



# Effectiveness of *Biebersteinia multifida* Root on Quality of Life and Heart Function in Patient With Systolic Heart Failure: A Randomized Clinical Trial

Ebadollah Salekmoghadam<sup>1</sup>, Hassan Ahangar<sup>2\*</sup>, Mohsen Bahrami<sup>3</sup>, Mohammad Kamalinejad<sup>4</sup>, Sepehr Gohari<sup>5</sup>

## Abstract

**Objectives:** The present study aimed to evaluate the effect of *Biebersteinia multifida* on the quality of life (QoL) in patients with systolic heart failure (HF).

**Materials and Methods:** This parallel, double-blind, placebo-controlled experiment was conducted from November 2018 to May 2020. A total of 60 patients aged 40-75 years with systolic HF were allocated into two groups of intervention (*B. multifida*) and placebo. All subjects received the *B. multifida* and placebo capsules twice daily for 60 days. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the 6-Minute Walk Test (6MWT) were used to determine the primary outcomes improving QoL. The secondary results were improved heart function by echocardiography and serum biochemical markers.

**Results:** There was no significant difference between the study groups before treatment in terms of demographic data and results ( $P > 0.05$ ). Following therapy, the primary outcomes were not different between the two groups ( $P > 0.05$ ), but the 6MWT was improved in the intervention group. Moreover, the left ventricular myocardial performance index (LVMPI) in the intervention group was significantly higher than the placebo group ( $P = 0.034$ ).

**Conclusions:** *B. multifida* root extract, as a supplemental drug, can improve myocardial function and modestly increase the QoL in patients with systolic HF.

**Keywords:** Echocardiography, Heart failure, Quality of life, *Biebersteinia multifida*, Randomized controlled trial

## Introduction

Out of an approximate number of 17.9 million death cases in 2019 globally, cardiovascular diseases (CVDs) accounted for about 32% of cases (1, 2). Heart failure (HF) is one the most prominent CVDs, affecting around 26 million individuals worldwide and making it a global pandemic (3). Insufficiency of the heart function is a clinical syndrome initiated by irregularities in the function or structure of the ventricle, draining or filling the blood, leading to dyspnea, fatigue, or symptoms such as edema and rales (4). Breathlessness, exhaustion, ankle swelling, and an objective sign of cardiac malfunction at rest are all symptoms of HF. The patient typically shows some improvement in symptoms and signs in response to the treatments in which a relatively fast symptomatic improvement could be predicted. A clinical response to treatment for HF alone is not adequate for diagnosis (5). Undoubtedly, pulmonary edema is partially caused by increased pulmonary capillary pressure. However, studies on congestive HF among patients exercising showed a tenuous correlation between capillary pressure

and exercise capacity (6). Breathlessness during exertion is caused by increased pulmonary capillary pressure; it is also influenced by variations in the degree of mitral regurgitation (7, 8).

In Asian countries, the causes of infectious illness mortality and morbidity or malnutrition have changed to lifestyle-related illnesses such as CVDs, cancers, diabetes, and so-called epidemiological transmission (9). Lifestyle changes can affect many of the predisposing factors for HF. These factors include maintaining a healthy weight, not smoking, exercising regularly, and maintaining a healthy diet (10).

Herbs are now being utilized to treat CVDs all over the world. According to a growing body of data, traditional medicine employing ethnobotanical treatments can prevent or even reverse cardiac disease (11). Several herbal remedies can treat various heart diseases. So far, several studies have been conducted on *Biebersteinia multifida* root. Thirty-six compounds are identified in the extract oils of *B. multifida* foliage, fruits, and roots that have antioxidant activity (12). This study aims to investigate

Received 21 October 2022, Accepted 15 July 2023, Available online 11 August 2023

<sup>1</sup>Department of Persian and Traditional Medicine, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. <sup>2</sup>Department of Cardiology, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran. <sup>3</sup>Department of Persian and Traditional Medicine, Academic Center for Education, Culture and Research Center, Tehran, Iran. <sup>4</sup>Department of Pharmacognosy, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>5</sup>Student Research Center, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

\*Corresponding Author: Hassan Ahangar, Tel: +989111512028, Email: hassan.ahangar2028@gmail.com



## Key Messages

- ▶ *Biebersteinia multifida* root extract, as a supplemental drug, can enhance cardiac function in people with systolic HF.
- ▶ *Biebersteinia multifida* root extract has a modest impact on QoL of people with systolic HF.

whether the *B. multifida* root will be able to improve the quality of life and myocardial functions with heart failure.

