several studies have shown hypoglycemic effects of Fenugreek seeds in type 1 and 2 diabetics (Madar *et al*., 1988; Sharma *et al*., 1990; Jain *et al*., 1995; Sharma *et al*., 1996) [12, 21, 9, 23]. Kaviarasan *et al*. (2007) [10] tested the effects of Fenugreek seed polyphenol extract (FPEt) on liver lipids and collagen in experimental hepatotoxic rats. They observed that administration of FPEt to alcohol-fed rats significantly improved lipid profile and reduced collagen content, aldehyde content and peroxidation. They regarded the observed hepato protective effect due to the bioactive phytochemicals in Fenugreek seeds (Kaviarasan *et al*. 2007) [10]. Anti-urolithiatic and anti-oxidative potential effects of

T. foenum-graecum in ethylene glycol induced kidney stone rats have been demonstrated (Shekha *et al*., 2014) [24]. Serum triglycerides were reduced from baseline in patients with newly-diagnosed, mild, type-2 diabetes mellitus who received a hydro alcoholic extract of Fenugreek seeds 1 g/day (Gupta *et al*., 2001) [8]. Diuretic effect of Fenugreek was investigated in two animal studies (Al-Atwi, 2010 [1]; Rohini *et al*., 2008) [19]. However, there are no human clinical data that support this action. The objectives of the present research was to investigate the safety, tolerability and possible diuretic efficacy of Fenugreek in cirrhotic ascitic patients.

Materials and Method

Subjects

A randomized controlled study was carried out in the Tropical Department, Tanta University, Tanta, Egypt after prior approval of the ethical committee on fifty grade 2 cirrhotic ascitic patients out of which 11 patients dropped out (5 developed hepatic encephalopathy, 3 were omitted due to electrolyte disturbance and 3 patients refused to complete the study). The study was carried out on the remaining 39 patients.

Inclusion Criteria

Cirrhotic patients with Grade 2 ascites (clinically detectable ascites with flank bulging and shifting dullness)

Exclusion Criteria

Grade 3 ascites (tense ascites), Hypotension (blood pressure < 90/60 mm Hg), Hypokalemia (serum potassium level < 3.5 mmol/liter), hyponatremia Na < 120 mml/ litre, impaired renal function (serum creatinine > 2mg/dl), Spontaneous Bacterial Peritonitis (SBP), cardiac problems (heart failure, arrhythmia) and Diabetes Mellitus.

Study Groups

The patients were randomly distributed into two groups:

Group I: [Furosemide 40 mg tablet and Spironolactone (100 mg tablet) treated, one tablet daily for 7 days] (n=20; 11 males, 9 females) (mean age 48.4± 4.37 years) and

Group II: (Fenugreek methanol extract 500 mg capsule twice daily for 7 days) (n= 19; 12 males, 7 females) with mean age 45.9 ±5.87.

Study Design

Diuretic therapy, K supplementation were discontinued 3 days prior to the commencement of the study. All patients were advised to restrict salt in their diet. Written consents were taken from patients. Basal and final assessment of body weight, mean arterial blood pressure, 24h urine volume, serum and 24h urine Na and K, liver, renal function test, fasting blood glucose and complete blood picture were recorded. Conscious level, lower limb edema, flapping tremors, cramps, body weight, 24h urine volume, blood pressure, Serum Na and K, serum creatinine and any unexpected side effects of Fenugreek such as allergy, nausea, vomiting, abdominal pain and diarrhea were followed up daily.

Plant Formulation

Methanol extraction of the herbs was followed by freeze drying and standardization using HPLC. Gelatinous capsules of 500 mg Fenugreek extract for each were formulated.

Primary Outcomes of the Study

Response to treatment was judged on the basis of total Na excretion in 24 hours urine**,** body weight loss**,** 24h urine secretion.

