

RESEARCH ARTICLE

The effect of *Cornus mas* fruit extract consumption on lipid profile, glycemic indices, and leptin in postmenopausal women – A randomized clinical trial

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Menopause, which occurs following a declined ovarian activity and reduced estrogen levels, can lead to long-term changes in lipid and glycemic profiles and increases the risk of cardiovascular disease and osteoporosis. Cornelian cherry (*Cornus mas*) is rich in phytochemicals and antioxidants, which appears to be useful in reducing the postmenopausal complications. This interventional, double-blinded, randomized clinical trial carried out on 84 menopausal women aged 45–60 years old. They were randomly divided into two groups. The treatment group received three capsules of 300 mg of *Cornus mas* extract (CME), and control group received three capsules of 300 mg of starch powder per day for 8 weeks. Then, BMI, waist circumference, glycemic indices, lipid profile, serum apoproteinase, apoprotein B100, fibrinogen, and leptin were measured. The dietary intakes were evaluated using 24-hr dietary recall questionnaire. The consumption of CME in comparison with the control group resulted in a significant reduction in weight, body mass index, waist circumference, LDL to HDL ratio, total cholesterol to HDL ratio, and fibrinogen. There was also a significant increase in HDL and ApoA1 levels in the treatment group. Furthermore, there was a significant decrease in BMI, waist circumference, fasting insulin, and insulin resistance index after 8 weeks of using CME. Summing up the results, it can be concluded that CME can have possible effects on decreasing BMI, waist circumference, and improving some aspects of lipid profile and glycemic indices in postmenopausal women.

KEYWORDS

Cornus, insulin resistance, leptin, lipidemia, menopause

1 | INTRODUCTION

Natural menopause is defined as a permanent menstrual cessation due to the lack of follicular activity of ovaries, which occurs 12 months after the last menstruation, without any physical or pathological cause (Rajaeefard, Mohammad-Beigi, & Mohammad-Salehi, 2011). Due to the increased rate of life expectancy in women from 47–50 years to

82–85 years old, in some countries (Kian, Golian, & Mehran, 2002), symptoms and complications of menopause and the management of them have attracted scientists' attention, because menopause is related to multiple diseases and can affect the women's quality of life. (Al-Azzawi, 2001).

Menopausal complications are caused by estrogen deprivation and can lead to cardiovascular disease, osteoporosis, atrophic changes,

Alzheimer's, cognitive disorders, and vasomotor symptoms (Chamberlain & Bowen-Simpkins, 2000). This condition can result in dyslipidemia by increasing the amount of LDL cholesterol and reducing the amount of HDL cholesterol (Saha et al., 2013). Based on previous studies, 1% increase in blood cholesterol brings about a higher incidence of CHD by 2% (Tavakkoli Darestani, Kimiagar, & Valaei, 2004). Estrogen can reduce the ratio of LDL-cholesterol to HDL-cholesterol, which can delay the progression of coronary artery disease and causes the absolute reduction in total cholesterol so in menopause status, hypoestrogenemia can increase the risk of cardiovascular disease. On the other hand, deprivation of estrogen can disrupt the modulation of growth factor and cytokines production from bone and bone marrow and result in osteoporosis (Lello, Capozzi, & Scambia, 2015). Estrogen deficiency can be responsible for glucose metabolism disorders and reduction of insulin secretion and insulin resistance. Furthermore, fibrinogen, a major factor for blood coagulation and a risk factor for cardiovascular disease, increases after menopause (DeSouza, Stevenson, Davy, Jones, & Seals, 1997).

There is a lot of evidence that polyphenols such as curcumin, resveratrol, and quercetin have potential to affect blood glucose and lipid profile. (Cherniack, 2011) Cornelian cherry with the scientific name of *Cornus mas* is a species of the Cornaceae family (Koçyiğit & Özhatay, 2006). *Cornus mas* contains a wide range of phytochemicals including tannins, phenols, organic acids, anthocyanins, and flavonoids (Deng, West, & Jensen, 2013) that major part of their functions is attributed to their phenolic compounds (Basu et al., 2010; Coates et al., 2010). The most important flavonoids in this fruit are quercetin, kaempferol, and aromadendrin. Studies have shown that quercetin and kaempferol have an important effect on estrogen receptors (Pawlowska, Camangi, & Braca, 2010). Cell culture studies have shown that polyphenols can help to improve the glycemic profile by inhibiting the alpha-glucosidase, α -amylase, and ACE-1 (angiotensin converting-enzyme inhibitor) enzymes (Basu et al., 2011). Also, anthocyanins, by preventing the formation of Proxyl nitrite and its oxidative damage, have potential to reduce the LDL oxidation and subsequently the foam cells production. Moreover, it can decrease the inflammatory mediators that have been induced by TNF α , insulin resistance, and lipid disorders that lead to cardiovascular diseases (Basu et al., 2010).

