Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2024; 9(4): 692-701 Website: jnfs.ssu.ac.ir

The Impact of Combined Cranberry Supplementation and Weight Loss Diet on Inflammatory, Antioxidant, and Apoptosis Biomarkers in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Controlled Clinical Trial

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ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 5 Mar 2023
Revised: 14 Feb 2023
Accepted:21 Feb 2023

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Keywords:
Vaccinium macrocarpon; Non-alcohlic fatty liver diseases; Inflammation; Oxidative stress; Apoptosis.

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disease. The aim of this study is to evaluate the effect of combined weight loss diet and cranberry supplementation on anthropometric measurements, inflammation and antioxidant biomarkers in patients with NAFLD. **Methods:** In this randomized, double-blinded, and controlled clinical trial, 41 NAFLD patients were supplemented with either cranberry or placebo tablets for 12 weeks. Both groups followed a diet of 500-1000 calories less than the estimated energy requirements. Serum levels of total antioxidant capacity (TAC), malondialdehyde (MDA), cytokeratin 18 M30 (CK-18 M30), chemokine C-C motif ligand 2 (*CCL2*) and tumor necrosis factor alpha (TNF-α) were measured at both baseline and the end of the study. **Results:** Significant improvements in TAC were observed in the cranberry group and between the two groups (P=0.006 and P=0.011, respectively), but the changes in the placebo group were not significant (P=0.325). There were no statistically significant differences in the serum levels of MDA, CK-18 M30, CCL2 and TNF-α between the cranberry and the placebo groups (P>0.05). **Conclusions:** It seems that daily consumption of cranberry supplement would be beneficial in increasing serum levels of TAC. Further studies are needed to investigate the effects of anti-inflammatory and antioxidant properties of cranberry on NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a condition in which excessive accumulation of triglycerides in the cytoplasm of hepatocytes (>0.5%) without the over-consumption of alcohol

This paper should be cited as: Hormoznejad R, Mohammad Shahi M, Mahboobi S, Rahim F, Helli B, Alavinejad P, et al. ***The Impact of Combined Cranberry Supplementation and Weight Loss Diet on Inflammatory, Antioxidant, and Apoptosis Biomarkers in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Controlled Clinical Trial.*** *Journal of Nutrition and Food Security (JNFS)*, 2024; 9(4): 692-701.

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[DOI: 10.18502/jnfs.v9i4.16898]

(Benedict and Zhang, 2017). NAFLD that embrace a broad spectrum of physio-pathological conditions from simple steatosis to non-alcoholic steatohepatitis (NASH), is highly related to obesity, diabetes, insulin resistance, hypertension, hyperlipidemia, and metabolic syndrome (Asrih and Jornayvaz, 2015). The prevalence of NAFLD is currently estimated to be about 25-30% (Le *et al.*, 2022). In terms of pathogenesis of NAFLD, it has been shown in both "two-hit" model and "multi-parallel hit" hypothesis that hepatic inflammation, oxidative stress, necrosis, apoptosis, and finally, fibrosis are caused by excessive fat accumulation in hepatocytes (Abenavoli *et al.*, 2017). A fundamental intervention for the management of NAFLD is lifestyle modification such as having healthy eating patterns and regular exercise (Friedman *et al.*, 2018, Kwon *et al.*, 2023). An increased serum content of free-radical oxidation products and a decreased total antioxidant capacity (TAC) in patients with NAFLD have been detected (Abenavoli *et al.*, 2017). It is recommended that antioxidant and anti-inflammatory supplements may be beneficial as adjuvant therapy along with healthy eating patterns in oxidative stress and inflammation among patients with NAFLD (Mansoori *et al.*, 2020). Available evidence shows that food ingredients such as phytochemicals, vitamins and minerals exhibit anti-inflammatory, antioxidant and immune-regulating activity in body (Hormoznejad *et al.*, 2021). One of the classes of phytochemicals are phenolics compounds, which include flavonoids and polyphenol (Nisar, 2022). Researchers have shown that these phytochemicals have the ability to scavenge free radicals, reduce inflammation, and modify the lipid profile. Cranberries (Vaccinium Macrocarpon) are rich in polyphenols such as flavonols, catechins, anthocyanins, resveratrol, organic acids, B-type proanthocyanidins (PACs) and a high amount of rare A-type PACs (Flammer *et al.*, 2013), and according to the United States Department of Agriculture (USDA), they have the highest free radical scavenging ability (Abenavoli *et al.*, 2016). The previous studies have shown that cranberry bio-actives have various beneficial effects, such as reducing inflammation in humans and in vitro. They also help in reducing blood markers of oxidative stress in humans (Glisan *et al.*, 2016) and hepatic inflammation and steatosis in mice that are fed a high-fat diet and hepatic inflammation and steatosis in mice fed a high-fat diet (Shimizu *et al.*, 2019). Impact of consumption of low-calorie cranberry juice on several cardiometabolic risk factors in overweight middle-aged population was investigated. There was a significant improvement in C-reactive protein (CRP) for intervention group after 8 weeks of evaluation (Novotny *et al.*, 2015).