Secondary Out Comes of the Study

Detection of changes of renal functions and serum electrolytes and assessment of safety (absence of pathological modifications in the biochemical tests), tolerability (absence of intense side effects), and efficacy of Fenugreek**.**

Criteria of Withdrawal

Development of gastro intestinal bleeding (hematemesis, melena)**,** hepatic encephalopathy, disturbance in serum electrolytes and hypotension less than 90/60 mm Hg.

Statistical Analysis

Data analysis was conducted using Microsoft SPSS Excel. Student t test was used to compare the variables before and after treatment in each group. A value of $P < 0.05$ was considered significant. Results are expressed as means ± SE.

Results

The diuretic response was evaluated by recording loss in body weight, 24 hours urine volume and Na excretion in 24 hours urine which was exhibited by both groups but with insignificant values.

In Group I the mean loss of body weight was -1.10±0.892 kg which is significantly (P<0.023) greater than that of Group II (-0.526±0.595 kg). Mean increase in 24 h urine volume in Group I was +232±173 and +130±108 in Group II with significant difference (P<0.036) (Table 1).

Table 1: Mean change in body weight (kg) and in 24h urine volume (ml)

	Mean change of body weight (kg)	Mean change in 24h urine volume (ml)
Group I	-.100±0.892	+232±173
Group II	-0.526±0.595	+130±108
p	0.023	0.036
t	2.37	2.17

The mean of Na excretion in 24 h urine in Group I before treatment was 119±6.26 mmol/l which increased significantly (P<0.03) after treatment to 123±4.25 mmol/l. On the other hand, in Group II, it showed insignificant increase (P>0.40) where it was 119±6.44 mmol/l before treatment and 121±6.09 mmol/l after treatment (Table 2, Fig 1). The mean of K excretion in 24 h urine increased insignificantly after treatment in both groups. Mean of serum Na decreased in both groups at the end of the study with significant decrease (P< 0.026) in Group I. Group II showed an insignificant change (P>0.362). Serum K decreased insignificantly in both groups at the end of the study (Table 2, Fig 1).

Table2: Mean of Na and K in 24h urine and serum before and after treatment

	Group I		Group II	
	Before Treatment	**After Treatment**	**Before Treatment**	**After Treatment**
Na in 24h urine (mean value) mmol/l	119+6.26	123+4.25	119+6.44	121+6.09
t test	2.20		0.844	
p value	0.03		0.40	
K in 24h urine (mean value) mmol/l	40.6±8.74	42.2±6.44	42.3±8.65	43.7±7.99
t test	0.658		0.501	
p value	0.51		0.62	
Serum Na (mean value) mmol/l	141+5.97	136+7.01	143.43+4.74	142.76+5.40
t test	2.23		0.424	
p value	0.026		0.362	
Serum K (mean value) mmol/l	4.19±0.46	4.01±0.46	4.42±0.30	4.41±0.20
t test	1.23		0.558	
p value	0.23		0.852	

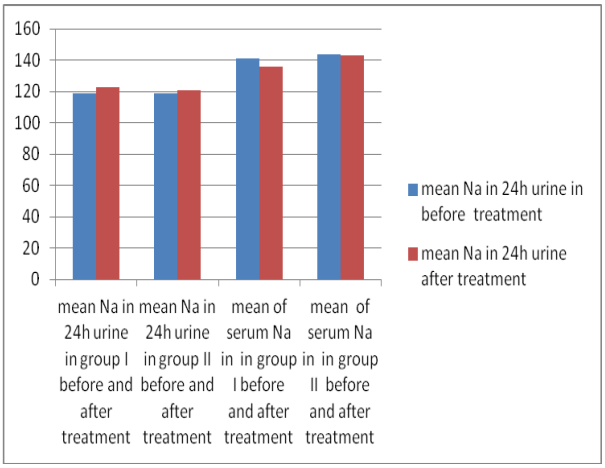

Fig 1: Mean of Na in 24 h urine and mean of serum Na before and after treatment in both groups

There were no significant changes in biochemical parameters and mean arterial blood pressure in both groups at the end of the study as shown in Table 3.

