Beneficial Health Effects of Fennel Seeds (Shamar) on Male Rats Feeding High Fat-Diet

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Abstract

Fennel has been known since antiquity as a medicinal and aromatic herb, it commonly used in household remedy for various medicinal purposes. The present study was conducted to investigate the effect of beneficial health effects of fennel seeds on feeding rats with high fat-diet. Histopathological changes of aorta, heart and liver were examined. Thirty five male albino rats of Sprague-Dawley strain weighing 201±5g were used. Animals were divided into five groups of seven rats each: group (1) fed on the basal diet and kept as a negative control group; group (2) fed on high fat–diet and kept as positive control group; groups (3), (4) and (5) fed on high fat diets supplemented with three different levels of fennel seeds (5, 10 and 15%, respectively. The present results revealed that rats fed on high fat-diet only (positive control group) had significant (at \( p < 0.05 \)) increase in serum TL, TG, TC, LDL-C, VLDL-C, AST, ALT, ALP and MDA concentrations, and significant decrease in serum HDL-C level as well as significant decrease in HDL-C/LDL-C ratio value and serum activity of CAT, GPX and SOD enzymes as compared to rats fed on basal diet only (negative control group). High fat-diet supplemented with the three different levels of fennel seeds significantly improved serum levels of TL, TG, TC, LDL-C, VLDL-C, AST, ALT, ALP and MDA concentrations, and significant raise in serum HDL-C level, values of HDL-C/LDL-C ratio and improve activities of CAT, GPX and SOD enzymes compared to the positive control group. Histopathological investigation showed vaculations of tunica media and narrowing in the lumen of aorta sections and congestion of cardiac blood vessel as well as fatty change of hepatocytes in positive control rats. Vaculations of tunica media in aorta sections and fatty changes of hepatocytes were showed in rats fed high fat-diet supplemented with 5% fennel seeds. Slight thickening in the wall of aorta sections was showed in rats treated with 10% fennel seeds, whereas, other sections showed apparent normal histological structure. Its liver sections had small vacuoles in the cytoplasm hepatocytes. Liver sections of treated rats with 15% fennel seeds showed small vacuoles in the cytoplasm of some hepatocytes and other sections revealed apparent normal hepatocytes. There were no histological changes in heart sections of all treated rats with fennel seeds and in aorta of rats treated with 15% fennel seeds. In conclusion, the present study revealed that fennel seeds improve dyslipidaemia by improving lipid profile, cholesterol and low density lipoprotein cholesterol, and decrease the risk of chronic heart diseases by increasing level of HDL-C as well as enhancing activities of antioxidant enzymes.

Key Words: Fennel – Hyperlipidemia – Hypercholesteremia – Liver functions – Antioxidant system.

Introduction

HYPERLIPIDEMIA is a heterogeneous disorder involving multiple etiologies. It is characterized by the elevated in serum levels of free fatty acids, triglycerides (TG), total lipid (TL), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and Apolipoprotein B, and reduced serum high-density lipoprotein cholesterol (HDL-C) concentration [1].

Hyperlipidemia contributes significantly in the development of atherosclerosis and coronary heart diseases. Atherosclerosis is the most common cause of mortality and morbidity worldwide [2]. High cholesterol diet leading to hyperlipidemia is regarded as an important factor in the development of ischemic heart disease. Ischemic stress of the heart is a major cause of mortality in civilized societies [3]. Although several factors, such as diet high in saturated fats and cholesterol, age, family history, hypertension and life style play a significant role in causing heart failure, the high levels of cholesterol particularly TC, TG and LDL-C is mainly responsible for the onset of cardiovascular diseases [2].

The use of medicinal plants for health started from thousands of years and still a part of the medical practice in Egypt and other developed countries. Foeniculum vulgare is an annual, biennial or perennial plant, depending on the variety and it is a well-known umbelliferous plant. The leaves, stalk and seeds are edible part. Fennel is the ripe fruit known as seed of Foeniculum Vulgare [4]. It
is a commonly used in household remedy for various medicinal purposes [8]. Fennel seed has been known since antiquity as a medicinal and aromatic herb, commonly used to flavor breads, fishes, salads and cheeses [6]. Some people use fennel as a diuretic, and it may be an effective diuretic and a potential drug for treatment of hypertension [7]. It can be add into syrup to treat babies with colic [8].

