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Simultaneous effect of one-month crataegus supplementation and rehabilitation program on cardiac contractile strength, blood pressure, heart rate and functional capacity of patients with heart failure

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Abstract

Background and Objective: Heart failure (HF) is one of the most prevalent and debilitating diseases of the current era, which is the leading cause of high mortality rates in human. This study aims to investigate the simultaneous effect of crataegus supplementation and a 4-week cardiac rehabilitation program on ejection fraction (EF), blood pressure (BP), heart rate (HR), and functional capacity in patients with heart failure.

Materials and Methods: 30 patients with heart failure (EF between 10 to 30%) with an average age of 50 to 75 voluntarily participated in the present study and randomly divided into three equal groups (n = 10), crataegus+exercise (cr+e), crataegus (cr), and control (c) groups. The cr+e and cr groups received the crataegus extract for one month. cr+e group did rehabilitation exercises for one month. The c group had their usual lifestyle and treatment without any regular exercise or supplement. Before and after the project, all subjects were tested for vital signs, (electrocardiogram) ECG, echocardiography, and a 6-minute walking test (6MWT).

Results: The findings showed a significant increase in EF in the cr+e group after 4 weeks ($P<0.00$). Results of 6MWT increased after 4 weeks in cr+e and cr groups ($P<0.05$) and BP and HR was improved in both groups.

Conclusion: Results indicate that 4 weeks of exercise program along with crataegus supplement will lead to the reduction of heart risk factors in patients with heart failure by increasing the contractile strength of the heart, lowering blood pressure and improving functional capacity.

Keywords: Crataegus, Rehabilitation, Ejection fraction

1. Introduction

Congestive heart failure (CHF) is one of the most important chronic diseases worldwide (1, 2). In HF, due to the delicacy of the heart, the blood needed for the peripheral circulation of the body is not provided adequately (3). Patients with HF experience several physical and psychological symptoms such as dyspnea, lack of energy and weakness, fatigue, limb edema, sleep disorders, depression, and chest pain (4), all of this symptoms can lead to limitations in daily activities, personal and social affairs and reduced quality of life (5). Pharmacotherapy and therapeutic interventions have been able to create very small to moderate

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improvement in the life quality of HF patients (6, 7).

Identifying new drugs for the prevention or treatment of cardiovascular disorders, especially herbal drugs, is vital because of their non-toxic nature (8). Crataegus plant is one of the most important herbal remedies for heart failure (9). Evidence has shown that flowers, leaves, and fruit of the crataegus plant have cardiovascular pharmacological properties, including antioxidant activity, positive inotropic effect, the protective effect of the heart in cases of ischemic-reperfusion damage, antiarrhythmic, and reducing effect on systemic hypertension (10).

