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Efficacy of Chamomile-Lemon Balm Syrup in Patients With Conventional Drug-Resistant Cardiac Syndrome X: A Single-Arm Clinical Trial

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Abstract

Objectives: Treatment of cardiac syndrome X (CSX) remains a major challenge for conventional medicine. In this regard, developing new natural treatments could be an alternative choice. This study was planned to appraise the efficacy of chamomile-lemon balm syrup on chest pain and quality of life in patients with conventional drug-resistant CSX.

Materials and Methods: 29 participants with conventional drug-resistant were enrolled in a single-arm clinical trial, and 14 participants completed the study protocol. Chamomile (*Matricaria chamomilla* L.)-lemon balm (*Melissa officinalis* L.) syrup was provided for the treatment for the 90-day study period. All conventional treatments of CSX remained unchanged. Efficacy assessment included Seattle Angina Questionnaires (SAQ), 36-item short form survey, and the Hospital Anxiety and Depression Scale (HADS).

Results: An improvement was observed in the total score of all questionnaires with statistically significant changes over time of the study ($P<0.001$).

Conclusions: Chamomile-lemon balm syrup showed promising results in improving effect on angina symptoms, quality of life, and anxiety and depression in the patients with drug-resistant CSX. However, a placebo-controlled trial should be performed to verify these data.

Keywords: Cardiac syndrome X, *Matricaria chamomilla* L., *Melissa Officinalis* L.

Introduction

Cardiac syndrome X (CSX), according to recent studies termed "microvascular angina", is characterized by typical exertional chest pain, a positive exercise stress test as evidence of transient myocardial ischemia, and normal coronary angiography in the absence of cardiac (for example, left ventricular dysfunction) or systemic (for example, uncontrolled diabetes) diseases causing microvascular dysfunction (1,2).

Although multiple mechanisms have been proposed for the pathophysiology of CSX, the etiology and pathology of CSX remain uncertain. Disturbance of endothelium-dependent vasodilation due to decreased nitric oxide-releasing and increased microvascular constriction following cardiac autonomic imbalanced or coronary hyperreactivity to constrictor stimuli are commonly proposed mechanisms of microvascular dysfunction attributed to CSX. These mechanisms are related to the raised genesis of reactive oxygen species (3-8). Anxiety and other psychological stresses can provoke chest pain in patients with CSX by altering the regulation of the cardiac autonomic system to sympathetic dominance. The other mechanisms proposed for CSX include inflammation and oxidative stress. Inflammation has been involved in the pathogenesis of microvascular dysfunction in CSX (8). In evidence, a significantly higher level of C-reactive protein as an inflammatory marker had been found in the patients with CSX when compared with controls (9).

CSX is frequently associated with significant suffering, impaired quality of life, and increased psychological morbidity (2,10,11). Treatment strategies of CXS include anti-ischemic medications (nitrates, calcium channel antagonists, and beta-blockers), alternative medications (angiotensin-converting enzyme [ACE] inhibitors, statins, xanthine derivatives, and tricyclic antidepressants), non-pharmacologic procedures and lifestyle modifications. There are 20% of patients with CSX experience worsening symptoms and difficulty handling them clinically (12). Treatment of CXS remains challenging because of failure to symptom control and recurring and disabling chest pain in patients under treatment (1,13), so investigations for new treatments seem to be necessary.

