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# Impact of astaxanthin on oxidative markers, uric acid, and clinical symptoms in heart failure: a randomized clinical trial

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## Abstract

**Background and aims** Chronic heart failure (HF) is often linked to increased oxidative stress and metabolic issues like high uric acid, which can worsen outcomes. Astaxanthin (ASX), a strong antioxidant, may help reduce these harmful effects. This study aimed to investigate the effects of ASX supplementation on oxidative stress markers as the primary outcome and clinical symptoms in patients with HF.

**Methods** In this randomized, double-blind, placebo-controlled clinical trial, 80 patients with HF were enrolled and randomly assigned to receive either ASX (20 mg/day) or a placebo (20 mg/day of maltodextrin) for 8 weeks. Biomarkers including total antioxidant capacity (TAC), malondialdehyde (MDA), superoxide dismutase (SOD), serum UA, and clinical symptoms (dyspnea, fatigue, appetite) were assessed pre-and post-intervention.

**Results** After eight weeks, compared to the placebo group, participants receiving ASX supplementation showed a significant increase in TAC (0.12 vs. -0.04 mmol/L, $P=0.002$) and SOD levels (156.92 vs. 36.14 U/mL, $P<0.001$). In contrast, the ASX group demonstrated significantly greater reductions in MDA (-2.19 vs. -0.68 nmol/L, $P<0.001$) and serum UA levels (-1.82 vs. -0.63 mg/dl, $P=0.003$) compared to placebo. Furthermore, among ASX treated patients, improvements in dyspnea and fatigue were statistically significant ($P<0.001$), while the increase in appetite was only marginally significant ($P=0.071$).

**Conclusion** These findings suggest that ASX supplementation may be effective in improving oxidative stress biomarkers and clinical status in patients with HF.

**Trial registration** Iranian Registry of Clinical Trials IRCT20200429047235N3. Registered on 26 March 2024, prior to the enrollment of the first participant. http://irct.behdasht.gov.ir/trial/75913.

**Keywords** Astaxanthin, Oxidative Stress, Uric Acid, Heart Failure, Dyspnea, Fatigue

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## Introduction

Heart failure (HF) is a chronic and progressive cardiovascular condition that imposes a significant burden on public health and healthcare systems worldwide [1]. It represents the final common pathway of many cardiovascular diseases. It is characterized by the heart's inability to pump blood effectively, resulting in fluid retention, dyspnea, fatigue, and reduced exercise tolerance [2]. Oxidative stress has been extensively recognized as a critical factor in the pathogenesis of HF. Under oxidative stress conditions, the balance between reactive oxygen species (ROS) production and the antioxidant defense system is disrupted, leading to cellular damage, mitochondrial dysfunction, and accelerated disease progression [3].

Among the laboratory markers used to evaluate oxidative stress are malondialdehyde (MDA), an indicator of lipid peroxidation; superoxide dismutase (SOD), an essential antioxidant enzyme; and total antioxidant capacity (TAC), which reflects the cumulative effect of all antioxidants present in plasma [4]. In addition, elevated serum uric acid (UA) levels have been recognized as an oxidative stress-related factor in HF patients. High UA concentrations have been associated with adverse cardiovascular outcomes and are considered an independent predictor of mortality and morbidity in these patients [4, 5]. Therefore, controlling oxidative stress and related biochemical factors may contribute to better clinical outcomes and an enhanced quality of life in HF patients.

ASX is a naturally occurring carotenoid with potent antioxidant properties, found abundantly in red-pigmented marine organisms such as microalgae, shrimp, and salmon [6]. Due to its ability to cross the blood–brain barrier, high stability, and integration into phospholipid membranes, ASX can effectively protect cells against oxidative damage [7]. Previous research has demonstrated its protective effects in diabetes, cancer, cardiovascular diseases, and chronic inflammatory disorders [8, 9]. However, clinical evidence regarding its efficacy, particularly in HF patients, remains scarce. Previous studies have often faced limitations by small sample sizes, suboptimal study designs, and a lack of comprehensive evaluation of both biochemical and clinical parameters.

Given these limitations, the present study was conducted to survey the impact of ASX supplementation on oxidative stress biomarkers, serum UA levels, and clinical outcomes in patients with HF.

## Methods and materials

### Study design and eligibility criteria

This study was designed as a randomized, double-blind, placebo-controlled clinical trial. The study was designed and carried out in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. A completed CONSORT checklist is provided in the supplementary file. A total of 80 patients with stage C or D HF, as defined by the American Heart Association (AHA) criteria [10] and with a left ventricular ejection fraction (LVEF) of less than 50% were recruited from a specialized Heart Hospital in Isfahan, Iran. Thus, only patients with heart failure with reduced ejection fraction (HFrEF) or mildly reduced ejection fraction (HFmrEF) were included, and patients with heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%) were not enrolled.

Inclusion criteria were as follows: age ≥ 18 years, confirmed diagnosis of heart failure, willingness to participate in the study, and provision of written informed consent before study initiation. Non-inclusion criteria included pregnancy or lactation, alcohol or drug addiction, uncontrolled diabetes, consumption of antioxidant supplements within three months prior to the study, warfarin use, adherence to a specific diet or exercise program, chronic hepatic, renal, or pulmonary diseases, inflammatory conditions such as Crohn's disease or ulcerative colitis, malignancy, and recent acute coronary syndrome or cardiac surgery within the past four weeks. Exclusion criteria were experiencing any adverse reaction or hypersensitivity not present before supplementation, consuming less than 80% of the total prescribed ASX capsules, undergoing changes in the prescribed medication regimen, or expressing unwillingness to continue participation.

The sample size was calculated based on a 5% significance level ($Z\alpha = 1.96$), 80% statistical power ($Z\beta = 0.84$), and a standardized effect size ($\Delta = 0.7$) for TAC as the primary outcome [11]. Based on these parameters, a total of 80 participants were enrolled, with 40 individuals allocated to each group. A detailed description of the study methodology is provided in the published study protocol in Trials journal [12]. This study has been officially registered in the Iranian Registry of Clinical Trials (ID: IRCT20200429047235N3). Additionally, the study protocol received approval from the Ethics Committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1402.099).

### Intervention protocol and implementation

Eligible individuals referred to specialized Heart Hospital who provided written informed consent were enrolled in the study. Participants were randomly assigned to either the intervention or placebo group and followed for 8 weeks. The intervention group received one 20 mg oral capsule of ASX daily in its non-esterified, cis-isomer form, manufactured by "Zist Fanavari Taravat Zendegi". The control group received a visually identical (same color, smell, and taste) 20 mg maltodextrin capsule, manufactured by Osina Shimi under the brand Foodchem. Both groups were instructed to take the capsule

with lunch each day for a total duration of 60 consecutive days.

