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The Effect of Foeniculum Vulgare Alcoholic Extract on Some Metabolic Changes in Liver and Kidneys of Alloxan Diabetic Mice

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Abstract

Background Some people used herbal extracts as a treatment for diabetes mellitus worldwide. Such treatment of considerable benefit especially during the early stages of the illness**.** Many phytoconstituents responsible for anti diabetic effects have been isolated from hypoglycemic plants; one of which is *Foeniculum vulgare*.

Objective To investigate the effects of alcoholic extract of *Foeniculum vulgare* on some biochemical parameters in liver and kidneys of alloxan-induced diabetic mice, in order to use this herb as natural products to the management of diabetes mellitus.

Methods Twenty four female mice (18 diabetic mice and 6 control) were divided into 4 groups, each contain 6 mice (I = control, II = alloxan-treated miceI, III and IV = extract treated mice). Oral administration of *Foeniculum vulgare* extract given for 30 days to group III and IV in doses of 1.2 mg/kg BW) and 2.2 mg/kg BW, respectively. The serum glucose, insulin, lipid profile, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, alkalinposphatase, creatinine, urea and calcium, were measured in fasting state.

Results As compared with group II, serum glucose was significantly reduced and serum insulin significantly elevated in groups III and IV following oral administration of extract for 21 days. Following 30 days, significant reduction in the total cholesterol, triglycerides, low density lipoprotein- cholesterol, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, very low density lipoprotein- cholesterol, and creatnin, whereas high density-cholesterol and calcium were significantly increased.

Conclusion Foeniculum vulgare extract have good hypoglycemic, antihyperlipidemic in Alloxan- induced diabetic mice, in addition to the improvement in the glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, creatinin, urea and calcium.

Keywords Diabetes militates, Antihyperlipidemia, Hypoglycemic effect, alloxan, medical plants, Foeniculum Vulgare.

List of abbreviation: ALP = Alkaline phosphatase, ANOVA = Analysis of variance, BW = Body weight, Ca = Calcium, CAMP = cyclic adenosine mono phosphate, DM = Diabetes mellitus, FV = Foeniculum vulgare, GOT = Glutamate oxaloacetate transaminase, GPT = Glutamate pyruvate transaminase, HDL-C = High density lipoprotein-cholesterol, LDL-C = Low density lipoprotein- cholesterol, T.Chol. = Total cholesterol, TG = Triglycerides, VLDL-C = Very low density lipoprotein- cholesterol, WHO = World health organization

Introduction

Diabetes mellitus (DM) is a chronic disease caused by inherited or acquired deficiency in production of insulin by beta cells of pancreas, or by the ineffectiveness of the insulin. It is an extremely common metabolic disorder affecting carbohydrate, fat and protein metabolism characterized by hyperglycemia, glucose urea and negative nitrogen balance. It is mainly due to lack of insulin secretion, or resistance to insulin action or both [(1)]. Two types of DM were noticed type 1 and type 2 [(2)]. It is the most prevalent disease in the world affecting 25% of population and afflicts 150 million People and is set to rise to 300 million by 2025. The disease

takes an ever-increasing proportion of national and international health care budgets. It is projected to become one of the world's main disablers and killers within the next 25 years. Regions with greatest potential are Asia and Africa [1,3]. DM causes number of complications like retinopathy, neuropathy and peripheral vascular insufficiencies [4]. The detrimental effects of diabetic complications are mainly mediated through oxidative stress [5]. DM is still not completely cured by using anti diabetic agents. Insulin therapy is the only satisfactory approach in it, even though it has several drawbacks like insulin resistance, anorexia and fatty liver in prolong treatment [6]. Synthetic anti diabetic agents can produce some side effects and they are not suitable for use in all patients. Treatment of diabetes without any side effects is still a challenge to the medical system. This leads to increasing demand for natural products with anti diabetic activity and fewer side effects [7]. Furthermore, after the recommendation made by World Health Organization (WHO) on diabetes mellitus, investigations on hypoglycemic agents from medicinal plants have become more important. WHO has estimated that 80% of population of developing countries still relies on traditional medicines mostly plant drugs for their primary health care needs and ensure patient safety by upgrading the skills and knowledge of traditional medicine providers [8].