Also, exercise and physical activity are normally prohibited in HF patients, and this theory has been accepted in most scientific medical texts that reducing physical activity is essential to prevent the symptoms of physical activity and exercise, especially increased hemodynamic load on the patient's ventricles (11). But it has recently been suggested that this form of inactivity (lack of exercise, watching TV, and rest in bed) can lead to loss of physical ability and may even worsen the symptoms of HF (12). Therefore, most European and American medical professionals today agree on the general recommendations for exercise training for all HF patients with stable conditions along with appropriate pharmacotherapy (13-15). Therefore, a careful and supervised endurance training program can improve the performance of work capacity in chronic heart failure (CHF) patients (12). Hwang et al. (2008) investigated the effect of 3 weeks of treatment with 3 doses of Hawthorne (low = 1.3, medium = 13, high = 130) on left ventricular function in male mice with developing stenosis aorta (SA) and cardiac hypertrophy. The results showed that AS increased the ratio of LV to body weight by 34% in both groups, and Hawthorne could significantly reduce the volume of the left ventricular chamber; AC also reduced the side shortening (VCFC) by 28%; this reduction was also reinforced by Hawthorne. They concluded that treatment with hawthorn corrected the change in myocardial contractility disorder in cardiac hypertrophy due to recent hypertension (16). Swaminathan et al. (2010) examined the effect of crataegus plant extract in the ischemia-reperfusion model on mice and infused crataegus ethanolic extract (1mg/ml/minute) for 10 minutes during reperfusion. The results showed a significant return on the contractile strength of the heart, a decrease in the size of the infarct area, and a decrease in creatine kinase and lactate dehydrogenase activity, a significant increase in anti-apoptosis factors and a decrease in pre-apoptosis proteins in cardiac treatment with extract (17). Abbasi et al. (2007) examined the effect of walking exercise program, 3 times a week for 2 months, on 60 HF patients (EF ≥ 40) with an average age of 40 to 75 on life quality and functional capacity; the results stipulated a significant increase in the distance traveled with the 6MWT test and a significant difference in the quality of life at the beginning and end of the activity (18). Considering the research on the effect of crataegus extract and sports activity in patients with heart failure is very limited and dispersed, and its exact effect is not clear, and considering that most research is in vivo and in vitro conditions, the present study was developed to investigate the simultaneous effect of one month of the extract of dried powder of flowers and leaves of crataegus and rehabilitation (walking program) on the contractile strength of the heart, BP, HR, and functional capacity in HF patients. Accordingly, the present study hypothesized that walking exercise with crataegus extract could lead to further improvement in the heart function indicators of HF patients after open-heart surgery.

2. Materials and Methods

2.1. Study Population

The subjects of this study included 30 HF patients with 10-30% LVEF (mean ±SD; age 67.4±4.5 y, BMI 27.5±7.3 kg/m2) from the Hazrat-e-Rasoul Hospital in the town of Javanroud, Kermanshah province, who were randomly divided into three even groups (n=10): crataegus +exercise (cr+e), crataegus (cr), and control (c) groups. The criteria for entering the study included patients who undergo echocardiography by a cardiologist and their LVEF is in the range of 10 to 30 percent and also have not been participating in any regular exercise during the last 6 months. Criteria for being excluded from the study were more than two sessions absent in the exercise program, the experience of any side effects during the intervention phase, and the person's objection to continuing the program. After consulting with the patients' physician, all the subjects completed the health-related questionnaire first. Before the study, all the subjects were asked to sign a written consent form. The protocol of the rehabilitation and supplement program was approved by the ethics committee of Shahed University of Medical Sciences in Tehran (the ethics code IR.SHAHED.REC.1399.023). All the subjects were asked to avoid taking drugs and supplements arbitrarily or without medical supervision, as well as they must have no smoking during and six months before the start of the study.

2.2. Research Design

This research is a semi-experimental project based on the pre-test-post-test model. After randomly subjects assignment in to study groups using blocked Web-based open source application for the randomization (https://www.random.org/), based on the their groups they were familiarized to the details of the study were needed; such as the steps of the rehabilitation program, the 6MWT test, and the control of vital signs, and after that, for 4 weeks they performed the rehabilitation program and received the crataegus

supplement under the supervision of the researcher and the specialist. Twenty-four hours before and after the end of the program, the subjects in the three groups were assessed for their height, weight, body fat percentage (body composition analyzer, zeus 9.9), blood pressure (BP) and heart rate (HR), 6MWT test, ECG and echocardiography at resting status.

2.3. Measurement of Height, Weight and Fat Percentage

Before and after the completion of the training protocol, height was measured to the nearest 0.5 cm using a calibrated stadiometer (Seca 206, Seca Corp, Harmans, MD) and body mass and body percent were measured using the Body Composition Analyzer (VENUS-5.5, Jawon Medical, Seoul, Korea) with correction for light indoor clothing.

2.4. Supplementation

The extract of the dried powder of the flowers and leaves of the plant crataegus, which is standardized at 4-6 mg of Vitexin-2-Ramnozide, was taken twice a day (morning and night) in both CR+E and CR groups while the control group did not take any supplements or placebo. Also, all patients' medications were evaluated weekly by the cardiologist based on the possibility of the effects of crataegus on patients and were adjusted if needed.