## Materials and Methods

### Study Design

This phase III, randomized, double-blind, placebo-controlled trial evaluated the effect of *B. multifida* capsules (500 mg/twice daily) on QoL of patients with systolic HF compared to a placebo group.

### Subjects

The population of this study included all patients referred to the Cardiology Clinic in Zanjan, Iran from 2018 to May 2020. According to epidemiological studies, the median age of 40 to 75 years old as a range of higher incidence of heart failure was determined (13). During the study period, 100 individuals were evaluated for eligibility. The sample size was calculated as 60 patients (in two equal groups of 30) according to the following formula:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\alpha})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

The inclusion criteria were as follows: age range 40-75 years, 2) systolic HF with an ejection fraction (EF) less than 40%, 3) diagnosed with HF and receiving therapy for it in the previous six months, and 4) meeting criteria by the New York Heart Association's (NYHA's) Functional Classification I and II. The exclusion criteria were as follows: 1) A history of collagen vascular disease, 2) breast feeding women, 3) a history of cancer, 4) a history of *B. multifida* root hypersensitivity, 5) patient's refusal to continue therapy or a lack of follow-up, 6) a long-lasting inflammatory condition, 7) severe renal failure, 8) pregnancy, 9) acute infectious disease with a rapid onset, and 10) an instance of decompensated HF during the trial.

### Study Procedure

#### Randomization and Follow-up

In this study, 60 subjects were randomly assigned into two equal groups (n=30 in each) of intervention (*B. multifida*) and placebo in a 1:1 ratio according to their age and gender using the Winpepi software (Version 11.6). Patients' demographic information, pharmacological history, and possible allergies were documented at enrollment. The medications were recommended for 60 days (500 mg capsule/twice daily). Patients were visited in the clinic every 14 days to check the vital signs. Even if the patients opted to leave the trial, they were instructed to keep attending clinic sessions.

## Results

We witnessed improvements in QoL after two months, as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the 6-Minute Walk Test (6MWT) (13). After 60 days of therapy, there were alterations in echocardiographic and biochemical results. At the beginning, all patients had a conventional 2-dimensional and a Doppler trans-thoracic echocardiography (Vivid7; GE). The heart function was also measured at the end of the study. To evaluate the left ventricular (LV) function, left ventricular ejection fraction (LVEF) was calculated by Simpson's method, isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and ejection time (ET). LV myocardial performance index (MPI) was calculated using  $\frac{IVCT+IVRT}{ET}$  and E/e' average. Also, using fractional area change (FAC), right ventricular (RV) was measured as follows:

$$\frac{RV \text{ area in diastol} - RV \text{ area in systol}}{RV \text{ area in diastol}} \times 100$$

To examine the biochemical and hematological markers, 3 mL blood was collected in a tube containing ethylenediaminetetraacetic acid and 10 mL venous blood was obtained and collected in an anticoagulant free tube from all patients at the first day of the trial, before therapy, and after 60 days of treatment. A biobank was developed to investigate the secondary outcomes, with patients' serums preserved in an ultra-low temperature freezer.

### Blinding

Both groups received capsules (*B. multifida* and placebo) in a similar appearance and container, but different identification numbers. Each patient received a unique code at the time of enrollment, which was utilized until the completion of the trial. All patients, investigators, outcome assessors, and healthcare professionals were blind to the grouping of patients. The Medical Documentation Council of Zanjan University of Medical Sciences kept track of the unblended therapy list.

### Drug Preparation

#### Preparation of Root Extract

The plant was thoroughly cleansed to remove impurities before preparing *B. multifida* concentrate capsules. Then, in a beaker, 100 grams of *B. multifida* was combined with 1.5 L of water and cooked over a flame. The beaker was cooled to its normal temperature after 15 minutes of boiling and the solution was filtered. The solution was purified and condensed, and the *B. multifida* concentrate was extracted using a rotatory evaporator. The excipient (corn starch) was added when the dry weight of main *B. multifida* extract was reduced to 10%. As a result, 500 mg capsules containing corn starch were made to deliver identical drugs with a neutral effect in the placebo group. So, 60 capsules were kept in special bottles. The entire drug preparation procedure was performed at Shahid

Beheshti University of Medical Sciences, Iran.

