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Randomized Controlled Trial

Effect of *Cornus mas L.* fruit extract on blood pressure, anthropometric and body composition indices in patients with non-alcoholic fatty liver disease: A double-blind randomized controlled trial

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SUMMARY

Background & aims: Obesity is linked to the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Patients with NAFLD are at increased risk for hypertension. Some investigations have hypothesized that *Cornus mas* L. fruit can improve obesity and hypertension. We investigated the effect of *C. mas* L. fruit extract on blood pressure, anthropometric and body composition indices in patients with NAFLD.

Methods: This 12-week double-blind randomized controlled trial was conducted on fifty patients with NAFLD. Patients received 20 cc/d *C. mas* L. fruit extract or placebo. We measured diastolic blood pressure (DBP), systolic blood pressure (SBP), weight, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), body fat mass (BFM), body fat percent (BFP) and fat free mass (FFM) before and after intervention.

Results: Treatment group compared to control group showed a significant reduction in DBP (-8.62 ± 11.86 mmHg vs. 0.53 ± 8.53 mmHg; $P_{crude} = 0.003$; $P_{adjucted} = 0.03$) and SBP (-8.63 ± 14.37 mmHg vs. 0.0 ± 12.67 mmHg; $P_{crude} = 0.02$; $P_{adjucted} = 0.02$). We found no difference between groups in weight, WC, HC, WHR, BFM, BFP and FFM ($P > 0.05$). After adjusting for confounding factors, a significant reduction was observed in treatment group compared to control group in BFM (-0.2 ± 3.9 kg vs. 0.7 ± 2.4 kg; $P = 0.01$) and BFP ($-0.2 \pm 4.9\%$ vs. $0.8 \pm 2.8\%$; $P = 0.02$).

Conclusions: C. mas L. fruit extract statistically reduced blood pressure and body fat. However, it had no effect on other anthropometric and body composition indices. Studies with larger sample sizes and higher dosages of extract are needed. Trial registration: Registered on 30/9/2018 at Iranian Registry of Clinical Trials IRCT20180419039359N1 (https://www.irct.ir/trial/30707).

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is known as the accumulation of fat (mainly triglyceride) in the liver (more than 5% of liver weight) without evidence of alcohol consumption [1,2]. The prevalence of NAFLD is high in both developed and developing countries [3–5]. It is the most common chronic liver disease worldwide and the main cause of liver transplantation [6,7].

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Obesity, disrupted lipid metabolism, inflammation and insulin resistance are the most important factors that contribute to the development and progression of NAFLD [8–10]. A strong association between NAFLD and both metabolic syndrome and cardiovascular disease (CVD) has been confirmed [11,12]. In addition, patients suffering from NAFLD compared to the healthy subjects are at higher risk for hypertension [13,14]. Modifiable lifestyle factors such as weight loss and adherence to the healthy plant-based dietary patterns are the important strategies to manage NAFLD [15–17].

Cornus mas L. (cornelian cherry) fruit is a rich source of compounds with anti-inflammatory and antioxidant properties such as anthocyanins, flavonoids and polyphenols [18–20]. It has been reported that *C. mas* L. fruit/anthocyanins can improve obesity and hypertension through several mechanisms [21–24]. The effects of *C. mas* L. fruit on some factors involved in the pathogenesis of NAFLD such as insulin resistance, dyslipidemia and inflammation have been examined [25–27]. A few number of studies have examined the effect of *C. mas* L. on anthropometric and body composition indices [25,26]. The studies that investigated the effect of *C. mas* L. fruit in patients with NAFLD are rare [28]. To the best of our knowledge, there is no study evaluating the effect of *C. mas* L. fruit on anthropometric and body composition indices in patients with NAFLD. In addition, there was no clinical trial that investigated the effect of *C. mas* L. fruit on blood pressure. Accordingly, we designed a clinical trial to examine the effect of *C. mas* L. fruit extract blood pressure variables, anthropometric and body composition indices in patients with NAFLD.