However, to the best of our knowledge, there is not any study on *Cornus mas* effects in postmenopausal women and their complications, we studied the effects of *Cornus mas* fruit extract consumption on glucose and lipid profiles and leptin in this group of patients.

2 | MATERIAL AND METHODS

2.1 | Study design

A randomized double-blind placebo-controlled trial was conducted over 8-week period in postmenopausal. The research protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC 1395.9313680004 IR), registered in the Iranian Center for Clinical Trials at www.irct.ir, IRCT201610259472N10.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were physical health, age range of 45–60 years old, lack of menstruation for at least past 12 months, lack of hormone replacement therapy for the past 6 months, not taking estrogen and medroxyprogesterone and any medications that can affect blood sugar, blood lipids, and blood pressure, at the time of admission, nonvaginal bleeding with unknown origin, absence of history of acute liver and/or kidney deficiency and inflammatory disease, no history of malignancy, thromboembolism and allergies to *Cornus mas* and its products, not using soy, not taking nutritional supplements in the last three months (multivitamin, minerals, and antioxidants), no smoking and alcohol consumption, and not following vegetarian diet. Exclusion criteria included lack of willingness to cooperate, nonacceptance of supplements (accepting less than 80%), changes in diet or physical activity for any reason, changes in the type, and amount of daily intake of medication.

2.3 | Sample size determination

Subjects were selected from women referring to Mohammadshahar Health center in Karaj. The participants included 84 postmenopausal women who had inclusion criteria. The sample size was determined based on total cholesterol, which is one of the main indicators in this study. (Tavakkoli Darestani et al., 2004) Data on dietary habits, dietary supplements, drug history, and smoking habits were obtained by face-to-face interviews by an expert.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

By the use of sample size determination formula, with the confidence level of 95% and power of 80%, and 10% drop in the number of participants, total sample size was measured 84 women.

2.4 | Intervention

Eighty four subjects were divided into two groups by using Balanced Block Randomization technique. Two groups in terms of the type of supplement intake were as follows: CME group received 900-mg *Cornus mas* extract daily as three capsules. Placebo group received 900-mg starch powder daily as three capsules. CME and its placebo were produced by the Barij Essence Pharmaceutical Company (Kashan, Iran).

Before and after the intervention, general information questionnaires, height, and weight measurements were recorded. In order to investigate variations in their food intake and to control diet-related confounding factors, 24-hr recall questionnaire (1 day) and food diary (2 days) were taken before and after the study. Also, the International physical activity questionnaire-short form (IPAQ-S) was used for recording physical activity.

Dietary intakes were analyzed by Nutritionist IV software (version 3.5.2, The Hearst Corporation, San Bruno, CA). The subjects were

asked not to alter their usual diet and physical activities throughout the study. Neither the researchers nor the patients were aware whether the patients belong to CME or placebo group.

2.5 | Measurements

The height was measured using a nonresilient SKA meter (without shoes) with a precision of 0.1 cm. Weight and body composition were measured by the Beurer scale of the BF54 toffee model with light clothing and without shoes. Body mass index was calculated for each individual, using the following equation at the beginning and end of the study and recorded in the form.

$$\text{Body mass index (BMI)} = \text{Weight (kg)} / \text{height (m)}^2$$

The waist circumference, which is the smallest circumference in the lower area of the chest and upper navel, was measured using tape measurements.

Before starting the supplementation and after 8 weeks, 10 cc of venous blood samples were taken following 12 hr of fasting. Blood serum was collected by centrifugation at 3,000 rpm; serum and plasma samples were stored at -70°C prior to biochemical measurements. Plasma glucose, triglyceride, HDL, serum cholesterol, LDL cholesterol, and total cholesterol were measured by colorimetric method with the Pars test company kit and using the Hitachi 911 autoanalyzer. The serum insulin was measured by ELISA technique using the Monobind Co. (California, United States). ApoA1 and ApoB100 were measured by ELISA technique using Zellbio kits (Ulm, Germany). The Clauss method was used to measure fibrinogen. In this method, thickened thrombin is added to the diluted plasma, thrombin converts fibrinogen to fibrin, and then the plasma clotting time is measured. The plasma clotting time is inversely related to the amount of fibrinogen in the sample, which is obtained by comparing the samples with the standard sample. Measurement of serum leptin was performed using ELISA method by use of Biovendor ELISA kit (Brno, Czech Republic).

