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Anti-diabetic effects of aqueous extracts of three Iranian medicinal plants in type 2 diabetic rats induced by high fructose diet

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ABSTRACT

Objectives: Insulin resistance has been considered as the most important component of type 2 diabetes mellitus (DM2). Plants used in folk medicine to treat diabetes mellitus represent a viable alternative for the control of this disease. This study was aimed to examine the antidiabetic effects of three Iranian medicinal plants i.e. *Urtica dioica, Trigonella foenum-graecum* and *Fumaria officinalis* in an animal model of DM2.

Methods: Diabetes was induced in male Wistar rats (6-8 weeks old) by feeding 21% fructose in drinking water for 8 weeks. They were treated with aqueous extracts (10%) of three medicinal plants (*Urtica dioica, Trigonella foenum-graecum* and *Fumaria officinalis)* for 8 weeks. After diabetes induction and the last day of the experiment, body weight, fasting blood glucose, plasma insulin, urine volume and glucose were assayed.

Results: Blood glucose, plasma insulin, urine glucose and urine volume were increased significantly after 8 weeks of high fructose feeding ($P<0.05$); the aqueous extracts of *Urtica dioica* reduced the blood and urine glucose and also the aqueous extracts of *Trigonell Foenum* diminished the insulin, weight and blood glucose in comparison with the high fructose-fed control group ($P<0.05$).

Conclusion: The obtained data in this study showed hypoglycemia effects of *Trigonell Foenum* and *Urtica dioica* extracts. Also our findings indicated that the hypoglycemia effect of *Trigonell Foenum* extract is in part by improvement of insulin resistance. These results can be extrapolated to humans and these extracts might be useful in the treatment of insulin resistance.

Keywords: *Glucose; Hypoglycemic Agents; Insulin Resistance; Trigonella; Urtica dioica*

Introduction

Primary treatment goals in diabetes include restoration and maintenance of normoglycaemia, avoidance of diabetic complications, and prevention of cardiovascular events. In addition to glycemic control, management of hyperinsulinemia is also essential for limiting the complications of type 2 diabetes mellitus (DM2) [1]. Feeding of a high fructose diet to normal Wistar rats provides a dietary model of type 2 diabetes associated with insulin resistance, hyperinsulinemia, hypertriglyceridemia[2] and hypertension [3]. The precise molecular mechanisms that high fructose diet induces the abnormalities in liver carbohydrate metabolism are not fully understood. Thus, fructose has been implicated as the useful tool to induce insulin resistance in animals [4].

We took the advantage of these fructose-induced metabolic characteristics to develop an animal model of advanced DM2. Plants used in folk medicine to treat diabetes mellitus represent a viable alternative for the control of this disease [5]. *Urtica dioica, Trigonella foenum-graecum* and *Fumaria officinalis* are traditionally consumed as herbal medicine in Iran and they are mentioned for treatment of diabetes. Some people in Iran use *Urtica dioica L.* (UD) or nettle as

food supplement like herbal tea or flavored food without any side effect. Moreover, UD is known in folk medicine in Iran as hypotensive and antidiabetic. The blood sugar lowering effect of UD has been introduced in old scripts such as those written by Avicenna [6]. Also other reports indicate the different benefits of UD extract for prostatic hyperplasia [7], inflammation [8], rheumatoid arthritis [9], hypertension and inhibition of platelet aggregation [10]. It is noteworthy that the mode of the effect has not been determined to date [6]. Although, some studies mentioned that this plant has no effect on diabetes [11], its antidiabetic activities in experimental diabetic rats have been well documented in scientific literature [12]. However in our knowledge, studies regarding its efficacy in preventing insulin resistance which plays a role in pathophysiology of type 2 diabetes mellitus have not been undertaken.

Trigonella foenum-graecum L. (TF) or Fenugreek dried ripe seeds is well known for its pungent aromatic properties [13]. TF seeds and leaves are said to have antidiabetic activity [14]. It seems that TF exerts its hypoglycemic effect by delaying glucose absorption through inhibition of disaccharidase enzyme in the gut [15] and enhancing its utilization [16], hence it considered to be potentially useful for glucose control and preventing hyperlipidaemia and atherosclerosis in diabetic subjects. TF showed a significant hypoglycemic effect in Type 2 diabetic model rats when it was fed simultaneously with glucose [17].

