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Effects of *Cornus mas* L. on anthropometric and biochemical parameters among metabolic associated fatty liver disease patients: Randomized clinical trial

Hatice Merve Bayram [a,*], Raim Iliaz [b], Fatma Esra Gunes [c]

[a] Department of Nutrition and Dietetics, Faculty of Health Sciences, Istanbul Gelisim University, Istanbul, Turkey
[b] Division of Gastroenterology and Hepatology, Istanbul Atlas University, Istanbul, Turkey
[c] Department of Nutrition and Dietetics, Faculty of Health Sciences, Medeniyet University, Istanbul, Turkey

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ABSTRACT

Ethnopharmacological relevance: *Cornus mas* L. (Cornelian cherry, CM) fruits have been utilized for decades in numerous European and Asian countries as traditional cuisine and folk medicine. CM has antioxidant, anti-diabetic, anti-inflammatory, anti-obesity, and hypolipidemic activities due to its rich bioactive compounds, and CM fruits and other parts have been used for the prevention and treatment of a diverse variety of diseases in folk medicine. Obesity, insulin resistance, and inflammation are strongly associated with metabolic-associated fatty liver disease (MAFLD), therefore, CM may be hope for MAFLD patients.

Aim of the study: The study aimed to evaluate the effect of lyophilized CM fruit powder with/without diet therapy on biochemical parameters and anthropometric measurements in patients with MAFLD.

Materials and methods: This randomized clinical trial was conducted on 87 patients with MAFLD and 21 healthy individuals. Patients were randomly assigned into 4 groups: group-1 receiving 30 g/d lyophilized CM fruit powder plus diet therapy, group-2 receiving only diet therapy, group-3 receiving only 30 g/d lyophilized CM fruit powder, and group-4 had not undertaken any pharmacological treatment and diet therapy or lyophilized CM fruit powder for 8 weeks. Biochemical parameters, and anthropometric measurements at baseline and after the intervention were taken.

Results: After 8 weeks of intervention, a significant decrease in body weight, body mass index, body fat mass, waist and hip circumferences, fasting blood glucose, insulin, hbA1c, liver enzymes, total triglycerides, low-density lipoprotein, total cholesterol were found in group-1, 2 and 3.

Conclusion: Lyophilized CM fruit powder in addition to diet therapy and only diet therapy had a positive and similar effect on anthropometric measurements and biochemical parameters in MAFLD patients. Furthermore, only lyophilized CM fruit powder improved glycemic parameters. Therefore, lyophilized CM fruit powder may be beneficial for adult patients with MAFLD.

1. Introduction

Metabolic (dysfunction)-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), constitutes one of the biggest health threats of the twenty-first century affecting nearly a quarter of the population (Eslam et al., 2020a,b; Bayram et al., 2021). However, the prevalence of MAFLD was found to be much higher at 45.5% in the general population in Turkey (Yilmaz et al., 2021). MAFLD is strongly associated with obesity, metabolic syndrome, insulin resistance, dyslipidemia, and hypertension (Huang et al., 2020). Additionally, MAFLD that coexists with other liver diseases is now referred to as dual (or more) etiology fatty liver disease. Given the rapidly increasing prevalence of MAFLD, this will further increase the prevalence of MAFLD, especially in developed and developing countries such as Turkey (Xian et al., 2021).

The therapeutical approach of MAFLD is currently based on dietary and lifestyle modifications, and there has never been a definitive pharmacologic treatment proposed for it (Patel et al., 2015; EASL-EASD-EASO, 2016). For these reasons, developing new treatment processes for MAFLD patients is critical. Plant-based foods have emerged as

* Corresponding author.
E-mail addresses: merve.bayrm@gmail.com (H.M. Bayram), raimiliaz@gmail.com (R. Iliaz), fatmaesra.gunes@medeniyet.edu.tr (F.E. Gunes).

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promising natural sources of bioactive compounds such as anthocyanins for the prevention and treatment of MAFLD in recent years (Zhang et al., 2015; Li et al., 2021).

Cornelian cherry (*Cornus mas* L., CM) is an important plant, which belongs to the Cornaceae family, that grows in Europe and Southwest Asia (Dinda et al., 2016; Bayram and Ozturkcan, 2020). The use of CM as a medicinal plant took root between 450 and 100 BCE (Lietava et al., 2019). The leaves, flowers, and fruits of the plant widely used in traditional medicine for over 1000 years for the treatment and prevention of diarrhea, sore throat, hemorrhoids, diabetes, measles, digestive ailments, measles, chicken pox, anemia, rickets, liver and renal diseases in especially the Caucasus and Central Asia (Işık et al., 2014; Dinda et al., 2016; Bayram and Ozturkcan, 2020). In Turkey, the fruits and leaves of the plant are widely used for cold and flu, and urinary inflammation (Polat et al., 2013); the fruits of the plant are used for diarrhea (Güler et al., 2015), gastrointestinal diseases (Celik et al., 2006), stomach ulcers and colitis, cough (Genç and Özhatay, 2006), constipation, bronchitis (Altundag and Ozturk, 2011); and the leaves, fruits, and seeds are used diarrhea and diabetes (Sezik et al., 1991).

CM fruit has antioxidant, anti-diabetic, anti-inflammatory, anti-obesity, hypolipidemic, and protective effects against liver, kidney, and cardiovascular diseases due to its rich bioactive compounds such as anthocyanins, iridoids, flavonoids, phenolic acids, and tannins (Dinda et al., 2016; Bayram and Ozturkcan, 2020). A small number of clinical trials were carried out investigating the effects of CM fruit on NAFLD. However, these studies were based on the efficacy of CM fruit extract, not CM fruit fully (Sangsefidi et al., 2021; Sangouni et al., 2022; Yarhosseini et al., 2023). The aim of the study was to evaluate the effect of lyophilized CM fruit powder with/without diet therapy on biochemical parameters and anthropometric measurements in patients with MAFLD.

2. Materials and Methods

2.1. Preparation of fruit

We provided the *Cornus mas* L. fresh fruits from Uzundere Gölbaşı District, Erzurum, Turkey. The analysis of whether the purchased fruits belong to the "*Cornus mas* L." family was performed by the Department of Pharmaceutical Botany, Faculty of Pharmacy, Marmara University, Turkey. The fruit belonged to the "*Cornus mas* L.", and was recorded with the number MARE 22458.

The fruits were cleaned and their seeds were removed using a 32 mm porous palper machine, and the lyophilized drying process was carried out free of charge by the Pol'S company in Karaman, Turkey. The drying process was performed by sublimation with a G-Ray 125 freeze-dry machine (Fig. 1).

2.2. Determination of total anthocyanin and carbohydrate contents

The carbohydrate profile of the fruit was analyzed using a high-performance liquid chromatography - refractive index detector (RID) (Agilent 1100, USA) and Hypersil APS-2 (5 μm, 250 × 4.6 mm) column.

The total anthocyanins content of the samples was determined according to the spectrophotometric pH differential described by Tepić Horecki et al. (2018).

2.3. Safety evaluation and dosage

Group-1 and 3 received 30 g/d lyophilized CM fruit powder, which provided 350 mg/d total anthocyanin and 18 g/d carbohydrates. This dosage was safe according to previous studies (Abdollahi et al., 2014; Alavian et al., 2014; Es Haghi et al., 2014; Mesgari-Abbasi et al., 2020). Additionally, it was observed that no side effects of CM fruit in human subjects based on the previous clinical trials (Asgary et al., 2013; Soltani et al., 2015; Sangouni et al., 2022; Yarhosseini et al., 2023). However, adverse effects were monitored every two weeks during the follow-up period.

2.4. Study design and participants

This randomized clinical trial was conducted in Gastroenterology Clinic in a private University Hospital in Istanbul, Turkey, between June 2021–May 2022. The inclusion criteria: patients were aged 18–65 years, without >20 g/day for men and 10 g/day for women alcohol consumption in the past 1 year, diagnosis of steatosis through ultrasonography, resident of the city of Istanbul, and approved written consent. The exclusion criteria were: patients with hepatitis B or C, chronic liver diseases associated with viral hepatitis, such as Wilson disease, hemochromatosis, and Cushing syndrome; autoimmune liver disease; history of cardiovascular diseases, cancer, mental diseases, severe liver, and kidney dysfunction; thyroid diseases such as goiter, hypothyroidism or hyperthyroidism; with prolonged use of estrogen or regular consumption of drug associated with fatty liver diseases, such as corticosteroid, methotrexate, tamoxifen, and amiodarone; pregnant, breastfeeding, allergic to CM fruit, and unwillingness to continue the study.