Traditional, complementary, and alternative medicines, such as Persian medicine, could be valuable sources for finding new remedies for cardiovascular diseases (14-16). In Persian medicine, CSX is conceived as a subtype of

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Key Messages

- Treatment of CSX remains a major challenge for current medicine.
- The Chamomile- Lemon balm syrup was provided for the treatment for the 90–day.
- This herbal product showed an improving effect on symptoms of patients.

angina-like and compressive chest pain with a non-life-threatening prognosis, induced by non-blockage, cold and moist dystemperament of the coronary artery. *Melissa Officinalis* L. (lemon balm) and *Matricaria chamomilla* L. (chamomile) are two of the plants that have been used to treat this disease in Persian Medicine (17-19). Based on animal studies, lemon balm had a vasorelaxant effect, reducing heart rate, protective effect against the injury of the ischemic heart and lethal ventricular arrhythmias followed it (20,21). Also, based on clinical studies, lemon balm had a reducing effect on heart palpitation and improved serum biomarkers of oxidative stress, inflammation, and lipid profile in a patient with chronic stable angina (22,23). Vasorelaxant and anti-ischemic effect of chamomile has been revealed in animal studies. Also, it showed a significant reduction in elevated blood pressure and heart rate in a clinical trial (24-26).

In this study, we aimed to evaluate the efficacy of a syrup made from lemon balm and chamomile on chest pain and quality of life in patients with drug-resistant CSX.

Materials and Methods

Study Design and Participants

This single-arm clinical trial was conducted at Tehran Heart Center Hospital of the Tehran University of Medical Sciences, Tehran, Iran, between November 17, 2019, and April 8, 2020.

Inclusion and Exclusion Criteria

We assessed and screened a database of 209 participants (2017-2019) with normal angiography and positive exercise stress test. Upon entry into the study, the inclusion/exclusion criteria were assessed.

Our inclusion criteria included typical angina chest pain, abnormal stress test, normal coronary angiography, recurrent chest pain despite conventional treatment for at least 6 months, including two anti-ischemic (beta-blockers, calcium antagonists, nitrate) or one anti-ischemic and one alternative (Statin, ACE inhibitor).

Exclusion criteria determined as sever valvular heart disease, cardiomyopathy, coronary spasm, LV dysfunction (EF <50%), uncontrolled diabetes (Fasting blood sugar >126 mg/d or random-sample glucose level >200), uncontrolled hypertension (systolic blood pressure >140 mm Hg or >90 mm Hg diastolic blood pressure), history of myocardial infarction.

Sample Size

The sample size was calculated based on scores of SAQ domains, using 12 as mean difference and 12 as the standard deviation of the difference between two phases of the study. This translated into a sample size of 10 participants to achieve a power of 80% and a level of significance of 5% (two-sided) (27).

Interventions

Preparation and Standardization of Chamomile-Lemon Balm Syrup

Dry plants of *M. officinalis* (aerial parts) and *M. chamomilla* (flower) were purchased from Shiraz, a city located the southwest Iran, and identified in the Herbarium of Tehran University of Medical Sciences, Tehran, Iran under the voucher numbers PMP-1322 and PMP-1323, respectively. To prepare 1000 mL of syrup, 30 g *M. officinalis* and 30 gr *M. chamomile* was weighed and crushed with the grinder and engulfed with 1000 mL boiling water. After half an hour of boiling, the extract was filtered and sweetened by adding 100 g of sugar. The syrup was heated until the sugar was completely dissolved. Then, it was packed in 250 mL bottles.

Standardization of Drug Based on Total Phenolic and Flavonoid Contents

Total phenolic content was determined by the spectrophotometric method. To determine the phenolic concentration in the syrup, an ethanol solution of syrup (1 mg/mL) was made, and the reaction mixture was used by mixing ethanol solution (0.5 mL), 7.5% Sodium bicarbonate (2.5 ml), and 10% Folin-Ciocalteu's reagent (2.5 mL). After that, the samples were incubated at 45°C for 45 minutes. The absorbance was detected using a spectrophotometer at 765 nm against a prepared blank. Gallic acid was used as a standard to construct the standard curve. The total phenolic content was expressed as mg gallic acid per milliliter of syrup (28). Total flavonoid content was estimated by a colorimetric method. To determine the flavonoid contents, the samples consisting of 1 ml of ethanol solution of syrup (1 mg/mL) and 1 mL of 2% aluminium chloride solution dissolved in methanol were prepared. After that, samples were incubated for 1 hour at room temperature. The absorbance was measured against blank at 415 nm. Quercetin was used as the standard to construct the standard curve. Total flavonoid content was expressed as mg quercetin equivalent per milliliter of syrup (29).