Fumaria species, known as "fumitory, earth smoke, beggary, fumus, vapor, fumittery or wax dolls" in English, have been reported to be used traditionally against hepatobiliary diseases in the folk medicines of various countries [18]. *Fumaria officinalis L*. (FO) is a widespread perennial herb in Europe and Asia which has played a traditional role in empirical medicine over centuries. Fumitory has been used in many countries for the treatment of skin diseases, rheumatism, hypertension or infections. Nowadays, this herb is a component in several phytopharmaceuticals, mainly used to treat functional diseases of the hepatobiliary system discernible as colicky pains affecting the gallbladder, biliary system and the gastrointestinal tract. These biological activities of fumitoryare mainly associated with the presence of isoquinoline alkaloids [19]. In Morocoo this plant is used as drug for hypertension and cardiac disease [20]. FO is also used against hepatic and gallbladder diseases as tea in northern Portugal [21]. In Italy this plant is used for Depurative, cholagogue, hypertensive, antispasmodic, respiratory stimulant, and anti-arteriosclerosis [22]. In Cyprus people use this plant as a medical herb for hypertension, constipation, liver detoxification, and spasmolytic [23]. A review of the literature, however, reveals very few studies about the effect of these plants on insulin resistance.

Therefore this study was designed to investigate the effects of three Iranian traditional plants (*Urtica dioica, Trigonella foenum-graecum* and-*Fumaria officinalis)* on insulin resistance and glycemia condition of type 2 diabetic rats induced by high fructose diet.

Materials and Methods

Plant material & Preparation of extracts

All plants were purchased from the local market in western area of Iran, identified and authenticated by a botanist. All parts of the plants were dried at room temperature and were grounded into powder.

Ten grams of these powders were boiled with 100 ml of distilled water for 5 minutes with occasional stirrings. The decoction preparation was then filtered through a gauze cloth followed by filtration through regular filter paper (Watman no. 1). Extract was kept at 4°C until its use within 1 week [15]

Animals

Male Wistar rats (6-8 weeks old weighing approximately 150–200 g) were housed in stainless steel cages (three animals per cage). The animals were kept 1 week prior to the experiment for full acclimatization in an air-conditioned animal room (22 ± 2°C) under a 12 h light/dark cycle with free access to standard pellet diet and water, the rats were kept for 17 weeks.

The study was approved by the ethics committee of Hamadan University of Medical Sciences, and the rats were maintained in accordance with the National Institute of Nutrition (Iran) guidelines for the care and use of laboratory animals.

Experimental design

The animals were randomly divided into five groups containing six rats in each group as given below:

(I) Normal control (NC) receiving only standard chow diet and normal drinking water; (II) Diabetic control (DC) receiving standard chow diet and a 21% fructose solution with drinking water; (III) *Urtica dioica* group (UD), (IV) *Trigonella foenum-graecum* group (TF) and (V) *Fumaria officinalis* group (FO) receiving standard chow diet and a 21% fructose solution as drinking water for 8 weeks and a 21% fructose solution plus either aqueous herbal extract with drinking water for another 8 wks.

On day 0, the animals were distributed into groups. Food and water were supplied ad libitum. DC, UD, TF and FO groups started to use fructose for diabetes induction (8 wk), after diabetes confirmation, UD, TF and FO groups started to be treated with the plants extracts for 8 wk more (till 16th wk).

The rats were considered to be diabetic and were used for the study if they developed hyperglycemia (blood glucose more than 150 mg/dl) after 8wk fructose consumption.

Sample collection and Biochemical measurements:

Body weight, 6 hour urine, and blood sample were taken on day 0, end of 8th and 16th week. Sample was collected from 12-h fasted rats.

Blood samples (Approximately, 1 ml) were taken from aorta under general anesthesia following intraperitoneal injection of ketamine HCl (50 mg/kg). The blood was placed into an Eppendorf tube, centrifuged at 3000 rpm for 5 min and the serum was aliquoted, frozen at −20°C and assayed for glucose and insulin later.