#### Total Phenol Content (TPC)

In this study, 1 mL of gallic acid with different concentrations (20, 40, 60, 80, and 100 g/mL) was combined with 5 mL Folin-Ciocalteu reagent. After 10 minutes, aqueous Na<sub>2</sub>CO<sub>3</sub> (4 mL, 7.5 mg/mL) was added and incubated for 30 minutes in dark. Finally, absorption rate at 765 nm was read by spectrophotometry and gallic acid standard curve was drawn. The extract solution (1 mL, 30 mg/mL) was measured and TPC was measured using the standard curve.

#### Total Flavonoid Content (TFC)

To measure TFC, 2.5 mL of rutin solution (20, 40, 60, 80, and 100 g/mL) was combined with 2.5 mL of aluminum chloride (20 mg/mL) in ethanol 80%. After 40 minutes, TFC absorption was read in 415 nm and rutin standard curve was drawn. Then, 2.5 mL of *B. multifida* extract (30 mg/mL) was used and TFC was calculated according to the standard curve.

#### Statistical Analysis

The Shapiro-Wilk test was used to test the normality of data and to create a Q-Q plot. A comparison of the descriptive baseline characteristics of the two groups was tabulated as means (SD) or percentages. The categorical data were statistically analyzed using chi-square or Fisher's exact test, and t-test was used for continuous data. Primary QoL efficacy data were analyzed using an intention-to-treat analysis. The general linear model (GLM) of the MLHFQ and the results of the 6MWT between the two groups were compared using the repeated measures analysis of variance (ANOVA) test. Evaluation time was considered a within-subjects factor, and intervention status (*B. multifida* vs. placebo) was considered a between-subjects factor. Group time (interaction period) was considered as the group difference in response over time. We tested Mauchly's sphericity test for the compound symmetry assumption. We also used generalized estimating equations (14) models to determine the difference in MLHFQ and 6MWT scores at each time point between the two groups, and time after

treatment after adjusting for other variables. A trend was also estimated. A *P* value <0.05 or equal to 0.05 was considered as statistically significant. The IBM Statistical Package for the Social Sciences (SPSS) version 16 and SATA version 10 were used for data analysis.

## Results

### Results of Drug Analysis

The TPC and TFC of capsules were calculated as 0.71 mg and 0.35 mg, respectively.

### Demographic Characteristics of Patients

A total of 60 patients were enrolled in this trial. Due to the incomplete treatment, five individuals were excluded (Table 1). The data of 55 patients was analyzed statistically. There were 32 male (58%) and 23 female (42%) among them. Patients were evenly distributed across the two trial arms in terms of demographic and basic characteristics (Table 1).

### Quality of Life Assessments

#### The results of MLHFQ and 6MWT

Table 2 shows the mean and SD before and after administrating the drug, as well as the results of the MLHFQ and 6MWT scales in each group. There was a downward trend in the MLHFQ in both groups, indicating no significant difference between the two group (*P*>0.05). Meanwhile, there was an upward trend in the 6MWT in both groups, indicating no significant difference between the two group (*P*>0.05).

After adjusting for other variables (age, physical activity, cool and dry temperament), the generalized estimating equation (GEE) model showed a higher score for MLHFQ in the placebo group than in the intervention group, but this difference was not statistically significant (4.52, 95% CI: -3.89, 12.93; *P*=0.29). In addition, this model revealed that the 6MWT score for placebo group was lower than the intervention group, but the difference was not statistically significant (-33.48, 95% CI: -83.04, 16.09; *P*=0.19).

#### The results of MLHFQ

Table 1. Patients' Basic Characteristics

Variables		<i>Biebersteinia multifida</i>		Placebo		<i>P</i>
		Frequency	Percent	Frequency	Percent	
Gender	Male	16	55.2	16	61.5	0.633
	Female	13	44.8	10	38.5	
Cigarette smoking	No	21	72.4	18	69.2	0.332
	Yes	4	13.8	3	11.5	
	Quit	4	13.8	5	19.2	
Regular exercise	Yes	14	48.3	8	30.8	0.186
	No	15	51.7	18	69.2	
NYHA class	I	8	27.6	9	34.6	0.938
	II	21	72.4	17	65.4	

NYHA, New York Heart Association.

The MLHFQ scores were much lower in both groups ( $P < 0.001$ ). After intervention, the decrease in the *B. multifida* group was not statistically different ( $23.13 \pm 18.14$  vs.  $28.00 \pm 16.92$ ,  $P = 0.311$ ) (Table 2).