2. Methods

2.1. Recruitment and eligibility screening

We recruited the subjects from Diabetes Research Center of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, between May 2019 and August 2019. A total of 50 subjects met the inclusion criteria including age 25–65 years, diagnosis of NAFLD by a gastroenterologist via ultrasonography, alanine aminotransferase (ALT) serum concentrations $\geq$30 U/L in men and $\geq$19 U/L in women [29–31], and resident of Yazd city. The exclusion criteria included alcohol consumption, viral hepatitis, cancer, Wilson, type 2 diabetes mellitus (T2DM), CVD, mental diseases, pregnancy, lactation, adherence to a special diet 1 month before the study, taking corticosteroids, non-steroidal anti-inflammatory drugs, hypoglycemic drugs, tamoxifen, sodium valproate, methotrexate, amiodarone and anti-retroviral agents for HIV, taking probiotics and consuming antioxidant and anti-inflammatory supplements such as vitamin D, vitamin E, omega-3 and resveratrol during 1 month before the study. In addition, poor compliance and unwillingness to continue the study were considered as drop-out criteria.

2.2. Trial design

We designed a double-blind randomized, placebo-controlled clinical trial (RCT) to evaluate the effect of *C. mas* L. fruit extract intake on blood pressure, anthropometric and body composition indices in patients with NAFLD. Based on the study of Zhang et al. [32], which was conducted among patients with NAFLD, the intervention duration was considered to be 12 weeks. At the beginning, the participants signed a written informed consent that was confirmed by the ethical committee of Shahid Sadoughi University of Medical Sciences and Health Services in Yazd (IR.SSU.SPH.REC.1399.019). We registered the protocol on 30/9/2018 at Iranian registry of clinical trials website (http://www.irct.ir) under code number IRCT20180419039359N1 (https://www.irct.ir/trial/30707). We stratified the participants according to their age (25–45; 45–65 years) and gender (male/female), and the participants were divided into the treatment group (n = 25) and the control group (n = 25) by a person who did not contribute to the study. To perform randomization, a random number table produced by random allocation software was used [33]. The patients and investigators were blinded until the end of the trial.

2.3. Extract preparation

We provided the *C. mas* L. fresh fruits from the forests of Ghazvin, Iran. Preparation of the *C. mas* L. fruit extract and placebo was performed in the Pharmacy Faculty of Shahid Sadoughi University of Medical Sciences. To determine total anthocyanins content of final extract we used pH differential method [34]. We reported the details of *C. mas* L. fruit extract preparation as well as total anthocyanins content determination in our previous articles [28,35].

2.4. Intervention

Based on previous clinical trials [25,27], we considered 20 cc/d *C. mas* L. fruit extract as the optimal dosage for treatment group. This amount provided 32 mg/d total anthocyanin. 20 cc liquid extract was equivalent to 2800 mg dried extract. The safety of this dosage was confirmed by previous studies [25,26,36,37]. The control group received 20 cc/d placebo without any anthocyanin. Purified water and red color carmoisine were the components of placebo. At the beginning of the study, the participants were asked not to follow special diets during intervention. The *C. mas* L. fruit extract and the placebo that had similar appearance were packed in bottles with the same color, shape and size. The participants received the bottles every 2 weeks. We assessed the rate of compliance every 2 weeks based on extract consumption. Consumption of extracts less than 80% of the prescribed amount was considered as poor compliance. Adverse events during follow-up were checked every 2 weeks.

2.5. Dietary intake and physical activity assessment

We evaluated the dietary intake of participants at the baseline and after intervention utilizing a 3-day (1 weekend day and 2 nonconsecutive weekdays) food record. Energy and macronutrients intakes were calculated using nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA) [38]. In addition, we used a short form of International physical activity questionnaire (IPAQ) [39,40] to assess physical activity at the baseline and after intervention.

2.6. Blood pressure measurement

Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured by a trained person using a mercury sphygmomanometer device (MicrolifeBP AG1-10) at the baseline and after intervention. Measurement were performed in accordance with the recommendations of American Heart Association (AHA) [41]. Briefly, the participant rested while seated in a chair for 5 min before the cuff was placed on the arm. The participant was asked to remove clothes that cover the location of cuff placement. The middle of the cuff was placed on the upper arm at the level of the right atrium (the mid-point of the sternum), and the arm was placed on a pillow. In each visit, three readings were taken at intervals of at least 1 min and the average of three readings was reported.

