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Effect of dietary lipids on liver lipid profile and antioxidant enzymes in male Wistar rats

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Key words: Monounsaturated fatty acids (MUFA); polyunsaturated fatty acids (PUFA); olive; hazelnut; lipids; antioxidants.

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Abstract

This study evaluated the effect of olive and hazelnut oil on liver lipid profile and antioxidant status in adult rats. A total of fifteen male wistar rats (150-170 grams) were randomized into three groups. Control group received 30 grams diet daily with soybean oil. OLVO and HAZO groups received 30 grams diet with olive and hazelnut oil, respectively. Total cholesterol, triglycerides, HDL-C, LDL-C, SOD, GSH-PX, catalase activity and MDA was determined in liver homogenates. The result demonstrates significant ($p \leq 0.05$) gain in animal body weight in OLVO group compared to control group. The lowest total cholesterol (2.49±0.17 mg/dl) was observed in HAZO group and difference was significant ($p \leq 0.05$) between control and treatment groups but insignificant within treated groups. Similarly, lowest value of triglyceride (11.48±0.78 mg/dl), LDL-C (6.04±0.41 mg/dl) and VLDL-C (2.29±0.14 mg/dl) and the highest HDL value (29.59±1.99 mg/dl) was also observed in OLVO group and a significant ($p \leq 0.05$) difference was found between control and treated group. Ratio LDL/ HDL and cholesterol/ HDL was lower in OLVO group, followed by HAZO and control. The highest activity of GSHPx was observed in OLVO (17.02 ±0.50 U/ml) group, but the results showed insignificant ($p \geq 0.05$) differences between control and treated group. Similarly, highest concentration of SOD (5.707±0.53 U/ml) and catalase (19.68 ±1.30 nmol/min/ml) and least concentration of MDA (0.67 nmol/ml) was also observed in OLVO. MUFA diets were found to have a beneficial effect on lipid profiles and antioxidant enzymes and may be used as nutritional alternatives to prevent lipid disturbances.

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Introduction

Globally, non-communicable diseases (NCDs) such as cardiovascular disease (CVD), cancer and type 2 diabetes (T2D) account for over 70% of all deaths (GBD 2016 Causes of Death Collaborators, 2016), and according to the report of World Health Organization, CVD alone accounts for almost 17.9 million deaths annually with a multifactorial etiology (WHO, 2021). The Global Burden of Disease Study has reported that suboptimal diet is the peril factor for about 50% of infirmities from CVDs (GBD 2017 Diet Collaborators, 2019), so dietary changes are the foremost approach applied to avert and treat CVDs. Fats and oils, commonly known as dietary lipids, provide a concentrated source of energy and while also contributing satiety, flavor, and palatability to the diet. The guidelines from the National Academy of Science (NAS) recommend that total fat intake should range from 20 to 35% of total calories and the endorsed range provides flexibility in planning diets according to the health and physical activity status of the individual (Institute of Medicine, 2002). An International survey reported that 95% of respondents were aware that vitamins are vital for a healthy diet, but only 41% of the respondents were aware that fat is also an essential part of the diet (Diekman and Malcolm, 2009). Various studies have reported that the type, amount and composition of lipid in the diet are determining factors of the serum lipid profile (Uauy, 2009; Baum *et al*., 2012).

Unsaturated fatty acids have been linked to a decreased risk of various diseases, which is particularly noteworthy. Over the past few decades, the studies have shown that modification in the diet can affect coronary events and the consumption of monounsaturated or polyunsaturated fat-enriched diets has been widely accepted as a therapy against increased levels of plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) associated with saturated fat intake (Chang and Huang, 1999; Hu and Willett 2002). The world is gradually engaging in the usage and research of medicinal plants because, unlike synthetic drugs and antibiotics, herbal drugs are said to be safe and free of side effects. Oxidative stress is defined as the state under which the production of reactive oxygen species (ROS) that are highly toxic molecules surpasses the capacity of antioxidants to detoxify and healthy antioxidant status and maintaining healthy antioxidants levels are vital for cellular homeostasis. Various enzymes such as catalase (CAT), superoxide dismutases (SODs), and glutathione peroxidase detoxify ROS. The liver is an organ that undergoes a variety of oxidative processes and is hence the prime target of OxS-induced damage (Arroyave-Ospina *et al*., 2021). Numerous studies suggest that nuts consumption has been linked to better plasma lipid profiles and reduced risk of coronary heart (Petersen *et al*., 2005; Kelly and Sabaté, 2006; Mercanlıgil *et al*., 2007). The lipid content of olive oil has been found to be quite similar to that of hazelnut[14] (Aparicio, 2000). In this study, we examined the effects of monounsaturated fatty acids (MUFA) (olive oil and hazelnut oil) on the liver lipid profile and antioxidant status in adult rats based on the hypothesis that MUFA diets might be utilized as nutritional alternatives to avoid lipid abnormalities.

