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Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats

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ABSTRACT

Purpose: The purpose was to investigate the effects of six weeks of resistance or aerobic exercise combined with the intake of Cornus mas extract on the lipid profile, metabolic parameters, and liver enzymes of obese rats. Methods: 49 male Wistar rats were divided into seven groups: 1) healthy control (n = 7); 2) hypercaloric fatty-food-based diet (n = 7); 3) aerobic exercise (AE, n = 7); 4) resistance exercise (RE, n = 7); 5) Cornus mas extract intake (C, n = 7); 6) Cornus mas combined with aerobic exercise (CAE, n = 7); and 7) Cornus mas combined with resistance exercise (CRE, n = 7). All the rats (except the controls) were induced fatty liver by six weeks of a hypercaloric diet before the intervention. After the six-week intervention, blood samples were taken to obtain levels of triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), cholesterol, glucose, c-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and urea. A one-way ANOVA or the Kruskal Wallis tests for the non-normally distributed variables, with post-hoc pairwise comparisons, assessed differences between groups. Results: All the intervention groups significantly ($p < .05$) improved the parameters compared to the hypercaloric group in almost all the assessed parameters, reaching in many cases significantly better values than the healthy group (control). Adding the Cornus supplementation to the exercise resulted in slightly non-significant better values. Conclusion: Cornus mas extract and aerobic or resistance training may be helpful to treat fatty liver and also reduce the lipid profile levels.
Keywords: Aerobic; Resistance training; Physical activity; Fatty liver; Cardiovascular disease; Wistar rats.

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INTRODUCTION

The concurrent epidemic of metabolic diseases such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) has been increasing in both developed and developing countries (El Hadi et al., 2019; Tomeno et al., 2020), being a major risk factor for cardiovascular disease (CVD) (Ismaiel et al., 2019). According to the World Health Organization, CVD is the cause of 18 million deaths per year.

NAFLD is the most common liver disease (Iloon Kashkooli et al., 2015) and is a key risk factor for CVD and diabetes type 2 (Della Pepa et al., 2017). NAFLD refers to a range of liver diseases caused by abnormal fatty deposits in the liver and a comprehensive spectrum of histological liver abnormalities ranging from simple triglyceride accumulation in hepatocytes to non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH; Tomeno et al., 2020). Furthermore, NAFLD can lead to death if it progresses to cirrhosis and/or hepatocellular carcinoma (liver cell cancer; Reid, 2006). Previous studies show that liver enzyme levels such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), formerly called serum glutamic pyruvic transaminase (GPT) and serum glutamic oxaloacetic transaminase (GOT), respectively (Huang et al., 2006), are some readily available factors (perhaps the best) for assessing liver status (Yıldırım et al., 2010). In this sense, the increase in ALT levels a common symptom of advanced fatty liver disease or hepatic steatosis in 80 to 90 percent of cases. ALT increases are associated with inflammation caused by fat accumulation in the liver, abdominal obesity, metabolic syndrome, dyslipidemia, hyperglycemia, hypertension, high blood pressure, and type 2 diabetes (Hallsworth et al., 2011). Determining the most appropriate treatment for NAFLD is very important due to its increasing trend and the financial, individual, and social burden of this disease.

Exercise is an important part of the overall approach to treating fatty liver disease. In many obese individuals, weight loss can be achieved through increased physical activity (Stevanović et al., 2020). Lipid profile is characterized by an increase in triglycerides and a decrease in high-density lipoprotein (HDL) levels, which is associated with other metabolic risk factors, including abdominal obesity and insulin resistance (a major cause of fatty liver) (Lehto et al., 1997). Aerobic exercise, due to the lipolysis processes involved in aerobic energy supply, reduces plasma triglycerides and increases HDL (Thompson & Rader, 2001), which is a good way to reduce liver fat and improve liver damage indicators in patients with NAFLD (Yavari et al., 2012). Based on their experiments, researchers have reported a significant inverse relationship between fitness and cardio-respiratory scores and liver fat in NAFLD patients (Nikroo et al., 2011; Zelber-Sagi et al., 2011). Resistance training can improve muscle mass, strength, and power; increase insulin sensitivity and daily energy expenditure (Dunstan et al., 2002); therefore, it is used as a health-promoting tool in the elderly and obese.

