International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

International Journal of Pharmacology 11 (1): 72-75, 2015
ISSN 1811-7775

ansinet
Asian Network for Scientific Information

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.72.75

Antihyperglycemic Properties of *Foeniculum vulgare* Extract in Streptozocin-Induced Diabetes in Rats

[1]Nizar M. Mhaidat, [2]Ahmed S. Abu-zaiton, [1]Karem H. Alzoubi, [1]Wael Alzoubi and [3]Rami S. Alazab
[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, 22110, Jordan
[2]Department of Biological Science, Al-Albayt University, P.O. Box 130040, Mafraq, 25113, Jordan
[3]Department of Surgery, Faculty of Medicine, Jordan University of Science and Technology, Irbid, 22110, Jordan

ARTICLE INFO
Article History:
Received: October 06, 2014
Accepted: December 31, 2014

Corresponding Author:
Nizar M. Mhaidat,
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Jordan University of Science and Technology, Irbid, 22110, Jordan
Tel: +962-2-720100
Fax: +96227201075

ABSTRACT
The present study aimed to evaluate the antihyperglycemic effects of *Foeniculum vulgare* extract in streptozotocin (STZ)-induced diabetes in rats. Diabetes was induced via an intraperitoneal injection of STZ (50 mg kg^{-1} b.wt.). Control and diabetic animals were treated by *F. vulgare* extract (100 mg kg^{-1}) or a similar volume of vehicle. Animals body weight and water intake were monitored and recorded. Blood glucose, amylase, total cholesterol alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea and creatinine were determined using standard biochemical methods. Results indicated that treatment of diabetic animals with *F. vulgare* extract restored body weight to be similar to control animals. Additionally, treatment with *F. vulgare* reduced hyperglycemia in diabetic animals, yet it did not affect glucose levels in control animals. Similarly, treatment of diabetic animals with *F. vulgare* significantly reduced the diabetes-associated elevation in levels of amylase, total cholesterol, ALT, AST, urea and creatinine suggesting a protective effect on the cardiovascular system, the liver and kidneys. These findings demonstrated the effectiveness of *F. vulgare* extract in management of STZ-induced diabetes and some of its related complications in animal models. Thus, a more comprehensive characterization of the medicinal potential of *F. vulgare* will provide understanding of its mechanisms of action and its possible use for diabetes.

Key words: Diabetes, *Foeniculum vulgare*, streptozotocin, liver enzymes, rat

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels resulted from either a peripheral resistance to insulin or insulin secretion defect (Kalra, 2013). The currently available treatment options for hyperglycemia, apart from lifestyle changes and weight reduction, are oral hypoglycemic agents with various modes of action and different types of insulin (Spasov *et al*., 2013). Thus, many classes of medicines are used for the treatment of diabetes but all of them have limited efficacy and are associated with adverse effects. Therefore, the search for new classes of compounds is essential to overcome these problems (Maiese *et al*., 2011; Maiese *et al*., 2013). Medicinal plants are considered to be a good alternative since they are generally less toxic and free from side effects as compared to synthetic drugs.

Foeniculum vulgare is umbelliferous plant traditionally used for medicinal purposes and as a food component. It is native to southern Europe and the Mediterranean area. Seeds of the plant have been shown to regulate menstruation, alleviate symptoms of female climacteric syndrome and increase libido (Albert-Puleo, 1980). Fennel is a common name of *F. vulgare*, it is also traditionally recommended for diabetes, bronchitis and chronic coughs and for the treatment of kidney stones. A previous study showed that *F. vulgare*

essential oil corrected hyperglycemia in streptozotocin-treated rats (El-Soud *et al.*, 2011). On the other hand, Dongare *et al.* (2012) reported the antidiabetic activity of trans-anethole in streptozotocin-induced diabetic rats through aldose-reductase inhibition (Dongare *et al.*, 2012). The species is also considered to have diuretic, stomachic and galactagogue properties (Ostad *et al.*, 2001). *Foeniculum vulgare* extract has been traditionally used as an antispasmodic, carminative, diuretic, lactation stimulant and as dressings for wounds (Baytop, 1984). The *F. vulgare* extract contains 1-3% of volatile oils, which are composed of 50-85% of anethole and about 20% of d-fenchone (Mimica-Dukic *et al.*, 2003; Dadalioglu and Evrendilek, 2004). In the current study, the possible antihyperglycemic properties of *F. vulgare* extract were evaluated in STZ-induced diabetic rats.

MATERIALS AND METHODS

Plant material: Aerial parts of *F. vulgare* was collected from local sources and the botanical identity was confirmed by a taxonomist Professor Jammel Lahaam, Department of Biological Sciences, Faculty of Science, Yarmouk University, Irbid-Jordan. A voucher specimen has been deposited at the herbarium of the Faculty of Pharmacy, Jordan University of Science and Technology. The plant material was air-dried at room temperature, grounded and protected from light at room temperature until required for extraction and analysis.

