112 mg Ca Fructoborate = 3 mg/day, not enough Boron
Resveratrol trans 10 mg (50% of 20mg)

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Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: Effects on lipid profiles, inflammation markers, and quality of life

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ABSTRACT

Objective: This study aimed to evaluate the effects of short-term (60-d) oral supplementation with calcium fructoborate, resveratrol, and their combination on the clinical and biological statuses of subjects with stable angina pectoris.
Methods: A randomized, double-blinded, active-controlled, parallel clinical trial was conducted in three groups of subjects. Of the total number of subjects included in study ($n = 166$), 87 completed the 60-d test treatment study period and 29 followed in parallel their usual medical care and treatment. The primary outcomes were inflammation biomarkers (high-sensitivity C-reactive protein), left ventricular function markers (N-terminal prohormone of brain natriuretic peptide), and lipid markers (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triacylglycerols). Quality of life was assessed by the Canadian Cardiovascular Society angina class and the number of angina attacks per week.
Results: There was a significant decrease of high-sensitivity C-reactive protein in all groups at the 30-d and 60-d visits. This decrease was greater (39.7% at 60 d) for group 3 (calcium fructoborate), followed by group 2 (resveratrol plus calcium fructoborate, 30.3% at 60 d). The N-terminal prohormone of brain natriuretic peptide was significantly lowered by resveratrol (group 1, 59.7% at 60 d) and by calcium fructoborate (group 3, 52.6% at 60 d). However, their combination (group 2) was the most effective and induced a decrease of 65.5%. Lipid markers showed slight changes from baseline in all groups. The improvement in the quality of life was best observed for subjects who received the resveratrol and calcium fructoborate mixture (group 2).
Conclusion: The results indicate that the combination of resveratrol and calcium fructoborate has beneficial effects in patients with angina (ClinicalTrials.gov, ISRCTN02337806; March 25, 2010).

Introduction

Atherosclerotic ischemic heart disease is a major health problem worldwide [1]. Inflammation is a main factor in the initiation, progression, and acute complications of an atherosclerotic plaque [2]. Resveratrol has shown significant cardiovascular protective effects [3] in models of myocardial injury [4,5], systemic and pulmonary hypertension [6], and type 2 diabetes [7]. Several cardioprotective mechanisms of resveratrol, including antioxidant, anti-inflammatory, and anti-fibrotic actions, have been identified [8]. The low *in vivo* bioavailability caused by rapid resveratrol metabolism and elimination, its major disadvantages, limits the results for patient studies [9]. Boron is a bioactive element for humans and boron-containing compounds present different biological activities [10]. Calcium fructoborate (CF) is a complex of calcium, fructose, and boron found naturally in fresh and dried

All the authors contributed equally to this work.

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fruits, vegetables, herbs, and wine [11,12]. In previous studies, the effect of CF on human polymorphonuclear neutrophils and macrophages, which play a central role in the inflammatory response, has been investigated [13,14]. Two very recent studies have provided important information on the possible molecular anti-inflammatory activity of CF in the treatment of osteoarthritis [15,16].

The purpose of this controlled pilot study was to assess the short-term synergistic effect of resveratrol in combination with CF on the clinical and biological statuses of subjects with stable angina pectoris. The combination of these two substances was based on the fact that CF acts as a stabilizer for resveratrol degradation in the digestive tract [17]. Furthermore, CF might present a positive synergism together with resveratrol, increasing the anti-inflammatory properties of the former and the biological efficacy of the latter as an antioxidant agent.