2.5. Rehabilitation Program

Patients in the cr+e group had a 4-week (three-session weekly) regular walking program and regular exercise under the supervision of a sports coach and nurse. At the beginning of each exercise session, the patients' blood pressure and heart rate were checked, and they were asked if they could work out on that day or postponed it to another day, and then if all conditions were right the exercise program began. The walking program for each session started from 30 to 35 minutes in the first week and gradually increased by 10 minutes per week to 60 to 65 minutes in the last week. The training program included warming up and preparation of the body for 5 minutes with stretching movements, five minutes of slow walking and then 10 minutes of brisk walking, which increased by 10 minutes each week based on the patients' tolerance (in case of dyspnea and fatigue, the subjects were recommended to walk slowly or rest), and at the end of session 10 minutes of slow walking and cooling down with stretching exercise and relaxation of the body.

2.6 Six Minute Walking Time (6MWT)

The 6 Minute Walk Test is a sub-maximal exercise test utilized to assess aerobic capacity and endurance of patients. The distance covered over a time of 6 minutes is used as the result by which to compare changes in performance capacity. With this test, we were able to compare the rate of progression of study subjects before and after the intervention. This test was taken from all the subjects under the precise supervision at the beginning and 48 h after the last training session. Subjects of all groups were asked to perform 6 minutes walking in a rectangular hall in Hazrat-e-Rasoul Hospital, and then the area paved in 6 minutes was recorded.

2.7. Measurement of EF, BP, HR and ECG:

To examine ECG, cardiac arrhythmias, as well as the heart rate, patients' ECG was taken 24 hours before and after the completion of the last training session. After 20 minutes resting ate sitting status resting HR and BP was measured. The patients were then referred to the echocardiography room for examination of the contractile strength and EF of heart and underwent echocardiography (US-made GE vivid7 echocardiogram machine) by the cardiologist.

2-8. Statistical analyses

Data were analyzed using SPSS statistical software. Shapiro-Wilk test was used to determine the normality of data. A paired t-test was used to compare the intra-group data. To evaluate the effect of rehabilitation practice and supplementation on the research variables, a one-way analysis of variance test was used to compare the changes in the three groups, and if there was a significant difference, the Bonferroni post hoc test was used. It should be noted that the significance level was considered $P < 0.05$ in all tests.

3. Results

The characteristics and body composition of the study participants are presented in Table 1. The results showed that after 4 weeks, weight, and BMI did not have any changes when comparing all groups. One-way analysis of variance demonstrated a significant difference between the fat percentage changes of the three groups before and after the intervention ($F2.25 = 5.23$, $P = 0.01$). Referring to the Bonferroni post hoc test, it was found that changes in the fat percentage in the cr+e group showed a significant difference with the c group ($P = 0.01$). But the other groups did not demonstrate a significant difference ($P > 0.05$).

Table 1. Demographic characteristics (Mean+SD) of the participants

Groups	CR+E			CR			C		
Demographic	before	after	sig	before	after	sig	before	after	sig
Age (y)	65.8 ± 7.1	N	N	69.4 ± 8.2	N	N	67.1± 11.1	N	N
Weigh (Kg)	72.6 ± 2.6	72.5 ± 2.4	P=0.56	72.9 ± 3.3	73.2 ± 3.4	P=0.35	70.6 ± 5.8	71.8 ± 6.1	P=0.53
BMI (kg/m²)	26.6 ± 1.7	26.6 ± 1.9	P=0.51	27.8 ± 1.1	27.9 ± 1.3	P=0.36	26.7 ± 1.5	26.8 ± 1.6	P=0.49
Fat Percent (%)	34.9± 2.8	32.3 ± 2.84	P<0.001	34.9 ± 2.3	33.6± 2.7	P=0.061	32.9 ± 3.5	33.1 ± 3.1	P=0.28

CR+E= *crataegus*+endurance group, CR= *crataegus* group, C=control group

Statistical analyses showed a significant difference in the EF changes (Fig. 1) of the three groups before and after the intervention ($F_{2.25}$ = 3. 68, P = 0.04). By referring to the Bonferroni *post hoc* test, it was found that the EF changes in the cr+e group were significantly more than c group (P < 0.05). But the other groups did not show any significant difference (P > 0.05).