Fennel seeds are rich in carbohydrates, moisture, and protein and fat [9]. Its mineral contents are calcium, phosphorous, iron, sodium and potassium. Vitamins content are thiamine, riboflavin, niacin and C [10]. The major fatty acid components of fennel seeds are oleic acid and linoleic acid. Fennel seeds are high in isoleucine and histidine. The seed oil yield varies according to variety and origin and the highest concentration of fennel oil ranging from 2-7%. Fennel volatile oil is a mixture of different chemicals and the main ingredients are anethole, fenchone and estragole [4].

Recently, fennel seeds were found to have a hypotensive effect [11], antispasmodic activities [12], anti-hirsutism [13], hepatoprotective [14], anti-inflammatory [15], antidementia [16], possess pain reliever in primary dysmenorrhoea [17], antiplatelet and antithrombotic [18], immunomodulatory [19], protective effect against ethanol induced gastric mucosal lesions [20], anticancer [21], potential in the treatment of glaucoma [22] and antioxidant [23].

The current study was aimed to investigate the beneficial health effects of fennel seeds (Foeniculum vulgare) administration on hyperlipidemic rats feed on high fat-diet. Histopathological changes of aorta, heart and liver were examined.

Material and Methods

Fennel seeds (foeniculum vulgare): Fennel seeds were obtained from Haraz market for herbs and medicinal plants market, Cairo, Egypt.

Rats and diet: Thirty five male albino rats of Sprague-Dawley strain weighing 200±5g were obtained from the Laboratory Animal Colony, Ministry of Health and Population, Helwan, Egypt. Basal diet constituents were purchased from El-Gomhorya Company for Pharmaceutical and Chemical, Cairo, Egypt.

Kits: Kits for biochemical analysis of serum TL, TG, TC, HDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), malondialdehyde (MDA), catalase (CAT), glutathione peroxidase (GPX) and superoxide dismutase (SOD) were purchased from The Gamma Trade Company for Pharmaceutical and Chemicals, Dokki, Egypt.

Preparation of fennel seeds: Dried fennel seeds (shamar) were washed with tap water to remove possible potential dust. Afterwards, it was dried by cotton cloth to remove the excess liquid prior to drying. Drying was achieved at room temperature for 48 hr. Then a grinder mill and sieves were used to obtain a powder particle size of less than 0.2mm.

Preparation of basal diets: The basal diet (AIN-93M) was prepared according to Reeves et al. Diet was formulated to meet recommended nutrients levels for rats.

Experimental design:

The experiment was conducted on thirty five male rats weighing approximately 200±5g for 4 weeks. The animals were housed in healthy condition at room temperature (21-23°C), with 40-60% humidity, exposed to a 12: 12-h light-dark cycle and fed on the basal diet and water was provided ad libitum for one week before starting the experimental for acclimatization. After acclimatization period rats were divided into five groups of seven rats each: group (1) fed on the basal diet and kept as a negative control group (normal rats); the remaining four groups fed high fat containing-diet. Group (2) kept as a positive control group; groups (3), (4) and (5) fed on high fat diets supplemented with the three different levels of fennel seeds (5, 10 and 15%, respectively). Hyperlipidemia in rats was done according to the method described by Balkan et al. [25]. In briefly, basal diet was formulated with 1% cholesterol, 2% sheep fat and 0.5% cholic acid to enhance the enteral absorption of lipids.

At the end of the experimental period, diets were withheld from experimental rats for 12-h and then rats were sacrificed. Blood samples were collected from the portal vein into dry clean centrifuge tubes. For serum separation, blood samples were left at room temperature to get clot, and then centrifuged for 15 minutes at 3000 rpm. Serum was carefully aspirated using a needle and transfers into dry clean test tubes and kept frozen at-10°C until chemical analysis.

Aorta and organs such as heart and liver were removed and washed with saline solution, dried, and kept in formalin solution (10%) for histopathological examination.

Biochemical analysis:

Lipid profile and lipoprotein cholesterol assay: Serum TL concentration was determined colori-
metric using spectrophotometer apparatus adjusted at 520nm as described by kit instructions (Randox Co., Ireland). TG, TC and HDL-C concentrations were determined using enzymatic methods as described in the instructions provided with the kits (Analyticon® Biotechnologies AG, Germany). The absorbance of the testes samples were read using spectrophotometer adjusted at 546nm for TG and TC, and 500nm for HDL-C.