This placebo-controlled, double-blind, randomized clinical trial study was designed to explore the possible role of combined weight loss diet and cranberry supplementation on inflammatory, antioxidant, and apoptosis biomarkers in patients with NAFLD because of the anti-inflammatory and antioxidant properties of cranberry and role of inflammation and oxidative stress in pathogenesis of NAFLD.

Materials and Methods

Samples and study design

In this randomized double-blind and placebo-controlled clinical trial, the patients with NAFLD were recruited from Ahvaz Golestan Hospital. Totally, 50 eligible patients were recruited. A signed consent form was collected by all participants. The recruited participants were randomly allocated to control (n=25) and intervention (n=25) groups based on the block design. The type of treatment was selected by numbering it in the envelope without the person studied, and the researcher was responsible for the intervention being aware of it. Elsewhere, the numbers were computerized to determine whether the number was a cranberry supplement or placebo. Being 18 or older, having body mass index (BMI) of 25–35 kg/m^2, and having confirmed NAFLD (the grade of steatosis higher or equal to 2 at ultrasonography) were the inclusion criteria; having a history of significant alcohol intake (more than 10 mL/day for women and 20 ml/d for men), smoking habits, being affected by other liver diseases, cardiovascular, respiratory, kidney disorders,

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malignancies, hypertension, dyslipidemia, hypothyroidism, and diabetes mellitus, pregnancy or breastfeeding, being under medication in the previous 6 months, having supplementation with antioxidants or vitamins, having weight loss over the past 3 months, and having metabolism and endocrine disorders pregnancy or breastfeeding, were the exclusion criteria. The placebo and cranberry groups received either placebo or cranberry tablets (two tablets; one tablet after lunch and another one after dinner) for 12 weeks. Cranberry tablets were purchased from Shari Nutraceutical Co., Tehran, Iran. Each tablet contained 144 mg of vaccinium macrocarpon extract with at least 36 mg proanthocyanidine (equal to 13 g dried cranberry fruit), while composition of the remaining 144 mg was unknown. Placebo tablets contained 288 mg starch. The cranberry and placebo tablets were similar in color, size, and weight. Both groups followed a diet of 500-1000 calories less than the estimated energy requirement. Energy requirements were calculated by Mifflin Jeor St equation. The distribution of macronutrients content in relation to the diet was as follows: 15% to 18% protein, 52% to 55% carbohydrate, and ≤ 30% fat (Bellentani et al. 2008). Dietary intakes were obtained from three 24 h dietary recalls (1 weekend day and 2 weekdays). Physical activity levels were assessed by metabolic equivalent of task (MET) questionnaire (Ainsworth *et al.*, 2000).