At baseline, participants' demographic/health history was collected by reviewing available past medical records and performing a physical examination. Chamomile-lemon balm syrup was prescribed 2 times a day, each as 10 cc, for 90 days. Follow-up visits were scheduled 45 days and 90 days after inclusion in the study. No changes were made to the participants' conventional medications, diet, or exercise.

Outcomes and Data Collection

Endpoint Assessment

All participants were assessed by a series of questionnaires at the baseline (T_1), 45 days (T_2), and 90 days (T_3) after inclusion in the study.

Primary outcome of the study was angina symptom. It was measured at baseline and follow-up visits at 45 days (T2), and 90 days (T3) after inclusion in the study by the valid and reliable Iranian version of the Seattle Angina Questionnaires (SAQ) (30,31).

Secondary outcomes of the study were quality of life and the status of anxiety and depression. They were assessed at baseline and follow-up visits at 45 days (T2), and 90 days (T3) after inclusion in the study by the valid and reliable Iranian version of the questionnaires, including 36-Item Short Form Survey (SF36) (32,33), and the Hospital Anxiety and Depression Scale (HADS) (34), respectively.

SAQ is a 19-item survey that quantifies 5 domains measuring the impact of angina on the patient's health status: physical limitations, angina stability, angina severity, treatment satisfaction, and perceived disease. Responses are graded on a 5- or 6-point Likert scale and transformed to a 0-100. Higher scores show better function or fewer symptoms, from 0-100 (30,31). The validity and reliability of the Iranian version of the questionnaire were approved by Taheri-Kharameh and co-workers (31).

SF36 is a general health questionnaire divided into eight aspects of quality of life: physical functioning, physical role limitation, Emotion role limitation, vitality, and mental health. Social functioning, bodily pain, general health. Responses are graded on a 2- to-6-point Likert scale, and scores are transformed from 0 (worst) to 100 (best). Scale scores for the S36 range from 0-100. Higher scores show better health status (32,33,35). its reliability and validity for the Iranian population were approved by Montazeri and colleagues (33).

HADS is a 14-item questionnaire divided into two subscales (anxiety and depression), measuring clinically significant anxiety and depression. Responses are graded on 4-point (0-3) Likert scales. The analyses score ranges from 0 (best) to 21 (worst), with a score of 11 or more on either scale described as clinically significant anxiety or depression. The validity and reliability of the Iranian version of the questionnaire were approved by Kaviani et al (34).

Statistical Analysis

Statistical analysis was done using SPSS software (IBM, Version 25.0). All variables were summarized by the mean and standard deviation. Repeated measures ANOVA and post hoc test Bonferroni were used to compare variables between all study phases (T_1, T_2, and T_3). $P<0.05$ is considered significant.

Results

The syrup is prepared according to the mentioned protocol. The standardization results show the total phenolic content, and flavonoid content in the syrup are 87 ± 0.58 mg gallic acid equivalent per mL of syrup and 31 ± 0.79 mg quercetin equivalent per mL of syrup, respectively (Figure 1). 209 subjects were screened, and among them, 41 were eligible, and 29 individual were enrolled. Finally, 14 participants completed the study, 11 participants elected to discontinue, and 4 were lost to follow-up (Figure 2). No side effects were observed during follow-up (Table 1).

After 90 days of the treatment, all of the dimensions of SAQ, SF36, and HADS were improved with the scores significant changed compared with the baseline ($P<0.001$; Table 2).

The SAQ, SF36, and HADS scores were improved with statistically significant changes after the treatment period (SAQ: from 47.81 ± 9.58 to 88.28 ± 4.98, ($P<0.001$), SF36: from 49.29 ± 13.47 to 95.75 ± 2.89, ($P<<0.001$), HADS: from 15.71 ± 7.16 to 2.28 ± 2.09, ($P<0.001$) (Figure 3).

