Original Article

Physiological and Histological Effects of Flaxseed Oil on the Liver and Heart Muscle

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Abstract

Background: Flaxseeds are the focus of medical nutrition due to their potential benefits for human health. Flaxseed oil is rich in unsaturated fatty acids and has many biological effects. **Objective:** This study aimed to assess the effects of flaxseed oil on lipid profile, liver, and heart. **Materials and Methods:** One hundred mice were randomly divided into 10 groups: 10 mice for each group (either male or female). Ten males and 10 females served as control groups, group 1 received flaxseed oil orally (60 mg/kg body weight/day). Twenty of them (10 of each gender) were treated for 1 week and another 20 mice (10 of each gender) were treated for 2 weeks. In the same way, group 2 was divided and treated with 120 mg/kg/day. Measurements of serum lipid profile, serum lactate dehydrogenase, serum total protein, and albumin were performed along with histological examination of the liver and heart. **Results:** The comparative data showed that there were statistically significant decreases in total cholesterol, low-density lipoprotein (LDL), serum albumin, and total protein levels. There were also statistically significant increases in levels of very low-density lipoprotein (VLDL), triglycerides, high-density lipoprotein (HDL), and lactate dehydrogenase enzyme. Histological examination revealed striking histological changes in the liver and heart. **Conclusion:** Consumption of flaxseed oil reduced total cholesterol and LDL levels and increased the levels of VLDL, triglycerides, HDL, and lactate dehydrogenase enzyme. Flaxseed oil in high doses causes damage to the liver and heart muscle.

Keywords: Flaxseed oil, heart, linseed oil, liver, serum lipid profile

Introduction

Flaxseed (*Linum usitatissimum* L.) is the focus of medical nutrition due to its potential benefits to human health.[1-5] Flaxseed is an herb believed to be found in Egypt. It belongs to the genus Linum, which belongs to the Linaceae family.[6] Mature flaxseed consists of an embryo with two cotyledons. The embryo is surrounded by a smooth seed coat and an endosperm.[7]

A fixed oil can be produced from the seeds called flaxseed oil or linseed oil. The flaxseed oil content of the seed is about 38–44% and this variation in its proportion is due to environmental and genotype parameters.[7-9] The majority of the oil (75%) is present in the cotyledons, while 22% is in the endosperm and seed coat.[10] Linseed oil is rich in unsaturated fatty acids, including alpha-linolenic acid (35–67%), oleic acid (12–30%), and linoleic acid (8–29%).[11]

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DOI: 10.4103/MJBL.MJBL_1603_23

Flaxseed oil has antimicrobial,[12,13] anti-inflammatory,[14] as well as analgesic and antipyretic effects.[6] It has a therapeutic effect in acute and chronic arthritis[15] and experimental esophagitis[16] in rats and an antiulcer effect in animals.[17] It also has dual effectiveness for constipation and diarrhea.[18] As the abnormalities in the lipid and lipoprotein are considered well-known risk factors for cardiovascular diseases because of their association with atherosclerosis,[19] we decided to assess the possible effects of flaxseed oil on the lipid profile, liver, and heart because flaxseed oil is rich in alpha-linolenic acid (ALA), which

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Submission: 24-Oct-2023 **Accepted:** 21-Dec-2023 **Published:** 24-Sep-2024

How to cite this article: Alaubody NMT, Al-Mousawi ZAH, Abdulwahid AB, Khudair ZW. Physiological and histological effects of flaxseed oil on the liver and heart muscle. Med J Babylon 2024;21:696-703.

Table 1: Effect of consumption of flaxseed oil on lipid profile (n = 100)