The selected dose of ASX was based on a review of the existing literature and known safe intake levels, with 20 mg/day identified as an appropriate and evidence-based dosage for this study [11, 13]. To reduce potential confounding variables, participants were asked to maintain their usual dietary patterns and physical activity levels throughout the study period.

Patients were reminded via regular phone calls and text message to ensure compliance. Also, each participant was provided with a daily supplement intake checklist to mark upon consumption, which was collected at the end of the study. Compliance percentage was calculated as the proportion of capsules consumed relative to the total capsules dispensed.

#### Randomization and blinding process

All eligible participants who met the inclusion criteria were randomly assigned to two groups using block randomization with permuted blocks of size four. Randomization was performed using an online random number generator (https://www.sealedenvelope.com/simple-randomiser/v1/lists).

A trained staff member, not involved in the recruitment or randomization process, was responsible for preparing the supplement containers. Both ASX and placebo capsules were labeled with codes (Code A and Code B) by this individual. These codes remained concealed from all study personnel, including participants, investigators, and laboratory staff, until the completion of the study to ensure allocation concealment and blinding.

#### Evaluation of nutritional intake and physical activity

To assess the participants' nutritional intake, each patient was instructed to complete three 3-day food records (two weekdays and one weekend day) at baseline, midpoint, and the end of the intervention. The validity and reliability of this dietary record method have been previously confirmed [14]. The dietary data were analyzed using the Nutritionist IV software (First Databank, Hearst Corp, San Bruno, CA, USA) to determine energy intake, macronutrients, and micronutrients. Physical activity levels were assessed at baseline, midpoint, and the end of the study using the International Physical Activity Questionnaire (IPAQ), whose validity and reliability have been previously validated [15].

#### Biochemical assessment

A total of 10 mL of venous blood after 10–12 h fasting was drawn from each participant. Blood samples were centrifuged at 3500 rpm, and the resulting serum was transferred into microtubes and stored at − 80 °C until analysis.

Serum UA levels were measured using the uricase method with Pars Peyvand diagnostic kits. Antioxidant markers including SOD, TAC, and MDA were assessed using commercial kits provided by Navand Salamat. TAC was evaluated using the Ferric Reducing Antioxidant Power (FRAP) method [16]. SOD activity was determined based on the inhibition of pyrogallol autoxidation [17]. MDA concentration was measured using the Thiobarbituric Acid Reactive Substances (TBARS) colorimetric method [18].

#### Fatigue severity score assessment

Fatigue severity was assessed using the Persian version of the Fatigue Severity Scale (FSS). The FSS consists of nine statements rated on a 7-point Likert scale, ranging from 0 ("strongly disagree") to 7 ("strongly agree"). The total possible score ranges from 0 to 63.

The content validity of the Persian version of the FSS has been previously confirmed in Iranian populations [19].

#### Dyspnea severity score assessment

Dyspnea was evaluated using the 5-point Modified Medical Research Council (MMRC) Dyspnea Scale. This scale ranges from 0 (no dyspnea during strenuous exercise or daily activities) to 4 (dyspnea during routine daily activities). Participants were asked to read the descriptive statements and select the score that best matched their experience of dyspnea [20]. The Persian version has demonstrated strong reliability and validated content via evaluations from experts in cardiology, pulmonology, and nursing [21].

#### Appetite score assessment

Appetite was assessed using the Simplified Nutritional Appetite Questionnaire (SNAQ). The total score ranges from 4 to 20, with higher scores indicating better appetite. The validity and reliability of the Persian version of the questionnaire have been previously confirmed in the Iranian population [22].

#### Demographic and basic clinical characteristics of study participants

Demographic variables, including age, gender, marital status, smoking status, medical history, family history of disease, educational level, occupation, and use of supplements and medications, were collected using a structured general information questionnaire. The socioeconomic status of participants at the beginning of the study was assessed using the socioeconomic status short-form questionnaire (SES-SQ). The questionnaire provides a total score ranging from 0 to 17. Participants with a score below 4.5 were classified as low socioeconomic status, those scoring between 4.5 and 8.5 as middle class, and

those above 8.5 as high socioeconomic status. The validity and reliability of this questionnaire have been previously confirmed [23].

### Statistical analysis

In this study, continuous variables were presented as mean ± standard deviation when data followed a normal distribution, and as median (interquartile range) for variables not normally distributed. Categorical variables were expressed as frequencies (percentages). The Shapiro–Wilk test and Q–Q plots were used to assess the normality of data distribution. Data analysis was conducted according to intention-to-treat (ITT) principle. Baseline comparisons between groups (both continuous and categorical variables) were performed using independent samples t-tests and chi-square tests, respectively. Within-group changes in continuous variables were analyzed using the paired t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables and ordinal categorical variables, such as dyspnea severity. Between-group comparisons for continuous normally distributed variables were done using analysis of covariance (ANCOVA) while for non-normal continuous variables and ordinal categorical variables were performed using generalized estimating equations (GEE) and adjustment was made for potential confounding variables in both methods.

Changes in dietary intake and physical activity levels over time between groups were analyzed using repeated-measures analysis of variance. All statistical analyses were conducted using SPSS version 20 (IBM Corp. IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp; 2011), with a significance level set at $P < 0.05$. A $P$ value between 0.05 and 0.1 was considered as marginally significant.

## Results

The study initially enrolled 80 participants. During the study period, 10 individuals withdrew (5 from the control group and 5 from the intervention group) (Fig. 1). Two participants in the intervention group experienced gastrointestinal adverse effects, including nausea and vomiting. Ultimately, data from all participants were analyzed according to the ITT principle. Adherence to supplementation was high in both groups. The compliance rate was 93.5% in the ASX group and 94.2% in the placebo group, with no statistically significant difference between groups ($P = 0.620$).

### Characteristic of participants

Table 1 summarizes the baseline characteristics of participants in both groups, including quantitative variables such as age, weight, height, body mass index (BMI), waist circumference, and blood pressure and qualitative variables, including gender, marital status, education level, medical history, family history, supplement use, smoking status, and medication use. No significant differences were observed between groups for any variables except smoking frequency, which differed significantly.