2.7. Anthropometric and body composition evaluations

Measuring height was performed according to the standard instructions via a stadiometer (Seca, Hamburg, Germany) with an accuracy of 0.5 cm. Weight, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), body fat mass (BFM), body fat percent (BFP) and fat free mass (FFM) was performed at the baseline and after intervention using a bioelectrical impedance analyzer (BIA) (In Body 770, Korea) based on the standard protocols while participants were with light clothes and without shoes.

2.8. Sample size and statistical analysis

We calculated the sample size (25 per group) based on fibrosis score, with 95% confidence interval, $\alpha = 0.05$, power = 80% in our previous article [28]. We performed a retrospective power analysis for the present study, and power = 80% was estimated for HC. Statistical package for social science (SPSS) software (Chicago, Illinois, USA) version 24 was utilized for statistical analyses. Kolmogorov–Smirnov test was utilized to evaluate the parameters distribution. We used independent t-test and chi-square test for continuous and categorical variables, respectively to compare differences between groups. Independent t-test was utilized to compare the means of variables at the end of the study, as well as the mean changes between groups. Parameters with abnormal distribution were compared between groups utilizing Mann–Whitney U test. In addition, we used paired t-test (for parameters with normal distribution), and Wilcoxon test (for parameters with abnormal distribution) to perform within group comparisons. Analysis of covariance (ANCOVA) was used to adjust the effects of confounding factors including energy intake, physical activity and menopausal status. The primary outcomes were reported based on intention-to-treat (ITT) approach.

3. Results

3.1. Characteristics and anthropometric variables

A total of 40 patients completed the study. Ten patients were excluded from the trial for reasons such as flatulence (n = 1), immigration (n = 2), unwillingness to continue the study (n = 3), surgery (n = 1), and corona virus pandemic (n = 3) (Fig. 1). There was no difference between the treatment group and the control groups in the baseline variables (Table 1). In addition, we found no difference between the treatment group and the control groups in dietary intakes and physical activity at the baseline and after intervention (Table 2). The patients reported no serious adverse event related to extracts during follow-up. One patient with history of gastrointestinal disorders had flatulence during intervention, and was excluded.

3.2. Outcomes

At the baseline, no significant difference was found between the treatment and the control groups in terms of DBP (P = 0.46) and SBP (P = 0.98) (Table 3). After intervention, a significant difference was observed between two groups in DBP (P = 0.01). However, there was no significant difference between groups in SBP (P = 0.07). The treatment group compared to the control group showed a significant reduction in DBP (−8.62 ± 11.86 mmHg vs. 0.53 ± 8.53 mmHg; P = 0.03), and SBP (−8.63 ± 14.37 mmHg vs. 0.0 ± 12.67 mmHg; P = 0.02) (Table 3).

In addition, there was no significant difference between the two groups in weight (P = 0.73), WC (P = 0.18), HC (P = 0.10), WHR (P = 0.71), BFM (P = 0.25), BFP (P = 0.29) and FFM (P = 0.67) at the baseline (Table 4). In addition, we found no significant difference between two groups in weight (P = 0.73), WC (P = 0.20), WHR (P = 0.82), BFM (P = 0.14), BFP (P = 0.14) and FFM (P = 0.49) after intervention. However, level of HC (P = 0.03) was significantly higher in the control group compared to the treatment group (Table 4). We found no significant difference between two groups in mean change of weight (0.5 ± 2.3 kg vs. 0.5 ± 1.5 kg; P = 0.99), WC (0.8 ± 3.3 cm vs. 1.0 ± 2.7 cm; P = 0.74), HC (0.1 ± 1.3 cm vs. 0.9 ± 2.5 cm; P = 0.24), WHR (0.01 ± 0.03 vs. 0.00 ± 0.03; P = 0.73), BFM (−0.2 ± 3.9 kg vs. 0.7 ± 2.4 kg; P = 0.36), BFP (−0.2 ± 4.9% vs. 0.8 ± 2.8%; P = 0.37), and FFM (0.7 ± 3.7 kg vs. −0.2 ± 2.4 kg; P = 0.32) (Table 4).

