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Efficacy of *Rhubarb* root extract on quality of life in patients with systolic heart failure: A randomized placebo controlled study

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ABSTRACT

Introduction: This study aimed to investigate the role of Rheum palmatum on quality of life and cardiac function in patients with systolic heart failure. *Material and Method*: This was a parallel double-blind, placebo-controlled trial study from April to August 2019. Total of 60 patients with systolic heart failure were randomly assigned to Rheum palmatum and placebo groups. The intervention group received Rheum palmatum capsules (containing 250 mg of dry extract of Rheum palmatum root and 250 mg corn starch) and the placebo group received capsules containing 500 mg corn starch twice-daily for 60 days. The primary outcomes were the enhancement of quality of life (QoL) based on the Minnesota questionnaire and the 6-minute walk test. The secondary outcomes were the improvement of cardiac function and serum biochemical markers. *Results*: Before treatment, no significant difference between study groups in terms of clinical, laboratory, imaging and QoL results were seen (P>0.05). After treatment, none of the study groups had superiority considering the QoL parameters and patients' exercise tests (P>0.05). The echocardiographic findings showed significant improvement in LV and RV systolic function (P<0.05). *Conclusion:* Short term treatment with Rheum palmatum extract has beneficial effect on cardiac function but not on patients' quality of life.

Keywords: Echocardiography, Heart Failure, Quality of Life, Rheum palmatum, Randomized Controlled Trial.

1. INTRODUCTION

Heart failure (HF) is a debilitating disorder which is caused by a reduced ability of the heart to provide sufficient circulation throughout the body and is already known as the end stage of several cardiovascular diseases (CVD), such as myocardial infarction, hypertension and valvular diseases (Yancy et

al., 2013; Wilkins et al., 2017; Asgary et al., 2014). HF is a syndrome, which results in complex clinical manifestations mainly due to structural or functional cardiac disorders that prohibit the cardiac muscle from meeting the metabolic demands (Francis and Tang, 2019). Therefore, the main challenge regarding the HF is the increasing amount of the costs and burdens of the disease on the health systems (Lesyuk et al., 2018).

In order to diminish the burden of the disease, over the last years, several medications has been suggested to treat and control related symptoms which ultimately may increase the quality of life (QoL) (Drazner and Stevenson, 2019; Mark et al., 2018). Despite the increasing efficacy of medications, low compliance to medical treatment remains the main concern among patients with HF. However, medical plants and herbs were used widely to treat various medical conditions, particularly cardiovascular diseases, including congestive heart failure, hypertension, angina pectoris and atherosclerosis. In addition, recently the overall popularity of the traditional medicine and herbs has increased (Rastogi et al., 2016). Thus, traditional remedies have been attended once again in different fields, especially in treatment of CVDs.

According to the Iranian traditional medicine resources, the heart, as a noble organ, has a special role and potential for survival, so there are numerous herbs has been introduced to strengthen the heart. The "Rheum palmatum" (RP), also known as Chinese Rhubarb, is one of these herbal plants which has been discussed in ancient literature, and has been referred to as a potent medicine. Previous studies have demonstrated several beneficial effects for RP, including antiviral, antioxidant, and anti-proliferative effects (Chang et al., 2014; Chen et al., 2017; El-Saied et al., 2018; Kang et al., 2008; Shojaei-Shad et al. 2019). The components are found (hydroxyanthracene derivatives) (e.g. sennoside B, rhein, glucofrangulin A, aloin, aloe emodin, etc.) in the root and rhizome of Rheum palmatum and their hybrids (Lesyuk et al., 2018). Many beneficial effects of this plant have been attributed to the mentioned compounds. The lipid-lowering and cardiovascular effects of this drug are previously investigated in animal models (Mark et al., 2018; Radcliffe, 2005). The cardiovascular benefit of this plant in heart failure, however, is not yet investigated.

On the other hand, the main role of this plant in many authentic sources of Iranian traditional medicine has been considered as a heart enhancer, as expressed in the book of al-Adawiyyah reserved for the herbs and properties of RP (Radcliffe, 2005). In al-Mansouri's book by Iranian ancient wisdom "Razi", RP has introduced to have several cardiovascular benefits (al-Razi, 2008). The current randomized controlled trial is the first study of the effect of Rheum palmatum on the improvement of the cardiac function and QoL in patients with systolic HF.

