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Original Research Article

The effect of rosehip on echocardiographic parameters and chest pain in patients with coronary slow flow: A double-blind, randomized, placebo-controlled trial

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Abstract

Objective: To investigates the effects of rosehip alcoholic extract on chest pain severity and echocardiographic parameters in patients with coronary slow flow (CSF).

Materials and Methods: Thirty patients presenting CSF in the left anterior descending (LAD) artery were randomly allocated into two groups of rosehip and placebo for eight weeks. Echocardiographic parameters and Canadian Cardiology Society (CCS) angina scores were evaluated at baseline and at the end of the study.

Results: Significant increases were observed in peak diastolic velocity (PDV), mean diastolic velocity (MDV), and velocity time integral (VTI) within the rosehip group as compared to control group (p=0.001, 0.006, and 0.020, respectively). Comparative analysis of echocardiographic parameters between the two groups demonstrated significant improvements in PDV and MDV in the rosehip group (p=0.031 and 0.003, respectively). Nonetheless, differences in PDP, MDP, VTI, and Dint between the two groups were not statistically significant. Furthermore, chest pain was significantly alleviated in the rosehip group (p=0.015).

Conclusion: Rosehip supplementation enhances microvascular coronary blood flow and diminishes chest pain in patients with CSF.

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Introduction

Coronary slow flow (CSF) phenomenon, also known as microvascular angina, is characterized by delayed opacification of distal coronary arteries without significant stenosis, a common angiographic finding with relatively high prevalence. It is commonly associated with recurrent rest angina or mixed angina and is associated with various clinical manifestations including ischemic heart disease, ST-elevation myocardial infarction, ventricular arrhythmia, and potentially sudden cardiac death, often linked to increased QTc dispersion (Aparicio et al. 2022). Smoking, underlying diseases such as hypertension, and genetic factors contribute to the incidence of CSF. Although the precise pathophysiology of CSF remains incompletely determined, hypotheses including endothelial dysfunction, oxidative stress, inflammation, and subclinical atherosclerosis have been proposed as underlying etiological factors (Wang and Nie 2011). Key disease mechanisms involve microvascular endothelial dysfunction stemming from reduced vasodilatory capacity and microvascular vasoconstriction due to hypersensitivity to vasoconstrictor stimuli. Several molecular pathways including nitric oxide, are involved in endothelial dysfunction and vasoconstriction. Nitric oxide is the most important endothelial-derived mediator; decreased production or activity of nitric oxide diminishes the vasodilatory capacity of the microvasculature (Chaudhary 2022).

Management of CSF typically involves modifying atherosclerotic cardiovascular disease (ASCVD) risk factors including hypertension, diabetes, dyslipidemia, obesity, and smoking through lifestyle changes and pharmacotherapy. Furthermore, treatments to alleviate angina symptoms such as nitroglycerin, β-blockers, and calcium channel blockers, are commonly prescribed (Chaudhary 2022). Nevertheless, effective strategies for controlling clinical symptoms and preventing the recurrence or severity of chest pain remain elusive, necessitating exploration of novel treatment modalities.

Over the recent past decades, there has been a tremendous interest in using natural products and phytochemicals for the management of cardiovascular risk factors and diseases (Sahebkar et al. 2015; Momtazi et al., 2017; Alidadi et al. 2020; Alum 2025). Rosehip fruit (*Rosa canina*), a member of the Rosaceae family, is a wild rose native to western Asia, northwest Africa, and Europe. It contains various active compounds including flavonoids, phenolic acids, ascorbic acid, proanthocyanidins, tannins, unsaturated fatty acids, phospholipids, galactolipids, carotenoids, and minerals (Chrubasik et al. 2008). *In vitro* and *in vivo* studies have highlighted its antioxidant, anti-inflammatory, anti-atherosclerotic, and nitric oxide-enhancing properties (Lattanzio et al. 2011; Ersoy et al. 2015). Notably, an *in vivo* study demonstrated that rosehip supplementation exerts anti-atherosclerotic effects and enhances nitric oxide-mediated dilation in ApoE-null mice following 24 weeks of treatment (Cavalera et al. 2017).

Given the pathophysiology of CSF and the documented effects of rosehip, it is plausible that rosehip consumption could offer benefits for individuals with CSF. This study aimed to evaluate whether rosehip supplementation improves echocardiographic markers of coronary microvascular function and reduces angina symptoms in CSF patients, given its potential vasodilatory and anti-inflammatory properties.

Materials and Methods

Study design

This study employed a prospective, randomized, double-blind, placebo-controlled design and was conducted at Ghaem Hospital, Mashhad, Iran, from August 2022 to March 2023.

