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Original Research

Eryngium carlinae Extract and Exercise Improve Blood Lipid Profile and Skeletal Muscle Function in Obese Rats

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Academic Editor: Paul J. Arciero

Collection: Nutrition and Exercise for Weight Loss

OBM Integrative and Complementary Medicine
2024, volume 9, issue 3
doi:10.21926/obm.icm.2403040

Received: January 08, 2024
Accepted: July 03, 2024
Published: July 10, 2024

Abstract

An excess of adipose tissue characterizes obesity; it is associated with complications such as diabetes and cardiovascular diseases due to an alteration in the lipid profile; this condition affects all tissues; even skeletal muscle is the most affected, causing its malfunction and bringing more significant consequences. Exercise has been described as one of the best treatments to combat obesity. At the same time, *E. carlinae* is a plant proven to have lipid-lowering and hypoglycemic effects, improving the function of various organs. However, its described effect has not been proven in skeletal muscle during obesity. Wistar male rats were

separated into 8 groups, 4 healthy and 4 obese, treated with exercise and *E. carlinae* extract; after 8 weeks, they were sacrificed, muscles were extracted to measure contraction force, and blood was extracted to perform biochemical tests. Both exercise and *E. carlinae* extract effectively lowered glucose, improved lipid profile, reduced visceral fat, and improved muscle function during obesity. Exercise and *E. carlinae* extract improved muscle function during obesity, concerning better utilization and lower absorption of lipids.

Keywords
Muscular fatigue; contraction force; lipidic profile

1. Introduction

According to the WHO, obesity is characterized by excess fatty tissue, causing an imbalance between energy intake and expenditure [1]. The adipose tissue excess affects the entire body. However, one of the most affected tissues is the skeletal muscle since it represents approximately 40% of the total weight of a healthy adult person and is responsible for the homeostasis of glucose and lipids, consuming up to 75% of the available energy during exercise [2-4]. A disproportionate increase in adipose tissue can lead to skeletal muscle inflammation, mitochondrial dysfunction, insulin resistance, decreased muscle mass, and fatigue resistance [5, 6], so better skeletal muscle function during obesity can lower the risks of complications such as cardiovascular disease and diabetes.

Various studies propose moderate-intensity exercise as an effective treatment for obesity since it brings multiple adaptations that improve muscle function, such as hypertrophy, increased strength and resistance to fatigue, and the secretion of biologically active substances that enhance metabolic flexibility and help glucose and lipid homeostasis [7].

On the other hand, dyslipidemia during obesity is associated with lipotoxicity and inflammation and is a causal factor for insulin resistance in skeletal muscle and type II diabetes. Moreover, lipotoxicity increases oxidative stress, further contributing to insulin resistance development [8]. In this regard, *E. carlinae* is a plant whose ethanolic extract decreases cholesterol and triglycerides and augments c-HDL in diabetic rats [9, 10]. Likewise, a hexanic extract of *E. carlinae* decreased hyperglycemia in both normoglycemic and diabetic rats and diminished oxidative stress in proteins and lipids in the liver, the kidney, and the brain. In addition, it had antioxidant activity in vitro in Saccharomyces cerevisiae cells subjected to oxidative stress by hydrogen peroxide [11]. Therefore, given the involvement of dyslipidemia and oxidative stress in lipotoxicity and insulin resistance in obesity, besides the antioxidant and hypolipemiant actions of *E. carlinae*, this study aimed to investigate if the administration of the hexanic extract of *E. carlinae* enhances the beneficial effects of exercise on muscle function and blood lipids in obese rats.

2. Materials and Methods

2.1 Biological Material and Diet

48 male Wistar rats, 12 weeks old and weighing between 300 and 350 g, were used and divided into 8 groups: control (C), obese (O), healthy treated with the extract (X), healthy exercised (E), healthy exercised treated with the extract (EX), exercised obese (OE), extract-treated obese (OX) and extract-treated exercised obese (OEX) who were kept under standard laboratory conditions and water ad libitum, healthy groups (C, E, X, EX) were fed a standard Rodent Chow® diet, which was available for free consumption. The obese groups (O, OE, OX, OEX) were subjected to a high-fat diet [12] containing 50% standard Rodent Chow® and 50% fat (Table 1) for 8 weeks. All procedures were carried out under the technical specifications for the production, care, and handling of animals (NOM-062-ZOO-1999, Ministry of Agriculture, Mexico) and were approved by the Institutional Committee for the Use and Care of Animals of the Instituto de Investigaciones Químico Biológicas of the Universidad Michoacana de San Nicolás de Hidalgo (Number 2018-06; April 2018).