2. MATERIALS AND METHODS

Study Design

This was a Phase III, parallel double-blind, and placebo-controlled randomized trial study of the effect of RP capsules versus placebo on the quality of life in patients with systolic heart failure. The study was conducted in accordance with the principles of the declaration of Helsinki and approved by the ethic committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1396.271) and also this study was submitted prospectively in the Iranian Registry of Clinical Trials (IRCT20180206038645N1). All the patients provided written informed consent.

Study Patients and settings

The study population was selected from patients with systolic heart failure who were under routine heart failure treatment in the cardiology special clinic in Zanjan, Iran. Patients' recruitment started from April 2018 and completed in August 2019. During this period 129 patients were assessed for eligibility and 69 were excluded (45 were not meeting the inclusion criteria, 17 declined to participate and 7 with other reasons). Ultimately, 60 patients were enrolled in the study.

The inclusion criteria were 1) Age between 40 to 75 years old 2) Systolic heart failure with the ejection fraction (EF) ≤ 40% 3) Under fix and continuous treatment for heart failure within last 6 months. 4) The New York Heart Association (NYHA) Functional Classification I and II.

The exclusion criteria were 1) Pregnancy 2) Breast feeding 3) History of malignancy 4) History of hypersensitive reaction to RP root 5) Unwillingness of the patient to continue the treatment or loss of follow up 6) Chronic inflammatory disease 7) Significant renal insufficiency 8) History of Collagen vascular disease 9) Acute infectious disease 10) occurrence of decompensated heart failure during the study.

Study procedure

Randomization and Follow up

Recruited patients were randomized in a 1:1 ratio into 2 groups of intervention and control groups (30 patients each) using the random numbers table. Generation of the random allocation sequence, participants' assignments and Coding of the drug and placebo was under the responsibility of a statistical adviser who was not blind. The intervention group received 500 mg twice-daily Rheum palmatum capsules for 60 days. Patients were followed up for 60 days and they were visited bimonthly at the clinic during this period to ensure the proper usage of the drug, record vital signs and evaluate the study progress (figure 1).

Drug preparation and analysis

To prepare a RP concentrate capsules, the plant washed completely, to eliminate contaminants. Then, 100 gr of RP was poured with 1.5 Liters water in a beaker and boiled over the flame. After boiling for 15 minutes, the beaker was cooled down at the room temperature, and the solution was filtrated. The rotatory evaporator was used to purify and condense the solution and to extract the RP concentrate. The dry weight of the extract was 10% of the primary RP weight, subsequently; the excipient (a corn starch) was added.

Finally, 500 mg capsules of RP concentrate were prepared, while 250 mg of the powder, containing active compound, was poured into the capsule, as well as the 250 mg of the supplementary material, described above. Accordingly, in order to provide similar medications with neutral effect in control group, 500 mg capsules with corn starch were prepared. Finally, capsules were prepared in specific bottles containing 60 capsules each, which were similar in shape, color, and batch in both groups. All the mentioned processes (drug preparation) were done at School of Pharmacy, Shahid Beheshti University of Medical Sciences with an institutional herbarium approval number of SBMU-8098. Each group of capsules containing the drug and placebo was identified by the respective code, due to double-blinded nature of the study.

The drug analysis was performed with the UV method based on the calculation of the percentage content of sample Hydroxyanthracene glycosides expressed as sennoside B using the following expression

$\frac{A \times 4.167}{m}$, where A= absorbance at 515 nm; m= mass of the herbal drug to be examined, in grams (16,17).

Outcomes

The Primary outcome was the changes in the quality of life (QoL) within 60 days of follow up based on the Minnesota questionnaire for quality of life and the 6-minute walk test (6MWT) (Bilbao et al., 2016). The secondary outcomes were changes in echocardiographic and biochemical parameters after 60 days of treatment. To assess the cardiac function, patients underwent standard 2-dimentional and Doppler trans-thoracic echocardiography (Vivid 7; GE) at the beginning of the study and the end of the treatment course. Left ventricular (LV) function was assessed by the following parameters: 1) LVEF calculated by Sympson method 2) Isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT) and Ejection time (ET) 3) LV myocardial performance index (MPI) using $\frac{IVCT+IVRT}{ET}$ formula. 4) Ratio between early diastolic mitral inflow velocity and mitral annular early diastolic velocity (Average E/e'). Right ventricular (RV) function assessed by Fractional area change (FAC) using

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

To assess the biochemical parameters, a sterile antecubital venous blood sample was taken from the patients at the beginning of the study prior to the treatment and after 60 days of treatment.

Blinding

All participants, care providers, Investigators and outcome assessors were blinded to the intervention-control groups.

