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ABSTRACT

Background: Grape-seed oil has diverse biological functions and is beneficial in treating metabolic complications, such as metabolic syndrome, obesity, diabetes, and dyslipidemia. The purpose of this study was to investigate the anti-hyperglycemic, anti-dyslipidemic, and anti-inflammatory effects of Grape-seed oil in diabetic rats.

Materials and methods: 16 streptozotocin-induced diabetic Wistar rats were used in this study. Diabetic rats were randomly allocated to either of two groups (n = 8): diabetic rats treated with grape-seed oil or diabetic control. Grape-seed oil (GSO) (25 mg/kg BW) was administered orally for 40 days, and at the end, blood samples were taken directly from the heart.

Results: Diabetic rats treated with oil compared to control diabetic rats demonstrated a significant ($p = 0.001$) decline in serum glucose concentration. High plasma concentrations of TG, LDL, and VLDL were reduced ($p = 0.001$, $p = 0.001$, $p = 0.001$, respectively). Surprisingly, between inflammatory markers, TNF-α was significantly ($p = 0.02$) increased. Furthermore, GSO-treated diabetic rats experienced a significant ($p = 0.014$) weight gain during the study. However, total cholesterol, HDL, and CRP levels did not change significantly.

Conclusion: Treatment with grape-seed oil ameliorated dyslipidemia and hyperglycemia in diabetic rats. However, further investigations in peculiar clinical studies are required.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a multifaceted chronic metabolic noncommunicable disease (NCD) and one of the major pandemics of the twenty-first century and causes numerous comorbidities and significant mortality worldwide. Based on International Diabetes Federation records, there were 425 million diabetic individuals worldwide in 2016. In both developed and emerging countries, the number of diabetic patients are expected to exceed 629 million people by 2045 without adequate management and supervision. About 5 million people died from diabetes worldwide in 2017, with an estimated annual cost exceeding $1.3 trillion (Berbudi et al., 2020; Braunwald, 2019). Impaired glucose tolerance and hyperglycemia are the major clinical features of diabetes, which are the consequences of insulin deficiency or resistance (Tsalamandris et al., 2019). In addition, some proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 can trigger inflammatory processes that eventually lead to impaired insulin and glucose metabolism (Shoelson et al., 2006). These factors can increase insulin resistance and are among the substantial risk factors for cardiovascular disease. Inflammation plays a leading role in initiating the immune attack against pancreatic beta cells and later stages in maintaining the pancreatic islets' inflammation. Inflammatory mediators may be involved in destroying beta cells and inhibit their function (Poitout and Robertson, 2008). There is currently no cure for this illness. In diabetic patients, insulin therapy is used to keep blood sugar levels under control. However, there are a number of drawbacks, including insulin resistance after a lengthy period of medication. On the other hand, oral antidiabetics are either prohibitively expensive or have undesirable side effects or contraindications (Xu et al., 2015). To prevent these difficulties, a significant part of the population has turned to herbal therapy to manage diabetes (Palici et al., 2015). Accordingly, it seems that focusing on inflammation by herbal treatment can be an interesting strategy for curing insulin resistance and overall complications of diabetes (AHMED et al., 2019; Celik et al., 2017). Moreover, supplementation with α-linolenic acid, eicosapentaenoic acid, and omega-3 fatty acid prevented alloxan-induced DM. Therefore, unsaturated fatty acids are closely associated with positive health benefits related to cardiovascular diseases and glucose metabolism (Su et al., 2015; Parsamanesh et al., 2021).

Grape-seed oil (GSO) is a byproduct of the winemaking process (Martin et al., 2020). These seeds contain lipid, protein, carbohydrates, and polyphenols (Chedea et al., 2010; Ekin et al., 2003). It was found to contain 8–20 percent of oil (dry basis depending on the variety) (Rombaut et al., 2015) that is extracted either by mechanical technique (cold pressing) or conventional solvent extraction (Garavaglia et al., 2016a; Shinagawa et al., 2015). Cold-pressed grape seed oil is rich in polyunsaturated fatty acids (PUFA), especially linoleic acid (Fruehwirth et al., 2020). GSO also contains a large number of hydrophilic constituents, such as phenolic compounds, and lipophilic constituents, such as vitamin E and phytosterols. Therefore, GSO is considered a potential antioxidant, anti-inflammatory, anti-microbial and reduced probable nephropathies complications (Garavaglia et al., 2016b; Kıvanç et al., 2018).