Materials and methods

Study design

The study was randomized, double-blinded, active-controlled, and paralleled with three groups of subjects who received the test drugs and one control group of subjects who were not randomized. This single-center trial was approved by the institutional ethics committee of the Craiova Cardiology Center (Craiova, Romania) according to decision no. 400 in February 2010. The trial also was in accord with the Declaration of Helsinki of 1975, which was last reviewed in 2008. Placebo was not admitted by the hospital bioethics commission owing to ethical considerations. Nevertheless, this trial had a control group with subjects who fulfilled inclusion criteria, but they received only their usual medical care and treatment, without any test materials, during the clinical trial. The number of total enrolled subjects was 166 (Fig. 1). Of 116 subjects who met the inclusion criteria, 87 were included in the intention-to-treat analysis, divided into three groups (29 subjects in each group), and all completed the entire protocol. The remaining 29 were included in the control group and underwent the same analysis as those who received the test materials. The subjects' ages ranged from 42 to 83 years (mean age 65 y). There were more men (71, 61.2%) than women (45, 38.8%). Most were in Canadian Cardiovascular Society (CCS) angina class III at inclusion (62%), 30% were in class II, and 8% were in class IV. Table 1 presents the baseline demographic characteristics of the subjects who successfully completed the study and the background medication. There were no significant differences among the groups. All subjects continued with their medical therapy as prescribed by their treating physicians. Subjects did not receive any nutritional supplements or other products. They were instructed to follow a diet low in salt or fat if they were hypertensive or dyslipidemic, respectively. Patients with diabetes mellitus were instructed to follow the recommendation of their treating physicians.

Inclusion criteria

Male and female subjects at least 18 y of age were included. All had been diagnosed with angina pectoris (CCS classes II–IV), and they had to be in stable clinical condition for at least 1 mo (angina class, angina frequency). The subjects' body mass index range was 24 to 27 kg/m^2 (overweight but not obese). Subjects had to be on standard and stable treatment for angina in the previous month.

Exclusion criteria

Subjects who were unlikely to cooperate in the study, had legal incapacity or limited legal incapacity, and were pregnant or breast-feeding or had child-

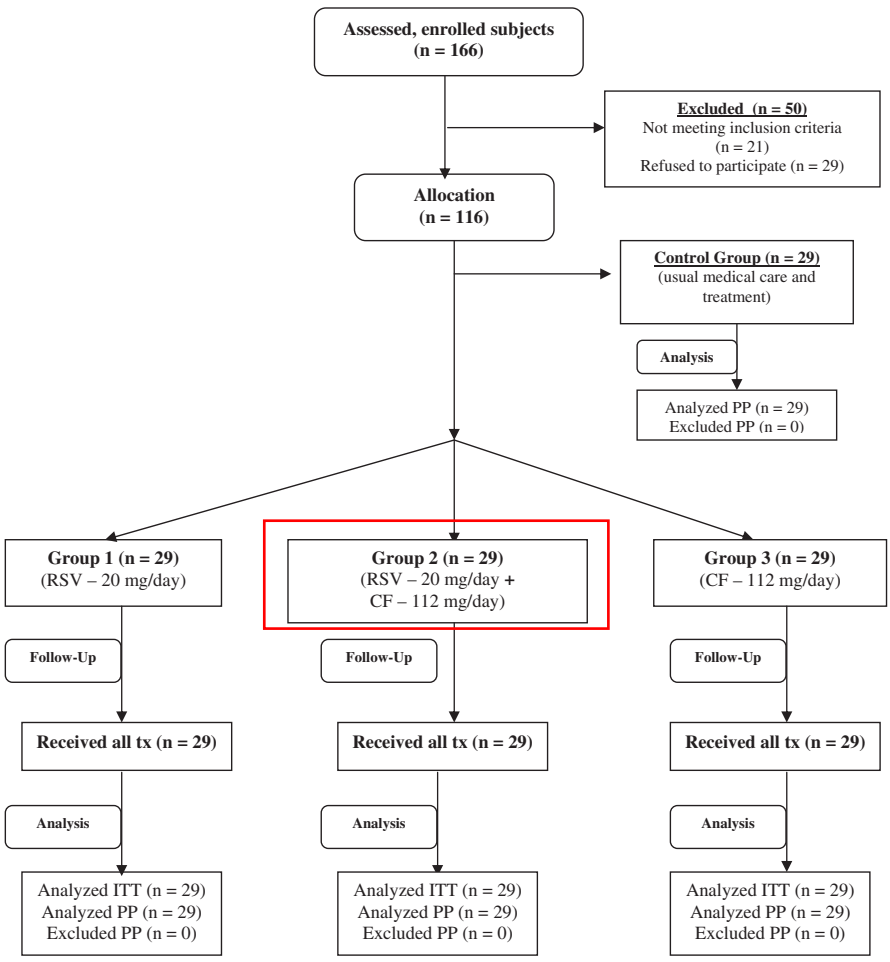

Fig. 1. Flow chart for subject recruitment. CF, calcium fructoborate; ITT, intention to treat; PP, patients; RSV, resveratrol; tx, study treatment.

