ARTICLE

Short-Term Caraway Extract Administration Improves Cardiovascular Disease Risk Markers in Streptozotocin-Induced Diabetic Rats: A Dose-Response Study

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ABSTRACT. \textbf{Objective:} This study examined the effects of caraway plant on blood levels of glucose, lipid profile, and C-reactive protein in diabetic rats. \textbf{Methods:} Thirty two male Wistar rats were randomly divided into four groups: group 1: nondiabetic control rats, group 2: diabetic rats, group 3, and 4 (caraway treated diabetic groups): each rat was treated with caraway at doses of 1 g/kg in group 3 and 2 g/kg in group 4. Diabetes was induced by a single intraperitoneal injection of 60 mg/kg streptozotocin. Caraway was administered as aqueous extract orally once a day for 3 weeks. Finally, blood samples were collected and fasting blood glucose, serum lipid profile, and C-reactive protein levels were determined. Data were analyzed statistically by one-way Analysis of Variance and considered to be significant when $p < .05$. \textbf{Results:} Diabetic rats receiving 1 and 2 g/kg caraway extracts had significantly lower total cholesterol ($p = .036$ and $p = .010$, respectively), low-density lipoprotein ($p = .001$ and $p = .002$, respectively), non-HDL-C ($p = .003$ and $p = .007$, respectively), LDL-C to HDL-C ratio ($p = .002$) and atherogenic index ($p = .001$) than that of diabetic control rats. Moreover, there were significant changes in fasting blood glucose in diabetic groups treated with 1 and 2 g/kg caraway extracts ($p = .001$ and $p = .027$, respectively) compared with the diabetic control. However, caraway did not have any significant effect on C-reactive protein level in diabetic rats. \textbf{Conclusion:} This study suggests that caraway can exhibit blood glucose and lipid lowering activities in diabetes, without any effect on C-reactive protein level.

KEYWORDS. caraway, cardiovascular disease, C-reactive protein, diabetes, lipid profile, rats

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INTRODUCTION

Diabetes, characterized mainly by chronic hyperglycemia, is the most common endocrine disorder and one of the major public health problems in the world (Cho et al., 2006). The World Health Organization (WHO) had estimated there were 171 million people around the world suffering from diabetes in the year 2000. This figure is growing with a fast rate and is predicted to double by the year 2030 (Wild, Roglic, Green, Sicree, & King, 2004).

The main causes of morbidity and mortality in the diabetic patients are vascular inflammation and cardiovascular disease (CVD), which are the main public health issues. The proinflammatory cytokine, C-reactive protein (CRP), is a recognized marker of vascular inflammation, which is increased in the blood of most of the diabetics (Jay, Hitomi, & Griendling, 2006) and is known to raise vascular inflammation and CVD (Andreozzi et al., 2006; Singh, Devaraj, & Jialal, 2005). Diabetes is also associated with the elevation of plasma lipids which can finally lead to CVD (Wilson Tang, Maroo, & Young, 2004). Therefore, targeting inflammation and lipid abnormalities could possibly aid in delaying the onset of diabetes complications and concomitant death in diabetic population.

Considering the increase in the prevalence of diabetes and mortality rate of CVD in diabetics, the need for new therapies which are more effective with less adverse effects, is highlighted (Kahn, Hull, & Utzschneider, 2006; Wild et al., 2004). Phytotherapies possess these properties (Gupta et al., 2005). Furthermore, the WHO has managed to promote safe herbal medicine worldwide and has recommended more investigations in this field (Ameh, Obodozie, Abubakar, & Garba, 2010).

