The effect of oral administration of *Carum carvi* on weight, serum glucose, and lipid profile in streptozotocin-induced diabetic rats

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ABSTRACT

الأهداف: تقييم تأثير تناول عشبة الكراوية عن طريق الفم على كل من: مستويات جلوكوز الدم، وتحليل الدهون، والوزن لدى الجرذان المصابة بالسكري.

الطريقة: أُجريت هذه الدراسة في جامعة الأحواز للعلوم الطبية، الأحواز، إيران وذلك خلال الفترة من أبريل إلى يونيو 2010م. شملت الدراسة 24 جرذي من النوع ويستر والتي تتراوح أوزانها ما بين 250–200 غرام، وقد قمنا بدراسة هذه الحيوانات على مدى 3 أسابيع وذلك بعد تقسيمها عشوائياً إلى 3 مجموعات كالتالي: المجموعة الطبيعية، والمجموعة المصابة بالسكري، والمجموعة المصابة بالسكري والتي تم علاجها بعشبة الكراوية. لقد أُصيبت الجرذان بالسكري بعد استحثاث المرض للتجربة وبواسطة حقن عقار الستربتوزوتوسين داخل الصفاق وبجرعة مقدارها 60 ملغ/كلغ. فيما تم إعطاء الكراوية للجرذان عن طريق الفم وبجرعة كان مقدارها 1 غرام/كلغ يومياً، وتمت متابعة أوزان الحيوانات يومياً. وأخيراً جُمعت عينات الدم من أجل تحليل مستويات الجلوكوز والدهون في الدم.

النتائج: أشارت نتائج الدراسة إلى أن تناول الكراوية عن طريق الفم قد أدى إلى انخفاض واضح في مستويات سكر الدم وذلك في المجموعة التي عولجت بهذه العشبة مقارنةً مع المجموعات الأخرى (p=0.001)، كما أنها أدت إلى تنقيص الوزن في هذه المجموعة مقارنةً مع المجموعات الأخرى (p=0.037). بالإضافة إلى ذلك فقد أدت هذه العشبة إلى خفض مستوى الكولسترول الكلي (p=0.036)، ومستوى الكولسترول المنخفض الكثافة (p=0.001) في المجموعة المُعالجة مقارنةً مع المجموعة المصابة بالسكري والتي لم تُعالج بهذه العشبة، غير أن تناولها لم يسبب تغيراً ملحوظاً في مستويات ثلاثي الجليسريد، والكولسترول العالي الكثافة.

خاتمة: أثبتت الدراسة دور عشبة الكرواية في خفض مستويات السكر والدهون في الدم لدى الجرذان المصابة بالسكري، إلا أنه يُنصح بإجراء المزيد من الاختبارات على الحيوانات والبشر لمعرفة مدى تأثير هذه العشبة وفعاليتها.

Objectives: To evaluate the effect of oral administration of caraway (*Carum carvi*) on the blood glucose level, lipid profile, and the weight of diabetic rats.

Methods: This investigation was carried out in Ahvaz University of Medical Sciences, Ahvaz, Iran between April and June 2010. Twenty-four male Wistar rats weighing 200-250 g were randomly divided into 3 groups: normal, diabetic, and caraway treated diabetic groups and were studied for 3 weeks. Diabetes was induced by intraperitoneal injection of 60 mg/kg body weight streptozotocin. Caraway was given orally at a dose of 1g/kg body weight daily, and the body weight of animals was measured every day. Blood samples were collected and blood glucose levels and lipid profile were determined.

Results: The results showed that oral administration of caraway caused a significant decrease in blood glucose level of treated rats (p=0.001) and alleviated their body weight loss (p=0.037). Furthermore, it caused significant decrease in total cholesterol (p=0.036), and low-density lipoprotein cholesterol levels (p=0.001) in the treated animals compared with the diabetic control rats, and with no significant change in triglyceride and high-density lipoprotein cholesterol levels.

Conclusion: Caraway has both antihyperglycemic and hypolipidemic activity in diabetic rats. Nevertheless, it is not recommended before further investigations in animals and humans.