After adjusting for confounding factors, a significant reduction was observed in treatment group compared to the control group in

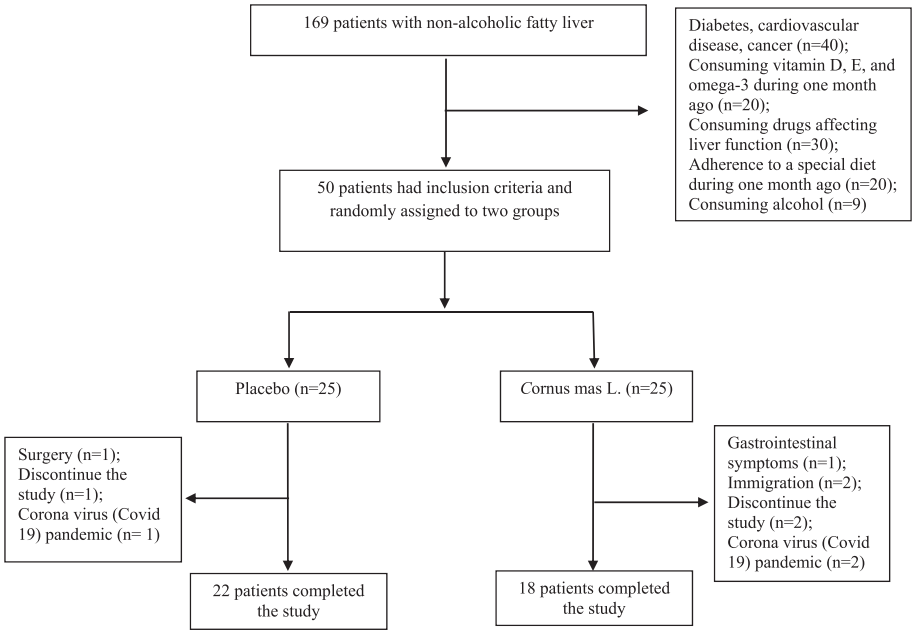

Fig. 1. Eligibility, screening, and follow-up.

Table 1
Baseline characteristics of patients with NAFLD.

Variables		*Cornus mas* L. (n = 25)	Placebo (n = 25)
Age[a], **y**		41.4 ± 9.5	42.6 ± 9.9
Gender[a]	Male, n (%)	12 (48)	11 (44)
	Female, n (%)	13 (52)	14 (56)
History of other chronic diseases[a]	Yes, n (%)	3 (12)	3 (12)
	No, n (%)	22 (88)	22 (88)
Menopausal status[a]	Yes, n (%)	4 (16)	5 (20)
	No, n (%)	21 (84)	20 (80)
DBP[a], mmHg		80.16 ± 12.06	78.0 ± 8.57
SBP[a], mmHg		121.08 ± 13.43	121.16 ± 15.96
Height[a], cm		168.0 ± 11.2	164.4 ± 9.6
Weight, kg		79.7 ± 12.5	80.9 ± 12.8
WC[a], cm		97.6 ± 9.1	101.1 ± 9.3
HC[a], cm		102.5 ± 5.7	104.9 ± 4.7
WHR[a]		0.95 ± 0.09	0.96 ± 0.08
BFM[a], kg		27.4 ± 6.5	29.9 ± 8.1
BFP[a], %		34.5 ± 7.3	36.8 ± 7.6
FFM[a], kg		52.3 ± 11.1	51.0 ± 10.5

P values are computed by independent t-test and data are expressed as mean ± standard deviation (SD), but for gender and history of other chronic diseases are computed by chi-square and data are expressed as numbers (percentage).
NAFLD: non-alcoholic fatty liver disease; DBP: diastolic blood pressure; SBP: systolic blood pressure; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; BFM: body fat mass; BFP: body fat percent; FFM: fat free mass.
[a] No significant difference was found between two groups at the baseline.

the mean change of BFM (P = 0.01) and BFP (P = 0.02). Other findings remained unchanged after adjusting for confounding variables.