Low density lipoprotein cholesterol concentration was calculated by using formula of Friedwald et al. [26]. Then ratio of high density lipoprotein cholesterol to low density lipoprotein cholesterol (HDL-C/LDL-C) was measured. Very low density lipoprotein cholesterol (VLDL-C) was calculated using the following equation:

\[ \text{VLDL-C (mg/dL)} = \frac{\text{TG}}{5} \]

Liver functions assay: Serum AST, ALT and ALP activities were determined using colorimetric methods as described in the kits instruction (Diamond Co., Hannover, Germany).The absorption of the test samples were read at 505nm for AST and ALT and at 510nm for ALP.

Malondialdehyde assay: Serum MDA concentration as indicator of lipid peroxidation was determined. The principle of the methods is spectrophotometric measurements of the color produced by the reaction of thiobarbituric acid (TBA) with MDA. The concentration of MDA was then calculated and expressed as \( \mu \)moles/dl \[27\].

Antioxidant defense system assays: Activity of CAT, GPX, SOD enzymes were determined by Autoanalyzer (Roche-Hitachi, Japan) using commercial kits according to the methods described by Sinha, [28], Hissin and Hiff, [29]; Kakkor et al. [30] respectively.

Histopathological examination: Aorta, heart and liver of the scarified rats were taken and immersed in 10% formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. Specimens were then cleared in xylol, embedded in paraffin, sectioned at 4-6 microns thickness, and stained with Hematoxylin and Eosin stain for histopathological examination as described by Carleton, [31].

Statistical analysis: Results were expressed as mean±SE. All data from the experiment were examined statistically by one-way analysis of variance with computerized SPSS package program (SPSS 6.00 software for Windows) by ANOVA test. A \( p \)-value <0.05 was considered statistically significant.

Results

Serum total lipids, triglycerides and total cholesterol concentrations: Recorded data in Table (1) illustrated that feeding animal with high fat diet (positive control group) produced a significant \( p<0.05 \) elevation in serum TL concentration (442.43±0.37mg/dL), as well as significant increase in TG and TC concentrations (135.43±0.30 and 99.14±0.26mg/dL, respectively) as compared to the feeding animal with normal basal diet only (371.29±0.42, 115.14±0.51 and 58.14±0.26mg/dL, respectively). Supplemented high fat diet with fennel seeds at different levels reduced significantly \( p<0.05 \) serum TL, TG and TC levels as compared to feeding animal with high fat diet only.

Serum LDL, HDL and VLDL-cholesterol concentrations: Data in Table (2) revealed that serum LDL-C and VLDL-C levels were higher significantly at \( p<0.05 \) (59.04±0.18 and 27.06±0.10mg/dL, respectively), while HDL-C level was lower significantly (13.00±0.31mg/dL) in positive control rats compared with negative control rats (11.11±0.11, 23.03±0.11mg/dL, 24.00±0.31mg/dL, respectively). High fat diets supplemented with fennel seeds at different levels reduced significantly serum levels of LDL-C and VLDL-C, and raised significantly serum HDL-C level compared with feeding rats with high fat diet.

HDL/LDL-C ratio: As shown in Fig. (1) results demonstrated that mean ±SE for value of HDL-C/LDL-C ratio was lower significantly \( p<0.05 \) in positive control rats (0.22±0.06) compared with the negative control rats (2.16±0.04). In contrast, feeding rats with high fat-diet supplemented with different levels of fennel seeds induced significantly higher in values of HDL/LDL-C ratio (0.61±0.11, 0.29 and 37.14±0.04), as compared to feeding animal with normal basal diet only.

Liver functions: Serum AST, ALT and ALP concentrations as indicator of liver function in rats are shown in Table (3). Data showed that positive control group had significant \( p<0.05 \) increase in serum AST, ALT and ALP levels (26.86±0.51, 21.86±0.26 and 50.29±0.18U/L, respectively) compared with the negative control group (16.14±0.40, 13.29±0.29 and 37.14±0.34U/L, respectively). Feeding high fat diet supplemented with 5, 10 and 15% of fennel seeds induced significant \( p<0.05 \) decrease in serum AST, ALT and ALP levels compared to the positive control group.