Preparation of plant extract: About 500 g of plant material was extracted exhaustively with n-hexane using Soxhlet apparatus to remove fatty materials followed by extraction with methanol. The solvent was evaporated under reduced pressure to yield about 23 g of MeOH extract.

Experimental animals: Wistar albino rats, of either sex, each weighing 160-210 g and their ages between 8-12 weeks, were obtained from the animal house at Jordan University of Science and Technology. They were kept in Plexiglas cages (6 rats per cage) at room temperature (22±1°C; 40-60% humidity) with a regular 12 h light and dark cycle and *ad libitum* access to standard rodent chow and water. Animals were treated humanely in accordance with guidance of Institutional Animal Care and Use Committee.

Induction of the experimental diabetes: After fasting, diabetes was induced by intraperitoneal injection of STZ dissolved in 0.1 M cold sodium citrate buffer (pH 4.4) at a dose of 50 mg kg^{-1} b.wt. (Alzoubi *et al.*, 2013). Animals were allowed to drink 5% glucose solution overnight to overcome the drug-induced hypoglycemia. After 72 h, STZ-treated animals were considered as diabetic when the fasting plasma levels were observed above 200 mg dL^{-1}. Blood was drawn from tip of the tail and blood glucose level was estimated daily using glucometer (One Touch Ultra, Johnson and Johnson Ltd., UK).

Animal groups and treatment: Four rats were used in each of the animal groups which were as follows: Group I: Control (vehicle-treated), Group II: Normal rats treated with extract, Group III: Diabetic animals (vehicle-treated), Group IV: Diabetic rats treated with *F. vulgare* extract (100 mg kg^{-1}) (Schone *et al.*, 2006), Tognolini *et al.*, 2007; Mohamad *et al.*, 2011). Vehicle and plant extract were administered once daily for 14 days beginning from the day of induction via oral gavage. As a positive control, an additional group of diabetic rats (n = 4) were treated with glibenclamide (0.25 mg kg^{-1} day^{-1}) for 14 days. For the glibenclamide treated diabetic rats, only serum glucose level was determined at the end of the 14 days treatment.

Blood biochemistry: Tests for amylase, total cholesterol (Syrbio, Syria), aspartate aminotransferase (AST; Syrbio, Syria), alanine aminotransferase (ALT; Biorex, UK), albumin (BioSystems, Spain), urea (Biorex, UK) and creatinine were all performed according to manufacturer's instruction using spectroscan 80D UV-VIS spectrophotometer (Biotech Engineering, UK).

Statistical analysis: All collected data represent the Mean±standard error (SE). Comparisons between the different groups were carried out by analysis of variance followed by the Tukey test. Differences were considered statistically significant when $p<0.05$.

RESULTS

Results in Table 1 revealed that induction of diabetes has significantly ($p<0.05$) decreased the body weight compared to controls and increased levels of water consumption by diabetic group. Oral treatment of diabetic animals with the extract of *F. vulgare* (100 mg kg^{-1}) has significantly ($p<0.05$) improved the body weight during the entire period of treatment and reduced water consumption.

The STZ was able to induce hyperglycemia in rats as indicated by significantly ($p<0.05$) increased levels of blood glucose compared with control values treated with vehicle (Table 2). Administration of glibenclamide (0.25 mg kg^{-1} day^{-1}) normalized serum glucose levels (103.4±2.3 mg dL^{-1}) compared to control (95.0±4.9 mg dL^{-1}). Similarly, treatment with *F. vulgare* partially restored levels of glucose. Moreover, there was a significant elevation ($p<0.05$) in the levels of serum cholesterol and amylase in diabetic rats when compared with the control group. Administration of *F. vulgare* extract partially normalized these levels.

In serum biochemistry analysis, ALT, AST, urea and creatinine were measured. As shown in Table 2, levels of creatinine, urea, ALT and AST were significantly ($p<0.05$) elevated in diabetic animals compared to control group. Administration of the *F. vulgare* extract to diabetic rats either partially or fully restored all these indices.