Table 1 Nutritional composition of rodent chow diet and high-fat diet (the Mexican equivalent of food system).

	Standard rodent chow® diet	High-fat diet
Caloric content	**336 cal/100 g**	**649.25 cal/100 g**
Protein	**28,507%**	**14.05%**
Fat	**13,496%**	**69.5%**
Carbohydrates	**57,996%**	**21.4%**

2.2 Collection and Preparation of the Hexanic Extract of Eryngium carlinae

The aerial part of *Eryngium carlinae* plants was collected in Morelia, Michoacán, at coordinates 19°38'02.0" N 101°16'14.0" E in an open field by the side of the road. It was identified by Miguel Angel Bello-Gonzalez, PhD (Faculty of Agrobiology, Universidad Michoacana de San Nicolás de Hidalgo). A voucher specimen was deposited at the biology faculty herbarium of the Universidad Michoacana de San Nicolás de Hidalgo (no. 15214). The name of the plant Ethics Statement was verified in "World Flora Online" (www.worldfloraonline.org). The flowers were separated from the stems and leaves of the fresh plant and allowed to dry for two weeks. The dry material was weighed and stored in plastic containers under refrigeration at -4°C for later use.

The dry material was macerated in n-hexane (1:10 ratio) for 7 days after it was filtered, discarding the solid material and storing the liquid, concentrated in a rotary evaporator at 60°C. Once the solvent was evaporated and the pure extracts were obtained, it was dissolved in dimethyl sulfoxide (DMSO) at 50 mg of extract per ml of DMSO. This solution was used as a stock, and deionized water was later added to the solvent at a 2% concentration. The hexanic extract of *Eryngium carlinae* was administered to the corresponding groups at 30 mg/kg of weight of each rat for 60 continuous days.

2.3 Exercise Protocol

The rats exercised on a treadmill for 8 weeks, 5 days a week; in addition to a week of physical conditioning, the protocol consisted of moderate-intensity training with a gradual increase in time and distance each week. The protocol is shown in Table 2.

Table 2 Moderate intensity exercise protocol applied for 8 weeks, 5 days a week.

Exercise protocol per week	
Week 1	10 m/min for 10 min
Week 2	10 m/min for 15 min
Week 3	10 m/min for 15 min 17 m/min for 5 min
Week 4	10 m/min for 15 min 17 m/min for 10 min
Week 5	10 m/min for 15 min 17 m/min for 10 min 22 m/min for 5 min
Week 6	10 m/min for 20 min 17 m/min for 10 min 22 m/min for 5 min
Week 7	10 m/min for 15 min 17 m/min for 15 min 22 m/min for 5 min
Week 8	10 m/min for 15 min 17 m/min for 15 min 22 m/min for 5 min

2.4 Muscle Extraction

Once the experimental stage was over, the animals were sacrificed. The soleus and extensor digitorum longus (EDL) muscles were removed from the right limb and placed in a Petri dish covered with clear Sylgard© resin with Krebs-Ringer buffer (118 mM NaCl, 4.75 mM KCl, 1.18 mM $MgSO_4$, 24.8 mM $NaHCO_3$, 1.18 mM KH_2PO_4, 2.08 g/L, pH 7.4) where they were prepared for stress tests (removal of connective tissue).

2.5 Stimulation for Fatigue Induction and Force Development

The soleus muscle and EDL were mounted in an isometric tension recording chamber; one of its ends was fixed to the bottom of the chamber, while the other end was attached to the hook of an optical transducer (World Precision Instruments, USA), which through an amplifier (World Precision Instruments, USA) and an analog-digital interface (World Precision Instruments, USA) allowed to acquire the muscular tension generated by each muscle through the MDAC software (World Precision Instruments, USA). The stimulation protocol was applied with platinum electrodes immersed in the recording chamber, using a stimulator (Grass, USA) that applied pulses of 100 Volts,

300 ms duration, and a frequency of 45 Hz for soleus and 50 Hz for EDL. The fatigue time was measured in seconds from the beginning of the stimulation until the tension decreased by 60-70% of the maximum tension reached.

