Original Article

Effect of *Ferula assa-foetida* oleo-gum-resin on renal function in normal Wistar rats

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ABSTRACT

In traditional Iranian medicine, asafoetida, an oleo-gum-resin obtained from the roots of Ferula assa-foetida, has been prescribed as a diuretic. This study was undertaken to investigate the diuretic effect of asafoetida in normal rats. Asafoetida was administered orally at the doses of 25 and 50 mg/kg and furosemide (10 mg/kg, intraperitoneal) was used as positive control. The diuretic effect was evaluated by measuring urine volume and sodium, potassium, urea, and creatinine content in urine and serum. Urine volume, excretion of sodium, and potassium were significantly increased by asafoetida as compared to the control group. A significant increase in creatinine clearance was observed in the groups treated with asafoetida at the doses of 25 and 50 mg/kg ($P < 0.05$). We conclude that asafoetida induced a diuretic effect comparable to that produced by the reference diuretic furosemide. This study provides a quantitative basis for explaining the folkloric use of asafoetida as a diuretic agent.

Key words: Asafoetida, diuretic activity, *Ferula assa-foetida*, furosemide, medicinal plant

Introduction

Medicinal plants are commonly used to treat renal diseases. Many medicinal plants have been studied and their activities confirmed in experimental animals.[1] Diuretics are used for treatment of hypertension, congestive heart failure, ascites, and pulmonary edema.[2] Thiazides and furosemide are also associated with a number of adverse effects, such as electrolyte imbalance, metabolic alterations, development of new-onset diabetes, activation of the rennin–angiotensin–neuroendocrine systems, and impairment of sexual function.[3] Hence, there is a need for new diuretics with lower potential adverse effects.

Medicinal plants are important sources of safe chemical substances with potential therapeutic effects. The World Health Organization has estimated that over 75% of the world's population still relies on plant-derived medicines, usually obtained from traditional healers.[4] Plants of the genus *Ferula,* family Apiaceae, include about 130 species distributed throughout central Asia and Mediterranean area.[5] *Ferula assa-foetida* L. grows wildly in the central area of Iran. Pharmacologically important part of this plant and several other species of *Ferula* is an oleo-gum-resin (asafoetida) obtained from incisions in the stem and/or roots of these plants.[6] In Iranian folk medicine, asafoetida is used as a diuretic, antispasmodic, carminative, and analgesic agent.[7] Recent pharmacological and biological studies have also shown several pharmacological activities such as antioxidant,[8] antileishmanial,[9] cancer chemopreventive,[10]

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anticonvulsant[11] anti-diabetic,[12] antispasmodic,[13] hypotensive,[14] and antinociceptive[15] for asafoetida. Phytochemistry of asafoetida showed that gum fraction contains the glucuronic acid, galactose, arabinose and rhamnose and its resin consists of umbelliferone, ferulic acid and its esters, coumarins, sesquiterpene coumarins and other terpenoids.[6] Despite the fact that in Iranian folk medicine asafoetida has been considered as a diuretic agent, to our knowledge, there is no comprehensive study on its effects on the renal function. Hence, this study set out to evaluate the acute diuretic effects of orally administered *F. assa-foetida* oleo-gum-resin in rats.

Materials and Methods

Animals

Twenty-four male Wistar rats weighing between 200 and 250 g were bred and maintained in the Animal House Unit of the Faculty of Medicine of Shahid Sadoughi University of Medical Sciences under controlled temperature 21°C ± 1°C in 12 h light: 12 h dark schedule. Animals were housed in plastic cages, and food and water were made available *ad libitum*. The study was approved by Institutional Animal Ethical Committee of Shahid Sadoughi University of Medical Sciences (Yazd, Iran).

Preparation of plant oleo-gum-resin

F. assa-foetida oleo-gum-resin was collected from Tabas region (Yazd Province, Iran) during the summer, and the plant species was botanically identified by Dr. Abbas Zarezadeh in Yazd Agricultural Research Center. The dried powder of asafoetida was soaked in distilled water overnight at room temperature, and the yielded suspension was used orally. Concentrations and dosages of the suspension were expressed as the crude amount of the dried oleo-gum-resin used in preparing the stock solution.

Experimental design

Each animal was placed in an individual metabolic cage 24 h prior to commencement of the experiment for adaptation. The animals were divided into four groups of six rats per group and were fasted overnight with free access to water and subjected to the stated treatment as described below. Before treatment, all animals received an oral dose of 5 mL/100 g body weight (BW) physiological saline (0.9% NaCl) to impose a uniform water and salt load.[16] The first group received orally physiological saline 10 ml/kg BW, and served as the control group. The second group was treated with an oral dose of 10 mg/kg furosemide as a positive control group. The third and fourth groups were orally administered asafoetida 25 and 50 mg/kg BW. Urine was collected and its volume was measured 8 h after the treatments and a sample of it was used for measuring sodium, potassium, urea, and creatinine concentrations.

