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The effect of *Foeniculum vulgare* (Fennel) hydroalcoholic extract on serum lipid profiles and liver enzymes in male rats fed a high cholesterol regimen

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Abstract

Background and Objective: Currently, hyperlipidemia is a major health-threatening factor in developed and developing countries. Hyperlipidemia induced by high cholesterol (HC) diet rapidly increases the risk of cardiovascular and liver diseases. F. vulgare is used in traditional medicine for a wide range of ailments and has hepatoprotective, hypolipidemic and cardiovascular activities. This study was done to evaluate the effect of F. vulgare hydroalcoholic extract on serum lipid profiles and liver enzymes in adult Wistar rats.

Materials and Methods: In this experimental study, 28 male rats (190-220 g) were divided into four different groups including: Control, HC diet, Control plus Fennel extract, and Fennel extract-treated high cholesterol-fed groups. Rats were fed a high-cholesterol diet (HC group) or normal rat chow (control group) for 8 weeks. The extract was administered at a dose of 150 mg/kg, once daily for 3 weeks. The blood samples were collected from retroorbital sinus. Then, the measurements of serum biochemical parameters were performed. The data was analyzed by one-way ANOVA test.

Results: Our study showed that the levels of triglyceride (TG), total cholesterol, LDL, LDH, ALT, and ALP significantly increase in HC group and the level of HDL in HC group significantly decreases by HC diet compared to control group ($p<0.001$) after 8 weeks. The levels of TG, total cholesterol, LDL, LDH, ALT, and ALP significantly reduced by treatment with fennel extract and the level of HDL in fennel extract-treated HC-fed group was significantly higher compared to HC group ($p<0.001$).

Conclusion: The results from the present research showed hypolipidemic and hepatoprotective effects of F. vulgare that leads to protection of the liver and cardiovascular system from high cholesterol damage in rats.

Keywords: Foeniculum vulgare, Liver enzymes, Lipid profiles, Hypercholesterolemia

1. Introduction

Currently, hyperlipidemia is a major health-threatening factor in developed and developing countries. It has reached epidemic proportions globally and has been correlated with various comorbidities, including dyslipidemia, fatty liver, as well as cardiovascular (CV) diseases such as heart failure (HF) and coronary heart disease (CHD) and diabetics (1, 2). In developed countries, most dyslipidemias are hyperlipidemias that is a very frequent metabolic disorder characterized by an increase in the rates of triglycerides (TG), total cholesterol (CT), low-density lipoproteins cholesterol (LDL-c) and a reduction of the high-density lipoprotein cholesterol (HDL-c) (3). Fatty liver disease (FLD) and hyperlipidemia are strongly correlated in patients and animal models (4). When energy intake exceeds energy expenditure, excessive

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cellular lipid accumulation occurs not only in adipose tissue but also in ectopic tissues such as liver. Therefore, excessive ectopic lipid deposition often disrupts normal cellular and physiological function, which if allowed proceeds unchecked, will lead to pathological progression. increased hepatic lipogenesis and serum fatty acids contribute to hyperlipidemia progression which cause the excessive accumulation of lipid in liver and result in fatty liver, impaired liver function, and eventually liver failure (5). Liver is an important organ in metabolism, secretion, and waste materials and plays a vital role in maintaining, implementing, and regulating homeostasis in the body and may be involved in several metabolic pathways for growth, to protect against diseases, nutrition supply, energy production, and reproduction. by liver damage, serum levels of many biochemical markers is increased such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), cholesterol, bilirubin, triglyceride, and albumin (ALB) synthesis and total protein (TP) is decreased (6). Cardiovascular disease illustrates that hypercholesterolemia has a proatherogenic and direct effect on the myocardium and results in contraction dysfunction. High cholesterol diet rises LDH, CK and homocysteine which are cardiovascular indices (7).

For many decades, medicinal plants have been used to prevent or treat various diseases. They are used worldwide for their hypoglycemia, hypolipidemia or antioxidant activities (8). *F. vulgar*e is an important medicinal plant which is cultivated in all country (9, 10). It is universally known as fennel. It is a traditional and popular herb has long been used as a medicine. Some studies showed that *F. vulgare* effectively controls numerous infectious disorders of bacterial, fungal, viral, mycobacterium, and protozoal. It has antioxidant, antitumor, chemopreventive, cytoprotective, hepatoprotective, hypoglycemic, and estrogenic activities (10). Some of the publications stated that *F. vulgare* has a special kind of memory-enhancing effect and can reduce stress (10, 11).