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Diabetes is one of the major public health problems and the most prevalent endocrine disease in the world.[1] It is growing with a fast rate and is likely to affect 340 million people, or more by the year 2030.[2] Diabetes is characterized mainly by chronic hyperglycemia and is also associated with elevation in the plasma lipid and lipoprotein profile,[3] which can lead to long-term damage and failure of various organs especially the eyes, kidneys, nerves, heart, and blood vessels. It produces an enormous economic burden for managing diabetic complications.[4] Regarding the alarming increase in the worldwide diabetic population, there is a need for novel therapies that are more effective with less adverse effects.[5] Herbal remedies have these properties.[6] The World Health Organization has encouraged and recommended that herbal therapy for diabetes needs further evaluation.[7] One of the medicinal plants, which have been getting increasing attention lately, is caraway. Caraway, *Carum carvi L.*, belonging to the Apiaceae family,[8] is a widely distributed annual herbaceous plant. Its seed is commonly known in Iran as '*Zireh Siah*' and has been used widely in foods and Iranian traditional medicine to cure several disorders. The plant has been used since ancient times, especially in the treatment of digestive disorders and is known worldwide as antibacterial,[9] anti ulcerogenic,[10] and is traditionally used to treat flatulence, colic pain, and bronchitis, diabetes, cardiovascular diseases, and hypertension. In several studies, it has shown antimutagenic, diuretic, and laxative activities.[8-10] Furthermore, it may serve as a dietary source of natural antioxidants for health promotion and may be used as a natural antioxidative food additive to increase food quality and stability.[11] The known main constituents of caraway have been demonstrated as monoterpens (carvone [40–60%], limonene, thymol), glycosides (carveol, dihydro carveol) and flavonoids (quercetin 3-glucuronide, quercetin 3-O-caffeylglucoside, kaempferol 3-glucoside, isoquercitrin).[12,13] Monoterpens and flavonoids in caraway help to inhibit colon carcinogenesis in rats,[14] and have a modulatory effect on tissue lipid peroxidation and antioxidant profile. They also prevent histopathological lesions in colon cancer,[15,16] and have a reno-protective effect against diabetic nephropathy in rats.[17]

This investigation is based on the hypothesis that bioactive compounds found in caraway (*Carum carvi*) have antidiabetic properties. The hypoglycemic and antihyperlipidemic effects of *Carum carvi* in normal and diabetic rats have been shown before.[18] However, its effect in diabetes has not been confirmed yet, and very little is known about its mechanisms. To verify our hypothesis, the current study aimed at exploring the possibility of oral administration of the aqueous extract of the *Carum carvi* seed for 21 days on plasma glucose and lipid profile in normal and streptozotocin (STZ)-induced diabetic rats.

Disclosure. This study was conducted with financial support provided by the Diabetes Research Center, Ahvaz Jondi Shapour University of Medical Sciences, Iran (Grant NO. D-8902).

Methods. ***Animals.*** Male Wistar rats (200-250 g), aged 6-8 weeks, were obtained from the Physiology Research Center of Ahvaz University of Medical Sciences, Ahvaz, Iran. The animals were held in an air-conditioned room (22 ± 3°C) with 55 ± 5% humidity and a 12-hour light/dark cycle. They were fed with a standard diet and had free access to water. The study was approved by the Ethical Committee, affiliated to Ahvaz Jondi Shapour University of Medical Sciences.

Induction of diabetes. Diabetes was induced by administration of a single intraperitoneal injection of 60 mg/kg body weight STZ (Sigma, Aldrich, USA), which was prepared freshly. Two days after administration of STZ, serum glucose levels were determined. Only rats with fasting blood glucose over 250 mg/dl were considered diabetic and included in the experiments. Each animal was used only once in the experiment.

Plant material and extraction. *Carum carvi* seeds were collected from the Kerman area in Iran. The seeds were dried at 40°C and were finely powdered. To prepare aqueous extract, 100 g of powdered seeds was mixed with 1000 ml distilled water and then at low temperature (50°C) evaporated for 72 hours gently, until the final volume reached 150 ml. Thereafter, the solvent was filtered to remove particulate matter. The obtained caraway aqueous extract was stored at -20°C until usage.