All participants provided written informed consent and the study protocol was approved by Marmara University Faculty of Medicine Clinical Research (Approval number: 09.2019.810). All authors had access to the study data and reviewed and approved the final manuscript. The protocol of the study was registered at the website of clinical trials (https://clinicaltrials.gov/) with identifier number NCT05546450.

2.5. Determination of MAFLD

MAFLD was defined according to the recent consensus criteria (Eslam et al., 2020a,b). Based on these criteria MAFLD was diagnosed as the presence of hepatic steatosis by ultrasonography with any one of the listed three criteria, namely overweight/obesity (Body mass index (BMI) ≥25 kg/m^2), presence of type 2 DM, or at least two or more of the following metabolic dysfunctions presented in Fig. 2.

Liver ultrasonography was performed after at least 8 h of fasting by an expert in gastroenterology, who was blind to participants' details using a GE Logiq S7 (Seongnam-Si, Seoul, Korea) ultrasound machine. Fatty liver was identified based on a combination of liver-kidney contrast (bright liver) and vascular blurring (Yajima et al., 1983).

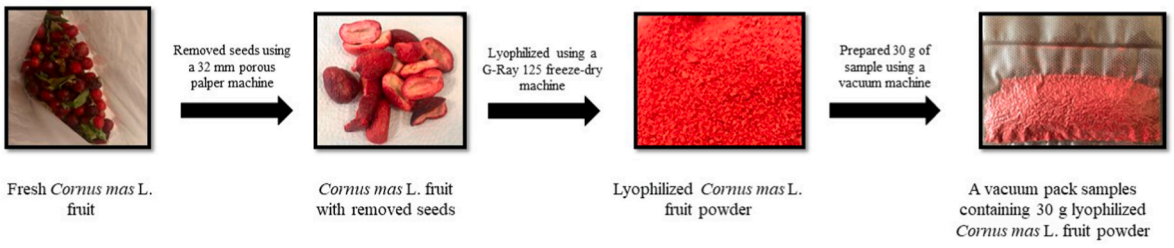

Fig. 1. The picture of lyophilized *Cornus mas* L. fruit powder.

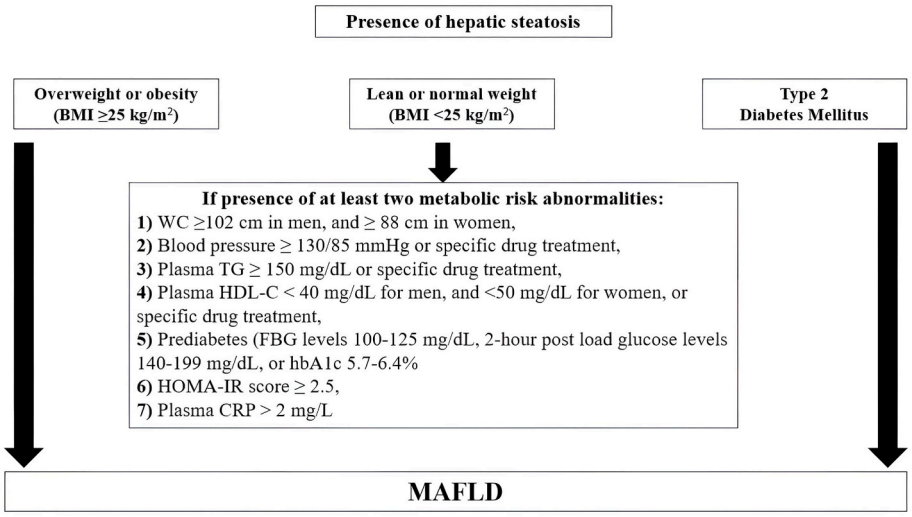

Fig. 2. Criteria defining Metabolic-associated fatty liver disease (MAFLD).

2.6. Sample size estimation

We calculated the sample size using power analysis with the prevalence as 20%, type I error rate as $\alpha = 0.05$, type II error rate as $\beta = 0.20$, and power of the test as $1\text{-}\beta = 0.80$ using previous studies (Sangsefidi et al., 2021; Yarhosseini et al., 2023). As a result, 20 individuals per group were found to be sufficient, but 25 individuals were included in all groups, considering that they may be left during the follow-up of the study.

2.7. Randomization and intervention

After an initial screening, potential subjects were assessed for inclusion in the run-in period of the trial. The subjects were given detailed information regarding the study through an information meeting in the Gastroenterology Clinic. Patients with MAFLD were randomly and equally assigned (1:1:1:1) into 4 groups, and healthy individuals were in the fifth group. A computer program was used to generate the randomization. Randomization and allocation were done by a trained nutritionist and were concealed from the patients until the primary analyses were completed. Although interventions cannot be performed in a double-blinded fashion (since study subjects clearly are aware of the type of intervention), the assessor was blinded for the tests and analyses during the entire study.

Group-1 (n: 22): This group was given 30 g/d lyophilized CM fruit powder plus a diet therapy which was performed based on the American Association for the Study of Liver Diseases (AASLD) Practice Guideline for 8 weeks. The diet is based on 500 kcal less than the patient's required energy. The proposed food plan included carbohydrates (40–45%), proteins (15–20%, about 50% of which were vegetable proteins), fats (30–35%), saturated fat (less than 10%), cholesterol (less than 200 mg/day) and fibers (25–30 g/day) (Chalasani et al., 2018). To ensure proper vitamin and mineral intake, the Turkish Recommended Dietary Allowances (RDAs) were incorporated (Turkish Ministry of Health, 2022). The diet was modified based on the number of units required from each food group for each person, and a list of food substitutes was provided.

Group-2 (n: 21): This group was only a diet therapy which was performed based on the AASLD Practice Guideline for 8 weeks. The diet is based on 500 kcal less than the patient's required energy. The proposed food plan included carbohydrates (40–45%), proteins (15–20%, about 50% of which were vegetable proteins), fats (30–35%), saturated fat (less than 10%), cholesterol (less than 200 mg/day) and fibers (25–30 g/day) (Chalasani et al., 2018). To ensure proper vitamin and mineral intake, the Turkish RDAs were incorporated (Turkish Ministry of Health, 2022). The diet was modified based on the number of units required from each food group for each person, and a list of food substitutes was provided.

Group-3 (n: 22): This group was given only 30 g/d lyophilized CM fruit powder without a low-calorie diet for 8 weeks.

Group-4 (n: 22): This group included patients with MAFLD and met the inclusion criteria. Additionally, patients in this group who had not undertaken any pharmacological treatment and diet therapy or lyophilized CM fruit powder were monitored for the same period.

Group-5 (n: 21): This group included healthy individuals who were not diagnosed with MAFLD according to Fig. 2 criteria and met the inclusion criteria.

At the beginning of the study, the necessary explanations about the observance of the diet were given to all study participants, and all patients were given and instructed on an exchange list to facilitate diet compliance. Diet adherence was monitored weekly with phone calls, two interviews for a month, and the collection of three 24-h recalls. All patients spent about 45 min with a dietitian for learning the basics of their diets every 15 days. Additionally, we gave a list of other fruits and vegetables containing anthocyanin to the participants, therefore, we ensured that they did not consume any anthocyanin-containing food other than CM.

2.8. Assessment of dietary intake

The 24-h dietary recall was used for the assessment of the dietary intake of participants for 3 consecutive days (one on weekends, 2 on weekdays). Additionally, all participants were given brief instructions on how to keep a food diary and completed a 24-h dietary recall (including food item, preparation, and amount) upon enrollment and every 15 days for 8 weeks during the study intervals. All 3-day food records were analyzed using Nutrition Information System Package Program version 8.2 for macronutrient distribution (Schmind, 2011), and the results were compared with the Turkish recommended daily (or dietary) allowance (RDA) according to the age and gender of Dietary Guidelines for Turkey. A nutrient intake of less than two-thirds of the RDA (67%) was considered inadequate (Turkish Ministry of Health, 2022).

2.9. Assessment of anthropometric measurements

Anthropometric measurements (height, body analysis, waist and hip circumferences) were taken every 15 days for 8 weeks by trained and qualified nutritionists using standardized procedures.