Biochemical analysis

At the end of the experiment, blood was collected in capillary tubes containing ethylenediaminetetraacetic acid by retro-orbital puncture under light diethyl ether anesthesia. Serum samples were obtained by centrifugation and stored at −20°C until analyzed. Serum levels of sodium, potassium, urea, and creatinine were measured. Urocolor test strips were used for quantitative determination of pH and specific gravity of urine samples.

Statistical analysis

Results were expressed as mean ± standard error of mean and statistically assessed by one-way ANOVA, followed by *post-hoc* Tukey's test using GraphPad Prism version 5 (San Diego, California). A value of $P < 0.05$ was considered as significant.

Results

Effect of asafoetida on urine volume

Asafoetida administration led to an increase in 8 h urine volume which was significantly more than the control rats (asafoetida 25 mg/kg 8.9 ± 1.7 mL, asafoetida 50 mg/kg 11.2 ± 1.9 vs. controls 3.7 ± 1.1 mL; $P < 0.01$) [Figure 1]. Furosemide in a single dose also induced a significant diuresis as compared to control group (14.1 ± 2.4 vs. 3.7 ± 1.1, $P < 0.01$) [Figure 1].

Effect of asafoetida on urine biochemistry

The effect of single furosemide doses and two doses of asafoetida on urine biochemical parameters (Na^+, K^+, urea and creatinine) is presented in Table 1. Asafoetida enhanced the excretion of the total amount of the electrolytes (Na^+ and K^+), as compared with control group. The Na^+/K^+ excretion ratio in furosemide group was higher than for the asafoetida. Urea concentration in furosemide and asafoetida treated animals was significantly increased as compared to control group.

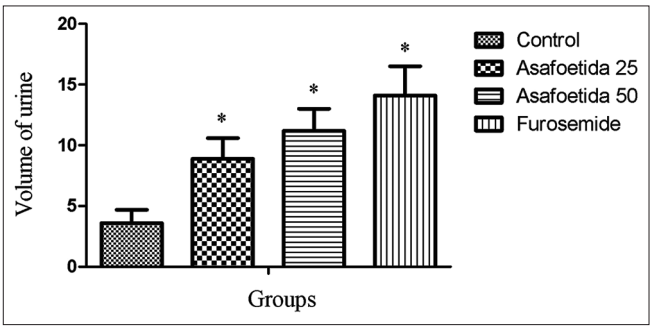

Figure 1: Effect of asafoetida 25 and 50 mg/kg on urine volume. The volume of excreted urine was measured at 8 h after the treatment. Mean ± standard error of mean, *n* = 5, **P* < 0.05

Table 1: Effect of oral administration of asafoetida on urinary factors at 8 h after treatment

Groups	Urea (mg/dl)	Urine pH	Specific gravity	Total Na^+ (μmoles/kg)	Total K^+ (μmoles/kg)	Na^+/K^+ ratio
Control	125.5±10	6±0.5	1.016±0.1	414.4±15	120.5±12	3.4±0.7
Asafoetida 25	179.9±11*	6.5±0.9	1.015±0.2	2329.2±49*	512.9±21*	4.5±1*
Asafoetida 50	381.7±16*	6.2±1	1.016±0.1	1716.2±38*	391.9±16*	4.4±0.8*
Furosemide	282.0±13*	6.8±1.1	1.015±0.1	1932±42*	301.5±18*	6.4±1.3*

Values are reported as mean±SEM for five rats in each group. *P<0.05 compared to control group. SEM: Standard error of mean

Creatinine clearance was measured on the last day of treatment. A significant increase in creatinine clearance was observed in the groups treated with asafoetida at the dose of 25 and 50 mg/kg [$P < 0.05$, Figure 2]. There was no significant difference between the pH and specific gravity of urine in different groups.

Effect of asafoetida on electrolytes, urea, and creatinine

The effect of two doses of asafoetida and furosemide on plasma electrolytes, urea and creatinine is presented in Table 2. There was no significant difference between Na, K, and creatinine concentration in different groups. Only urea concentration of plasma in animals that received furosemide was significantly higher than control animals ($P < 0.05$).

