DOI: *http://dx.doi.org/10.48305/arya.2022.11840.2515*

A randomized, Double-blind Clinical Trial of the Three-month Effect of Garlic Administration on Cardiac Outcomes in Patients with Heart Failure

Sima Azish[1], Mohammad Garakyaraghi[3], Mehrbod Vakhshoori[2], Maryam Heidarpour[3], Mohaddeseh Behjati[4], Kiyan Heshmat-Ghahdarijani[2], Sepehr Omoomi[2], Mohammad Fakhrolmobasheri[2], Davood Shafie[2], Nizal Sarrafzadegan[5]

Original Article

Abstract

BACKGROUND: Garlic may have anti-oxidanmayti-hypertensive and anti-hyperlipidemic properties. However, the effects of its administration on cardiac function in heart failure (HF) patients impact require further investigation. We aimed to evaluate garlic prescription effects on cardiac outcomes and quality of life scores in Iranian HF patients.

METHOD: From August to December 2020, a randomized, double-blind clinical trial was conducted. Individuals with heart failure (New York heart association (NYHA) functional class of II and III) referred to private clinics in Isfahan, Iran, were randomly assigned to intervention (n=80) and control (n=80) groups. They have received 500 mg of odorless garlic tablets or the same shape and dosage of placebo twice daily for three months. Laboratory data, cardiac outcomes (end-diastolic diameter, ventricular septal thickness, NYHA functional class, left ventricular ejection fraction), quality of life score (Minnesota living with HF questionnaire), and the Modified Borg Scale (MBS) were all evaluated at the baseline and the end of the trial.

RESULTS: The population's mean age was 58.1±13.5 years (55% males). Patients who consumed garlic had remarkably improved functional class compared to placebo takers and their baseline (NYHA practical class of II, 79.4% vs. 50.6%, P<0.001 and 79.4% vs. 54%, P=0.006, respectively). MBS levels were significantly lower among garlic consumers (baseline: 2.52±0.5, after three months: 2.2±1.06, P= 0.040).

CONCLUSIONS: Garlic administration may improve cardiac function and breathe in HF patients. Complementary research is necessary to confirm our findings.

Keywords: Heart Failure, Garlic, Randomized Controlled Trial, Quality of Life

Date of submission: *2021-Sep-12,* ***Date of acceptance:****2022-Nov-12*

Introduction

Heart failure (HF) is a clinical syndrome caused by any functional or structural defect in either blood ejection or ventricular filling.[1] Worldwide, approximately 26 million individuals are affected by HF.[2] This global concern's prevalence has been reported to rise with age. About 20 and more than 80 per 1000 individuals aged 65-69 and over 85 years suffer from HF, respectively.[3]

How to cite this article: Azish S, Garakyaraghi M, Vakhshoori M, Heidarpour M, Behjati M, Heshmat-Ghahdarijani K, Omoomi O, Fakhrolmobasheri M, Shafie D, Sarrafzadegan N. **A randomized, Double- blind Clinical Trial of the Three-month Effect of Garlic Administration on Cardiac Outcomes in Patients with Heart Failure.** ARYA Atheroscler 2022; 18(6): 2515.

1- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
4- Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Address for correspondence: Davood Shafie; Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran. Email: d.shafie87@gmail.com

Furthermore, the prevalence of HF is expected to rise by 46% by 2030.[4] The most common manifestations of this disease are fatigue and dyspnea, which cause fluid retention and limit exercise tolerance.[1] This complex syndrome severely affects health-related quality of life and failure to improve after hospital discharge and is classified as a significant predictor of mortality or hospital readmission.[5, 6] The total annual HF management expenditure has been estimated to be $108 billion, which includes both direct ($65 billion) and indirect ($43 billion) costs.[7] Aside from common prognostic and traditional medications used in HF management, alternative pharmacotherapy, such as dietary supplementations, herbal remedies, and vitamins, has recently gained popularity.[8-10] Allium Sativum (Garlic) is a plant in the Alliaceae family. This plant has been used medicinally for approximately 5000 years, and the Chinese population began using this herbal drug around 3000 years ago.[11] Garlic has been suggested to have cardiovascular disease (CVD) preventive properties. *Allicin* is an active garlic metabolite that has been shown to lower cholesterol and blood pressure while inhibiting platelet aggregation.[12]