Experimental design. Twenty-four rats were divided randomly into 3 groups (n=8) and treated as follows: Group 1: nondiabetic control rats; Group 2: diabetic rats; and Group 3: caraway treated diabetic rats. Caraway extract was given by oral gavage at a dose of one g/kg body weight daily. The volume of administration was 1 mL, and the treatments lasted for 21 days. Groups 1 and 2 animals received distilled water at the same volume. The animals were carefully monitored and weighed every other day. Fasting blood samples were collected from the tail vein at the beginning and directly from the heart under light ether anesthesia at the end of the study. During fasting, rats were deprived of food for 12 hours, but had free access to water. Plasma glucose,

Table 1 - Means of body weight and blood glucose in experimental groups at the beginning and the end of study.

Parameter	Normal	Diabetic	Diabetic + caraway	P_a	P_b	P_c
Initial weight (g)	227.25±7.9	238.87±7.1	230.12±6.5	0.268	0.781	0.401
Final weight (g)	244.37±9.2	155.43±11.7	164.75±9.06	0.000	0.000	0.520
Initial glucose (mg/dl)	100.12±3.1	106.12±1.2	105.12±1.5	0.058	0.110	0.740
Final glucose (mg/dl)	160.75±4.8	330.00±29.4	142.87±21.2	0.002	0.703	0.001

All values are expressed as mean ± SE (n=8). One way ANOVA test was used for statistical significance assessment. P_a indicates *p*-value between normal and diabetic animals, P_b indicates *p*-value between normal and caraway treated diabetic animals, and P_c indicates *p*-value between diabetic and caraway treated diabetic animals.
SE - standard error

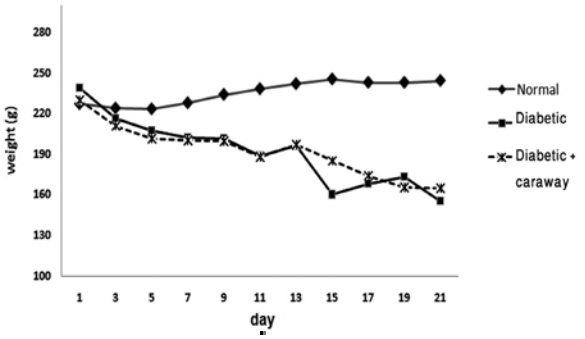

Figure 1 - Effect of orally administered caraway on body weight changes of diabetic rats (n=8).

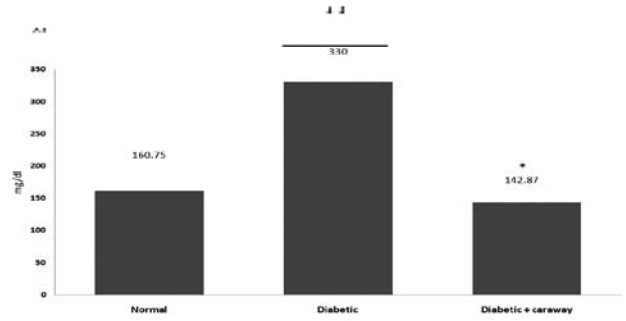

Figure 2 - Effect of orally administered caraway on blood glucose of diabetic rats (n=8). *indicates *p*=0.001 versus untreated diabetic rats.

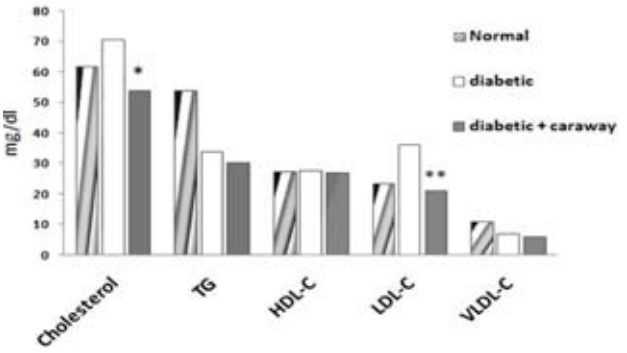

Figure 3 - Effect of orally administered caraway on lipid profile of diabetic rats (n=8). *indicates *p*=0.036 and **indicates *p*=0.001 versus untreated diabetic rats. TG - triglyceride, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, VLDL - very low density lipoprotein cholesterol.

triglycerides (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-c) levels were determined enzymatically using standard methods. The low density lipoprotein cholesterol (LDL-c) level was calculated by the Friedewald formula as follows: LDL cholesterol = TC - HDL cholesterol - (triglyceride/5).