F. vulgare is an upright, branching perennial herb with soft, feathery, almost hair-like foliage, growing up to 6.6 ft (2 m) long. This plant looks like a dill. It has a green, sleek, and slippery stem with upright stiff branches and much-divided leaves in linear segments. Flowers are small, yellow, and found in large flat-topped umbels. Fruits are oblong to ovoid. The fruits are elongation and have strong ribs. The most esteemed fennel seeds vary from three to five lines in length and are elliptical, slightly curved, and somewhat obtuse at the ends (10).

F. vulgare has been extensively used in traditional medicine for a wide variety of ailments. Its stem, fruit, leaves, seeds, and entire plant itself are medicinally used in different forms in the treatment of a range of diseases other health-related conditions (10, 12, 13). Phytochemical research carried out on *F. vulgare* has led to the isolation of fatty acids, phenolic components, Flavonoids, hydrocarbons, volatile components, and several other classes of secondary metabolites from different part of it (10, 14). Dietary flavonoids are generally regarded as an important category of antioxidants in the human diet. Among the flavonoids found in *F. vulgare*, quercetin-3-glucuronide, isoquercitrin, quercetin-3-arabinoside, kaempferol-3-glucuronide and kaempferol-3-arabinoside, and isorhamnetin glucoside are major flavonoids in fruit (10, 15). These flavonoids exhibit significant antinociceptive and anti-inflammatory activities (10, 16). Many of phenolic components have antioxidant activities and hepatoprotective properties (10, 17) with decreased levels of AST, ALT and ALK-P (18).

Considering all above reports, the current investigation was carried out to evaluate the effect of hydroalcoholic extract of *F. vulgare* on serum lipid profiles and liver enzymes in HF diet male rats.

2. Materials and Methods

2.1. Animals

In this study, 28 male Wistar rats (190-220 g) were provided from Pasteur Institute of Iran. Animals were maintained in plastic cages with 12/12 h light/dark cycle at 21 ± 2°C. These conditions were kept constant in all experiments. All the ethical issues were based on Ethical Committee of Shahed University Ethical Protocols in animal experiments.

2.2. Extraction

Fennel seeds were purchased from common market of medicinal herbs in Tehran and the Shahid Beheshti University verified the voucher codes (SUMS8034). To prepare the extract by maceration method, at first 100 grams of fennel seeds was weighed and after milling was poured into an Erlenmeyer flask. Then, 80% ethanol solution (Merck, Germany) was added four times more than the weight of the plant and kept for three to four days on the shaker at lab temperature. After this period, the mixture was passed through filter paper and the solvent extracts were evaporated on a watch glass at 45°C Ben Marie. Extract powder was obtained and kept at 4°C until to be used (19, 20).

2.3. Grouping and prescribing the extract

Rats were randomly divided into four different groups with 7 rats in each group, including:

A) Control: received standard pellet for 8 weeks.

B) HC: received high cholesterol diet for 8 weeks + 3 weeks (standard pellet+cholesterol 0.1%+ cholic acid 0.25%) (21).

C) Control plus Fennel extract: received normal standard pellet for 8 weeks and administration of the hydroalcoholic extract of Fennel through

intraperitoneal route at a dose of 150 mg/kg body weight for 3 weeks.

D) Fennel extract-treated high cholesterol-fed group: received high cholesterol diet for 8 weeks and administration of the hydroalcoholic extract of Fennel through intraperitoneal route at a dose of 150 mg/kg body weight for 3 weeks.

In order to adapt, rats were fed with diet (food and water) for 10 days. The extract was administrated into groups C and D once a day. Measurements of body weight were recorded before and after feeding with high cholesterol diet.

2.3. Experimental test

The blood samples were collected from retro-orbital sinus. Then, samples were centrifuged at 8000 rpm for 15 minutes at 4°C to separate the plasma. For further analysis, plasma is separated to proper transfer/storage tubes at -20°C. Then, plasma concentrations of total cholesterol, triglycerides, LDL, LDH, HDL and activities of plasma ALT, ALP were determined using diagnostic kits, supplied by Pars Azmoon according to manufacturer-provided standards and protocols.

2.4. Statistical analysis

The results were statistically analyzed using SPSS software. Several comparisons were made among the treatment and control groups by ANOVA. In all the tests, the criterion for statistical significance was considered to be $p<0.05$.

3. Results

Table 1 shows lipid profile levels after 8 weeks feeding with high cholesterol diet. As can be seen, the dietary fat feeding high cholesterol for 8 weeks increased the levels of TG, total cholesterol and LDL-c and decreased the level of HDL in HC group compared to control group. Extract-treated high cholesterol-fed group significantly increased the level of HDL-c in group D compared to group C. On the other hand, Extract-treated high cholesterol-fed group significantly decreased the levels of TG, LDL-c and total cholesterol in group D compared to group C.

