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# Hemp Seed Oil Effects on Female Rats Fed a High-Fat Diet and Modulating Adiponectin, Leptin, and Lipid Profile

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**Abstract:** Background: The prevalence of obesity is increasing dramatically worldwide. Obesity injuries have been linked to the alteration of many health biomarkers in humans. Consuming a 2.5:1 ratio of omega-6 and omega-3 helps to restore standard health biomarkers. Hemp, the non-psychoactive variety of *Cannabis Sativa* L., has a long history of being used as a source of food, fiber, and medicine. One of its attractive features is the favorable omega-6:omega-3 ratio found in its seed oil (HSO), making it a promising functional food for mitigating obesity-related injuries. Methods: A total of 84 female Wistar rats were randomly allocated into four groups. Two control groups ($n = 21$ each) were fed with a standard diet supplemented with 10% HSO. Two other equivalent groups consumed a high-fat diet, and one was supplemented with 10% HSO. Rats were euthanized from each group at 5, 10, or 15 weeks to measure body weight change, food intake, and several health biomarkers. Results: The results demonstrated that body weight gain and triglycerides were lower ($p \leq 0.05$) for the control group supplemented with HSO compared with the other groups. Adiponectin concentration was lower ($p \leq 0.05$) in both the control and high-fat treated groups. Other biomarkers were comparable among treatment diets. Conclusion: Our results suggest the usefulness of HSO supplementation for the overall health status.

**Keywords:** hemp seed oil (HSO); obesity; lipid profile; omega-6:omega-3 ratio; adiponectin



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## 1. Introduction

Worldwide, obesity has become an everyday health problem. As with other countries, in Jordan, obesity is a common health problems, with 38.8% of Jordanian women considered obese [1]. Obesity could be linked to many health problems including heart disease, infertility, and diabetes mellitus altered lipid profile [2,3].

Awareness of the functional role of plants as a source of bioactive compounds has been increasing over the last few years. Therefore, incorporating these compounds into the diet through plant-based sources has become an important way to promote health and reduce the risk of chronic illnesses [4]. An example of such a compound is poly unsaturated fatty acids, e.g., omega-6 and omega-3, which have anti-inflammatory properties. A balanced ratio of omega-6 to omega-3 is crucial for reducing the risk of chronic illnesses and promoting health [5].

In this study, we focused on finding a readily available product in the Jordanian market that can be used as a defense against obesity-related health problems. We selected hemp seed oil (HSO), which is derived from Cannabis Sativa L. (commonly referred to as hemp) and is widely cultivated for food, fiber, and medicines [6,7]. *Cannabis* is an annual, dioecious, green, and leafy plant [8,9]. Many studies have confirmed the unique omega-6:omega-3 ratio of HSO, which is thought to have a lowering effect on serum total

triglycerides and a semi-protective effect on induced hepatoxicity [7,10–12]. The HSO used in this trial had an omega-6:omega-3 ratio of 2.6:1, which is within the recommended range for optimal health, as suggested by previous researchers. Studies suggest that a ratio of between 1:1 and 4:1 per day is ideal for preventing or treating cardiovascular diseases and other health issues [13,14].

Hemp, also known as Hashish or Qunbuz, is found in the southern part of Jordan [15]. The HSO is available in Jordan as a cold-pressed oil, sold over counters in many organic markets. Therefore, to find the beneficial effects of hemp seed oil supplementation in the Jordanian markets as an adjunct therapy to diet on serum adiponectin, leptin, insulin, body weight, and lipid levels, we conducted the presented trial on induced obese female rats.

## 2. Materials and Methods

### *2.1. Experimental Design*

Eighty-four female Wistar rats were randomly allocated to four groups ($n$ = 21 for each group). The first group was offered standard chow. The second group was given standard chow with 10% HSO added. The third group was offered a high-fat (HF) diet, and the fourth group was given a HF diet with 10% HSO added. All diets were offered throughout the duration of the trial period. Animals were allocated in a completely randomized design, with the factors being obesity-inducing diet and HSO supplementation.