### Echocardiographic Parameter Changes

The LVEF was significantly increased in both groups, but the level of increment was higher in *B. multifida* group ( $P < 0.001$  vs.  $P = 0.039$ ). The intergroup analysis, however, revealed no significant difference between *B. multifida* and placebo groups ( $34.879 \pm 5.630$  vs.  $34.288 \pm 5.630$ ,  $P = 0.701$ ). Also, the *B. multifida* group had superiority in left ventricular myocardial performance index (LVMPI) compared to placebo ( $0.581 \pm 0.124$  vs.  $0.653 \pm 0.119$ ,  $P = 0.034$ ). As demonstrated in Table 3, none of the RV echocardiographic parameters showed a significant difference between *B. multifida* and placebo groups ( $P > 0.05$ ).

### Laboratory Measurements

There was a statistically significant increase in the levels of blood urea nitrogen (BUN) and red blood cell (RBC) and a downward trend in the levels of Alanine transaminase (ALP), mean corpuscle hemoglobin (MCH), and mean corpuscle hemoglobin concentration (MCHC) regardless of study groups (within-subject differences or time effect) ( $P < 0.05$ ). The trends of BUN and alanine transaminase (ALT) were different between the study groups ( $P < 0.05$ ). After adjusting for other variables (age, physical activity, cool and dry temperament state), GEE demonstrated that the level of AST in placebo group was higher and statistically significant compared to *B. multifida* group ( $P = 0.02$ ) (Table 4).

### Discussion

Recently, the application of herbal medicines has increased globally because of their miraculous therapeutic effects and fewer side effects on patients compared to modern medicines (15).

HF is a clinical phenomenon in which cardiac output is reduced due to a variety of factors, such as coronary artery disease, cardiomyopathies, etc. The most frequent type is systolic HF, which is mostly caused by a dysfunction in cardiac muscle contractility (16). Management of HF includes different strategies, such as drug therapy, physical examination, and multi-disciplinary interventions (14). A

significant percentage of patients prefer to use traditional methods instead of chemical treatments. Some studies demonstrated different applications of *B. multifida* in traditional treatments and as a medication. The present study evaluated the effect of *B. multifida* on the QoL in patients with systolic HF.

Marjorie L. in a prospective cohort study, enrolled 38,180 men and 60,289 women in the Cancer Prevention Study II Nutrition Cohort. The seven-year follow-up of CVD patients demonstrated that flavonoid containing drugs were associated with lower CVD mortality. *B. multifida* derivatives are attributed to the phenolic and flavonoid compounds, including kaempferol, quercetin, luteolin, myricetin, and catechin which act as free radical scavengers (17). A recent study by Coe et al showed that rich flavonoid diet improved 6MWT results in patients affected with Parkinson's disease. In this study 30 people with Parkinson's (PwP) were divided into two high and low flavonoid groups and analyzed. They reported changes on 6MWT as follows: The energy of statistical samples (ES) 0.11 (95% CI:  $-0.11-0.26$ ,  $Z = 0.81$ ) (18). According to the findings of this study, the 6MWT score considerably improved in the intervention group after the treatment period compared to the placebo. According to the results of echocardiographic tests, the LVMPI, which measures left ventricular function, was considerably better from starting point in the intervention group but not in the placebo group.

The anti-inflammatory, anti-oxidant, and physical stamina-boosting properties of *B. multifida* root extract are well-known (19, 20). It is also reported that the *B. multifida* leaves and root have the maximum effects on antioxidant activity rather than other effects (12). Reduction of oxidative stress may result in regulation of intracellular metabolism, particularly in cardiomyocytes which are highly active and need huge amount of energy (21). In a study, Xu et al linked early HF with increased apoptosis, mitochondrial respiratory impairment, and redox stress due to abnormal opening of the mitochondrial permeability transition pore, which was associated with failure of the antioxidant response. They showed that uncompensated oxidative stress had a fundamental role in HF development (22). Raeesi et al reported that the hydro-methanolic extract of *B. multifida* increased the gastro-protection against oxidative stress due to its antioxidant properties. They also reported

**Table 2.** The MLHFQ and 6MWT Scores Before and After Drug Administration

		Time		Time	Effect (P Value)	
		Pre	Post		Time* Group	Group <sup>a</sup>
MLHFQ	<i>B. multifida</i>	33.5 (17.99)	23.57 (17.99)	<0.001	0.11	0.29
	Placebo	40.17 (17.5)	25.93 (16.64)			
6MWT	<i>B. multifida</i>	352.83 (138.47)	408.87 (98.82)	0.001	0.18	0.19
	Placebo	351.1 (114.78)	376.67 (115.24)			

<sup>a</sup> After adjusting for other variables (age, physical activity, cool and dry temperament state) in GEE model.