Recently, much thought has been given to the role of natural products in the treatment of various diseases such as diabetes, different microbial strains, inflammation, oxidative stress, and also cancer. Besides physical exercise for weight loss and treatment of fatty liver, the use of herbal medicines for this purpose could be a good alternative to non-toxic treatments for curing some diseases (Tiptiri-Kourpeti et al., 2019), due to their fewer side effects among other reasons (Abdollahi et al., 2014; Lietava et al., 2019). One of these herbs is Cornelian cherry. Its scientific name is Cornus mas-land and it belongs to the genus Cornaceae. Its fruits are rich in anthocyanins such as cyanidin, peonidin, pelargonidin, and petunidin, and also contain bioflavonoids, vitamin C, and ursolic acid. The anthocyanins lead to increased insulin secretion (pelargonidin increases insulin secretion up to 1.4 times), amelioration of insulin resistance, and improvement of hyperlipidemia (Dayar et al., 2020). Cornuse mas is used in Chinese and Iranian traditional medicine to treat diabetes and high blood lipids and their complications (Abdollahi et al., 2014; Lietava et al., 2019).

Due to all the aforementioned facts, the purpose of the present study was to explore the effects of physical exercise (aerobic and resistance training), intake of Cornuse mas, and their combination on the lipid profile (triglycerides, HDL, low-density lipoprotein [LDL], cholesterol), metabolic parameters (glucose, creatinine, c-reactive protein [CRP], urea), and liver enzymes (ALT, AST) in obese male rats. We hypothesized that the combination of physical exercise and Cornuse mas extract will improve to a greater extent the assessed parameters, with no big difference between the aerobic and resistance exercise.

MATERIAL AND METHODS

Participants

49 male Wistar rats (age: six weeks; average weight: 200g) were randomly assigned to seven experimental groups: [1] control (n = 7) following a normocaloric diet and no treatment; [2] hypercaloric (n = 7) following a high-fat diet and no treatment; [3] aerobic exercise (AE, n = 7); [4] resistance exercise (RE, n = 7); [5] Cornus mas extract intake (C, n = 7) following no exercise program; [6] Cornus mas extract intake in combination with aerobic exercise (CAE, n = 7); [7] Cornus mas extract intake in combination with resistance exercise (CRE, n = 7). All the groups were homogeneous in terms of number, breed, age, and weight. All ethical considerations and working protocols of this study were approved by Shahrekord's committee for monitoring Laboratory Animal Rights in Medical Sciences University with code 2-1-94.

The rats were kept for 12 weeks in the Shahrekord University Animal Laboratory Medical Sciences at a temperature between 22 and 27ºC. The room was illuminated in a controlled manner (12 hours off and 12 hours on). Six weeks were used to induce the fatty liver in the rats and six weeks to carry out the intervention. The hypercaloric, AE, RE, C, CAE, and CRE groups (n = 42) were induced with hyperlipidemia and hypercholesterolemia by diet (see below "*Diet formulation*" section) and 7 rats remained healthy following a normocaloric diet (controls).

Intervention

Diet formulation

During the six weeks before the intervention, the selected 42 rats were daily fed by gavage with a specific diet to induce hyperlipidemia and hypercholesterolemia. More concretely, Persintra-M was prepared from egg yolk to induce hyperlipidemia (1g of cholesterol, palm oil of 80% purity, and intralipid fluid per 100g of egg yolk) and 25mg of cholesterol were condensed to 2ml to induce hypercholesterolemia. In addition, the rat's meal was brought to 1% cholesterol and 20% sugar using palm oil, sugar, and cow fat.