Caraway, Carum carvi L., belonging to the Apiaceae family, is an annual herbaceous plant which has been traditionally used especially in treating digestive disorders, bronchitis, diabetes, CVDs and hypertension (de Carvalho & da Fonseca, 2006; Tahraoui, El-Hilaly, Israili, & Lyoussi, 2007). The plant may also serve as a dietary source of antioxidants (Yu, Zhou, & Parry, 2005). The most important components of caraway seed have been shown as monoterpens (carvone, limonene, and thymol), flavonoids (quercetin 3-glucuronide, quercitin 3-O-caffeylglucoside, isoquercitrin, and kaempferol 3-glucoside), and glycosides (carveol and dihydrocarveol) (Laribi, Kouki, Mougou, & Marzouk, 2010). Flavonoids and monoterpenes in caraway help to prevent colon carcinogenesis and histopathological lesions of colon cancer in rats (Deeptha, Kamaleeswari, Sengottuvelan, & Nalini, 2006; Mazaki et al., 2006). They also modulate antioxidant profile and tissue lipid peroxidation (Kamaleeswari & Nalini, 2006).

The inflammatory, oxidative, and hyperlipidemic state of diabetes and the antioxidant, hypolipidemic, and antidiabetic properties of caraway plant and its bioactive compounds, shaped our hypothesis that caraway may exert positive effects on diabetes. Antioxidant effects of caraway have been shown in vivo and in vitro (Kamaleeswari & Nalini, 2006; Satyanarayana, Sushruta, Sarma, Srinivas, & Subba Raju, 2004; Yu et al., 2005). However, its effect on inflammation in diabetes has not been shown and its hypolipidemic effect has not been confirmed yet. The present study was undertaken to evaluate the beneficial effects of the aqueous extract of caraway seeds for 21 days on serum levels of CRP as well as lipid profile in streptozotocin (STZ)-induced diabetic rats.
**METHODS**

**Plant Material and Extraction**

Fresh caraway seeds were obtained from Kerman area in Iran. After air-drying at 40°C, the dehydrated seeds were milled into fine powder. In the present study, an aqueous extraction method was used, since it is more similar to the routine consumption method of herbal remedies. The powdered seeds (100 g) were mixed with distilled water (1,000 mL) and evaporated gently at low temperature (50°C) for 72 hr, until a volume of 150 mL of extract was yield. The obtained caraway extract was then filtered and stored at −20°C until it was used.

**Experimental Animals and Induction of Diabetes**

Experiments involving animals were conducted according to the ethical policies and procedures approved by the Animal Care and Use Committee of Ahvaz University of Medical Sciences, Ahvaz, Iran. Thirty two male wistar rats (6–8 week old) with a body weight ranging from 200 to 250 g were purchased from physiology research center of Ahvaz University of Medical Sciences. The animals were housed in a room with controlled temperature (22 ± 3°C), humidity (55 ± 5%) and a 12-hr cycle of light and dark and allowed free access to standard laboratory rat food (35% carbohydrates, 25% proteins, 7% lipids, and 3% vitamins) and water. The diet was purchased from Pars-Dam food service, Tehran, Iran. There was not any difference in the combination of foods among the experimental groups.

After acclimatization for 2 weeks, 24 rats were fasted for 12 hr and then made diabetic by a single intraperitoneal injection of a freshly prepared STZ solution (Sigma, Aldrich, USA) (60 mg/kg body weight). Forty eight hours after STZ injection, the animals with hyperglycemia (fasting blood glucose over 250 mg/dL) were considered diabetic and included in the study. Each animal was used only once in the study.

**Experimental Procedure**

Thirty two rats were randomly divided into the following four experimental groups, each group including eight animals; group 1: normal control rats, group 2: diabetic control rats, group 3 and 4: caraway treated diabetic rats, in which each rat was treated with the caraway plant at doses of 1 g/kg body weight in group 3 and 2 g/kg body weight in group 4. Caraway was administered as aqueous extract by oral gavage (48 hr after induction of diabetes), once a day for 3 weeks, while the normal group and the control diabetic group were administered the same volume of distilled water.