Safety considerations

In every follow up visit, patients were evaluated regarding the potential adverse effects and allergic reactions with open-ended questions.

Statistical analysis

Chi-square test was used to analyze the demographic data and student T test was used to compare quantitative variables (primary and secondary outcomes) between groups and paired T test was used for intra group assessments. The level of significance was set at 0.05, and all results were expressed by frequency (percent) for qualitative variables and Mean±SD for quantitative variables. All analysis was done IBM SPSS Statistics software (version 16.0, SPSS, Chicago, Illinois).

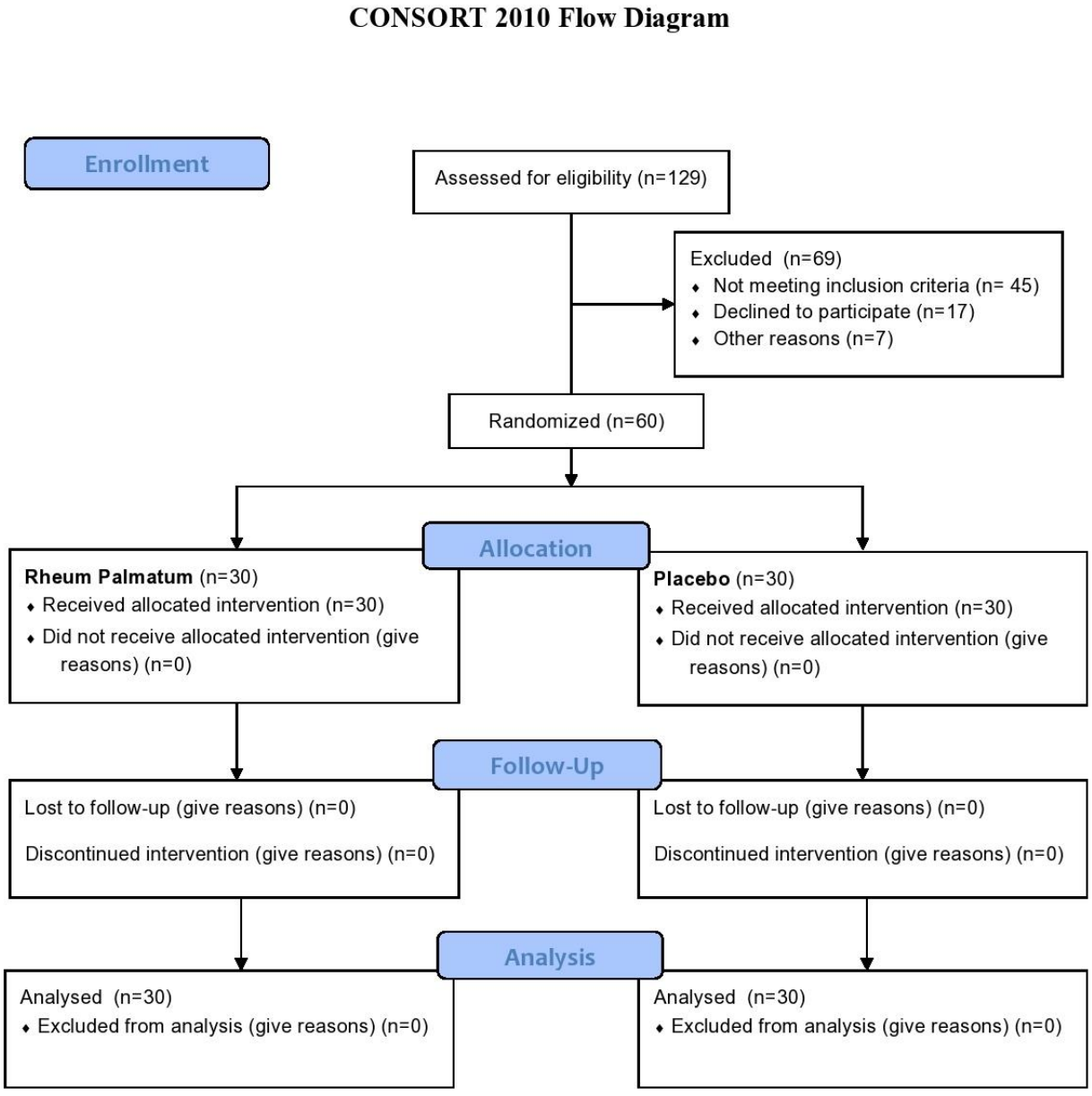

Figure 1 CONSORT 2010 Flow diagram of the study.