During the intervention period (six weeks) only the hypercaloric group continued with the above explained hypercaloric diet and the rest of the groups switched to a normocaloric animal diet. The controls remained all the 12 weeks with a normocaloric diet. Water and food was freely available to all the rats throughout the study.

Aerobic training program

The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the aerobic training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention.

To stimulate the rats to walk, an auditory stimulus (tapping on the wall of the treadmill) was used. For this purpose, a low-voltage electrical stimulus was initially used together with an audio stimulus. After the rats were conditioned to two stimuli simultaneously, the single audio stimulus was used in later sessions to comply with the ethics of animal experimentation.

Table 1. Aerobic training program.

	Adaptation phase		**Overload phase**		**Maintenance phase**	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Speed	8 m/min	12 m/min	18 m/min	20 m/min	20 m/min	20 m/min
Time	10 min	20 min	30 min	40 min	40 min	40 min

Resistance training program

A one-meter ladder with 50 steps separated by 2cm, a width of 50cm, and an inclination of 85º was used for the resistance training. A load pouch attached to the proximal portion of the rats' tail (1-2cm after the hair growth point) was used as resistance. Prior to the six weeks of the resistance training program, a familiarization period without external weight was carried out. The number of repetitions of the training program (see Table 2) in each session ranged from 8 to 12 repetitions, with a two-minute rest in between; each repetition had to be completed in 8 seconds. At the beginning and end of the exercise, 5 repetitions without weight were used as warm-up and cool-down. The rats were placed at the bottom of the ladder and were motivated to climb the ladder by gently pushing on their backside. No rewards or abnormal stimuli such as electrical stimulation, cold water, or air pressure were used in this study.

Table 2. Resistance training program.

	Adaptation phase		**Overload phase**		**Maintenance phase**	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Rats' weight average	240g	252g	260g	266g	277g	287g
Ratio overload per bodyweight	50%	75%	85%	95%	110%	120%
Average weight used	120g	189g	221g	253g	305g	344g

Cornus mas extraction and use

Samples of Cornus mas were procured from reputable suppliers and used after confirmation from the Center for Herbal Medicine Research of the University. The plant was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and dissolved in 2 litres of alcohol (70%) and water (30%). The solution was left to stand for 72h at laboratory temperature. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400mg of Cornus mas per one kilogram of body weight was administered daily to the rats by gavage.

Measures

After the six-week intervention, another session was used to extract the blood samples. The rats were anesthetized by an intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from their hearts and were introduced in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. At this point, the serum was transferred using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) to a BT3000 analyser (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea), and liver enzymes (ALT, AST) were calculated.

Data analysis

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. Only the triglycerides complied with normality and homoscedasticity assumption among the seven groups. Therefore, a one-way analysis of variance (ANOVA) for the triglycerides and Kruskal Wallis testing for the non-normally distributed variables were conducted. The effect size was reported as the eta squared (η^2) where $0.01 < \eta^2 < 0.06$ constitutes a small effect, $0.06 \leq \eta^2 \leq 0.14$ a medium effect and $\eta^2 > 0.14$ constitutes a large effect. After this, paired post-hoc tests with Tukey adjustments for the parametric analysis and with no adjustment for the non-parametric evaluated significant differences. A 95% confidence level (significance $p < .05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

RESULTS

Twelve weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The ANOVA and the Kruskal Wallis test indicated that significant differences existed among the study variables, with AST: $H(6) = 29.01$, $p < .001$, $\eta^2 = 0.55$; ALT: $H(6) = 18.09$, $p = .006$, $\eta^2 = 0.29$; CRP: $H(6) = 24.20$, $p < .001$, $\eta^2 = 0.43$; creatinine: $H(6) = 35.29$, $p < .001$, $\eta^2 = 0.70$; urea: $H(6) = 31.57$, $p < .001$, $\eta^2 = 0.61$; cholesterol: $H(6) = 34.13$, $p < .001$, $\eta^2 = 0.67$; glucose: $H(6) = 21.58$, $p = .001$, $\eta^2 = 0.37$; triglycerides: $F(6) = 14.78$, $p < .001$, $\eta^2 = 0.68$; LDL: $H(6) = 24.84$, $p < .001$, $\eta^2 = 0.45$ and HDL: $H(6) = 13.33$, $p = .038$, $\eta^2 = 0.18$. Tables 3 and 4 present the outcomes of the intervention in the liver enzymes and metabolic parameters.