Discussion

CSX represents a major clinical challenge because conventional treatment is often not successful (1,13). Developing new drugs from medicinal plants used in complementary and alternative medicine, such as Persian medicine, could be a promising option. In Persian medicine, chamomile and lemon balm are two plants suggested to treat angina-like and compressive chest pain with a non-life-threatening prognosis known as CSX in conventional medicine.

This study revealed that 90 days of treatment with chamomile-lemon balm syrup significantly improved SAQ, SF36, and HADS scores during the study. In other words, chamomile-lemon balm syrup significantly improved angina symptoms, quality of life, and anxiety and

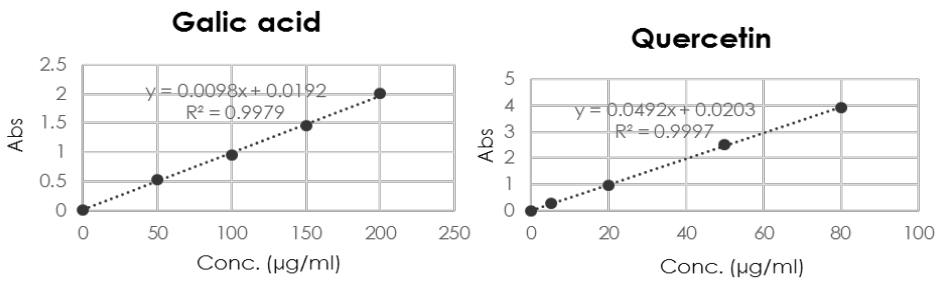

Figure 1. Calibration Curves for Gallic Acid and Quercetin Standards to Determine Total Phenol and Flavonoid Contents of Syrup, Respectively.

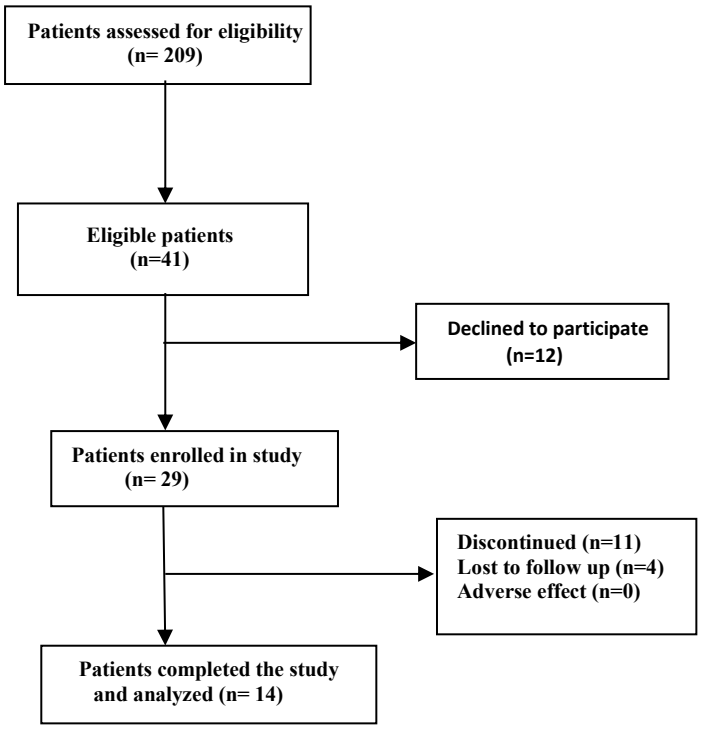

Figure 2. Study CONSORT Flowchart.

depression over time of the study. In this study, there were no significant adverse effects. According to a systematic review and several clinical trials, the average duration of conventional treatment of cardiac syndrome was 3 months (36,37). Similar to a performed systematic review in 2013 by Jia-Ying Wan that showed Chinese herbs compared with conventional treatment had an improving effect on chest pain in the patients with CSX after an average duration of one-month treatment (38), in our study, the significant improvement of CSX initiated after one and a half months of treatment. Improvement of the patients with CSX in this clinical study could be contributed to improving or protecting endothelial function effect of chamomile and lemon balm, as the systematic review of the effect of Chinese herb on chest pain of patients with CSX showed this effect of all 48 types of herbs (38).