The index of insulin resistance (HOMA-IR) and insulin sensitivity (QUICKI) was also calculated according to the following formulas (Mashavi et al., 2008):

$$\text{HOMA-IR} = \{[\text{fasting insulin } (\mu\text{U}/\text{mL})] \times [\text{fasting glucose } (\text{mmo1}/\text{1})]\} / 22.5,$$

$$\text{QUICKI} = 1 / [\log (\text{fasting insulin}, \mu\text{U}/\text{ml}) + \log (\text{fasting glucose}, \text{mg}/\text{dL})].$$

2.6 | Statistical analysis

SPSS software version 22 (IBM, Chicago) was used to analyze the data. The Kolmogorov–Smirnov test was used to determine the quantitative dependence of the normal distribution. In this study, the assessment of quantitative variables between the two groups at the beginning of the study as well as at the end of the study were performed using independent *t* test (in the case of normal data distribution) or the Mann–Whitney test. In order to compare the mean of

the quantitative variables before and after the intervention, *t*-paired *t* test (if data distribution was normal) or Wilcoxon test was used in each group. Qualitative variables such as physical activity were analyzed by Chi-square test. All values were reported based on (mean \pm S.E.M). The *p* value of $<.05$ was considered as a significant level of statistical significance.

3 | RESULTS

A total of 99 postmenopausal women aged 45 to 60 years old entered the study of which 84 patients completed the study; 15 subjects were excluded of which nine were from the group that used CME (five were uncooperative, one had gastrointestinal symptoms, one underwent angiography, and one of them had waist fracture), and six were from the group that took Placebo (four were uncooperative, one did not answer, and one did not take the supplements; Figure 1).

3.1 | Anthropometric characteristics

Anthropometric characteristics of the participants are presented in Table 1. As the results show, there is no statistically significant difference between the two groups at the beginning of the study.

At the end of the eighth week, there was a significant decrease in weight, waist circumference, and body mass index within CME group and also between the groups ($p = .01$). There were no statistically significant differences between anthropometric variables before and after 8 weeks in the placebo group.

3.2 | Glycemic indices

There was no statistically significant difference in fasting blood glucose, fasting insulin, insulin resistance index (HOMA-IR), and insulin sensitivity index (QUICKI) after 8 weeks between the two groups (Table 2). Only insulin serum concentration and insulin resistance index (HOMA-IR) showed a statistically significant decrease in the CME group ($p = .01$).

3.3 | Serum lipids

In accordance with Table 3, there was no statistically significant difference in mean of triglyceride, LDL-cholesterol and total cholesterol before and after intervention between the groups ($p = .2$ for TG; $p = .9$ for LDL-c; and $p = .57$ for Total-chol). In the group receiving CME, the mean HDL cholesterol after 8 weeks of intervention was significantly higher before the beginning of the study ($p = .001$). Also, changes in HDL cholesterol levels were significant between the groups before and after 8 weeks of intervention ($p = .002$). The mean serum lipoprotein level of ApoA1 increased significantly in the group receiving CME ($p = .00$), but there was no significant difference in the mean ApoA1 lipoprotein level in the placebo group before and after 8 weeks of intervention. Comparison of ApoA1