Herbal drugs or natural products are gaining popularity in the treatment of DM, it prescribed widely considering their safety, low incidence of side effects, effectiveness, availability and low cost [5,6]. The anti diabetic activity of herbs depends upon variety of mechanisms such as; Pancreatic beta cell potassium channel blocking, cyclic adenosine mono phosphate (cAMP) stimulation, inhibition of renal glucose re absorption, stimulation of insulin secretion from beta cells, reduction in insulin resistance , providing certain elements for the beta-cells like calcium, zinc, magnesium, manganese and copper, regenerating of pancreatic beta cells, stimulation of insulin secretion, stimulation of glycogenesis and hepatic glycolysis, protective effect against the destruction of the beta cells, inhibition of β-galactocidase and α-glucocidase, cortisol lowering activities, inhibition of alpha-amylase and preventing oxidative stress in beta cell [6].

Several medicinal plants are used in the management of DM [7]. Many phytoconstituents responsible for anti diabetic effects have been isolated from hypoglycemic plants [9]. One of such plants is *Foeniculum vulgare* (*FV*). It is a member of family of Apiaceae. This plant is an aromatic plant [10-13]. The name Foeniculum was given by Romans to this plant and is derived from a latin word (Foenum) which means (hay) perhaps because smell of fennel rell of fennel resembles that of hay. Fennel is a native of Mediterranean region and Europe but is commonly cultivated throughout India especially in Assam, Maharashtra, Punjab and Gujarat [14]. An analysis of fennel shows it to consist of moisture 6.3%, protein 9.5%, fat 10%, minerals 13.4%, fiber 18.5% and carbohydrates 42.3%. Its mineral and vitamin contents are calcium, phosphorous, iron, sodium, potassium, thiamine, riboflavin, niacin and vitamin C. Main components of *FV* are trans-anethol (50-70%), estrogen-dianthol. Flavonoids and organic acids [10,14]. Fennel is chiefly known as culinary herb but it is a commonly used household remedy for various medicinal purposes. Fruits are used as spice and condiment, as carminative and stimulant, also employed as flavoring agent in culinary preparations, confectionary etc. Fennel is often added to purgatives in order to allay their tendency to cause gripe. In a study carried out on rats, *FV* has shown a protective effect against ethanol induced gastric mucosal lesions. Fennel has shown anti-inflammatory; antioxidant, anti platelet and antithrombotic; antispasmodic activities.

It has also been reported to possess bronchodilatory; diuretic; hepatoprotective; hypotensive; insecticidal; nematicidal; and oculohypotensive properties; and pain reliever in primary dysmenorrhoea. Anethole has a chemical structure similar to a chemical substance called dopamine, naturally present in the body. Dopamine is known to have a relaxing effect on

the intestine and perhaps, explains why fennel has a beneficial effect on infantile colic. Also *FV* have antimicrobial properties. Therefore it is used in traditional medicine as antibacterial and antiviral [10,14,15].

The present study was undertaken to investigate the effects of alcoholic extract of *Foeniculum vulgare* on some biochemical parameters in liver and kidneys of alloxan-induced diabetic mice, in order to use this herb as natural products to the management of diabetes mellitus.

Methods

FV were purchased from the local gardens and identified in a Biotechnology Research Centre, Al-Nahrain University. The leaves were cleaned and finely powdered and extracted by: 50 gm of plant was extracted with 250 ml of methanol by soxhlet apparatus for 6 hour at 40-60 ^{o}C, then the cooled solution was evaporated to dryness by rotary evaporator at 40 ^{o}C, and and crude extract was kept until used [16].

The doses prepared from the extracted material with a concentration of (1.2 and 2.2 mg/kg BW) this methanol extracts, administrated daily for 30 days.

Healthy adult albino females of Swiss albino strain were obtained from animal house of Biotechnology Research Center, Al-Nahrain University. Twenty four mice were used in this study, the age of the mice were in the range of 2.5 to 3 months old, and the weight in the range 25-30 grams. The animals were housed in small plastic cages, which were cleaned weekly by washing with soap and tap water and sterilized with 70% ethyl alcohol throughout the period of the study. The room temperature was maintained at 24 ± 2 ^{o}C, and the animals were exposed to 14 hours light program. The period of treatment extended from 20th Jun. 2011 till 20th Jul. 2011.