Side effects (nausea, vomiting, diarrhea, abdominal pain, allergy) in the patients receiving Fenugreek at the given dose were not detected**.**

Table 3: Biochemical tests before and after treatment in both groups

	Group I		Group II	
	Before Treatment	**After Treatment**	**Before Treatment**	**After Treatment**
Hb(gm/dl) (mean value)	11.5±0.643	11.6±0.57	11.4±0.62	11.2±0.64
t test	0.388		1.35	
p value	0.70		0.18	
WBCs (cell/mm)³ (mean value)	4.21±0.589	4.33±0.464	4.29±0.522	4.45±0.531
t test	0.696		0.992	
p value	0.49		0.33	
Platelet (cell/mm)³ (mean value)	127.±23.4	124.±23.8	130± 23.2	130±26.3
t test	0.476		0.524	
p value	0.64		0.96	
S creatinine (mg/dl) (mean value)	0.98±0.2	0.95±0.1	0.94±0.2	0.96±0.2
t test	0.651		0.259	
p value	0.52		0.80	
Serum bilirubin (mg/dl) (mean value)	0.85±0.21	0.84±0.16	0.87±0.20	0.85±0.161
t test	0.166		0.268	
p value	0.87			0.79
S albumin (g/dl) (mean value)	3.22+0.174	3.15+0.147	3.23±0.176	3.15±0.147
t test	1,48		1.40	
p value	0.15		0.17	
AST(IU/l) (mean value)	41.9±8.40	40.3±7.7	42.3±8.47	40.8±7.51
t test	0.628		0.547	
p value	0.53		0.53	
ALT (IU/l) (mean value)	36.4±3.08	36.2±2.4	36.4± 3.15	36.3±2.45
t test	0.172		0.173	
p value	0.86		0.86	
Blood glucose mg/ Fasting dl (mean value)	96.2±10.7	91.8+8.49	96.2±11	92.2±8.62

t test	1.41		1.24	
p value	0.17		0.22	
INR (mean value)	1.30±0.19	1.25+0.15	1.25±0.14	1.26±0.14
t test	0.844		0.238	
p value	0.40		0.81	
Mean arterial blood pressure (mmHg) mean value	83.5±5.88	80.5±5.34	82.8±7.14	80.7±6.63
t test	1.68		0.942	
p value	0.10		0.35	

Discussion

Fenugreek (*Trigonella foenum graecum*) is an annual Mediterranean and Asiatic herb having aromatic seeds (Petropoulos, 2002) [16]. It has many therapeutic properties such as hypolipidemic (Anita *et al*., 2007) [4], hypoglycemic (Sharma *et al*., 1990; Analava and Debaprasad 2004) [21, 2] antioxidant (Birjees Bukhari *et al*., 2008) [6], antibacterial (Dash *et al*., 2011) [7] and diuretic (Rohini *et al*., 2008; Al-Atwi, 2010) [19, 1]. However, there is no previous clinical data on humans to support the traditional use of Fenugreek as a diuretic agent.

In an effort to investigate the possible diuretic efficacy, safety and tolerability of Fenugreek, we performed this randomized controlled clinical trial in 39 cirrhotic ascitic patients. Fenugreek exerted a weak diuretic efficacy where the mean change of body weight and 24h urine volume was significantly lower than Group I. Na excretion in 24h urine increased insignificantly at the end of the study while in the control group, significant increment was noticed. Insignificant increment of K excretion in 24h urine was observed in both groups. Serum Na insignificantly decreased in the Fenugreek group as compared to the significant diminution in the control group. In both groups, serum K decreased insignificantly. Fenugreek was found to be safe and tolerable as no significant changes in biochemical tests nor any side effec tswere bserved.