Serum malondialdehyde concentration and activity of catalase enzyme: Tabulated results as shown in Table (4) revealed that positive control
rats had significant \((p<0.05)\) increase in serum MDA level (2.79±0.003 µmol/dL) and significant decrease in the activity of CAT enzyme (42.19±0.27 µmol/dL) compared with the negative control rats (1.25±0.002 and 68.56±0.49 µmol/dL). However, feeding rats with high fat-diet supplemented with 5%, 10% and 15% of fennel seeds significantly reduced serum MDA (1.68±0.003, 1.48±0.004 and 1.41±0.004 µmol/dL., respectively) levels and significant increase activity of CAT enzyme compared with the positive control rats.

**Activity of GPX and SOD enzymes:** Recorded results in Table (5) demonstrated that the positive control rats fed on high fat-diet only had significant \((p<0.05)\) decrease in the activity of GPX enzyme (8.09±0.16mmol/dL) compared with the negative control rats fed on the basal normal diet (18.67±0.16 mmol/dL). Feeding rats with high fat-diet supplemented with fennel seeds at different levels (5, 10 and 15%) increased significantly activity of GPX enzyme (9.28±0.03, 10.74±0.04 and 15.65±0.16 mmol/dL, respectively) compared with the positive control rats.

With regard to the activity of SOD enzyme in serum of rats, tabulated results revealed that positive control rats had significant \((p<0.05)\) decrease in serum activity of SOD (55.95±0.17U/dL) enzyme compared with the negative control rats (95.30±0.14 U/dL). Feeding supplemented diets with the three different levels of fennel seeds increased significantly \((p<0.05)\) the serum activity of SOD (68.98±0.17, 75.99±0.04, 87.88±0.04U/dL, respectively) enzyme compared to the positive control rats (55.95±0.17U/dL).

**Histopathological examination:**

**Aorta:** Fig.s (2-5) showed histopathological structure of aorta sections in experimental animals. Normal histological structure was showed in normal rats fed on normal basal diet (Fig. 2). However, vaculations of tunica media in the lumen was showed in rats fed on high fat-diet (Fig. 3). Aorta sections of feeding rats with high fat diet supplemented with 5% fennel seeds revealed vaculations of tunica media as showed in Fig. (4). However, slight thickening in the wall was showed in aorta sections of feeding rats on high fat diet supplemented with 10% fennel seeds (Fig. 5), whereas, other sections revealed apparent normal histological structure. Normal histological structure of aorta was showed in feeding rats with high fat diet supplemented with 15% fennel seeds.

**Heart:** Normal histological pattern of heart tissue of negative control rats and feeding rats with high fat diet supplemented with the three different levels of fennel seeds was detected as showed in Fig. (6). However, congestion of cardiac blood vessel and hyalinosis of its wall was showed in rats from positive control group (Fig. 7).

**Liver:** Liver sections of rats from negative control rats revealed normal histological structure of hepatic lobule as shown in Fig. (8). Liver sections of rats from positive control rats revealed fatty change of hepatocytes and congestion of hepatic sinusoid, vacuolization of hepatocytes and necrosis of sporadic hepatocytes as shown in Figs. (9,10, respectively). Treated rats with 5% fennel seeds revealed fatty change of hepatocytes as shown in Fig. (11). Examined liver sections of hyperlipidemic rats treated with 10% fennel seeds revealed only small vacuoles in the cytoplasm of hepatocytes as shown Fig. (11). Meanwhile, liver sections of treated rats with 15% fennel seeds showed small vacuoles in the cytoplasm of some hepatocytes as shown in Fig. (12), whereas, other sections revealed apparent normal hepatocytes.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters as Mean±SE</th>
</tr>
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<tbody>
<tr>
<td>TL (mg/dL)</td>
<td>TG (mg/dL)</td>
</tr>
<tr>
<td>Negative group</td>
<td>371.29±0.42e</td>
</tr>
<tr>
<td>Positive group</td>
<td>442.43±0.37a</td>
</tr>
<tr>
<td>5% fennel</td>
<td>399.29±0.23b</td>
</tr>
<tr>
<td>10% fennel</td>
<td>388.43±0.43a</td>
</tr>
<tr>
<td>15% fennel</td>
<td>375.86±0.26d</td>
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</table>