2.6 Determination of Lipids in Blood Serum

At the end of the treatments and after sacrifice, blood serum was obtained from each rat after a 12 h fast for subsequent measurement of the lipid profile by enzymatic methods with VITROS Chemistry Products kits (Ortho Clinical Diagnostics Inc. Rochester, NY, USA). According to the manufacturer's instructions.

2.7 Statistical Analysis

The results were expressed as the mean ± the standard error of the independent experiments using samples from different animals; the statistical differences of the data were determined by T-tests that allowed comparison between the most important groups. Statistically significant differences were defined as $p \leq 0.05$.

3. Results

3.1 Effect of E. Carlinae Extract and Exercise on Weight, Glucose, and Visceral Fat in Obese Rats

Glucose (Figure 1A) was significantly increased in the obese (O) group, and the obese group was treated with exercise (OE) compared to the healthy control group (C). However, the treatment with extract (OX) and the mixture of exercise with extract (OEX) efficiently reduced glucose levels in obese rats. Glucose levels also decreased in healthy rats treated with exercise only (E) or combined exercise plus the extract (EX). In the weight at the end of the treatments (Figure 1B), a significant increase was observed in the O group, and the treatment of obese rats with exercise, the extract, or the extract plus exercise (OEX) did not modify this outcome. Regarding visceral fat (Figure 1C), the levels in the O group were several-fold higher than in the C group. The treatments with exercise or extract alone, or exercise plus the extract, were equally effective in reducing the amount of visceral fat in obese rats, as the OE, O, and OEX groups underwent a ~40% reduction in this parameter compared to the O group. Likewise, the exercise or exercise plus extract treatment also decreased visceral fat in healthy rats compared to the C group.