Table 1. Lipid profile levels in different groups

Fats / Groups	Triglyceride (TG) (mg/dl)	Total cholesterol (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)
A: control	228.14 ± 3.35 a	57.98 ± 2.33 a	157.5 ± 2.55 a	29.9 ± 1.76 a
B: Control+Fennel extract	203 ± 3.7 a	50.17 ± 2.14 a	169.82 ± 2.71 a	25.35 ± 1.75 a
C: HC	254.45 ± 4.24 b	107.37 ± 4.15 b	57.5 ± 2.14 b	41.56 ± 1.57 b
D: HC + Fennel extract	185.47 ± 3.56 a	81.14 ± 1.88 a	93.6 ± 2.31 a	32.31 ± 1.68 a

Values were expressed as means ± S.E.M, n = 7. Different p-values are considered to be $P < 0.001$, a vs b, control vs HC or HC vs treatment.

3.1. Effect of normal and HC diet on entire body weights after 8 weeks

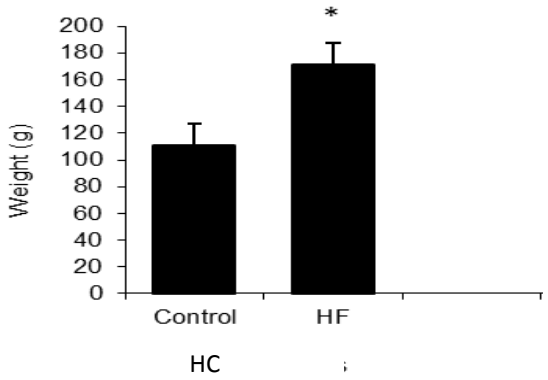

Figure 1. Effect of normal and HC diet on entire body weights. Body weight was significantly increased in rats fed on the HC diet during 8 weeks compared with controls. Values were significantly different compared to normal weight *P < 0.05.

Body weight was significantly increased in rats on the HC diet compared to control (p<0.05) (Figure 1).

3.2. Plasma TG levels before and after treatment with the hydroalcoholic extract of fennel

Figure 2 shows a significant increase in TG level in HC group compared to control group (p<0.001) and it was significantly lower in extract-treated high cholesterol-fed group compared to HC group (p<0.001). In addition, there was a significant reduction in extract- treated control group compared to control group (p<0.001).

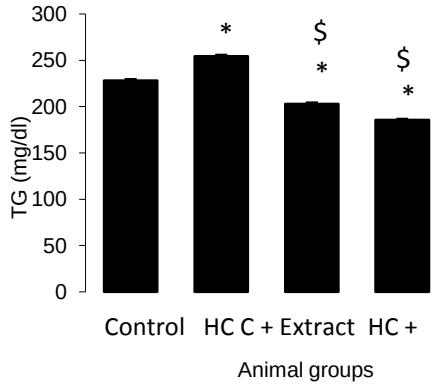

Figure 2. Plasma TG levels before and after treatment with the hydroalcoholic extract of fennel. For each group, *p<0.001(as compared to control) and $ p<0.001(as compared to HC group).

3.3. Plasma TC levels before and after treatment with the hydroalcoholic extract of fennel

Figure 3 shows a significant increase in TC level in HC group compared to control group (p<0.001) and it was significantly lower in extract-treated control group compared to control group (p<0.001). Furthermore, there was a significant decline in extract-treated high cholesterol-fed group compared to HC group (p<0.001).

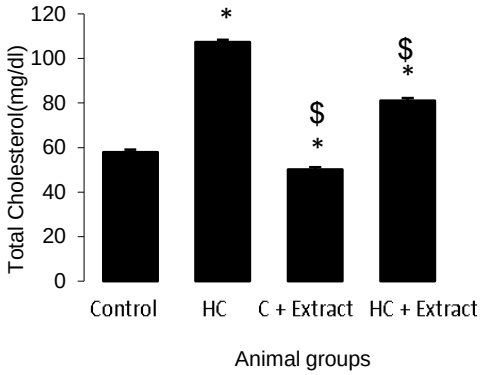

Figure 3. Plasma TC levels before and after treatment with the hydroalcoholic extract of fennel. For each group, *p<0.001(as compared to control) and $ p<0.001(as compared to HC group).