### *2.2. Animals and Treatments*

Eighty-four 3-month-old female Wistar rats were obtained from the animal house at the Jordan University of Science and Technology (JUST). All rats were housed individually in a room with controlled temperature (22 °C ± 2 °C), humidity (55% ± 5%), and a 12-h light–darkness cycle throughout the study period (15 weeks). All rats were in an adaptation period for one week before the 15-week treatment period started. All procedures were approved by the JUST Institutional Animal Care and Use Committee.

### *2.3. Diet Composition*

The two diets used in the trial were the standard chow (control diet; COD) and HF diet. The COD was obtained from the animal house at JUST and the HF diet recipe contained COD 25%, sucrose 15%, fat 20% (margarine butter supplemented with vitamins), and dry milk 40% (Table 1).

**Table 1.** Diet composition.

| Ingredients | COD | COHSO | HF | HFHSO |
|---|---|---|---|---|
| Standard Chow | 100 | 90 | 25 | 25 |
| Sucrose | - | - | 15 | 15 |
| Powder Milk | - | - | 40 | 40 |
| Margarine | - | - | 20 | 20 |
| HSO | - | 10 | - | 10 |
| Kcal/100 g Diet | 332.89 | 389.6 | 488.99 | 504.71 |
| Calories From Fat % | 4.89 | 23.1 | 51.11 | 52.37 |

COD: control diet, COHSO: control diet supplemented with 10% HSO, HF: high-fat diet, HFHSO: high-fat diet supplemented with 10% HSO, HSO: hemp seed oil. All compositions are in kg to produce 100 kg of diet.

The 100% pure cold-pressed HSO used in this trial was obtained from Green Shop Organic Food company located in Amman. Table 2 shows a duplicate of the nutritional facts found on the oil.

These four diets were selected to improve the comparability of the results. The regular rat chow was not considered an appropriate control group as it was not supplemented, unlike the other supplemented diets.

**Table 2.** Hemp seed oil profile.

| Type of Fat | Amount in 100 g |
|---|---|
| Saturated Fat | 11 |
| Unsaturated Fat | 89 |
| Of Which Monounsaturated | 13 |
| Polyunsaturated | 76 |
| Of Which Omega-6 | 55 |
| Omega-3 | 21 |

The profile is based on the nutritional fact table from the HSO used in the trial. All number are in grams.

### *2.4. Data Collection*

The rats' weights were measured weekly by electrical balance, and daily feed intake was calculated. All data were recorded to assess weight gain and growth.

### *2.5. Blood and Serum Markers*

The blood samples were collected from rats by cardiac puncture after deep terminal anesthesia (Ketamine 100 mg/kg body weight and Xylazine 10 mg/kg body weight, with 25% of total volume normal saline used as the drug carrier to speed up the process). Around 6 mL of blood was collected from each rat, which was left to clot at room temperature for 20 min in gel test tubes, then the samples were centrifuged at 4 °C, 4000 rpm for 10 min. The serum was preserved in a −20 °C freezer for later assays. Several tests were completed at the Veterinary Health Center at JUST to detect the impact, if any, of the diet and the HSO supplementation on health. All tests were performed using ELISA commercial kits, except for the low-density lipoprotein (LDL) concentration, which was calculated using the Friedewald formula: LDL = total cholesterol − (HDL + "TG/5") [16].

### *2.6. Data Analysis*

Statistical analysis was performed using the MIXED procedure of SAS (version 8.1, 2000, SAS Inst. Inc., Cary, NC, USA). One-way analysis of variance (ANOVA) was conducted for the normally distributed variables. The least square difference (LSD) test was performed to determine the differences between groups. A $p$-value of <0.05 was considered statistically significant.

## 3. Results

### *3.1. Weight, Weight Gain, and Intake*

The COD group intake was the highest among all groups during the trial period ($p \leq 0.05$). At week 5, body weight gains and body weight did not differ among all the treatment groups. However, at week 10, weight gains and body weights were greater ($p \leq 0.05$) for the HF group than COHSO. At the end of the trial (i.e., week 15), weight gains and body weight were higher ($p \leq 0.05$) for the HF and HFHSO groups compared with the COD and COHSO groups (Figure 1).