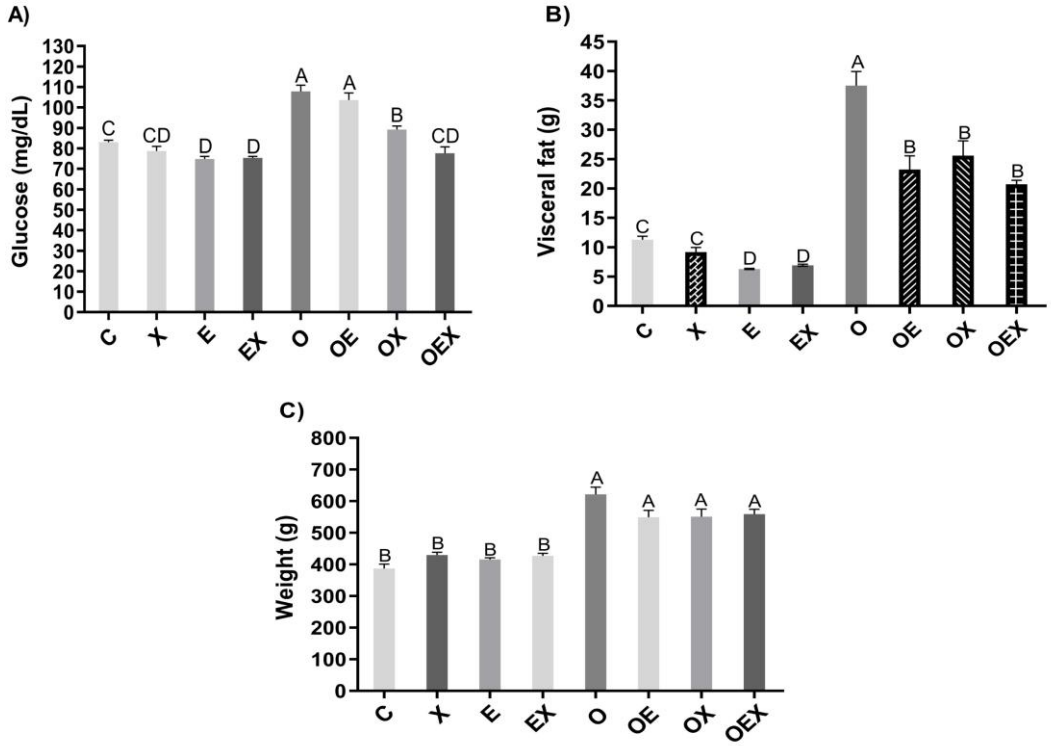

Figure 1 Effects of exercise*, E. carlinae* extract, and exercise plus *E. carlinae* extract in fasting serum glucose (1A), final weight (1B), and visceral fat (1C) in obese rats. (n = 6; data are presented as mean ± standard error). The letters at the top of each bar indicate statistically significant differences between groups ($p \leq 0.05$). T-test analysis. C, controls; X, extract; E, exercised; EX, exercised with extract; O, obese; OE, exercised obese; OX, extract-treated obese; OEX, extract-treated exercised obese.

3.2 Effects of E. Carlinae Extract and Exercise on Maximal Tension, Total Tension, and Time to Fatigue of EDL and Soleus Muscles

Figure 2 shows the effects of the *E. carlinae* extract and exercise in the function of both the soleus (Figure 2A) and EDL (Figure 2B) muscles, respectively. It is observed that there is a decrease in both the maximal tension (black bars) and total tension (gray bars) in the O group in comparison to the C group in both the soleus (panel A) and EDL (panel B) muscles, indicating an overall loss of muscle strength. As expected, the treatment with exercise increased the muscle strength in both types of muscles in healthy rats, while the extract diminished the muscle strength in the soleus and had no effect on the EDL muscle of healthy rats. The adverse effects in muscle strength in the soleus of the obese rats were entirely prevented either by applying the exercise protocol, the treatment with the extract, or the combination of exercise plus the extract as observed in the OE, OX, and OEX groups, respectively. In contrast, the decrease in muscle strength in the EDL muscle of the O group was partially recovered only by 55% in the OE, OX, and OEX groups (Figure 2B).