DISCUSSION

This study aimed to assess the effectiveness of physical exercise (aerobic and resistance) and Cornus mas extract intake in improving blood parameters (lipid profile, liver enzymes, and metabolic parameters) of rats with fatty liver and obesity. For such purpose, a control group was kept healthy from the beginning and the other six groups were induced fatty liver and obesity by diet. Of these six groups, one continued having the hypercaloric diet and the other five joined different treatment programs (aerobic or resistance exercise, Cornus mas extract intake, and aerobic or resistance exercise combined with the intake of Cornuse mas extract). The most notable findings were that all the intervention groups after six weeks of treatment reverted their levels and significantly improved compared to the hypercaloric group in almost all the assessed parameters, reaching in many cases better values than the healthy group (control). These interesting results provide a strong foundation for the management and treatment of obesity and other associated conditions such as fatty liver, cardiovascular disease, metabolic syndrome, diabetes mellitus, atherosclerosis, and dyslipidemia (Dayar et al., 2020; El Hadi et al., 2019; Huang et al., 2009; Tomeno et al., 2020; Wong et al., 2016).

The outcomes presented are in accordance with previously published investigations that found improvements in different hepatic and lipidic parameters after intaking Cornuse mas extract both in rats (Alavian et al., 2014; Asgary et al., 2013, 2014) and humans with type 2 diabetes (Soltani et al., 2015). This beneficial effect of the Cornuse mas extract may be due to its content in antioxidants, phenolic compounds, and vitamins, which help in the prevention of inflammatory processes and oxidative stress associated with different metabolic and cardiovascular conditions (Abdollahi et al., 2014). What is new from this study, is the combination of the intake of Cornuse mas extract with aerobic and resistance exercises, which slightly improved (only significant for the cholesterol and glucose) the levels in almost all the variables compared to only performing the exercise programs or only intaking Cornuse mas extract.

Table 3. Levels of liver enzymes (AST/GOT and ALT/GPT) and metabolic parameters (CRP, creatinine, and urea) in all experimental groups (all n = 7).