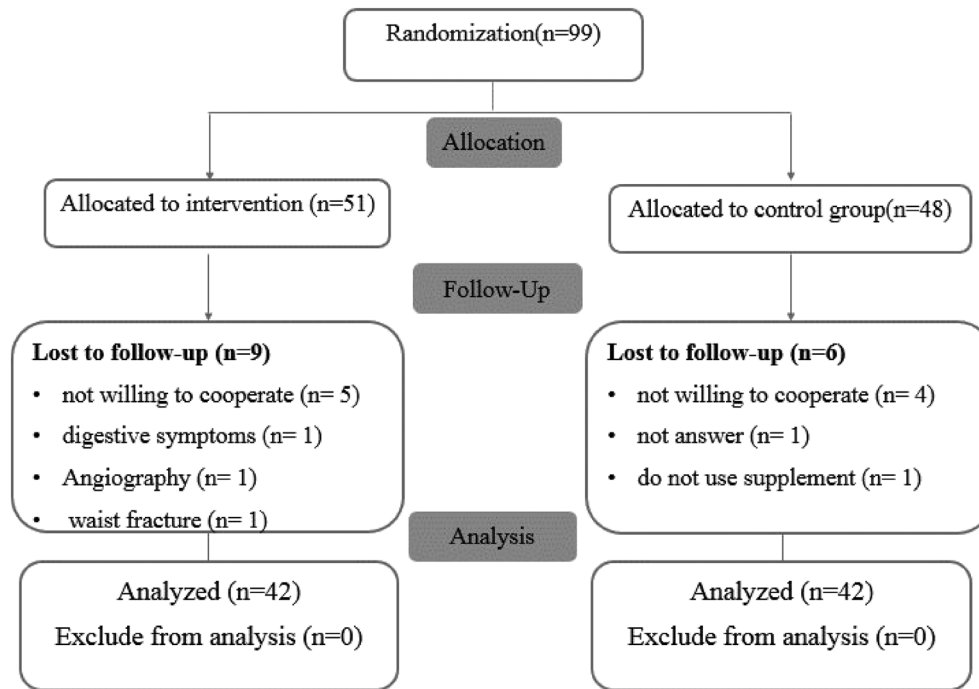


FIGURE 1 Consort flow diagram

TABLE 1 Comparison of mean and standard deviation of anthropometric indices between the two groups

Variable	CME (Mean ± S.E.M)			Placebo (S.E.M ± Mean)			p value ^a	p value ^b
	Before	After	Change	Before	After	Change		
Weight	74.81 ± 1.87	74.12 ± 1.81	-0.68 ± 0.22	71.87 ± 1.71	71.97 ± 1.68	0.09 ± 0.22	.38	.01
BMI	30.81 ± 0.73	30.54 ± 0.71	-0.27 ± 0.09	29.56 ± 0.79	29.60 ± 0.78	0.03 ± 0.09	.37	.01
WC	107.28 ± 1.70	105.07 ± 1.56	-2.21 ± 0.38	106.4 ± 1.75	105.59 ± 1.62	-0.8 ± 0.43	.81	.01

Note. Data are presented as means ± SEM. *p* value <0.05 is significant.

Abbreviations: BMI, Body Mass Index; WC, waist circumference.

^aBetween groups (independent *t* test).

^bCompare changes between groups (independent *t* test).

TABLE 2 Comparison of mean and standard deviation of blood glucose indexes between two groups

Variable	CME (Mean ± S.E.M)			Placebo (Mean ± S.E.M)			p value ^a	p value ^b
	Before	After	Change	Before	After	Change		
FBS	91.49 ± 0.98	90.81 ± 0.89	-0.67 ± 0.63	90.26 ± 1.04	90.42 ± 1.06	0.16 ± 0.64	.77	.35
Ins	4.76 ± 0.49	4.64 ± 0.49	-0.11 ± 0.04	5.7 ± 0.49	5.54 ± 0.50	-0.15 ± 0.19	.20	.85
HOMA-IR	1.08 ± 0.74	1.04 ± 0.72	0.04 ± 0.01	1.27 ± 0.71	1.25 ± 0.76	0.02 ± 0.04	.18	.72
QUICKI	0.4 ± 0.01	0.41 ± 0.01	0.002 ± 0.00	0.38 ± 0.00	0.38 ± 0.00	0.005 ± 0.00	.11	.53

Note. Data are presented as means ± SEM. *p* value <.05 is significant.

^aBetween groups comparison (independent *t* test or Mann-Whitney test).

^bCompare changes between groups (independent *t* test).

lipoprotein changes showed significant difference between two groups within intervention and placebo (*p* = .003). ApoB100 lipoprotein did not show any significant difference between the two groups in the intervention and placebo groups as well as in the two groups.

The ratio of LDL-c/HDL-c and total cholesterol to HDL-cholesterol ratio did not show significant difference between two groups after 8 weeks of intervention, but the mean difference between two groups after the study was significant (*p* = .02 and *p* = .01).

TABLE 3 Comparison of mean and standard deviation of lipid profiles between the two groups

Variable	CME (Mean ± S.E.M)			Placebo (Mean ± S.E.M)			p value ^a	p value ^b
	Before	After	Change	Before	After	Change		
TG	131.83 ± 6.94	128.45 ± 6.45	-3.38 ± 1.92	141.62 ± 8.2	141 ± 7.29	-0.61 ± 2.71	.2	.34
LDL-c	48.76 ± 1.29	50.46 ± 1.16	1.88 ± 0.54	47.02 ± 1.25	46.71 ± 1.21	-0.3 ± 0.42	.90	.16
HDL-c	48.76 ± 1.29	50.64 ± 1.16	1.88 ± 0.54	47.02 ± 1.25	46.71 ± 1.21	-0.3 ± 0.42	.02	.002
Total-c	184.83 ± 5.07	180.52 ± 4.8	-4.3 ± 2.19	178.29 ± 4.69	176.62 ± 4.93	-1.66 ± 1.63	.57	.33
ApoA1	104.22 ± 3.16	107.85 ± 3.23	3.62 ± 0.85	107.25 ± 3.98	107.82 ± 3.93	0.56 ± 0.48	.99	.003
ApoB100	107.25 ± 2.39	107.42 ± 2.65	0.17 ± 0.7	106.43 ± 2.56	106.95 ± 2.57	0.52 ± 0.39	.90	.66
LDL-c/HDL-c	2.29 ± 0.09	2.13 ± 0.08	-0.16 ± 0.05	2.3 ± 0.09	2.3 ± 0.08	-0.00 ± 0.04	.15	.02
TC/HDL-c	3.89 ± 0.14	3.63 ± 0.11	-0.26 ± 0.07	3.88 ± 0.13	3.85 ± 0.12	-0.02 ± 0.05	.19	.01

Note. Data are presented as means ± SEM. *p* value <0.05 is significant.