Materials and methods

Experimental animals

A total of fifteen male rats (Wister strain) weighing 150-170 grams were obtained from Experimental Animals Care Center, College of Pharmacy, King Saudi University, Saudi Arabia. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee for Scientific Research and Post Graduate Studies at the King Saud University, Saudi Arabia (reference: KSU-SE-19-68). Animals were maintained in a controlled environment at 25°C with a 12/12 light / dark cycle and they had free access to water and a chow diet throughout the study period.

Experimental design

Grain silos and flour mills Riyadh Saudi Arabia provide a commercial rodent diet. In order to avoid oil oxidation, the fresh chow was weekly mixed with oil and stored at 4°C until fed.

The experimental diets for the male Wistar rats were made by adding the oil (spraying under pressure with continuous mixing during the spraying) to the basal diet (Table 1).

Animals were housed in single rat cages to allow them to adjust and then divided randomly into three groups of five rats each, as follows:

Groups 1 (Control group): assigned to receive 30 grams of the control diet with soybean oil per day for a month.

Group 2 (OLVO): assigned to receive 30 grams of the diet with olive oil per day for a month.

Group 3 (HAZo): assigned to receive 30 grams of the diet with hazelnut oil per day for a month.

Assessment of body weight

Growth

In the non-fed state, weight was noted at the commencement (initial weight) and at the end of the study (final weight).

Weight gain (g) = final body weight (g)-initial body weight (g).

Preparation of liver samples

At the end of the study, the animals were sacrificed and the liver samples were removed and cleaned from other tissues, then refrigerated at -80°C, to make liver homogenates. A portion of each liver sample was homogenized with phosphate buffer (pH 7.4) and the homogenates were centrifuged at 4000 rpm for 10 minutes to obtain clear supernatants. Supernatants were stored at -80 °C until further analysis.

Biochemical analyses

Liver lipid profile

Total cholesterol, triglycerides, HDL-C, LDL-C was determined in liver homogenates. The lipid profile kits were obtained from Randox Laboratories Ltd. Crumlin, UK. The analyzes were performed according to the instructions provided by the manufacturer.

Analysis of oxidative stress markers

The activity of superoxide dismutase (SOD) and GSH-PX in liver homogenates was determined using a commercially available kit (ELISA Kit, MyBioSource, USA) according to the manufacturer's instructions. Catalase activity was determined in liver homogenates using a commercially available kit (ELISA Kit, Cayman Chemical Company, USA) in accordance with the manufacturer's instructions.

Assay of Lipid peroxidation

MDA in plasma was determined using a commercially available kit (ELISA Kit, MyBioSource, USA) according to the manufacturer's instructions.

Statistical analysis

The data were analyzed using the SPSS statistical software. Data were expressed as mean ± standard deviation. The differences between the treatment groups were analyzed using one-way ANOVA at a significance level of $p \leq 0.05$ and if differences were found to be significant, a Post-hoc analysis using Duncan's multiple range tests was performed.

Results and discussion

Effect of MUFA enriched diet on growth of animals

The effect of MUFA enriched diet on animals' weight has been presented in Fig. 1. At baseline, there was an insignificant difference in the average weight of the animals between the control and experimented groups or even within the experimented group. The result demonstrates that there was a significant ($p \leq 0.05$) gain in body weight of the animals in OLVO group compared to the control group. Wistar rats are very selective in the aromas and flavors of the food they consume and control the total energy intake of their diet (Jean *et al.*, 2002; Diane *et al.*, 2008; Boudalia *et al.*, 2014).

The increase in diet consumption justifies the weight gain of animals during the course of the study. Some investigators found an inverse relationship between frequent nut consumption and body mass index (BMI), which contradicts the results of this study (Sabate, 2003; Natoli and McCoy, 2007).