Height was measured to the nearest 0.1 cm using a stadiometer. Tanita SC-330 (Accurate Technology Co., Ltd. Tianjin, China) was used to analyze body composition, and the subjects' body weight, percentage of lean mass, and fat were recorded. Waist circumference (WC) was measured using a non-stretch plastic tape measure with an accuracy of 1 mm on the midaxillary line at the midpoint between the lowest rib and the iliac crest. Hip circumference (HC) was measured at the widest point between the waist and the knee using a non-stretch plastic tape measure with an accuracy of within 1 mm.

BMI was calculated by dividing the weight (in kg) by the square of the height (in square m).

2.10. Biochemical parameters

At the beginning and the 8 weeks of intervention, blood samples were collected after fasting for 8–10 h, and laboratory data such as fasting blood glucose (FBG), fasting insulin, glycated hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), C reactive protein (CRP) were analyzed.

Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the equation: HOMA-IR = Fasting insulin (μU/mL) x fasting glucose (mg/dL)/405 (Matthews et al., 1985).

2.11. Statistical analysis

The study data were analyzed with SPSS software, version 24.0 (Statistical Package for the Social Sciences). Quantitative and qualitative data were described using mean (SD) and frequency (%), respectively. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Parameters with a normal distribution were energy, protein, fat, height, body fat mass, body fat percentage, body muscle mass, body muscle percentage, and HC. In contrast, parameters without a normal distribution were carbohydrates, body weight, BMI, WC, FBG, insulin, HOMA-IR, hbA1c, AST, ALT, ALP, GGT, Total TG, HDL-C, LDL-C, TC, and CRP. The ANOVA test was used to compare the mean values of data for groups that had normal distribution, and Tukey's test was used to determine which groups caused the difference in significant data. On the contrary, the Kruskal-Wallis test was used to compare the data from more than two groups that did not fit the normal distribution, and the Mann-Whitney *U* test was used to determine which groups caused the difference in significant data. Additionally, we carried out within-group comparisons (pre and post-intervention) using the paired *t*-test (for parameters with normal distribution) and the Wilcoxon test (for parameters with abnormal distribution). Statistical significance was defined as a P-value < 0.05.

3. Results

As shown in Fig. 3, a total of 87 patients with MAFLD and 21 healthy individuals completed the study. Notable, no adverse effects were reported following lyophilized CM fruit powder throughout the study.

The general characteristics of the participants are shown in Table 1. There was no statistically significant difference in demographic characteristics between the groups diagnosed with MAFLD. There was no statistically significant difference between all groups in demographic characteristics, except age and education ($p < 0.001$, and p: 0.014, respectively).

At the baseline, there was no statistically significant difference between the energy, carbohydrate, protein, and fat intakes of the participants. Additionally, energy intake from baseline to the end of the study in group-1, group-2, and group-3 (p: 0.005, $p < 0.001$, and p: 0.022, respectively); carbohydrate intake in group-2 (p: 0.007); protein intake in group-1 (p: 0.021); fat intake in group-1 and group-2 ($p < 0.001$ in both) were statistically different (Table 2).

Table 3 comparatively shows the effects of interventions on anthropometric measurements. A statistically significant decrease was found from baseline to the end of the study in body weight and BMI in group-1, group-2, and group-3 ($p < 0.001$, $p < 0.001$, p: 0.001, respectively). Similar results were found for WC and HC (for WC $p < 0.001$ for group-1, group-2, and group-3; for HC $p < 0.001$, $p < 0.001$, and p: 0.016, respectively). Body fat mass showed a statistically significant difference from baseline to the end of the study in all groups ($p < 0.001$ for group-1, $p < 0.001$ for group-2, p: 0.017 for group-3, p: 0.047

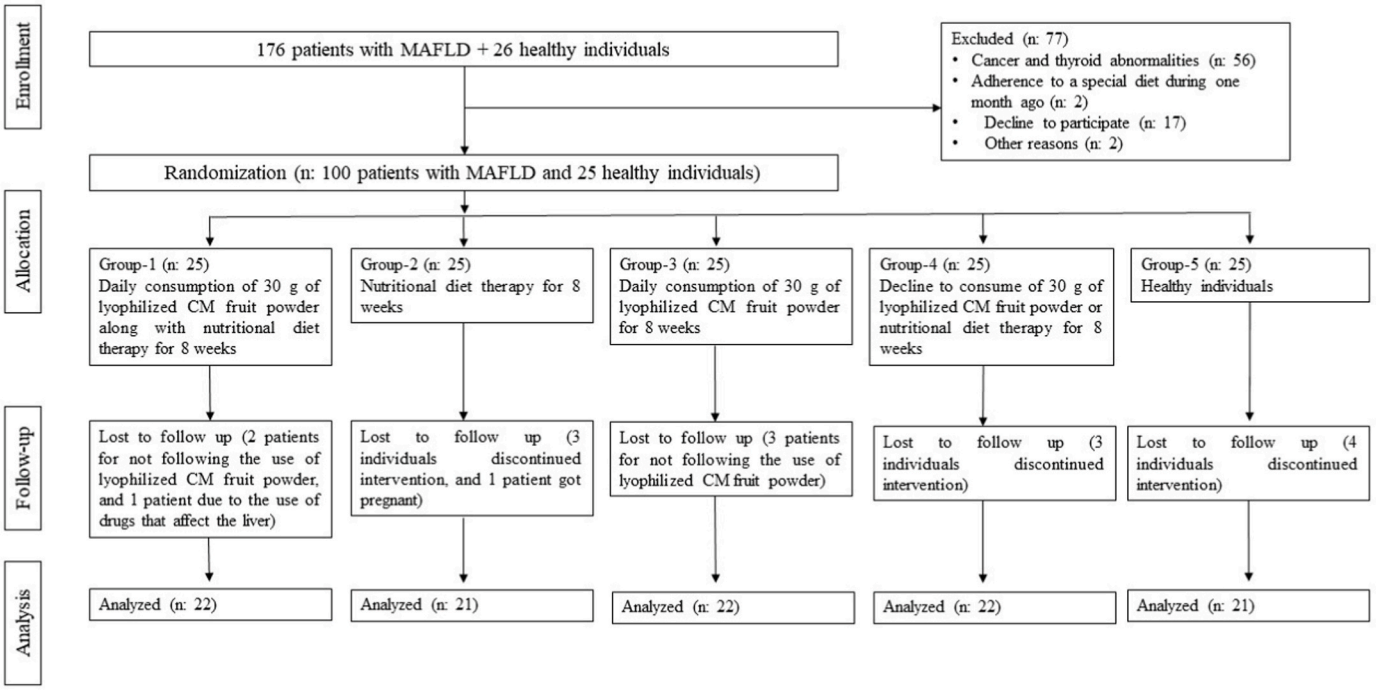

Fig. 3. Flowchart of the study.

Table 1
General characteristics of participants (n = 108).

	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	Group-5 (n = 21)	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Age[¥]	48.72 ± 11.90	41.52 ± 11.12	43.90 ± 10.44	43.40 ± 12.46	30.90 ± 4.91	0.213[a], < **0.001**[*,b]
Sex						0.999[a], 1.000[b]
Female	12 (54.5)	11 (52.4)	12 (54.5)	12 (54.5)	11 (52.4)	
Male	10 (45.5)	10 (47.6)	10 (45.5)	10 (45.5)	10 (47.6)	
Education						0.336[a], **0.014**[*,b]
Elementary school or lower	6 (27.3)	2 (9.5)	5 (22.7)	6 (27.2)	–	
High school	4 (18.2)	4 (19.0)	4 (18.2)	8 (36.4)	1 (4.8)	
University or higher	12 (54.5)	15 (71.5)	13 (59.1)	8 (36.4)	20 (95.2)	
Occupation						0.520[a], 0.232[b]
Non-Employee	8 (36.4)	3 (14.3)	4 (18.2)	5 (22.7)	2 (9.5)	
Self-employed	2 (9.1)	6 (28.6)	5 (22.7)	6 (27.3)	2 (9.5)	
Employee	12 (54.5)	12 (57.1)	13 (59.1)	11 (50.0)	17 (81.0)	
Marital status						0.747[a], 0.766[b]
Married	18 (81.8)	15 (71.4)	16 (72.7)	18 (81.8)	15 (71.4)	
Single/ Divorced	4 (18.2)	6 (28.6)	6 (27.3)	4 (18.2)	6 (28.6)	
Smoking history						0.221[a], 0.335[b]
Yes	15 (68.2)	9 (42.9)	15 (68.2)	11 (50.0)	13 (61.9)	
No	7 (31.8)	12 (57.1)	7 (31.8)	11 (50.0)	8 (38.1)	
Physical activity						0.530[a], 0.667[b]
Yes	4 (18.2)	3 (15.0)	2 (9.1)	1 (4.5)	3 (14.3)	
No	18 (81.8)	17 (85.0)	20 (90.9)	21 (95.5)	18 (85.7)	
History of chronic disease						0.921[a], 0.661[b]
Yes	2 (9.1)	2 (9.5)	1 (4.5)	2 (9.1)	–	
No	20 (90.9)	19 (90.5)	21 (95.5)	20 (90.9)	–	

*p < 0,005; **p < 0,001, [a]Differences between groups which diagnosed MAFD (Group-1 to group-4). [b]Differences between all groups. p-values (except age) were calculated using the chi-square test. [¥]Differences were calculated using Kruskall-Wallis test.

for group-4, and group-p for 5: 0.023). There was no statistically significant difference between group-1 and group-2 in the weight loss (%), body fat mass, WC, and HC.