Statistical analysis. Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 17 for windows. Data were expressed as mean ± standard error. Statistical analysis was performed using one-way ANOVA with 95% confidence interval. Differences were considered to be significant when $p<0.05$.

Results. The initial and final body weight and blood glucose in the control and treated groups are summarized in **Table 1**. The results show that the mean final body weights in both diabetic control and diabetic treated rats were significantly lower than those of normal rats ($p=0.000$). A significant increase in blood glucose levels in the untreated diabetic rats compared to the normal group was also obvious at the end of the study ($p=0.002$). The body weight changes during the study in normal and diabetic groups are presented in **Figure 1**. At the end of the study, the body weight of the diabetic control rats significantly decreased ($p=0.000$). However, treatment of the diabetic rats with caraway extract improved their body weight loss compared with the control group ($p=0.037$). The effects of oral administration of caraway on blood glucose and the lipid profiles are shown in **Figure 2** and **Figure 3**. As obvious in **Figure 2**, the caraway treated diabetic group had significantly lower levels of glucose in comparison with the untreated diabetic rats ($p=0.001$). The serum LDL-c levels were significantly higher in the untreated diabetic group than those of the normal control group ($p=0.005$). The present data also indicated that caraway administration caused a significant decrease in TC and LDL-c levels of the treated animals compared with the diabetic control rats ($p=0.036$, and $p=0.001$) while serum triglyceride, VLDL-c, and HDL-c levels did not change significantly (**Figure 3**).

Discussion. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both,[19] and is also associated with disorders in lipid metabolism and hyperlipidemia.[3] A number of medicinal herbs have been reported to yield hypoglycemic and hypolipidemic effects in patients with diabetes. The caraway plant is a native shrub widely distributed throughout Iran and there have been some hypothesis on its useful effects in diabetes. Thus, this study was undertaken to examine caraway potency to attenuate hyperglycemia, hyperlipidemia, and associated weight lose in STZ-induced diabetic rats.

In the present study, decreased body weight in diabetic rats was in agreement with other studies,[20,21] and clearly characterized the diabetic condition, which could be due to poor glycemic control. The excessive catabolism of protein to supply amino acids for gluconeogenesis in insulin deficiency results in muscle wasting and weight loss in diabetic untreated rats.[20] In this study, dietary supplementation with *Carum carvi* significantly inhibited the weight loss trend of diabetic animals. It is speculated that the improved glycemic control in caraway treated rats may be responsible for this effect.

In this study, the elevated blood glucose concentration at the beginning and at the end of the experimental period clearly proves the persistent hyperglycemia in the STZ-induced diabetic rats, which is as a result of the destruction of the beta cells of the pancreas by STZ. However, administration of aqueous extract of *Carum carvi* at a dosage of 1 g/kg in diabetic animals tended to lower blood glucose levels toward near normal levels. This finding indicates that *Carum carvi* seeds act as an antihyperglycemic agent rather than a hypoglycemic agent. The hypoglycemic effect of caraway seed has been previously shown by investigators. Ene et al[21] reported that caraway oil altered the hyperglycemic condition of alloxan-induced diabetic rats to normal. They suggested that the oil might contain substances that mimic the action of insulin. In another study, Eddouks et al[18] found that after oral administration of the aqueous extract of caraway for 2 weeks, blood glucose levels in STZ diabetic rats also significantly decreased and even were nearly normalized. However, unlike Ene et al's[21] findings, no changes were observed in basal plasma insulin concentrations after treatment with these plants in STZ diabetic rats, indicating that the underlying mechanism of this pharmacological activity seems to be independent of insulin secretion.