Lipid group			Total cholesterol (mg/dL)	TG (mg/dL)	VLDL (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Control	M (n = 10)		140 ± 0.96 a	48.03 ± 1.55 f	9.6 ± 0.31 f	76.52 ± 2.09 a	53.87 ± 1.74 g
	F (n = 10)		136.42 ± 0.78 b	45.28 ± 1.43 f	9.06 ± 0.3 f	71.14 ± 1.13 b	56.22 ± 1.2 f
Group 1 (60 mg/kg)	1w	M (n=10)	130.57 ± 3.62 c	146.24 ± 6.53 d	29.25 ± 1.3 d	41.75 ± 3.7 c	59.57 ± 1.04 e
		F (n = 10)	129.03 ± 1.76 cd	138.2 ± 3.95 e	27.64 ± 0.9 e	38.7 ± 2.07 d	62.68 ± 0.97 d
	2w	M (n = 10)	129.05 ± 0.86 cd	169.17 ± 5.36 b	33.83 ± 1.1 b	32.9 ± 1.75 e	62.31 ± 1.01 d
		F (n = 10)	127 ± 0.55 e	157.23 ± 2.3 c	31.45 ± 0.46 c	29.92 ± 1.2 f	65.6 ± 1.15 c
Group 2 (120 mg/kg)	1w	M (n = 10)	127.44 ± 1.6 de	169.59 ± 3.22 b	33.92 ± 0.64 b	30.6 ± 1.34 f	62.93 ± 1.4 d
		F (n = 10)	124.19 ± 2.19 fg	157.33 ± 3.9 c	31.47 ± 0.8 c	26.6 ± 2.31 g	66.13 ± 1.26 bc
	2w	M (n = 10)	125.42 ± 2 ef	202.54 ± 13.38 a	40.5 ± 2.68 a	18.42 ± 4.13 i	66.49 ± 0.83 ab
		F (n = 10)	123 ± 2.8 g	170.15 ± 4.2 b	34.03 ± 0.84 b	21.35 ± 2.93 h	67.57 ± 0.82 a
LSD	2.02	8.05	1.61	2.31	1.08		

TG: triglyceride, VLDL: very low-density lipoprotein, LDL: low-density lipoprotein, HDL: high-density lipoprotein, LSD: lowest significant difference

is considered precursor to omega-3 fatty acids. Although omega-3 reduces high blood pressure,[20] which is a major risk factor for cardiovascular diseases,[21] human studies regarding the hypolipidemic effects of flaxseed oil are controversial.[22,23]

Methods and Materials

Experiment design

The study included one hundred albino mice (Bulbe C) from a laboratory animal house where they were fed ad libitum. The mice were randomly divided into 10 groups, 10 mice for each group (either male or female). Ten males and 10 females served as control groups, group 1 received (60 mg/kg body weight/day) flaxseed oil orally. Twenty of them (10 of each gender) were treated for 1 week and another 20 mice (10 of each gender) were treated for 2 weeks. In the same way, group 2 was divided and treated with 120 mg/kg/day.

Preparation of flaxseed oil

The seeds of *L. usitatissimum* (flaxseed) were cleaned and grounded using an electric grinder. Samples of 50 g were placed in the thimble of the Soxhlet apparatus, defatted in a Soxhlet apparatus using 250 mL of normal hexane at a boiling point of 50–60°C for 4 h, then, the separated oil was extracted from the solvent using a rotary evaporator at 50°C for 1 h. The extracted oil was dried at room temperature for 5 days,[24] and then stored in a dark glass vial in the refrigerator at 4°C.

Blood collection

The blood samples were collected from the hearts and then the sera were isolated by centrifugation to assess the biochemical parameters.

Biochemical assay

Measurements of serum lipid profile, serum lactate dehydrogenase (LDH), serum total protein, and albumin were performed using commercial kits (Human, Germany) and a spectrophotometer.

Histopathological examination

After the end of the experiment, the heart and liver specimens were subjected to histological examination using Ziehl–Neelsen staining. The organ specimens were fixed in 10% natural buffered formalin and the preparation of the slide included dehydration with increasing alcohol concentration, clearing with xylene, embedding with paraffin, cutting by microtome, and staining with hematoxylin and eosin, and finally examination under a light microscope.[25]

Statistical analysis

We used one-way analysis of variance (ANOVA) for statistical analysis of our data. SPSS program version 24 was used. Data were tabulated as mean ± standard deviation. We then relied on the calculation of the least significant different test (LSD) to find the difference between the means in different groups. $P \leq 0.05$ was considered significant.

Results

Effect of consumption of flaxseed oil on lipid profile

There was a significant decrease in total cholesterol levels in both male and female mice. In male mice, this decrease was dose-dependent and not duration-dependent reduction, whereas in female mice, it was both a dose- and duration-dependent decrease, as shown in Table 1 and Figure 1.

Regarding triglyceride (TG), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL), there were significant dose and duration-dependent increases in triglyceride and VLDL levels in both mouse genders, as shown in Table 1 and Figures 2–4. There was a significant dose- and duration-dependent decrease in low-density lipoprotein (LDL) levels in both mouse genders, as shown in Table 1 and Figure 5.