Group	AST	ALT	CRP	Creatinine	Urea
	94.14±9.56^{2,4,6,7}	39.71±6.77$^{(3)}$	16.42±1.54	0.72±0.04^{3,4,5,6,7}	34.42±3.59*
1	[85.29-102.98]	[33.44-45.98]	[14.99-17.85]	[0.68-0.77]	[31.10-37.75]
(Control)	Median: 97.00	Median: 41.00	Median: 17.00	Median: 0.70	Median: 34.00
	IQR: 15.00	IQR: 11.00	IQR: 0.80	IQR: 0.10	IQR: 7.00
	161.00±25.60*	74.57±17.62^{1,4,5,6,7}	23.15±0.79*	1.01±0.13^{3,4,5,6,7}	60.85±15.29^{4,5,6,7}
2	[137.46-184.82]	[58.27-9087]	[22.41-23.89]	[0.88-1.13]	[46.71-74.99]
(Hyper)	Median: 150.00	Median: 68.00	Median: 23.20	Median: 1.00	Median: 53.00
	IQR: 45.00	IQR: 20.00	IQR: 0.80	IQR: 0.10	IQR:22.00
	83.85±14.39$^{(4)}$	56.71±18.04$^{(4),7}$	17.04±1.27$^{(5)}$	0.44±0.07	48.71±2.62^{5,7}
3	[70.54-97.16]	[40.02-73.40]	[15.85-18.22]	[0.37-0.51]	[46.28-51.14]
(AE)	Median: 86.00	Median: 60.00	Median: 17.20	Median: 0.50	Median: 49.00
	IQR: 24.00	IQR: 34.00	IQR: 3.00	IQR: 0.10	IQR: 4.00
	65.85±11.82	42.42±11.02	17.24±0.975	0.47±0.07	45.28±4.27
4	[54.92-76.79]	[32.22-52.62]	[16.34-18.14]	[0.40-0.54]	[41.33-49.23]
(RE)	Median: 66.00	Median: 39.00	Median: 16.80	Median: 0.50	Median: 45.00
	IQR: 29.00	IQR: 8.00	IQR: 1.30	IQR: 0.10	IQR: 9.00
	79.57±19.90	47.51±35.00	15.61±0.93	0.42±0.07	42.85±3.18
5	[61.16-97.98]	[32.61-62.41]	[14.75-16.47]	[0.35-0.49]	[39.91-45.80]
(C)	Median: 88.00	Median: 45.00	Median: 15.80	Median: 0.40	Median: 42.00
	IQR: 23.00	IQR: 35.00	IQR: 1.60	IQR: 0.00	IQR: 4.00
	71.42±14.03	45.00±10.67	16.12±1.73	0.42±0.07	47.14±6.54
6	[58.44-84.40]	[35.12-54.87]	[14.52-17.72]	[0.35-0.49]	[41.09-53.19]
(CAE)	Median: 79.00	Median: 43.00	Median: 16.20	Median: 0.40	Median: 47.00
	IQR: 29.00	IQR: 24.00	IQR: 3.00	IQR: 0.10	IQR: 8.00
	63.57±22.04	39.14±10.38	15.47±1.76	0.40±0.00	42.71±3.45
7	[43.18-83.95]	[29.54-48.74]	[13.84-17.10]	[0.40-0.40]	[39.52-45.90]
(CRE)	Median: 61.00	Median:39.00	Median: 15.50	Median: 0.40	Median: 45.00
	IQR: 48.00	IQR: 8.00	IQR: 3.40	IQR: 00	IQR: 7.00

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference (p < .05) with all the rest of the groups;* ^{1,2,3,4,5,6,7}*: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5 < p < 1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornuse mas intake group; CAE: Cornuse mas intake in combination with aerobic exercise; CRE: Cornuse mas intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.*

Regarding the effects of the exercise on the assessed parameters, a six-week program of both exercise methodologies was enough to improve the values of almost all the assessed variables, as happened in previous research (de Piano et al., 2012; Carbajo-Pescador et al., 2019; Slentz et al., 2011; Shamsoddini et al., 2015). On the other hand, one study reported inconsistent results in this regard (Barani et al., 2014). It is worth mentioning that resistance exercise showed trends of further improving liver enzymes and HDL than aerobic exercise. In fact, the six-week aerobic training program was not enough to significantly modify the ALT, urea, and HDL levels. These positive results associated with the exercise could be due to its regulator effect on insulin resistance and glucose levels. In this regard, insulin resistance is associated with fatty liver and metabolic diseases. The main mechanisms of insulin resistance are negative regulation of deep insulin receptors and a decrease in signalling caused by excessive signalling of free fatty acids in the bloodstream (Akyüz et al., 2007). To perform muscle contractions during the exercise the levels of the glucose transporter type 4 protein, secondary messengers (Richter & Hargreaves, 2013), and insulin-1 receptors rise to increase glucose uptake in the skeletal muscle (Chibalin et al., 2000). As a result, glucose is better absorbed, and insulin resistance is reduced. Furthermore, visceral fat represents a source of free fatty acids that can be preferentially oxidized to glucose. Reducing visceral fat by decreasing abdominal obesity may be another important benefit of exercise leading to significant improvement in metabolic indicators (Albright et al., 2000; Houttu et al., 2020). Due to all these aforementioned factors, we can state that physical exercise has a positive impact on the treatment of fatty liver and metabolic diseases.