### *3.2. Lipid Profile*

LDL content was greater ($p < 0.05$) for the COHSO and HF groups than the HFHSO groups, whereas the COD group was intermediate. At week 10, TG concentration showed a significant difference between all groups ($p \leq 0.05$). However, for the HDL, LDL, and cholesterol, the significant differences ($p \leq 0.05$) were between the COD and all other groups, HF/HFHSO and the two other groups, the high-fat diet groups and the control diet groups, respectively. Moreover, at week 15, there was a statically significant difference between the COD and HF/COHSO groups in HDL and cholesterol concentration ($p \leq 0.05$), but there were no differences between the COD and HFHSO groups for the same biomarkers. For TG concentration, there was a statically significant difference between the COD and HFHSO groups ($p \leq 0.05$, Figure 2).

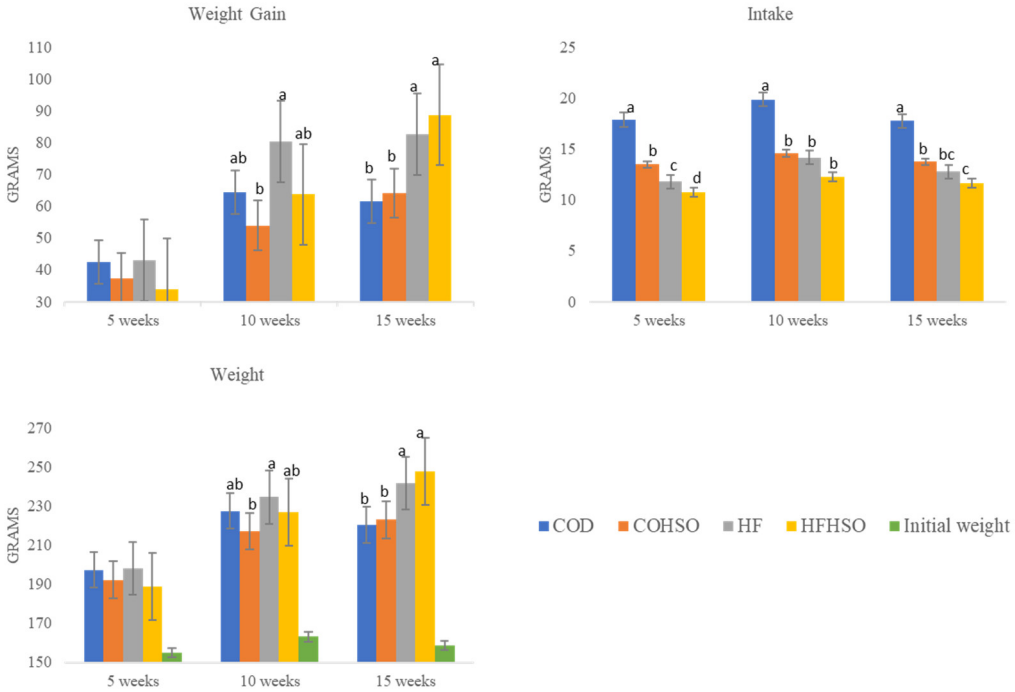


**Figure 1.** Weight, Weight Gain, and Total Food Intake for Rats. Significant $p \leq 0.05$, a: the most significant result. All groups were compared with each other within the same week. The same bar with different superscript letters is significantly different among groups within the same week ($p < 0.05$). COD: control diet, COHSO: control diet supplemented with 10% HSO, HF: high-fat diet, HFHSO: high-fat diet supplemented with 10% HSO, HSO: hemp seed oil.