Table 1. Formulation of diet**.**

Ingredient (g/kg diet)	Control	OLVO	HAZO
Corn starch	465.6	465.6	465.6
Casein	140	140	140
Maltodextrin	145	145	145
Sucrose	100	100	100
Soy oil	50	-	-
Olive oil	-	50	-
Hazelnut oil	-	-	50
Cellulose	50	50	50
Minerals mix (AIN-93-MX)	35	35	35
Vitamin mix (AIN-93-VX)	10	10	10
L-Cystine	1.8	1.8	1.8
Choline	2.5	2.5	2.5
tert-Butylhydroquinone (TBHQ), mg	8	8	8

Effect of MUFA oil-enriched diet on liver lipid profile of animals

Table 2 depicts the effect of MUFA enriched diet on animals' liver lipid profiles. The lowest total cholesterol levels (TC, 2.49±0.17 mg/dl) were observed in the HAZO group and the difference was significant ($p \leq 0.05$) between control and treatment groups but insignificant between OLVO and HAZO groups. Similarly, much lowest value of triglyceride (TG, 11.48±0.78 mg/dl), low-density lipoprotein cholesterol (LDL-C, 6.04±0.41 mg/dl) and very-low-density lipoprotein (VLDL-C, 2.29±0.14 mg/dl) and highest value of HDL (29.59±1.99 mg/dl) was also observed in OLVO group followed by HAZO group and a significant ($p \leq 0.05$) difference was found between control and treated group. Cardiovascular diseases are the predominant cause of death globally. Diets added to oil-rich in PUFA and MUFA should be consumed because of their antiatherogenic, antiplatelet and vasodilation action (Aquino *et al.*, 2015). Foods rich in MUFA have been shown to favorably impact blood lipid concentrations, thus decreasing the risk of CVD (Garg, 1998). The normal range of the lipid profile in rats is usually lower than in humans (de la Torre-Carbot *et al.*, 2015). The control diet showed a higher percentage of polyunsaturated fatty acids, especially linoleic acid and the diet added to the experimented group was rich in monounsaturated fatty acids, mainly oleic acid. The present study demonstrated that MUFA oil-enriched diet (Olive and hazelnut) significantly reduced the TG, LDL-C, VLDL-C and increased HDL-C. The possible mechanism that could be responsible for the favorable lipid profile might be the various micronutrients and bioactive substances and MUFA found in olive oil and hazelnut oil. Jenkins *et al.* (2020) stated that viscous fiber in a portfolio diet is supposed to reduce cholesterol by forming a thick, sticky gel in the intestine, which delays absorption of nutrients, like glucose, in the small intestine, resulting in reduced insulin response and a reduction in cholesterol. Apart from this, the gel may also reduce the reabsorption of bile salts in the small intestine, increasing fecal cholesterol loss and further reducing blood cholesterol. A study on the effect of dietary oils on serum lipid calcium absorption and bone mineralization demonstrated insignificant differences in TG and LDL-c and significant differences in TC and HDL-c between soybean and olive oil (Rezq *et al.*, 2010). Various studies conducted on normal and hyperlipidemic subjects have shown that the addition of nuts into the diet has significantly reduced TC and LDL-C (Wamoto *et al.*, 2002; Ros *et al.*, 2004). A study showed improvement in the plasma lipid profile in a hamster fed a high-fat diet with the supplementation of hazelnut skin extract (Caimari *et al.,* 2015). Trautwein and colleagues reported that MUFA-rich dietary fats, such as olive oil, rapeseed and 18:1-rich sunflower oil, have similar hypo-cholesterolemic potential and have similar effects on plasma cholesterol as 18:2-rich sunflower oil in hamsters when the dietary cholesterol intake is moderate (Trautwein *et al.*, 1999). Similarly, another study of the diabetic patients' has reported that a