Fasting blood samples were obtained alternatively from the tail vein for confirming diabetes and animals were weighed every other day. At the termination of the treatment, the animals were anesthetized using light ether, and blood was collected directly from the heart. Blood samples were then centrifuged at 4,000 × g for 10 min, and the serums were stored at −20°C until assayed.
Biochemical Assay

Serum glucose, total cholesterol (TC), triglycerides (TG), and HDL-C levels were determined enzymatically using standard methods. The LDL-C, Non-HDL-C, and Atherogenic Index (AI), were calculated using the following formulas:

\[
\text{LDL cholesterol} = \text{Total cholesterol} - \text{HDL cholesterol} - \left(\frac{\text{triglyceride}}{5}\right)
\]

\[
\text{Non-HDL-C} = \text{Total cholesterol} - \text{HDL-C} \quad \text{(Aryal et al., 2010)}
\]

\[
\text{AI} = \frac{\text{LDL-C} + \text{VLDL-C}}{\text{HDL-C}} \quad \text{(Santos et al., 2012)}
\]

The pro-inflammatory cytokine; CRP level in the serum was determined by the sandwich ELISA method with commercially available kit (BioVendor). The whole instructions and appropriate standards and controls of manufacturer’s kit were used.

Statistical Analysis

To examine the normality of distribution, the Kolmogorov-Smirnov goodness-of-fit test was used. Data were analyzed statistically by one-way Analysis of Variance followed by LSD test using SPSS version 17 (SPSS, Chicago, IL) and were expressed as mean ± SE and considered to be significant when \( p < .05 \).

RESULTS

As suggested in Table 1, at baseline there were no significant differences in weight and serum glucose among groups. The administration of the caraway at 1 and 2 g/kg doses significantly decreased serum glucose level in diabetic rats in comparison with the untreated diabetic rats (\( p = .001 \) and \( p = .027 \), respectively) (Table 1). The body weight changes of all experimental groups during the study and the effect of two doses of caraway extract in target animals are demonstrated in Figure 1. As it is clear in the picture, at the end of the study, the diabetic control rats lost weight significantly compared to the normal control group (\( p = .000 \)). However, administration of caraway at 1 and 2 g/kg to the diabetic rats ameliorate their body weight loss compared to the diabetic control group (\( p = .037 \) and \( p = .000 \), respectively).

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma glucose (mg/dL)</th>
<th>Body weight (g)</th>
<th>Weight change (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 day</td>
<td>21st day</td>
<td>0 day</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>106.12 ± 1.23</td>
<td>330.00 ± 29.49(^a)</td>
<td>238.87 ± 7.17</td>
</tr>
</tbody>
</table>
| D + C (1 g/kg) | 105.12 ± 1.50 | 142.87 ± 21.21\(^c\) | 230.12 ± 6.56 | 164.7 ± 9.06\(^b\) | -65.37 ± 7.68\(^b\).
| D + C (2 g/kg) | 103.75 ± 2.13 | 189.75 ± 28.93\(^d\) | 236.75 ± 10.36 | 227.25 ± 15.38\(^c,e\) | -9.5 ± 10.41\(^a,c,e\) |

N, normal; D, diabetic; D + C, diabetic + caraway. The data were expressed as mean ± SE (\( n = 8 \)) and evaluated by one-way ANOVA test.

\(^a\)\( p < .05 \) vs. to normal group; \(^b\)\( p < .001 \) vs. to normal group; \(^c\)\( p < .001 \) vs. to control diabetic group; \(^d\)\( p < .05 \) vs. to control diabetic group; \(^e\)\( p < .001 \) vs. to diabetic + caraway (1 g/kg) group.
FIGURE 1. The effect of oral administration of caraway extract at doses of 1 and 2 g/kg on body weight changes in diabetic rats (n = 8).