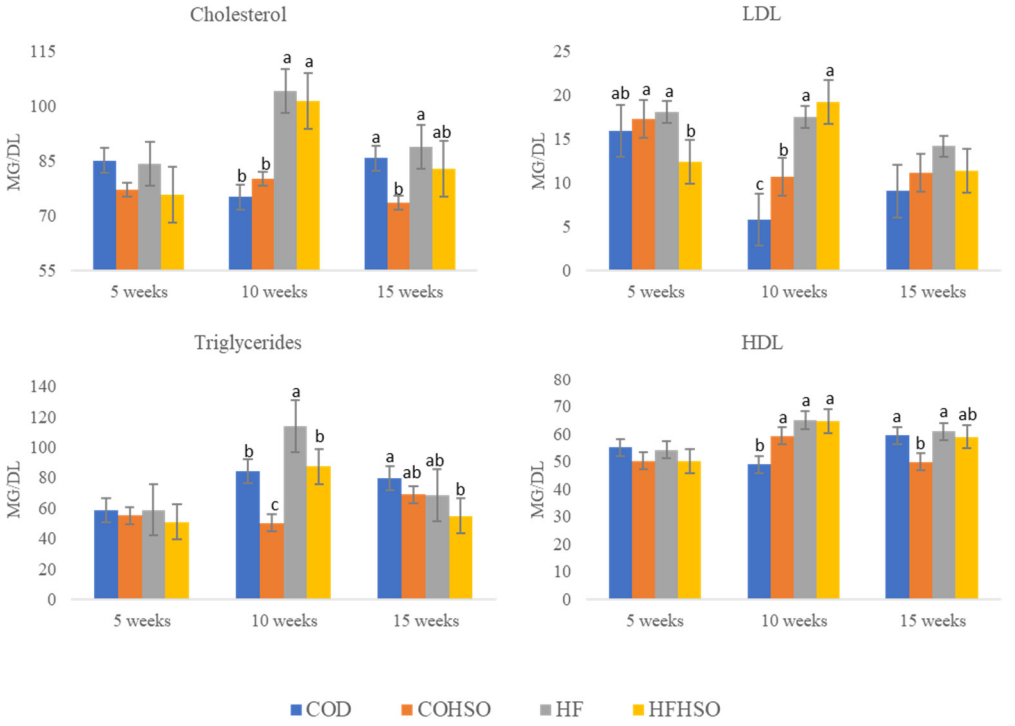


**Figure 2.** Lipid profile for rats. Significant $p \leq 0.05$, a: the most significant result. All groups were compared with each other within the same week. The same bar with different superscript letters is significantly different among groups within the same week ($p < 0.05$). COD: control diet, COHSO: control diet supplemented with 10% HSO, HF: high-fat diet, HFHSO: high-fat diet supplemented with 10% HSO, HSO: hemp seed oil.

### *3.3. Pancreas Function*

Only at week 5 was there a significant difference ($p \leq 0.05$) between the HF and COHSO groups regarding random glucose concentration. However, there was a statically significant difference between the HFHSO and COD groups at 10 and 15 weeks ($p \leq 0.05$). At week 5, insulin concentration showed a significant difference between all groups, except for the HF and HSO-supplemented groups ($p \leq 0.05$). Also at week 5, HbA1c concentration showed statically significant differences between the HFHSO group and all other groups, as well as again at week 15 ($p \leq 0.05$). A statically significant difference was observed at week 10 between the COHSO and COD groups ($p \leq 0.05$, Figure 3).