The trial was registered in the Iranian Clinical Trials Registry (registration number IRCT20120520009801N8) and received approval from the Internal Review Board and Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1401.125).

Preparation of rosehip and placebo tablets

The rosehip fruit was collected from the vicinity of Ardabil city in Iran. Following macroscopic examination at the herbarium of Mashhad faculty of pharmacy, an identification code was assigned by a botanist. The ethanolic extract of rosehip was prepared by extracting powdered dried rosehip with 70% ethanol (Dr. Mojallali Co., Iran) using a percolator. The resulting filtrate was concentrated at 37°C using a rotary evaporator (Heidolph, Germany).

Rosehip tablets were formulated using the wet granulation method. A granulation mixture comprising equal parts of corn starch and microcrystalline cellulose (Avicel®) (FMC Biopolymer, Iceland) served as granulation excipients, with the concentrated extract employed as the wet granulation liquid (binder). After lubrication of the granules with 1% magnesium stearate (Merck, Germany), tablet compression was performed using a single punch tableting machine (Korch-Erweka, Germany) equipped with a 13 mm convex die and punch. The resultant tablets had an average weight of 600 mg and contained 50% w/w dry extract. Tablet standardization was achieved based on total phenol content using the Folin-Ciocalteu method (Koczka et al. 2018), with each tablet exhibiting a total polyphenol content of 26.43% w/w.

Placebo tablets were fabricated using an identical process to that of rosehip tablets and they were similar in terms of shape, size, and color. Corn starch and Avicel® were utilized for wet granulation, and a small quantity of FD&C Yellow No. 6 served as a coloring agent.

Patient selection

Following the assessment of inclusion and exclusion criteria, a total of 30 patients of both sexes were randomly allocated into two groups: rosehip (n = 15) and placebo (n = 15). Comprehensive baseline information including demographic data, laboratory results, atherosclerotic cardiovascular disease (ASCVD) risk factors, and medication history, was collected and recorded in the case report form. Prior to enrollment, all patients were provided with detailed information about the study, and written informed consent was obtained from each participant.

The inclusion criteria were as follows: (1) Diagnosis of CSF in the left anterior descending (LAD) based on angiography results, (2) Corrected thrombolysis in myocardial infarction (TIMI) frame count exceeding 27, and (3) Provision of informed consent.

Exclusion criteria were as follows: (1) Presence of coronary artery aneurysm or epicardial coronary vessel ectasia detected via echocardiography, (2) Presence of myocarditis, pericarditis, cardiomyopathy, or heart failure as determined by echocardiography, (3) Pre-existing coronary artery disease or heart valve disorders, (4) Inadequate visual acuity for echocardiographic assessment. (5) Pregnancy or lactation, (6) Renal impairment defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or requiring dialysis, or (7) Hepatic dysfunction indicated by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding three times the upper limit of normal.

Randomization and blinding

Randomization was conducted using the block method with varying block sizes. A random chain consisting of two groups, treatment (T) and control (C), with a 1:1 ratio was generated in blocks of size 4 and 6 (7 blocks of 4 and 3 blocks of 6) for 46 volunteers, utilizing www.sealedenvelope.com. Additionally, a

unique 4-digit personal ID was assigned to each volunteer. To ensure concealment of the random allocation, identical boxes were used for both the drug and placebo. These boxes were labeled with the random sequence of T and C, the corresponding drug or placebo, row numbers 1 to 46, and the assigned ID code. The process of generating and arranging the random sequence was solely managed by the study's epidemiologist. The numbered box corresponding to each participant's ID was provided upon enrollment.

Blinding was maintained throughout the study period. All study participants, including the patients, attending physician, and the project manager, were unaware of the group allocation and the medication received. Only the epidemiologist, responsible for randomization and final data analysis, was informed about the allocation method. The epidemiologist was not involved in prescribing or evaluating the intervention and solely managed the codes and provision of numbered boxes containing the drug or placebo to the attending physician. The boxes were labeled with rows 1 to 46 and the ID code, with rosehip or placebo tablets inside having identical shape, size, and color. Thus, distinguishing between the drug and placebo was impossible for patients, attending physicians, and the project manager.

Following eight weeks of treatment, patients underwent evaluation at the hospital by attending physicians who remained unaware of whether the patient received the drug or placebo and only had access to the ID code. Subsequently, evaluation results were communicated to the epidemiologist based on the assigned code.