^abetween groups (independent *t* test).

^bCompare changes between groups (independent *t* test).

Also as shown in Table 3, there was no statistically significant difference in mean of changes in triglyceride, LDL-cholesterol, and total cholesterol between the two groups before and after 8 weeks of intervention ($p = .34$, $p = .16$, and $p = .33$). In the CME group, mean HDL-cholesterol after 8 weeks of intervention had a significant difference compared with the beginning of the study ($p = .00$). There was also a significant difference in HDL-cholesterol between two groups before and after the 8 weeks of intervention ($p = .00$). The mean serum lipoprotein level of ApoA1 increased significantly in the group receiving CME ($p = .00$), but there was no significant difference in the mean ApoA1 lipoprotein level in the placebo group before and after 8 weeks. Comparison of ApoA1 lipoprotein changes showed a significant difference between two groups in intervention and placebo ($p = .00$). The ApoB100 lipoprotein had no significant difference in the placebo and placebo groups ($p = .8$ and $p = .19$). There was no significant difference in ApoB100 lipoprotein levels between the groups before and after study ($p = .66$).

The LDL/HDL ratio was not statistically different between two groups before the study ($p = .93$) and after the intervention ($p = .15$). There was a significant difference between the LDL/HDL ratio in the experimental group before and after the intervention ($p = .004$). However, there was no significant difference in the LDL/HDL ratio in the placebo group before and after the intervention ($p = .98$). The total serum cholesterol/HDL ratio was also calculated. There was no statistically significant difference between two groups before and after the intervention. Significant differences were observed in the intervention

group before and after the study ($p = .001$). There was no significant difference in placebo group before and after study ($p = .65$). Changes in ratio of total cholesterol level to HDL level of serum before and after intervention were significant ($p = .014$).

3.4 | Plasma fibrinogen and leptin

The results presented in Table 4 showed a significant decrease in plasma fibrinogen after 8 weeks of intervention in the group receiving the CME ($p = .004$). Also, comparison of fibrinogen changes between two groups was significant ($p = .007$). Serum leptin before and after intervention between and within each group did not change significantly.

As you can see in Table 4, Fibrinogen showed a significant decrease after 8 weeks of intervention in the CME group ($p = .004$). Also, the changes between two groups were statistically significant ($p = .007$). The serum leptin level did not show statistically significant difference between the groups before and after the intervention. Table 5 shows the *p* value after the 8-week study within the groups.

3.5 | Dietary assessment

The analysis of dietary intake showed no significant difference between groups before and after the intervention.

TABLE 4 Comparison of mean and standard deviation of fibrinogen and leptin between the two groups

Variable	CME (Mean ± S.E.M)			Placebo (Mean ± S.E.M)			p value ^a	p value ^b
	Before	After	Change	Before	After	Change		
Fibrinogen	270.45 ± 17.4	267 ± 17.17	3.45 ± 1.14	261.05 ± 15.15	262.31 ± 14.7	1.26 ± 1.27	.83	.007
Leptin ψ	14.18 ± 0.99	14.04 ± 0.95	-0.14 ± 0.11	13.88 ± 1.02	13.99 ± 0.99	0.10 ± 0.10	.72	.11

Note. Data are presented as means ± SEM. *p* value <0.05 is significant.

^aBetween groups comparison (independent *t* test or Mann-Whitney test).

^bCompare changes between groups (independent *t* test).

TABLE 5 Comparison of study variables at the end of the eighth week in the intervention and placebo groups

variable	p value (CME)	p value (Placebo)	variable	p value (CME)	p value (Placebo)
Weight	.003	.66	HDL-c	.001	.46
BMI	.004	.68	Total-cholesterol	.057	.31
WCR	.00	.06	ApoA1	.001	.24
FBS	.33	.80	ApoB100	.80	.19
Ins	.01	.43	LDL-c/HDL-c	.004	.98
HOMA-IR	.01	.53	TC/HDL-c	.001	.65
QUICKI	.13	.26	Fibrinogen	.004	.32
TG	.08	.77	Leptin	.33	.60
LDL-c	.06	.91			

Note. Within group comparison (paired *t* test or Wilcoxon test). *p* value <0.05 is significant.