Diabetes was induced by a single intraperitoneal injection of alloxan monohydrated (5% w/v) in physiological saline at a dose of 150 mg/kg BW in a volume of 0.1 ml. The diabetic state was confirmed 48 hours after alloxan injection by weight loss and hyperglycaemia. There was 75% mortality in animals treated with alloxan. Surviving mice with a fasting blood glucose level higher than 200 ml/dl were included in the study. Four groups consisting of six animals for each group were maintained as follows [17].

In the present investigation, total of 24 female's mice (18 diabetic surviving mice and 6 normal mice) were taken and divided into four groups of 6 mice each.

Group I: Normal untreated mice (control),

Group II: Alloxan-induced diabetic mice,

Group III: Alloxan-induced diabetic mice treated with *FV* alcoholic extract (1.2 mg/kg BW) daily for 30 days, and

Group IV: Alloxan induced-diabetic mice treated with *FV* alcoholic extract (2.2 mg/kg BW) daily for 30 days.

At the end of 15 day and 30 day, the mice fasted over night and killed by cervical dislocation, and then blood was collected from heart puncture. Fasting blood (glucose and insulin) level was evaluated at the day 15 and 30 for (control, diabetic and treated groups). Lipid profiles, Ca^{2+}, creatinin, urea, serum glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate transaminase (GOT) and serum alkalin phosphatase (ALP) were evaluated at the day 30 for all groups.

All the above biochemical parameters were assayed by the reported methods in their kits, while low density lipoprotein - cholesterol (LDL-C) concentration are most commonly calculated by using the Friedwald formula which was based on the assumption that very low density lipoprotein - cholesterol (VLDL-C) is present in serum at a concentration equal to one fifth of the TG concentration.

Friedwald formula as follow [18]:

LDL-C mg/dl = total cholesterol – (HDL-C + TG/5), when all concentrations are given in milligrams per deciliter.

Data were analyzed by 1-way analysis of variance with ANOVA test is presented as means ±SE. The level of significance was $P < 0.05$ [19].

Results

The alloxan-induced diabetic mice (group II) in the present study showed a significant increase in the

mean of serum glucose level and significant decrease in the mean of serum insulin after 21 days. Also the results showed after 30 days significant increase in the means of GOT, GPT, ALP, T.Chol., TG, LDL-C, VLDL-C, creatinine and urea, while the means of HDL-C and Ca were significant decrease as compared with control (group I), with $P < 0.05$, (Tables 1,2,3 and 4).

After oral administration of FV extract in doses (1.2 and 2.2 mg/kg BW) for groups III and IV respectively, the results showed after 21days significant decrease in the means of serum glucose and significant increase in the means of serum insulin. After 30 days the results showed significant decrease in the means of cholesterol, TG, LDL-C, GOT, GPT, ALP and creatinine, in contrast to a significant increase in HDL- C and Ca but there were no significant differences in the means of urea, as compared with group II at $P < 0.05$ (Tables 1,2,3 and 4).

There was no significant difference in the mean of VLDL-C in group III as compared with group II at $P < 0.05$ (Table 2), while there was significant difference in the mean of VLDL-C in group IV as compared with group II.

Table 1. Effect of methanol extract of *Foeniculum vulgare* on serum glucose and serum Insulin level in alloxan-induce diabetic mice

N	Groups	Serum Glucose (mg/dl) (mean ± SD)		Serum Insulin (mg/dl) (mean ± SD)	
		21 days	30 days	21 days	30 days
I	Control	A , a 98.53±4.72	A , a 93.75±10.05	A , a 20.23±3.27	A , a 26.59±5.40
II	Alloxan	B , a 308.22±17.83	B , a 320.41±25.91	B , a 8.51±2.94	B , b 5.21±1.08
III	Alloxan + *FV* (1.2 mg/kg BW)	C , a 204.60±12.28	C , a 192.74±12.41	C , a 13.22±2.73	C , a 11.45±3.27
IV	Alloxan + *FV* (2.2 mg/kg BW)	D, a 166.20±9.85	D, b 132.69±9.72	C , a 14.68±3.01	D, a 18.40±5.54

Letters A,B,C are significant at $P < 0.05$ (comparison between columns), Letters a,b,c are significant at $P < 0.05$ (comparison between rows).