The mechanism by which caraway acts as an antihyperglycemic plant includes inhibition of hepatic glucose production, and/or stimulation of glucose utilization by peripheral tissues, especially muscle and adipose tissue.[22] The plant could also act as an inhibitor of renal glucose reabsorption and intestinal glucose absorption.[23] The known main constituents of caraway have been demonstrated as monoterpens (carvone, limonene, thymol), glycosides (carveol, dihydro carveol) and flavonoids (quercetin 3-glucuronide, quercetin 3-O-caffeylglucoside, kaempferol 3-glucosid, isoquercitrin).[12,13] It seems that further studies are needed to identify the principle components of this powder and the mechanism of hypoglycemic effect of them in diabetes. Flavonoids are active principles in many medicinal plants and natural products, which have positive effects on human health. However, other components other than flavonoids may act as bioactive hypoglycemic agents.

Diabetes is associated with profound alterations of plasma lipids and lipoprotein profile and also with an increased risk of coronary heart disease.[24] Lemhadri et al[25] displayed significant hypotriglyceridemic and hypocholesterolemic activities in both normal and STZ diabetic rats 15 days after *Carum carvi* treatment.

The results of the present study exhibit an elevation in total serum cholesterol and LDL-c in diabetic animals. These findings may be due to the insulinopenic state, which causes an important lipolytic activity contributing to the elevated serum lipid profiles in diabetic rats.[25] The results demonstrate that the aqueous extract of *Carum carvi* significantly decreases serum cholesterol and LDL-c in treated rats, although it does not affect the concentration of serum TG, VLDL-c, and HDL-c. The possible mechanism by which *Carum carvi* can exert cholesterol lowering activities is not known. Several mechanisms, however, could be proposed. Caraway fibers might bind bile acids to reduce their absorption and entry into enterohepatic circulation, which then leads to an increase in gut bile acid excretion. This mechanism could be contributed to the observed cholesterol lowering activity of caraway. Moreover, *Carum carvi* can also act by decreasing the cholesterol biosynthesis especially by decreasing the HMG-CoA reductase activity (key enzyme of cholesterol biosynthesis),[26] and/or by reducing the NADPH required for fatty acids and cholesterol synthesis. *Carum carvi* may also act by modifying lipoprotein metabolism: it enhances uptake of LDL by increasing LDL receptors, and/or by increasing the lecithin–cholesterol acyl transferase (LCAT) activity,[27] which may contribute to the regulation of blood lipids and help to take lipoproteins back by the liver cells.[28] Caraway may also facilitate rapid catabolism of LDL.[23] The findings of this study also display a reduction in serum TG concentration in diabetic animals compared with the normal group rats. This is not in agreement with other studies.[19,21,25] There has been a positive correlation between body weight and serum TG in our study, which could simply explain that this reduction could be due to the weight loss of diabetic animals. The

present study also shows that caraway administration has no significant effect on serum TG concentration in diabetic animals. This could be due to the short period of the study, which was not long enough to affect serum TG.

Nevertheless, this study had some limitations. Firstly, the type of diabetes induced by STZ in the current study would rather represent type 1 diabetes, although most diabetic patients are type 2. Therefore, it may not be suitable for study of type 2 diabetes. However, the STZ-induced diabetic rat model can cause hyperglycemia, hyperlipidemia, and inflammation and made it useful for the evaluation of compounds that are able to alleviate these high risk conditions in diabetes. Secondly, the insulin concentration was not evaluated in this study, so it is not elucidated if the hypoglycemic and hypolipidemic effects of caraway are due to its potential to increase serum insulin levels or not.

This study concludes that caraway seed is effective in controlling hyperglycemia to a significant extent in STZ-diabetic rats and possesses antidiabetic activities. The data obtained also implies that caraway may be beneficial in reducing diabetic complications arising due to insulin deficiency and metabolic perturbations such as hypercholesterolemia and LDL increment in diabetic rats. The mechanism underlying the protective effect against hyperglycemia and the lipid-lowering action by caraway is unknown. Hence, further studies are needed to isolate the principle components of caraway and clarify the possible mechanism(s) of their action in the diabetes condition. The plant, thus, should be considered as an excellent candidate for future studies on diabetes.

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