Effect of flaxseed oil consumption on total protein and serum albumin and LDH

In both group 1 and group 2, there were significant transient decreases in total protein levels and serum albumin in the first week, which returned to the control group level after 2 weeks as shown in Table 2 and Figures 6 and 7.

Regarding LDH, there was a significant increase in LDH levels in both group 1 and group 2. This increase was duration-dependent rather than dose-dependent, as shown in Table 2 and Figure 8.

Histopathological examination

1. Histopathological examination of the liver:

Histopathological examination of the liver showed dilation of the central vein and enlargement of hepatocytes [Figure 9], but showed minimal periportal fibrosis in G2 [Figure 10]

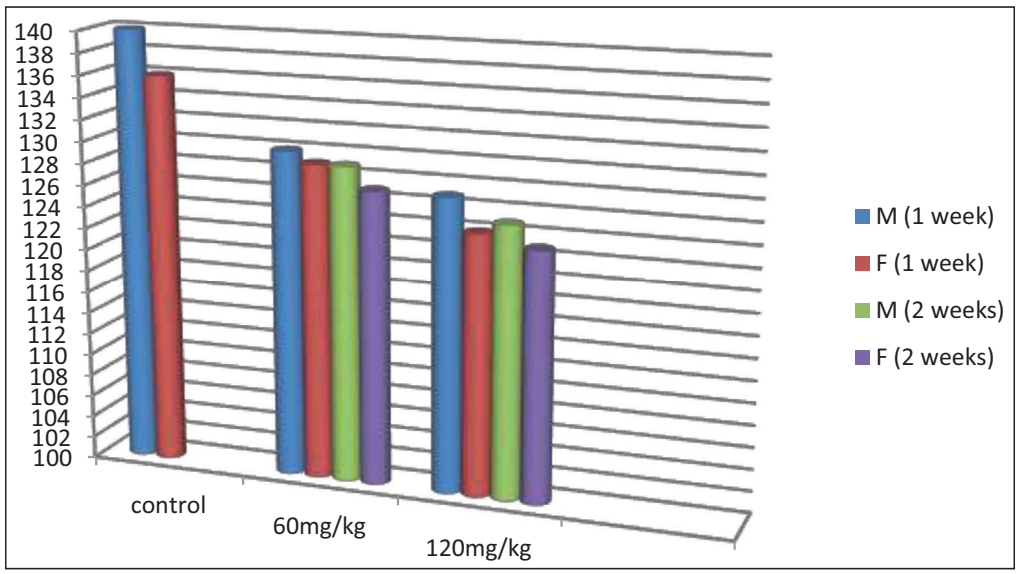

Figure 1: Effect of consumption of flaxseed oil on total cholesterol

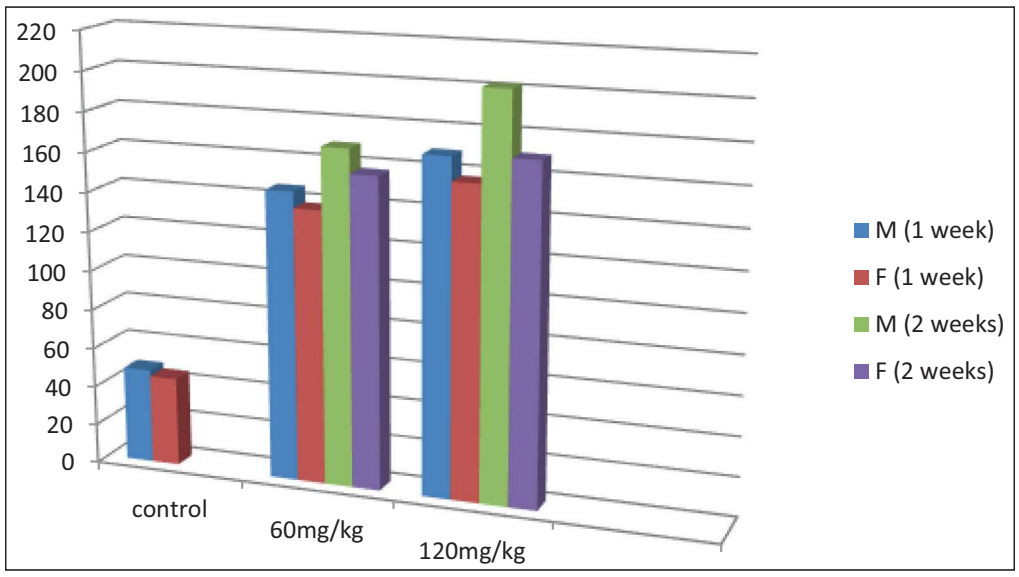

Figure 2: Effect of consumption of flaxseed oil on triglyceride