Table 1
Baseline demographic characteristics and concomitant therapy of subjects who successfully completed the study

	Group 1	Group 2	Group 3	Control
Characteristics				
Age (y), mean ± SD	64.9 ± 5.8	66.3 ± 5.5	63.7 ± 6.2	64.2 ± 7.1
Men/women (*n*)	17/12	18/11	18/11	18/11
History of MI (%)	41.37	41.37	48.27	44.82
Previous PCI or CABG (%)	13.79	17.24	13.79	13.79
History of hypertension (%)	100	96.55	93.1	96.55
History of DM (%)	44.82	41.37	44.82	41.37
History of PAD (%)	20.68	20.68	17.24	17.24
Medication				
β-Blocker (*n*)	27	26	28	26
ACEI/ARB (*n*)	23	24	22	23
Calcium channel blocker (*n*)	8	10	7	5
Nitrate (*n*)	12	14	11	12
Statin (*n*)	18	16	21	20
Other lipid-lowering drug (*n*)	5	7	4	6
Antiplatelets (*n*)	23	21	25	25
Acenocoumarol (*n*)	6	7	4	3

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DM, diabetes mellitus; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention

bearing potential were excluded from the study. Participants in another drug or device trial at the same time or within the previous 30 d or within five drug half-lives of the investigational materials or within the time legally required by the regulatory authorities, whichever was longer, and those with recent (<3 mo) hospitalization for unstable angina, myocardial infarction, or coronary revascularization were also declared non-eligible for this study. In addition, subjects with known alcohol or drug abuse, known moderate or severe liver disease (Child–Pugh score >7), known severe renal disease (serum creatinine >220 μmol/L) or known anemia (blood hemoglobin <11 g/L), and known chronic inflammatory disease did not participate in the study.

not enough B

The study used a patented, commercially available dietary supplement that was previously shown to be identical to a naturally occurring plant-based boron carbohydrate, i.e., CF [12]. A powdered extract standardized to 50% resveratrol also was used. Subjects were randomized into three groups for treatment. Supplementation for the groups was double-blinded. Group 1 received a single daily capsule of resveratrol 20 mg/d (*trans*-resveratrol 10.0 mg) in addition to their usual medical care and treatment. Group 2 received a single daily capsule of resveratrol 20 mg/d (*trans*-resveratrol 10.0 mg) combined with CF 112 mg/d (boron 3.0 mg/d) in addition to their usual medical care and treatment. Group 3 received a single daily capsule of CF 112 mg/d (boron 3.0 mg/d) in addition to their usual medical care and treatment. The non-randomized control group received only their usual medical care and treatment.

weak references

The daily serving size of CF was based on the recommended daily levels of boron intake (0.5–7.0 mg/d per person) [18,19]. Using the boron content database of foods commonly consumed by urban and rural Romanians, the boron intake was calculated for the population of Craiova and its surroundings and was equal to 2.0 ± 0.7 mg/d per person (mean ± standard deviation) and uniformly distributed between men and women [15]. During the trial, we did not measure the CF content from food, but from data in the literature, and knowing the boron intake for the local population, the CF amount from nutrition should not exceed 5 mg as boron [11].

In humans, less than 5% of the oral dose has been observed as free resveratrol in blood plasma [9,20]. In our trial, we did not measure plasma levels of resveratrol because previous research has stated that CF stabilizes resveratrol degradation in the digestive tract [17]. The optimum amount of resveratrol was administered to subjects as a function of the amount of boron. The stability ratio between resveratrol and boron is 1:10. In the present study, we used the optimum boron concentration for nutrition; thus, the amount of resveratrol could not have exceeded this determined ratio [17].

The follow-up included three visits: inclusion, at 1 mo (30 d), and at 2 mo (60 d). The study treatments were well tolerated.

Noninvasive two-dimensional echocardiography was performed only at inclusion to exclude left ventricular systolic dysfunction or heart failure.

Coronary angiography was not performed because, it is highly unlikely that a regression of atherosclerotic plaques would be observed in such short time (e.g., 2 y in one study [21]). Platelet function was not assessed.