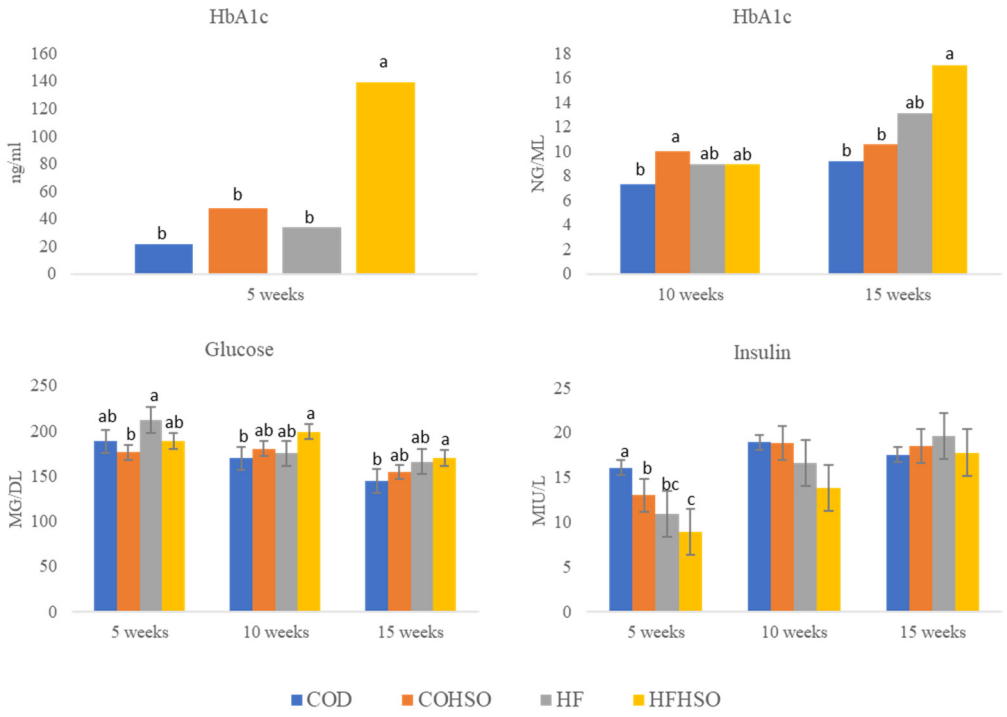


**Figure 3.** Pancreas function for rats. Significant $p \leq 0.05$, a: the most significant result. All groups were compared with each other within the same week. The same bar with different superscript letters is significantly different among groups within the same week ($p < 0.05$). COD: control diet, COHSO: control diet supplemented with 10% HSO, HF: high-fat diet, HFHSO: high-fat diet supplemented with 10% HSO, HSO: hemp seed oil.

### *3.4. Adiponectin and Leptin*

As shown in Figure 4, there were no statically significant differences ($p > 0.05$) between any group in leptin concentration, except in week 5, when a significant difference ($p \leq 0.05$) was observed between the COHSO and HF groups. Adiponectin concentration showed statically significant differences ($p \leq 0.05$) between the COD group and all groups at week 5. At weeks 10 and 15, statically significant differences were observed between the HF group and all other groups ($p \leq 0.05$, Figure 4).

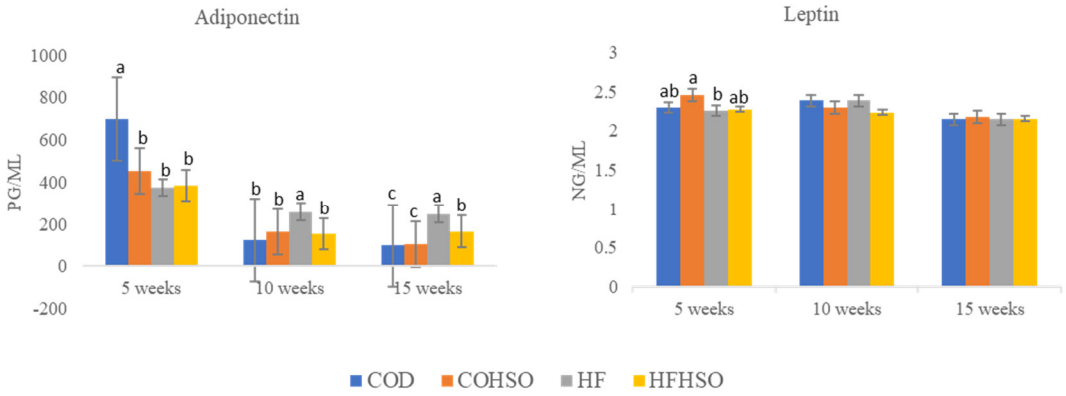


**Figure 4.** Adiponectine and leptin for rats. Significant $p \leq 0.05$, a: the most significant result. All groups were compared with each other within the same week. The same bar with different superscript letters is significantly different among groups within the same week ($p < 0.05$). COD: control diet, COHSO: control diet supplemented with 10% HSO, HF: high-fat diet, HFHSO: high-fat diet supplemented with 10% HSO, HSO: hemp seed oil.