Biochemical and anthropometric measurements

At baseline, 6th weeks and after 12 weeks, all participants underwent anthropometric measurements: Height was measured to the nearest 0.1 cm using a non-stretched tape measure. Weight, body fat (BF), and BMI were measured using a bioelectrical impedance analysis (OMRON device BF-511). Waist circumference (WC) (the widest area between the lower rib and the superior iliac crest) was also measured to the nearest 0.1 cm. A fasting blood sample (12 ml) was collected from participants at baseline and the end of intervention. Blood samples were centrifuged at 3500 rpm for 10 min, and then, the supernates were stored at -70 °C until analysis. The serum samples were used to analyze TAC, tumor necrosis factor alpha (TNF-α), Malondialdehyde (MDA), Cytokeratin *18 M30* (CK-18 M30), and C-C Motif Chemokine Ligand 2 (CCL2). Serum levels of CCL2, CK-18 M30, TNF-α and TAC were measured using ELISA method by laboratory kits (Biotech Day Crystal for CCL2, CK-18 M30, TNF-α; and LDN, PLabor Diagnostika Nord GmbH, Germany for TAC). Serum MDA levels were assessed utilizing thiobarbituric acid reactive substances (TBARS).

Ethical considerations

The research protocol was approved by the ethics committee of the Research Deputy of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1397.678). This clinical trial study was registered in "Iranian Registry of Clinical Trials" with IRCT number IRCT20150124020765N2.

Data analysis

Considering 95% confidence interval with an estimated standard deviation and difference in fasting blood glucose (Shidfar *et al.*, 2012), the sample size was calculated, and 25 subjects in each group were determined. Statistical analyses were performed using IBM SPSS (version 19.0, SPSS Inc., Chicago, IL, USA). The results were presented as mean±SD, and P-value of lower than 0.05 was considered significant. Kolmogorov-Smirnov test was used to assess the normal distribution of variables. Independent samples comparisons in terms of quantitative variables were performed using two independent samples t-tests and repeated measures ANOVA. In order to analyze nutrient intakes, "Nutritionist IV" software was applied.

Results

In this study, 9 out of 50 patients were excluded due to non-adherence to diet and medication. Therefore, 21 participants in the group received cranberry supplements, and 20 in the placebo group remained in the study (**Figure 1**). Patients' compliance with this randomized clinical trial study was 82%. The characteristics of participants are shown in **Table 1**. No statistically significant difference was seen between the two groups in

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terms of their demographic characteristics or their baseline biomedical, and anthropometric measurements. **Table 2** shows dietary intake and anthropometric indices of the two groups. Statistical analysis showed that after 12 weeks, weight, BF, BMI, and WC significantly decreased in both groups. There was no significant difference in weight, BMI, BF, and WC between the two groups. No significant differences were also observed between two groups for dietary data including the intakes of energy and macronutrients at the end of the study.

Table 3 shows the inflammatory, antioxidant and apoptosis biomarkers at baseline after 12 weeks for the two groups. Significant improvements in TAC were observed in the cranberry group and between the two groups (P=0.006 and P=0.011, respectively), but the changes in the placebo group were not significant (P=0.325). The mean MDA was reduced (but not significantly) in the cranberry group after intervention; moreover, no significant differences were seen in serum levels of MDA between the cranberry and the placebo groups. Also, both within cranberry and placebo groups, there were no significant changes in the mean levels of CK-18 M30 in post-intervention compared with baseline. There were no statistically significant differences in the serum levels of CCL2 and TNF-α between the cranberry and the placebo groups.

Table 1. Baseline characteristics and dietary intakes of study participants.