Considering the role of inflammatory mediators in the etiology of diabetes-associated complications, as well, the anti-inflammatory and anti-diabetic effects of GSO, this study aimed to investigate the effect of GSO on inflammatory markers, blood glucose and lipid profiles in diabetic rats.

2. Materials and methods

2.1. Chemicals

All the chemicals used in this study were in analytical grade, kept in a standard condition and purchased from legal commercial suppliers. GSO was provided from the finest quality in the market. Streptozotocin (STZ) was provided from Sigma-Aldrich Chemical Co. (Steinheim, Germany).

2.2. Experimental animals

Male albino rats of the Wistar strain, weighing 200–220 g and six weeks old, were used as an animal models. They were provided from the Ahvaz Jundi Shapour University of Medical Sciences' Physiology Research Facility and held in standard condition, polypropylene cages, with daily chow and water available ad-libitum. The rats were maintained for two weeks - prior to the initiation of the trial - for ambient acclimatization and trainer handling. To minimize the influence of the circadian rhythm, all animal manipulations were conducted in the morning. The experimental design adhered to the ethical guidelines set out by the Animal Care and Use Committee of Ahvaz Jundi Shapour University of Medical Sciences.

2.3. Induction of experimental diabetes

After 12 h of fasting, streptozotocin (50 mg/kg body weight, dissolved in a cold citrate buffer (0.1 M, pH = 4.5)) was injected intraperitoneally (i.p.) to induce diabetes (Rakieten et al., 1963). Since STZ can cause fatal hypoglycemia subsequent to massive pancreatic insulin secretion, all animals were supported by 10 percent glucose solution for the next 24 h to avoid plausible consequences. Neither death nor the opposite outcome was detected. Rats with fasting blood sugar concentrations above 250 mg/dl were selected for the experimental diabetes model.

2.4. Experimental design

Sixteen rats were divided randomly into two groups (n = 8 and aged 6 weeks) as follows: Control group (diabetic rats with no treatment) and treatment group (diabetic rats that treated with 25 mg/kg GSO daily) (Cuevas et al., 2011; Yurt et al., 2019). The animals' food intake and body weight were monitored twice a week and the study was conducted for 8 weeks. After the treatment period, the mice were fasted overnight with unrestricted access to water before being anesthetized and sacrificed by direct blood collection

from the heart. Blood samples were centrifuged immediately and the isolated plasma samples were kept refrigerated in standard condition for further measurements.

Fasting blood sugar (FBS) (mg/dl), total cholesterol (TC) (mg/ml), high-density lipoprotein (HDL) (mmol/L), and triglyceride (TG) (mmol/L) were measured enzymatically in a medical diagnostic laboratory using laboratory kits (Parsa Azmoon, Iran). Very low density lipoprotein (VLDL) (mg/dL) was calculated as TG/5 and low-density lipoprotein (LDL) (mmol/L) cholesterol was calculated using the Friedewald formula. Proinflammatory cytokine levels, CRP (μg/ml) and TNF-α (pg/mL) were measured by proper kits using the ELISA method (Karmania Pars gene, Iran).

2.5. Statistical analysis

The results were expressed as mean ± SD. The statistical significance was evaluated by independent sample *t*-test and one-way analysis of variance (ANOVA) using the SPSS (version 25.0) followed by Tuky. Values were considered statistically significant when $p < 0.05$.

3. Results

Weight was measured in 14 days during the study (every 4 days). Lipid profiles values (LDL, HDL, VLD, TG, TC) and inflammatory markers (TNF-α, CRP) were measured at the end of the study. Blood glucose levels were measured at the beginning and the end of the study. Analyzes were performed using SPSS 25 and R software version 4.0.1. Bar plot of lipid profiles, inflammatory markers, and blood glucose are shown in Fig. 1.

The variables in the treatment and placebo groups are compared and depicted in Fig. 2. The upper left, middle and right diagrams demonstrate the difference in LDL, CHOL and TG respectively. In the middle row differences of HDL, VLDL and TNF-αbetween both groups are presented, and the lower row show the difference of CRP, the mean weight difference over time, and the mean blood sugar at the beginning and end of the study. According to the chart, there was a noticeable difference between LDL, TG and VLDL levels between treatment and placebo groups. The Mann-Whitney test was used to compare inflammatory markers. The CRP test results showed that the amount of CRP in both groups was almost equal (p-value = 0.053). Nevertheless, TNF-α levels in the treatment group was higher than the control (p-value = 0.026). The Wilcoxon test results to compare blood sugar levels showed that FBS in treatment group were significantly higher in the beginning of the study (p-value = 0.018), and after treatment for 8 weeks, FBS levels decreased. However, the difference was not significant in control group (p-value = 0.753) (see Fig. 3).