4. Discussion

Based on our knowledge, our study was the first study that examined the effect of *C. mas* L. fruit extract on blood pressure, anthropometric and body composition indices in patients with

Table 2
Dietary intakes and physical activity in patients with NAFLD.

variables	*Cornus mas* L. (n = 25)	Placebo (n = 25)	*P*†
Energy intake, kcal/d			
Baseline	2960.80 ± 885.15	2576.24 ± 617.81	0.11
Week 12	2943.50 ± 758.81	2635.78 ± 621.91	0.16
P	0.85	0.31	
Carbohydrates, g/d			
Baseline	425.08 ± 185.33	375.33 ± 128.80	0.32
Week 12	460.46 ± 172.58	379.39 ± 132.36	0.10
P	0.32	0.80	
Proteins, g/d			
Baseline	95.25 (83.30–120.22)	88.36 (67.44–99.17)	0.14[a]
Week 12	93.99 (81.58–134.23)	96.34 (74.94–113.18)	0.48[a]
P	0.83[b]	0.19[b]	
Fats, g/d			
Baseline	93.18 (54.68–156.09)	69.37 (53.85–106.85)	0.23[a]
Week 12	83.46 (59.56–99.97)	72.12 (61.25–100.25)	0.76[a]
P	0.30[b]	0.45[b]	
Physical activity, (MET/hr/week)			
Baseline	660.45 (307.12–791.25)	341.5 (0–1705.50)	0.75[a]
Week 12	850.50 (111.37–881.29)	283.75 (0–1234.12)	0.49[a]
P	0.31[b]	0.28[b]	

Values of total energy and carbohydrates are presented as mean ± standard deviation (SD), while for proteins, fats and physical activity are presented as median and quartile range.
P: resulted from comparisons within groups.
P†: resulted from comparisons between two groups.
NAFLD: non-alcoholic fatty liver disease.
[a] P values are computed by Mann–Whitney U test.
[b] P values are computed by Wilcoxon test.

Table 3
Effect of *Cornus mas L.* fruit extract on blood pressure in patients with NAFLD*.

Indices	*Cornus mas* L. (n = 25)	Placebo (n = 25)	*P*†	*P*††
DBP (mmHg)				0.03
Baseline	80.16 ± 12.06	78.0 ± 8.57	0.46	
Week 12	71.54 ± 7.82	78.53 ± 10.67	0.01	
P	0.001	0.75		
Mean change of DBP	−8.62 ± 11.86	0.53 ± 8.53	0.003	
SBP (mmHg)				0.02
Baseline	121.08 ± 13.43	121.16 ± 15.96	0.98	
Week 12	112.45 ± 16.63	121.16 ± 16.87	0.07	
P	0.006	0.99		
Mean change of SBP	−8.63 ± 14.37	0.0 ± 12.67	0.02	

Values are presented as mean ± standard deviation (SD).
P: resulted from comparisons within groups by paired t-test.
P†: resulted from comparisons between two groups by independent t-test.
P††: resulted from comparisons mean changes between two groups after adjusting for mean changes of energy intake, physical activity and menopausal status using analysis of covariance (ANCOVA).
NAFLD: non-alcoholic fatty liver disease; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 4
Effect of *Cornus mas L.* fruit extract on body composition in patients with NAFLD*.

Indices	*Cornus mas* L. (n = 25)	Placebo (n = 25)	*P*†	*P*††
Weight (kg)				0.45
Baseline	79.7 ± 12.5	80.9 ± 12.8	0.73	
Week 12	80.2 ± 12.5	81.4 ± 13.0	0.73	
P	0.32	0.13		
Mean change of weight	0.5 ± 2.3	0.5 ± 1.5	0.99	
WC (cm)				0.51
Baseline	97.6 ± 9.1	101.1 ± 9.3	0.18	
Week 12	98.4 ± 10.2	102.1 ± 10.5	0.20	
P	0.29	0.08		
Mean change of WC	0.8 ± 3.3	1.0 ± 2.7	0.74	
HC (cm)				0.07
Baseline	102.5 ± 5.7	104.9 ± 4.7	0.10	
Week 12	102.6 ± 5.3	105.8 ± 4.9	0.03	
P	0.54	0.11		
Mean change of HC	0.1 ± 1.3	0.9 ± 2.5	0.24	
WHR				0.63
Baseline	0.95 ± 0.09	0.96 ± 0.08	0.71	
Week 12	0.96 ± 0.10	0.96 ± 0.09	0.82	
P	0.44	0.82		
Mean change of WHR	0.01 ± 0.03	0.00 ± 0.03	0.73	
BFM (kg)				0.01
Baseline	27.4 ± 6.5	29.9 ± 8.1	0.25	
Week 12	27.2 ± 6.9	30.6 ± 8.3	0.14	
P	0.94	0.10		
Mean change of BFM	−0.2 ± 3.9	0.7 ± 2.4	0.36	
BFP (%)				0.02
Baseline	34.5 ± 7.3	36.8 ± 7.6	0.29	
Week 12	34.3 ± 7.6	37.6 ± 7.8	0.14	
P	0.82	0.16		
Mean change of BFP	−0.2 ± 4.9	0.8 ± 2.8	0.37	
FFM (kg)				0.37
Baseline	52.3 ± 11.1	51.0 ± 10.5	0.67	
Week 12	53.0 ± 11.7	50.8 ± 10.4	0.49	
P	0.30	0.82		
Mean change of FFM	0.7 ± 3.7	−0.2 ± 2.4	0.32	