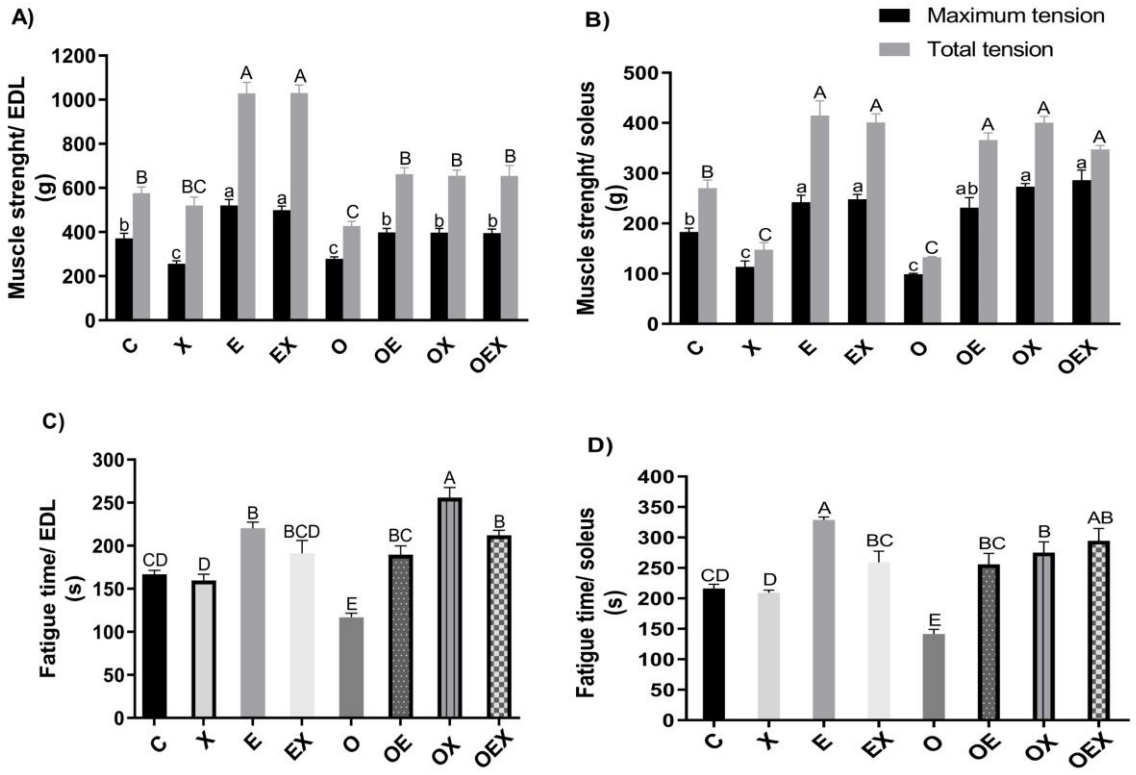

Figure 2 Effect of *E. carlinae* extract and exercise on soleus muscle strength development (2A) and EDL (2B). Effect of *E. carlinae* extract and exercise on soleus muscle fatigue time (2C) and EDL (2D). (n = 6; data are presented as mean ± standard error). The letters at the top of each bar indicate statistically significant differences between groups ($p \leq 0.05$). T-test analysis. C, controls; X, extract; E, exercised; EX, exercised with extract; O, obese; OE, exercised obese; OX, extract-treated obese; OEX, extract-treated exercised obese. Black bars in panels A and B are maximal tension; gray bars in panels A and B are total tension.

Regarding muscle fatigue, the obese rats underwent a shortening in fatigue time in both the soleus and EDL muscles of 44% (Figure 2C) and 30% (Figure 2D), respectively, compared to the C group. In the soleus and EDL muscles of healthy rats, there was an increment in fatigue time in the exercised rats and the rats with exercise plus the extract but not in healthy rats supplemented only with the extract. The shortening in fatigue time in the soleus muscle of the O group was prevented by the exercise protocol, the extract, or the combination of the exercise protocol plus the extract above of the fatigue time of the C group, as observed in the OE, OX, and OEX groups, respectively (Figure 2C).

In the EDL muscle of obese rats, there was an increase in fatigue time with the exercise protocol and rats treated with the combination of exercise plus the extract at the level of the healthy exercised rats, as observed in the OE, OEX, and E groups, respectively (Figure 2D). Moreover, the obese rats treated only with the extract underwent an increase in fatigue time even at a higher level than the healthy, exercised rats, as observed in the OX and E groups, respectively (Figure 2D). Overall, these results indicate that the exercise protocol or the extract improved the muscle

function of obese rats at a variable degree and that the combination of exercise plus the extract does not enhance the effects of exercise or the extract alone.

3.3 Effect of E. Carlinae Extract and Exercise on Serum Triglycerides and Cholesterol of Obese Rats

Obesity significantly increased the levels of triglycerides (Figure 3A), total cholesterol (Figure 3B), c-LDL (Figure 3C), and c-VLDL (Figure 3D) in blood serum compared to healthy rats; however, exercise was efficient in improving cholesterol levels in all cases where obesity was present.