### Dietary intake and physical activity of participants in the intervention and control groups

Table 2 presents the dietary intake data of study participants indicated that a statistically significant difference was observed only in the intake of vitamin A between the intervention and control groups. No significant differences were found over the study period between two groups regarding the intake of other macronutrients and other micronutrients. Table 3 presents the physical activity levels of participants at the baseline, midpoint, and end of the study. Repeated-measures ANOVA showed no significant group × time interaction for physical activity levels ($P = 0.597$). The main effect of group was also non-significant ($P = 0.646$). Within-group analyses revealed no significant changes from baseline to study end in either the ASX group ($P = 0.41$) or the placebo group ($P = 0.36$). Thus, physical activity levels remained stable throughout the 8-week study in both groups.

### Comparison of oxidative stress markers and clinical symptoms in intervention and control groups

Table 4 presents the results of the effect of ASX supplementation on oxidative stress markers, UA, and, the severity of dyspnea, fatigue, and appetite levels. The mean MDA levels in both groups significantly decreased post-intervention compared to baseline. Moreover, the between-group comparison of mean changes indicated a greater reduction in the intervention group than the control group ($P < 0.001$), and this difference remained statistically significant after adjusting for potential confounders (including baseline values, gender, smoking, and mean vitamin A) ($P < 0.001$). The mean TAC in the intervention group showed a statistically significant increase at the end of the study compared to baseline ($P = 0.001$). The between-group comparison of changes in TAC from baseline revealed a significant difference ($P < 0.001$), which remained significant even after controlling for confounding variables ($P = 0.002$). The mean SOD levels significantly increased in both groups compared to the start of the intervention. However, the intervention group demonstrated a significantly greater increase than the control group ($P < 0.001$), and this difference persisted after adjusting for confounders ($P < 0.001$). In both groups, mean UA levels significantly decreased post-intervention compared to baseline. The between-group comparison showed that the reduction in UA was significantly greater in the intervention group ($P = 0.001$),

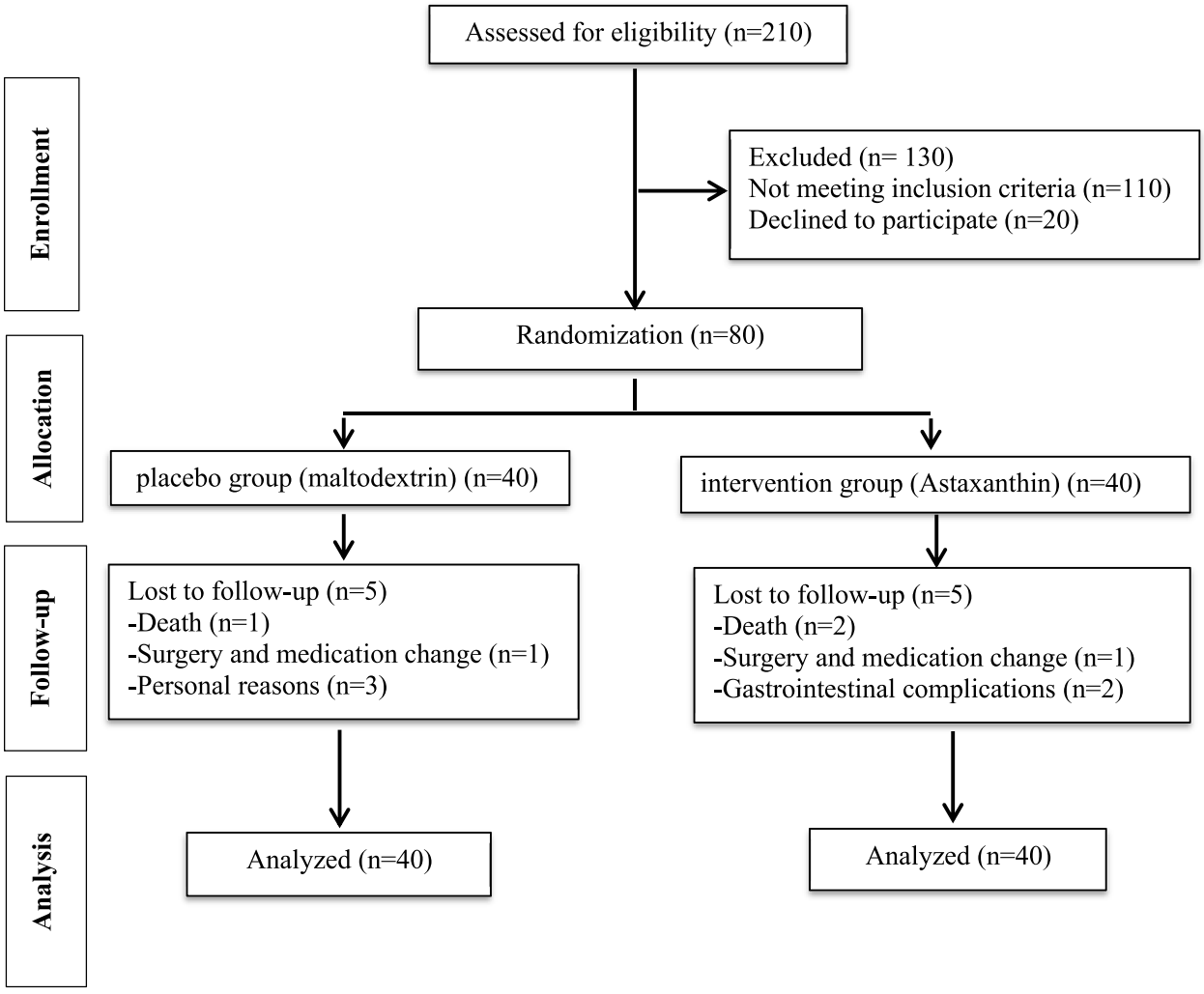


**Fig. 1** Flow diagram of study

and this difference remained statistically significant after adjustment for confounders ($P = 0.003$).

The severity of both dyspnea and fatigue decreased in both study groups at the end of the intervention period compared to baseline. However, this reduction was statistically significant only in the ASX group ($P < 0.001$). Furthermore, eight weeks of ASX supplementation led to a significantly greater reduction in the severity of dyspnea and fatigue in the intervention group compared to the control group ($P < 0.001$). Following the intervention, both groups experienced a significant increase in appetite levels compared to baseline. However, the between-group comparison of mean changes did not show a statistically significant difference ($P = 0.130$). After adjusting for potential confounding variables, a marginally significant difference was observed between the two groups after eight weeks of supplementation ($P = 0.071$). For visual representation, changes in oxidative markers are presented in Fig. 2, and changes in clinical symptoms are shown in Fig. 3.

## Discussion

The findings of this study indicated that daily supplementation with 20 mg of ASX for eight weeks in patients with HF resulted in significantly greater improvements in oxidative stress biomarkers compared to placebo group. This improvement included reductions in uric acid and MDA, along increases in TAC and SOD.