The 6 hours urine was collected from fasted overnight rat that had free access to tap water. Urine volume and urine glucose were measured. The blood and urine glucose were determined by glucose oxidase method, using Pars Azmun kit (Iran). Serum insulin was assayed by an enzyme-linked immune sorbent assay (ELISA kit Alpco).

Statistical analysis

Values are given as mean ± standard deviation (SD). The statistical analysis of biochemical parameters were conducted using the SPSS 10.1. Within-group comparisons were performed by Wilcoxon (2-related samples) and between groups' comparisons by Mann Whitney U test (2-Independent samples). Kruskal–Wallis test was applied to check for statistical evaluations between 2 groups. In all analyses, P<0.05 was considered significant.

Result

Values for blood glucose, urine glucose, plasma insulin and urine volume increased significantly (compared to day 0) in induced diabetes groups (DC, UD, TF &FO) after 8 weeks of high fructose feeding (P<0.05, Fig. 1), while no significant difference was observed in these parameters in NC group during this period of time (Table 1). Although two exceptions were observed, increase in weight in this period in NC group and no increase in urine volume in FO group.

Table 1: The levels of weight, plasma insulin, and urine volume in different rat groups (n= 6) on day 0 and after 8 weeks high fructose fed†

Group	Weight(g)		Plasma insulin(ng/ml)		Urine volume(ml)	
(n=6)	0 day	8 wk	0 day	8 wk	0 day	8 wk
NC	171.8±18.3*	310.8±41.8	1.088±0.50	1.77±0.94	3.60±1.20	2.40±2.10
DC	184.3±16.8	312.2±36.8	1.23±0.76	2.70±0.65	2.80±0.76	7.60±1.60
TF	172.3±26.2	352.3±41.3	1.043±0.40	2.80±0.50	3.40±1.18	8.32±0.80
FO	175.3±14.1	332.5±38.2	0.94±0.51	2.81±2.10	4.10±1.54**	6.60±2.77
UD	175.4±26.8	288.7±33.9	1.21±0.88	2.80±1.19	2.80±0.60	6.35±0.78

† All comparisons between day0 and 8wk in each group, except NC (Normal control), were significant (P<0.05)
* Significant difference in NC group between 0day and 8th wk.
**no significant difference between 0day and 8 wk in urine volume of FO group
NC, Normal control; DC, Diabetic control; TF, Trigonella foenum-graecum; FO, Fumaria officinalis; UD, Urtica dioica

In the NC group in the 16th wk no significant differences was observed in the studied parameters compared to those of 8th wk, however in DC group the changes were notable. The mean (SD) of rat`s weight in DC group was 184.3 g (16.8) and 344 g (37.0) after 8 and 16 weeks respectively, and the difference was significant.

No significant difference was detected in urine volume and urine glucose in the TF group, while blood glucose, weight and plasma insulin experienced significant changes (P<0.05). Obtained data from the FO group did not show any significant changes in the studied parameters between the 8th and the 16th week. In UD group, weight,

urine volume and plasma insulin remained unchanged (p>0.05), whereas blood glucose and urine glucose decreased considerably (P<0.05) (Fig. 2).

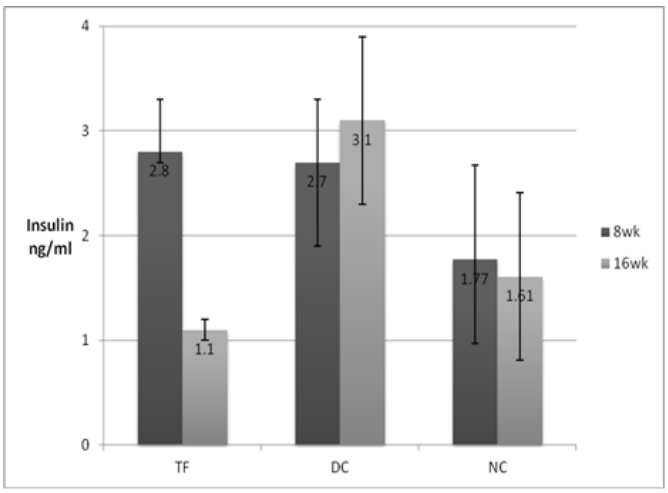

Figure 1. Plasma insulin in 8th and 16th week in TF , DC and NC groups. (NC; Normal control, DC; Diabetic control, TF; Trigonella foenum-graecum)

Urtica extract significantly decreased blood glucose and urine glucose but had no effect on plasma insulin. Trigonella extract significantly affected blood glucose and plasma insulin (P<0.05), however aqueous extract of Fumaria did not have any effect on the mentioned factors.