Tolerance was evaluated at each visit by asking subjects about the appearance of any adverse events. Compliance was assessed after each subject returned the test material boxes by counting the remaining capsules and calculating the percentage of compliance.

Statistical analyses

SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. The sample size was determined by a power analysis based on the preliminary results that were obtained in the cardiology center. After 30 and 60 d, respectively, differences between mean values obtained for each marker under evaluation were analyzed using Student's *t* test and the Wilcoxon signed-rank test. The former was used for the primary outcomes (Tables 2 and 3) and the number of angina episodes and nitroglycerin consumption per week (Table 4), and the latter was used for Seattle Angina Questionnaire (SAQ) results and CCS angina class (Table 5). The statistical significance was defined at the level of 95% ($P < 0.05$) for Student's *t* test and the significance level was an α value equal to 0.001 for the Wilcoxon signed-rank test. All the obtained results were compared with baseline values. In Tables 2, 3, and 4, the results are expressed as mean ± standard deviation. In the same tables, values within parentheses represent the percentage of differences compared with baseline. This was computed as $(x_0 - x)/x_0 \times 100\%$, where x_0 is the initial value (at inclusion) and x the actual value (after 30 and 60 d, respectively). Owing to the number of subjects (29) in each group, we chose *t* repartition, which requires a near-gaussian distribution of data and similar standard deviations in the compared groups. Before the statistical analysis, variables were examined for normal distribution as determined by the Kolmogorov–Smirnov and Shapiro–Wilk tests. To verify the similarity of dispersions, the Levene test was used.

Primary outcome measurements (biochemical parameters)

For biochemical analyses, blood samples of fasting venous blood were taken in the morning and after 30 d and then 60 d of treatment. Commercial tubes were used to collect the blood for biochemical parameter determination. Basic biochemical parameters such as lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triacylglycerols) and inflammatory markers (serum high-sensitivity C-reactive protein [hs-CRP]) were analyzed in serum by standard biochemical procedures using the Cobas Integra 400 Plus automatic analyzer and kits (Roche, Switzerland). N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was determined using the Cobas h232 analyzer and tests (Roche Diagnostics GmbH, Mannheim, Germany).

Secondary outcomes measurements (quality of life)

Secondary outcomes were the CCS angina class as assessed by a physician during the subject's interview, the mean number of angina attacks per week, and the SAQ scores obtained at inclusion and the final visit after 60 d. The questionnaires were completed by the subjects or with the help of a relative or nurse. Regarding the number of angina episodes per week and nitroglycerin consumption, subjects were instructed to keep a diary with the number of angina episodes they had and the number of nitroglycerin tablets they used. The SAQ is a 19-item questionnaire intended to measure functional status in subjects with coronary artery disease [22,23].

Safety assessment

Two emergency telephone numbers were given to the subjects to maintain contact during the study in case of adverse events or other concerns related to the study. Participants were instructed to inform the test supervisor if they chose to discontinue the study owing to adverse effects.

Table 2
Changes in hs-CRP and NT-proBNP

	Inclusion	Month 1	Month 2	*P**
hs-CRP (mg/L)				
Group 1	6.9 ± 2.5	5.7 ± 1.9 (−17.3%)	5.2 ± 1.7 (−24.6%)	0.03
Group 2	6.6 ± 2.6	6.2 ± 2.5 (−6%)	4.6 ± 1.8 (−30.3%)	0.02
Group 3	6.8 ± 1.9	5.3 ± 2.5 (−22%)	4.1 ± 1.5 (−39.7%)	0.005
Control	6.6 ± 2.4	6.2 ± 2.1 (−6%)	5.9 ± 2.6 (−10.6%)	0.04
NT-proBNP (pg/mL)				
Group 1	674 ± 192	552 ± 232 (−18.1%)	271 ± 137 (−59.7%)	0.02
Group 2	662 ± 238	498 ± 147 (−24.7%)	228 ± 84 (−65.5%)	0.01
Group 3	684 ± 151	531 ± 165 (−22.3%)	324 ± 102 (−52.6%)	0.03
Control	671 ± 218	582 ± 197 (−13.2%)	514 ± 207 (−23.3%)	0.04

hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide
Data are presented as mean ± SD (percentage of differences from baseline)
* Statistical significance from baseline, computed at the end of trial (Student's *t* test).