Variable	Placebo group (n=21)	Cranberry group (n=20)	P-value[a]
Age (years)	40.00 ± 9.91	43.55 ± 11.51	0.296
Gender			
Female	7 (38.9)[b]	11 (61.1)	0.215
Male	14 (60.9)	9 (39.1)	
Weight (kg)	89.66±13.39	89.94±11.58	0.944
Height (m)	1.68±0.08	1.67±0.12	0.758
Body mass index (kg/m^2)	31.67±4.72	32.46±6.09	0.645
Waist circumference (cm)	105.64±9.19	106.52±11.15	0.783
Body fat (%)	40.12±11.01	39.46±10.72	0.847
MET (min/d)	35.77±4.81	33.68±2.44	0.090
Total antioxidant capacity (mmol/l)	1.42±0.50	1.21±0.47	0.197
*M*alondialdehyde (nmol/ml)	13.14±7.11	12.28±6.33	0.686
CK-18 M30 (ngl/ml)	16.01±7.88	18.76±7.06	0.248
CCL2 (ng/l)	851.05±875.96	916.94±374.78	0.669
TNF-α (ng/l)	433.98±300.22	547.13±242.38	0.193
Energy (kcal/day)	2714.98±799.72	2743.85±706.31	0.903
Carbohydrate (g/day)	340.15±90.84	364.51±121.15	0.469
Protein (g/day)	96.94±33.76	83.66±35.69	0.228
Fat (g/day)	104.10±55.04	95.90±19.40	0.535

***MET**: Metabolic equivalent of task; **CK-18 M30: C**ytokeratin 18-M30; **CCL2:** Chemokine C-C motif ligand 2; **TNF-α**: Tumor necrosis factor alpha; [a]: Student t-test and Ch-square test used for quantitative and categorical variables, respectively; [b]: n(%).*

Discussion

The present study was conducted to evaluate the effects of cranberry supplementation and weight loss diet on markers of inflammation (TNF-α and CCL-2), oxidative stress (MDA and TAC) and hepatic cell apoptosis (CK-18 M30) in NAFLD patients. Supplementing a weight loss diet with cranberry for a period of 12 weeks could significantly increase TAC. However, changes in other variables remained insignificant. Different studies have been conducted on the effects of cranberry with or without dietary interventions on these markers with different intervention types (extract, juice, tablet, etc), variable doses, and different findings.

Cytokine imbalances occur in the “second hit”

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of NAFLD. Therefore, the issue has gained a considerable attention as a target for therapeutic interventions (Speliotes and George, 2022). Glisan et al. evaluated the effects of polyphenol enriched cranberry extract (CBE) on markers of hepatic inflammation in HFD-fed obese rats and found that CBE can decrease hepatic protein levels of TNF-α and CCL-2, as well as hepatic mRNA levels of toll like receptor-4 (TLR-4) and nuclear factor κB (NFκB) (Glisan *et al.*, 2016). Another study was performed to evaluate possible anti-fibrotic effects of cranberry nutraceuticals in high fat cholesterol diet induced (HFCD)-NAFLD rats.

Table 2. Anthropometric measurements and dietary intakes at the baseline, 6 weeks and after 12 weeks.

Variable	Placebo group (n=21)	Cranberry group (n=20)	P-value[b]
Weight (kg)			
Baseline	89.66±13.39[c]	89.94±11.58	0.984
6 weeks	86.20±11.98	88.19±11.60	0.858
12 weeks	84.50±11.65	85.85±10.64	0.341
P-value[a]	< 0.001	<0.001	
Body mass index (kg/m^2)			
Baseline	31.67±4.72	32.46±6.09	0.749
6 weeks	30.44±4.12	31.85±6.20	0.493
12 weeks	29.87±4.32	31.04±6.02	0.551
P-value	<0.001	< 00.1	
Waist circumference			
Baseline	105.64±9.19	106.52±11.15	0.888
6 weeks	102.19±8.39	105.55±12.95	0.378
12 weeks	101.04±8.24	103.60±11.33	0.429
P-value	<0.001	<0.001	
Body fat (%)			
Baseline	40.12±11.01	39.46±10.72	0.704
6 weeks	37.13±9.96	37.76±10.38	0.676
12 weeks	34.19±9.39	34.54±10.27	0.721
P-value	<0.001	<0.001	
Energy (kcal/day)			0.067
Baseline	2714.9±799.0	2743.8±706.0	0.612
6 weeks	1956.5±344.0	2063.3±569.0	0.406
12 weeks	1749.5±395.0	1794.0±329.0	
P-value	<0.001	<0.001	
Carbohydrate (%)			
Baseline	51.18 ± 7.60	52.54 ± 6.64	0.124
6 weeks	52.84 ± 6.40	52.25 ± 6.37	0.387
12 weeks	52.94 ± 6.48	56.23 ± 7.25	0.500
P-value	<0.001	<0.001	
Protein (%)			
Baseline	15.54±4.69	14.86±4.02	0.180
6 weeks	16.68±4.86	14.97±4.77	0.472
12 weeks	16.08±5.28	14.31±3.70	0.486
P-value	0.005	0.007	
Fat (%)			
Baseline	33.28±10.49	32.60±7.28	0.069
6 weeks	30.48±11.82	32.78±6.44	0.308
12 weeks	30.98±8.53	29.46±6.52	0.364
P-value	<0.001	<0.001	