**Table 3.** Cardiac Parameters Level Before and After Drug Administration

		Time		Effect (P Value)		
		Pre	Post	Time	Time* Group	Group <sup>a</sup>
LVEDV	<i>B. multifida</i>	5.68 (0.73)	5.64 (0.74)	<b>0.002</b>	<b>0.05</b>	0.83
	Placebo	5.94 (0.98)	5.75 (0.95)			
LVESV	<i>B. multifida</i>	4.76 (0.77)	4.6 (0.8)	<b>&lt;0.001</b>	0.61	0.71
	Placebo	4.96 (0.98)	4.74 (0.95)			
LAD	<i>B. multifida</i>	3.73 (0.53)	3.69 (0.6)	0.33	0.92	0.47
	Placebo	3.89 (0.7)	3.86 (0.69)			
EF	<i>B. multifida</i>	33.73 (5.1)	35.62 (4.71)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.43
	Placebo	34.2 (6.17)	34.47 (6.24)			
EFS	<i>B. multifida</i>	32.77 (6.34)	35.25 (5.94)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.48
	Placebo	33.67 (5.42)	34.28 (5.42)			
E	<i>B. multifida</i>	0.71 (0.27)	0.73 (0.25)	0.67	0.71	0.85
	Placebo	0.73 (0.2)	0.73 (0.26)			
A	<i>B. multifida</i>	0.75 (0.23)	0.78 (0.22)	0.42	0.48	0.68
	Placebo	0.71 (0.19)	0.71 (0.18)			
E/A	<i>B. multifida</i>	0.84 (0.41)	0.83 (0.28)	0.98	0.86	0.08
	Placebo	1.09 (0.76)	1.11 (0.66)			
DT	<i>B. multifida</i>	208.03 (67.43)	222.07 (66.77)	0.95	0.11	0.59
	Placebo	228.27 (60.55)	215.33 (52.97)			
E'	<i>B. multifida</i>	0.07 (0.02)	0.07 (0.02)	0.27	0.92	<b>0.02</b>
	Placebo	0.08 (0.03)	0.08 (0.02)			
IVCT	<i>B. multifida</i>	78.33 (22.66)	76.2 (18.73)	0.8	0.21	0.52
	Placebo	76.73 (24.46)	79.93 (19.15)			
IVRT	<i>B. multifida</i>	94.57 (16.73)	88.13 (21.37)	0.62	<b>0.05</b>	0.22
	Placebo	90.42 (15.04)	94.27 (17.11)			
ET	<i>B. multifida</i>	279.23 (38.07)	287.23 (29.25)	0.12	0.88	0.08
	Placebo	262.9 (53.84)	272.7 (30.97)			
LAA	<i>B. multifida</i>	17.31 (4.25)	16.71 (3.44)	0.96	0.21	<b>0.01</b>
	Placebo	19.96 (6.08)	20.52 (6.51)			
RAA	<i>B. multifida</i>	14.14 (3.69)	14.86 (3.48)	0.18	0.72	<b>0.03</b>
	Placebo	17.21 (5.83)	17.63 (4.36)			
RVAD	<i>B. multifida</i>	16.72 (3.8)	15.76 (5.14)	0.21	0.6	0.43
	Placebo	17.14 (3.73)	16.74 (5.07)			
RVAS	<i>B. multifida</i>	11.3 (2.74)	10.5 (3.97)	0.14	0.56	0.17
	Placebo	12.36 (3.51)	12.02 (4.42)			
LVDV	<i>B. multifida</i>	152.76 (55.78)	143.45 (59.19)	<b>0.04</b>	0.55	0.65
	Placebo	158.83 (72.23)	153.7 (67.96)			
LVSV	<i>B. multifida</i>	106.66 (50.75)	93.14 (47.22)	<b>0.05</b>	0.07	0.71
	Placebo	100.53 (53.05)	100.15 (57.1)			
RV size	<i>B. multifida</i>	3.07 (0.5)	3.02 (0.56)	0.37	0.91	0.18
	Placebo	3.3 (0.68)	3.23 (0.54)			
IVC	<i>B. multifida</i>	1.57 (0.34)	1.62 (0.38)	0.99	0.18	0.68
	Placebo	1.72 (0.5)	1.66 (0.42)			
PAP	<i>B. multifida</i>	25.83 (4.56)	26.33 (4.9)	0.19	0.6	0.24
	Placebo	27.03 (6.58)	28.2 (7.77)			
MPI	<i>B. multifida</i>	0.63 (0.12)	0.58 (0.12)	0.26	<b>0.006</b>	<b>0.04</b>
	Placebo	0.62 (0.13)	0.65 (0.11)			
FAC	<i>B. multifida</i>	32.3 (7.11)	33.57 (10.68)	0.43	0.73	0.09
	Placebo	28.26 (9.82)	28.76 (8.64)			
E/E'	<i>B. multifida</i>	10.58 (4.33)	10.85 (5.04)	0.51	0.21	0.17
	Placebo	10.19 (4.78)	9.3 (4.02)			