Consistent with our findings, a study reported that supplementation with 6 mg of ASX for 12 weeks in women with endometriosis significantly reduced MDA levels and increased TAC and SOD [24]. Additionally, a meta-analysis conducted in 2022 showed that ASX significantly decreased MDA and increased SOD levels [25]. Contrary to our results, a study by Fereidouni et al. found that supplementation with 6 mg of ASX for 8 weeks in women with polycystic ovary syndrome did not affect MDA and

**Table 1** Comparison of the demographic and basic clinical characteristics of the two groups at the beginning of the study

| Variable | Group | | $P^a$ |
|---|---|---|---|
| | ASX ($n=40$) | Placebo ($n=40$) | |
| Age (year) | 61.82 ± 11.75 | 60.20 ± 12.81 | 0.556 |
| Weight (kg) | 73.95 ± 13.05 | 76.11 ± 13.74 | 0.474 |
| Height (cm) | 169.85 ± 7.51 | 170.28 ± 10.48 | 0.831 |
| BMI (kg/m2) | 25.72 ± 4.42 | 26.37 ± 4.82 | 0.535 |
| Waist circumference (cm) | 100.14 ± 15.45 | 102.60 ± 15.10 | 0.472 |
| SBP (mmHg) | 121.67 ± 19.92 | 119.90 ± 25.40 | 0.729 |
| DBP (mmHg) | 82.92 ± 12.12 | 78.75 ± 13.75 | 0.154 |
| Gender (male) | 30 (75) | 27 (67.5) | 0.459 |
| Education level | | | 0.995 |
| Academic | 5 (12.5) | 5 (12.5) | |
| Non-academic | 35 (87.5) | 35 (87.50 | |
| Socioeconomic status | | | 0.958 |
| Low | 15 (37.5) | 15 (37.5) | |
| Moderate | 15 (37.5) | 16 (40) | |
| High | 10 (25) | 9 (22.5) | |
| Medical history (yes) | 24 (60) | 30 (75) | 0.365 |
| Family history (yes) | 28 (70) | 29 (72.5) | 0.805 |
| Supplement intake (yes) | 3 (7.5) | 2 (5) | 0.644 |
| Smoking (yes) | 11 (27.5) | 4 (10) | 0.045 |
| Medications | | | |
| Blood thinners | 25 (62.5) | 29 (72.5) | 0.340 |
| Beta-blocker | 16 (40) | 20 (50) | 0.369 |
| Diuretic | 27 (67.5) | 27 (67.5) | > 0.99 |
| Calcium channel blocker | 2 (5) | 1 (2.5) | 0.556 |
| Angiotensin II blocker | 22 (55) | 21 (52.5) | 0.823 |
| ACE inhibitor | 2 (5) | 0 (0) | 0.152 |
| Diabetes drugs | 22 (55) | 27 (67.5) | 0.251 |
| Lipid-reducing drugs | 31 (77.5) | 26 (65) | 0.217 |
| Antiarrhythmic | 3 (7.5) | 5 (12.5) | 0.456 |
| Levothyroxine | 4 (10) | 8 (20) | 0.210 |

Data are expressed as mean ± SD for quantitative variables and numbers (%) for qualitative variables

*Abbreviations*: *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *ACE* Angiotensin-converting enzyme

[a]performed by an independent samples t-test for quantitative variables and the Chi-square test for qualitative variables

$P < 0.05$ was considered statistically significant

SOD levels [26]. Another study reported that supplementation with 8 mg of ASX for 40 days only increased TAC without affecting MDA and SOD [27]. A meta-analysis by Wu et al. concluded that high-dose ASX (20 mg per day) and a minimum intervention duration of 3 weeks yielded significant antioxidant effects, whereas lower doses or shorter durations did not produce meaningful outcomes [28].

Oxidative stress in HF is closely linked to mitochondrial dysfunction [3]. Mitochondria, as the primary source of ROS, can, when impaired, create a vicious cycle of oxidative stress and cellular damage that accelerates HF progression [29]. ASX, a potent antioxidant carotenoid, exerts its protective effects by preventing lipid peroxidation, enhancing antioxidant enzyme activities, and regulating gene expression [30]. ASX indirectly promotes antioxidant activity by activating the nuclear transcription factor Nrf2 and upregulating its downstream antioxidant genes [31].

In our study, participants received the cis-isomer form of ASX. The cis-isomer of ASX demonstrates greater anti-inflammatory and antioxidant properties than the trans-isomer, along with enhanced bioavailability [32]. Therefore, inconsistencies among studies may be attributed to differences in participants' baseline antioxidant status, underlying medical conditions, dosage, isomeric form and formulation of ASX used, and the duration of intervention.

UA, the final product of purine catabolism, plays a dual role in the body. While it is considered a major antioxidant in plasma, it also acts as a pro-oxidant by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and promoting superoxide generation [4]. Elevated serum UA levels are recognized as prognostic markers in HF, especially among patients with hypertension, coronary artery disease, and post-myocardial infarction. Hyperuricemia is common in chronic HF and is associated with adverse long-term outcomes [5]. Animal studies have demonstrated that ASX inhibits UA synthesis by downregulating mRNA expression of xanthine oxidase and adenosine deaminase and enhances UA excretion by modulating urate transporter proteins. These mechanisms have led to significant reductions in serum UA levels in animal models [33]. In line with our findings, the results of a clinical trial demonstrated that supplementation with 8 mg of ASX for 7 days led to a significant reduction in UA levels among individuals with gout [34].

Another interesting finding of our study is the greater improvement in clinical symptoms, including fatigue and dyspnea, and a marginally significant increase in appetite in the ASX group, which is clinically valuable since heart failure is commonly associated with symptoms such as fatigue, appetite loss, dyspnea, and exercise intolerance, all of which affect quality of life [2]. Studies have shown that oxidative stress not only contributes to exercise-induced fatigue but also plays a role in chronic fatigue syndrome and its associated psychological effects [35]. ASX is a potent antioxidant with the ability to cross the blood–brain barrier, enabling it to protect the nervous system from acute injury and chronic degeneration [36]. Its protective effects are attributed to its antioxidant, anti-apoptotic, and anti-inflammatory properties [7]. Research has shown that ASX enhances endurance capacity and promotes fat utilization during exercise by activating carnitine palmitoyl transferase I (CPT-I), thereby improving physical stamina [37]. One study found that supplementation with 3 mg of ASX for