A uses harmonic mean sample size \(= 7\) rats.
Data represented as Mean±SE.
Means with different superscript letters are significantly different at \(p<0.05\).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters as Mean±SE</th>
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<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>HDL-C (mg/dL)</td>
</tr>
<tr>
<td>Negative group</td>
<td>11.11±0.11e</td>
</tr>
<tr>
<td>Positive group</td>
<td>59.04±0.18a</td>
</tr>
<tr>
<td>5% fennel</td>
<td>28.80±0.16b</td>
</tr>
<tr>
<td>10% fennel</td>
<td>21.71±0.19c</td>
</tr>
<tr>
<td>15% fennel</td>
<td>17.20±0.33d</td>
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</table>

A uses harmonic mean sample size \(= 7\) rats.
Data represented as Mean±SE.
Means with different superscript letters are significantly different at \(p<0.05\).
Table (3): Serum AST, ALT and ALP concentrations in hyperlipidemic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST (U/L)</td>
<td>ALT (U/L)</td>
<td>ALP (U/L)</td>
<td></td>
</tr>
<tr>
<td>Negative group</td>
<td>16.14±0.40d</td>
<td>13.29±0.29e</td>
<td>37.14±0.34c</td>
<td></td>
</tr>
<tr>
<td>Positive group</td>
<td>26.86±0.51a</td>
<td>21.86±0.26a</td>
<td>50.29±0.18a</td>
<td></td>
</tr>
<tr>
<td>5% fennel</td>
<td>23.00±0.53b</td>
<td>17.57±0.20b</td>
<td>38.43±0.20b</td>
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</tr>
<tr>
<td>10% fennel</td>
<td>19.71±0.57c</td>
<td>15.71±0.29c</td>
<td>37.43±0.37c</td>
<td></td>
</tr>
<tr>
<td>15% fennel</td>
<td>17.14±0.40d</td>
<td>14.43±0.20d</td>
<td>36.00±0.31d</td>
<td></td>
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</tbody>
</table>

A uses harmonic mean sample size = 7 rats.
Data represented as Mean±SE.
Means with different superscript letters are significantly different at p<0.05.

Table (4): Serum MDA concentration and activity of CAT enzyme in hyperlipidemic rats.

<table>
<thead>
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<th>Groups</th>
<th>Parameters</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>MDA (µmol/dL)</td>
<td>CAT (mmol/dL)</td>
<td></td>
</tr>
<tr>
<td>Negative group</td>
<td>1.25±0.002e</td>
<td>68.56±0.49a</td>
<td></td>
</tr>
<tr>
<td>Positive group</td>
<td>2.79±0.003a</td>
<td>42.19±0.27e</td>
<td></td>
</tr>
<tr>
<td>5% fennel</td>
<td>1.68±0.003b</td>
<td>52.43±0.23d</td>
<td></td>
</tr>
<tr>
<td>10% fennel</td>
<td>1.48±0.004c</td>
<td>56.53±0.17c</td>
<td></td>
</tr>
<tr>
<td>15% fennel</td>
<td>1.41±0.004d</td>
<td>63.04±0.23b</td>
<td></td>
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</tbody>
</table>

A uses harmonic mean sample size = 7 rats.
Data represented as Mean±SE.
Means with different superscript letters are significantly different at p<0.05.

Table (5): Serum activity of GPX and SOD enzymes in hyperlipidemic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GPX (mmol/dL)</td>
<td>SOD (U/dL)</td>
</tr>
<tr>
<td>Negative group</td>
<td>18.67±0.16a</td>
<td>95.30±0.14a</td>
</tr>
<tr>
<td>Positive group</td>
<td>8.09±0.16e</td>
<td>55.95±0.17e</td>
</tr>
<tr>
<td>5% fennel</td>
<td>9.28±0.03d</td>
<td>68.98±0.17d</td>
</tr>
<tr>
<td>10% fennel</td>
<td>10.74±0.04c</td>
<td>75.99±0.04c</td>
</tr>
<tr>
<td>15% fennel</td>
<td>15.65±0.16b</td>
<td>87.88±0.04b</td>
</tr>
</tbody>
</table>

A uses harmonic mean sample size = 7 rats.
Data represented as Mean±SE.
Means with different superscript letters are significantly different at p<0.05.
Fig. (5): Aorta of rat from hyperlipidemic rats treated with 10% fennel seeds showing slight thickening in the wall (H & E x 400).

Fig. (8): Liver of normal rats showing normal histological structure of hepatic lobule (H & E x 400).

Fig. (6): Heart of rat from normal group showing no histopathological change (H & E x 400).

Fig. (9): Liver of positive control rats showing fatty change of hepatocytes (H & E x 400).