Due to the normality of lipid profile and homogeneity of variance, multivariate regression was used to examine the differences between the groups. Table 1 shows the results of the multivariate regression.

The results of multivariate regression for variables that had significantly changed are depicted in Table 1. The coefficient of GSO in the regression output is negative, indicating that treatment is associated with a decrease in lipid profiles. The estimation of the regression coefficient for TG, LDL and VLDL was significant (all p-values <0.001), which predicts that, on average, in the GSO group, TG, LDL, and VLDL levels are 114.96, 56.96, and 22.99 units less than control group respectively.

Table 2 summarizes the weight (gram) information of mice by type of treatment. Two-way repeated-measures ANOVA was used to analyze the weight information of mice. The interaction between treatment and time was significant (p-value = 0.014) according to Table 3. In other words, the weight of mice over time in the placebo group is significantly different from the weight (gram) in the treatment group.

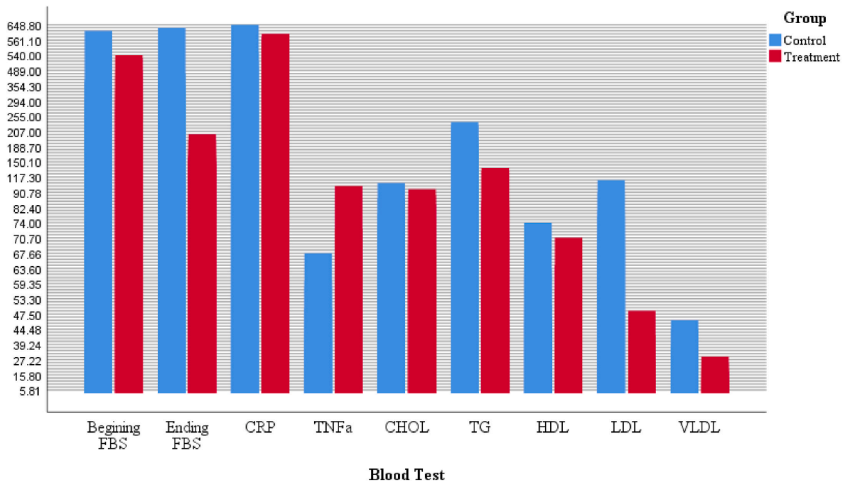

Fig. 1. Cluster bar plot of blood test by group.