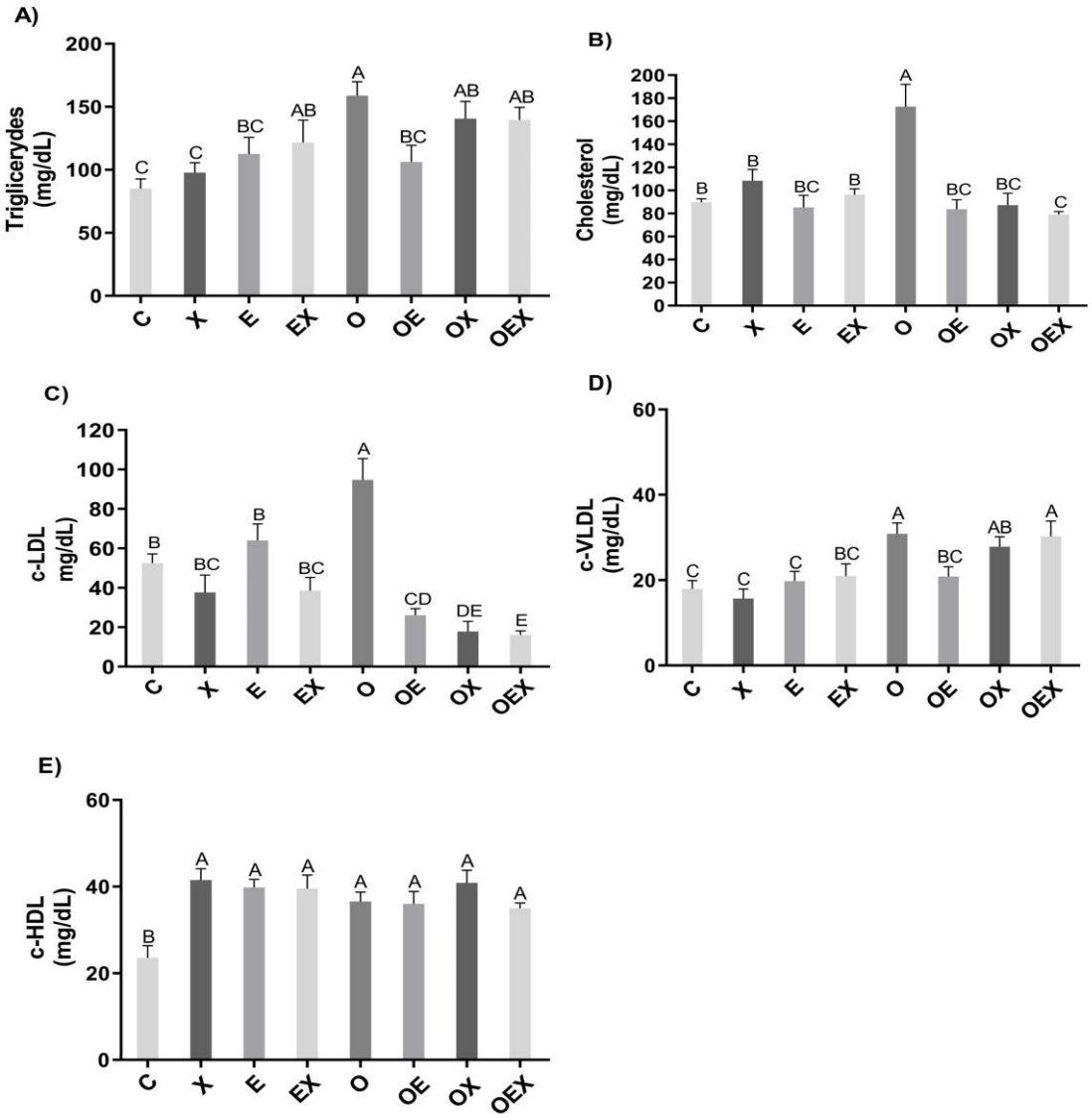

Figure 3 Effects of the *E. carlinae* extract and exercise on the levels of triglycerides (3A), total cholesterol (3B), low-density cholesterol (3C), very low-density cholesterol (3D), and high-density cholesterol (3E). (n = 6; data are presented as mean ± standard error). The letters at the top of each bar indicate statistically significant differences between groups ($p \leq 0.05$). T-test analysis. C, controls; X, extract; E, exercised; EX, exercised with extract; O, obese; OE, exercised obese; OX, extract-treated obese; OEX, extract-treated exercised obese.

E. carlinae extract significantly decreased total and LDL cholesterol levels without affecting triglycerides or c-VLDL levels in obese rats. Something similar is observed when both treatments (exercise + extract) are mixed during obesity, where the extract seems to inhibit the effects of exercise on triglycerides and c-VLDL. In the case of c-HDL (Figure 3E), there is a significant increase in all groups compared to the control.

4. Discussion

A diet rich in fat caused an increase in the weight of the rats, characteristics present in obesity since it is a component of the equation to determine the body mass index (BMI), where a BMI greater than or equal to 30 is considered obese, according to the WHO. Although the treatments were not effective in reducing body weight, it is essential to take into account that weight does not discriminate between the percentage of different tissues, such as skeletal muscle or fat, or between the location of fat in the body, which is essential since an increase in the amount of visceral fat is associated with a greater risk of suffering from cardiovascular diseases because there is a blood supply up to three times greater in visceral fat than in subdermal adipose tissue, this suggests that abdominal adipocytes constantly export fatty acids to the circulation, the high-fat diet also caused an increase in the amount of visceral fat [13]. However, moderate-intensity training decreased the amount of fat located in this area. These results agree with previous studies [14, 15], where it has been observed that moderate-intensity exercise reduces visceral fat. This is because it generates adaptations that favor fat oxidation as a source of energy.