**Table 2** Dietary intakes of the participants

| Nutrients | Group | | $P^a$ |
|---|---|---|---|
| | ASX ($n=40$) | Control ($n=40$) | |
| Energy (kcal/day) | | | 0.182 |
| Baseline | 1830.84 ± 468.32 | 2000.13 ± 655.94 | |
| Midpoint | 1705.74 ± 384.88 | 1922.17 ± 509.04 | |
| End | 1810.35 ± 417.78 | 1863.21 ± 486.43 | |
| Carbohydrate (g/day) | | | 0.155 |
| Baseline | 253.99 ± 66.37 | 280.76 ± 92.46 | |
| Midpoint | 243.46 ± 55.77 | 275.85 ± 80.31 | |
| End | 262.64 ± 65.65 | 272.40 ± 75.40 | |
| Protein (g/day) | | | 0.398 |
| Baseline | 75.92 ± 23.76 | 79.54 ± 26.82 | |
| Midpoint | 64.60 ± 17.99 | 70.33 ± 18.75 | |
| End | 67.08 ± 18.03 | 68.85 ± 17.54 | |
| Fat (g/day) | | | 0.394 |
| Baseline | 61.48 ± 27.02 | 67.08 ± 26.66 | |
| Midpoint | 58.18 ± 24.62 | 65.44 ± 22.69 | |
| End | 60.98 ± 23.15 | 61.58 ± 22.44 | |
| Cholesterol (mg/day) | | | 0.060 |
| Baseline | 261.94 ± 108.63 | 295.63 ± 138.23 | |
| Midpoint | 230.19 ± 94.44 | 269.06 ± 114.22 | |
| End | 190.66 ± 78.62 | 226.92 ± 102.98 | |
| SFA (g/day) | | | 0.137 |
| Baseline | 17.37 ± 6.33 | 19.24 ± 7.02 | |
| Midpoint | 15.96 ± 5.57 | 17.79 ± 5.87 | |
| End | 15.61 ± 4.28 | 17.54 ± 7.11 | |
| MUFA (g/day) | | | 0.093 |
| Baseline | 18.78 ± 6.74 | 21.39 ± 9.28 | |
| Midpoint | 17.09 ± 5.15 | 20.65 ± 6.48 | |
| End | 18.61 ± 5.29 | 18.72 ± 6.72 | |
| PUFA (g/day) | | | 0.961 |
| Baseline | 18.91 ± 17.68<br>14.26 (4.60–86.99) | 18.87 ± 13.74<br>14.51 (5.52–71.71) | |
| Midpoint | 18.37 ± 16.85<br>14.76 (5.49–102.22) | 19.61 ± 12.61<br>17.77 (4.57–76.65) | |
| End | 19.42 ± 16.07<br>14.34 (5.64–86.25) | 17.74 ± 12.99<br>15.31 (3.85–86.02) | |
| Total dietary fiber (g/day) | | | 0.409 |
| Baseline | 16.36 ± 7.10 | 17.65 ± 6.84 | |
| Midpoint | 17.17 ± 5.06 | 19.48 ± 5.84 | |
| End | 22.93 ± 8.11 | 22.18 ± 6.48 | |
| Sugar (g/day) | | | 0.873 |
| Baseline | 86.69 ± 38.95 | 87.35 ± 28.50 | |
| Midpoint | 92.79 ± 30.16 | 98.48 ± 36.75 | |
| End | 95.17 ± 32.20 | 91.65 ± 21.44 | |
| Vitamin A (RAE) | | | 0.023 |
| Baseline | 825.12 ± 426.62<br>650.75 (320.75–1892.04) | 1070.98 ± 683.83<br>909.22 (120.81–2976.12) | |
| Midpoint | 746.70 ± 312.10<br>720.06 (274.99–1305.98) | 892.80 ± 423.99<br>791.77 (324.49–1923.69) | |
| End | 745.38 ± 387.52<br>671.18 (199.31–1766.53) | 889.13 ± 559.32<br>756.70 (177.03–2712.85) | |
| Vitamin E (mg/day) | | | 0.851 |
| Baseline | 4.18 ± 3.77<br>2.63 (0.81–16.73) | 6.02 ± 5.62<br>4.19 (0.63–23.93) | |

**Table 2** (continued)

| Nutrients | Group | | $P^a$ |
|---|---|---|---|
| | ASX ($n=40$) | Control ($n=40$) | |
| Midpoint | 6.17 ± 4.62<br>4.24 (0.87–16.48) | 5.69 ± 4.65<br>4.01 (1.12–22.65) | |
| End | 6.83 ± 6.18<br>5.70 (1.94–37.79) | 5.97 ± 3.76<br>4.66 (1.12–17.49) | |
| Vitamin C (mg/day) | | | 0.363 |
| Baseline | 97.71 ± 41.65 | 109.85 ± 67.07 | |
| Midpoint | 104.05 ± 50.58 | 102.97 ± 48.42 | |
| End | 110.61 ± 51.48 | 121.10 ± 46.09 | |
| Copper (mg/day) | | | 0.682 |
| Baseline | 1.27 ± 0.83<br>0.93 (0.55–4.25) | 1.34 ± 0.69<br>1.15 (0.58–3.59) | |
| Midpoint | 1.18 ± 0.67<br>0.98 (0.63–4.49) | 1.31 ± 0.54<br>1.26 (0.59–3.71) | |
| End | 1.41 ± 0.76<br>1.22 (0.68–4.55) | 1.39 ± 0.61<br>1.30 (0.61–3.89) | |
| Selenium (mg/day) | | | 0.813 |
| Baseline | 64.83 ± 55.40<br>44.13 (3.37–240.75) | 60.19 ± 60.33<br>41.02 (3.59–277.00) | |
| Midpoint | 49.42 ± 38.28<br>37.00 (5.52–165.60) | 46.45 ± 34.48<br>39.18 (3.66–151.55) | |
| End | 45.37 ± 39.73<br>33.99 (2.66–170.74) | 48.31 ± 34.44<br>52.93 (2.98–102.67) | |
| Zinc (mg/day) | | | 0.752 |
| Baseline | 11.08 ± 6.178.49 (5.44–32.32) | 11.34 ± 4.93 | |
| Midpoint | 9.32 ± 4.458.44 (5.24–32.20) | 10.03 ± 3.47 | |
| End | 9.92 ± 4.68<br>8.56 (5.53–26.69) | 9.88 ± 3.96<br>9.16 (4.08–26.72) | |
| Manganese (mg/day) | | | 0.845 |
| Baseline | 3.75 ± 3.56<br>2.65 (0.71–18.37) | 3.61 ± 2.42<br>2.78 (1.15–14.87) | |
| Midpoint | 3.56 ± 3.00<br>2.67 (1.65–19.01) | 3.50 ± 2.24<br>3.14 (1.61–15.71) | |
| End | 3.82 ± 2.91<br>3.17 (1.74–18.05) | 3.66 ± 2.37<br>3.39 (1.67–16.81) | |