Table 1: Body weight and water intake variations in Wistar rats

Parameters	Control group	STZ	Extract	STZ+Extract
Initial body weight (g)	206.25±13.1	203.75±24.1	202.5±11.0	203.3±10.9
Final Body weight (g)	238.75±18.0	172.50±12.5*	220.7±15.0	211.0±12.0
Water intake (mL day^{-1})	20.20±2.4	91.10±11.1*	33.5±5.1	43.1±4.2

*Significant difference ($p<0.05$) from all other groups

Table 2: Serum biochemical analysis

Parameters	Control group	STZ	Extract	STZ+Extract
Glucose (mg dL^{-1})	95.00±4.9	420.00±23*	121.50±12.1	225.00±18.2*#
Amylase (U L^{-1})	65.02±5.1	152.30±7.2*	66.80±6.9	114.81±7.0*#
Total cholesterol	41.30±5.0	86.00±9.1*	34.50±5.3	56.80±5.2*#
ALT (U L^{-1})	31.40±4.0	47.80±3.1*	38.55±3.8	33.70±2.9
AST (U L^{-1})	27.10±3.42	46.98±4.8*	29.60±3.2	35.60±4.0*#
Albumin (g dL^{-1})	7.48±2.50	12.46±3.6	14.86±2.18	12.72±3.22
Urea (mg dL^{-1})	52.55±6.2	95.46±7.1*	55.45±6.3	58.10±5.4
Creatinine (mmol L^{-1})	0.521±0.01	2.57±0.1*	0.563±0.09	1.299±0.19*#

*Significant difference ($p<0.05$) from all other groups, #Significant difference ($p<0.05$) from the STZ group, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

DISCUSSION

In the present study, a number of biochemical indicators of diabetes mellitus were recorded in animals such as significant increase in blood glucose and increased water consumption. Administration of *F. vulgare* extract was effective in preventing polydipsia and elevated levels of blood glucose indicating the antidiabetic activity of the extract. Additionally, diabetes-associated increases in total cholesterol, ALT, AST, urea and ceatinine were restored, at least partially, via treatment with *F. vulgare*.

Despite the increase in the body weight of the untreated diabetic rats, the body weight of extract-treated animals was significantly reduced. This effect of the extract might be attributed to the increase in metabolic activity and increased glucose metabolism.

Medicinal plants with antidiabetic potential have been found to contain a variety of substances responsible for the reported effects (Loew and Kaszkin, 2002). Phytochemical tests of *F. vulgare* revealed the presence of triterpenes, steroids, saponins and phenolic compounds (Barros *et al.*, 2009). It has been demonstrated that triterpenes and phenols stimulate insulin secretion through their antioxidant activities (Jang *et al.*, 2000; Sarkhail *et al.*, 2007). Oxidative stress has been shown to play a key role in the causation of diabetes and diabetes complications (Stadler, 2012; Alzoubi *et al.*, 2013). The STZ produces oxygen radicals causing pancreatic injury and could be responsible for the increased blood glucose and lipid peroxidation. Thus, components of *F. vulgare* such as triterpenes and phenols may have a role in the alleviation of diabetes and its complications, probably via their antioxidant properties (Wolff, 1993; McCue *et al.*, 2004; Barros *et al.*, 2009) and ability to stimulate insulin secretion (Stadler, 2012; Alzoubi *et al.*, 2013). Identifying the active components in *F. vulgare* and determining their mechanism of action to reduce elevated blood glucose, are important aspects to be studied. These points will definitely be the matter of our future investigations.

Abnormalities in lipid profile are common during diabetes (Pari and Umamaheswari, 2000). As one of the complications that follow diabetic hyperglycemia is hypercholesterolemia leading to increased risk of ischemic heart disease (Boodhwani and Sellke, 2009). The increased levels of cholesterol in the blood vessels are largely attributed to the increase in the mobilization of free fatty acids from peripheral depots since insulin inhibits the hormone-sensitive lipase (Al-Shamaony *et al.*, 1994). Administration of *F. vulgare* to diabetic rats significantly decreased the plasma cholesterol level, which could be associated with lower risk of cardiovascular disease.

The liver is the main tissue for the detoxification and metabolism of most chemicals. Liver enzymes including ALT and AST usually help to detect chronic liver diseases by monitoring their concentrations. Both ALT and AST are considered as indicator of liver injury (Mehta *et al.*, 2009). Elevation in serum activities of both transaminases as observed in diabetes suggests damage to liver cells (Kramer and Retnakaran, 2013). Administration of the *F. vulgare* extract attenuated the elevation of ALT and AST in diabetic rats. This may indicate that the extract is nontoxic and might protect liver complications associated with diabetes.

Creatinine and urea are molecules used to assess kidney function. The elevation in urea and creatinine levels in the untreated diabetic rats is an indication of impaired kidney functions. Administration of *F. vulgare* extract restored urea and creatinine levels. Thus, the extract of *F. vulgare* could have protective effect against renal damage commonly noticed during diabetes.

CONCLUSION

Administration of the extract of *F. vulgare* showed antihyperglycemic activity in STZ-induced diabetes in experimental animals. It also showed potential to restore some of the cardiovascular, renal and hepatic complications of diabetes. Thus, the *F. vulgare* extract might be potential future herbal remedy for diabetes and its complications.

ACKNOWLEDGMENT

Many thanks for Jordan University of Science and Technology for support of this project.

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