Moreover, this plant has been linked to antioxidant properties and the healing of endothelial injuries.[13] Hara et al. discovered that rats who received garlic extract had lower left ventricular (LV) fibrosis and improved LV diastolic dysfunction.[14] However, more clinical research is needed to prove garlic's possible effect on cardiovascular outcomes.

This study aimed to investigate the effects of prescribing garlic tablets on cardiac outcomes and the quality of life in Iranian HF patients.

Materials and Methods

Study design

This double-blinded randomized clinical trial was conducted from August 2020 to December 2020 according to the Consort Standards of Reporting Trials (CONSORT) guidelines. Individuals with stable HF referred to outpatient clinics in Isfahan, Iran, were recruited to compare the effects of garlic tablets on cardiovascular outcomes and quality of life. The Isfahan University of Medical Sciences (IUMS) ethical committee approved this study (IR.MUI.MED. REC.1398.273). This trial was also registered in the Iranian Registry of Clinical Trials (IRCT20181121041715N1).

Study population

We enrolled anyone over the age of 18 who had previously proven HF (New York Heart Association (NYHA) functional class of II and III) and a left ventricular ejection fraction (LVEF) of less than 45%. Participants with cancer, malignancy, thyroid, liver, or renal diseases, anemia, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, uncontrolled diabetes mellitus, or blood pressure ≥ 180/120 mmHg were excluded. Other exclusion criteria included patients' unwillingness to continue participating in project phases, using herbal drugs other than garlic tablets, or discontinuing medications. We also excluded women who became pregnant during the trial. After selecting appropriate candidates, the principal investigator explained the study's primary goals in the first session. Finally, everyone who took part signed a written consent form.

Clinical evaluation

Each patient's medical profile was used to collect data on demographic characteristics and past medical and drug history. Patients were referred to pre-determined laboratory centers before the trial's start date. A fasting blood sample was drawn to measure the serum levels of indices, including a lipid profile, renal function, coagulation factors, hemoglobin (Hb) (g/dl), platelets (10^9/l), fasting blood sugar (FBS) (mg/dl), and thyroid-stimulating hormone (TSH) (uIU/ml).

Moreover, echocardiography was used to assess the following parameters: end-diastolic diameter (10) (mm), ventricular septal thickness (VST) (mm), and LVEF (%). All previously performed laboratory and para-clinical data were collected in the following session.

The Minnesota Living with HF Questionnaire (MLHFQ) was administered to the participants [15]. This questionnaire is

intended to assess the quality of life in HF patients. It consists of 21 questions, with each item graded on a 6-point Likert scale (0 to 5). The minimum and maximum total scores range from 0 to 105, with higher scores indicating a reduced quality of life. The Modified Borg Scale (MBS) was used to assess breathing [16]. This scale is rated from 0 (no breathless at all) to 10 (maximal), with higher scores indicating impaired breathing. After five minutes of sitting in a quiet room, blood pressure was measured three times with a minute interval from the right arm using an appropriate sized-cuff calibrated brachial manometer, and the mean value was reported.

Study intervention Randomization

We used a block randomization method with a 1:1 ratio to assign participants to intervention or control groups. One hundred blocks were created, each with a block size of four and a different combination of "A" or "B" groups. Then, at random, one of these various combinations was selected. The "A" group was given a garlic tablet or placebo, while the "B" group was given the other agent. Neither the participants nor the investigator knew the pre-determined codes assigned to each group. The person who knew the codes and was not involved in the research project was the person who performed the block randomization method.

