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

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**Abstract**

The present study aimed to evaluate the antihyperglycemic effects of *Foeniculum vulgare* extract in streptozocin (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.

**Keywords:** Diabetes, *Foeniculum vulgare*, streptozocin, 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-fenchene (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, ground 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 hours 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 diabetics: 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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>STZ</th>
<th>STZ + Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>206.25±13.1</td>
<td>203.75±24.1</td>
<td>203.5±10.9</td>
</tr>
<tr>
<td>Final Body weight (g)</td>
<td>238.75±18.0</td>
<td>172.50±12.5*</td>
<td>220.7±15.0</td>
</tr>
<tr>
<td>Water intake (mL/week)</td>
<td>20±5.2</td>
<td>3.5±1.1</td>
<td>43.1±4.2</td>
</tr>
</tbody>
</table>

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

Table 2: Serum biochemical analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>STZ</th>
<th>STZ + Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg dL⁻¹)</td>
<td>95.00±4.9</td>
<td>420.00±23*</td>
<td>225.00±18.2</td>
</tr>
<tr>
<td>Amylase (U L⁻¹)</td>
<td>65.02±5.1</td>
<td>152.30±7.2*</td>
<td>114.81±7.0</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>41.30±5.0</td>
<td>86.00±9.1*</td>
<td>56.80±5.2*</td>
</tr>
<tr>
<td>ALT (U L⁻¹)</td>
<td>31.40±4.0</td>
<td>47.80±3.1*</td>
<td>33.70±2.9</td>
</tr>
<tr>
<td>AST (U L⁻¹)</td>
<td>27.10±3.42</td>
<td>46.98±4.8*</td>
<td>35.60±4.0*</td>
</tr>
<tr>
<td>Albumin (g dL⁻¹)</td>
<td>7.48±2.50</td>
<td>12.45±3.6</td>
<td>12.72±3.22</td>
</tr>
<tr>
<td>Urea (mg dL⁻¹)</td>
<td>52.55±6.2</td>
<td>95.46±7.1*</td>
<td>58.10±5.4</td>
</tr>
<tr>
<td>Creatinine (mmol L⁻¹)</td>
<td>0.52±0.01</td>
<td>2.57±0.1*</td>
<td>1.29±0.19*</td>
</tr>
</tbody>
</table>

*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 anti-diabetic activity of the extract. Additionally, diabetes-associated increases in total cholesterol, ALT, AST, urea and creatinine 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 anti-diabetic 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; Sarkhai et al., 2007). Oxidative stress has been shown to play a key role in the causation of diabetes and diabetes complications (Stadler, 2012; Alzouabi 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; Alzouabi 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-Shamaory 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**

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REFERENCES