On the other hand, the hexane extract of *E. carlinae* also significantly decreased visceral fat during obesity. This may be due to the hypolipidemic effects attributed to this plant [9]. The decrease in circulating lipids caused by the *E. carlinae* extract also decreased the amount of fatty acids available for energy storage and use in visceral adipocytes. In addition, fatty tissue is also considered an endocrine organ since it secretes various hormones called adipokines. Intramuscularly stored lipids also release these cytokines that cause skeletal muscle inflammation. Proinflammatory cytokines may also contribute to the development of insulin resistance by intervening in signaling pathways that induce phosphorylation of insulin receptor 1 (IRS1) on serine residues instead of tyrosine, thereby inhibiting glucose receptor translocation (in muscle, GLUT4 [8]). High glucose levels can occur in obesity, as observed in the present study. However, treatment with hexane extract of *E. carlinae* also effectively reduced them during pathology, which is consistent with recent studies where the hypoglycemic effect of the plant was reported [11]. This may also be a consequence of the decrease in visceral fat and circulating lipids that do not allow fat accumulation in skeletal muscle and reduce lipotoxicity.

The obese group also presented an altered lipid profile. This is one of the most common complications of obesity since when the need to store body fat exceeds the ability of the adipocyte to function normally, and fatty acids are released into the bloodstream. Excessive release of free fatty acids, as well as dyslipidemia in obesity, is associated with increased visceral fat and insulin resistance characterized by hyperglycemia and hyperinsulinemia [16]. Exercise was found to be effective in reducing lipidemia during obesity. This fact agrees with the results of recent studies [17], where it was shown that obese individuals subjected to both moderate-intensity training and high-intensity interval training had an improvement in the lipid profile by decreasing LDL and VLDL; however, they did not find improvements in triglycerides as was found in the present study.

It is known that resistance training can activate lipoprotein lipase (LPL), which promotes the breakdown of triglycerides (TG) and TG-rich lipoproteins such as VLDL-c, providing additional substrates for HDL-c synthesis, thereby, in turn triggers the decrease in the plasma concentration of LDL-C, in addition to this, exercise can also decrease the catabolism of HDL-C, further increasing the concentration of this lipoprotein [18]. On the other hand, exercise can increase the expression of mitochondrial proteins, as well as enzymes that participate in β-oxidation, the Krebs cycle, and the electron transport chain, increasing the respiratory capacity of cells by up to 40%, substantially improving the ability to oxidize fatty acids, ketones, and pyruvate. Furthermore, these same skeletal muscle adaptations to exercise allow less dependence on carbohydrate oxidation for energy and better utilization of fatty acids [19]. These adaptations could contribute to the decline in total cholesterol sterol, VLDL-c, LDL-c, and triglycerides that were observed in the obese group that was exercised for 8 weeks. On the other hand, hexane extract of *Eryngium carlinae* effectively reduced total cholesterol and LDL-C, but not triglycerides and VLDL-C during obesity. It is believed that the mechanism of action of this plant to reduce lipidemia is through the ABCG5 and ABCG8 receptors in the intestine and liver [20]. These proteins form a heterodimer that functions as a reverse cholesterol transporter; in the intestine, it opposes the absorption of cholesterol and phytosterols from the diet, taking them back to the intestinal lumen for elimination through feces, while in the liver, it contributes due to the elimination of cholesterol by bile secretion, this represents 70% to 90% of biliary cholesterol secretion [21]. However, the ABCG5 and ABCG8 transporters do not transport triglycerides (only cholesterol), so VLDL-c, which is made up mainly of triglycerides that it transports from the liver, where it is synthesized, to the organs and tissues, was not affected. When the extract was administered during obesity, increased lipoprotein (c-VLDL) in the blood can also increase triglyceride levels.

Obesity decreases the contraction force of skeletal muscle. It causes more significant fatigue because a high-fat diet has been observed to promote muscle atrophy and muscle proteolysis due to an increase in the rate of atrophic factors such as atrogin-1/MAFbx and MURF1. In addition, the infiltration of lipids into muscle fibers during obesity does not allow adequate muscle contraction and causes lipotoxicity. On the other hand, there is inflammation of the skeletal muscle due to the high concentration of lipids stored intramuscularly that they release. Constantly proinflammatory adipokines in the muscle lead to the infiltration of immune system cells, oxidative stress, and lipid oxidation, reflected in the loss of strength and fatigue of skeletal muscles [7, 8, 22]. Treatment with moderate-intensity exercise considerably improved these parameters in both muscles in both the healthy and obese groups. Adaptations achieved with exercise have been described at the systemic and muscular level, resulting in better skeletal muscle performance even during pathologies such as obesity. These adaptations can translate into skeletal muscle hypertrophy by activating insulin-like growth factor 1 (IFG-1). Exercise can also activate AMPK, a metabolic sensor responsible for turning anabolic and catabolic processes on or off. Another vital function of skeletal muscle enhanced by exercise is the secretion of anti-inflammatory cytokines such as IL-10, IL-6, and adiponectin that counteract inflammation caused by adipose tissue.