Intervention

Participants in the intervention group were instructed to take odorless garlic tablets (Garcin® 500 mg) every 12 hours daily for 12 weeks. Patients in the control group received placebo tablets of the same size and shape as those in the intervention groups, with the same dosage frequency. All participants were asked about the remaining tablets in the middle of the trial (6 weeks after study initiation). Patients were also asked about the possibility of any probable adverse effects from recent changes in their HF medications. Any positive findings in this regard were excluded.

Outcomes

The trial's primary endpoints were assessing cardiovascular outcomes and quality of life. Patients were invited to investigate cardiac and laboratory data similar to those assessed at the baseline three months after the study concluded. The same cardiologist used 2-dimensional (2D) echocardiography (Phillips IE 33, Netherlands) to measure EDD, VST, and LVEF. Participants also completed the MLHFQ, and changes from the baseline were evaluated.

Sample size

The total sample size for each group was estimated to be 70, considering the 95% confidence interval and type I error (α) of 0.05, as well as study power of 80% plus mean (standard deviation (SD)) of 81.1 (34.7) and 61.4 (45.7) based on the quality of life score in the general population and HF patients [17]. During sample recruitment, we added more than ten subjects and divided them into two groups with even numbers using random numbers (n=160).

Statistical analysis

Continuous and categorical variables were presented as mean ±SD and frequency (percentage). We used Shapiro-Wilk to determine the normality status of variables. The relationship between categorical variables was investigated using the Chi-square test. We used an independent t-test/Mann-Whitney in continuous variables to assess the association between intervention and control groups. An Analysis of Covariance (ANCOVA) with baseline variables adjusted as covariates was used to compare the differences in LVEF, EDD, VST, NYHA, MLHFQ, and MBS scores between garlic or placebo groups. The paired t-test/Wilcoxon or McNemar tests were utilized, as appropriate, to examine the relationship of variables above between the baseline and end date of the trial. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., version 22.0, Chicago, IL, USA), and P-values less than 0.05 were considered statistically significant.

Results

After recruiting all eligible patients, 160 were randomly assigned to one of two groups: garlic (n=80) or placebo (n=80). Figure 1 depicts the current trial's CONSORT flow diagram. During the study period, 17 and 3 participants from the intervention and placebo groups dropped out. The reasons given were that they had changed their previous medications, were using new herbal agents other than garlic on their own, or unwillingness to complete the trial due to personal beliefs. Finally, 63 (garlic group) and 77 (placebo group) participants finished the entire trial.

The normality test failed to demonstrate that the recruited variables had a normal distribution. Table 1 shows the general characteristics of the study population. Our study population had a mean age of 58.1 ± 13.5 years, and more than half of them (55%) were male. At baseline, none of our assessed variables showed significant differences between groups. Except for BUN, which revealed lower means in garlic-consuming patients than placebo takers, there was no significant difference between groups at the end of the study. Garlic-tablet users had significantly lower BUN means than placebo consumers (25.4 ± 8.9 mg/dl vs. 30.2 ± 8.2 mg/dl, P=0.001). Compared to baseline, BUN levels were significantly lower at the end of the study among subjects who received garlic (25.4 ± 8.9 mg/dl vs. 28.8 ± 9.9 mg/dl, P= 0.013).

The distribution of cardiac outcomes and quality of life scores across different categories of garlic or placebo groups is shown in Table 2.