4 | DISCUSSION

In the present study, daily consumption of 900 mg of *Cornus mas* extract did not affect fasting blood glucose, serum insulin, insulin resistance index, and insulin sensitivity between the groups, although the fasting blood glucose level in both groups decreased. These changes were not statistically significant; however, serum insulin and insulin resistance index within the intervention group were significantly decreased. Two studies conducted by Apostolidis et al. and Pinto et al., at the cellular level, showed the capability of *Cornus mas* to control blood glucose by inhibiting the alpha-amylase and alpha-glucosidase enzymes that is due to the polyphenols content of this fruit (Apostolidis, Kwon, Shetty, Apostolidis, & Kwon, 2006; Pinto, Ghaedian, Shinde, & Shetty, 2010). Many in vivo and in vitro studies have investigated the effects of polyphenols on blood glucose regulation. These studies have shown that phenolic acids can inhibit SGLT1, thereby intestinal absorption of glucose (Törrönen et al., 2010). Zhang et al., in a study, showed that Ureolic acid in *Cornus mas* can stimulate the phosphorylation of insulin receptor and stimulate glucose uptake by tissues (Zhang et al., 2006). The study by Teodoro et al. showed that oleanolic acid in *Cornus mas* fruit, in addition to its inhibitory effect on the alpha-glycidase enzyme, activates G protein receptors, and it seems that through these receptors can improve insulin function (Teodoro et al., 2008). Yamahara and colleagues conducted a study on diabetic rats indicating that the use of hydroalcoholic extract of *Cornus mas* could increase the expression of GLUT4 mRNA (Yamahara et al., 1981). In a study by Seymour et al. on diabetic rats after 12 weeks of intervention with Tart Cherry, the mean fasting insulin level was significantly reduced compared with control group (Seymour et al., 2009). In a study by Eftekhari et al., on 48 women with metabolic syndrome, supplementation of 400 mg of *Cornus mas* fruit extract in 8 weeks did not change insulin level of serum and insulin resistance index (HOMA-IR) significantly. Although insulin resistance and insulin resistance index (HOMA-IR) decreased in the treatment group and increased

in the control group, this difference was not significant between two groups. (Eftekhari, Khosrowpanah, & Rajaifard, 2014). These studies were in line with our study, but in another study by Lee et al., the daily intake of 1,500 mg of *Cornus mas* over 12 weeks in insulin-dependent diabetic patients did not bring about any statistically change in insulin level (Lee, Chan, Lin, Lee, & Sheu, 2008). In the present study, fasting blood sugar decreased in the intervention group and increased in the control group, which was statistically nonsignificant. A possible explanation for the insignificant fasting blood glucose, serum insulin, resistance, and insulin sensitivity between two groups in our study, comparing with the result of other studies previously performed on diabetic patients, can be the normal blood glucose levels of women who participated in our study.

HDL cholesterol and ApoA1 levels at the end of the study showed a significant increase in the intervention group as well as in the placebo group. Also, there was a decrease in the level of total cholesterol in the CME group ($p = .057$). Triglyceride, LDL cholesterol, and total cholesterol did not show any significant difference. Results of studies conducted in this field are inconsistent with that of current study. In many studies, *Cornus mas* have not been effective in altering lipid profiles (Basu et al., 2011; Chamberlain & Bowen-Simpkins, 2000). In the study performed by Eftekhari et al., on 48 women with metabolic syndrome, total cholesterol, triglyceride, and LDL cholesterol did change significantly after 8 weeks of treatment with 400 mg of *Cornus mas* extract. Only at the end of the eighth week HDL showed a significant increase (Eftekhari et al., 2014). Abdullahi et al. conducted a study on 40 healthy male rats fed with a same diet, and dosage of 50, 200, and 400 mg per kg of body weight *Cornus mas* per day. After 3 weeks of intervention, there was no significant difference in mean serum triglyceride, LDL-cholesterol, HDL-cholesterol, and total cholesterol. Only a slight decrease, but not significant, was observed in cholesterol and HDL-cholesterol, respectively (Abdollahi et al., 2014). Mirbeldzadeh et al. in a study showed that the extract of *Cornus mas* fruit significantly reduced serum triglyceride and LDL cholesterol levels compared with diabetic control group. LDL cholesterol decreased in the group receiving the *Cornus mas* as the group receiving glibenclamide and the triglyceride in the *Cornus mas* group decreased more than the group receiving the glibenclamide drug; as well, the *Cornus mas* increase HDL cholesterol compared with the control group (Miroddanzadeh, 2010). Lee et al. in a study on 30 patients with diabetes showed that taking 1,500 mg of *Cornus mas* extract for 12 weeks can result in a significant decrease in total cholesterol and LDL cholesterol between two groups but HDL cholesterol and triglyceride at the end. The intervention did not show any significant difference (Lee et al., 2008). *Cornus mas* extract seems to be effective in reducing triglycerides in hyperlipidemic patients, such as diabetic and dyslipidemic patients, but those who participated in our study were not hyperlipidemic. This effect may be due to the improved insulin function, because insulin plays a role in the metabolism of lipids. Anthocyanin in blueberries can also inhibit lipase in the pancreas and intestinal absorption of lipids. According to previous studies, there are mechanisms for the effect of blueberries on lipid profiles. The possible mechanism for reducing total cholesterol is to increase the