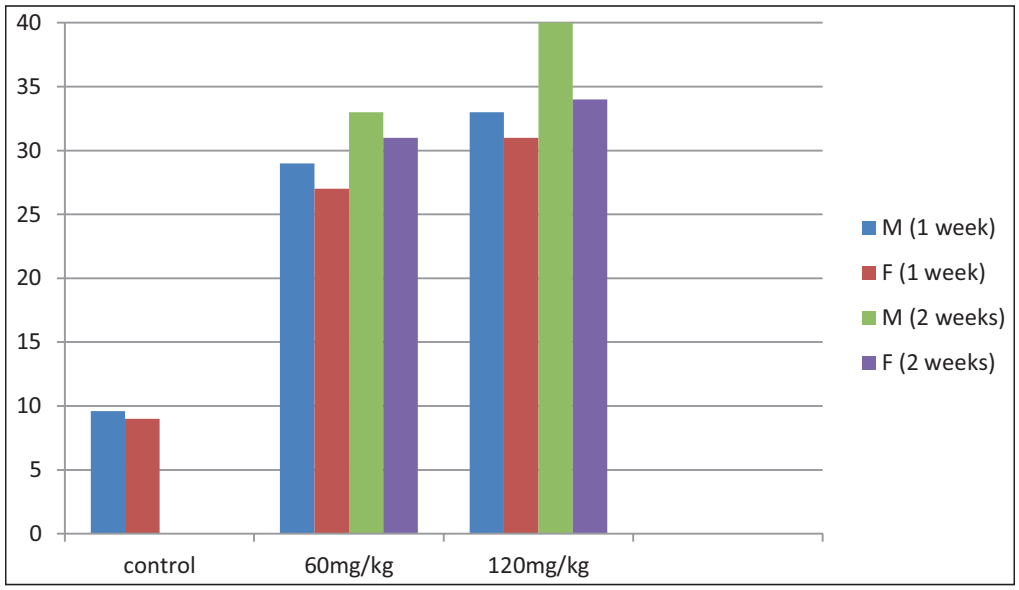

Figure 3 : Effect of consumption of flaxseed oil on very low-density lipoprotein

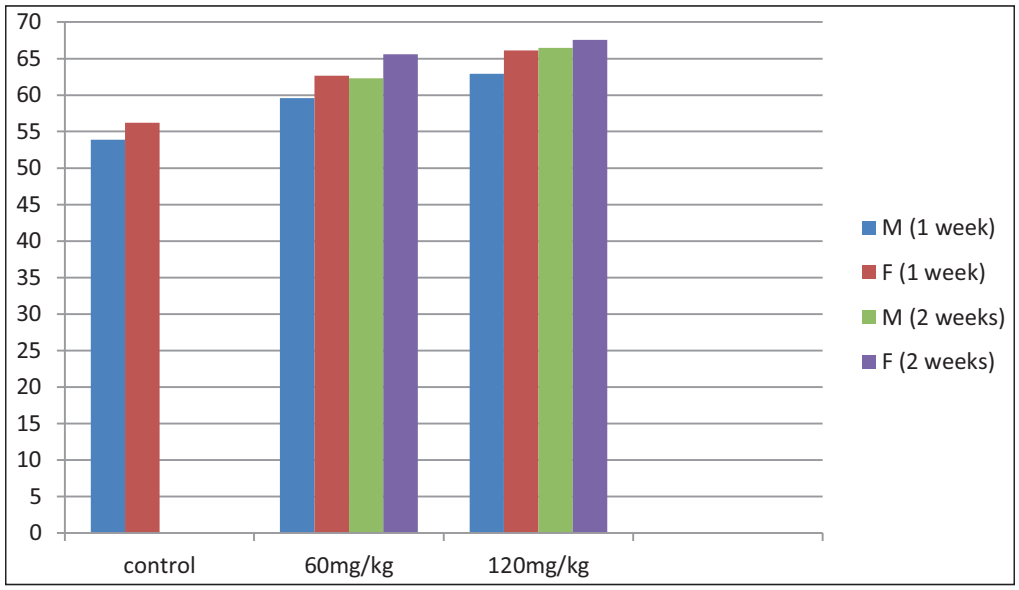

Figure 4: Effect of consumption of flaxseed oil on high-density lipoprotein

2. Histopathological examination of the heart:

After necropsy, there were formed cells and fibrosis among the myocardial cells as a focal area [Figure 11], congestion of blood vessels [Figure 12], and the hemorrhagic area between the myocardial cavities [Figure 13], as well as peripheral fibrosis in the pericardium of the second group of mice [Figure 14].

Discussion

The effect of consuming flaxseed oil on lipid profile was studied in mice and there were significant decreases in total cholesterol and LDL levels, accompanied by significant increases in HDL levels. This effect could be explained by the presence of -linolenic acid in flaxseed oil.