Intervention groups and measurements

The study group (n = 15), in addition to receiving standard treatment, consumed rosehip alcoholic extract tablets twice daily for a duration of eight weeks. Conversely, individuals in the control group (n = 15) received an equivalent number of placebo tablets resembling rosehip tablets, administered over the same eight-week period.

At the commencement of the study, all patients underwent comprehensive blood tests, including complete blood count (CBC), blood glucose assessment, and measurement of serum levels of urea, creatinine, sodium, and potassium. Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were also evaluated at baseline.

TIMI frame count was calculated as the number of cineangiographic frames (at 30 frames/second) required for contrast to reach standardized distal landmarks in the LAD artery, with values >27 defining CSF (Gibson et al. 1996). Echocardiographic parameters such as peak diastolic velocity (PDV), mean diastolic velocity (MDV), peak diastolic pressure (PDP), mean diastolic pressure (MDP), diastolic flow interval (Dint), and velocity time integral (VTI), were assessed both at baseline and after eight weeks of treatment specifically in LAD artery (Figure 1). Furthermore, the impact of rosehip on chest pain severity was evaluated using the Canadian Cardiology Society (CCS) angina score (Members et al. 2013) at baseline and the end of the study.

Patients were monitored biweekly via phone calls for adverse events (e.g. gastrointestinal symptoms, skin reactions) and compliance.

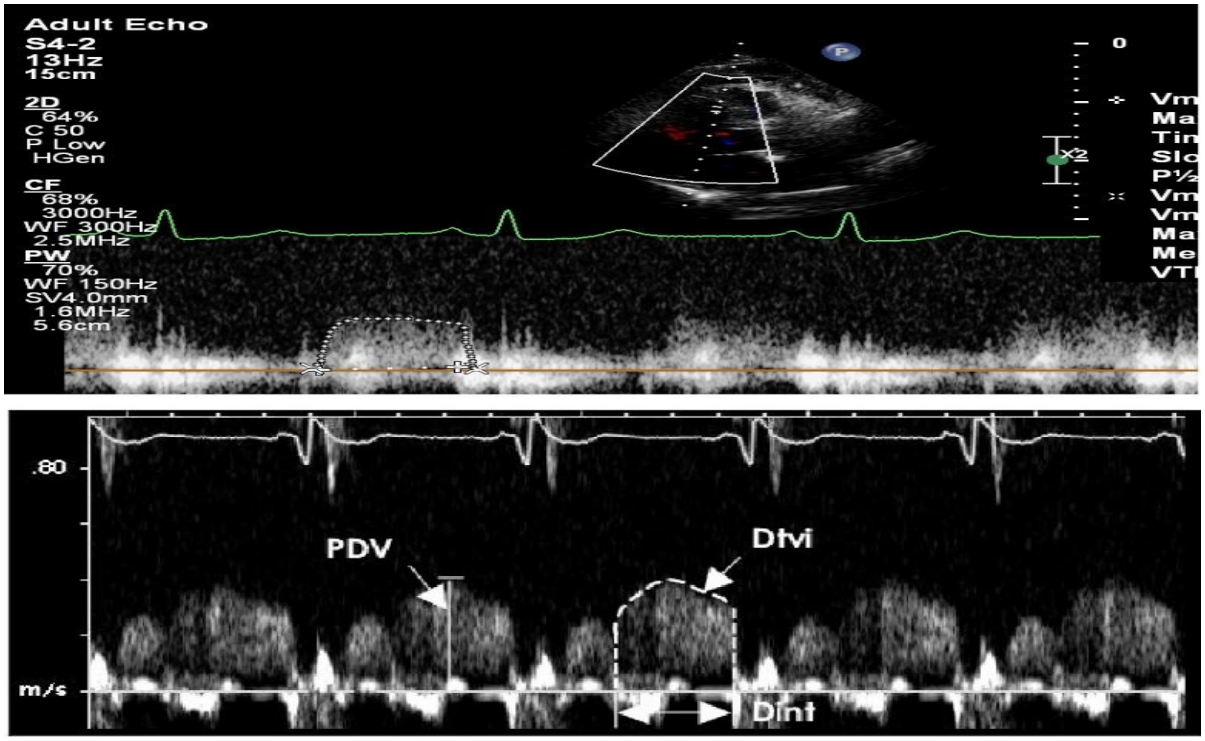

Figure 1. Echocardiography was performed with a Phillips echocardiography machine (affinity 50) so that the patients were in the left decubitus position and the short axis echo view of large vessels. With a brief rotation of the probe, the passage of the LAD under the pulmonary artery is evident. Its flow was evaluated by the pulsed wave Doppler.