change in the diet from linoleic to oleic acid showed better improvement in LDL and HDL (Madigan *et al.*, 2005). Improvement in the lipid profile in rats fed on a diet containing olive oil may be explained on the basis that it is a rich source of MUFA, primarily oleic and palmitoleic, that improves the lipid profile (Hayes *et al.*, 1994), and apart from MUFA the higher ingredients of antioxidants such as carotenoids, chlorophyll, polyphenolic compounds also contribute in the improvement of lipid profile as all of these compounds have free radical scavenging ability (Morello *et al.*, 2007). Jenkins *et al.* (2020) reported that the replacement of carbohydrates with MUFA will allow HDL-C to stay in circulation longer, providing a positive effect on the ratio of "good" cholesterol to "bad" cholesterol. Plant sterols reduce the absorption of dietary cholesterol as well as cholesterol generated by the body, thus lowering LDL cholesterol. Duavy *et al.* (2017) reported that oleic acid-rich olive oil containing MUFA was able to ameliorate the serum lipid profile when compared to a cholesterol-free and linoleic acid-rich diet. Due to the higher absorption velocity of MUFA diet in acinar zone 1 of the liver as compared to PUFA, a significant reduction of the serum LDL-C, VLDL-C and CT levels in the animal treated with HC+OO diet have been reported. Dietary linolenic acid raises the concentration of PUFA in lipoproteins which in turn increases their sensitivity to oxidation, while dietary oleic acid results in LDL particles less prone to their oxidation sensitivity (Reaven *et al.*, 1993). The high content of MUFA is an important factor in preventing the early development of atherosclerosis (Uauy, 2009), although the cardioprotective benefits of a MUFA-rich diet have been argued when compared to diets high in PUFAs (Degirolamo and Rudel, 2010; Schwingshackl *et al.*, 2011). But it is generally accepted that the substitution of saturated fatty acids and trans fatty acids with MUFAs and/or PUFA is beneficial for cardiovascular health (Marai and Massalha, 2014; Weech *et al.*, 2014). Instead of analyzing isolated parameters only, it is recommended to analyze LDL/HDL ratio and cholesterol /HDL ratio as they are key indicators of vascular risk and is considered more sensitive and specific than individual parameters. Due to an imbalance between the cholesterol carried by atherogenic and protective lipoproteins, individuals with high LDL/HDL cholesterol and total cholesterol/ HDL ratios have greater cardiovascular risk (Millan *et al.*, 2009). Olive oil and hazelnut oil has been evaluated in this study as beneficial lipid profile as it has the lowest LDL/HDL and cholesterol /HDL index.

Table 2. Effect of MUFA oil enriched diet on liver lipid profile in male albino rats.

Parameters	Control	OLVO	HAZO
TC (mg/dl)	8.44±2.03^{c}	3.62±0.49^{a}	2.49±0.17^{a}
TG (mg/dl)	26.16±10.08^{c}	11.48±0.78^{a}	17.81±4.57^{ab}
LDL-C (mg/dl)	13.77±5.31^{a}	6.04±0.41^{a}	9.37±2.41^{ab}
HDL-C (mg/dl)	20.65±7.96^{ab}	29.59±1.99^{c}	14.99±3.85^{a}
VLDL-C (mg/dl)	5.23±1.80^{c}	2.29±0.14^{a}	3.56±0.82^{ab}
LDL/HDL	0.667±0.0007	0.204±0.0008	0.625±0.0004
Cholesterol/HDL	0.464±0.194	0.122±0.014	0.174±0.039

OLVO- olive oil, HAZO- hazelnut oil, TC- total cholesterol, TG-triglycerides, LDL-C-low density lipoprotein, HDL-C- high density lipoprotein, VLDL-C –very low density lipoprotein.

Data were expressed as mean ± standard deviation. The differences between the treatment groups were analyzed using one-way ANOVA at a significance level of $p \leq 0.05$. Different alphabetical superscript defines differences in each row.

Effect of MUFA oil-enriched diet on antioxidant enzymes and lipid peroxidation in the liver of male albino rats