Data are presented as mean ± standard deviation for normally distributed variables and median (first quartile-third quartile) for non-normally distributed variables

*Abbreviations*: *SFA* Saturated fatty acids, *MUFA* Monounsaturated fatty acids, *PUFA* Polyunsaturated fatty acids, *RAE* Retinol activity equivalent

[a] *P* value obtained from a repeated measures ANOVA test

**Table 3** Comparison of mean changes in physical activity in the intervention and control groups

| Variable | Group | | $P^a$ (Group effect) |
|---|---|---|---|
| | ASX ($n=40$) | Placebo ($n=40$) | |
| Physical activity (MET/Min/Week) | | | 0.646 |
| Baseline | 335.75 ± 682.27<br>0.00 (0.00–3360) | 438.94 ± 1010.11<br>0.00 (0.00–3840) | |
| Midpoint | 272.87 ± 503.07<br>33.00 (0.00–31460 | 359. 67 ± 802.66<br>0.00 (0.00–3516) | |
| End | 305.00 ± 619.03<br>0.00 (0.00–2880) | 355.22 ± 803.03<br>0.00 (0.00–3417) | |

Data are presented as mean ± standard deviation for normally distributed variables and median (first quartile-third quartile) for non-normally distributed variables

*Abbreviations*: *MET* Metabolic equivalent of task, *Min* Minute

[a] *P* value obtained from a repeated measures ANOVA test

4 weeks significantly improved mental fatigue, although its effect on physical fatigue was less pronounced [38]. In another study, supplementation with 12 mg of ASX over 12 weeks reduced daily fatigue caused by both psychological and physical stress [39].

While the effect of ASX on dyspnea has not been extensively studied, its anti-inflammatory and antioxidant properties may confer indirect benefits to the respiratory system. One study suggested that ASX may be beneficial in regenerating small airways affected by chronic obstructive pulmonary disease (COPD). The mechanism of action involves inhibition of AKT serine/threonine kinase 1 (AKT1) signaling, leading to reduced inflammation and airway fibrosis [40]. Furthermore, antioxidants including ASX have demonstrated potential protective effects against air pollution, not only through

**Table 4** Comparison of oxidative stress markers and clinical symptoms before and after intervention in each group and between groups

| Variable | Group | | $P^b$ | $P^c$ |
|---|---|---|---|---|
| | ASX ($n=40$) | Placebo ($n=40$) | | |
| TAC (mmol/L) | | | | |
| Baseline | 0.82 ± 0.30 | 0.86 ± 0.26 | | |
| End | 0.94 ± 0.26 | 0.82 ± 0.21 | | |
| Mean changes | 0.12 ± 0.03 | - 0.04 ± 0.03 | < 0.001 | 0.002 |
| $P^a$ | 0.001 | 0.184 | | |
| SOD (U/ml) | | | | |
| Baseline | 194.50 ± 7.64 | 198.06 ± 26.60 | | |
| End | 351.41 ± 63.83 | 234.20 ± 41.83 | | |
| Mean changes | 156.92 ± 10.17 | 36.14 ± 5.70 | < 0.001 | < 0.001 |
| $P^a$ | < 0.001 | < 0.001 | | |
| MDA (nmol/ml) | | | | |
| Baseline | 4.92 ± 0.88 | 4.84 ± 1.21 | | |
| End | 2.72 ± 0.85 | 4.17 ± 1.21 | | |
| Mean changes | - 2.19 ± 0.20 | - 0.68 ± 0.10 | < 0.001 | < 0.001 |
| $P^a$ | < 0.001 | < 0.001 | | |
| Uric acid (mg/dl) | | | | |
| Baseline | 8.03 ± 3.42 | 8.11 ± 2.35 | | |
| End | 6.21 ± 2.21 | 7.48 ± 2.56 | | |
| Mean changes | - 1.82 ± 0.33 | - 0.63 ± 0.31 | 0.001 | 0.003 |
| $P^a$ | < 0.001 | 0.046 | | |
| Dyspnea | | | | |
| Baseline | 2.90 ± 1.03<br>3.00<br>(2.00–4.00) | 3.22 ± 0.89<br>3.00<br>(3.00–4.00) | | |
| End | 2.43 ± 0.96<br>3.00<br>(2.00–3.00) | 3.20 ± 0.88<br>3.00<br>(3.00–4.00) | | |
| Mean changes | - 0.47 ± 0.08<br>0.00<br>(−1.00–0.00) | - 0.02 ± 0.02<br>0.00<br>(0.00–0.00) | < 0.001 | < 0.001 |
| $P^a$ | < 0.001 | 0.317 | | |
| Fatigue | | | | |
| Baseline | 48.05 ± 14.12 | 50.22 ± 12.58 | | |
| End | 35.12 ± 11.52 | 49.44 ± 11.09 | | |
| Mean changes | - 12.92 ± 1.20 | - 0.79 ± 0.64 | < 0.001 | < 0.001 |
| $P^a$ | < 0.001 | 0.224 | | |
| Appetite | | | | |
| Baseline | 12.80 ± 2.57 | 13.15 ± 3.25 | | |
| End | 13.78 ± 1.78 | 13.75 ± 2.59 | | |
| Mean changes | 0.98 ± 0.19 | 0.60 ± 0.18 | 0.130 | 0.071 |
| $P^a$ | < 0.001 | 0.002 | | |

Values are presented as mean ± standard deviation (SD) for baseline and end-of-study values, and mean ± standard error (SE) for changes. Median (first quartile-third quartile) is presented for variables with non-normal distribution

*Abbreviations*: *MDA*, Malondialdehyde, *TAC* Total antioxidant capacity, *SOD* Superoxide dismutase

[a]Paired t-test or Wilcoxon signed-rank test to compare baseline and end-of-study values in each group

[b]ANCOVA or GEE for comparing the end-of-study values of outcomes between the two groups by adjusting the baseline values

[c]ANCOVA or GEE for comparing the end-of-study values of outcomes between the two groups by adjusting the baseline values and confounding variables including gender, smoking, and mean vitamin A