Abbreviations: LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume; LAD, left atrium diameter; EFM, Ejection fraction M mode; EFS, Ejection fraction Simpson; E, early diastolic; A, atrial contraction; D.T, deceleration time; E', early diastolic (Tissue Doppler Imaging); IVCT, Isovolumic contraction time; IVRT, Isovolumic relaxation time; ET, ejection time; LAA, Left atrium area; RAA, Right atrium area; RVAD, Diastolic right ventricular area; RVAS, Systolic right ventricular area; LVDV, Left ventricular diastolic volume; LVSV, Left ventricular systolic volume; RV size, Right ventricular size; IVC, Inferior vena cava; PAP, Pulmonary artery pressure; MPI, Myocardial performance index; FAC, Fractional area change.

<sup>a</sup> After adjusting for other variables (age, physical activity, cool and dry temperament state) in GEE model.

**Table 4.** Laboratory Parameters Level Before and After Drug Administration

		Time		Effect (P Value)		
		Pre	Post	Time	Time* Group	Group <sup>a</sup>
BUN	<i>B. multifida</i>	15.27 (3.69)	20.27 (7.68)	<0.001	0.03	0.05
	Placebo	15.6 (4.6)	17.27 (4.86)			
Cr	<i>B. multifida</i>	1.06 (0.19)	1.13 (0.2)	0.35	0.1	0.27
	Placebo	1.09 (0.24)	1.07 (0.23)			
AST	<i>B. multifida</i>	21.83 (8.72)	22.28 (7.08)	0.7	0.87	0.02
	Placebo	25.37 (10.11)	26.37 (8.86)			
ALT	<i>B. multifida</i>	20.9 (8.04)	24.24 (10.2)	0.93	0.04	0.54
	Placebo	28.73 (12.48)	25.1 (10.52)			
ALP	<i>B. multifida</i>	202.1 (56.96)	188.03 (48.81)	<0.001	0.9	0.59
	Placebo	205.1 (61)	190.07 (45.84)			
CRP	<i>B. multifida</i>	5.5 (8.17)	6.4 (3.71)	0.2	0.9	0.65
	Placebo	4.87 (3.94)	5.93 (4.99)			
WBC	<i>B. multifida</i>	6.95 (1.48)	6.87 (1.89)	0.58	0.96	0.99
	Placebo	7.23 (1.93)	7.13 (1.88)			
RBC	<i>B. multifida</i>	4.96 (0.52)	5.07 (0.49)	0.04	0.15	0.9
	Placebo	5.15 (0.58)	5.17 (0.46)			
Hb	<i>B. multifida</i>	14.36 (1.69)	14.46 (1.68)	0.85	0.26	0.49
	Placebo	15.14 (1.82)	15 (1.51)			
Hct	<i>B. multifida</i>	41.83 (4.54)	42.67 (3.87)	0.13	0.21	0.65
	Placebo	43.7 (4.53)	43.78 (3.85)			
MCV	<i>B. multifida</i>	84.47 (4.5)	84.41 (4.13)	0.67	0.81	0.6
	Placebo	85.07 (4.31)	84.85 (5.08)			
MCH	<i>B. multifida</i>	29 (1.92)	28.55 (1.85)	<0.001	0.71	0.32
	Placebo	29.45 (2)	20.07 (2.03)			
MCHC	<i>B. multifida</i>	34.3 (0.85)	33.82 (1.32)	0.006	0.69	0.31
	Placebo	34.62 (1.41)	34.25 (1.31)			
PLT	<i>B. multifida</i>	231.83 (58.58)	233.1 (55.68)	0.51	0.64	0.31
	Placebo	214.65 (61.14)	222.3 (51.58)			

Abbreviations: BUN, Blood urea nitrogen; Cr, Creatinine; AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase; CRP, C-reactive protein; WBC, White blood cell; RBC, Red Blood Cell; Hb, Hemoglobin; Hct, Hematocrit; MCV, mean corpuscle volume; MCH, mean corpuscle hemoglobin; MCHC, mean corpuscle hemoglobin concentration; PLT, Platelet.