## 4. Discussion

Obesity can damage the structure and function of many organs and it is known that a high-fat diet can induce obesity in animal models. The focus of this study was to characterize high-fat effects on weight, lipid profile, pancreas, leptin, and adiponectin hormones. All results compared the HFHSO and COHSO groups with the HF and COD groups to determine the HSO impact. We chose a 10% level of supplementation because it is believed to closely resemble dietary interventions in humans. This conclusion is based on the understanding that similar levels of supplementation with flaxseed at 10% are considered adequate [17]. The present study has shown, in line with many recent studies, a direct link between a high-fat diet and obesity.

According to our results for intake and weight gain, the COD group had the highest intake during the trial period. However, the HF and HFHSO groups exhibited higher weight gain between 10 and 15 weeks. At the beginning of the trial, the rats were not accustomed to the new diet, which may explain why the COD group had the highest intake. As the trial progressed, the rats began to adapt to and prefer the high-fat diet, leading to higher weight gain. This may be because fat provides more calories per gram than carbohydrates and proteins combined [18]. Typically, high-fat meals are smaller and denser, which can satisfy hunger faster with excess calorie intake. However, the group supplemented with HSO showed a lower intake than the same diet group without supplementation. This may be due to the bitter taste and strong smell of HSO [6]. On the other hand, the COHSO group had the lowest weight gain compared to all other groups. Additionally, the weight gain of the HFHSO group was similar to that of the HF group. These observations suggest that HSO has a weight-lowering effect in non-obese individuals. Our findings are supported by previous research, which has shown that a high-fat diet can lower intake and increase weight gain [19–21]. For example, Schwab et al. (2006) found that weight reduction occurred with HSO supplementation [11]. This supports our suggestion that the reduced weight gain in the COHSO group was due to HSO. The weight reduction may be caused by the presence of omega-6:omega-3 ratios, which have a protective effect against obesity [22]. Similarly, Mohammadi-Sartang et al. (2017) suggested that supplementing a high-fat diet with omega-3 can reduce body weight [23]. This weight reduction may occur through increased apoptosis in the adipose tissue and an increase in the adipogenic transcription factor due to omega-3 [24].

Regarding lipid profile results, many studies have shown that offering a high-fat diet will elevate TG, cholesterol, and LDL concentration in serum and decrease HDL concentration [21,25]. At week 15, our results concur with studies by Schwab et al. (2006), Fotschki et al. (2020), and Suzuki et al. (2021) on the decreasing effect on TG serum concentra-

tion [10,11,19,26]. However, in our trial, the cholesterol concentration was lowered at week 15. In our opinion, this may be due to the oleic acid present in the HSO as a considerable amount of the literature has recommended it for its lowering effect on serum cholesterol concentration [27,28]. It is possible that oleic acid stimulates the extra-hepatic efflux of cholesterol in bile acid and increases the expression of the ATP-binding cassette transporter, which transports dietary sterols from the liver and small intestine and prevents its accumulation [27].

In addition, the concentration of HDL tended to be higher in the HF and HFHSO groups. This may be because we used margarine supplemented with vitamin E. A study suggested that vitamin E supplementation may affect both HDL and LDL concentrations by increasing them [29]. In agreement, a study reported that HSO could elevate LDL concentration [11]. This finding is consistent with Baumgartner et al. (2017), who suggested that this elevation may occur due to vitamin E but did not explain why this could happen [29]. Simopoulos (2016) also mentioned that the omega-6:omega-3 ratio could alter lipid homeostasis and increase LDL concentration by raising the expression of the responsible genes [22]. On the other hand, canola oil has a similar omega-6:omega-3 ratio, but it also showed a slight decrease in the total lipid profile after canola oil treatment [30].