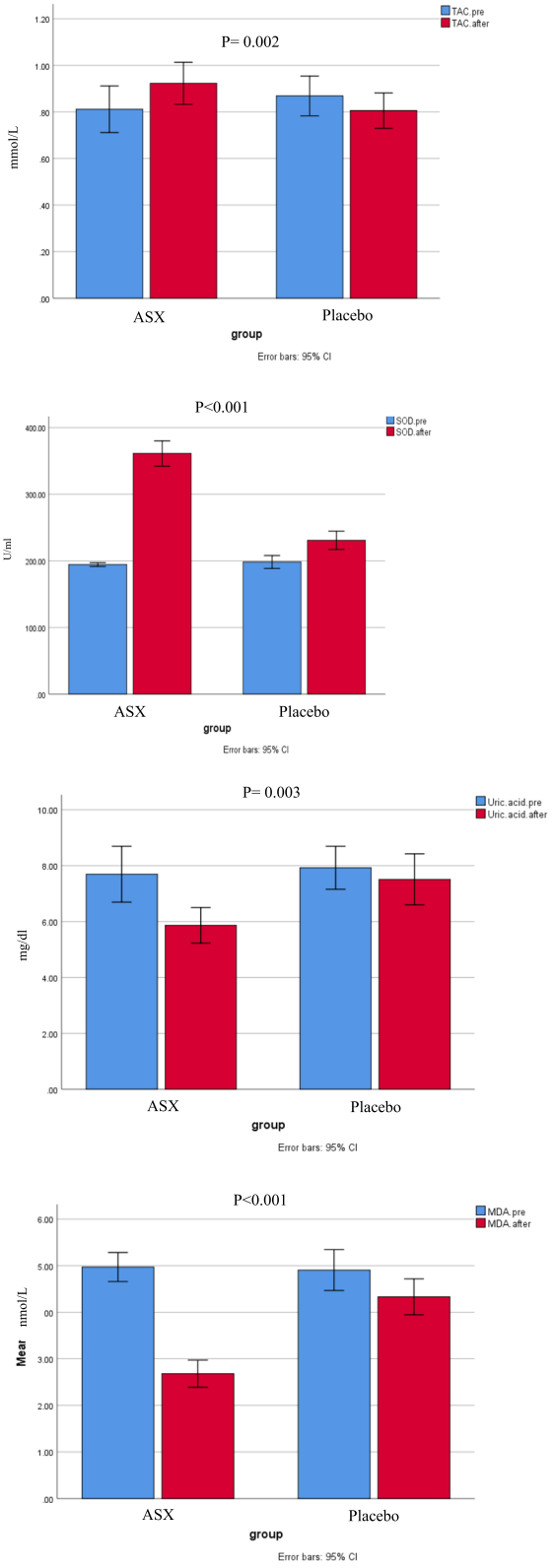


**Fig. 2** Effects of ASX supplementation on oxidative/biochemical markers (TAC, SOD, MDA, UA). Data are presented as mean ± SD. Adjusted *P*-values indicate between-group differences

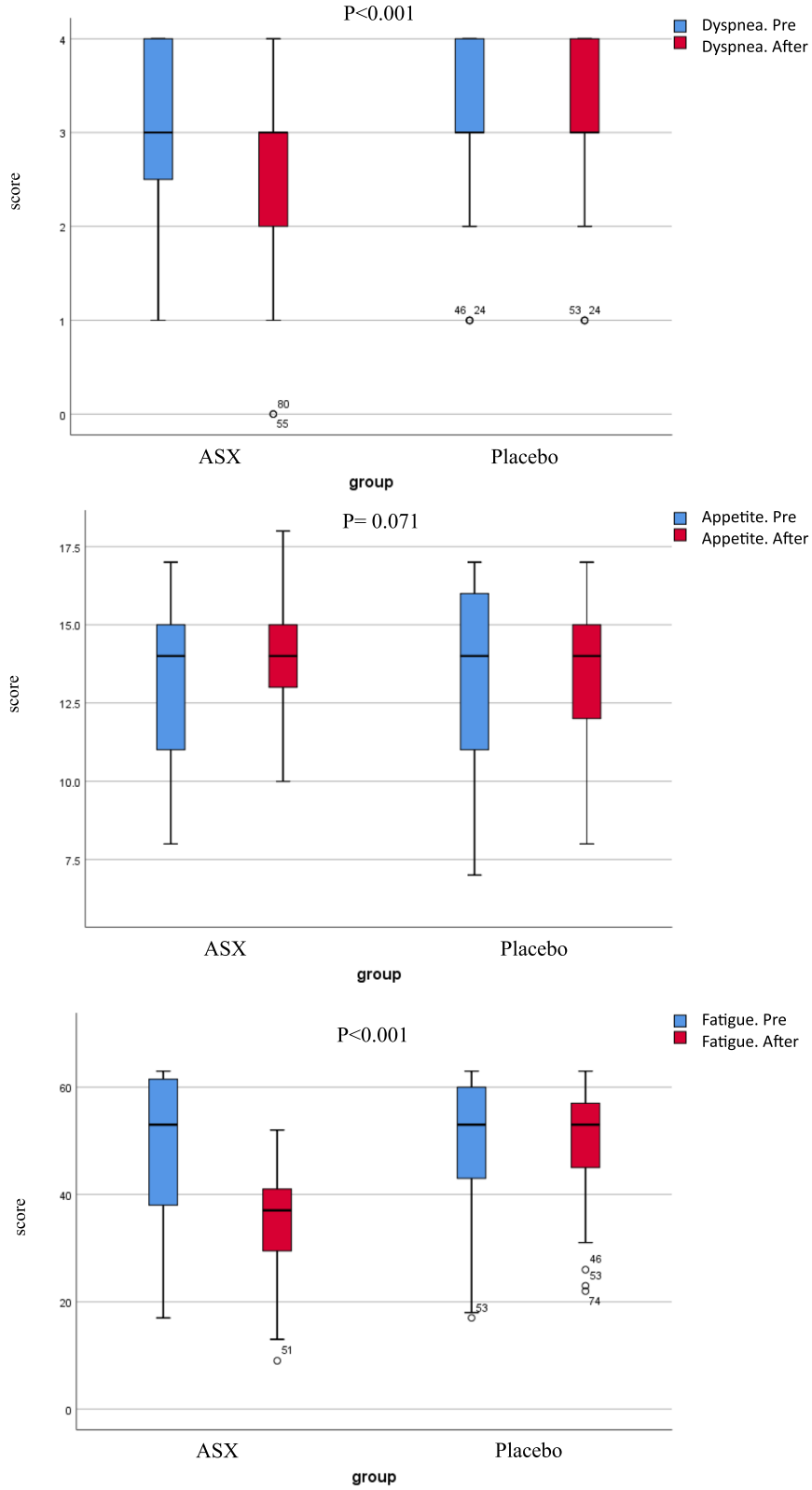


**Fig. 3** Effects of ASX supplementation on clinical symptoms (dyspnea, fatigue, appetite). Data are presented as median (IQR). Adjusted *P*-values indicate between-group differences

direct scavenging of reactive oxygen species but also via their anti-inflammatory actions, potentially aiding respiratory function in pulmonary patients [41].