excretion of sterols and bile acids from the stool. Eliminating bile acids can lead to stimulation of the liver to convert more cholesterol to bile acid and thereby reduce cholesterol (Eftekhari et al., 2014; Neto, 2007). Reducing the expression of HMG-CoA hepatocyte reductase gene by anthocyanin in cranberry fruit can be possible. The potential mechanism for *Cornus mas* to reduce triglycerides may be due to its effect on improving insulin status and consequently reducing insulin levels. Insulin regulates the expression of the SREBP-1 gene, which regulates genes linked to glucose and fat metabolism. Insulin via SREBP-1 increases the expression of GPAT gene, the first enzyme in the pathway for triglyceride production. In our study, LDL cholesterol decreased, but this decrease was not statistically significant. The probable mechanism of *Cornus mas* is to reduce LDL cholesterol by controlling the cholesteryl ester transferase (CETP) protein. Also, anthocyanins can increase the expression of LDL receptor-derived cholesterol and increase cholesterol excretion (Liu, Sun, Lu, & Bo, 2016). An increase in the concentration of HDL cholesterol is explained by changes in plasma ApoA1 (Ruel et al., 2006). Also, Quercetin and flavonoid, found in large quantities in *Cornus mas*, can increase in the expression of paraoxonase-1 associated with HDL (Gouédard, Barouki, & Morel, 2004). Serum paroxinase enzyme, which located on HDL cholesterol has antioxidative function. This enzyme is known as a stimulant for the reverse transfusion of cholesterol; thus, it can justify an increase in HDL cholesterol (Eftekhari et al., 2014; Rosenblat, Karry, & Aviram, 2006). The potential mechanism for *Cornus mas* to increase HDL cholesterol can be referred to as the CETP inhibitory function, because studies have shown an inverse relationship between the activity of this protein and the level of HDL cholesterol (Beyer et al., 2008). Anthocyanins have a potential effect on increasing the expression of PPAR α , which can increase HDL cholesterol and lower LDL cholesterol and total cholesterol (Du et al., 2015).

In the present study, complementary supplementation with 900 mg of CME significantly decreased the fibrinogen level in the intervention group as well as changes between the two groups at the end of the eighth week (Table 4).

Asgari et al. in a study compared the effect of lovastatin and cranberry extract on fibrinogen levels in hypercholesterolemic rabbits. In this study, blueberries were shown to reduce fibrinogen levels as compared with control group (Asgary, Rafieian-Kopaei, Adelnia, Kazemi, & Shamsi, 2010). Our findings on the effect of cranberries extract on fibrinogen reduction are consistent with the findings of Asgari et al. Fibrinogen, in addition to being involved in the pathogenesis of some vascular events, is also known as an acute inflammatory reaction agent. Fibrinogen is increased among people with type 2 diabetes, hypertension, obesity, and those with low levels of physical activity. Also, in inflammation and infection, fibrinogen liver synthesis can increase up to four times. By increasing LDL cholesterol, the level of fibrinogen increases too (Asgary et al., 2010). It seems that cranberries can reduce fibrinogen levels by weight loss, reducing LDL cholesterol and inflammation (AKh, Zaichkina, Ruzieva, & Ganassi, 1993; Asgary et al., 2010; Gülçin, Beydemir, Şat, & Küfrevioğlu, 2005). Another mechanism for anthocyanins is disruption of coagulation process by inhibiting the COX enzyme. (Mulabagal, Lang, DeWitt, Dalavoy, &

Nair, 2009; Seeram, Momin, Nair, & Bourquin, 2001; Seeram, Schutzki, Chandra, & Nair, 2002)

In our study, there was no significant change in leptin levels after 8 weeks of exposure to hydroalcoholic extract of *Cornus mas* fruit. Wu et al. in a study of 48 mice showed that blubbery and mulberry water reduces leptin levels (Wu et al., 2013). Prior and colleagues in a 10-week study on low-fat and high-fat diet mice showed that the use of blueberries or blueberry anthocyanins reduced serum leptin levels in high-fat diet mice (Prior et al., 2010).