[a]: Kruskal-Wallis test; [b:] student t-test; [c]: Means±SD

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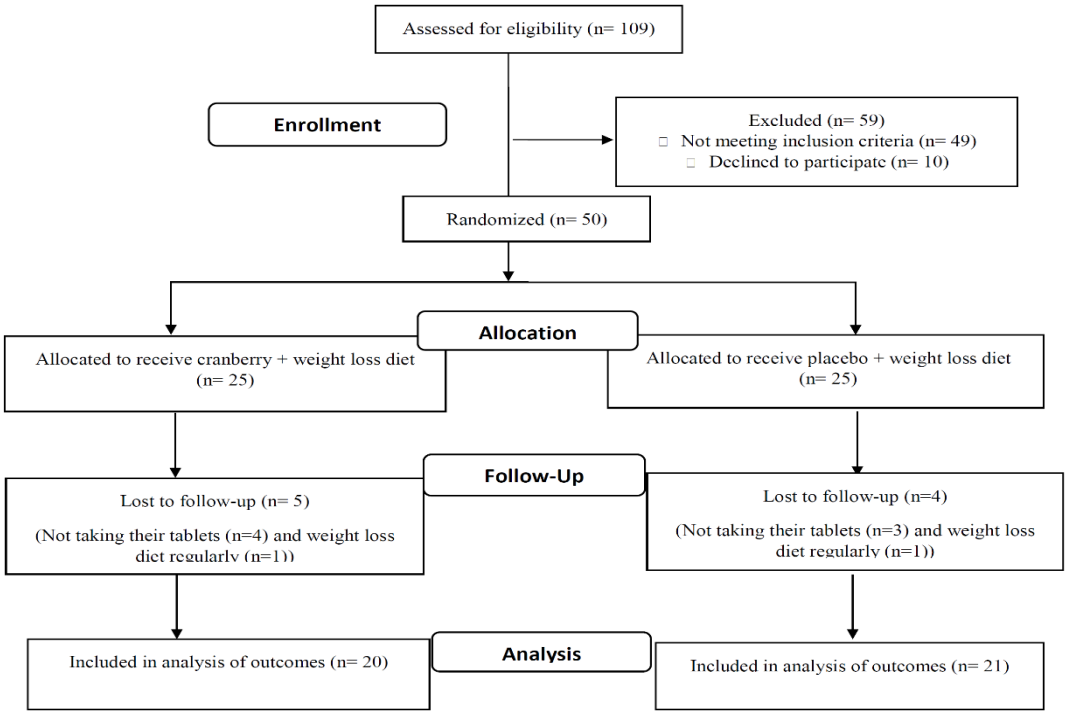

Figure 1. The study flow diagram.

Table 3. Biochemical parameters at the baseline and after 12 weeks.