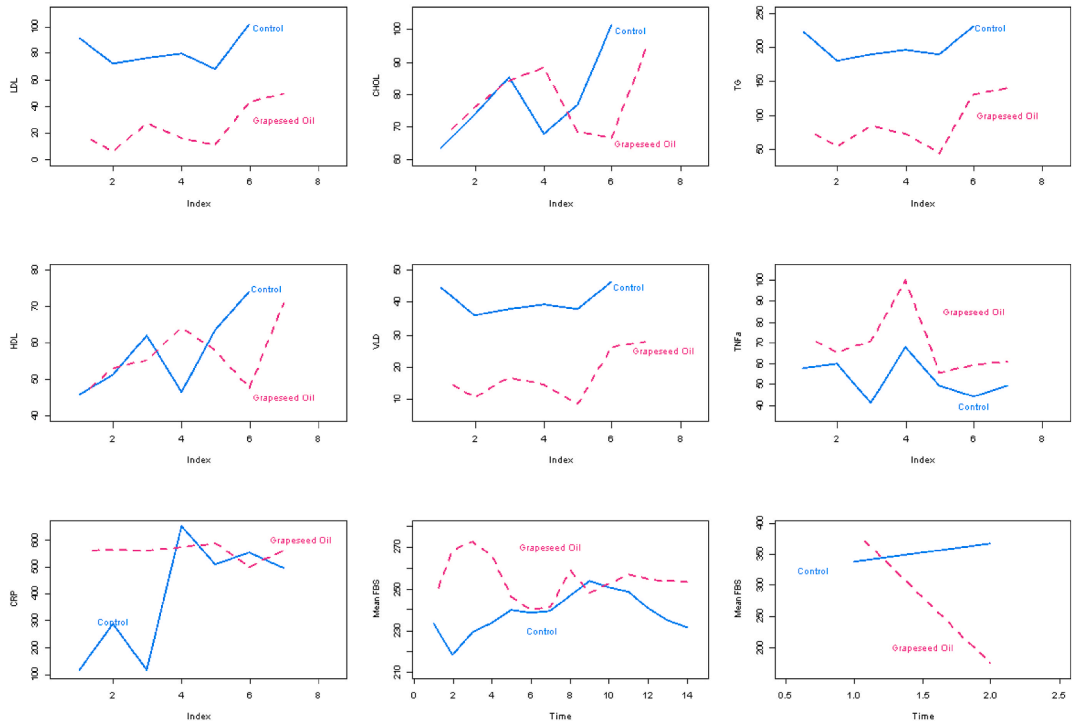

Fig. 2. The variables in the treatment and placebo groups are compared and depicted. The upper left, middle and right diagrams demonstrate the difference in LDL, CHOL and TG, respectively. In the middle row, differences of HDL, VLDL and TNF-αbetween both groups are presented, and the lower row shows the difference of CRP, the mean weight difference over time, and the mean blood sugar at the beginning and end of the study. The Mann-Whitney test was used to compare inflammatory markers. The CRP test results showed that the amount of CRP in both groups was almost equal (p-value = 0.053). Nevertheless, TNF-α levels in the treatment group were higher than the control (p-value = 0.026). The Wilcoxon test results to compare blood sugar levels showed that FBS in the treatment group was significantly higher in the beginning of the study (p-value = 0.018), and after treatment for 8 weeks, FBS levels decreased.

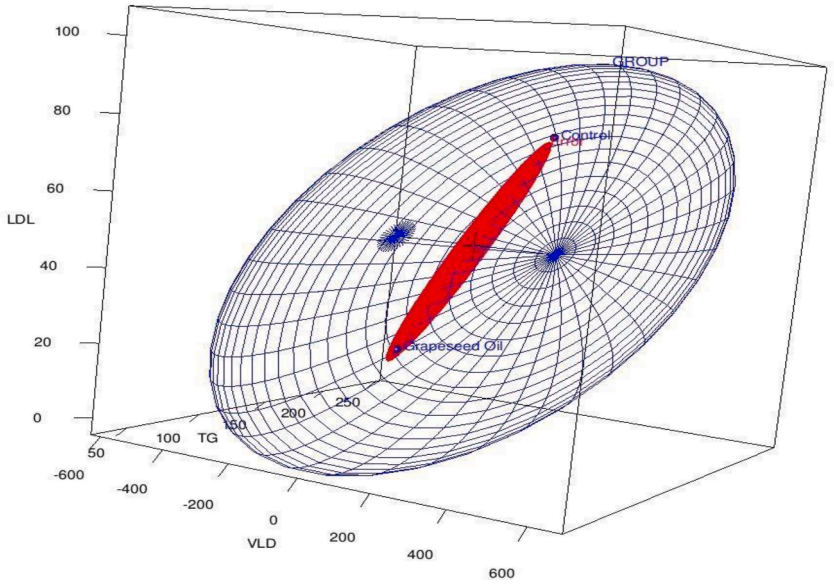

Fig. 3. 3D Plot of Multivariate Regression Analysis. The red part inside the globe indicates the model error. Because it covers a small part, it means that the model was appropriate. Considering the location of control and treatment points, it is clear that the values of variables for the control group were higher than the treatment group. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Multivariate regression analysis for lipid profiles.

Dependent Variable	Coefficients Estimate		S.E	T value	Sig.	F	Sig.	Multiple R^2	Adjusted R^2
CHOL (mg/ml)	β_0	78.06	5.06	15.43	< 0.001	0.004	0.95	0.0003	−0.09
	β_1	−0.44	6.89	−0.06	0.95				
TG (mmol/L)	β_0	201.3	12.36	16.28	< 0.001	46.57	< 0.001	0.81	0.79
	β_1	−114.96	16.84	−6.824	< 0.001				
HDL (mmol/L)	β_0	57.16	4.12	13.84	< 0.001	0.033	0.86	0.003	−0.09
	β_1	−1.02	5.62	−0.18	0.86				
LDL (mmol/L)	β_0	81.58	6.04	13.5	< 0.001	47.85	< 0.001	0.8131	0.7961
	β_1	−56.96	8.23	−6.91	< 0.001				
VLDL (mg/dL)	β_0	40.26	2.47	16.28	< 0.001	46.57	< 0.001	0.8089	0.7916
	β_1	−22.99	3.36	−6.82	< 0.001				

Table 2
Rats weight (gram) summary.