Although the impact of ASX on appetite has not been widely investigated, some studies indicate that it may influence metabolic regulation and appetite signaling pathways. Chronic inflammation can disrupt appetite-regulating mechanisms, and ASX, through inhibition of inflammatory pathways such as NF-κB and JAK-STAT, may help restore normal appetite regulation [9]. Additionally, HF is associated with downregulation of subunits in the mitochondrial electron transport chain, leading to decreased mitochondrial activity. ASX has been shown to enhance mitochondrial function and improve ATP synthase complex activity [42]. Given its role in improving mitochondrial performance, ASX may indirectly support appetite regulation by increasing energy levels, improving nutrient utilization, and mitigating fatigue-induced appetite suppression [3, 43]. The observed improvement in appetite following astaxanthin supplementation was only marginally significant ($P = 0.071$) after controlling for potential confounders, indicating a trend rather than definitive evidence of effect. This finding should be interpreted with caution. While statistical significance was not firmly established, even a modest improvement in appetite may have clinical relevance in patients with HF, where appetite loss can contribute to malnutrition, diminished quality of life, and worse outcomes [44]. However, the lack of a strong statistical signal suggests that larger studies with extended intervention periods are needed to clarify whether astaxanthin can meaningfully enhance appetite in this population. Future investigations incorporating more sensitive or objective measures of nutritional intake and body composition may provide further insights into the clinical impact of astaxanthin on appetite regulation.

The present study employed a high-dose (20 mg/day) cis-isomer form of synthetic ASX, which is associated with enhanced bioavailability. While this formulation allowed us to observe significant biochemical and symptomatic effects, caution is warranted when generalizing these results to natural sources of ASX. Prior reviews have noted that the safety and pharmacokinetic profile of synthetic ASX may differ from algal-derived ASX [13]. In our study, gastrointestinal adverse effects occurred in two participants receiving ASX, which may be related to the specific formulation used. Therefore, while our findings support the potential efficacy of ASX in HF, further trials are required to evaluate whether similar effects and tolerability are observed with natural algal-derived ASX formulations.

One of the strengths of this study is that it represents the first randomized clinical trial to evaluate the effects of ASX supplementation on oxidative stress markers, UA levels, and clinical symptoms in patients with HF. Additionally, potential confounding factors were controlled as much as possible. However, several limitations were identified, including the relatively short intervention duration, limited sample size, limited generalizability of the findings due to the single-center design, absence of blood ASX level measurements, and lack of long-term follow-up. It should be noted that our inclusion criteria (LVEF < 50%) encompassed both patients with HFrEF (≤ 40%) and those with HFmrEF (41–49%). Because detailed subgroup data were not available, we were unable to report the exact distribution of these patients or perform separate analyses. This heterogeneity may have influenced our results, and larger studies with stratified recruitment are warranted to clarify whether the effects of ASX differ between HFrEF and HFmrEF populations. Assessing blood concentrations of ASX could have provided important insights into dose–response relationships and enabled a more accurate evaluation of the intervention's effectiveness.

To enhance the robustness and generalizability of future research, it is recommended that, studies be conducted with larger sample sizes and extended intervention periods; A broader range of biomarkers, including inflammatory markers and indicators of cardiac function, be assessed; Blood levels of ASX be measured to investigate pharmacokinetics and dose–response correlations; Long-term follow-up assessments be incorporated to evaluate the sustainability of the intervention's effects over time.

## Conclusion

In this randomized clinical trial, supplementation with ASX at a daily dose of 20 mg for eight weeks resulted in improvements in oxidative stress markers, reductions in serum UA levels, and symptomatic benefits in patients with HF. While these findings are promising, they should be interpreted cautiously due to the limited duration and sample size. ASX may therefore be considered a potential adjunctive option, but further large-scale and long-term studies are warranted before firm clinical recommendations can be made.

**Abbreviations**

| | |
|---|---|
| AHA | American heart association |
| AKT1 | AKT serine/threonine kinase 1 |
| ANCOVA | Analysis of covariance |
| ASX | Astaxanthin |
| BMI | Body mass index |
| COPD | Chronic obstructive pulmonary disease |
| CPT-I | Carnitine palmitoyl transferase I |
| FSS | Fatigue severity scale |
| FRAP | Ferric reducing antioxidant power |
| GEE | Generalized estimating equations |
| HF | Heart failure |
| HFrEF | Heart failure with reduced ejection fraction |
| HFmrEF | Heart failure with mildly reduced ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |

| | |
|---|---|
| IPAQ | International physical activity questionnaire |
| ITT | Intention-to-treat |
| LEVF | Left ventricular ejection fraction |
| MDA | Malondialdehyde |
| MMRC | Modified medical research council |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| ROS | Reactive oxygen species |
| SES-SQ: | Socioeconomic status short-form questionnaire |
| SNAQ | Simplified nutritional appetite questionnaire |
| SOD | Super oxide dismutase |
| TAC | Total antioxidant capacity |
| TBARS | Thiobarbituric acid reactive substances |
| UA | Uric acid |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-05260-z.

Supplementary Material 1

Supplementary Material 2

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**Authors' contributions**
SGM and MK were responsible for designing the study. SGM and DS managed the collection of samples and data from the participants involved in the study. AF conducted the statistical analysis, while SGM drafted the initial version of the article. DS, AF, AA, MB, and MK were involved in critically revising it for significant intellectual content. All authors made contributions to the article and approved the version submitted.

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**Data availability**
Data from this study include laboratory measurements and questionnaire responses collected from human participants. Due to ethical restrictions and confidentiality agreements outlined in the informed consent forms, the raw data cannot be publicly shared. However, the SPSS data files used for the analyses can be made available from the corresponding author upon reasonable request, subject to ethical and confidentiality considerations.

## Declarations

**Ethics approval and consent to participate**
The study protocol was reviewed and approved by the Ethics Committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1402.099, approved on 19 March 2024) and trial registration (IRCT20200429047235N3, registered on 26 March 2024) were both completed before the enrollment of the first participant. Written informed consent was obtained from all participants prior to their enrollment in the study, ensuring their voluntary participation and adherence to ethical standards in research. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note