Statistical analysis

According to a previous study, the mean and standard deviation of the PDV in patients with CSF were reported as 0.228 and 0.029 m/s, respectively (Nie et al. 2011). At the initiation of our study, assuming no significant difference in PDV between the two groups and anticipating a 16% increase in PDV, based on the similarity of the observed variance with the aforementioned study. Utilizing the obtained effect size ($\Delta = 1.3$), and assuming equal sample sizes in both groups ($\lambda = 1$), a correlation coefficient of 0.5 for observations before and after each intervention group ($\rho = 0.5$), one measurement before the intervention ($\nu = 1$), and one measurement after the intervention ($w = 1$), it was determined that a final sample size of 15 individuals in each group would be sufficient. Considering 30% attrition rate, the final sample size required would be 22 individuals in each group.

$$R = [\frac{1 + (w-1)\rho_T}{w} - \frac{v\rho_T^2}{[1 + (v-1)\rho_T}]$$

$$m_{repeated} = R[\left(1 + \frac{1}{\lambda}\right)^2 \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\Delta_{plan}^2} + \frac{z_{1-\frac{\alpha}{2}}^2}{4}]$$

The data obtained following the clinical stages of the study were initially described using described using central and dispersion indicators. The normality of quantitative variables was assessed using the Shapiro-Wilk test. For qualitative variables in the study groups, comparison was conducted using the chi-square test (or exact test if necessary). The two independent samples t-test (or Mann-Whitney U test for non-normally distributed variables) was employed to compare the quantitative variables between the study groups. Changes in echocardiographic parameters such as PDV within the study groups were evaluated using paired t-tests or Wilcoxon tests. All statistical analyses were performed using SPSS version 21 at a significance level of 0.05.

Results

Patient characteristics

Initially, 70 patients were assessed for eligibility. Of these, 24 did not meet the inclusion/exclusion criteria, and one declined to provide informed consent. The remaining 45 patients were randomized into the rosehip (n=23) and placebo (n=22) groups. During the 8-week follow-up period, 8 patients in the rosehip group and 7 in the placebo group were lost to follow-up (due to non-attendance for secondary assessments) or withdrew from the study. Notably, no patients reported drug-related adverse effects during the trial. Finally, a total of 30 patients participated in the study, with 15 individuals assigned to each group. The mean age was 48.33 ± 9.053 years in the rosehip group and 52.67 ± 8.853 years in the placebo group (p = 0.196). The CONSORT flowchart illustrating participant enrollment and allocation is presented in Figure 2. Baseline demographics, laboratory data, atherosclerotic cardiovascular disease (ASCVD) risk factors, and medication history of the two groups are shown in Table 1. There were no statistically significant differences in these parameters between the two groups (p>0.05).

Table 1. Baseline characteristics of the patients

		Placebo (n = 15)	Rosehip (n = 15)	p value
Demographic	Gender (men/women)	3/12	9/6	0.457$
	Age (year)	52.67±8.853	48.33±9.053	0.196$
	Height (cm)	162.67±8.466	167.93±12.441	0.188$
	Weight (kg)	69.93±16.153	82.07±16.939	0.054$
Lab data	Blood Sugar (mg/dl)	97.428±25.674	112.600±31.420	0.305*
	Urea (mg/dl)	36.266±11.404	34.357±7.781	0.601$
	Creatinine (mg/dl)	1.086±0.274	1.126±0.231	0.558*
	Na (mEq/L)	138.133±2.531	138.000±2.645	0.889$
	K (mEq/L)	4.060±0.297	4.140±0.528	0.950*
	WBC ($\times10^3/\mu l$)	7.366±2.417	7.300±2.052	0.937$
	RBC ($\times10^6/\mu l$)	4.484±0.470	4.610±0.401	0.444$
	Hemoglobin (g/dl)	13.540±1.599	14.050±1.515	0.386$
	Platelet ($\times10^3/\mu l$)	222.200±43.237	201.214±76.012	0.376$
	ESR 1h (mm/h)	32.875±24.660	15.818±11.522	0.059$
	CRP (mg/L)	4.976±2.906	6.366±7.464	0.935*
ASCVD risk factors	Hypertension	6 (40%)	3 (20%)	0.060#
	Diabetes	4 (26%)	3 (20%)	1.000#
	Dyslipidemia	4 (26%)	7 (46%)	0.450#
	Smoking	1 (6%)	2 (12%)	1.000#
	Family History	11 (73%)	7 (46%)	0.264#
	Older age	8 (53%)	7 (46%)	1.000#
Medication history	Aspirin	11 (73%)	9 (60%)	0.700#
	Statins	8 (53%)	9 (60%)	1.000#
	β-blockers	10 (66%)	6 (40%)	0.272#
	Nitroglycerin	5 (33%)	5 (33%)	1.000#
	Nicorandil	1 (6%)	0 (0%)	1.000#
	ACEi/ARB	4 (26%)	1 (6%)	0.330#

*Mann-Whitney U test; $ two independent samples t-test; # chi-squared test

Comparison of the echocardiographic parameters

Echocardiographic parameters were measured at baseline and after eight weeks in both the rosehip and placebo groups. At baseline, there were no significant differences in echocardiographic parameters between the two groups (p>0.05).