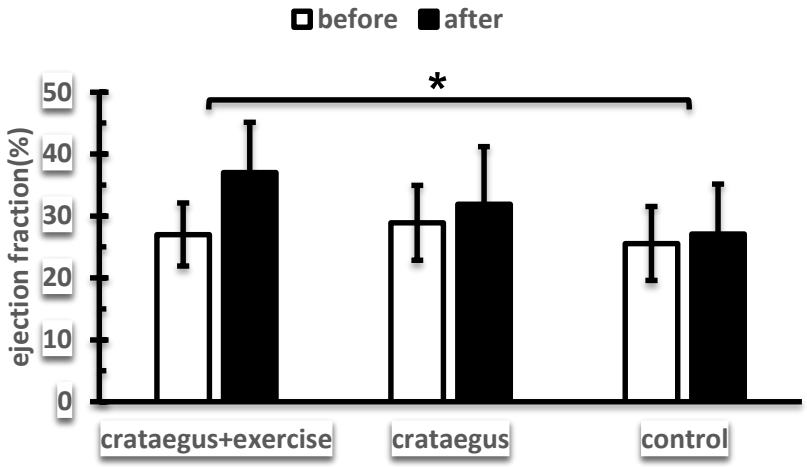

Fig. 1. Mean ± standard deviation of ejection fraction (EJ) data in the cr+e, cr and c group before and after 4 weeks of intervention. * indicated significant differences between CR+E and C groups.

Within group comparison showed a significant increase in 6MWT results in both cr + e and cr groups (P<0.05), and the c group records remained unchanged after 4 weeks (P>0.05). The results of one-way analysis of variance (Fig. 2) showed a significant difference between the 6MWT of the three groups before and after the intervention ($F_{2.25}$=3.47, P =0.047). Referring to the Bonferroni *post hoc* test, the cr + e group showed a significant difference with the c group (P=0.03) and the cr group also have a significant difference with the c group (P=0.02).

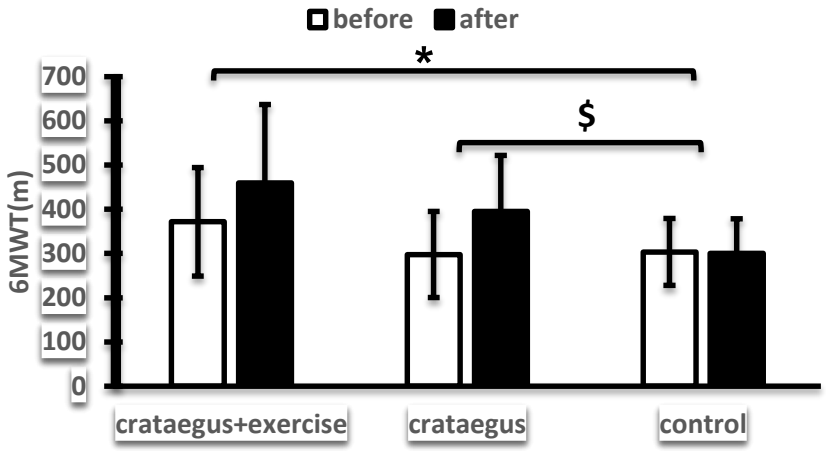

Fig. 2. Mean ± standard deviation of 6MWT data in the cr+e, cr and c group before and after 4 weeks of intervention. * indicated significant differences between CR+E and C groups. $ indicated significant differences between CR and C groups.