Table 2. Effect of methanol extract of *Foeniculum vulgare* on serum lipid profiles in alloxan-induced diabetic mice

N	Group	T Chol. mg/dl (mean±SD)	TG mg/dl (mean±SD)	HDL-C mg/dl (mean±SD)	VLDL-C mg/dl (mean±SD)	LDL-C mg/dl (mean±SD)
I	**Control**	A 133.28±25.05	A 101.24±16.93	A 32.57±6.83	A 20.25±4.22	A 80.46±13.04
II	**Alloxan**	B 251.28±31.06	B 212.24±37.62	B 19.48±8.33	B 42.45±7.05	B 189.35±36.41
III	**Alloxan+ *FV* (1.2 mg/kg BW)**	C 174.29±31.76	C 178.46±25.72	C 25.08±4.82	B 35.69±8.71	C 113.52±21.01
IV	**Alloxan + *FV* (2.2 mg/kg BW)**	C 157.03±19.22	D 130.96±13.94	AC 30.12±6.77	C 26.19±7.29	C 100.72±15.48

FV = Foeniculum vulgare

Differences letters A,B,C are significant at ($P < 0.05$) to compare columns

Table 3. Effect of methanol extract of Foeniculum vulgare on serum biomarkers in alloxan induced diabetic mice

N	Groups	GOT IU/ml (mean±SD)	GPT IU/ml (mean±SD)	ALP IU/ml (mean±SD)
I	Control	A 174.36±21.26	A 76.24±6.84	A 82.19±13.38
II	Alloxan	B 286.26±19.05	B 132.51±24.46	B 161.34±20.55
III	Alloxan + *Foeniculum vulgare* (1.2 mg/kg BW)	C 203.05±33.84	A 84.76±8.93	C 103.61±16.53
IV	Alloxan + *Foeniculum vulgare* (2.2 mg/kg BW)	A 185.25±20.73	A 80.33±12.04	AC 91.75±11.79

Differences letters A,B,C are significant at ($P < 0.05$) to compare columns.

Table 4. Effect of methanol extract of *Foeniculum vulgare* on serum creatinine, urea, Ca^{2+} in alloxan-induced diabetic mice

N	Groups	Creatinine mg/dl (mean±SD)	Urea mg/dl (mean±SD)	Ca mg/dl (mean±SD)
I	Control	A 0.56±0.031	A 20.13±3.38	A 14.53±2.94
II	Alloxan	B 0.84±0.068	B 32.58±6.40	B 12.68±2.74
III	Alloxan + *Foeniculum vulgare* (1.2 mg/kg BW)	C 0.72±0.044	B 28.22±5.11	A 15.18±1.94
IV	Alloxan + *Foeniculum vulgare* (2.2 mg/kg BW)	A 0.59±0.039	AB 23.14±4.02	A 16.09±2.33

Differences letters A,B,C are significant at ($P < 0.05$) to compare columns.

Discussion

In the present study oral administration of *FV* extract reduced serum glucose. This result were in agreement with the results of Abou El-Soud *et al*, in which they reported that the reduction was observed in blood glucose in diabetic rats treated with the tested essential oil of FV Mill. Also they reported that research studies on the effect of fennel oil on blood glucose are not numerous [15]. A single study by Barros et al reported that fennel can improve rat glucose tolerance obviously [20]. The antidiabetic effect of methanol extract of *FV* may be due to the presence of more than one antihyperglycemic principle and their synergistic effects [17]. Abou El-Soud *et al*. reported that the chemical constituents of *FV* for anti-diabetic are (flavonoids and terpenoids) [15].