Table 3 shows the effect of a MUFA oil-enriched diet on antioxidant enzymes in the plasma of male albino rats. The highest activity of enzymatic antioxidant glutathione peroxidase (GSHPx) was observed in OLVO (17.02 ±0.50 U/ml) group, but the results show insignificant ($p \geq 0.05$) differences between the control and treated group. Similarly, the highest

concentration of other enzymatic antioxidants such as superoxide dismutase (SOD, 5.707±0.53 U/ml) and catalase (19.68 ±1.30 nmol/min/ml) was also observed in OLVO group and the difference was significant (p≤0.05) between control and treated group. Lipid peroxidation was assessed by measuring malondialdehyde (MDA). The highest level of MDA (0.93±0.10 nmol/ml) was seen in the control group and the least (0.67 nmol/ml) value was observed in OLVO group. The activity of SOD, catalase and MDA levels were found to be a significant difference in the control and treatment groups. Oxidative damage is a major contributor to the development of cardiovascular disease, cancer and neurodegenerative disorders. In healthy individuals, the generation of reactive oxygen species (ROS) is well balanced by the counterbalancing act of antioxidant defenses. The main enzymes responsible for inactivating reactive oxygen species are glutathione peroxidase, superoxide dismutase, and catalase (Forsberg *et al.*, 2001). In this study, different dietary fats have been evaluated in animal experiments for their effects on antioxidant enzymes and indicators of oxidative stress. Excess oxidative stress injures membranes by causing an imbalance in redox homeostasis, which then allows malondialdehyde (MDA) to accumulate, which is harmful because it causes extra damage to biomolecules (Łuczaj *et al.*, 2017). Studies have shown that PUFAs upsurge the vulnerability of the organism to lipid peroxidation and intrude the prooxidant-antioxidant balance in favor of peroxidation (Berry *et al.*, 1991; Nardini *et al.*, 1995).

There has been significant evidence in the literature supporting the beneficial effects of MUFA-containing oils (especially olive oil) on lipids and lipid peroxidation in relation to atherosclerosis (Heyden, 1994; Gorinstein *et al.*, 2002).

Table 3. Effect of MUFA oil enriched diet on antioxidant enzymes in the liver of male albino rats.

Parameters	Control	OLVO	HAZO
GSHPx (U/ml)	16.94±0.94^{a}	17.02±0.50^{a}	15.70±1.62^{a}
SOD (U/ml)	5.53±0.32^{c}	5.707±0.53^{bc}	4.71±0.46^{ab}
Catalase (nmol/min/ml)	18.39±2.07^{ab}	19.68±1.30^{b}	16.09±1.38^{a}
MDA (nmol/ml)	0.93±0.09^{c}	0.67±0.10^{a}	0.84±0.09^{bc}

GSHPx -Glutathione peroxidase, SOD- superoxide dismutase, MDA-malondialdehyde.
Data were expressed as mean ± standard deviation. The differences between the treatment groups were analyzed using one-way ANOVA at a significance level of p ≤ 0.05. Different alphabetical superscript defines differences in each row.

While comparing the extra virgin olive oil and genetically modified soybean combined group with genetically modified soybean-fed animals only, El-Kholy *et al.* (2014) reported a significant decline in the lipid peroxidation level and a significant upsurge in glutathione dehydrogenase level. Olive oil has been linked to a number of favorable benefits on liver regeneration due to its antioxidant content, which may serve as an explanation for this result (Nakbi *et al.*, 2010). In another study, the hazelnut oil given to normal rabbits did not alter the plasma or tissue lipids or pro-oxidant-antioxidant status but reduced aortic cholesterol levels and reduced MDA and Diene conjugate plasma liver, and aorta in hypercholesterolemic rabbits. They reported that the antioxidant system parameters remained unchanged in the livers of rabbits (Hatipoglu *et al.*, 2004). Parthasarathy *et al.* (1990) suggested that in the place of PUFA, supplementation of MUFA shields LDL against oxidative modification by simply reducing the number of PUFAs available as targets for peroxidation. Scaccini *et al.* (1992), in their study, demonstrated that instead of the fatty acid unsaturation of dietary oils, the optimal balance between the natural antioxidants and unsaturated fatty acids content in dietary oils appears to be determining factor in the antioxidant capacity of lipoproteins in an animal model.