Variable	Baseline	12 weeks	P-value[b]	Change
Total antioxidant capacity (mmol/l)				
Placebo	1.42±0.50[c]	1.20±0.67	0.325	-0.21±0.99
Cranberry	1.21±0.47	1.73±0.72	0.006	0.52±0.75
P-value[a]	0.197	0.004		0.011
Malondialdehyde (nmol/ml)				
Placebo	13.14±7.11	15.52±14.59	0.512	2.38±16.34
Cranberry	12.28±6.33	9.95±3.67	0.208	-2.33±8.00
P-value	0.686	0.106		0.252
CK-18 M30 (ngl/ml)				
Placebo	16.01±7.88	16.27±6.84	0.914	0.26±10.94
Cranberry	18.76±7.06	18.12±7.18	0.736	-0.63±8.29
P-value	0.248	0.403		0.316
CCL2 (ng/l)				
Placebo	851.05±875.96	960.16±591.13	0.585	109.10±900.31
Cranberry	916.94±374.78	890.02±410.38	0.752	-26.91±375.66
P-value	0.669	0.663		0.535
TNF-α (ng/l)				
Placebo	433.98±300.22	512.57±305.90	0.443	78.59±460.21
Cranberry	547.13±242.38	502.12±252.72	0.505	-45.01±296.46
P-value	0.193	0.906		0.316

CK-18 M30: *Cytokeratin 18-M30,* ***CCL2:*** *Chemokine C-C motif ligand 2 (*CCL2*),* ***TNF-α:*** *Tumor necrosis factor alpha; [a]: Student t-test; [b:] Paired t-test; [c]: Means±SD.*

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The results showed that cranberry could alleviate markers of oxidative stress (MDA, glutathione, catalase and superoxide dismutase), inflammation (TNF-α, IL-6 and NFκB) and improved markers of insulin resistance (Faheem *et al.*, 2020). Apoptosis is a key mechanism in the progression of steatosis to NASH, and apoptosis markers are related to histologic severity of NAFLD (He *et al.*, 2023). CK-18 M30 is a well-known substrate of caspase activity during apoptotic hepatocyte death (Yip *et al.*, 2023) and has been shown to have a high accuracy in differentiating NAFLD from control subjects (Zhang *et al.*, 2015). Accordingly, in the current study, CK-18 M30 was assessed as a marker of apoptosis which did not significantly change during intervention. There are few studies regarding anti-apoptotic effects of cranberries. However, some studies have been conducted on other polyphenol-rich compounds in this area. In a randomized clinical trial, 44 participants were given either 250 ml of bayberry juice or placebo twice a day for 4 weeks. Bayberry consumption could significantly improve markers of inflammation and apoptosis including polypeptide specific antigen and CK-18 M30 (Zhang *et al.*, 2015). In another study, 14 days of dark chocolate consumption, as a source of polyphenols, led to a significant reduction in CK-18 M30 in NAFLD patients (Loffredo *et al.*, 2016). According to the findings, multistage processing of fruit extraction leads to a considerable loss in phytochemical content through thermal degradation and polyphenol oxidation which could have been considered as a reason for null findings. Therefore, future research should focus on comparisons between different forms of cranberry supplements.

On the other hand, a significant improvement in TAC was observed in intervention group which indicated possible anti-oxidative effects of cranberry supplements in NAFLD patients. Oxidative stress is the result of an imbalance between pro-oxidants and anti-oxidants and plays a crucial role in pathogenesis of NAFLD (Su *et al.*, 2016). A considerable amount of research has been conducted regarding anti-oxidative effects of berries. In one study, mulberry treatment in HFD rats significantly suppressed hepatic reactive oxygen species (ROS) overproduction and mitochondrial oxidative stress (Yang and Jo, 2018). Another research team investigated the effects of raspberry on obese diabetic (db/db) mice for 8 weeks. The findings showed that raspberry intake could improve antioxidant status and lessen IL-6 in treatment group (Noratto *et al.*, 2017). Results of a double-blind randomized trial showed that 4 weeks supplementation with maqui berry (delphinol) significantly reduced markers of oxidative stress (ox-LDL and urinary F2-isoprostane) in intervention group (Davinelli *et al.*, 2015). Wild blueberry consumption significantly improved postprandial oxidative stress in male subjects. Oxygen radical absorbance capacity (ORAC) assay and the total antioxidant status (TAS) were evaluated as markers of oxidative stress in the study (Kay and Holub, 2002). On the other hand, in a randomized controlled trial, 40 post-menopausal women consumed either 22 grams of blueberry or placebo for 8 weeks. As a result, blood markers of oxidative stress, inflammation, and antioxidant defense did not change in blueberry group after 8 weeks (Johnson *et al.*, 2017).