Table 4. Levels of lipid profile in all experimental groups (all n = 7).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 (Control)	47.28±9.12^{2,3,4,5,7} [38.84-55.72] Median: 48.00 IQR: 18.00	125.00±7.18^{2} [118.35-131.64] Median: 126.00 IQR: 10.00	64.00±18.61$^{2,3,4,(5)}$ [46.78-81.21] Median: 59.00 IQR: 27.00	10.10±2.92* [7.39-12.81] Median: 9.70 IQR: 4.90	37.97±6.00^{2,3} [32.41-43.52] Median: 37.90 IQR: 12.00
2 (Hyper)	123.71±40.38$^{(3),4,6,7}$ [86.36-161.06] Median: 108.00 IQR: 71.00	216.85±29.65* [189.43-244.27] Median: 216 IQR: 57.00	142.28±24.23* [119.78-164.69] Median: 139.00 IQR: 47.00	39.05±5.29* [34.15-43.95] Median: 37.20 IQR: 9.30	28.11±6.45$^{4,(5),7}$ [22.11-34.08] Median: 30.50 IQR: 12.30
3 (AE)	81.85±5.45^{6} [76.80-86.90] Median: 80.00 IQR: 10.00	124.42±3.99 [120.73-128.12] Median: 125.00 IQR: 7.00	97.57±15.45 [83.27-11.86] Median: 99.00 IQR: 21.00	13.95±2.28 [11.83-16.06] Median: 14.20 IQR: 2.80	31.84±3.20$^{(4),7}$ [28.87-34.81] Median: 31.40 IQR: 3.70
4 (RE)	79.42±2.22 [77.37-81.48] Median: 79.00 IQR: 3.00	125.00±8.56 [117.08-132.91] Median: 125.00 IQR: 11.00	93.00±21.97 [72.67-113.32] Median: 91.00 IQR: 37.00	14.94±2.73 [12.41-17.47] Median: 15.20 IQR: 4.50	35.81±3.91 [32.19-39.43] Median: 36.30 IQR: 2.50
5 (C)	85.57±8.99^{6} [77.25-93.89] Median: 85.00 IQR: 9.00	132.42±12.24$^{(6),(7)}$ [121.10-143.75] Median: 131.00 IQR: 21.00	89.71±10.45 [80.04-99.38] Median: 87.00 IQR: 16.00	14.06±4.12 [10.24-17.88] Median: 11.40 IQR: 7.00	35.05±4.48 [30.90-39.20] Median: 36.20 IQR: 9.70
6 (CAE)	70.00±6.75 [63.75-76.24] Median: 70.00 IQR: 11.00	119.28±10.30 [109.75-128.81] Median: 121.00 IQR: 19.00	73.85±10.33 [64.29-83.41] Median: 73.00 IQR: 18.00	13.76±2.42 [11.52-16.00] Median: 14.20 IQR: 4.70	34.52±6.84 [28.19-40.85] Median: 30.80 IQR: 8.90
7 (CRE)	78.42±6.80 [72.13-84.72] Median: 81.00 IQR: 12.00	121.85±5.61 [116.66-127.04] Median: 123.00 IQR: 7.00	78.85±15.98 [64.07-93.63] Median: 81.00 IQR: 28.00	13.87±2.14 [11.89-15.86] Median: 12.80 IQR: 4.30	37.92±4.54 [33.72-42.13] Median: 36.50 IQR: 6.00

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p < .05$) with all the rest of the groups; ^{1,2,3,4,5,6,7}: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5 < p < 1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornuse mas intake group; CAE: Cornuse mas intake in combination with aerobic exercise; CRE: Cornuse mas intake in combination with resistance exercise; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

CONCLUSION

According to the results of this study, Cornus Mas extract intake in combination with aerobic or resistance training may be recommended to improve fatty liver and obesity by improving the blood lipid profile, metabolic parameters, and liver enzyme levels. Therefore, the Cornuse mas extract and the exercise may be a good alternative or adjuvant to the use of chemical medicine.

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