3. RESULTS

Drug analysis results

The percentage content of Hydroxyanthracene glycosides was calculated 0.28% per capsule.

Demographic status and basal characteristics

The totals of 129 patients were assessed for eligibility. Finally, 60 patients were randomized into 2 groups of RP and placebo (60% of patients were male and 40% were female, Mean±SD of age was 61.5±7.5 years). According to the demographic status, patients were well balanced between the two groups (Table 1).

Table 1 Patients baseline characteristics

Variables		RP1		Placebo		p	OR	95% C.I.: OR	
		Frequency	Percent	Frequency	Percent			Lower	Upper
Gender	Male	18	60	18	60	1.000	1.000	0.356	2.809
	Female	12	40	12	40				
Cigarette Smoking	No	17	56.7	20	66.7	0.810			
	Yes	5	16.7	3	10				
	Quit	8	26.7	7	23.3				
Regular Exercise	Yes	9	30	9	30	1.000	1.000	0.331	3.017
	No	21	70	21	70				
NYHA class	I	6	20	9	30	0.890			
	II	24	80	21	70				

1 Rheum Palmatum

Quality of life assessments

Six Minute Walk Test

The Intergroup analysis showed that patients in the RP group had better results in both before and after treatment but the difference was not significant (P=0.809 and P=0.314, respectively). In addition, no significant difference was observed in the intragroup analysis in both groups (P=0.125 and P=0.091, respectively) (Table 2).

Minnesota questionnaire for quality of life

The Intergroup analysis showed that there was no significant difference between the groups before and after the treatment (P=0.382 and P=0.596, respectively). The intragroup analysis showed that the Minnesota questionnaire scores were significantly dropped in both groups after the treatment (P=0.001 and P<0.001, respectively). Consequently, none of the study groups had superiority after treatment considering the QoL parameters (Table 2).

Table 2 Inter-group and intra-group analysis for 6MWT and Minnesota questionnaire for quality of life

Variables		RP1	Placebo	Student-t: P	Mean Difference	95% C.I.: Mean Difference	
		Mean±SD	Mean±SD			Lower	Upper
6 minute walk test (m)	Before	366.63±106.52	351.10±114.78	0.809	15.533	-41.69	72.76
	After	388.36±94.79	376.66±115.23	0.314	11.70	-42.83	66.23
	Paired : P	0.125	0.091				
Minnesota questionnaire	Before	33.37±20.65	40.16±17.49	0.382	6.43	-16.32	3.46
	After	25.00±18.26	25.93±16.6	0.596	0.93	-9.96	8.09
	Paired: P	0.001	<0.001				

Secondary outcomes assessment

Cardiac function

In the evaluation of the LV systolic function, a significant improvement in LVEF was seen in both RP and placebo groups after the treatment (P<0.001 in RP group and P=0.005 in placebo groups) but there was no significant difference between the 2 groups regarding this parameter (P>0.05). The analysis showed that in the RP group, the IVCT and IVRT were significantly reduced and ET was increased (P=0.017, P=0.04 and P=0.02, respectively) and in the placebo group these parameters increased but not significantly

(P>0.05). Consequently, the MPI which is dependent to the mentioned parameters was improved significantly in the RP group (P<0.001). In the evaluation of the LV diastolic function our finding showed that E/e′ ratio was improved in both RP and placebo group but the level of difference was not significant (P>0.05). However, the mitral annular early diastolic velocity (e′) was improved significantly in RP group (P=0.019). Finally, in the assessment of RV function our findings showed that the FAC was increased significantly in the RP group (28.922±8.135 % vs 32.839±7 %.458, P=0.001) which represents the improvement in RV function. Extra information has shown in table 3.