Our study is supposed to be the first human clinical trial that evaluates the possible diuretic efficacy of Fenugreek in ascetic cirrhotic patients. The observed diuretic potential seems to be parallel to the previous experimental research on other animals.

Rohini *et al*. (2008) [19] tried to evaluate the diuretic activity of petroleum ether, benzene, ethanol and aqueous extract of Fenugreek seed in wistar rat, divided in seven groups of six animals in each. The first group received normal saline (25 ml/kg, p.o.), the second, furosemide (10 mg/kg i.p.), other groups received doses of extract 150 mg/kg and 350 mg/kg (i.p). Urine volume and Na+, K+ and Cl^- ion concentrations were estimated. The volume of urine increased significantly at 150 mg/kg ($p<0.05$) and 350 mg/kg ($p<0.01$) and the electrolytes excretion increased in a dose-dependent manner from petroleum ether, benzene chloroform, ethanol and aqueous extracts of Fenugreek seeds respectively. There was significant increase in the volume of urine and marked increase in excretion of sodium, potassium and chloride ($P< 0.01$) in Furosemide group as compared to the control (Schrier *et al*., 1988) [20].

In another clinical trial (Al-Atwi, 2010) [1] Fenugreek alcoholic extract (1.375gm of Fenugreek extract dissolved in 7.5 ml distilled water per 12 hrs) was compared with equal volume of distilled water given to two groups of five healthy adult male albino rabbits. The duration of the study was 4 weeks through which serum and 24-hr urine samples were analyzed weekly for electrolyte level, osmolality and pH. Fenugreek caused a significant increase in sodium and potassium excretion with a significant hypocalciuric effect. No significant changes were observed in serum sodium, potassium, chloride, calcium, pH and osmolality with respect to the control values. She concluded that Fenugreek has a very powerful diuretic effect which is thiazide-like (Al-Atwi, 2010) [1].

Some limitations may be the cause of weak diuretic response that was achieved in our study. The used dose and formula of Fenugreek may be one of them. Larger dose with special pharmaceutical formula may help in better absorption and delivery of Fenugreek. Longer duration may present more potent diuretic effect which may form the basis for future studies.

In spite of salt restriction in all patients, calculation of daily Na and K intake seems to be more accurate for taking up further studies. The actual diuretic mechanism of Fenugreek maybe explained by using *in situ* kidney perfusion technique.

Conclusion

Insignificant diuretic efficacy of Fenugreek was observed in our study, these findings may pave way for further trials to get benefit of its diuretic activity in cirrhotic ascites especially, after demonstrating its safety and tolerability that may protect the patients from other diuretic complications.

References

1. Al-Atwi LF, Clinical evaluation for the diuretic effect of the alcoholic extract of *Trigonella faenum-gracum* seeds (fenugreek) on rabbits. Koufa Journal of Veterinary Science. 2010; 1(1):116-121.
2. Analava M, Debaprasad B, Dose-dependent effects of fenugreek composite in diabetes with dislipidaemia. International Journal of Food Safety. 2004; 8:49-55.
3. Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, Galioto A, Salinas F, D'aquino M, Sticca A, Gatta A, Combined versus sequential diuretic treatment of ascites in non azotemic patients with cirrhosis: results of an open randomized clinical trial. Gut. 2010; 59:98-104.
4. Anita K, Malkit N, Rajbir S, Effect of supplementation of traditional medicinal plants on serum lipid profile in non-insulin dependent diabetics. Journal of Human Ecology. 2007; 22(1):35-40.
5. Bernardi M, Optimum use of diuretics in managing ascites in patients with cirrhosis. Gut, 2010; 59: 10–11.
6. Birjees Bukhari S, Bhanger ML, Memon SH, Antioxidative activity of extracts from fenugreek seeds (*Trigonella foenum graecum*). Pakistan Journal of Anna Environmental Chemistry. 2008; 9:78-83.
7. Dash BK, Sultana S, Sultana N, Antibacterial activities of methanol and acetone extracts of Fenugreek (*Trigonella foenum*) and Coriander (*Coriandrum sativum*). Life Science Medical Research. 2011, LSMR-27.
8. Gupta A, Gupta R, Lal B, Effect of *Trigonella foenum graecum* (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double-blind placebo controlled study. Journal of Association of Physicians India. 2001; 49:1057-1061.
9. Jain V, Jain P, Sharma S, Kakani R, Hypolipidaemic