It is well known that in uncontrolled diabetes mellitus, there will be an increase in total cholesterol, Triglycerides and LDL-C associated with decrease in HDL-C and contributes to coronary artery disease, which is related with significant changes in lipid metabolism and structure. Although abnormalities in cellular cholesterol level in diabetes occur, the precise mechanisms underlying these enzymatic changes have not been elucidated. Such a significant increase in TG may be due to the lack of insulin under diabetic condition, while insulin activates the enzyme lipoprotein lipase and hydrolyze TG under normal condition [17]. In the present study the total cholesterol, triglycerides and LDL-C increased in diabetic group (II) and it was reduced after 30 days treatment with *FV* extract as well as the HDL-C level was

significantly increased. This may be due to saponin in *FV* which is reduces the uptake of certain nutrients including glucose and cholesterol at the gastro intestinal tract. Hence, it has been reported to have hypocholesterolemic effect and thus may aid lessening metabolic burden that would have been placed in the liver; this suggests that the extract may inhibit the pathway of cholesterol synthesis and increased HDL-C / LDL-C ratio may be due to activation of LDL-C receptors in hepatocyte, which is responsible for taking up LDL-C into the liver and reduce the serum LDL-C level [(21)].

Some studies found in a trial of fenugreek *FV* in twenty-five patients with type II diabetes, a trial group of thirteen patients received one gram per / day of an evaporated hydro- alcoholic extract of fenugreek seeds for two months. At the end of the period, blood sugar response to meal was significantly lower in fenugreek group. Insulin secretion was also lower, as were serum TG, HDL- C was improved, and a standard measure of insulin sensitivity showed increased insulin sensitivity. Several trials showed that evaporated hydro-alcoholic extract as effective as the aqueous extract [(22)]. Other study of Oulmouden *et al*, in which they found that the administration of the methanol extract of fennel caused a hypolipidemic and anti-atherosclerotic effect in reducing the lipids concentrations of serum and liver [(23)]. These results agreed with the results of glucose and lipid profile in the present study.

Serum GOT and GPT levels increase as a result of metabolic changes in the liver, such as administration of toxin, cirrhosis of the liver, hepatitis, liver cancer and inflammatory conditions including diabetes. In some studies and in the present study, it was observed that the levels of serum GOT and GPT in alloxan induced diabetic mice were elevated. It may be due to leaking out of enzymes from the tissues and migrating in to the circulation by the adverse effect of alloxan. The transaminase enzymes were used as markers to assess the extent of liver damage in streptozotocin induced diabetic mice [(17)].

In the present study oral administration of *FV* extract reduce serum GOT, GPT, ALP. These results were in agreement with the results of Selvan *et al* (2008) who found that hepatic damage was restored and the elevated transaminase activities were significantly reduced by hypoglycemic plant. The diabetic complication such as increased gluconeogenesis and ketogenesis may be due to elevated transaminase activities [(6)].

Renal disease is a common complication in diabetic patients. More than ten percent of people with diabetes die from renal complications as (renal failure) [(4)]. Significant elevations in serum creatinine and urea indicate impaired renal function in diabetic animals [(24)].

The recovery of renal function with treatment of fennel oil can be explained by the regenerative capability of the renal tubules. Similar results have been observed with the treatment of Streptozotocin induced diabetic rats with other herbal extracts as fenugreek alkaloid extract and onion oil. The role of fennel oil in reversing the diabetic state at the cellular level besides the metabolic normalization further proves its potential as an anti diabetic assert [(15)].

These results are in agreement with the results of the present study in which *FV* extract can partially inhibit Alloxan renal toxicity as observed from serum urea and creatinine levels Table 4.

Also *FV* extract correct the concentration of calcium in group III and IV as shown in Table 4. This result were in agreement with the result of Mohamed *et al* (2006) who reported that some herbs Provide certain necessary elements like Calcium, Zinc, Magnesium, Manganese and Copper for the beta- cells. Therefore the hypoglycemic effect of these herbs is probably due to stimulation of insulin release via modulation of intracellular Ca^{2+} concentration in pancreatic beta-cells [(25)].

Finally, the results about the effects of *FV* extracts in this study were in agreement with the results of Abou El-Soud *et al* (2011) who reported that essential oil of *FV* mill corrected the hyperglycemia and pathological abnormalities in diabetic rats which could be in part through its antioxidative effect and restoring redox homeostasis. This makes the possibility for included it as in anti diabetic drug industry [(15)].

So we can conclude from all the above biochemical parameters investigated that, *FV* extract showed exhibit anti-hyperglycemic, hyperlipidemic effects on alloxan diabetic mice.

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Declaration of interest

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