The effect of diabetes and caraway administration on serum lipid profile of control and treated groups is given in Table 2. Serum TC, LDL-C, LDL-C to HDL-C ratio, and atherogenic index were significantly higher in the untreated diabetic rats than those in normal control (p = .014, p = .007, p = .006, and p = .029, respectively). It is noteworthy that the diabetic rats receiving 1 and 2 g/kg caraway had significantly lower level of TC than that of diabetic control rats (p = .036 and p = .010, respectively). However, no significant difference was observed between two treated groups with respect to TC level. The present data also indicated that treatment of diabetic rats with caraway extracts resulted in a significant decrease in LDL-C level compared to the untreated diabetic rats (p = .001 and p = .002, respectively), although LDL-C level did not differ significantly between caraway treated groups. The LDL-C to HDL-C ratio and atherogenic index of diabetic rats receiving 1 g/kg caraway were also significantly lower than those of diabetic

TABLE 2. The Effect of Caraway Seeds on the Atherosclerotic Risk Markers in the Experimental Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>D</th>
<th>D + C (1 g/kg)</th>
<th>D + C (2 g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>51.75 ± 3.53</td>
<td>70.30 ± 3.63a</td>
<td>53.90 ± 6.56c</td>
<td>47.25 ± 5.76a</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>23.45 ± 1.94</td>
<td>36.10 ± 4.10b</td>
<td>20.95 ± 2.45d</td>
<td>18.25 ± 5.82a</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>27.50 ± 1.22</td>
<td>27.40 ± 1.83</td>
<td>26.90 ± 2.68</td>
<td>21.00 ± 3.58</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>54.00 ± 3.45</td>
<td>33.67 ± 3.44</td>
<td>32.25 ± 6.74</td>
<td>40.00 ± 7.78</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>10.80 ± 0.69</td>
<td>6.70 ± 0.68</td>
<td>6.05 ± 1.94</td>
<td>8.00 ± 3.55</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>34.25 ± 2.44</td>
<td>42.83 ± 4.23</td>
<td>27.00 ± 4.05c</td>
<td>26.25 ± 3.01c</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>0.84 ± 0.04</td>
<td>1.36 ± 0.20a</td>
<td>0.77 ± 0.05c</td>
<td>0.95 ± 0.27</td>
</tr>
<tr>
<td>AI</td>
<td>1.24 ± 0.05</td>
<td>1.61 ± 0.23a</td>
<td>0.98 ± 0.07d</td>
<td>1.33 ± 0.19</td>
</tr>
<tr>
<td>CRP (µg/mL)</td>
<td>173.22 ± 22.67</td>
<td>185.43 ± 28.32</td>
<td>216.85 ± 40.80</td>
<td>113.52 ± 11.16</td>
</tr>
</tbody>
</table>

N, normal; D, diabetic; D + C, diabetic + caraway. The data were expressed as mean ± SE (n = 8) and evaluated by one-way ANOVA test. a p < .05 vs. to normal group; b p < .01 vs. to normal group; c p < .05 vs. to control diabetic group; d p ≤ .001 vs. to control diabetic group; e p ≤ .01 vs. to control diabetic group.
control rats ($p = .002$ and $p = .001$, respectively). Moreover, caraway administration at 1 and 2 g/kg doses resulted in a significant decrease in the level of non-HDL-C compared to the untreated diabetic rats ($p = .003$ and $p = .007$, respectively). Furthermore, there were not any significant changes in serum HDL-C, triglyceride and VLDL-C levels of experimental groups during the study.

The present results showed a positive correlation between serum TG concentration and body weight ($r = 0.548$, $p = .001$). However, it is notable that there were not any significant correlation between body weight and neither serum TC concentration ($r = 0.41$, $p = .822$), and nor serum LDL-C concentration ($r = −0.162$, $p = .36$).

The effect of caraway on serum CRP of the experimental groups is depicted on Table 2. The results showed no significant change in the level of serum CRP in diabetic rats. Furthermore, caraway at 1 and 2 g/kg doses did not have any significant effect on CRP level in treated diabetic rats and there was not any significant difference between two treated groups in their serum CRP level.