Exercise activates transcription factors that promote the expression of mitochondrial proteins and enzymes that participate in β-oxidation, the Krebs cycle, and the electron transport chain, improving the oxidation of acids stored in the muscle. Furthermore, exercise promotes insulin-independent glucose uptake in skeletal muscle [6, 22-24]. *E. carlinae* treatment was also effective in improving the contraction strength of the EDL and soleus and improving the time to fatigue of

both muscles in obese rats. However, to date, the effects of extracts of this plant on skeletal muscle have not been described. However, beneficial effects have been obtained in other organs, such as improving lipid peroxidation and protein carbonylation in the liver, kidneys, and brain of diabetic rats [11]. It has also been described that this plant has anti-inflammatory effects thanks to the increase in the production of IL-10 [25]. This anti-inflammatory cytokine activates the ERK transcription factor and negatively regulates the production of TNF-α and IL-1β. These inflammatory adipokines are very abundant in obesity. This anti-inflammatory capacity of the extract is very similar to exercise in skeletal muscle through the production of myokines such as IL-10, so we can see similar results in both treatments in both types of muscles. In addition, the *E. carlinae* extract also decreased total cholesterol and LDL-C in blood serum, which may contribute to the good results of the improvement in contraction force and fatigue resistance time of both muscles. A decrease in these parameters decreases the bombardment of lipids received by the muscle, thus reducing lipotoxicity and local inflammation caused by lipids stored intramyocellular and improving glucose absorption and insulin resistance [22].

Exercise should never be discarded from the comprehensive treatment of obesity since by doing it, multiple benefits are obtained beyond muscular health, such as better cardiopulmonary health, a lower risk of suffering from comorbidities, and a lower risk of suffering from a heart attack. However, It is challenging to maintain adherence to exercise when you suffer from obesity since multiple factors intervene in regular exercise, such as excess weight and difficulty moving, low confidence, and lack of time, among others [26]. Although in the present study, potential effects of the benefits of the extract were found in conjunction with exercise during obesity, it was shown that they could be used together, obtaining good results, making the extract a more straightforward method to follow to maintain good health, while the subject is living with obesity, achieve good adherence to exercise.

5. Conclusions

Exercise and *E. carlinae* extract improved muscle function of obese rats due to a decrease in hyperlipidemia and hyperglycemia. *E. carlinae* extract is a promising treatment for obesity that could be used as an adjunct while building good exercise adherence.

Author Contributions

Conceptualization, R.M.P., A.S.M., and K.M.M.C.; methodology, K.M.M.C., M.G.B., D.J.P.M., and O.O.A.; validation, R.M.P., A.S.M., and K.M.M.C.; formal analysis, R.M.P., A.S.M., C.C.R., A.R.R.O., and K.M.M.C.; investigation, R.M.P., A.S.M., and K.M.M.C.; resources, R.M.P., A.S.M. A.R.R.O., and C.C.R.; data curation, R.M.P., A.S.M., and K.M.M.C.; writing—original draft preparation, R.M.P., A.S.M., and K.M.M.C.; writing—review and editing, R.M.P., A.S.M., and K.M.M.C.; supervision, R.M.P., A.S.M. and K.M.M.C.; project administration, R.M.P., A.S.M. and K.M.M.C.; funding acquisition, R.M.P., A.S.M. and C.C.R. All authors have read and agreed to the published version of the manuscript.

Funding

This research was partially funded by Coordinación de la Investigación Científica, Michoacana de San Nicolás de Hidalgo, R.M.P. CIC-UMSNH2019-2022; A.S.M. CIC-UMSNH2019-2022.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

All data has been included in the document.

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