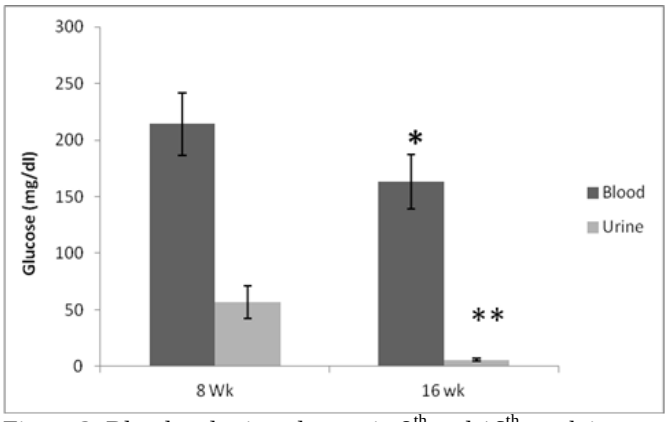

Figure 2. Blood and urine glucose in 8th and 16th week in rats receiving UD (Urtica dioica) extract.
* Significant difference in Blood Glucose between 8th wk and 16 wk
** Significant difference in urine Glucose between 8th wk and 16 wk

Discussion

A variety of oral active hypoglycemic agents are frequently used to help the management of glucose intolerance in type 2 diabetic patients. However the effectiveness of these drugs is limited and suffers from a variety of the side effects including hypoglycemia.

Our results indicated a decrease of plasma glucose and plasma insulin level in the fructose-rich diet rats receiving an oral administration of TF that was significant compared to the control diet group. In our study the observed hypoglycemic effect was similar to those of Farzami et al. [7] and Bnouham et al. [13]. Our findings regarding the effect on insulin were also consistent with those of Golalipour [24] study. Although we think the effect of the extracts on inhibition of intestinal absorption, mentioned in some studies [12, 25], is correct but since Farzami et al. [7] showed that IP injection of the extract had hypoglycemic effects, another mechanism may be involved.

TF seeds are found to remarkably suppress the clinical symptoms of diabetes such as polyuria, polydypsia, weakness and weight losses [26]. A possible mode of action of *TF* is an effect on intestinal carbohydrate digestion. It was found that *TF* decreases digestion of starch and also glucose absorption both in vivo and in vitro [27]. This may be the result of a direct inhibitory effect on the digestive enzymes [28]. Zia et al. [15] showed aqueous and methanolic extract of TF seed have hypoglycemic effect on normal mice, also they specified that the substance responsible for hypoglycaemic activity is probably polar in nature, being more soluble in water than in methanol or could be the presence of two different substances in TF but with different hypoglycaemic activities.

In diabetic rats receiving UD extract, while insulin remained unchanged, blood and urine glucose decreased significantly. Various studies showed the controversial effect of Urtica extract on blood glucose [9, 14, 15, 24, 25]. Farzami et al. (2003) suggested that the aqueous extract of UD leaves could enhance the secratogogue function of islets of langerhans, they also showed an interaperitoneal injection of purified UD had a hypoglycemic effect in both STZ diabetic and normal rats, however the effect in STZ group was less [7]. They concluded the reason was islet destruction. In contrast to Farzami`s findings, Domola et al. [25] mentioned that active fraction of UD did not stimulate insulin secretion in glucose-responsive in MIN6 clonal beta-cells.

Golalipour et al. [24] reported that UD extract did not decrease blood glucose and did not have any effect on beta cell regeneration. Onal et al. [29] established that the antidiabetic effect of UD is related to inhibition of alpha glycosidase in

intestine and Golalipour et al. [24] agreed with Onals conclusion.