Table 3 2D Trans-thoracic Echocardiographic findings

Variables		RP1	Placebo	Student-t : p	Mean Difference	95% C.I.: Mean Difference	
						Lower	Upper
EF2 (%)	Before	33.550±4.090	33.666±5.422	0.925	0.116	-2.598	2.365
	After	36.566±4.132	34.283±5.424	0.072	2.283	-0.208	4.775
	Paired : P	<0.001	0.005				
E3 (m/s)	Before	0.82±0.26	0.73±0.19	0.151	0.087	-0.032	0.208
	After	0.81±0.27	0.73±0.26	0.283	0.074	-0.063	0.211
	Paired : P	0.618	0.974				
e'4 (m/s)	Before	0.07±0.02	0.08±0.03	0.285	0.006	-0.018	0.005
	After	0.08±0.02	0.08±0.02	0.850	0.001	-0.011	0.009
	Paired : P	0.019	0.455				
IVCT5 (msec)	Before	90.833±37.109	76.733±24.463	0.088	14.100	-2.143	30.343
	After	78.800±23.577	79.933±19.152	0.839	1.133	-12.234	9.968
	Paired : P	0.017	0.198				
IVRT6 (msec)	Before	97.433±29.04	90.423±15.038	0.247	7.010	-4.942	18.962
	After	91.600±25.818	94.266±17.108	0.639	2.666	-13.985	8.652
	Paired : P	0.040	0.259				
ET7 (msec)	Before	277.166±29.556	262.900±53.836	0.208	14.266	-8.178	36.711
	After	289.600±29.231	272.700±30.974	0.034	16.900	1.334	32.465
	Paired : P	0.020	0.330				
LVMPI8	Before	0.689±0.181	0.6233±0.114	0.112	0.066	-0.016	0.149
	After	0.645±0.113	0.6233±0.113	0.092	0.050	-0.108	0.008
	Paired : P	P<0.001	0.188				
RVFAC9 (%)	Before	28.922±8.135	28.262±9.818	0.778	0.660	-3.999	5.320
	After	32.839±7.458	28.763±8.644	0.055	4.076	-0.098	8.250
	Paired : P	0.001	0.651				
E/ e'10	Before	11.618±4.631	10.190±4.779	0.245	1.428	-1.003	3.860
	After	10.630±6.014	9.299±4.021	0.318	1.331	-1.313	3.975
	Paired : P	0.115	0.234				

1. Rheum palmatum 2. Left ventricular ejection fraction 3. mitral inflow velocity 4. mitral annular early diastolic velocity 5. Isovolumic contraction time 6. Isovolumic relaxation time 7. Ejection time 8. Myocardial performance index 9. Fractional area change 10. Ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

Laboratory measurements

The Mean±SD of Bound urea nitrogen (BUN) in RP group was 18.43±6.621 mg/dl and 21.27±7.94 mg/dl before and after the treatment which was significant (P=0.037). the intragroup analysis showed that in the RP group, there was a significant reduction in aspartate aminotransferase (AST) (26.93±9.97 U/L vs 20.70±8.17 U/L, P=0.001), and significant increment in white blood cells (WBC) and C-reactive protein (CRP) (6.80±2.03 103/µL vs 7.29±1.77103/µL, P=0.009 for WBC and 4.13±4.21 mg/L vs 6.56±5.13 mg/L, P=0.001 for CRP) but not in placebo group (P>0.05). The intergroup and intragroup analysis have not shown significant differences regarding the other laboratory parameters (P>0.05) (Table 4).

Table 4 Laboratory measurements

Variables		RP 1	Placebo	Student-t: p	Mean Difference	95% C.I.: Mean Difference	
		Mean±SD	Mean±SD			Lower	Upper
BUN 2 (mg/dl)	Before	18.43±6.621	15.60±4.59	0.313	2.833	-0.113	5.779
	After	21.27±7.94	17.27±4.85	0.054	4.000	0.596	7.404
	Paired : P	0.037	0.050				
Cr 3 (mg/dl)	Before	1.15±0.21	1.093±0.23	0.850	0.063	-0.052	0.179
	After	1.127±0.29	1.073±0.22	0.294	0.053	-0.082	0.189
	Paired : P	0.543	0.645				
AST 4 (U/L)	Before	26.93±9.97	25.37±10.10	0.786	1.567	-3.623	6.757
	After	20.70±8.17	26.37±8.86	0.201	5.667	-10.072	-1.262
	Paired : P	0.001	0.692				
ALT 5 (U/L)	Before	26.40±14.60	28.73±12.47	0.872	2.333	-9.353	4.686
	After	23.10±11.54	25.10±10.51	0.599	2.000	-7.708	3.708
	Paired : P	0.068	0.175				
CRP 6 (mg/L)	Before	4.13±4.21	4.87±3.93	0.875	0.733	-2.841	1.375
	After	6.56±5.13	5.93±4.98	0.968	0.633	-1.982	3.248
	Paired : P	0.001	0.101				
WBC 7 (103/μL)	Before	6.80±2.03	7.22±1.93	0.820	0.423	-1.449	0.602
	After	7.29±1.77	7.12±1.88	0.732	0.166	-0.778	1.111
	Paired : P	0.009	0.715				
HGB 8 (g/dl)	Before	14.19±1.91	15.14±1.82	0.806	0.950	-1.916	0.016
	After	14.34±2.00	15.00±1.50	0.585	0.660	-1.576	0.256
	Paired : P	0.116	0.420				
PLT 9 (103/μL)	Before	219.93±68.05	214.65±61.13	0.358	5.283	-28.151	38.717
	After	226.33±67.50	222.30±51.57	0.088	4.033	-27.012	35.079
	Paired : P	0.098	0.552				