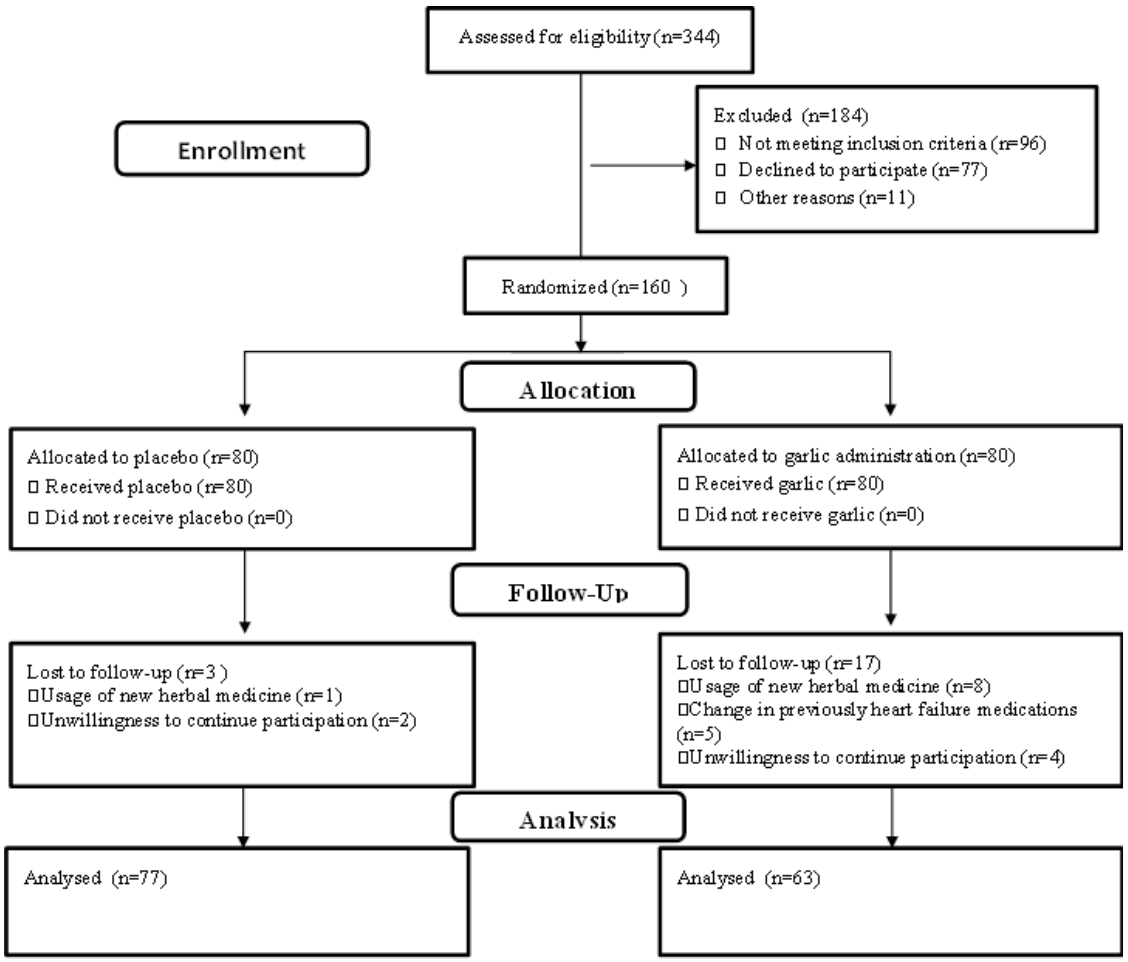

Figure 1. Flow diagram of the trial profile

Table 1. Characteristics of the study population according to placebo or intervention groups