Fig. (7): Heart of positive control rats showing congestion of cardiac blood vessel and hyalinosis of its wall (H & E x 400).

Fig. (10): Liver of positive control rats showing congestion of hepatic sinusoid, vacuolization of hepatocytes and necrosis of sporadic hepatocytes (H & E x 200).
Discussion

Hyperlipidemia is known as a risk factor for cardiovascular disease, especially atherosclerosis, which is one of the major causes of premature death globally and it is expected to be the most important cause of mortality. It has been well established that nutrition plays an important role in the etiology of hyperlipidemia and atherosclerosis. The current study was aimed to investigate the beneficial health effects of fennel seeds (Foeniculum vulgare) administration on hyperlipidemic rats feed on high fat-diet. Histopathological changes of aorta, heart and liver were examined.

Hyperlipidemia or dyslipidaemia is the presence of elevated or abnormal levels of lipids and/or lipoproteins in the blood. Lipid and lipoprotein abnormalities are regarded as a highly modifiable risk factor for cardiovascular disease due to the influence of cholesterol, one of the most clinically relevant lipid substances in atherosclerosis [32]. Ample of evidence exists with respect to the fact that HDL cholesterol is inversely related to total body cholesterol and a reduction of plasma HDL cholesterol concentration may accelerate the development of atherosclerosis leading to ischemic heart diseases, by impairing the clearing of cholesterol from the arterial wall [33]. From the obtained results it was observed that keeping the animal on high fat-diet resulted in dyslipidemic changes as illustrated by the significant increase in serum TL, TG, TC, LDL-C and VLDL-C, as well as a significant reduce in serum HDL-C level and value of HDL-C/LDL-C ratio compared to the rats on normal diet. These results were confirmed with histopathological changes of feeding rats with high fat diet only, which showed vaculations of tunica media and narrowing in the lumen of aorta sections as well as congestion of cardiac blood vessel and hyalinosis of its wall. This result was in accordance with Farmer and Gotto, [34] who reported that plasma levels of LDL are associated with the occurrence of atherosclerosis and impairment of endothelial function of arteries in hyperlipidemic patients. Parathasarathy et al. [35] reported that hypercholesterolemia is one of the major risk factors for coronary artery disease and atherosclerosis. LDL-C plays a crucial role in the atherogenesis and it is the oxidative modification that imparts an atherogenicity to LDL. This result was confirmed by Szilvassy et al. [36] who indicated that although hyperlipidemia increases oxidative stress in the cardiovascular system, it renders the heart and the vasculature more susceptible to stress. Recently, Ouwens et al. [37] identified that development of hypercholestremia, which is one of the
risk factors for cardiovascular diseases is associated with increased blood levels of TC, LDL-C and VLDL-C as well as lowered levels of HDL in rats fed on high fat-diet. Jain et al. [38] reported that coronary heart disease is caused by the narrowing of the artery that supplies nutrients and oxygen to the heart. The main reason for this narrowing is atherosclerosis. Moreover, there is a relationship between the elevated in plasma lipids and the development of atherosclerotic plaques. Woo et al. [39] showed that high fat-diet caused significantly elevated in serum TG and TC levels, significantly decreased in serum HDL-C compared to the controls rats.