3.4. Plasma LDL-c levels before and after treatment with the hydroalcoholic extract of fennel

Figure 4 shows a significant increase in LDL-c level in HC group compared to control group (p<0.001) and it was significantly lower in Extract-treated control group compared to control group (p<0.001). Furthermore, there was a significant decline in Extract-treated high cholesterol-fed group compared to HC group (p<0.001).

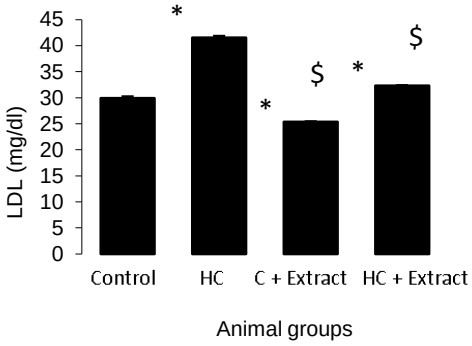

Figure 4. Plasma LDL-c levels before and after treatment with the hydroalcoholic extract of fennel. For each group, *p<0.001(as compared to control) and $ p<0.001(as compared to HC group).

3.5. Plasma HDL-c levels before and after treatment with the hydroalcoholic extract of fennel

Figure 5 shows a significant decrease in HDL-c levels in HC group compared to control group ($p<0.001$) and it was significantly higher in extract-treated control group compared to control group ($p<0.001$). Furthermore, there was a significant increase in extract-treated high cholesterol-fed group compared to HC group ($p<0.001$).

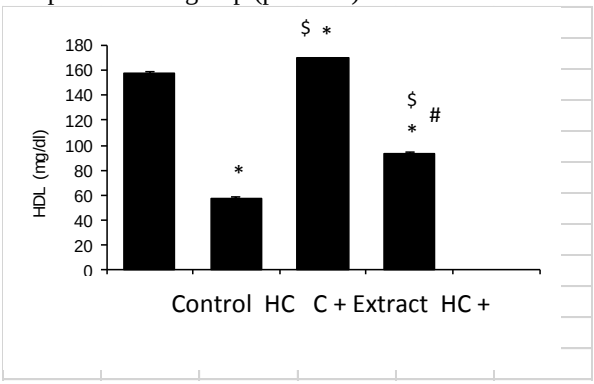

Figure 5. Plasma HDL-c levels before and after treatment with the hydroalcoholic extract of fennel. For each group, * $p<0.001$(as compared to control), $ $p<0.001$(as compared to HC group) and # $p<0.001$(as compared to C + Extract group)

3.6. Plasma ALT levels before and after treatment with the hydroalcoholic extract of fennel

Figure 6 shows a significant increase in ALT levels in HC group compared to control group ($p<0.001$) and there was a low reduction in Extract-treated control group compared to control group. In addition, there was a significant decline in Extract-treated high cholesterol-fed group compared to HC group ($p<0.001$).

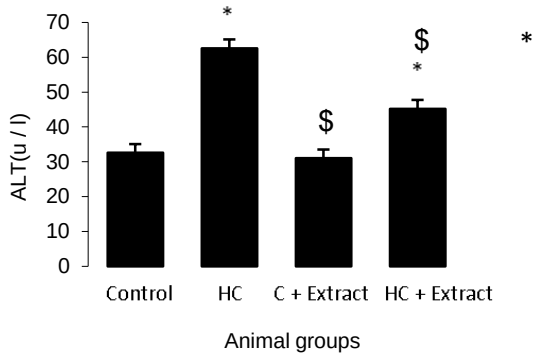

Figure 6. Plasma ALT levels before and after treatment with the hydroalcoholic extract of fennel. For each group, * $p<0.001$(as compared to control), $ $p<0.001$(as compared to HC group)

3.7. Plasma ALP levels before and after treatment with the hydroalcoholic extract of fennel

Figure 7 shows a significant increase in ALP levels in HC group compared to control group ($p<0.001$) and it was lower in extract-treated control group compared to control group ($p<0.001$). Furthermore, there was a significant decline in extract-treated high cholesterol-fed group compared to HC group ($p<0.001$).

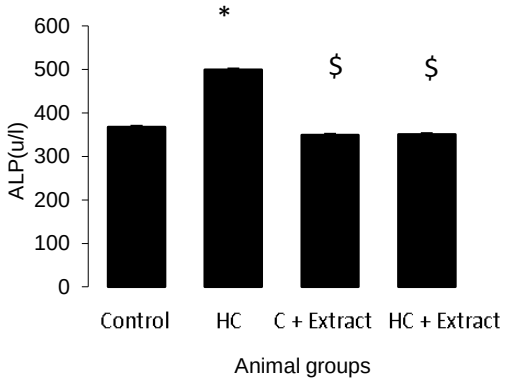

Figure 7. Plasma ALP levels before and after treatment with the hydroalcoholic extract of fennel. For each group, * $p<0.001$(as compared to control), $ $p<0.001$(as compared to HC group)

3.8. Plasma LDH levels before and after treatment with the hydroalcoholic extract of fennel

Figure 8 shows a significant increase in LDH levels in HC group compared to control group ($p<0.001$) and it was lower in Extract-treated control group compared to control group ($p<0.001$). Furthermore, there was a significant decline in Extract-treated high cholesterol-fed group compared to HC group ($p<0.001$).