Systolic blood pressure (BPs) decreased significantly in both cr + e and cr groups (P<0.05), but no change was observed in the c group (P>0.05). The one-way analysis of variance test indicated a significant difference between BP_S changes in the three groups before and after the intervention ($F_{2.25}$=5.26, P=0.013), referring to the Bonferroni *post hoc* test, the cr+e (P=0.03) and Cr (P=0.02) group showed a significant difference with the c group (Fig 3).

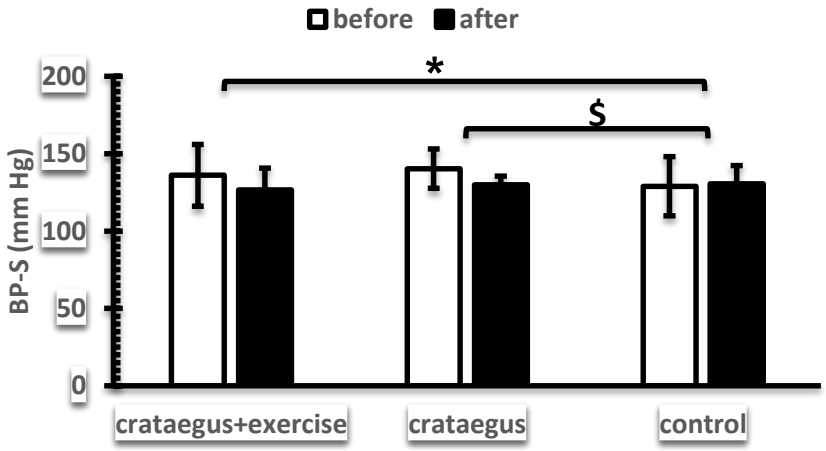

Fig. 3. Mean ± standard deviation of BPs data in the cr+e, cr and c group before and after 4 weeks of intervention. * indicated significant differences between CR+E and C groups. $ indicated significant differences between CR and C groups.

Diastolic blood pressure (BP_D) stipulated a significant decrease in cr + e group (P<0.05), but no significant change was observed in other groups (P 0.05). Also, the results of one-way variance analysis test did not show a significant difference in BP_D level changes (Fig 4) of the three groups before and after the intervention ($F_{2.25}$ = 1.51, P = 0.239).

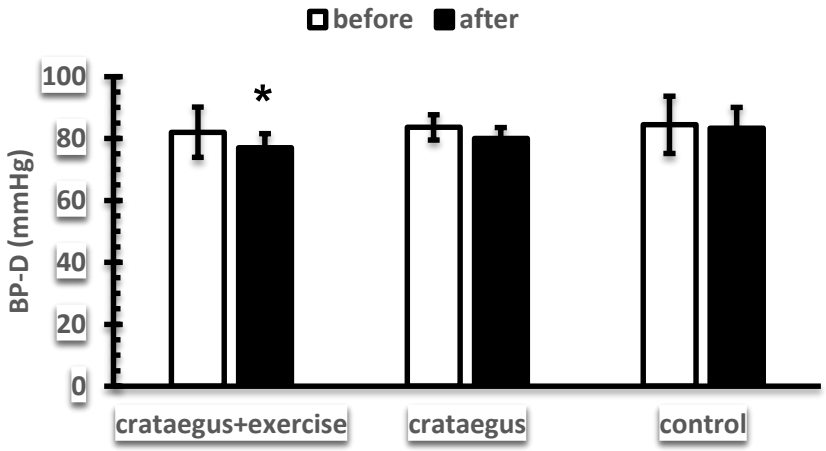

Fig. 4. Mean ± standard deviation of BP_D data in the cr+e, cr and c group before and after 4 weeks of intervention. * indicated significant differences between before and after BP_D in CR+E group.

Within group comparisons of resting HR showed significant decreased in both cr+e and cr groups ($P<0.05$), but the c group remained unchanged ($P>0.05$). However, the results of one-way analysis of variance did not show a significant difference between HR level changes (Fig. 5) of the three groups before and after the intervention ($F_{2.25}=3.03$. $P=0.067$).