[26] Serum concentrations of total and lipoprotein lipids are generally affected by the quality of dietary fat.[27] Serum cholesterol concentrations generally decrease with unsaturated fatty acids and increase with saturated fatty acids.[28,29] Alpha-linolenic acid is found in high amounts in flaxseed. Through a series of reactions, ALA is metabolized to docosahexaenoic acid and eicosapentaenoic acid[30] and could therefore provide a readily accessible source of dietary omega-3 polyunsaturated fatty acids (PUFAs). Flaxseed oil has a role in elevating omega-3 status by activating the key enzymes for polyunsaturated fatty acids (PUFAs) synthesis, particularly delta-5-desaturase and delta-6-desaturase (D5D and D6D).[31] Dietary omega-3 fatty acids are elemental parts of the cell membrane and

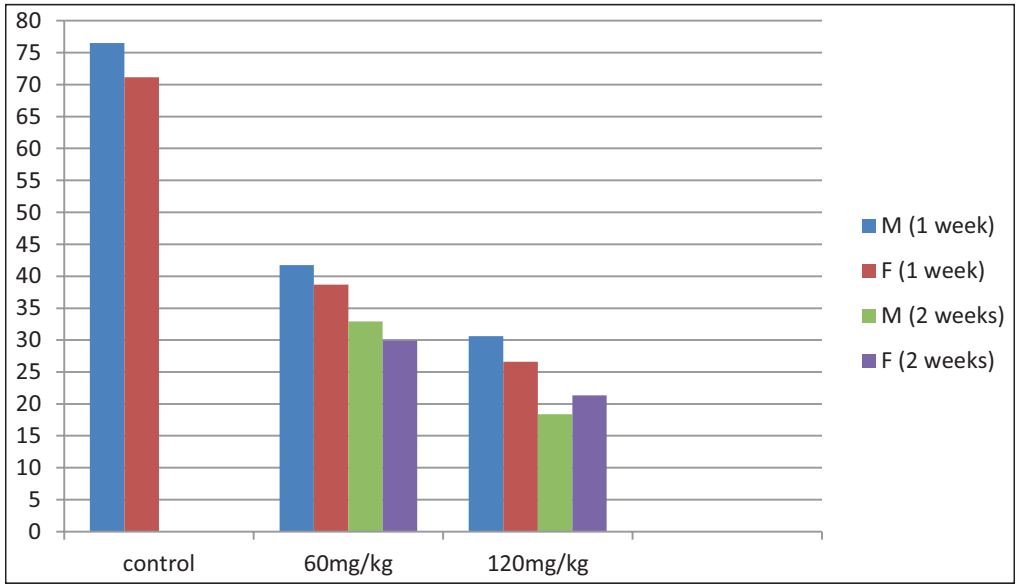

Figure 5: Effect of consumption of flaxseed oil on low-density lipoprotein

Table 2: Effect of consumption of flaxseed oil on total protein and serum albumin and LDH