Health benefits of fruits and vegetables have been demonstrated in nutrition, not only for their vitamins and minerals, but also for their phytochemical components (Slavin and Lloyd, 2012). The American cranberry (species *Vaccinium macrocarpon*) has been particularly considered a healthy fruit for centuries (Henig and Leahy, 2000). Cranberries, as a uniquely rich source of phytochemicals, contain over 150 phytochemicals with flavonoids as the most predominant component. Some cranberry flavonoids include anthocyanins, proanthrocyanidins, catechins, organic acids, resveratrol, and flavonols which are responsible for the fruit's color and sour astringent flavor (Pappas and Schaich, 2009). Several in vivo animal models have confirmed anticarcinogenic, antitumorogenic, antiangiogenic, anti-inflammatory, and antioxidant properties of cranberry polyphenols (Côté *et al.*, 2010). NAFLD has been linked to gut dysbiosis and metabolic endotoxemia which are the

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initial triggers of inflammatory cascade (Wieland *et al.*, 2015). NF-kβ is a key regulator in this cascade and has the potential to control the production of pro-inflammatory cytokines including TNF-α and IL-6 (Anhê *et al.*, 2013). Cranberries as a great source of polyphenols might exert prebiotics which can have immunomodulatory and anti-inflammatory effects by interacting with gut microbiota (Alves-Santos *et al.*, 2020). In one study, dietary cranberry supplementation in a mouse model of IBD, not only suppressed colonic levels of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) but also increased the abundance of beneficial gut bacteria including *lactobacillus* and *bifidobacterium* (Cai *et al.*, 2019). It has also been shown that phenolic compounds can suppress IL-1β secretion and exert anti-inflammatory effects through inhibition of cyclo-oxygenase and lipoxygenase activity (Lopez-Corona *et al.*, 2022). Antioxidant properties of cranberry are attributed to free radical scavenging properties of polyphenols against ROSs as well as inhibition of lipid and protein oxidation (Côté *et al.*, 2010). According to the studies, cranberry supplementation has also the potential to decrease NO synthase activity, improve homocysteine levels and endothelial function, thus suppressing oxidative stress (Lozovoy *et al.*, 2013).

Certain limitations of the present study include a small sample size and the short study duration. Another limitation might be the lack of polyphenol measurements in cranberry tablet via high performance liquid chromatography (HPLC) method.

Conclusion

In conclusion, this randomized, double-blind, placebo-controlled trial indicates that 288 mg/d of cranberry supplementation in addition to weight loss diet may not change MDA, CK-18 M30, CCL2, and TNF-α, but it will be beneficial in improving serum levels of TAC in NAFLD patients. Further studies are needed to investigate the effects of anti-inflammatory and antioxidant properties of cranberry on NAFLD.

Acknowledgements

This study was part of a PhD thesis by MS Hormoznejad. The authors would like to thank Golestan Hospital of Ahvaz Jundishapur University of Medical Sciences for their support.

Conflict of interests

The authors declared no conflict of interests.

Funding

The present study was financially supported by a grant (NRC-9718) from Vice-Chancellor for Research Affairs of Ahvaz Jundishapur University of Medical Sciences.

Authors' contributions

Mohammad Shahi M, Rahimi F, and Hormoznejad R were involved in the conception and design of the study. Sharhani A, Helli B, and Alavinejad P contributed to the methodology. Sharhani A performed data analysis and interpretation. Hormoznejad R, Sadeghi N, Dehghanseresht N, and Mahboobi S participated in conducting the study and drafting the manuscript. All the authors read and approved the final manuscript.

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