Table 3
Changes in lipid profile

	Inclusion	Month 1	Month 2	P*
Total cholesterol (mg/dL)				
Group 1	176.5 ± 89	171.1 ± 97	164.3 ± 79 (−6.9%)	0.02
Group 2	167.5 ± 95	165.2 ± 89	163.7 ± 71 (−2.2%)	0.04
Group 3	172.5 ± 75	166.8 ± 77	162.2 ± 69 (−5.9%)	0.03
Control	169.4 ± 85	166.3 ± 91	164.8 ± 82 (−2.7%)	0.04
LDL cholesterol (mg/dL)				
Group 1	123.2 ± 63	118.4 ± 59	115.3 ± 57 (−6.4%)	0.03
Group 2	118.5 ± 57	115.2 ± 54	113.2 ± 56 (−4.4%)	0.04
Group 3	122.6 ± 46	115.1 ± 49	111.2 ± 55 (−9.2%)	0.02
Control	121.2 ± 61	118.7 ± 57	116.6 ± 52 (−3.7)	0.04
HDL cholesterol (mg/dL)				
Group 1	53.2 ± 25	52.8 ± 27	54.1 ± 33 (1.6%)	0.03
Group 2	52.3 ± 45	51.9 ± 27	52.8 ± 35 (0.9%)	0.04
Group 3	50.1 ± 20	51.3 ± 23	52.7 ± 26 (5.1%)	0.03
Control	51.8 ± 23	51.2 ± 32	51.6 ± 29 (−0.3%)	0.04
Triacylglycerols (mg/dL)				
Group 1	134.1 ± 64	131.2 ± 72	128.8 ± 58 (−3.9%)	0.03
Group 2	127.1 ± 72	127.8 ± 67	125.7 ± 68 (−1.1%)	0.04
Group 3	137.6 ± 54	135.8 ± 62	132.7 ± 64 (−3.5%)	0.03
Control	132.4 ± 69	130.4 ± 81	129.8 ± 72 (−1.9%)	0.04

HDL, high-density lipoprotein; LDL, low-density lipoprotein
Data are presented as mean ± SD (percentage of differences from baseline)
* Statistical significance from baseline, computed at the end of trial (Student's *t* test).

Results

There was a significant decrease of hs-CRP in all groups at the 30-d and 60-d visits (Table 2). This decrease was greater for group 3 (CF), followed by group 2 (resveratrol plus CF). After 30 d, group 3 continued to show the greatest decrease (22%), followed by groups 1 and 2 (almost insignificant). After 60 d, group 2 exceeded group 1 (30.3% versus 24.6%), but group 3 (CF) still showed the most significant decrease (39.7%).

Table 2 presents the changes in NT-proBNP in all groups. NT-proBNP was significantly lowered by resveratrol (group 1, by 59.7% at 60 d) and by CF (group 3, by 52.6% at 60 d). Their combination was the most effective (group 2) and induced a decrease of 65.5% ($P = 0.01$, statistical significance from baseline). The downward trend for group 2 was the greatest after the first month and at the end of the study. The decrease in the control group was very low (10.6% for hs-CRP and 23.3% for NT-proBNP) compared with the other groups.

The lipid profile (Table 3) showed a favorable trend in all groups. Total cholesterol, LDL cholesterol, and triacylglycerols decreased, whereas HDL cholesterol increased. Based on the percentage of differences from baseline computed at the end of study, the greatest decrease in LDL cholesterol (−9.2%) and the greatest increase in HDL cholesterol (5.1%) were for subjects taking CF (group 3). Group 1 (resveratrol) presented the most significant decreases for total cholesterol (−6.9%) and for triacylglycerols (−3.9%), although the latter value was very close to that obtained for group 3 (−3.5%). It is important to note that during the study, subjects previously prescribed statins by their treating physician continued their statin therapy. Statins may have had an influence on the obtained results, but the results from the control group were rather low (−3.7% versus −9.2% for LDL cholesterol, −0.3% versus 5.1% for HDL cholesterol, −2.7% versus −6.9% for total cholesterol, and −1.9% versus −3.9% for triacylglycerols) compared with groups 1 and 3.