Time	Characteristics	Total (n=140)	Placebo group (n=77)	Garlic group (n=63)	P*
Baseline	Age(years)	58.1±13.5	57.9±14.4	58.3±12.5	0.942
	Males (%)	81(57.9)	47(61)	34(54)	0.399
	BMI(kg/m^2)	28.2±5.6	28.4±5.6	28.0±5.6	0.609
	Systolic blood pressure (mmHg)	113.7±19.7	112.45±19.0	115.22±19.0	0.381
	Diastolic blood pressure (mmHg)	74.5±9.9	73.9±10.0	75.2±9.8	0.486
	Hemoglobin (g/dl)	12.9±1.5	12.8±1.6	13.0±1.5	0.555
	Platelets (10^9/l)	204±32.3	205.7±29.7	201.8±35.3	0.246
	PT (seconds)	13.4±0.7	13.4±0.7	13.3±0.7	0.289
	PTT (seconds)	31.8±4.3	32.1±4.4	31.5±4.1	0.430
	Cholesterol (mg/dl)	166.1±31.0	168.6±33.6	163.1±27.5	0.308
	Triglyceride (mg/dl)	145.1±48.2	147.2±49.8	142.6±46.5	0.660
	LDL-C (mg/dl)	95.2±17.3	95.8±18.2	94.4±16.3	0.764
	HDL-C (mg/dl)	44.1±8.4	45.0±8.7	43.0±7.8	0.195
	Fasting blood sugar (mg/dl)	130.1±25.0	132.5±25.4	127.1±24.3	0.184
	TSH (uIU/ml)	4.6±2.3	4.7±2.2	4.4±2.4	0.326
	Blood urea nitrogen (mg/dl)	27.8±9.5	26.9±9.0	28.8±9.9	0.276
	Creatinine (mg/dl)	1.0±0.5	1.0±0.5	1.0±0.5	0.680
After three months	Systolic blood pressure (mmHg)	118.0±17.0	112.4±20.2	115.2±19.0	0.479
	Diastolic blood pressure (mmHg)	75.0±9.4	73.9±10.0	75.2±9.8	0.690
	Hemoglobin (g/dl)	13.6±1.6	13.6±1.7	13.0±1.6	0.818
	Platelets (10^9/l)	237.5±53.9	240.1±56	234.4±51.5	0.606
	PT (seconds)	13.1±0.7	13.2±0.8	13.0±0.7	0.345
	PTT (seconds)	33.1±4.6	33.3±4.6	32.9±4.6	0.609
	Cholesterol (mg/dl)	147.2±31.4	148.2±33.2	146.0±29.4	0.631
	Triglyceride (mg/dl)	143.3±35.6	142.4±33.9	144.4±37.8	0.755
	LDL-C (mg/dl)	88.8±21.3	90.3±20.8	86.9±22.1	0.293
	HDL-C (mg/dl)	44.6±8.1	44.3±8.6	45.0±7.4	0.411
	Fasting blood sugar (mg/dl)	105.9±13.4	107.3±14.4	104.1±12.0	0.203
	TSH (uIU/ml)	3.9±2.5	4.2±2.4	3.5±2.5	0.092
	Blood urea nitrogen (mg/dl)	28.1±8.8	30.2±8.2	25.4±8.9	0.001
	Creatinine (mg/dl)	1.0±0.5	1.0±0.5	0.9±0.4	0.078

BMI: body mass index, **PT:** prothrombin time, **PTT:** partial thromboplastin time, **LDL-C:** low-density lipoprotein cholesterol, **HDL-C:** high-density lipoprotein cholesterol, **TSH:** thyroid-stimulating hormone
*: P-values are calculated using the Mann-Whitney test for all variables except males (chi-square test)

The two groups' baseline characteristics were distributed evenly. Patients who took garlic tablets improved significantly from baseline (NYHA functional class II, before treatment: 54%, after treatment: 79.4%, P= 0.006). Moreover, garlic users improved their NYHA scores more frequently than placebo consumers (NYHA functional class II, garlic: 79.4%, placebo: 50.6% and NYHA functional class III, garlic: 20.6%, placebo: 49.4%, P< 0.001). On the other hand, MBS significantly improved after three months in patients who consumed garlic tablets (2.2 ± 1.06 vs. 2.52 ± 0.5, P= 0.040). However, no significant difference between groups was found (garlic group: 2.2 ± 1.06 vs. placebo group: 2.49 ± 1.04, P= 0.107). Other pre-defined variables, including LVEF, EDD, VST, and MLHFQ scores, had no significant association between them. During the trial period, no side effects from garlic or placebo were reported.