Values are presented as mean ± standard deviation (SD).
P: resulted from comparisons within groups by paired t-test.
P†: resulted from comparisons between two groups by independent t-test.
P††: resulted from comparisons mean changes between two groups after adjusting for mean changes of energy intake, physical activity and menopausal status using analysis of covariance (ANCOVA).
NAFLD: non-alcoholic fatty liver disease; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; BFM: body fat mass; BFP: body fat percent; FFM: fat free mass.

NAFLD. *C. mas* L. fruit extract (20 cc/d) could reduce blood pressure, BFM and BFP. However, weight, WC, HC, WHR and FFM did not change after intake of extract for 12 weeks.

C. mas L. fruit and its biological compounds through various mechanisms and pathways such as inducing endothelial nitric oxide gene expression, regulating nitric oxide synthase and increasing endogenous production of nitric oxide, modulating nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, reducing pro-inflammatory cytokines, decreasing peroxynitrate and reactive oxygen species (ROS) levels, and attenuating vasoconstriction by regulating angiotensin-converting enzyme (ACE) and angiotensin II receptor activity can improve hypertension [22,42–45]. There is no study investigating the effect of *C. mas* L. fruit on blood pressure in subjects in NAFLD. Johnson et al. [46] reported that daily consumption of blueberry, a rich source of anthocyanins, for 8 weeks in postmenopausal women with pre- and stage 1-hypertension can reduce DBP and SBP. In addition, the study of Broncel et al. [47] found that intake of 300 mg/d *Aronia melanocarpa* extract (another rich source of anthocyanins) for 2 months reduces DBP and SBP in subjects with metabolic syndrome. Moreover, the study conducted by Basu et al. [48] suggested that freeze-dried blueberry beverage (50 g freeze-dried blueberries) daily for 8 weeks can reduced DBP and SBP in participants with metabolic syndrome. However, a clinical study conducted by Hassellund et al. [49] demonstrated that anthocyanins supplementation (320 mg twice per day) after 4 weeks did not reduce blood pressure variables in subjects with hypertension. A meta-analysis found that anthocyanins supplementation has no effect on DBP and SBP [50]. Health status of participants, duration of follow-up, type of supplement and dosage of supplement are the most important differences between these studies. It seems, difference in type of supplements is the main factor explaining discrepancies between findings of mentioned studies. In general, anthocyanins supplementation did not show promising results in this field, while receiving sources of anthocyanins reported the beneficial effects on blood pressure. We used *C. mas* L. fruit extract containing several biological compounds that probably have synergistic effects.

On the other hand, the evidence suggested that *C. mas* L. fruit and its main compounds by inhibiting hepatic lipogenesis, increasing hepatic lipid oxidation and clearance, regulating the expression of peroxisome proliferator-activated receptors (PPARs), increasing the activity of AMP-activated protein kinase (AMPK) pathway in the white adipose tissue, decreasing adiponectin levels and activating adiponectin signaling, decreasing levels of adipocytokines, reducing the activity of pancreatic lipase and absorption of lipids can reduce obesity [21,51–55]. We found no similar study investigating the effect of *C. mas* L. fruit on obesity in patients with NAFLD. Gholamrezayi et al. [26] have examined the effect of 8-week *C. mas* L. fruit extract intake (900 mg/d) on anthropometric variables of postmenopausal women, and found a significant decrease in weight and WC. The dosage of *C. mas* L. fruit extract in the mentioned study was higher than our study. However, the study of Asgary et al. [25] showed no beneficial effect of *C. mas* L. fruit (100 g/d) for 6 weeks in dyslipidemic children and adolescents. Some studies have examined the effect of other rich sources of anthocyanins on body composition. It has been reported that 12-week cranberry extract intake (1500 mg/d) did not change the mean of WC in subjects with T2DM [56]. Likewise, Basu et al. [48] did not find the beneficial effect of blueberry intake on weight and WC among subjects suffering from metabolic syndrome. The pilot trial of Zhang et al. [32] reported that purified anthocyanins supplementation (320 mg/d) derived from bilberry and black currant for 12 weeks has no effect on weight, WC, HC and WHR in patients with NAFLD. It seems, dosage and type of extract are important in this field, and probably higher dosages of *C. mas* L. fruit extract can improve the indicators of obesity.