There was an improvement in the subjects' quality of life in all groups. Tables 4 and 5 present the significant decreases in the number of angina episodes per week and nitroglycerin consumption, increases in SAQ scores, and improvement in angina class in all groups. In Table 4, the improvement in the quality of life was best observed for subjects in group 2 (resveratrol plus CF), because the percentages of differences obtained from baseline were the highest compared with the other groups. Thus, the decrease in angina episodes per week was 59%. Nitroglycerin consumption followed a similar trend, with a decrease of 67.6%. For groups 1 and 3, the results were comparable and significant: the decreases in angina episodes per week were 50% for group 1 (resveratrol) and 48.8% for group 3 (CF). For nitroglycerin consumption, the decreases after 60 d were 56.2% for group 1 and 54.8% for group 3. For the control group, the decrease was almost half (23.8% and 29.4%, respectively) compared with the other groups.

All SAQ measurements showed a significant improvement from baseline to the 60-d follow-up (Table 5). The greatest difference was observed in SAQ angina stability, for which the resveratrol plus CF treatment produced an increase from 44.2 to 86.5. As presented in Table 5, an improvement in CCS angina class at the 2-mo follow-up in all treatment groups was observed. There were significantly fewer subjects in classes III and IV; most were in class II, and only a few subjects were in class I.

Table 4
Angina episodes and weekly nitroglycerin consumption

	Inclusion	Month 1	Month 2	P*
Angina episodes/wk				
Group 1	4.2	3.3	2.1 (−50%)	0.02
Group 2	4.4	3.2	1.8 (−59%)	0.002
Group 3	4.5	3.5	2.3 (−48.8%)	0.02
Control	4.2	3.8	3.2 (−23.8%)	0.03
Nitroglycerin consumption (tablets or puffs/wk)				
Group 1	3.2	2.3	1.4 (−56.2%)	0.006
Group 2	3.4	2.1	1.1 (−67.6%)	0.003
Group 3	3.1	2.4	1.4 (−54.8%)	0.007
Control	3.4	2.8	2.4 (−29.4%)	0.02

Data are presented as number (percentage of differences from baseline)
* Statistical significance from baseline, computed at the end of trial (Student's *t* test).

Discussion

All subjects in this study had been diagnosed with stable angina pectoris. Coronary artery disease, the main cause of angina, is caused by atherosclerosis of the coronary arteries. Atherosclerosis is an inflammatory disease and not merely the passive accumulation of lipids within the artery walls. The literature provides information that oxidized LDL is one risk factor for atherosclerotic inflammation. HDL has a protective effect against the development of atherosclerosis, which results partly from its anti-inflammatory and antioxidant properties [24–26]. Studies of the mechanisms of atherosclerosis have suggested that anti-inflammatory and antioxidant agents might be protective [24,27].

The two substances being tested in this trial, CF and resveratrol, were well tolerated. From the literature, the highest dose of CF administered was 37.5 mg/kg. No toxicity was noted at this dosage [28]. Resveratrol presents a low toxicity [29].

Orally ingested boron has been observed to be well absorbed (>90%) from the gastrointestinal tract in humans, rats, and rabbits. Boron as borate is readily and almost completely absorbed (>90%) from the human gut [30,31]. About 70% of the resveratrol dose given orally as a pill is absorbed; nevertheless, the oral bioavailabilityof resveratrol is low because it is rapidly metabolized in the intestines and liver into conjugated forms, i.e., glucuronateand sulfonate. Only trace amounts (<5 ng/mL) of

Table 5
SAQ results and CCS angina class*

	Group 1		Group 2		Group 3		Control	
	Baseline	Month 2	Baseline	Month 2	Baseline	Month 2	Baseline	Month 2
SAQ								
Physical limitations	52.2	64.3	50.5	66.4	53.4	64.4	55.3	59.1
Angina stability	46.7	81.2	44.2	86.5	47.3	82.6	49.3	61.2
Angina frequency	48.6	69.4	46.5	73.1	46.8	70.2	47.2	59.4
Treatment satisfaction	67.5	78.1	68.4	81.3	66.2	78.3	69.1	73.2
Disease perception	33.4	52.1	32.1	54.4	34.7	55.6	34.1	41.2
Visual scale score	63.2	74.5	64.5	77.1	61.8	75.6	62.4	68.1
CCS angina class								
I	0	4	0	5	0	7	0	2
II	8	13	8	11	10	13	9	10
III	19	10	18	12	17	8	18	16
IV	2	1	3	1	2	1	2	1

CCS, Canadian Cardiovascular Society; SAQ, Seattle Angina Questionnaire
* $P < 0.001$ (Wilcoxon signed-rank test).

unchanged resveratrol have been detected in the blood after a 25-mg oral dose [9].