Table 1. Demographic Characteristics of the Study Participants

Characteristics	
Age (years), Mean± SD	50.57±6
Gender, No. (%)	
Male	6 (42.9)
Female	8 (57.1)
BMI (kg/m^2), Mean± SD	28.02 ± 3.8
Hypertension, No. (%)	1 (7.1)
Diabetes, No. (%)	0
Hyperlipidemia, No. (%)	9 (64.3)
Smoking, No. (%)	2 (14.3)
Drug treatment, No. (%)	
Beta-blockers	11 (78.6)
Calcium antagonists	11 (78.6)
Nitrate	4 (28.6)
Statin	9 (64.3)
ACE inhibitor	1 (7.1)

SD: Standard Deviation, BMI: body mass index.

Medicinal herbs featuring multi-constituents, multi-targets, and multi-effects are valuable resources for multi-target drug discovery (39-41). Several studies designed to investigate the effects of either chamomile, lemon balm, or its major flavonoid components, namely apigenin, quercetin, and luteolin, on the cardiovascular system (22-26). Based on available studies, improving the effect induced by chamomile and lemon balm in this clinical study could be attributed to the effective functions of these plants in the pathology of CSX. An *ex vivo* study demonstrated that chamomile-derived compounds cause a slow vasorelaxation of isolated blood vessels through blockage of calcium channels and produce rapid, transient endothelium-dependent vasorelaxation through nitric oxide-releasing (25). Another *ex vivo* study showed that aqueous extract of lemon balm exerts an endothelium-dependent vasorelaxant effect caused by endothelial nitric oxide production (42). Based on an animal model, an oral intake of methanol extract of chamomile before induction of cardiac ischemia-reperfusion showed potent anti-ischemic activity due to its anti-oxidant properties (24). Based on a clinical study on patients with chronic, stable angina, oral administration of powdered lemon balm effectively improved biomarkers of oxidative stress and inflammation (22). The anti-anxiety of the syrup was observed in this study according to the results of the

Table 2. SAQ, SF36, and HADS domains Score During the Entire Study Period, Baseline, and After 6 Months of Treatment