	Group		Albumin	Total protein	LDH
Control	M	3.13 ± 0.24 b	6.41 ± 0.35 bc	150.9 ± 2.73 f	
	F	2.93 ± 0.15 c	6.1 ± 0.17 c	147 ± 2.12 f	
Group 1	1 week	M	2.35 0.22 e	4.15 ± 0.2 e	380.06 ± 32.57 e
		F	1.88 ± 0.12 f	3.24 ± 0.37 f	420.09 ± 19.96 d
	2 week	M	3.51 ± 0.38 a	7.88 ± 0.86 a	529.25 ± 17.72 b
		F	3.05 ± 0.17 bc	5.92 ± 0.25 c	693.2 ± 15.56 a
Group 2	1 week	M	3.11 ± 0.2 bc	3.87 ± 0.37 e	458.01 ± 27.45 c
		F	1.6 ± 0.12 g	2.92 ± 0.25 f	419.78 ± 12.81 d
	2 week	M	3.41 ± 0.21 a	6.73 ± 0.72 b	550.06 ± 52.31 b
		F	2.67 ± 0.25 d	4.9 ± 0.27 d	429.13 ± 1 2.33 d
LSD			0.2	0.49	28.87

LDH: lactate dehydrogenase, LSD: lowest significant deference

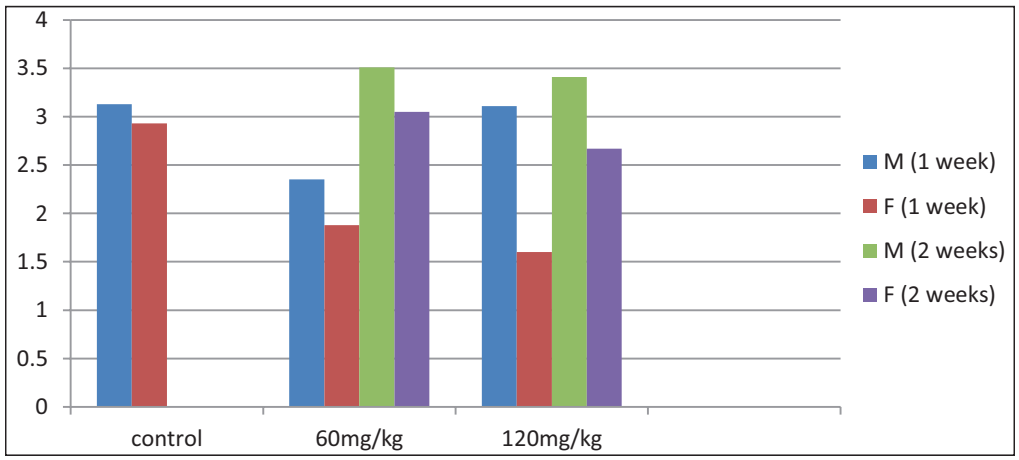

Figure 6: Effect of consumption of flaxseed oil on serum albumin

have the ability to sustain a status of well-being[32-35] through their role in modifying the expression of genes such as the pro-atherogenic and pro-inflammatory genes.[35-37] Ventura *et al.*[38] in their study on fish oil, eicosapentaenoic acid,