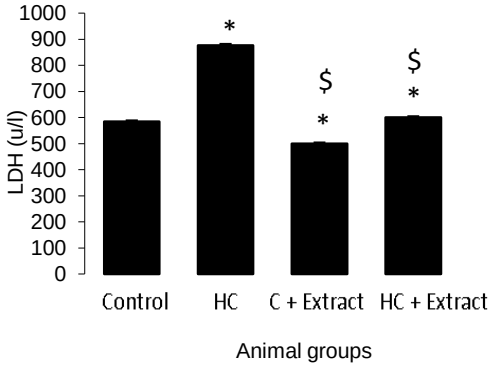

Figure 8. Plasma LDH levels before and after treatment with the hydroalcoholic extract of Fennel. For each group, * $p<0.001$(as compared to control), $ $p<0.001$(as compared to HC group)

4. Discussion

Studies have demonstrated that overproduction or deficiency in lipoproteins leads to a disorder of lipoprotein metabolism so-called dyslipidemia, which is determined by an increase in serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, and decrease in high-density lipoprotein cholesterol (22). Hyperlipidemia induced by high-fat diet escalates the risk of cardiovascular and liver diseases (1). Also, medicinal plants have long been used throughout the world to prevent various diseases. Thus, this study evaluates the potential effects of fennel hydroalcoholic extract on serum lipid profiles and changes in the activities of ALT and ALP indicators of liver cell and tissue damage and LDH levels.

The obtained results showed that body weight increased significantly in the HF diet group compared to the normal group (Figure 1), it is a result in line with study by Xu et al and Kamal et al (2, 23). Obesity resulting from overconsumption of the HF diet since it facilitates the development of a positive energy balance leading to an increase in visceral fat deposition; this led to specifically abdominal obesity (22).

This study illustrated a HF diet with a significant increase in serum TC, TG, LDL, LDH levels and a significant decrease in serum HDL level, which is line with study of Amin et al and Woo et al and Al-Muzafar (2, 7, 24)**.** Lipid in adipose tissue are largely derived from TG especially during HF diet feeding. The increased serum LDL level in HF rats has been recorded. This fact was explained by the decreased HDL level, thus the reverse cholesterol transport is decreased from the blood stream via liver (25). In addition, high cholesterol diet increases lipid profiles like TG, TC, and LDL. As well, it disturbs cardiac markers such as LDH. These factors interfere with endothelial dysfunction and increase the risk of cardiovascular disorders (7). TC, TG, LDL and LDH levels are significantly decreased by fennel extract and serum HDL level increased in HF treated extract group compared with HF group (Figures 2, 3, 4, 5, 8). The result is in line with study of Shahat et al (25). This result indicated that the constitution of fennel extract is appropriate to improve blood lipid profile by increasing HDL level and stimulating the reverse cholesterol transport from the blood steam via the liver. Also, the fennel is capable of delaying upper gastrointestinal transit that decreases fat absorption (25). Moreover, flavonoids and phenolic compounds of fennel have anti-hyperlipidemic action by regulation of blood lipids (22).

This study showed that there is a significant increase in the activity of enzymes ALP and ALT in the HF diet group compared to control rats (Figures 6 and 7). The result is in line with studies by Keskin et al and Amin et al (2, 26). Liver is bombarded by the free fatty acids that pour out of the adipose tissue into the portal blood. This can directly cause inflammation within the liver cells and releases further pro-inflammatory cytokines, leads to more hepatocyte injury and affects the integrity of liver cells (2). Administration of fennel extract decreases significantly the activity of ALP and ALT in extract-treated HF rats compared to HF group (Figures 6 and 7). The result is in line with studies of Parsayan et al and Ozbec et al (18, 27). Many phenolic components and fennel flavonoids have antioxidant activities and hepatoprotective properties by decreasing ALP and ALT levels (10, 16, 17).

Conclusion

To conclude, *F. vulgare* has a promising effect on hyperlipidemia and prevents cardiovascular disorders and also protects the liver against hypercholesterolemia.

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