In general, our findings regarding the effects of 12-week intervention with *C. mas* L. fruit extract (20 cc/d) on anthropometric and body composition indices did not demonstrate promising evidence from a clinical perspective. In other words, although we reported a significant reduction in BFM and BFP, the reduction of these variables were statistically significant, and their slight changes are not clinically important. This may be due to our important limitations such as low dosage of extract.

To comply with principles of ethics in research, we declare that our research group reported the findings of liver function [28], lipid accumulation product and cardiovascular indices [57]. We used the same data for the present article, and Fig. 1, sample size information, some baseline characteristics, dietary intakes and physical activity of our previous articles were added to the present article.

The present study had some important advantages. This study was the first RCT that examined the effect of *C. mas* L. fruit extract on blood pressure variables and body composition indices in patients with NAFLD. In addition, the extract was standardized according to total anthocyanin content. Similar to other RCTs, this study had some limitations. The dosage of *C. mas* L. fruit extract in our study was low. Liver ultrasonography was used for diagnosis of NAFLD, while Fibroscan has higher accuracy than ultrasonography [58,59]. In addition, we did not measure the serum levels of anthocyanins to evaluate the bioavailability of anthocyanins. As another important limitation, we did not measure all compounds of the cornelian cherry fruit extract. Moreover, there were some menopausal women in this study. Due to small sample size, we did not eliminate menopausal women.

5. Conclusions

Overall, 12-week *C. mas* L. fruit extract intake (20 cc/d) reduced blood pressure. In addition, body fat was decreased after 12-week intervention. It should be noted that reduction of body fat was statistically significant, and slight change of body fat is not clinically important. *C. mas* L. fruit extract had no effect on other anthropometric and body composition indices. Further studies with larger sample sizes and higher dosages of *C. mas* L. fruit extract are required to clarify the real effects of *C. mas* L. fruit extract.

Declarations

Ethics approval and consent to participate

The research council of Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences and Health Services approved the study protocol. The methods were performed in accordance with the Helsinki Declaration. The ethical committee of Shahid Sadoughi University of Medical Sciences and Health Services in Yazd approved the written informed consent (code number: IR.SSU.SPH.REC.1399.019). The written informed consent was obtained from all participants before the data collection.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials of the current study is available from the corresponding author on reasonable request.

Competing interests

The authors have declared no competing interests.

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Authors' contributions

H.M-Kh, M.H, F.Y and Z.S: conducted the study; H.M-Kh, M.A-M and A.R: provided material and technical support; H.F, A.S and F.Y: carried out the statistical analysis, and interpreted the finding; A.S: drafted the manuscript; H.M-Kh: critically revised the manuscript; and H.M-Kh: supervised the study. All authors reviewed the manuscript.

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List of abbreviations:

ACE	angiotensin-converting enzyme
AHA	American Heart Association
AMPK	adenosine monophosphate activated protein kinase
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
BFM	body fat mass
BFP	body fat percent
CVD	cardiovascular disease
DBP	diastolic blood pressure
FFM	fat free mass
FPG	fasting plasma glucose
HC	hip circumference
ITT	intention-to-treat
IPAQ	international physical activity questionnaire
MAPK	mitogen-activated protein kinase
MET-h	metabolic equivalent task hours
NAFLD	nonalcoholic fatty liver disease
NF-κB	nuclear factor-κ B
PPARs	peroxisome proliferator-activated receptors
RCT	randomized controlled trial
ROS	reactive oxygen species
SBP	systolic blood pressure
SPSS	statistical package for social science
T2DM	type 2 diabetes mellitus
WC	waist circumference
WHR	waist-to-hip ratio

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