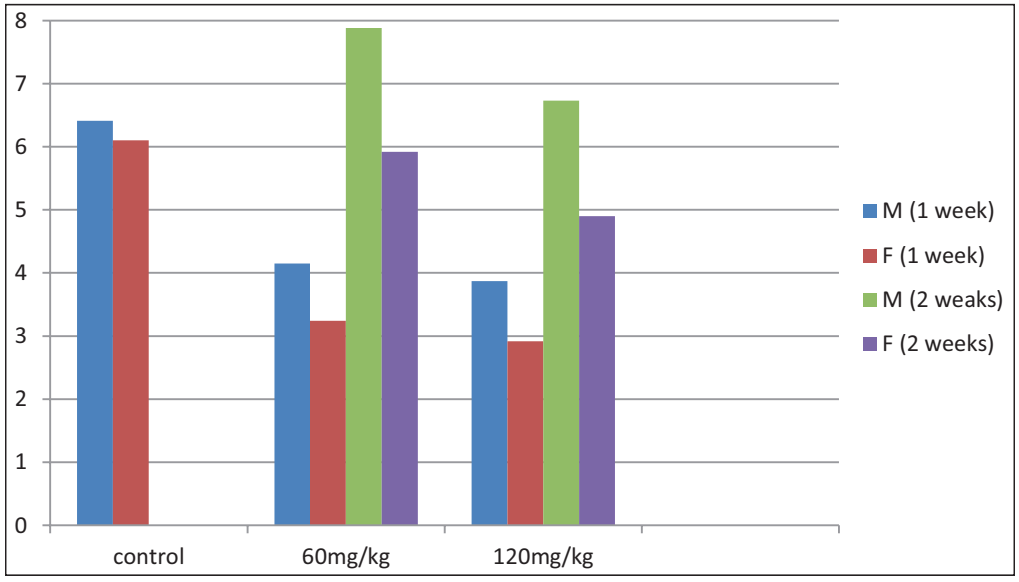

Figure 7: Effect of consumption of flaxseed oil on total protein

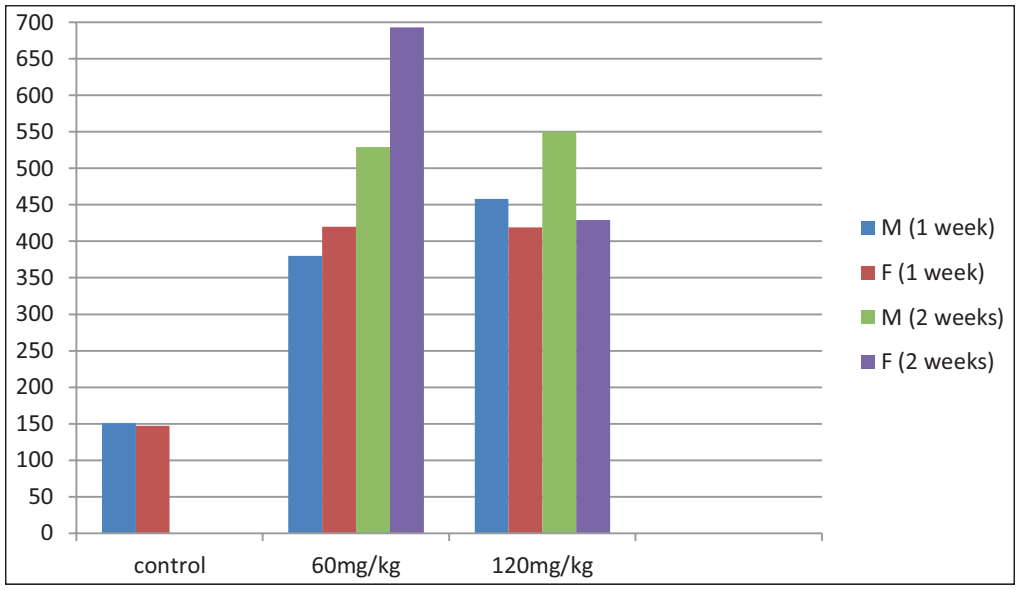

Figure 8: Effect of consumption of flaxseed oil on lactate dehydrogenase

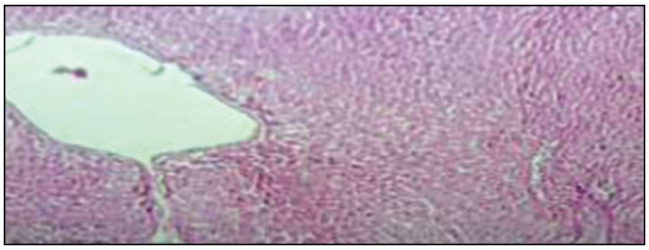

Figure 9: Section of G1 mice liver shows dilation of central vein and enlargement of hepatocyte

and docosahexaenoic acid mentioned that enhanced hepatic LDL receptor activity is the cause of diminished plasma LDL levels. Peroxisome proliferator-activated receptor-α (PPAR-α) is a transcription factor that plays an important role in controlling carbohydrate and lipid levels.[39] It is significantly up-regulated by the flaxseed oil diet.[22] Wallace *et al.*[40] found that agonists of this factor have multiple effects on HDL-C levels. Induction of delta-5-desaturase (D5D) and delta-6-desaturase (D6D) enzymes has been previously reported to be caused by the activation of PPAR in rat liver.[41]

Beta-oxidation of fatty acids has been found to be stimulated by the activation of PPAR-α,[42] and thereby the activation of PPAR-α is supposed to be a decreasing factor for serum TG level but unexpectedly in our study there was significant increase in serum TG and VLDL levels. This may indicate that flaxseed oil has another regulatory effect on serum and VLDL levels. The increased VLDL level and decreased LDL level may indicate the inhibitory