In group-1, group-2, and group-3, FBG (p: 0.009, p: 0.009, and p: 0.020, respectively), insulin (p < 0.001, p < 0.001, and p: 0.002, respectively), HOMA–IR (p < 0.001, p < 0.001, p: 0.001, respectively), hbA1c (p < 0.001 for all groups), TG (p < 0.001, p: 0.001, p < 0.001, respectively), LDL-C (p: 0.001, p: 0.001, p: 0.003, respectively), TC (p < 0.001, p < 0.001, p: 0.004, respectively) showed a statistically significant decrease from baseline to the end of the study. In group-4, these values increased statistically significantly (p: 0.024, p: 0.004, p < 0.001, p: 0.007, p: 0.003, and p: 0.033, respectively). Additionally, liver enzymes (AST, ALT, ALP, and GGT) decreased significantly from baseline to the end of the study in group-1, group-2, and group-3. However, AST, ALT, and GGT values increased statistically at the beginning and end of the study in group-4 (p: 0.027, p < 0.001, p: 0.007, respectively). CRP levels decreased statistically significantly from baseline to the end of the study in group-1 and group-2 (p: 0.003 and p: 0.013, respectively). There was no statistically significant difference between group-1 and group-2 in mean changes of FBG, HOMA-IR, hbA1c, TG, LDL-C, TC, liver enzymes, and CRP (Table 4).

At baseline, 27.3% of patients with grade I, 50.0% with grade II, and 22.7% with grade III in group-1. At the end of the study, the degree of steatosis was found to be grade 0 at 9.1%, grade I at 22.7%, grade II at 59.1%, and grade III at 9.1%. In group-2, 14.3% of patients with grade I and a total of 85.7% with grade II at baseline. At the end of the study, the degree of steatosis was found to be grade I in 28.6%, and grade II in 71.4% of patients. It was observed that the severity of hepatic steatosis in the study group-3 did not change at the baseline and the end of the study. In the study group-4, there were 27.3% of patients with grade I, 68.2% with grade II, and 4.5% with grade III at baseline. However, at the end of the study, these values were determined as 18.2%, 77.3%, and 4.5%, respectively (p < 0.001) (Table 5).

4. Discussion

Based on our knowledge, the present study was the first study that determined the effect of lyophilized CM fruit powder with/without diet therapy on nutritional status and biochemical parameters in patients with MAFLD. Lyophilized CM fruit powder with/without diet therapy showed a significant reduction in abdominal obesity parameters (such as body weight, body fat mass, WC, and HC), serum glycose profile (FBG, insulin, HOMA-IR, and hbA1c), lipid profile (TG, LDL-C, and TC), and liver enzymes (AST, ALT, and GGT). There was no statistically significant between lyophilized CM fruit powder with diet therapy and only diet therapy on anthropometric and biochemical parameters in MAFLD patients.

Currently, there is no pharmacological treatment for MAFLD. The only treatment method is lifestyle modification with diet therapy which will reduce body weight together with an increase in physical activity (Patel et al., 2015; EASL-EASD-EASO, 2016). It was reported that only 53.9% of MAFD patients intended to lose weight. However, energy intake was found to be similar in groups that dieted and did not diet (Nguyen et al., 2021). We found that 50.6% of patients with MAFLD did not intend to do diet therapy which was composed of group-3, and group-4. Additionally, energy and macronutrient intakes were similar in all groups at baseline and end of the study. However, energy intakes were statistically significantly decreased in groups-1, 2, and 3. These findings highlight the significance of diet composition, rather than just energy intake.

It is emphasized that at least 3–5% body weight loss is required to improve steatosis, but 7–10% body weight loss to improve most histopathological features of NASH, including fibrosis according to the AASLD (Chalasani et al., 2018). According to the literature, an increase in the extent of weight loss indicates a more improvement in liver histology. It has been demonstrated that losing 7% or more of one's body weight results in a significant reduction in inflammation, hepatocyte ballooning (Promrat et al., 2010), and also a greater extent of weight loss was related to the level of improvement in all histological parameters related to MAFLD (Vilar-Gomez et al., 2015). In this study, the mean change in weight loss was 6.53% in group-1 and 6.26% in group-2, and there was no statistically significant difference between the two groups. Furthermore, diet therapy reduced BMI, WC, and HC, as well as the expected body weight loss in MAFLD patients. Our results showed that reduction of abdominal obesity along with weight loss is still beneficial effects patients with MAFLD.

Evidence suggests that CM fruit and its compounds may have an anti-obesity effect (Azzini et al., 2017; Gholamrezayi et al., 2019). The possible mechanism of action of consumption of CM fruit in reducing

Table 2
Macronutrients intake across groups at the beginning and end of the study (n = 108).

Parameters	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	Group-5 (n = 21)	p-value
Energy (kcal/d)						
Baseline	2076.11 ± 616.31	2134.55 ± 586.39	2190.00 ± 702.23	2175.89 ± 464.53	1879.87 ± 547.24	0.325
Week 8	1633.74 ± 121.69	1564.79 ± 174.76[b,*]	1775.54 ± 718.30	1897.34 ± 636.48	1951.74 ± 50.154[b,*]	**0.018***
p[g] value	**0.005***	< **0.001****	**0.022***	0.069	0.593	
Change	−552.67 (−938.04–87.39)	−619.77 (−972.00 to −145.09)[b,*]	−205.03 (−939.34–−43.05)	−356.21 (−694.04–93.04)	21.16 (−377.00-629.20)[b,*]	**0.030***
Carbohydrates (g/d)						
Baseline	173.81 (107.09–241.11)	158.00 (148.56–198.16)	183.88 (117.48–240.84)	203.02 (128.34–228.69)	162.63 (130.78–201.23)	0.749
Week 8	160.79 (146.49–173.19)[g,*]	132.15 (120.85–155.27)[b,g,i,*]	140.37 (89.68–188.03)	178.86 (124.12–229.52)[i,*]	172.95 (144.34–218.69)[b,*]	**0.043***
p[g] value	0.634	**0.007***	0.148	0.459	0.874	
Change	−13.54 (−79.20–42.34)	−29.88 (−67.00–0.47)	−21.79 (−82.66–23.37)	−23.49 (−59.76–59.89)	−8.28 (−44.87–54.77)	0.362
Proteins (g/d)						
Baseline	67.88 ± 20.93	81.04 ± 26.53	83.48 ± 41.35	79.56 ± 28.57	68.26 ± 18.76	0.348
Week 8	82.54 ± 17.58	89.81 ± 16.19[b,i,*]	84.96 ± 49.65	73.90 ± 47.27[i,*]	68.71 ± 15.25[b,*]	**0.001***
p[g] value	**0.021***	0.228	0.888	0.577	0.925	
Change	15.87 (−7.33–28.28)	6.66 (−9.06–25.56)	0.12 (−15.67–18.80)	−6.40 (−28.55–9.69)	3.03 (−10.77–13.71)	0.145
Fats (g/d)						
Baseline	112.72 ± 42.71	108.72 ± 34.35	118.68 ± 63.88	119.46 ± 39.43	98.59 ± 32.68	0.555
Week 8	70.10 ± 7.96[a,*]	69.81 ± 14.01[b,*]	88.54 ± 56.24	99.55 ± 55.51	107.19 ± 40.35 [a,b,*]	**0.002***
p[g] value	< **0.001****	< **0.001****	0.070	0.150	0.416	
Change	−42.14 (−70.44 to −6.79) [a,*]	−36.52 (−63.75 to −21.61) [b,*]	−25.64 (−62.14–19.80)	−23.87 (−54.57–16.62)	−1.65 (−19.55–44.07) [a, b,*]	**0.009***