When high fat-diet was supplemented with the three different levels of fennel seeds (5, 10 and 15%), the elevated levels of TL, TG, TC, LDL-C and VLDL-C condition has shown considerable decline which were significantly. This decline as effect by feeding fennel seeds was more detectable with increasing the level of it. Moreover, serum level of HDL-C and mean values of HDL-C/LDL-C ratio were significant increase, compared to feeding rats with high fat-diet only. Elevated level of HDL-C is considered as cardio protective effect. This result was confirmed by histological study, which revealed apparent normal histological structure of heart in all treated rats with fennel seeds. Epidemiologic studies have shown an inverse correlation between HDL-C level and the risk of cardiovascular disease. Increasing the HDL cholesterol level by 1mg may reduce the risk of cardiovascular disease by 2 to 3 percent [40]. The present data agreed with Fatiha et al. [41] who reported that hyperlipidemic rats treated with fennel extract had significant decrease in plasma levels of TL, TG, TC, LDL-C and VLDL, and significant increase in HDL-C level. This result suggests that cholesterol-lowering activity of the fennel can result from a rapid catabolism of LDL-C through its hepatic receptors for final elimination in the form of bile acids as demonstrated by Guimaraes et al. [42]. Cao and Prior, [43] suggested that the hypolipidemic activity of fennel could be attributed to the presence of the valuable polyphenolic compounds especially tannins, and flavonoids. Eleni and Bairaktari, [44] demonstrated that flavonoids and anthocyanins, a heterogeneous group of polyphenols, have exhibited a variety of pharmacological activities, including the antiatherogenesis effect. Anethole (t-anethole) that is the main compound in all fennel volatile oils possesses significant antioxidant activity. The presence of t-anethole and flavonoids content in fennel may be associated with lowering TL, TC, TG and LDL-c levels. So fennel suggested being a new alternative for clinical management of hyperlipidemic patients [44]. Anti-oxidative properties and radical scavenging activity may be the possible mechanisms by which fennel ameliorated the TL, TC, TG and LDL-C [20]. Flavonoids are reported to increase HDL-C concentration and decrease in LDL and VLDL levels in hypercholesteremic rats [45]. Furthermore, Gibney et al. [46] reported that hypolipidemic effect of fennel may be due to the high content of polyunsaturated fatty acids from omega-6 and omega-3 families that found in this plant and these compounds have strong biological properties in low concentrations.

Liver function tests, which include liver enzymes, are groups of clinical biochemistry laboratory blood assays designed to give information about the state of liver functions. The used serum liver chemistry test in the present study includes serum AST, ALT and ALP. The activities of AST and ALT are cytosolic marker enzymes reflecting hepatocellular necrosis as they are released into the blood after cell membrane damage. Therefore, we used the activities of AST, ALT and ALP in the circulation as indicators of hepatic functions.

In the current study data revealed that significant increase in the activities of liver enzymes (AST, ALT and ALP) in feeding rats with high fat-diet. These elevations in liver enzymes may be attributed to their release from the cytoplasm into the blood circulation after rupture of the plasma membrane, cellular damage. This result confirmed by histological changes of liver sections of positive control rats, which showed congestion of hepatic sinusoid, vacuolization of hepatocytes and necrosis of sporadic hepatocytes as well as fatty changes of hepatocytes. This observed in the elevations were agreed with Arkkila et al. [47] who reported that elevated activity of serum AST are a common sign of liver and cardiovascular diseases. The observed increases in serum AST and ALT levels may be attributed to excessive release of such enzymes from the damaged liver cells as a result of hyperlipidemia into the blood circulation. Where, there is an inverse relationship between the liver activity and the level of enzymes in serum. Since AST and ALT were significantly higher in fatty liver and the severity of fatty liver was positively related to increases in hyperlipidemia, so AST and ALT were significantly higher in hyperlipidemic cases [48]. This result was in accordance with Tebib and Rouanet, [49] who showed that an activity of liver enzymes increases in hypercholesterolemic animals. The uptake of LDL-C is dependent on receptors in plasmatic membrane. This may be happened in hepatic cells of the animal fed cholesterol-supplemented diets,
explanatory their higher LDL-C. Eman et al. [50] showed highly significant increase in serum levels of AST and ALT. In addition to, many histopathological and histochemical changes were detected in liver tissue of the hyperlipidemic rats. Jain et al. [38] demonstrated that hyperlipidemia is associated with hepatic fat accumulation. Amin and Nagy, [51] also, indicated that serum AST and ALT concentrations was significantly higher in the high fat diet rats compared to the control rats. The elevation effect of high fat diet on liver functions may be related to oxidative stress, which increased in metabolic syndrome due to dyslipidaemia resulting from increased levels of free fatty acids and TG that led to increased formation of foam cells, rendering LDL-C less dense and more vulnerable to oxidation and uptake by macrophages [52].

In contrast, the present results revealed that feeding rats with high fat-diet supplemented with different levels of fennel seeds produce significant decrease in serum AST, ALT and ALP levels and improved liver functions compared to the feeding rats with high fat diet only. This effect may be related to antioxidant properties of fennel. Ozbek et al. [14] reported that essential oil of fennel had hepatoprotective activity against carbon tetrachloride (CCI4) which induces liver injury in rat’s model as it decreases levels of serum AST, ALT, ALP and bilirubin. Fennel contains several types of phenolic and flavonoids that is known as antioxidants and had strong free radical scavenging. It is of the most effective antioxidants in the food industry [15]. D-limonene and β-myrcene compounds found in fennel (Foeniculum vulgare) have a potent hepatoprotective action [53]. Lately, chemical composition of fennel demonstrated the presence of anethole as the most potent antioxidant [54]. Presumably, fennel functions as an antioxidant, stops the propagation of the peroxidative chain reaction, by inhibiting 5-hipoxigenase [55].