Graf et al. performed a study on 60 fetal rats and evaluated the effect of anthocyanin-rich beverages on lipids, glucose, insulin, and adipocytes compared with the control group. At the end of the study, it was shown that anthocyanin reduced serum leptin levels, whereas weight in the two groups did not change significantly (Graf, Seifert, Jaudszus, Bub, & Watzl, 2013).

Our study results are different from those of other studies. However, in our study, in CME group, the mean leptin level decreased and in the placebo group increased, but none of them was statistically significant. The reason for this could be diets with high content of fat, weight gain, and diet type in samples. Another possible reason is supplementation with high dose of *Cornus mas* extract in animal studies.

The results of our study showed that supplementation with hydroalcoholic extracts of *Cornus mas* could significantly reduce weight, body mass index, and waist circumference. A study by Jayaprakasam et al. compared the effect of anthocyanin and peroric acid in *Cornus mas* in a high-fat diet, and it was observed that the reduction in weight gain in the anthocyanin group was higher, although in the group receiving ursolic acid showed a decrease in weight gain but was not significant in comparison with the control group (Jayaprakasam, Olson, Schutzki, Tai, & Nair, 2006). In the study of Rasoulia et al., cranberries powder could reduce weight gain as compared with control group (Rasoulia, Shahryar, Abbaspour, & Lotfi, 2012). Ataei Jafari et al. also conducted a pilot study on 19 women with diabetes, and it was observed that daily consumption of 40 g of cherry concentrate for 6 weeks resulted in a significant reduction in body weight and body mass index (Ataie-Jafari, Hosseini, Karimi, & Pajouhi, 2008). In another study, *Cornus mas* juice significantly decreased body weight, body mass index, and waist circumference in healthy obese men (Basu et al., 2011). In the Eftekhary et al. study, the mean of waist circumference in the intervention group with a 400-mg extract of *Cornus mas* was significantly decreased (Eftekhari et al., 2014). But in the study of Lee et al., *Cornus mas* did not change the mean waist circumference of diabetic patients (Lee et al., 2008). The probable mechanism for the effect of this intervention on the anthropometric indicators can be related to the anthocyanin present in the fruit. According to the studies, anthocyanin can alter the MAPK and the NF- κ B signaling stress pathway, thereby decreases inflammation and cellular protection and contributing to the pathology of obesity. Also, anthocyanin can cause changes in the adipose tissue, alter the expression of adipocytokines, and increase adiponectin levels. The suppression of visceral fat accumulation through inhibiting the activity of the pancreatic lipase, and thus reducing intestinal

absorption of fat, is another anthocyanin activity. Also, anthocyanin may increase the expression of Peroxisome proliferator-activated receptor alpha (PPAR α), peroxisome proliferator-activated receptor delta (PPAR δ), uncoupling protein 2 (UCP-2), uncoupling protein 3 (UCP-3), and mitochondrial transcription factor A genes mRNA expression (Azzini, Giacometti, & Russo, 2017).

In the present study, for the first time, the effect of hydro alcoholic extract of *Cornus mas* on lipid profiles, blood glucose, and leptin parameters in postmenopausal women has been investigated. The strengths of this study include blindness, randomized sampling, and controlled sample size. One of the weaknesses of this study is the lack of measurement of adiponectin hormone, resistin and visfatin, and the use of the formula to measure insulin resistance index instead of using glucose clamping due to financial constraints. More suggestions are made to find the mechanisms of cranberry effect by measuring genes' expression and measuring proteins involved in blood glucose metabolism such as adiponectin, PPAR α , and PPAR δ . Also, the effects of different doses of cranberry supplement and its simultaneous comparison with the consumption of blueberry juice can also be helpful.

5 | CONCLUSION

Supplementation with 900-mg hydro alcoholic extract of *Cornus mas* fruit significantly reduced the body mass index, waist circumference, some aspects of lipid profile, fibrinogen, and HOMA-IR and increased HDL-cholesterol, fasting insulin, and ApoA1 in comparison with control group. An implication of these findings is that, daily use of *Cornus mas* fruit is believed to help reduce anthropometric, blood sugar variables, and risk of cardiovascular disease.

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CONFLICT OF INTEREST

None of the authors report conflicting interests.

COMPLIANCE WITH ETHICAL STANDARDS

FUNDING INFORMATION

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ETHICAL APPROVAL

The study was approved by the Ethics Committee of Iran University of Medical Sciences IR.IUMS.REC 1395.9313680004 IR. Registered in

the Iranian Center for Clinical Trials at www.irct.ir, IRCT201610259472N10.

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