Upon analyzing the echocardiographic parameters after eight weeks, it was observed that changes within the placebo

group were not statistically significant (p>0.05) for all parameters. However, within the rosehip group, significant increases were noted in PDV, MDV, and VTI (p=0.001, 0.006, and 0.020, respectively). Additionally, a comparison between the two groups revealed that PDV and MDV were significantly higher in the rosehip group compared to the placebo group (p = 0.031 and 0.003, respectively). However, differences in PDP, MDP, VTI, and Dint were not statistically significant between the two groups (Table 2).

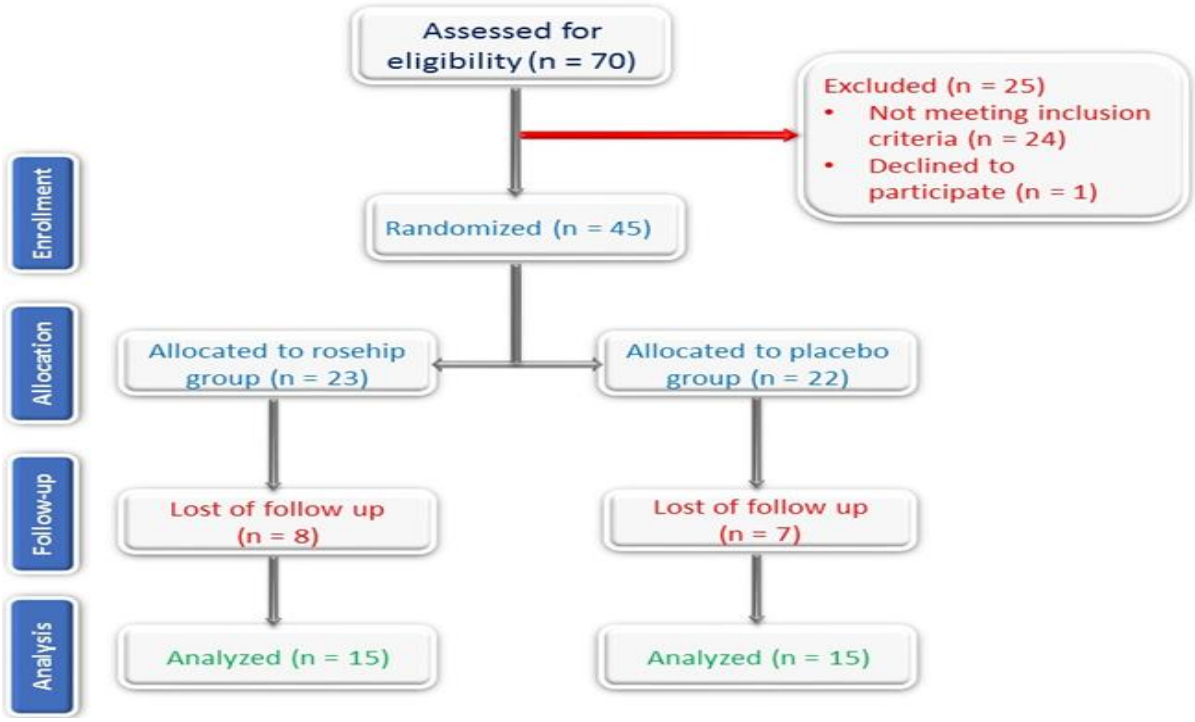

Figure 2. The CONSORT flowchart of the study

Table 2. Echocardiographic parameters of the patients

		Placebo (n = 15)	Rosehip (n = 15)	Between-group p value
PDV (m/s)	Baseline	29.960 ± 8.263	32.200 ± 10.745	
	8th weeks	31.933 ± 8.013	40.533 ± 10.418	**0.031**
	Within-group p value	0.316	**0.001**	
PDP (mmHg)	Baseline	4.861 ± 16.932	1.292 ± 2.994	
	8th weeks	3.880 ± 13.871	3.231 ± 9.638	0.312
	Within-group p value	0.243	0.481	
MDV (m/s)	Baseline	20.266 ± 5.202	20.024 ± 5.881	
	8th weeks	18.933 ± 3.453	24.066 ± 6.933	**0.003**
	Within-group p value	0.248	**0.006**	
MDP (mmHg)	Baseline	0.195 ± 0.513	0.614 ± 2.049	
	8th weeks	0.077 ± 0.181	1.822 ± 6.148	0.450
	Within-group p value	0.413	0.489	
VTI (m)	Baseline	9.626 ± 5.484	9.173 ± 2.091	
	8th weeks	10.293 ± 5.680	10.913 ± 2.836	0.171
	Within-group p value	0.095	**0.020**	
Dint (s)	Baseline	437.538 ± 103.929	436.066 ± 69.334	
	8th weeks	473.69 ± 130.241	449.20 ± 74.984	0.461
	Within-group p value	0.120	0.559	