Table 2: Effect of asafoetida on urea, creatinine, Na and K levels of plasma after 8 h of treatment

Groups	Urea (mg/dl)	Creatinine (mg/dl)	Na^+ (mEq/L)	K^+ (mEq/L)
Control	36.3±5.1	0.8±0.1	141.4±14.3	4.1±0.5
Asafoetida 25	38.1±5.9	0.9±0.12	143.5±13.5	4.8±0.8
Asafoetida 50	40.7±6.3	0.8±0.13	142.8±12.9	4.5±1.2
Furosemide	54.3±7.4*	1±0.2	141.4±13.5	4.0±0.9

Values are reported as mean±SEM for five rats in each group. *P<0.05 compared to control group. SEM: Standard error of mean

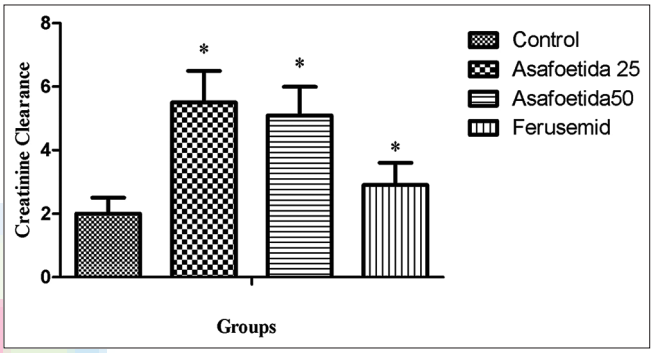

Figure 2: Effect of asafoetida on creatinine clearance. Creatinine clearance was measured at 8 h after the treatment. Mean ± standard error of mean $n = 5$, *$P < 0.05$ versus control, respectively

Discussion

In this study, the diuretic effect of orally administered asafoetida was evaluated in normal rats and the pharmacological response was compared with that produced by furosemide, a widely used diuretic in clinical practice. The oleo-gum-resin of *F. assa-foetida* selected for the study because it is commonly available and used in Iranian traditional medicine to induce dieresis.[7] The oral route was chosen because that is the way people use these plants in traditional medicine. Our results showed that asafoetida caused a significant increase in urine volume 8 h after treatment as compared to the control values. This effect was dose-dependent and a higher dose of asafoetida increased the urine exertion more than three times of control group. Diuresis also was accompanied by increased urinary excretion of Na and K. To investigate the mechanism of action of asafoetida; furosemide was used as positive control. Furosemide increases urine output and urinary excretion of sodium by inhibiting $Na^+/K^+/2Cl^-$ symporter (co-transporter system) in the thick ascending limb of the loop of henle.[17] The Na/K ratio could define the nature of the diuretic mechanism. The Na/K ratio for furosemide is approximately 6.4, which means that it eliminates Na more than K ion. On the other hand, this ratio was less in asafoetida treated groups as compared to furosemide indicating that the amount of K excretion was higher in animals received asafoetida compared to furosemide group. Both groups treated with asafoetida at the doses of 25 and 50 mg/kg significantly increased the creatinine clearance and urea exertion. The renal effects of asafoetida could be resulted from the decrease in tubular reabsorption of electrolytes and water and/or by modulating the flow of filtration. The urinary pH and specific gravity remained mostly unchanged throughout the study for both concentrations of asafoetida. The diuretic effect of *F. assa-foetida* oleo-gum-resin can be related to the presence of naturally bioactive compounds such as flavonoids and other phenolic compounds. Phytochemical analysis showed that asafoetida consists of phenolic compounds such as ferulic acid and its esters, coumarins, sesquiterpene coumarins and other terpenoids.[18] Flavonoids have shown a diuretic effect, and several flavonoids have been reported to inhibit Na-K-2Cl co-transporter, as well as an increase in natriuresis and kaluresis.[19,20] In an experimental study, hypotensive and vasodilatory effects of *F. assa-foetida* gum extract has reported.[14] There are evidences about the effect of asafoetida on the smooth muscles.[13] Asafoetida could affect the isolated pulmonary artery, so may affect the renal gemodynamics and led to an increase

in glomerular filtration rate. Although evidences for the diuretic efficacy of the asafoetida have been obtained, further investigations are necessary to determine the precise mechanism by which the extract affects diuresis and urinary electrolyte excretion. In conclusion, this study demonstrates that asafoetida has a diuretic action. The observed properties seem to validate the folk medicinal use of this plant, a fact which encourages the investigation of its phytochemical composition to isolate the bioactive compound(s) as well as pharmacological mechanisms of diuretic action.

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Conflicts of interest

There are no conflicts of interest.

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