Discussion

This study aimed to see how garlic administration affected cardiac outcomes and quality of life in HF patients. We discovered that those who consumed odorless garlic tablets significantly improved in NYHA functional class. Furthermore, MBS data analysis revealed that garlic consumers improved breathing. We also discovered that participants in the intervention group had significantly lower BUN values than controls. Garlic administration may appear to be an effective therapeutic strategy in clinical settings because managing HF symptoms is critical to improving patients' status.

Table 2. Distribution of cardiovascular outcomes and quality of life scores at baseline and three months after study initiation across different categories of intervention or control groups

Endpoint		Placebo group (n=77)		P*	Garlic group (n=63)		P*	P¶	P ؞
		Baseline	After three months		Baseline	After three months			
LVEF (%)		30.33±9.5	29.16±8.8	0.653	30.49±9.77	28.76±9.23	0.338	0.587	0.423
End diastolic diameter (mm)		6.01±1.12	6.08±1.04	0.530	5.96±1.02	6.06±1.14	0.821	0.820	0.946
Ventricular septal thickness (mm)		0.99±0.54	1.08±0.57	0.388	0.98±0.47	0.91±0.48	0.258	0.710	0.070
NYHA	Class II	43 (55.8)	39 (50.6)	0.617	34 (54)	50 (79.4)	0.006	0.870	<0.001
	Class III	34 (44.2)	38 (49.4)		29 (46)	13 (20.6)			
MLHFQ score		27.32±15.44	26.11±15.47	0.524	24.5±16.22	23.92±16.26	0.627	0.713	0.219
MBS score		2.45±0.5	2.49±1.04	0.682	2.52±0.5	2.2±1.06	0.040	0.238	0.581

L**VEF:** left ventricular ejection fraction, **NYHA:** New York Heart Association, **MLHFQ:** Minnesota living with heart failure questionnaire, **MBS:** modified Borg scale

* P-value between baseline and after three months (Wilcoxon test for all variables except NYHA (McNemar test))

¶ P-value between garlic and placebo group at baseline

؞ P-value between garlic and placebo group after three months (results from ANCOVA test when adjusted for baseline variables)

Regarding our findings, Liu et al. conducted a study investigating garlic's potential effects in chronic HF patients. They enrolled 120 individuals with NYHA functional classes II and III and randomly assigned them to the garlic or placebo groups to evaluate cardiac functions and quality of life. LVEF was not significantly different between groups at baseline. Interestingly, after a six-month follow-up, they discovered that LVEF improved significantly in both groups (garlic group: from 29.36 ± 9.34% to 36.82 ± 10.43%, P= 0.01, placebo group: from 28.24 ± 8.15% to 32.73 ± 10.21%, P= 0.01). This improvement was also more noticeable in garlic-consuming patients than in those placebo-taking patients (P= 0.03). Further, both groups' quality of life improved significantly, with a notable difference in garlic takers (P= 0.02). Concerning our findings, garlic consumers had significantly lower BUN levels at the end of the study, even when compared to placebo takers (garlic group, before treatment: 19.03 ± 6.85 mg/dl, after treatment: 15.23 ± 5.24 mg/dl, P= 0.01) (garlic group: 15.23 ± 5.24 mg/dl, placebo group: 17.05 ± 5.98 mg/dl, P= 0.02).[18] Although we found no significant improvement in EDD or VST, additional complementary research is required to evaluate the potential effect of garlic on these cardiac parameters.

Several studies have found that garlic has cardioprotective properties due to its various effects on cardiovascular risk factors. [19-22] Reid et al., for instance, conducted a systematic review and meta-analysis of randomized double-blinded clinical studies to determine the probable effect of garlic on blood pressure (BP) levels. After final data analysis, they reported that garlic is more effective than placebo in lowering BP among hypertensive individuals, with systolic BP (SBP) and diastolic BP (DBP) decreased by 8-9 mmHg and 6-7 mmHg, respectively (P< 0.0001).19 In contrast, our findings failed to demonstrate any significant difference in BP indices between garlic or placebo consumers. Two additional double-blinded randomized placebo-controlled trials suggested that garlic improved endothelial function and decreased C-reactive protein (CRP) levels, resulting in improved cardiovascular outcomes.[20, 21] Another study on 167 ischemic heart disease-free patients with hyperlipidemia found that after 12 months of taking a long-acting garlic agent called allicor in males, the 10-year absolute risk of developing ischemic heart disease and acute myocardial infarction was reduced by 10.7% and 22.7%, respectively (P< 0.05).[22]