<sup>a</sup> After adjusting for other variables (age, physical activity, cool and dry temperament state) in GEE model.

that *B. multifida* had protective properties in ethanol-induced ulcer model. They demonstrated that *B. multifida* antioxidant effects increased nitric oxide production (23). The improvement in cardiomyocyte metabolism results in enhancement in cardiac muscle contractility, which leads to the improvement of cardiac performance. The 6MWT is one of the most widely used objective tests to evaluate ventricular function, particularly LV function in HF patients (24). In parallel with the mentioned studies above, this may be a rational mechanism to explain the beneficial effects of this extract on cardiac performance and 6MWT results obtained in this study. The use of *B. multifida* extract, however, had no superiority in contrast with the placebo on the primary outcomes. The reason may be due to the lack of randomization on specific parameters on the primary outcomes between the two groups or the small sample size, which resulted in a low study power in the inter-group analysis. Moreover, a variety of variables are affecting the QoL in HF and we

should not expect massive changes in these parameters after using an additive supplement for a short duration of time. No adverse effect was reported in this study and all the changes in laboratory measurements were in the normal range, which was not clinically significant.

There are different ways to prevent HF as follows: hypertension treatment can decrease the incidence of HF by about 50%; diuretics,  $\beta$ -blockers, and angiotensin-converting enzyme (ACE) inhibitors; hydroxy methylglutaryl coenzyme A reductase inhibitors reduce the incidence of HF by about 20% between patients affected with hyper-cholesterolemia and CVD; and ACEIs reduce HF incidence by approximately 37% among patients with decreased systolic function and 23% among patients with coronary artery disease and normal systolic function (25).

Also, besides the current therapeutic drugs, consuming dietary and herbal supplements has become a widely accepted therapeutic method. This herbal is useful for

independent prediction of mortality in patients with HF. However, more research and clinical trials are needed to confirm these results. To understand the effect of *B. multifida* in herbal medical, increasing knowledge about the effect mechanism of the extract of the *B. multifida* root is necessary. It is also recommended to perform more humans and animals studies with a greater sample size and more extended time.

## Conclusions

In individuals with systolic HF, *B. multifida* root extract as a supplemental treatment may improve cardiac function. However, further research with longer administration and follow-up times and a larger sample size is required to fully understand the positive benefits described in this study.

## Data Availability

The raw data supporting the conclusions of this study may be obtained from the corresponding author upon request.

## Authors' Contribution

**Conceptualization:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari.

**Data curation:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari.

**Formal analysis:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari

**Investigation:** Ebadollah Salekmoghadam, Hassan Ahangar.

**Methodology:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami.

**Project Administration:** Hassan Ahangar, Funding Acquisition: Hassan Ahangar.

**Resources:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari.

**Supervision:** Hassan Ahangar, Mohsen Bahrami.

**Validation:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari.

**Visualization:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari

**Writing—original draft:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami, Mohammad Kamalinejad, Sepehr Gohari.

**Writing—review and editing:** Ebadollah Salekmoghadam, Hassan Ahangar, Mohsen Bahrami.

## Conflict of Interests

Authors have no conflict of interest.

## Ethical Issues

The ethics committee of Zanjan University of Medical Sciences approved the research protocol (code: IR.ZUMS.REC.1396.273) and the study was registered in the Iranian Registry for Clinical Trials (identifier: IRCT20180130038565N1). All participants signed an informed consent form prior to the study.

## Financial Support

This research was not financially supported by any organization.

## Acknowledgments

Prof. Soghrat Faghihzadeh and Mr. Naser Reshadmanesh provided valuable statistical analytic consultations. We would also like to express our gratitude to all the patients for their involvement and cooperation during the research.