*p < 0,005; **p < 0,001; [g]: for comparison of within-group differences. P[g] values were calculated using paired sample *t*-test or Wilcoxon test was used for pre and post-intervention. Parameters with homogeneous distribution were given as mean ± standard deviation and were analyzed with the ANOVA test, those without homogeneous distribution were given as the median (25-75th interquartile range) and analyzed with the Kruskall-Wallis test. [a]: Differences between group-5 and group-1; [b]: Differences between group-5 and group-2; [c]: Differences between group-5 and group-3; [d]: Differences between group-5 and group-4; [e]: Differences between group-4 and group-1; [f]: Differences between group-3 and group-1; [g]: Differences between group-2 and group-1; [h]: Differences between group-4 and group-3; [i]: Differences between group-4 and group-2; [i]: Differences between group-3 and group-2.

body weight is thought to be due to anthocyanins. The first possible effect is that anthocyanins may alter the mitogen-activated protein kinase (MAPK) and NF-κB stress signaling pathway, implying a cytoprotective and anti-inflammatory role in obesity pathology (Azzini et al., 2017). The second possible effect is that they may reduce body weight loss by increasing adiponectin levels and reducing leptin secretion and fat deposition (Azzini et al., 2017). The third possible effect is the suppression of visceral fat accumulation through the inhibition of pancreatic lipase activity, thereby reducing intestinal fat absorption (Azzini et al., 2017). However, clinical trials on the role of anthocyanins in obesity remain contentious (Soltani et al., 2015; Gholamrezayi et al., 2019; Yarhosseini et al., 2023). It was observed that there were no significant differences between 20 cc/d CM fruit extract and placebo in body weight, body fat mass, HC, and WC in NAFLD patients (Yarhosseini et al., 2023). In T2DM patients, CM extract containing 300 mg anthocyanin reduced BMI, however, this reduction was not statistically significant compared to placebo (Soltani et al., 2015). It was observed that CM extract containing 900 mg anthocyanin decreased body weight, BMI, and waist circumference after 8 weeks in postmenopausal women (Gholamrezayi et al., 2019). Our findings showed that the change in body weight was 1.55% in group-3, and this decrease was statistically significant. However, there was also a statistically significant reduction in BMI, body fat mass, WC and HC. The reason for this is the mechanism of action of CM fruit on anti-obesity, as well as the dose and type of extract consumed. Higher doses of CM fruit extract may improve obesity indicators (Yarhosseini et al., 2023).

Anthocyanin-containing foods have been shown to improve body inflammatory status and insulin sensitivity in obese patients (Stull et al., 2010; Wright et al., 2013). Administration of CM extract containing 300 mg anthocyanins showed no significant reduction in AST and ALT levels after 6 weeks in T2DM patients (Soltani et al., 2015). Administration of 20 mL CM fruit extract decreased in ALT after 12 weeks, however, this decrease was not statistically significant in NAFLD patients. Additionally, there was no significant effect on AST levels (Sangsefidi et al., 2021). In this study, we found that AST, ALT, ALP, and GGT levels were statistically significantly decreased in group-1 and group-2. The reason for this could be a decrease in abdominal obesity, a decrease in hepatic steatosis, and an improvement in liver enzyme levels in diet therapy groups. A statistically significant decrease in liver enzyme levels was also found in study group-3. The fact that the CM fruit was given whole rather than as an extract may have contributed to the statistical significance of the results in this study. Polyphenols have a synergistic effect, and an increase in polyphenol content contributes to antioxidant capacity (Cheshchevik et al., 2012). However, it is well known that reducing body weight and fat with diet therapy lowers liver enzymes and has a positive effect on liver fat (Mundi et al., 2020).

Some beneficial effects have been demonstrated attributable to CM's flavonoids, including anthocyanins. According to cell studies, the polyphenols in CM fruits have the ability to control blood glucose by inhibiting α-amylase and β-glucosidase enzymes (Apostolidis et al., 2006; da Silva Pinto et al., 2010). Berry polyphenols were shown o inhibit SGLT-1 and prevent glucose absorption from the intestines *in vitro* and *in vivo* studies (Törrönen et al., 2010). Another study found that CM fruit polyphenols can stimulate insulin receptor phosphorylation and glucose uptake by tissues (Zhang et al., 2006). However, there are limited clinical trials on this issue. Administration of CM extract containing 300 mg of anthocyanins decreased FBG, and hbA1c, but increased fasting insulin levels in patients with T2DM after 6 weeks (Soltani et al., 2015). In NAFLD patients, administration of 20 mL of CM extract reduced FBG, insulin levels, and HOMA-IR after 12 weeks, the results were not statistically significant (Sangsefidi et al., 2021). In this study, FBG, insulin, HOMA-IR, and hbA1c levels were statistically significantly lower at the end of the study in groups 1, 2, and 3. However, there was no statistically significant difference between group-1 and group-2 among the mean changes. This may be due to the amount and duration of the CM fruit.

CM fruit has been shown to improve lipid profile, especially in patients with dyslipidemia and hyperlipidemia (Asgary et al., 2013; Soltani

Table 3
Anthropometric characteristics across groups at the beginning and end of the study (n = 108).