Domains	(Min, Max)	(Mean ± SD)	P (Repeated measures ANOVA)	*P* (Bonferroni)
SAQ physical limitation			<0.001	
T1	35.56 ,77.78	83.92 ± 11.54		(T1, T2) <0.05
T2	57.78, 84.44	71.90 ± 9.08		(T1, T3) <0.05
T3	68.89, 82.22	78.41 ± 4.12		(T2, T3) <0.05
SAQ angina stability			<0.001	
T1	0, 50	28.57 ± 16.57		(T1, T2) <0.05
T2	25,100	73.21.22.92±		(T1, T3) <0.05
T3	50,100	87.50 ± 16.26		(T2, T3) <0.05
SAQ angina severity			<0.001	
T1	30,70	63.57 ± 11.50		(T1, T2) <0.05
T2	70,100	84.28 ± 8.51		(T1, T3) <0.05
T3	90,100	97.14 ± 4.68		(T2, T3) <0.05
SAQ treatment satisfaction			<0.001	
T1	32.5, 57.5	42.41 ± 7.52		(T1, T2) <0.05
T2	57.5, 76.25	70.89 ± 6.87		(T1, T3) <0.05
T3	76.25, 95	82.94 ± 9.32		(T2, T3) <0.05
SAQ perceiving disease			<0.001	
T1	0, 58.33	30.35 ± 18.08		(T1, T2) <0.05
T2	58.33,91.67	77.97 ± 10.64		(T1, T3) <0.05
T3	83.33, 100	94.64 ± 5.27		(T2, T3) <0.05
SAQ total score			<0.001	
T1	26.08, 60.90	47.81 ± 9.58		(T1, T2) <0.05
T2	62.99, 86.42	76.26 ± 7.2		(T1, T3) <0.05
T3	80.73, 94.31	88.28 ± 4.98		(T2, T3) <0.05
SF36 physical functioning			<0.001	
T1	25, 90	59.64 ± 19.94		(T1, T2) <0.05
T2	60, 100	86.78 ± 11.02		(T1, T3) <0.05
T3	90, 100	96.42 ± 4.12		(T2, T3) <0.05
SF36 physical role			<0.001	
T1	0, 100	40.26± 28.57		(T1, T2) <0.05
T2	50,100	96.42 ± 13.36		(T1, T3) <0.05
T3	100,100	100 ± 0		(T2, T3) >0.05
SF36 emotion role			<0.001	
T1	20, 51	40.57±9.93		(T1, T2) <0.05
T2	61,100	77.85±12.08		(T1, T3) <0.05
T3	84,100	96.57±6.81		(T2, T3) <0.05
SF36 vitality				
T1	25, 70	52.5 ± 14.37		(T1, T2) <0.05
T2	62, 100	79.57 ± 11.28	<0.001	(T1, T3) <0.05
T3	82, 100	94.28 ± 5.7		(T2, T3) <0.05
SF36 mental health			<0.001	
T1	0, 60	42.85 ± 14.5		(T1, T2) <0.05
T2	50,95	78.92 ± 13.32		(T1, T3) <0.05
T3	75, 100	88.21 ± 7.99		(T2, T3) <0.05
SF36 social functioning			<0.001	
T1	38,100	63.07 ± 23.23		(T1, T2) <0.05
T2	50,100	93.78 ± 16		(T1, T3) <0.05
T3	100,100	100 ± 0		(T2, T3)> 0.05
SF36 bodily pain			<0.001	
T1	0,100	42.71 ± 40.18		(T1, T2) <0.05
T2	67, 100	97.64 ± 8.81		(T1, T3) <0.05
T3	100,100	100 ± 0		(T2, T3) >0.05

Table 2. Continued

Domains	(Min, Max)	(Mean ± SD)	P (Repeated measures ANOVA)	*P* (Bonferroni)
SF36 general health			<0.001	
T1	0,88	59.42 ± 21.04		(T1, T2) <0.05
T2	68,100	84 ± 12.05		(T1, T3) <0.05
T3	80,100	90.57 ± 7.29		(T2, T3) >0.05
SF36 total score			<0.001	
T1	21.25, 67.75	49.29 ± 13.47		(T1, T2) <0.05
T2	75.88, 96.13	86.87 ± 6.8		(T1, T3) <0.05
T3	89.5, 100	95.75 ± 2.89		(T2, T3) <0.05
HADS anxiety			<0.001	
T1	3 ,17	9.14± 4.53		(T1, T2) <0.05
T2	0, 12	4.42 ± 3.34		(T1, T3) <0.05
T3	0, 5	1.35 ± 1.33		(T2, T3) <0.05
HADS depression			<0.001	
T1	2, 16	6.57 ± 3.75		(T1, T2) <0.05
T2	0, 5	2.21 ±1.84		(T1, T3) <0.05
T3	0, 3	1.14 ± 0.92		(T2, T3) <0.05
HADS total score			<0.001	
T1	5, 32	15.71 ± 7.16		(T1, T2) <0.05
T2	0, 16	6.64 ± 4.53		(T1, T3) <0.05
T3	0, 7	2.28 ± 2.09		(T2, T3) <0.05

HADS questionnaire, which was reported in a clinical study of the effect of lemon balm on the anxiety of patients undergoing coronary artery bypass surgery (43) and in a clinical study of chamomile on Generalized Anxiety Disorder (44).