Oxidative stress is known to describe the lack of equilibrium between the production of free radicals and the antioxidant protective activities in a given organism [56]. Hyperlipidemia enhanced oxidative stress with the oxidation of low density LDL-C [57]. Free radicals have been implicated in the pathogenesis of many degenerative disease, including diabetes, and atherosclerosis and cancer [58].

The present study showed that lipid−peroxidation was increased significantly in hyperlipidemic control rats as indicated by the increased in serum MDA level compared with the normal control rats. The activities of CAT and GPX enzymes were significantly decreased in hyperlipidemic control rats when compared with normal control rats. GSH is known as antioxidant, which is usually present as the most abundant low-molecular mass thiol in most organisms. It has various functions in the defense against oxidative stress and xenobiotic toxicity. It can act as an electron donor for glutathione peroxidase (GPX) in animal cells, and also directly reacts with ROS. GSH is readily oxidized to glutathione disulfide (GSSG) by glutathione peroxidase, as well as by the reaction with ROS, which may subsequently cause the reduction in GSH levels. The efficiency by which glutathione peroxidase can scavenge peroxides increases with increasing GSH concentration. Increasing intracellular GSH is associated with increasing the ability of cells to scavenge strong oxidants. Conversely, decreases activities of GSH and GPX enzymes results in greater damage as a result of oxidative stress [59].

It is well known that free radical scavenging enzymes like SOD protects the biological systems from oxidative stress. The current study showed a significant decrease in the activities of SOD in hyperlipidemic rats as compared to normal rats. This depletion could be due to an enhanced production of free radicals as a result of lipid peroxidation. The increased in MDA was consistent with the observation that these free radicals reduced the activity of the endogenous antioxidant enzyme SOD [60].

The present results agreed with Prasad et al. [61] who showed significant increase in serum MDA levels, a decrease in SOD activity in hypercholesterolemic. These results suggest that hypercholesterolemia produces oxidative stress in the myocardium which may be due to a decrease in the antioxidant reserve. Amin and Nagy, [51] reported that high-fat diet generates oxidative stress in rats as shown by a marked increase in the levels of MDA and a distinct diminution in GSH enzyme, as well as activities of the antioxidant enzyme catalase. All showed reduced activity in hyperlipidemic rats. Recently, Yogendrashinh and Rajendra, [62] found that there was significant lipid-peroxidation in hyperlipidemic rats as indicated by increased MDA levels compared with normal rats.

The levels of reactive oxygen species are controlled by antioxidant enzymes namely, SOD, GSH, CAT, and non-enzymatic scavengers [63]. These antioxidants are produced either endogenously or received from exogenous sources and protect cells against oxidative stress [64]. The protective antiox-
Fennel has potent antioxidant activity including total antioxidant, free radical scavenging, superoxide anion radical scavenging, and hydrogen peroxide scavenging. Antioxidant activity of the fennel protects against lipid peroxidation and free radical damage; its extracts will probably be useful for the development of safe food additives [72]. Fennel seed extracts may possess a radical scavenging antioxidant activity due to the occurrence of some phenol compounds in fennel being responsible for such an activity [21]. Anethole was isolated as the potent antioxidant component [54].

Conclusion:
In generally, hyperlipidaemia is associated with abnormalities in fatty acid metabolism. It is characterized by an increase cardiovascular risk. Treating with fennel turned back total lipids to the normal values. Fennel exhibited good radical scavenging activity and enhance the activities of antioxidant enzymes. Essential oil of fennel has also strong radical scavenging and has a strong protective effect against lipid peroxidation. Antioxidative properties and radical scavenging activity may be the possible mechanisms by which fennel ameliorated the total lipids, cholesterol, triglycerides and LDL-C. Anethole (β-anethole) is the main compound in all fennel volatile oils possesses significant antioxidant activity. The presence of β-anethole and flavonoids content in fennel may be associated with lowering total lipids, cholesterol, triglycerides and LDL-C levels. So fennel suggested being a new alternative for clinical management of hyperlipidemic patients.

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