1. Rheum palmatum 2. Blood urea nitrogen 3. Creatinine 4. Aspartate transaminase 5. Alanin transaminase 6. C-reactive protein 7. White blood cell 8. Hemoglobin 9. Platelet.

Adverse effect evaluations

No related adverse effect or allergic reaction was reported during the study.

4. DISCUSSION

The main concern of health-care providers is prevention as well as appropriate treatments for life-threatening diseases, in order to reduce mortality and increase life expectancy (Francis and Tang, 2019; Daubert and Douglas, 2019). Also, the severity of the chronic diseases (such as HF) is strongly associated with QoL of individuals and has a significant impact on life expectancy. Therefore, effective treatment should aim to enhance the patients' daily function, and subsequently their QoL (Al-Razi, 2008). In the present randomized controlled trial, the main aim was evaluation the effects of RP on enhancing the QoL and cardiac function in HF patients. In this study the primary outcome in which quality of life was assessed comprised of one subjective (Minnesota questionnaire) and one objective (6MWT) parameters for the quality assurance. Totally the results showed that RP does not have a beneficial nor adverse effect on QoL in patients with HF. Although this herbal plant was reported to have beneficial effects on cardiovascular system in Iranian complementary medicine, our study did not support this specific effect (Rastogi et al., 2016; Wilkins, 2017).

The result of this study showed that RP can significantly reduce the AST level. The possible underlying mechanism may be dependent to the lipid lowering effects induced by rhein and danthron which is reported that these active ingredients in RP promotes the phosphorylation of AMPK and acetyl-CoA carboxylase in both HepG2 and C2C12 cells; ultimately, reduces sterol regulatory element-binding protein 1c synthesis and fatty acid synthase gene expressions, contributing to the inhibitory effect on

lipid metabolism (Radcliffe, 2005). Also, the serum levels of CRP and WBC were also increase significantly in RP group but they were in normal range values. The possible reason is that CRP and WBC rise in many conditions like inflammation or infections; thus, these factors are not considered clinically significant as long as they are in normal range. The important part of this study was in the assessments of echocardiographic parameters.

The results of this study showed that short term use of RP improves the LV systolic function and RV function but has little effects on LV diastolic function. The exact underlying mechanism is not fully understood but recently Mark et al., (2018) reported that Emodin (as the major ingredient of RP) has therapeutic potential for cardiac hypertrophy (which is one of the major risk factors for heart failure development) through mitochondrial protection due to the modulation of SIRT3 signaling. Thus, the improvements in LV MPI and RV FAC may relate to this factor which is needed to be evaluated in future studies. In the present study no side effect or adverse effect reported; however, some side effects such as gastrointestinal discomfort, diarrhea, headache and vomiting are reported for RP (Yancy et al., 2013).

Limitations

One of the important limitations of this study was that we did not separate the active ingredients in our extract so we could not determine the ingredient/s which is/are contributed to the cardiac function improvements. Another limitation of this study was the occurrence of placebo effects through the study which may be due to some potential confounder factors we did not notice and need to be considered in future studies.

5. CONCLUSION

Totally, the short term use of RP extract has beneficial effects on cardiac function through LV systolic and RV systolic improvement but has neutral effects in patients with heart failure on the quality of their life. Further research is required to accredit our results and discover possible underlying mechanisms. This study, however, could be a basis for future studies.

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Authors' Contribution Statement

Zohre Gholami: Main Investigtor and outcome assessor
Mohsen Bahrami: Conceptualization and Supervision
Mohammad Kamalinejad: Providing resources and making herbal extract
Hassan Ahangar: Study design, methodology, project administration and outcome assessor
Tara Reshadmanesh: Statistical analysis and data curation and methodology
Sepehr Gohari: Study design, literature review, manuscript drafting and revision.

Ethics

The study was approved by the Medical Ethics Committee of Zanjan University (ethical approval code: IR.ZUMS.REC.1396.271).

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This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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