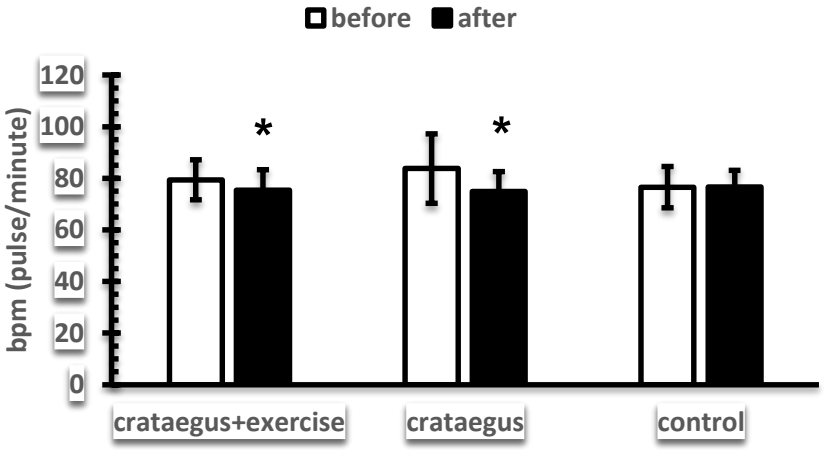

Fig. 5. Mean ± standard deviation of BP_D data in the cr+e, cr and c group before and after 4 weeks of intervention. * indicated significant differences between before and after BP_D in CR+E and CR groups.

4. Discussion

The results of the present study supported that taking one month of crataegus supplement along with controlled physical activity can improve the contractile strength of the heart and increase the EF by 5 to 20% in patients with HF. In a similar study performed on 120 embolic patients, Zick et al. (2009) noticed that taking crataegus extract for 6 months improved left ventricular EF compared to the control group, but their results did not reach significant levels (19). In another study conducted by Swaminathan et al., (2010) with the ischemic/reperfusion model on the mice, the results asserted that the heart of mice treated with Crataegus oxycantha extract showed a significant return in cardiac contractile strength, decreased infarct area size, and decreased activity of creatine kinase and lactate dehydrogenase and reduced oxidative stress; it also affirmed a significant role in inhibiting apoptotic pathways that may lead to heart protection (17). One

of the mechanisms proposed for the crataegus positive inotropic effect may be inhibition of the Na-K ATPase pump, thereby it can increase the effective transfer of Ca+2 into the cardiomyocyte (20). It is suggested that the underlying mechanisms for this shift are the concentration-dependent displacement of specifically bound cardiac glycoside [3H] ouabain from its receptor and the sarcolemmal Na+/K+-ATPase, seems to increase the force of contraction by inhibition of the sodium pump. Also, they can enhance the peak intracellular Ca2+ concentration as well in human myocardium from patients with congestive heart failure (21).

Also, the strong antioxidant properties of crataegus extract can collect harmful substances such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, which, by preserving the membrane structure, prevent the release of reactive oxygen species (ROS) and removal of free radicals produced. Therefore, the factors that can lead to changes in heart rate, increase in blood pressure, decrease in contractile strength of heart, and changes in the activity of some ion channels will be eliminated and heart-pumping returns to its normal state (22, 23). Animal studies also affirm that oligomeric procyanidins will increase coronary circulation (24). Another evidence of improved heart function following crataegus is the results of the 6MWT test, which increased significantly after 4 weeks in both cr + e and cr groups. In this context, Rainer et al. (2000) examined the effect of long-term exercise training on left ventricular function and peripheral vascular resistance on HF patients. The results demonstrated a significant increase in maximum ventilation, exercise time, exercise capacity, as well as a decrease in HR and an increase in stroke volume (SV) at rest time in the exercise group (12). On the other hand, the group that exercised with the use of crataegus supplement expressed a decrease in dyspnea and fatigue in doing daily activities and a more pleasant feeling than before. Because walking exercise in patients with HF was well tolerated in the present study and no adverse exercise-related events were observed in patients in the exercise group, it may be argued that exercise along with taking crataegus supplements can improve heart function. In a study by Karapolat et al. (2009), the effect of 8 weeks of exercise (at home or in hospital) on patients with HFPEF heart failure on functional capacity factors, life quality, psychological symptoms, and hemodynamic parameters were reviewed. The results proved a significant improvement in peak VO2, 6MWT, and physical function subsets, LVEF, depression symptoms, and life quality in both home and hospital exercise groups comparing which did not show a significant difference between the two groups (25). Therefore, walking can lead to an improvement in endurance capacity and a change in the abnormal left ventricle function in HF patients; based on these results, a precise controlled supervised physical activity by a physician at home is recommended to patients with HF; however, more research is needed in this case for sure.