Dint (diastolic flow interval); MDP (mean diastolic pressure); MDV (mean diastolic velocity); PDP (peak diastolic pressure); PDV (peak diastolic velocity); and VTI (velocity time integral).

Comparison of the CCS angina score between the two groups

The CCS angina score was evaluated at baseline and after eight weeks in both the rosehip and placebo groups. At baseline, there were no significant differences in CCS angina scores between the two groups (p=0.819). However, following eight weeks of treatment with rosehip or placebo, the distribution of angina grades differed significantly between the rosehip and placebo groups (p = 0.015). As illustrated in Figure 3, this difference was driven by a reduction in grade III angina and an increase in grade I angina frequency within the rosehip group.

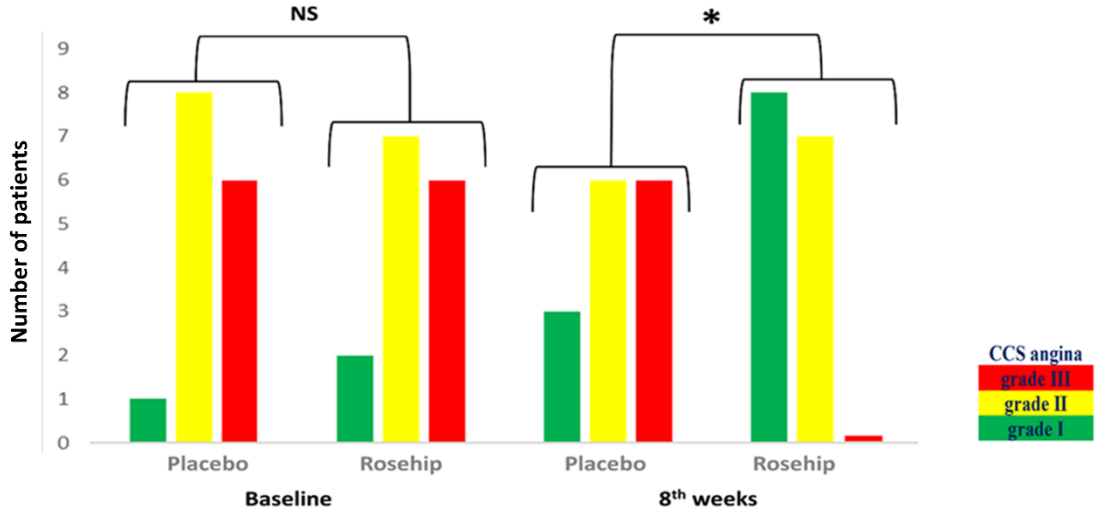

Figure 3. CCS angina scores of the patients at baseline and week 8 in the rosehip and placebo groups. A significant reduction in angina severity was observed in the rosehip group at week 8 (p =0.015), while no significant differences were detected at baseline. Colors indicate CCS grades I (green), II (yellow), and III (red).

Discussion

To our knowledge, this is the first randomized trial demonstrating that rosehip extract improves both hemodynamic (PDV and MDV) and symptomatic (CCS angina score) outcomes in CSF patients, extending beyond prior studies focused solely on antioxidant and antiatherosclerotic effects. The results of this research showed that daily consumption of rosehip alcoholic extract for eight weeks significantly improves the severity of the chest pain and certain echocardiographic parameters, including PDV, MDV, and VTI in the LAD artery of patients with CSF.