**DISCUSSION**

In the present study, serum TC and LDL-C in the STZ-induced diabetic rats were significantly increased, while administration of the aqueous extract of caraway had a significant effect on reducing cholesterol and LDL-C levels. These results are in agreement with Lemhadri et al. study in which administration of 20 mg/kg caraway extract for 15 days exhibited a significant cholesterol lowering and triglyceride lowering activities in STZ-induced diabetic rats (Lemhadri, Hajji, Michel, & Eddouks, 2006). However, the levels of other lipoproteins such as VLDL-C, LDL-C, and HDL-C, were not measured in their study. Furthermore, cholesterol lowering and LDL-C lowering activity of caraway in this study were associated with lower atherogenic index, non-HDL-C, and LDL-C to HDL-C ratio levels. To the best of our knowledge, no study has ever studied effects of caraway plant on these factors.

Although the mechanism by which caraway can exert its beneficial effects on diabetic hyperlipidemia is not clear, it may be attributed to the presence of a combination of bioactive components in the plant. Of the 41 compounds, representing 98.3%–99.9% of total essential oils of caraway seed, carvone (76.8%–80.5%), and limonene (13.0%–20.3%) are the major components (Laribi et al., 2010) In vivo studies have demonstrated that these bioactive compounds in the extracts from *Anethum graveolens* and *Nigella sativa* plants caused a significant reduction in the serum levels of plasma TC, LDL-C, and the activity of hydroxyl methyl glutaryl CoA reductase, which is the key enzyme in the cholesterol biosynthesis pathway (Ahmad & Beg 2013; Hajhashemi & Abbasi 2008). Furthermore, limonene has been shown to decrease hydroxyl methyl glutaryl CoA reductase synthesis (Peffley & Gayen, 2003). So, it is possible that these components in caraway act as inhibitors for some enzymes such as hydroxyl methyl glutaryl CoA reductase or maybe they can act as promoters for lecithin-cholesterol acyl transferase activity, which can help to take lipoproteins back by the liver cells (Wang et al., 2011). The extract might also increase lipoprotein lipase (LPL) activity (Ravi, Ramachandran, & Subramanian, 2004) thus enhance uptake of LDL-C (Ravi et al., 2005). In addition, it may probably act by reducing the NADPH required for cholesterol biosynthesis or
increasing LDL-C receptors (Sharma, Nasir, Prabhu, Murthy, & Dev, 2003). On the other hand, it is likely that the dietary fiber present in caraway plant may be responsible for hypocholesterolemic effect by decelerating fat absorption (Hannan et al., 2003) or binding bile acids within the intestine and increasing their excretion (Anderson et al., 2009). So far, the mechanism of action of caraway as a hypolipidemic agent has not established and is a matter of future evaluation.

Our results also revealed that STZ injection did not affect serum VLDL-C and TG concentration of diabetic rats significantly during the study. However, a slight decrease was observed in diabetic rats compared to the normal ones. Zhang et al. also demonstrated a reduction in serum TG level in STZ-induced diabetic animals after 70 days which is similar to our results (Zhang, Zhang, Xia, Zhao, Cai, & Li, 2008). However, other studies are not in accordance with this study (Cho et al., 2006; Lemhadri et al., 2006). A positive correlation between serum TG concentration and body weight was observed in this study. This might possibly suggest that low level of serum TG may be due to the severe weight loss of diabetic animals because of high blood glucose in the present study. Studies have shown an increase in adipose tissue LPL activity with weight loss (Patalay, Lofgren, Freake, Koo, & Fernandez, 2005). This enzyme is necessary for uptake and storage of serum VLDL-C and TG into fat cells (Wang & Eckel, 2009). Therefore, after weight reduction lower levels of VLDL-C and triglyceride, is expected (Laimer et al., 2009).