Time	Control Group (n = 8)			Treatment Group (n = 8)		
	MeanSD(gram)	95% Confidence Interval		MeanSD (gram)	95% Confidence Interval	
		Lower Bound (gram)	Upper Bound (gram)		Lower Bound (gram)	Upper Bound (gram)
1	233.38 ± 20.98	214.88	239.972	242.25 ± 23.34	220.981	266.733
2	218.0 ± 15.12	202.412	232.445	267.00 ± 30.39	237.766	298.234
3	229 ± 25.01	205.706	239.151	271.25 ± 32.12	240.700	304.443
4	233.5 ± 30.33	201.550	256.165	264.88 ± 31.17	235.017	296.983
5	239.63 ± 21.74	217.244	260.471	244.75 ± 32.29	214.316	278.255
6	238.63 ± 26.17	213.561	265.582	235.75 ± 27.69	214.104	265.039
7	239.13 ± 34.85	207.013	275.558	237.00 ± 30.16	212.471	268.957
8	246.75 ± 29.70	220.018	277.982	258.71 ± 53.01	209.690	307.739
9	254 ± 25.14	231.765	280.521	248.29 ± 27.39	222.954	273.618
10	250.63 ± 26.21	227.208	278.220	252.43 ± 29.37	225.260	279.597
11	248.5 ± 27.91	223.309	277.834	256.57 ± 31.49	227.448	285.695
12	240.38 ± 33.11	213.400	275.457	254.57 ± 31.74	225.214	283.929
13	234.88 ± 38.06	203.936	275.206	253.29 ± 32.13	223.567	283.004
14	231.63 ± 41.71	198.816	275.756	253.00 ± 33.09	222.391	283.609

Table 3
Results of Two-way repeated measures ANOVA for Weight. The interaction between treatment and time was significant (p-value = 0.014).

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Treatment	10845.735	1.000	10845.735	1.021	.351
Time	5769.918	1.715	3364.733	1.293	.309
Treatment * Time	15428.265	2.526	6107.020	5.230	.014
Error(Time)	26783.724	78	343.381		
Error(Treatment)	63737.051	6.000	10622.842		
Error(Treatment*Time)	17698.949	15.158	1167.639		

4. Discussion

Diabetes mellitus is a metabolic condition characterized by chronic hyperglycemia caused by a lack of insulin secretion, insulin activity or both (Kharroubi and Darwish, 2015). Diabetes is also strongly associated with dyslipidemia and inflammation. Due to various reasons, patients with diabetes may prefer the usage of herbal remedies, including disappointment with traditional therapy, adverse effects associated with treatment, and perceived suitability of herbal remedies with patients' values and moral beliefs (Mekuria et al., 2018). The winemaking process leads to GSO production as a byproduct. Rich in phenolic compounds, fatty acids, and vitamins, GSO is economically essential for the medicinal, cosmetic, and food industries. The health benefits of GSO include anti-inflammatory, cardioprotective, anti-microbial, and anticancer effects and can interact with cellular and molecular pathways (Garavaglia et al., 2016b). Therefore in this study, the effect of GSO on glucose metabolism, lipid profile, and inflammation was assessed in STZ-induced diabetic rats.

Irandoost et al. (2013) studied the grape-seed oil effect on inflammation and insulin resistance in overweight or obese females aged 20–50 years (n = 44). Treatment with grape seed oil for 8 weeks decreased inflammatory markers such as hs-CRP and TNF-α. Furthermore, grape seed oil lowered HOMA-IR (homeostatic model measurement of insulin resistance) ratings, indicating that insulin resistance in obese females improved (Irandoost et al., 2013). Söğütlü and colluges (2021) studied the role of Grape Seed

Extract on Insulin, Adiponectin and Resistin Levels in Diabetic Rats. They results showed The rats in the diabetes + grape seed extract group were discovered to have higher levels of insulin and adiponectin than the rats in the diabetes category. The variations in resistin concentration between the groups did not vary significantly. It is plausible to conclude that grape seed extract increases insulin levels while decreasing adiponectin levels in diabetic rats and having no discernible impact on resistin levels (Söğütlü et al., 2021). Another study on the hepatic function of adult male rabbits reported a significant reduction ($P < 0.05$) in serum glucose concentration in the GSO consuming group (124.8 ± 1.52) compared to the other (124.8 ± 1.52) (Khudiar and AJAiASciences, 2015). It has been reported that procyanidins in GSE exhibit insulin-mimetic properties by stimulating glucose uptake in insulin-sensitive cell lines and decrease hyperglycemia in STZ-induced diabetic rats (Suwannaphet et al., 2010). Our study also confirmed a significant decrease in FBS in diabetic rats consuming GSO.