Parameters	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	Group-5 (n = 21)	p-value
Height (cm)	164.18 ± 10.74	168.71 ± 11.21	167.95 ± 10.39	167.59 ± 8.61	169.61 ± 8.60	0.491
Body weight (kg)						
Baseline	83.15 (73.85–91.05)	92.70 (77.35–106.45) [b,*]	83.75 (72.77–95.82)	88.00 (79.75–97.00)[d,*]	70.00 (58.05–81.65) [b,d,*]	**0.001****
Week 8	79.05 (69.03–86.57)[e,*]	87.50 (72.65–101.30) [b,*]	82.25 (72.97–92.15)	87.70 (80.60–95.72)[d,e,*]	70.10 (58.50–81.60)[b,d,*]	**0.001****
p^g value	< **0.001****	< **0.001****	**0.001****	0.372	0.861	
Change	−5.25 (−6.32 to −2.60) [a,e,f,*]	−5.70 (−7.20 to −3.85) [b,i,i,**]	−1.20 (−1.87–0.02) [i,**]	0.05 (−0.90–1.00) [e,f,i,i,**]	0.00 (−0.30–0.25) [a,b,**]	< **0.001****
Change (%)	−6.53 (−7.76 to −4.36) [a,e,f,*]	−6.26 (−7.91 to −4.96) [b,i,i,**]	−1.55 (−2.21–0.03) [f,i,**]	0.06 (−1.04–1.25) [e,i,**]	0.00 (−0.39–0.28) [a,b,**]	< **0.001****
BMI (kg/m^2)						
Baseline	31.17 (28.59–33.05) [a,*]	32.25 (30.09–36.41) [b,*]	29.81 (26.81–32.39) [c,*]	32.16 (28.78–34.08) [d,*]	23.87 (21.60–25.90) [a,b,c,d,*]	< **0.001****
Week 8	28.54 (26.56–31.39) [a,e,*]	30.64 (28.64–34.35) [b,*]	29.67 (26.66–32.03) [c,*]	32.29 (28.86–34.42) [d,e,*]	23.91 (21.88–25.93) [a,b,c,d,*]	< **0.001****
p^g value	< **0.001****	< **0.001****	**0.001****	0.420	0.711	
Change	−2.05 (−2.49 to −1.35)[a,e,f,*]	−2.17 (−2.51 to −1.41)[b,i,i,*]	−0.44 (−0.68–0.00)[f,h,i,*]	0.01 (−0.30–0.34)[f,h,i,*]	0.00 (−0.10–0.08)[a,b,*]	< **0.001****
Body fat mass (kg)						
Baseline	29.73 ± 7.02[a,**]	36.34 ± 11.09[b,**]	28.84 ± 9.13[c,**]	32.30 ± 8.40[d,*]	17.81 ± 8.49[a,b,c,d,*]	< **0.001****
Week 8	24.81 ± 6.72[e,*]	32.01 ± 9.88[b,**]	27.38 ± 9.16[c,*]	33.00 ± 8.46[d,e,*]	18.34 ± 8.77 [b,c,d,*]	< **0.001****
p^g value	< **0.001****	< **0.001****	**0.017***	**0.047***	**0.023***	
Change	−4.30 (−6.10 to −3.17) [a,e,f,*]	−4.00 (−5.75 to −2.60) [b,i,i,*]	−0.90 (−1.82 to −0.22) [f,h,i,*]	0.30 (−0.22–1.25) [e,h,i,**]	0.10 (−0.10–1.00) [a,b,*]	< **0.001****
Body fat percentage (%)						
Baseline	35.84 ± 7.72[a,*]	38.21 ± 6.59[b,**]	33.10 ± 7.16	35.89 ± 7.59[d,**]	24.77 ± 9.44[a,b,d*]	< **0.001****
Week 8	31.91 ± 8.05	35.78 ± 6.57[b,*]	32.58 ± 7.54	36.42 ± 7.57[d,*]	25.43 ± 9.34[b,d,*]	< **0.001****
p^g value	< **0.001****	< **0.001****	0.160	0.054	**0.017***	
Change	−3.20 (−4.65 to −2.00) [a,e,f,*]	−2.40 (−3.30 to −1.40) [b,i,i,*]	−0.35 (−1.55–0.02) [f,h,i,*]	0.40 (−0.05–1.12) [e,h,i,**]	0.10 (−0.10–1.25) [a,b,*]	< **0.001****
Body muscle mass (kg)						
Baseline	51.71 ± 10.78	46.41 ± 17.47	54.87 ± 12.28	46.18 ± 14.85	49.42 ± 11.52	0.195
Week 8	50.66 ± 10.17	45.20 ± 17.14	54.53 ± 11.79	45.51 ± 14.64	49.03 ± 11.37	0.125
p^g value	**0.028***	< **0.001****	0.332	**0.032***	**0.041***	
Change	−1.10 (−2.35–0.25)[a,e,f,*]	- 0.80 (−1.90 to −0.40)[b,i,*]	−0.45 (−1.50–1.00)[f,h,*]	−0.50 (−1.07–0.00)[e,h,i,*]	−0.10 (−0.60–0.05)[a,b,*]	0.097
Body muscle percentage (%)						
Baseline	61.64 ± 7.32	49.02 ± 15.29 [b,i,*]	63.69 ± 6.99[i,h,*]	50.99 ± 13.59 [d,h,*]	70.79 ± 10.47[b,d,**]	< **0.001****
Week 8	64.68 ± 7.68[e,*]	50.79 ± 15.30[b,*]	64.42 ± 7.32[h,*]	50.05 ± 13.62 [d,e,h,*]	69.87 ± 10.78 [b,d,**]	< **0.001****
p^g value	< **0.001****	< **0.001****	0.075	**0.008***	0.243	
Change	2.81 (1.48–4.30) [a,e,f,*]	1.85 (0.84–2.48) [b,i,**]	0.26 (−0.02–1.66) [f,h,*]	−0.71 (−1.68–0.00) [e,h,i,*]	−0.28 (−1.13–0.16) [a,b,**]	< **0.001****
Waist circumference (cm)						
Baseline	103.00 (101.50–112.25)[a,**]	106.00 (98.50–111.50)[b,**]	103.00 (95.75–112.50)[c,**]	105.00 (96.00–117.25)[d,**]	89.00 (76.50–94.50) [a,b,c,d,**]	< **0.001****
Week 8	100.00 (94.75–106.00) [a,*]	102.00 (94.00–108.00) [b,*]	101.50 (93.75–112.25) [c,*]	105.50 (97.75–117.50) [d,*]	90.00 (76.00–94.50) [a,b,c,d,*]	< **0.001****
p^g value	< **0.001****	< **0.001****	< **0.001****	0.185	0.206	
Change	−6.00 (−7.25 to −3.00)[a,e,f,*]	−4.00 (−6.00 to −2.00)[b,i,i,*]	−1.00 (−2.00 to −0.75) [e,h,i,*]	0.00 (0.00–1.00)[e,h,i,*]	0.00 (−0.50–0.00)[a,b,*]	< **0.001****
Hip circumference (cm)						
Baseline	113.63 ± 6.38[a,**]	113.85 ± 9.64[b,*]	113.22 ± 10.02[c,*]	113.54 ± 10.35[d,*]	103.33 ± 8.04[a,b,c,d,*]	**0.001****
Week 8	109.18 ± 7.15	110.80 ± 9.20	112.31 ± 10.44[c,*]	113.59 ± 9.58[d,*]	103.09 ± 7.87[c,d,*]	**0.006***
p^g value	< **0.001****	< **0.001****	**0.016***	0.874	0.382	
Change	−4.00 (−7.00 to −2.00) [a,e,f,*]	−3.00 (−3.50 to −2.00) [b,i,i,*]	−0.50 (−2.00-0.00) [f,i,*]	0.00 (0.00–1.00) [e,i,**]	0.00 (−1.00-0.50) [a,b,*]	< **0.001****

*p < 0,005; **p < 0,001; [g]: for comparison of within-group differences. P^g values were calculated using paired sample *t*-test or Wilcoxon test was used for pre and post-intervention. Parameters with homogeneous distribution were given as mean ± standard deviation and were analyzed with the ANOVA test, those without homogeneous distribution were given as the median (25-75th interquartile range) and analyzed with the Kruskall-Wallis test. [a]: Differences between group-5 and group-1; [b]: Differences between group-5 and group-2; [c]: Differences between group-5 and group-3; [d]: Differences between group-5 and group-4; [e]: Differences between group-4 and group-1; [f]: Differences between group-3 and group-1; [g]: Differences between group-2 and group-1; [h]: Differences between group-4 and group-3; [i]: Differences between group-4 and group-2; [i]: Differences between group-3 and group-2.

Table 4
Biochemical parameters across groups at the beginning and end of the study (n = 108).