The difference between Farzami et al. [7] and Golalipour et al. [24] studies can be due to the difference between times of administration, since in the former it was acute and short time but in the later was chronic (4wk). Bnouham et al. [13] demonstrated that oral administration of the aqueous extract of the UD did not modify the blood glucose level in alloxan-induced diabetic rats. On the contrary, a strong antihyperglycemic effect of UD is reported in normal rats. Bnouham et al. [13] also observed a significant reduction in the absorption of glucose in jejunum segment of intestine through treatment of nettle–water extract. GÜnes et al. [30] described; not only UD had no effect on diabetes, but also caused some side effects in the kidney and liver.

Another plant that we investigated for its effect on diabetes type 2 was *Fumaria Officinalis* that is used in Iran folklore medicine. Our literature survey showed the hepatoprotective activity of FO and also approved effect on gallbladder, biliary system; gastrointestinal tract in an early article [22], whereas our results did not show any special effect on diabetes parameters, therefore the traditional use of FO may be superstition.

Vats et al [27] results revealed a well defined alcoholic extract of Trigonella in suppressing blood glucose levels in normal, glucose fed hyperglycemic and alloxanized diabetic rats as compared to normal and standardized controls. Vats et al [27] also mentioned that TF may inhibit intestinal glucosidase and insulin release. It has shown that Tf-sdf (soluble dietary fiber fraction of TF*)* can effectively reduce postprandial rise of glucose in rats [31]. It has also been shown earlier that Tf-sdf fraction does not stimulate insulin secretion during a single feeding [32].

Hannan et al [28] findings, as well as previous studies, suggest that the hypoglycemic activity of Tf-sdf is not related to stimulation of insulin secretion. Thus, this material may lead to postprandial glucose reduction without any extra load on the pancreatic B cells. It has been previously shown by Hannan et al [28] that Tf-sdf fraction effectively inhibits carbohydrate absorption in the gut.

Not only did we not observe significant increase in weight that is noticed in literature [31], (showing obesity with fructose feeding in comparison to chow-fed controls) but also after receiving an oral treatment of TF a reduction in weight (that gained in diabetes induction period) was observed that can be due to diarrhea which is one of TF side effects. However it should be mentioned that in our study the rats were type 2 diabetics while in the above study alloxanized rats were used. Our findings that TF affects on plasma insulin and improves insulin resistance are against of Hannan et al. [28] results that indicated no effect when they induced type 2 diabetes with STZ IP injection and gave the extract twice a day. Our results showed not only decreased hyperglycemia but also improved insulin resistance; therefore we could deduce that TF can be one of the suitable choices for diabetes type 2. Moreover another report [13] mentioned that TF not only may increase plasma insulin levels *in vivo* but also stimulates insulin secretion from perfused pancreas *in vitro*. Despite of this report, Vijayakumar and Bhat [32] reported that I.P injection of TF extract can reduce serum insulin concentration and they suggested extra-pancreatic mechanism and insulin mimetic properties for TF. These results are consistent with our findings.

Our studies on the hypoglycemic activity of the aforementioned plant remedies are in progress for the isolation of active constituents and to elucidate their mode of action. Other experiments are necessary to determine the mechanisms of hypoglycemic action of UD & TF and the active fractions involved in this effect. Overall these results can be extrapolated to humans and these extracts might show usefulness in the treatment of insulin resistance in non-diabetic states such as obesity and impaired glucose tolerance. UD and TF have been used for long periods in Iran and other countries as medicine for wide range of diseases and as food ingredients without any side effects or toxicity, however it is important to confirm the dose of drugs that has beneficial effects.

Conclusion

In summary, feeding high fructose diet to normal rats led to insulin resistance, hyperinsulinemia and hyperglycemia. Only hyperglycemia was attenuated by aqueous extract of *Urtica dioica*. Urtica extract was found ineffective in reducing mean plasma insulin level while significantly decreased hyperglycemia.

Against traditional belief we found Fumaria aqueous extract has no especial effect on diabetes parameters. In agreement with some reports we showed Trigonella aqueous extract has hypoglycemic effect and also the novel effect that we found was improvement in insulin resistance in fructose fed rats.

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Conflict of interest

The authors report there are no conflicts of interest.

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