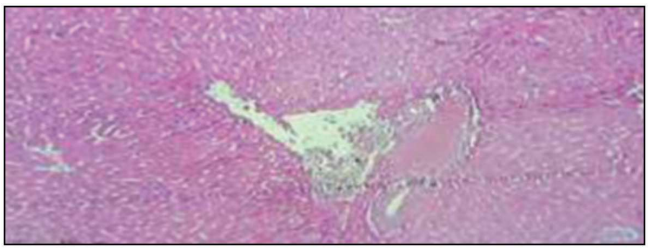

Figure 10: Section of G2 mice liver shows minimal periportal fibrosis, congested portal vein, and central vein

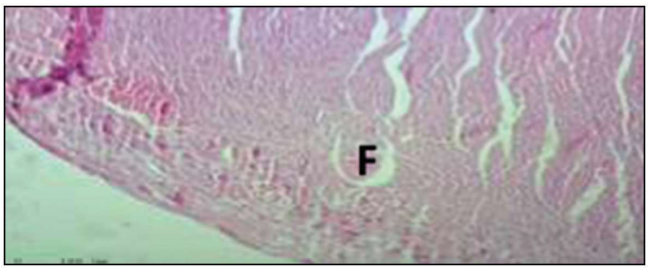

Figure 11: Section of G1 mice heart shows focal fibrosis (indicated by letter F) among myocardial cells

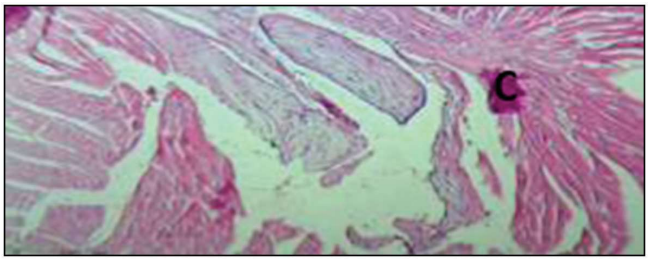

Figure 12: Section of G1 mice heart shows area of congestion of blood vessels (indicated by letter C)

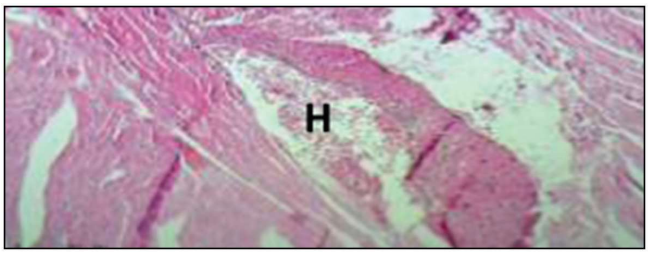

Figure 13: Section of G2 mice heart shows micro-hemorrhagic area (indicated by letter H) among myocardial cavities

effect of flaxseed oil on the lipolysis process which is responsible for the conversion of VLDL into LDL by the effect of the enzyme lipoprotein lipase (LPL).

Although some studies found a protective role for flaxseed on the liver and the heart,[23,43,44] our study found that the consumption of high doses of flaxseed oil leads to unfavorable histological changes in these two organs which indicates a harmful effect for these high doses on the liver and the cardiac muscle. The liver damage explains the decrease in total protein and serum albumin levels while cardiac muscle damage explains the increase in LDH level.

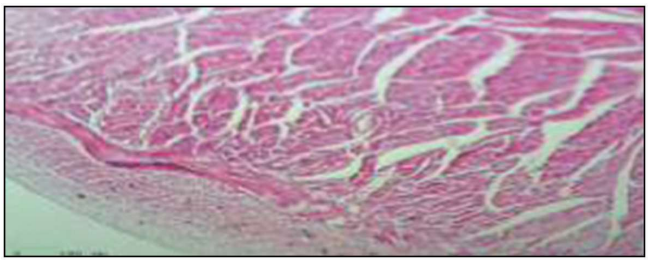

Figure 14: Section of G2 mice heart shows peripheral fibrosis in the pericardium

Conclusion

Consumption of flaxseed oil decreased the levels of total cholesterol and LDL levels and increased the levels of VLDL, TG, and HDL. Flaxseed oil in high doses causes damage to the liver and heart muscle.

Data availability statement

Data availability is under the authors' responsibility.

Financial support and sponsorship

No fundings were used in this study.

Conflicts of interest

None declared.

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