activity of syndrex, a hydroalcoholic extract of fenugreek seeds Single blind clinical study. International Medicine Journal. 1995; 89:1-41.
10. Kaviarasan S, Viswanathan P, Anuradha CV, Fenugreek seed (*Trigonella foenum graecum*) polyphenols inhibit ethanol-induced collagen and lipid accumulation in rat liver. Cell Biol. Toxicology. 2007; 23:373-383.
11. Lucena MI, Andrade RJ, Tognoni G, Hidalgo R, De La Cuesta FS, Fraile JM, Cabella R, Multicenter hospital study on prescribing patterns for prophylaxis and treatment of complications of cirrhosis. European Journal of Clinical Pharmacology. 2002; 58:435-440.
12. Madar Z, Rachel A, Shlomith S, Joseph A, Glucose lowering effect of fenugreek in non-insulin dependent diabetics. European Journal of Clinical Nutrition. 1988; 42:51-54.
13. Moller S, Henriksen JH, The systemic circulation in cirrhosis. *In*: P. Ginès, V. Arroyo, J Rodés, R.W. Schrier (eds.): Ascites and renal dysfunction in liver disease, Malden: Blackwell. 2005, 139-155.
14. Muralidhara, Narasimhamurthy K, Viswanatha S, Ramesh BS, Acute and subchronic toxicity assessment of debitterized fenugreek powder in the mouse and rat. Food Chem. Toxicology. 1999; 37:831-838.
15. Opdyke DL, Fenugreek absolute. Food Cosmet Toxicol. 1978; 16:S755-S756.
16. Petropoulos GA, Fenugreek -The genus *Trigonella*. 1st ed. Taylor and Francis, London and New York. 2002, 1-127.
17. Rao PU, Sesikeran B, Rao PS, Naidu AN, Rao VV, Ramachandran EP, Short term nutritional and safety evaluation of fenugreek. Nutrition Research, 1996; 16:1495-1505.
18. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J, Hepatic venous gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007; 133:481-488.
19. Rohini RM, Nayeem M, Das AK, Diuretic effect of *Trigonella foenum graecum* seed extracts. International Journal of Alternative Medicine. 2008; 6(2):1-4.
20. Schrier RW, Arroyo V, Bernardi M, Bernardi M, Epstein M, Henriksen JH, Rodés J, Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988; 8:1151-1157.
21. Sharma RD, Raghuram TC and Rao NS, Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. European Journal Clinical Nutrition. 1990; 44:301-306.
22. Sharma RD, Sarkar A, Hazra DK, Hypolipidaemic effect of fenugreek seeds: a chronic study in non-insulin dependent diabetic patients. Phytotherapy Research. 1996; 10:332-334.
23. Sharma RD, Sarkar A, Hazra DK, Misra B, Singh JB, Maheshwari BB, Toxicological evaluation of fenugreek seeds: a long term feeding experiment in diabetic patients. Phytotherapy Research. 1996; 10:519-520.
24. Shekha MS, Qadir AB, Ali HH, Selim XE, Effect of Fenugreek *Trigonella foenum-graecum* on Ethylene Glycol induced kidney stone in rats. Jordan Journal of Biological Science. 2014; 7(4):257-260.
25. Vuorelaa MP, Leinonenb M, Saikkuc P, Tammelaa P, Rauhad JP, Wennberge T and Vuorela H, Natural products in the process of finding new drug candidates. Current Medicinal Chemistry. 2000; 11(11):1375-1389.