In agreement with our finding regarding insulin and glucose concentrations, Rios et al. (2017) observed a decrease in insulin and glucose concentrations when a high-fat diet was offered to rats [19,31]. On the other hand, a study by Suzuki et al. (2021) on a mice model showed opposite results, and a similar finding on rats was achieved by Panchal et al. (2011) [20,21]. This difference in outcomes for high-fat diets can be linked, first, to the variation in animal species and how their bodies respond to the diet. Second, the length of time that the high-fat diet was administered for may have played a role. However, our treatment did not show any effect on improving the function of the pancreas. Additionally, serum HbA1c levels showed a significant elevation when diets with a high sugar content were given. It is well-established that HbA1c levels increase when glucose concentrations in the blood remain elevated for a prolonged period [18].

Obesity is typically associated with lower adiponectin concentration. Nevertheless, this study found elevated levels of adiponectin in the induced obese groups (HF and HFHSO), which was unexpected. This finding may be explained by the vitamin supplementation in the margarine used in diet preparation as Banerjee et al. (2017) reported a positive relationship between vitamin D and serum adiponectin concentration [32]. The HSO groups did not show any other effect on adiponectin levels. A study by Pusparini et al. (2017) also confirms this finding, but it is not yet clear how vitamin D affects adiponectin levels [33].

In general, obesity and a high-fat diet tend to increase leptin concentration in the serum [13]. Unexpectedly, our results did not show any significant differences in leptin levels among all groups (Figure 4). All the groups, except for the COD group, had one active compound in common, which was the presence of tocopherol (vitamin E) in their diet. A previous study on rats found that a high-fat diet supplemented with vitamin E was associated with lower leptin levels compared to a high-fat diet without vitamin E (1.8 ng/mL and 0.8 ng/mL for a high-fat diet and high-fat diet with vitamin E, respectively) [31]. The exact mechanism by which vitamin E might regulate leptin levels is not well understood but it is possible that its antioxidant activity may inhibit leptin secretion. A cross-sectional study also found that consuming antioxidants may reduce leptin levels [34].

At 5 and 15 weeks, all charts obtained the same spread. However, at week 10, the data spread was a little different. This can be explained by the age at which the rats were euthanized, as a study by Ihedioha et al. (2011) observed a sudden alteration of the serum lipid biomarkers around 20 weeks of age [35]. Therefore, we believe that all the serum biomarkers could be affected by this alteration, but more research is needed to confirm this. Additionally, our results may differ from previous studies due to the use of HSO, as there are 51 genotypes of hemp seed that vary in the phytochemical ingredients [7,36].

Therefore, our study is important because it contributes to the data available on the health benefits of HSO, especially for individuals with obesity. A few scientific studies have

examined the contribution of HSO to the injuries caused by obesity. Our results support the potential effect of HSO as a functional food. However, more studies are warranted to determine the exact mechanism.

## 5. Conclusions

In this study, the effects of high-fat diet with and without HSO supplementation on weight, lipid profile, pancreas, and hormones were examined in a rat model. The results demonstrated that HSO had a weight-lowering effect for non-obese individuals and influenced the lipid profile by decreasing serum TG concentration and increasing serum HDL concentration. In addition, HSO appeared to protect the pancreas and alter the levels of the hormones leptin and adiponectin. These findings suggest that HSO may have the potential as a functional food that can help in mitigating the adverse effects of a high-fat diet on weight, lipid profile, and organs' function. However, further research is needed to confirm and fully understand these effects of HSO.

**Author Contributions:** Conceptualization and visualization, T.S.A.G. and B.S.O.; methodology, B.S.O. and M.S.A.; validation, B.S.O., H.S.S. and M.S.A.; formal analysis, resources, writing (review and editing), funding acquisition, B.S.O.; investigation, data curation, writing (original draft preparation), T.S.A.G.; supervision, H.S.S.; project administration, B.S.O. and H.S.S. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The animal study protocol was approved by the Institutional Ethics Committee of Jordan University of Science and Technology.

**Data Availability Statement:** The data will be available upon request.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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