The pathogenesis of CSF remains incompletely understood, with hypotheses suggesting involvement of factors such as small vessel disease, structural factors, undiagnosed atherosclerosis, inflammation, endothelial dysfunction, and vasoconstriction (Wang and Nie 2011). Notably, endothelial dysfunction is regarded as a pivotal factor, with oxidative stress playing a significant role in inducing endothelial cell (Baysal and Koc 2019). Previous studies have indicated that selective β-blockers like nebivolol can reduce corrected TIMI frame count in CSF patients, possibly by mitigating oxidative stress and improving nitric oxide levels (Akçay et al. 2010). Rosehip, rich in antioxidant compounds, including phenolic compounds and ascorbic acid, can counteract free radicals (Daels-Rakotoarison et al. 2002, Egea et al. 2010). Therefore, rosehip prevents endothelial dysfunction mediated by free radicals and subsequently improves CSF (Daels-Rakotoarison et al. 2002). In addition to its antioxidant properties, rosehip components such as flavonoids and polyphenols have been shown to preserve nitric oxide bioavailability by reducing oxidative stress,

thereby supporting endothelial function and vascular tone (Wenzig et al. 2008, Cavalera et al. 2017).

Inflammation also contributes to the development of CSF, with C-reactive protein levels positively correlated with corrected TIMI frame count (Barutcu et al. 2007). Indeed, a chronic inflammatory response occurs as a result of abnormal vascular remodeling and increased resistance to blood flow in the pathophysiology of CSF (Zhang et al. 2021). In a randomized clinical study on 108 patients with CSF, atorvastatin significantly improved corrected TIMI frame count compared to the control group, by anti-inflammatory effects and enhancing endothelial function (Niu et al. 2018). In addition, in a recent clinical study that examined the effects of alprostadil and isosorbide dinitrate in CSF patients, the severity and number of chest pains were lower in the alprostadil group. These results have been attributed to the pharmacological properties of alprostadil, such as direct dilatory effects on coronary vessels, reduction of platelet aggregation, and anti-inflammatory effects (Zhang et al. 2022). Rosehip also exhibited anti-inflammatory effects in preclinical and clinical studies. In an *in vitro* study, rosehip reduced the secretion of chemokines and cytokines, such as interleukin-6 (IL-6) and interleukin 12 (IL-12) in peripheral blood leukocytes and primary chondrocytes (Schwager et al. 2014). The anti-inflammatory property of rosehip was also investigated in a rat model of carrageenan-induced edema. Results showed that the anti-inflammatory power of rosehip is similar to indomethacin (Lattanzio et al. 2011). In a randomized clinical trial involving 100 patients with osteoarthritis, daily consumption of rosehip powder for a duration of 4 months resulted in a significant enhancement of joint mobility and a reduction in pain (Warholm Odd et al. 2003). Furthermore, the galactolipid (GOPO®) found in rosehip has demonstrated significant inhibition of neutrophil chemotaxis and inflammatory mediator release, supporting the notion that rosehip may reduce vascular inflammation implicated in CSF pathogenesis (Chrubasik et al. 2006).

Vasoconstriction and increased tonicity of coronary microvessels are among the other proposed pathophysiologies in CSF. Microvessels typically exhibit lower levels of nitric oxide synthase enzyme, diminishing their capacity to convert inactive nitric oxide into its active form (Beltrame et al. 2014). Nitric oxide plays a crucial role in preventing the growth and migration of vascular smooth muscle cells and enhancing vascular endothelial function (Tsihlis et al. 2011). Our previous study indicated an increase in induced nitric oxide synthase concentration and a decrease in endothelial nitric oxide synthase in CSF patients (Shamsara et al. 2023). However, the use of nitroglycerin and other nitrate derivatives often yields unsatisfactory results in microvessels due to the lack of activating enzymes. A study investigating the effects of telmisartan, an angiotensin receptor blocker, revealed that endothelial function and small vessel resistance improved with telmisartan. Reducing the production of oxygen radicals and increasing the production of nitric oxide were proposed as involved mechanisms (Scalera et al. 2008). Similar findings were reported in another study involving telmisartan (Jin et al. 2018). Perindopril, an angiotensin-converting enzyme inhibitor, has been shown to reduce QT interval and QT dispersion while improving diastolic filling in patients with CSF. It is suggested that perindopril may prevent endothelial damage by improving small vessel resistance and alleviating ischemia through increased release of nitric oxide and other endothelial-derived hyperpolarizing factors (Guntekin et al. 2011). Similarly, in another study, the administration of nicorandil (15 mg/day for 90 days) in CSF patients significantly ameliorated chest pain by elevating plasma concentration of nitric oxide and reducing endothelin 1 levels (Chen et al. 2015).