## References

1. Global Burden of Disease (GBD) 2016 Mortality and Causes

- of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388: 1459-544. doi:10.1016/S0140-6736(16)31012-1
- Pega F, Nafradi B, Momen NC, et al. Global, regional, and national burdens of ischemic heart disease and stroke attributable to exposure to long working hours for 194 countries, 2000-2016: A systematic analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. *Environ Int*. 2021;154:106595. doi:10.1016/j.envint.2021.106595
- Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3:7-11. doi:10.15420/cfr.2016.25:2
- Mann DL, Chakinala M. Heart Failure: Pathophysiology and Diagnosis In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed. USA: McGraw-Hill Professional; 2015.
- Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115-40. doi:10.1093/eurheartj/ehi204
- Breitling S, Ravindran K, Goldenberg NM, Kuebler WM. The pathophysiology of pulmonary hypertension in left heart disease. *Am J Physiol Lung Cell Mol Physiol*. 2015;309:L924-41. doi:10.1152/ajplung.00146.2015
- Puri S, Baker B, Oakley C, Hughes J, Cleland J. Increased alveolar/capillary membrane resistance to gas transfer in patients with chronic heart failure. *Br Heart J*. 1994;72(2):140-144. doi:10.1136/hrt.72.2.140
- Young AL, Langston CS, Schiffman RL, Shortsleeve MJ. Mitral valve regurgitation causing right upper lobe pulmonary edema. *Tex Heart Inst J*. 2001;28:53-6.
- Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013; 77: 2209-17.
- Djoussé L, Driver JA, Gaziano JM. Relation Between Modifiable Lifestyle Factors and Lifetime Risk of Heart Failure. *JAMA*. 2009;302:394-400. doi:10.1001/jama.2009.1062
- Bianchi I. *Integrative Cardiology*. 1st ed. Springer International Publishing; 2017.
- AMIRI H. Antioxidant activities of the essential oils and extracts of *Biebersteinia multifida* DC. *Herba Polonica*. 2009; 55:59-68.
- Bilbao A, Escobar A, García-Pérez L, Navarro G, Quirós R. The Minnesota living with heart failure questionnaire: comparison of different factor structures. *Health Qual Life Outcomes*. 2016;14:23. doi:10.1186/s12955-016-0425-7
- Jaarsma T, Strömberg A, De Geest S, et al. Heart failure management programmes in Europe. *European Journal of Cardiovascular Nursing*. 2006;5:197-205.
- Fong HH. Integration of herbal medicine into modern medical practices issues and prospects. *Integr Cancer Ther*. 2002;1(3):287-293. doi:10.1177/153473540200100313
- Kemp CD, Conte JV. The pathophysiology of heart failure. *Cardiovasc Pathol*. 2012;21(5):365-371. doi:10.1016/j.carpath.2011.11.007
- Dabaghian FH, Entezari M, Ghobadi A, Hashemi M. Antimutagenicity and anticancer effects of *Biebersteinia multifida* DC. *Ann Res Rev Biol*. 2014;4:906-913. doi:10.9734/ARRB/2014/7193
- Coe S, Andreoli D, George M, et al. A feasibility study to determine whether the daily consumption of flavonoid-rich pure cocoa has the potential to reduce fatigue and fatigability in people with Parkinson's (pwP). *Clin Nutr ESPEN*. 2022;48:68-73. doi:10.1016/j.clnesp.2022.01.023
- Jahromy MH, Mohajer AJ, Adibi L, Khakpour S. Effects of *Biebersteinia multifida* DC. Root extract on physical stamina in male mice. *Food Nutr Sci*. 2015;6:326.
- Javidnia K, Miri R, Soltani M, Khosravi A. Essential oil composition of *Biebersteinia multifida* DC. (Biebersteiniaceae) from Iran. *Journal*

- of Essential Oil Research. 2010;22:611-612.
21. Mattera R, Benvenuto M, Giganti MG, et al. Effects of polyphenols on oxidative stress-mediated injury in cardiomyocytes. *Nutrients*. 2017;9:523.
  22. Xu X, Jin K, Bais AS, et al. Uncompensated mitochondrial oxidative stress underlies heart failure in an iPSC-derived model of congenital heart disease. *Cell Stem Cell*. 2022;29:840-55e7. doi:10.1016/j.stem.2022.03.003
  23. Raeesi M, Eskandari-Roozbahani N, Shomali T. Gastro-protective effect of *Biebersteinia multifida* root hydro-methanolic extract in rats with ethanol-induced peptic ulcer. *Avicenna J Phytomed*. 2019;9(5):410-418.
  24. Berisha V, Bajraktari G, Dobra D, Haliti E, Bajrami R, Elezi S. Echocardiography and 6-minute walk test in left ventricular systolic dysfunction. *Arq Bras Cardiol*. 2009;92:121-134.
  25. Baker DW. Prevention of heart failure. *J Card Fail*. 2002;8:333-346. doi:10.1054/jcaf.2002.0805333

**Copyright** © 2023 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.