The present study also demonstrated that caraway administration did not have any significant effect on serum VLDL-C and TG concentration in diabetic rats. In addition, there were no significant difference in the level of HDL-C in STZ-induced diabetic controls and in caraway treated diabetic rats after 21 days. To our knowledge, no investigation has ever studied caraway’s specific effect on HDL-C level in diabetes. However, longer period of study is suggested for next studies to better investigate effect of this seed on HDL-C.

We also observed that administration of two doses of caraway extract significantly reduced serum glucose level in STZ-induced diabetic rats compared with control diabetic rats, with no significance difference between caraway treated groups and normal group. In addition, because of beneficial decrease in serum glucose, body weight loss in caraway treated diabetic groups were significantly less than diabetic control group. These results were in accordance with other studies (Eddouks, Lemhadri, & Michel, 2004; Ene, Nwankwo, & Samdi, 2008). Furthermore, there was not any significant difference between two caraway treated groups in their serum glucose level. The mechanism of hypoglycemic activity of this plant may be through its main bioactive compounds. The effect of D-limonene on lowering serum glucose and glycosylated hemoglobin levels in STZ-induced diabetic rats has been previously shown. It has been reported that these effects were along with decreasing the activities of gluconeogenic enzymes such as, glucose 6-phosphatase and fructose 1, 6-bisphosphatase and increasing the glycolytic enzyme, glucokinase activity as well as liver glycogen (Murali & Saravanan, 2012). It is also possible that components in caraway seed act by stimulating glucose utilization by peripheral tissues and inhibiting intestinal glucose absorption or renal glucose reabsorption. This activity seemed to be independent of insulin secretion (Ene et al., 2008).

The results of the present study showed that STZ injection did not cause any significant change in serum CRP level in diabetic rats during 21 days. Studies in the
literature have reported both, no change in CRP level, 7 weeks after STZ injection (Jain, Rains, & Croad, 2007; Lei, Hwang, Chan, Lee, & Cheng, 2005) or an increase in CRP level, 8 weeks after STZ injection in diabetic rats (Cho et al., 2006). This study also found that administration of caraway extract did not have any significant effect on CRP level of treated rats. To the best of our knowledge, until now, there is no report on the effect of caraway extract on proinflammatory factor, CRP. Regarding the anti-inflammatory effects of different flavonoids, Song et al. showed that serum concentration of CRP was not significantly related to total intake of dietary flavonoids, including quercetin, kaempferol, myricetin, apigenin, and luteolin (Song, Manson, Buring, Sesso, & Liu, 2005), which is partially in accordance with our study.

Based on a review of the literature, there is no information on caraway toxicity in eukaryotic systems. In addition, during the experimental period, no clinical signs of toxicity or adverse events were observed in rats administered 1 and 2 g/kg caraway plant. However, additional investigations have to be conducted to confirm the lack of renal toxicity and to rule out other organ toxicity, especially after chronic treatment.

In conclusion, the results of the present study revealed that the aqueous extract of caraway plant can significantly decrease the levels of glucose, cholesterol, LDL-C, LDL-C to HDL-C ratio, atherogenic index and non-HDL-C in STZ-induced diabetic rats, showing that it may be of use to prevent cardiovascular complications arising due to lipid abnormalities. In addition, caraway dose of 1 g/kg showed the same results as compared to the dose of 2 g/kg in lowering cholesterol and LDL-C levels. The data obtained also indicated that when two doses of caraway were tested for their anti-inflammatory effects, caraway extracts did not exhibit any significant effect on inflammatory factor, CRP, in treated diabetic rats. Hence, further comprehensive investigations are needed to determine long-term anti-inflammatory and antihyperlipidemic effects of caraway as an adjuvant therapy on CVD and diabetes and to clarify the underlying mechanisms of action.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>STZ</td>
<td>streptozotocin</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>TC</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
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<tr>
<td>VLDL</td>
<td>very low density lipoprotein</td>
</tr>
<tr>
<td>AI</td>
<td>atherogenic index</td>
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*Declaration of interest:* The authors report no conflicts of interest.

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