Parameters	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	Group-5 (n = 21)	p-value
FBG (mg/dL)						
Baseline	101.00 (96.25–105.50)	97.67 (89.50–107.50)	104.50 (93.75–114.00) [c,*]	92.00 (86.75–101.92)	90.00 (85.50–97.50) [c,*]	**0.006***
Week 8	91.00 (84.00–103.00)	92.00 (87.00–99.50)	99.00 (90.75–108.00) [c,*]	98.50 (90.75–108.75) [d,*]	90.00 (84.50–97.00) [c,d,*]	**0.041***
p[g] value	**0.009***	**0.009***	**0.020***	**0.024***	0.740	
Change	−6.50 (−19.25–3.25) [e,*]	−3.00 (−8.00-1.00) [i,*]	−3.15 (8.52–1.25) [h,*]	2.50 (−0.25–8.00) [e,h,i,*]	1.00 (−3.00–3.50)	**0.001****
Insulin (μIU/mL)						
Baseline	17.95 (16.00–20.05) [a,**]	16.00 (12.75–18.60) [b,**]	16.35 (10.55–19.85) [c,**]	16.85 (14.17–20.10) [d,**]	5.00 (2.65–7.00) [a,b,c,d,**]	< **0.001****
Week 8	9.65 (8.50–10.85) [e,f,*]	11.30 (9.50–13.30) [i,i,*]	13.70 (10.32–16.02) [f,i,*]	17.55 (14.77–21.12) [e,i,*]	6.00 (4.05–7.63) [a,b,d,*]	< **0.001****
p[g] value	< **0.001****	< **0.001****	**0.002***	**0.004***	0.357	
Change	−8.15 (−10.32 to −4.20) [a,e,f,**]	−4.70 (−5.40 to −2.80) [b,i,*]	−2.55 (−4.00 to −1.48) [f,h,*]	1.70 (0.47–3.92) [e,h,i,*]	0.80 (−1.20–2.25) [a,b,**]	< **0.001****
HOMA-IR						
Baseline	3.82 (3.43–4.57) [a,**]	3.38 (2.78–4.15) [b,**]	3.78 (2.63–4.77) [c,**]	3.49 (2.85–4.50) [d,**]	0.97 (0.57–1.41) [a,b,c,d,**]	< **0.001****
Week 8	1.90 (1.62–2.43) [a,e,f,*]	2.39 (1.98–2.73) [b,i,*]	2.94 (2.12–3.65) [c,f,h,*]	4.21 (3.29–4.97) [d,e,h,i,*]	1.09 (0.81–1.50) [a,b,c,d,**]	< **0.001****
p[g] value	< **0.001****	< **0.001****	**0.001***	< **0.001****	0.322	
Change	−1.94 (−2.71 to −1.24) [a,e,f,*]	−1.03 (−1.44 to −0.50) [b,i,*]	−0.72 (−1.24 to −0.25) [f,h,*]	0.60 (0.23–0.98) [e,h,i,**]	0.13 (−0.19–0.46) [a,b,**]	< **0.001****
HbA1c (%)						
Baseline	5.95 (5.57–6.32) [a,**]	5.70 (5.60–6.10) [b,**]	5.80 (5.50–6.02) [c,**]	5.90 (5.60–6.10) [d,**]	4.80 (4.50–5.20) [a,b,c,d,**]	< **0.001****
Week 8	5.50 (5.17–5.90) [a,e,**]	5.50 (5.35–5.80) [b,i,*]	5.65 (5.37–5.90) [c,h,*]	6.05 (5.90–6.30) [d,e,h,i,*]	4.90 (4.45–5.30) [a,b,c,d,*]	< **0.001****
p[g] value	< **0.001****	< **0.001****	< **0.001****	**0.003***	0.433	
Change	−0.30 (−0.52 to −0.20) [a,e,f,*]	−0.20 (−0.35 to −0.10) [b,i,*]	−0.10 (−0.20 to −0.10) [f,h,*]	0.20 (0.02–0.30) [e,h,i,*]	0.00 (−0.10–0.10) [a,b,**]	< **0.001****
AST (u/L)						
Baseline	24.00 (18.00–43.50)[a,*]	21.00 (20.50–39.00) [b,*]	30.00 (20.50–39.00) [c,*]	34.00 (20.75–47.25) [d,*]	15.00 (14.00–20.00) [a,b,c,d,*]	< **0.001****
Week 8	18.00 (16.50–21.00) [e,*]	21.00 (15.50–32.50) [i,*]	19.00 (15.00–24.25) [h,*]	38.50 (21.00–50.25) [d,e,h,i,*]	17.00 (15.00–19.50) [d,**]	< **0.001****
p[g] value	**0.001***	< **0.001****	**0.001***	**0.027***	0.187	
Change	−5.00 (−20.25 to −0.75) [a,e,*]	−4.00 (−12.40 to −1.50) [b,i,*]	−9.00 (−17.37 to −1.50) [c,h,*]	2.00 (−1.00-6.00) [e,h,i,**]	1.00 (−1.00-2.00) [a,b,c,*]	< **0.001****
ALT (u/L)						
Baseline	33.50 (22.50–74.25) [a,*]	35.00 (24.00–52.75) [b,*]	29.70 (22.00–49.25) [c,*]	26.00 (22.50–49.55) [d,*]	18.00 (9.50–27.00) [a,b,c,d,*]	< **0.001****
Week 8	23.00[e,*]	25.00 (16.00–38.00)	25.50 (17.90–34.75)	37.00 (25.75–77.50) [d,e,*]	18.00 (9.50–27.00) [d,*]	< **0.001****
p[g] value	< **0.001****	**0.001***	**0.009***	< **0.001****	0.252	
Change	−14.00 (−35.00 to −1.00) [a,e,*]	−7.00 (−20.50 to −1.04) [b,i,*]	−5.00 (−21.25–2.25) [h,*]	5.00 (3.00–10.00) [e,h,i,**]	0.00 (−1.00-2.00) [a,b,*]	< **0.001****
ALP (u/L)						
Baseline	96.71 ± 32.33[a,*]	87.62 ± 15.89[b,*]	74.00 ± 17.86	73.46 ± 23.56	56.40 ± 20.43[a,b,*]	< **0.001****
Week 8	65.28 ± 19.09	64.93 ± 12.80	61.00 ± 13.57	75.33 ± 23.23	57.55 ± 21.94	0.216
p[g] value	< **0.001****	< **0.001****	< **0.001****	0.492	0.295	
Change	−19.00 (−52.00–−7.00)	−19.00 (−26.25–−7.00)	−8.50 (−21.25–−3.75)	2.00 (−3.00–4.00)	0.00 (−1.00–2.00)	
GGT (u/L)						
Baseline	35.50 (19.00–73.00)[a,*]	37.50 (24.00–60.00) [b,*]	39.00 (26.80–49.50) [c,*]	38.00 (21.50–43.50) [d,*]	12.00 (10.00–25.50) [a,b,c,d,*]	**0.001****
Week 8	18.00[e,*]	25.00 (21.25–46.25) [b,*]	30.00 (21.00–43.50) [c,*]	40.00 (23.50–47.00) [d,e,*]	14.00 (11.00–25.75) [b,d,c,*]	< **0.001****
p[g] value	< **0.001****	**0.001***	**0.021***	**0.007***	0.141	
Change	−12.5 (−20.50 to −3.75) 0[a,e,**]	−5.50 (−29.75 to −2.00) [b,i,*]	−3.00 (−14.50–1.50) [h,*]	2.00 (1.00–4.50) [e,h,i,**]	0.50 (−0.75–1.00) [a,b,*]	< **0.001****
Total TG (mg/dL)						
Baseline	168.50 (136.75–221.00) [c,**]	147.00 (111.50–211.00) [f,k,*]	187.00 (150.50–210.00) [e,i,k,**]	135.50 (105.00–192.00) [d,i,*]	78.00 (66.50–90.00) [c,d,e,f,*]	< **0.001****
Week 8	107.00 (79.75–129.62) [e,*]	115.00 (68.00–148.50) [i,*]	123.00 (94.75–145.00) [c,*]	158.00 (121.25–197.00) [d,e,i,*]	76.00 (69.00–86.50) [c,d,*]	< **0.001****
p[g] value	< **0.001****	**0.001***	< **0.001****	**0.007***	0.588	
Change	−60.50 (−108.00 to −34.75) [a,e,*]	−34.20 (−55.50 to −2.85) [i,*]	−59.00 (−97.75 to −34.17) [c,h,*]	9.50 (0.25–41.75) [e,h,i,*]	−1.00 (−3.30–2.50) [a,c,*]	< **0.001****
HDL-C (mg/dL)						
Baseline	45.35 (35.75–56.00)	50.00 (45.75–61.00)	40.00 (35.00–56.25)	44.00 (24.87–52.00) [d,*]	52.00 (46.50–66.00) [d,*]	**0.005***
Week 8	46.00 (38.57–57.75)	53.00 (47.00–56.00) [i,*]	44.00 (37.50–56.25)	42.00 (33.50–50.75) [d,i,*]	53.00 (48.50–65.50) [d,*]	**0.003***
p[g] value	**0.040***	0.968	0.614	**0.025***	0.251	
Change	2.00 (−0.35–7.55)	0.00 (−4.80–3.35)	−1.60 (−4.50–6.00)	−1.00 (−3.00–0.00)	1.00 (−1.00–2.00)	0.050
LDL-C (mg/dL)						

(*continued on next page*)

Table 4 (*continued*)