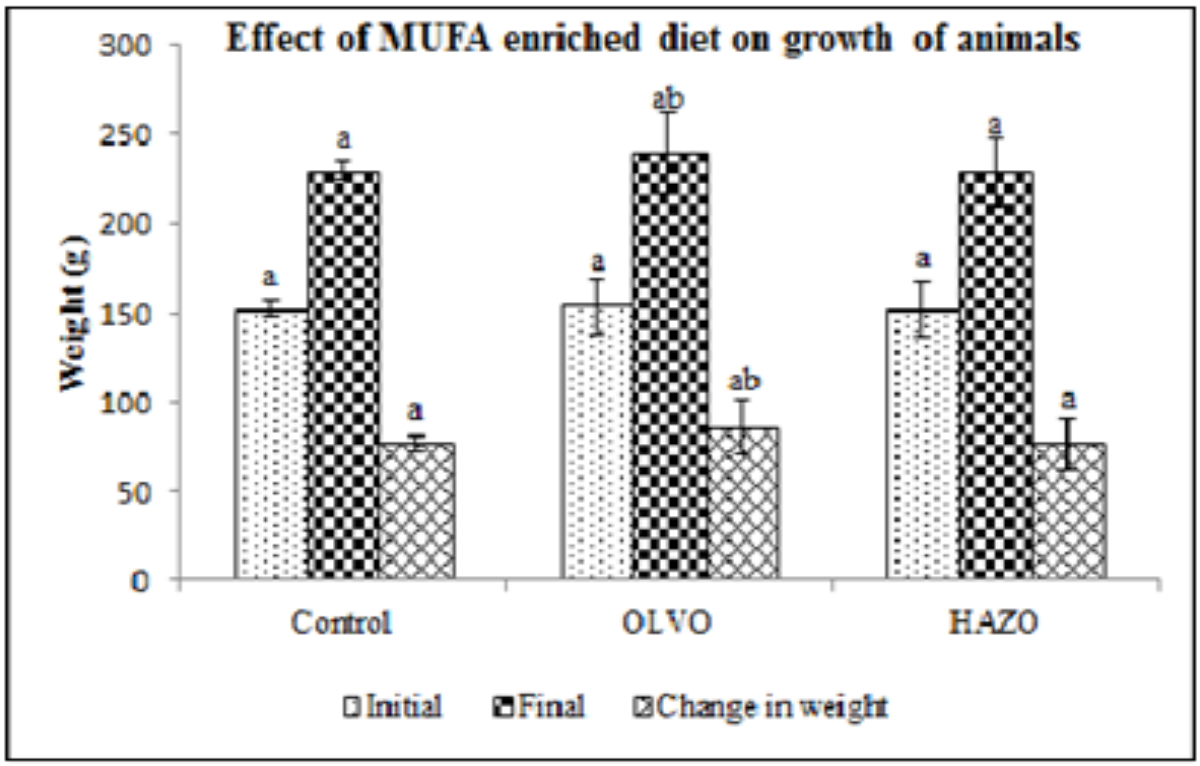

Fig. 1. Effect of MUFA enriched diet on growth of animals.

OLVO- olive oil, HAZO- hazelnut oil.

The differences between the treatment groups were analyzed using one-way ANOVA at a significance level of $p \leq 0.05$. Different alphabetical superscript defines differences in each row.

The oxidative degradation of PUFAs occurs in biological membranes as lipid peroxidation, which causes membrane function and structural integrity impairment, reduced membrane fluidity and even inactivation of several membrane-bound enzymes (Gutteridge and Halliwell, 2000). Enzymes such as superoxide dismutase and catalase are free radical scavengers that reduce oxidant molecules' effects on tissue and work against oxidative cell injury in the defense system. The majority of studies comparing the effects of a MUFA-rich diet with a PUFA-rich diet on LDL oxidation parameters have found that LDL particles are less prone to oxidation after consuming MUFA-rich diets (Aguilera *et al.*, 2004; Kratz *et al.*, 2002).

Conclusion

This study examined the effects of monounsaturated fatty acids (MUFA) (olive oil and hazelnut oil) rich oil on the liver lipid profile and antioxidant status in adult rats. It has been observed that MUFA enriched diet (OLVO and HAZO) caused a significant ($p \leq 0.05$) decrease in TC, TG, LDL-C, and VLDL-C and an increase in the level of HDL-C. Ratio LDL/ HDL and cholesterol/ HDL were also least in the treated group (OLVO), followed by HAZO and control. Similarly, the highest concentration of enzymatic antioxidant GSHPx, SOD and catalase, as well as the lowest concentration of MDA, was also observed in the OLVO group but with an insignificant difference between the control and treated group for GSHPx. This study has shown that MUFA diets can be used as nutritional alternatives to prevent lipid disturbances as it has shown a beneficial effect on lipid profiles and antioxidant enzymes.

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Conflicts of Interest

The authors declare no conflict of interest.

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