Acute effects of intracoronary injection of nicorandil and nitroglycerin were compared in patients with CSF. Both medications led to the recovery of TIMI frame counts, with superior improvement observed in the nicorandil group. This disparity is attributed to the opening of potassium channels sensitive to nicorandil, adenosine triphosphate, and the differential effect of nitroglycerin on microvessels (Zhang et al. 2016). Additionally, in an animal study involving 12 Apo-null mice fed with rosehip supplementation for 24 weeks, rosehip increased nitric oxide-mediated dilation of the caudal artery and prevented atherosclerotic plaque formation by the end of the study (Cavalera et al. 2017). This suggests that rosehip may enhance endothelial-dependent vasodilation, potentially improving microvascular function and coronary blood flow in CSF. Moreover, tiliroside, a flavonoid component of rosehip, has been shown to activate PPAR-α signaling, improving lipid metabolism and reducing oxidative stress, further contributing to vascular protection (Norum et al. 2019).

A randomized, double-blind, cross-over trial by Andersson et al. (2012) investigated the effects of rosehip intake on metabolic and cardiovascular risk markers in obese individuals. The study demonstrated that rosehip supplementation significantly reduced systolic blood pressure, total cholesterol, and low- density lipoprotein (LDL) cholesterol, suggesting potential cardioprotective benefits. Notably, rosehip also attenuated postprandial glucose levels, indicating improved glycemic control (Andersson et al. 2012). These findings align with our observations of enhanced coronary microvascular flow and reduced angina symptoms, further supporting the hypothesis that rosehip may improve endothelial function and vascular health. However, unlike our study, Andersson et al. focused on metabolic endpoints rather than hemodynamic parameters, highlighting the need for future research to bridge these mechanistic gaps.

In the current study, for the first time, the effects of the alcoholic extract of rosehip on the severity of chest pain and echocardiographic parameters in patients with CSF have been investigated. CSF was evaluated using echocardiography. It was chosen as a non-invasive, repeatable, and clinically feasible tool to assess microvascular function and diastolic flow parameters in the LAD artery before and after the intervention. This approach allowed us to monitor dynamic changes in coronary microcirculation without subjecting patients to repeated invasive procedures. However, our study has some limitations. Firstly, the small sample size necessitates further clinical trials with larger cohorts to validate the results of this study. The small sample size may limit the generalizability of our findings. However, our pilot data provide a foundation for larger trials. A post-hoc power analysis confirmed adequate power (>80%) for detecting significant changes in PDV and MDV. Secondly, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to broader populations. Multi-center studies with diverse demographic representation are needed to confirm our results. Fourthly, the clinical efficacy of an eight-week treatment should not be overstated, emphasizing the need for long-term studies to assess efficacy and compare with other available treatments. Fifthly, identifying the active ingredients in rosehip that positively impact CSF is important. While we observed improvements in echocardiographic parameters and angina symptoms, the study did not measure potential mechanistic biomarkers (e.g. nitric oxide levels, inflammatory cytokines, or oxidative stress markers) to elucidate the underlying pathways of rosehip effects. Future studies should incorporate these assessments to provide deeper insights into the pharmacodynamics of rosehip. Lastly, our echocardiographic method only measured blood flow velocity in the LAD artery. While angiography remains

definitive for CSF diagnosis, echocardiography was selected for its practicality in serial assessments of microvascular flow parameters. However, the inability to directly compare echocardiographic findings with post-intervention angiographic data is a limitation.

Overall, rosehip appears to increase blood flow in microvessel coronary arteries and alleviate chest pain in CSF patients, possibly mediated through vasodilatory effects due to enhancing nitric oxide synthesis, and antioxidant and anti-inflammatory properties attributed to high levels of ascorbic acid and phenolic compounds. Larger and long-term clinical studies are warranted to confirm these results.

Acknowledgment

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Conflicts of interest

The authors have declared that there is no conflict of interest.

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Ethical Consideration

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants prior to enrollment.

Code of Ethics

The study protocol was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethics code: IR.MUMS.REC.1401.125).

Authors' Contributions

F.A., Z.A., and F.A. prepared the initial manuscript draft. M.D., H.A., and A.H.M. supervised patient recruitment and clinical evaluations. S.A.E., A.T., and M.A. conducted the formulation and preparation of rosehip and placebo tablets. V.G. performed statistical analyses. V.J. assisted with clinical data acquisition. A.S. and S.A.E. critically revised the manuscript and provided scientific oversight. A.H.M supervised the project, finalized the manuscript, and approved the final version for submission. All authors read and approved the final manuscript.

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