Parameters	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	Group-5 (n = 21)	p-value
Baseline	152.90 (122.25–190.00) [a,**]	134.00 (122.50–168.70) [b,*]	142.90 (115.50–160.75) [c,*]	132.50 (93.00–150.80) [d,**]	87.00 (76.50–110.50) [a,b,c,d,*]	< **0.001****
Week 8	129.50 (102.50–146.75) [a,**]	121.00 (111.10–137.50) [b,*]	113.00 (100.50–152.50) [c,*]	145.00 (116.00–162.25) [d,**]	88.00 (78.00–104.50) [a,b,c,d,*]	< **0.001****
p^g value	**0.001***	**0.001***	**0.003***	**0.003***	0.265	
Change	−24.00 (−43.25 to −10.25)[a,e,**]	−12.00 (−24.85–0.00) [i,**]	−17.00 (−22.50 to −1.75) [h,**]	7.00 (0.50–29.25) [e,h,i,**]	2.00 (−2.15–6.00) [a,**]	< **0.001****
TC (mg/dL)						
Baseline	239.50 (206.50–257.50) [a,e,**]	208.00 (184.20–241.00) [b,*]	207.50 (185.75–231.50) [c,*]	197.50 (160.50–220.25) [e,*]	162.00 (140.00–177.00) [a,b,c,*]	< **0.001****
Week 8	199.00 (185.25–205.00) [a,*]	186.00 (171.50–203.60)	199.50 (171.75–215.75)[c,*]	196.50 (163.75–232.25) [d,*]	155.00 (143.00–177.50) [a,c,d,*]	**0.001****
p^g value	< **0.001****	< **0.001****	**0.004***	**0.033***	0.767	
Change	−42.00 (−60.25 to −26.50) [a,e,f,**]	−20.00 (−33.00 to −6.70) [b,i,**]	−6.00 (−16.75–0.02) [f,i,*]	5.50 (−1.25–14.50) [e,h,i,**]	4.00 (−11.00-8.50) [a,b,**]	< **0.001****
CRP (mg/L)						
Baseline	2.05 (0.20–4.10) [a,*]	4.50 (2.00–14.67) [b,*]	2.61 (1.37–5.98)	1.50 (0.30–2.35)	0.40 (0.08–1.50) [a,b,*]	**0.006***
Week 8	0.75 (0.20–2.15)	2.00 (0.95–6.62)	1.99 (0.97–6.40)	1.48 (0.20–2.70)	0.50 (0.25–3.15)	0.200
p^g value	**0.003***	**0.013***	0.181	0.638	0.535	
Change	−0.69 (−2.52–0.00) [a,e,*]	−0.08 (−1.70–0.00) [b,*]	−0.51 (−1.01–0.19)	0.00 (−0.60–0.31) [e,*]	0.00 (−0.14–0.65) [a,b,*]	**0.045***

*p < 0,005; **p < 0,001; [g]: for comparison of within-group differences. P^g values were calculated using paired sample *t*-test or Wilcoxon test was used for pre and post-intervention. Parameters with homogeneous distribution were given as mean ± standard deviation and were analyzed with the ANOVA test, those without homogeneous distribution were given as the median (25-75th interquartile range) and analyzed with the Kruskall-Wallis test. [a]: Differences between group-5 and group-1; [b]: Differences between group-5 and group-2; [c]: Differences between group-5 and group-3; [d]: Differences between group-5 and group-4; [e]: Differences between group-4 and group-1; [f]: Differences between group-3 and group-1; [g]: Differences between group-2 and group-1; [h]: Differences between group-4 and group-3; [i]: Differences between group-4 and group-2; [i]: Differences between group-3 and group-2.

Table 5
The severity of hepatic steatosis across groups at the beginning and end of the study.

The severity of hepatic steatosis	Group-1 (n = 22)	Group-2 (n = 21)	Group-3 (n = 22)	Group-4 (n = 22)	p-value
	(n, %)	(n, %)	(n, %)	(n, %)	
Grade 0					<0.001*
Baseline	–	–	–	–	<0.001**
Week 8	2 (9.1)	–	–	–	
Grade I					
Baseline	6 (27.3)	3 (14.3)	5 (22.7)	6 (27.3)	
Week 8	5 (22.7)	6 (28.6)	5 (22.7)	4 (18.2)	
Grade II					
Baseline	11 (50.0)	18 (85.7)	15 (68.2)	15 (68.2)	
Week 8	13 (59.1)	15 (71.4)	15 (68.2)	17 (77.3)	
Grade III					
Baseline	5 (22.7)	–	2 (9.1)	1 (4.5)	
Week 8	2 (9.1)	–	2 (9.1)	1 (4.5)	

*p < 0.001 for comparison of across-group differences at baseline, **p < 0.001 for comparison of across-group differences at 8 weeks. p-values were calculated using chi-square test.

et al., 2015; Gholamrezayi et al., 2019; Sangsefidi et al., 2021). The potential mechanism for CM to lower triglycerides may be due to its effect on improving insulin status and, as a result, lowering insulin levels. Insulin controls the expression of the SREBP-1 gene, which controls genes involved in glucose and fat metabolism (Gholamrezayi et al., 2019). Insulin stimulates the expression of the glycerol-3-phosphate acyltransferase gene, the first enzyme in the triglyceride production pathway. CM can also inhibit lipase in the pancreas and intestinal absorption of lipids (Gholamrezayi et al., 2019). In a study conducted with dyslipidemic children and adolescents, the consumption of 50 g of CM fruit twice a day decreased total TG levels at the end of 6 weeks, the results were not statistically significant (Asgary et al., 2013). The intervention of CM extract containing 300 mg anthocyanins reduced total TG after 6 weeks in T2DM patients (Soltani et al., 2015). Another study showed that 20 mL CM extract showed no statistically significant effect on TG levels after 12 weeks in NAFLD patients (Sangsefidi et al., 2021). In this study, total TG levels were statistically significantly decreased in group-1, group-2, and group-3.

Moreover, it is thought that polyphenols lower TC by increasing the excretion of sterols and bile acids in the feces (Neto, 2007). Eliminating bile acids can stimulate the liver to convert more cholesterol to bile acid, lowering cholesterol ((Neto, 2007). Furthermore, polyphenols can increase the expression of paraoxonase-1, an antioxidant enzyme associated with HDL-c ((Neto, 2007). This enzyme is known as a stimulant for reverse cholesterol transfusion, which can justify an increase in HDL-c (Neto, 2007). However, since an inverse relationship between the activity of this protein and HDL level has been demonstrated, the potential mechanism of CM fruit to increase HDL-c can be referred to as the cholesterol ester transferase inhibitory function (Beyer et al., 2008). Additionally, anthocyanins have a potential effect on increasing PPARα expression, which can increase HDL-c and lower LDL-c and TC (Du et al., 2015). A 6-week study on children and adolescents with dyslipidemia found that consuming 50 g of CM fruit twice a day had no statistically significant effect on LDL-c, TC, or HDL-c (Asgary et al., 2013). Similarly, CM extract containing 900 mg/day of anthocyanin did not result in a statistically significant change in LDL-c, TC, or HDL-c after 8 weeks in postmenopausal women (Gholamrezayi et al., 2019). In this study, LDL-c and TC levels were statistically significantly lower in groups 1, 2, and 3. Although HDL-c increased in these 3 groups at the end of the study, the results were statistically significant for only group-1. Our findings suggest that the dose and duration of CM fruit can help improve the lipid profile. A higher dose and duration of CM fruit consumption could have resulted in more positive effects.

Additionally, we found that the severity of hepatic steatosis was decreased in 27.3% of patients in group-1, and 14.3% of patients in group-2. However, the severity of hepatic steatosis in patients did not change at the baseline and the end of the study in group-3. In the line with our study, it can be concluded that adding lyophilized CM fruit powder to the diet therapy and only diet therapy reduces the degree of hepatic steatosis, while consumption of lyophilized CM fruit powder alone could prevent progression of the steatosis in MAFLD patients.

The present study has some strengths. First, the present study was the first clinical trial evaluating the effect of lyophilized CM fruit powder on anthropometric measurements and biochemical parameters in MAFLD

patients. We tried standardizing the lyophilized CM fruit powder according to the carbohydrate profile and total anthocyanin content. We also measured the levels of flavonoids, total polyphenols, and ascorbic acid. Moreover, we controlled for dietary intake and physical activity status as critical confounding factors. Second, there is no clinical study that investigated the effect of lyophilized CM fruit powder plus diet therapy. Therefore, our study may shed light on future studies.

The present study has some limitations. First, ultrasound was used to identify the presence of hepatic steatosis. Although ultrasound is the most widely used diagnostic method, fibroscan and biopsy have higher accuracy. Second, nutritional status was evaluated with a 24-h dietary recall. Since this method is based on recall, the participants may have under-reported the foods they consumed.

5. Conclusion

In this study, lyophilized CM fruit powder in addition to diet therapy and only diet therapy had a positive and similar effect on anthropometric measurements or biochemical parameters in MAFLD patients. Furthermore, only lyophilized CM fruit powder consumption showed to reduce body weight, BMI, body fat mass, waist and hip circumferences as well as ameliorate lipid profile and glycemic parameters in MAFLD patients. Therefore, lyophilized CM fruit powder may be beneficial for adult patients with MAFLD. However, further studies with larger sample sizes and longer duration are required to confirm these results.

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CRediT authorship contribution statement

Hatice Merve Bayram: Conceptualization, Methodology, Software, Investigation, Writing – original draft. **Raim Iliaz:** Investigation, Writing - review & editing. **Fatma Esra Gunes:** Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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