Diabetes is linked to significant plasma lipid and lipoprotein profile complications. GSO has a high linoleic acid content (60%–75%). It is confirmed that its intake may result in lipid profile refining (Pardo et al., 2009). Also, high amounts of tocotrienols and vitamin E derivatives may inhibit HMG-COA reductase and improve lipid profiles (Choi and Lee, 2009; O'Byrne et al., 2000). Our study is in accordance with this notion, as we found a significant reduction in TG plausibly by phenolic acid in the GSO group. Some studies like Kasab's did not find any significant TG changes due to the usage of refined GSO with no phenolic content (Kaseb et al., 2016).

In numerous studies (Mokhtar RA. 2013) hypocholesterolemic effect of GSO was reported (Mokhtar et al., 2016). However, in this study, changes in total cholesterol levels were not significant ($p = 0.95$). In GSO treated group, LDL and VLDL significantly decreased (p-values $= 0.001$) compared to the control group. Other researchers have reported controversial results considering HDL alteration. Few studies have shown a significant increase, while others have reported unchanged HDL levels (Al-Attar, 2015; Kim et al., 2010). This study demonstrated no significant change in HDL levels ($p = 0.86$) in the GSO group. Additional studies are required to confirm the effect of GSO in HDL levels.

Whereas there appear to be few studies assessing the health impacts of GSO on inflammatory markers, Tocotrienols seemed to be able to modulate inflammatory factors in diabetic rats in in-vitro studies (Kuhad and Chopra, 2009). Different researches imply that Tocotrienols can play a role in suppressing inflammatory factors and prevented nuclear factor κB (NF-κB) activation (Matsunaga et al., 2012). Apparently, Tocotrienols in GSO can suppress HMG-COA and thereby act as an anti-inflammatory transcriptional factor, inhibiting the actions of NF-κB, INOS, and COX-2, lowering hs-CRP and TNF-α. (Aggarwal et al., 2010; Wu et al., 2008). However, unlike other experiments, CRP levels in the treated animals did not change significantly ($p = 0.05$), whereas, surprisingly, TNF-α levels were unexpectedly elevated ($p = 0.02$). It may be due to conflicting factors impacting TNF-α levels, such as weight fluctuations and/or obesity-related complications (Poniachik et al., 2006). Others studies showed that the administration of GSE to diabetic individuals aided in the recovery of DNA damage and a deteriorating kidney state (Kıvanç et al., 2018; Sogutlu et al., 2022). Also, evidences indicated that grape seed extrac have positive influence on the pancreas activities and structure and cloud improved enzyme function in Langerhans islets (Irak et al., 2018; Amit et al., 2019).

5. Conclusion

Our findings imply that regular administration of GSO improved dyslipidemia and hyperglycemia in diabetic rats in an experimental model. The data almost certifies the positive benefits of grape-seed oil in treating metabolic disturbances, including FBS, LDL, VLDL, TG, and TC, and no positive effect on HDL and inflammation. The rats also experienced weight gain during the course of the study. Nevertheless, other investigations suggested no positive effect of GSO on dyslipidemia and hyperglycemia and inflammation. Finally, since GSO has a substantial hypoglycemic capacity, it may be used to treat diabetes. GSO appears to have several beneficial effects on metabolic disorders and diabetes. Hence, it may help prevent and treat a variety of other diseases, according to recent research. However, further studies are required to distinguish discrepancies in the literature. Besides, despite evidence representing promising effects in rodents, human studies are deficient, and either therapeutic or preventive values of GSO in humans remain to be elucidated.

Ethical issues

The ethic of this article, which was resulted from the PhD thesis number U-89210, has been approved in letter number 8/20/620 by Ahvaz Jundishapur University of Medical Sciences.

CRediT authorship contribution statement

Mohammad Reza Shiri-Shahsavar: Conceptualization, Supervision, Investigation, Methodology. **Sepideh Alijani:** Data curation. **Negin Parsamanesh:** Writing – review & editing. **Sara Moazzen:** Software, Validation. **Narges Sadeghi:** Investigation. **Amin Majnouni:** Investigation. **Ahmadreza Rasouli:** Methodology, Writing – original draft.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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