Several animal studies have also revealed that garlic has cardioprotection properties. Abdel-Daim et al. selected 40 mice to test the efficacy of active garlic ingredients against doxorubicin-induced cardiac toxicity. After cardiac tissue harvest, they realized that garlic significantly improved inflammation a nd oxidative damage.[23] Adriamycin, another anthracycline, was administered to 40 rats. After 30 days, those who received chronic garlic had lower tu- mor necrosis factor-α (TNF-α) expression and, consequently, less myocardial injury.[24]

The precise pathophysiological mechanism of garlic in cardioprotection remains unknown. However, several potential mechanisms have been proposed. The nitric oxide (NO) pathway is frequently disrupted in patients with cardiovascular diseases, and increasing NO production may be beneficial. Garlic has been shown to increase endothelial NO synthase (eNOS) activity, resulting in heightened NO levels.[25] Another mechanism could be linked to the hydrogen disulfide (H_2S). This gaseous molecule has been suggested to have cardioprotective properties, and garlic has been linked to increasing H_2S production due to several H_2S donor compounds.[26, 27]

This plant also has antioxidant properties. Studies show that garlic increases catalase, superoxide dismutase, glutathione peroxidase, and glutathione in vascular endothelial cells.[28, 29] Therefore, garlic administration might improve cardiac functions and the lives of those suffering from cardiovascular diseases.

To the best of our knowledge, this was the first study to investigate garlic administration's effect on cardiac outcomes and quality of life among Iranian HF patients. Another strength of the study was its relatively small sample size. However, the current study has several limita

tions. Other laboratory indices associated with HF, including pro-brain natriuretic peptide (pro-BNP), were not evaluated. Our relatively short follow-up period may have an impact on our reported outcomes. A telephone survey was used to assess participants' drug consumption status, which may have affected accurate usage. However, the investigator's remaining tablet supply during the follow-up period may have helped to mask this limitation. We recently enrolled stable HF patients in NYHA functional classes II and III. Therefore, extrapolating our findings to other HF functional classes should be done with caution.

In conclusion, this study suggests that garlic consumption in stable HF patients can improve cardiac function and breathing and could be considered an adjuvant HF therapy. However, additional research is needed to confirm these findings.

Ethical approval and consent to participate

All procedures in studies involving human participants were carried out per the institutional and national research committee's ethical standards, as well as the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards. The ethics committee approved this study at Isfahan University of Medical Sciences (IUMS) proved this study (IR.MUI.MED.REC.1398.273).
The patients provided written informed consent. The Editor-in-Chief of this journal has a copy of the written consent for review.

Consent for publication

Not applicable.

Availability of data and materials

Due to confidentiality concerns, the datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Competing interests

None of the authors had any personal or financial conflicts of interest.

Funding

This research did not receive any specific grant from any public, commercial, or non-profit funding agency.

Authors contribution

1. Study concept and design: M. V., S. A., M. B, D. S., M. H.
2. Acquisition of data: S. A., S. O., M. F.
3. Analysis and interpretation of data: M. V., D. S.
4. Drafting the manuscript: S. A., M. V, D. S., M. B., M. H., M. F.
5. Critical revision of the manuscript for valuable intellectual content: M. V., D. S., M. GY., K. H., M. G., S. A., N. S., M. H.
6. Statistical analysis: M. V., S. A., D. S.
7. Administrative, technical, and material support: K. H., D. S., M. GY., M. H., N. S.
8. Supervision: D. S., N. S., M. GY., M. H.

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