Boron supplements have been reported to lower the platelet count and potentially decrease the risk of thrombosis [32], and experimental evidence has been obtained for the likely usefulness of boron-containing thrombin inhibitors in the treatment of cardiovascular disorders [33]. Recent studies in animal models have suggested that boron deprivation increases the concentrations of plasma homocysteine [34] and insulin [35], which have been suggested as risk factors for heart disease.

For this trial, we chose this combination of CF and resveratrol because previous research has suggested that CF stabilizes resveratrol degradation in the digestive tract [17], CF has been shown to be an important anti-inflammatory agent [11,15], and resveratrol has been found to have antioxidant properties [36]. CF also is an antioxidant [11]. The objective was to assess their synergetic effect on the markers under investigation: inflammation, left ventricular function, and lipids.

The increase in CRP levels in the blood is recognized as a marker of cardiac disease risk, and it has a prognostic value in coronary artery disease [37]. Regarding the systemic inflammation measured by hs-CRP, the obtained results showed that resveratrol and especially CF (after 60 d, the decrease was 39.7%) have the beneficial effects of significantly decreasing the hs-CRP level. The CF results are consistent with previous studies in which CF in similar serving sizes caused significant decreases in hs-CRP [15,16]. This is further confirmation of the strong anti-inflammatory effects of CF.

The 76-amino acid NT-proBNP fragment is the most frequently used plasma marker of congestive heart failure [38]. According to the obtained results, the observed decrease was rather high (65.5% in group 2).

According to data from the literature, hs-CRP and NT-proBNP were monitored. Levels of NT-proBNP have been reported to be significantly higher (182.8 pg/mL) in ischemic patients compared with those without ischemia (88.4 pg/mL), with a median hs-CRP level of 2.2 mg/mL [39]. Moreover, in a study of different antianginal therapies, after 12 mo of treatment with valsartan and enalapril, patients with stable, symptomatic heart failure presented significantly decreased levels of NT-proBNP (−15.3% versus −13.6% changes, respectively) and hs-CRP (−105.7% versus −73.3% changes, respectively) compared with baseline [40]. In the present study, hs-CRP and pro-BNP showed significant changes in a relatively short time (2 mo). This finding opens new directions of research regarding the use of natural adjuvants (CF plus resveratrol) for improving the standard antianginal therapies.

Regarding lipid markers, improvements in levels of LDL cholesterol and HDL cholesterol were most numerically significant in the CF group (group 3), whereas the resveratrol group (group 1) showed the best results for total cholesterol and triacylglycerols, although the values were rather close to those in group 3. The observed changes seem small (<10%) but are nonetheless important because any statistically significant changes in these important cardiovascular markers may decrease the risk of heart disease.

Furthermore, this study showed that the combination of resveratrol and CF (group 2) elicited significant improvements in the number of angina episodes and nitroglycerin consumption per week and in the quality of life for subjects with stable angina pectoris.

In the three experimental groups, CF, resveratrol, and their combination presented positive effects, with the marker values being significantly different from baseline. For the control group, some changes were noticed, but these were of little significance. Thus, the addition of this control group to the trial highlights the improvements in the parameters under investigation in the presence of CF, resveratrol, or their combination in the other groups.

Although the study would have been improved by a larger number of subjects and a longer duration, to our knowledge this is the first clinical study that has evaluated the synergistic effects of resveratrol and CF in patients with ischemic cardiac disease from a clinical point of view (symptoms) and the beneficial effects (anti-inflammatory and antioxidant) of their combination on lipid profiles and inflammation markers. The obtained data are promising and represent an important base for further trials (the next trial has been registered in the international database at http://www.controlled-trials.com/ISRCTN90543844).

Conclusion

The combination of resveratrol and CF has beneficial effects in subjects with stable angina pectoris and the outcome of this study supports the use of these products as dietary supplements for improving quality of life. This trial is a starting point for studying the action of a resveratrol and CF mixture in patients with stable angina.

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