On the other hand, recent studies indicate an association between mental stress and endothelial dysfunction induced by exaggerated sympathetic vasoconstriction (45-47). So, the improvement of angina symptoms in patients in this study could be contributed to improving endothelial function through the anti-anxiety effects of lemon balm and chamomile.

Based on pharmacological activities, flavonoids such as apigenin, luteolin, quercetin, and caffeic acid, are the major cardioprotective phytochemicals present in chamomile and lemon balm (48,49). Based on current pharmacological evidence, these active constituents in chamomile and lemon balm have an improving effect on mechanisms involved in the pathophysiology of CSX. These improving effects include vasodilatory effects through stimulating endothelial nitric oxide synthase activity and blockage of calcium channels, improved endothelial function, anti-oxidant activities, and anti-inflammatory effects (25,50-52).

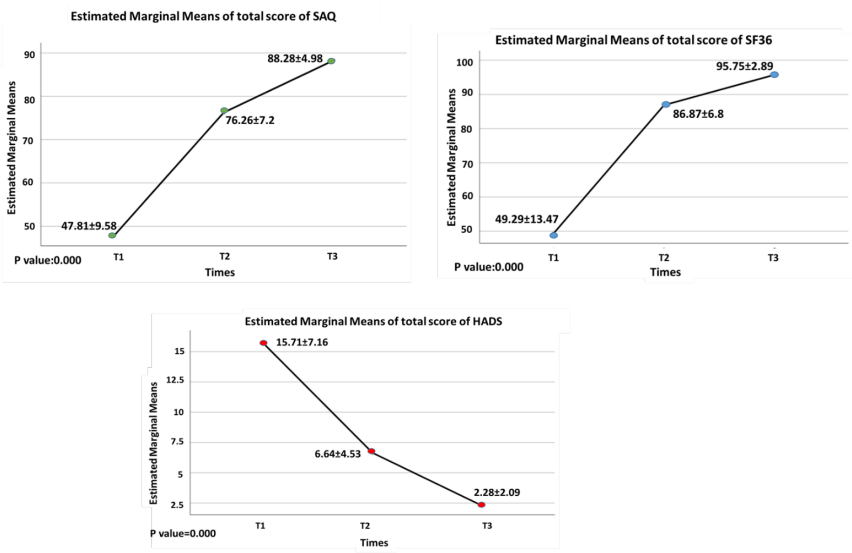

Figure 3. Changes in SAQ, SF36, and HADS Scores During Study. (SAQ: Seattle Angina Questionnaires; SF36: 36-Item Short Form Survey HADS: Hospital Anxiety and Depression Scale; T1: base line of study; T2:45 days after inclusion in the study; T3:90 days after inclusion in the study).

Limitations of the Study

However, this study is limited by the lack of a control group and small sample size due to enrollment of drug-resistant CSX instead of newly diagnosed CSX, considerable improvement in scores of SAQ, SF36, and HADS without any significant side effects should be further investigated in a placebo-controlled trial with larger sample size.

Conclusions

According to the findings of this investigation, an herbal preparation of chamomile-lemon balm has a significant improving effect of angina symptoms, quality of life, and status of anxiety and depression in the patients with drug-resistant CSX. A further placebo-controlled trial with a larger sample size is necessary to confirm our results.

Authors' Contribution

SN and MK designed the study and conducted the research. SN and SO monitored, evaluated, and analyzed the result of the study. Further, AVF, AZ, SS, FS and HR reviewed the article. All authors approved the final manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

This clinical trial was guided in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (code:IR.TUMS.VCR.REC.1397.618) and was registered at the Iranian Registry of Clinical Trials (identifier:IRCT20180608040014N1). Written informed consent was obtained from each participants after clarifying the aim of the trial.

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