On the other hand, in this study, the systolic blood pressure dropped significantly in both cr + e and cr groups after 4 weeks. Diastolic blood pressure also decreased significantly in the cr + e group, but this decrease in the cr group was not significant. In a study conducted by Asgari et al. (2004) on the hypotensive effect of the hydroalcoholic extract of flowers and leaves of crataegus plant on 92 men and women with hypertension, the results affirmed a significant decrease in both systolic and diastolic BP after 3 months which indicates the hypotensive effect of crataegus plant (26). In animal studies, Rowghani et al. (2009) examined the effect of oral consumption of hawthorn branches for 6 months on the contractile response and the removal of endothelium-dependent contraction of the thoracic aorta in diabetic rats. The results explain that the oral and long-term prescription of hawthorn will reduce the contractile response and the increased response to the contraction in the aortic tissue of the diabetic rats by affecting the endothelium-related factors and the effect of quercetin in crataegus on NO release from endothelium; it will also decline ROS due to the antioxidant properties of the crataegus (27). Studies on the crataegus and its flavonoid and polyphenolic components, including quercetin, catechin, and epicatechin, can be considered as a response to the hypotensive results of the crataegus plant. Quercetin can increase the release of endothelium-dependent nitric oxide vasodilator and enhance its availability (28). Another beneficial effect of crataegus can be attributed to the reduction of oxidative stress and lipid peroxidation in the vascular tissue that may have an important role in improving cardiovascular function and aerobic function improvement (29). Also, in the present study, 4 weeks of intervention on patients with HF led to a significant reduction in HR at rest in patients in the cr + e group by 5.03% and in the cr group by 10.63%. A study by Dyant et al. (2014) examined the extract of the crataegus plant in comparison with the amiodarone in the rat model; the results specified a significant reduction in the incidence of cardiac arrhythmias; short-term use of the extract did not alter the HR either (30).

Limitations and suggestions for further studies

Because an exact cellular mechanism for the effect of crataegus in combination physical activity on the contractile strength of the heart in HF patients is not known until now, further research is needed for the survey the heart muscles and vascular cells function in animals' model with HF in response to crataegus supplementation. The simultaneous effect of different rehabilitation modalities and long-term use of

crataegus supplement in the larger statistical population on patients with HF is also recommended.

Conclusion

Overall, the results of the present study showed that 4 weeks of crataegus supplementation and walking in patients with HF would reduce cardiac risk factors, including decreased systolic blood pressure and resting HR, improved cardiac contractility, and increased EF, quality of life and aerobic capacity. Therefore, according to the results of this study, it can be suggested that the extract of hawthorn plant as a herbal medication with high antioxidant properties and its cardiovascular protection effects can be used in cases of some cardiovascular impairment, atherosclerosis, and fatty liver and diabetic diseases. However, it is highly recommended that more research be done on the commercial use of crataegus for heart patients. Also, the rehabilitation program in the form of walking exercise is effective in improving the quality of life, increasing cardio-respiratory function, more independence in doing daily activities, and reducing dyspnea and fatigue. Therefore, in patients with HF, it can be recommended that taking crataegus supplements along with walking exercise can have a greater impact on improving and controlling the effects of heart failure, and most importantly, improving their quality of life and increasing their functional capacity.

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