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ORIGINAL RESEARCH

Effect of E-OJ-01 on Left Ventricular Ejection Fraction and Myocardial Oxygen Consumption: A Randomized, Double-Blind, Placebo-Controlled Study

Shalini Srivastava[1], Robert N Girandola[2], Bruce Abedon[3]

[1]Clinical Development, Enovate Biolife, Wilmington, DE, USA; [2]Department of Human Biology, University of Southern California, Los Angeles, CA, USA; [3]R&D, Innophos LLC, Cranbury, NJ, USA

Correspondence: Shalini Srivastava, Enovate Biolife, 913 N Market Street, Suite 200, Wilmington, DE, 19801, USA, Tel +1 650 855-4832, Email shalini@enovatebiolife.com

Purpose: E-OJ-01 (Oxyjun^{TM}), a proprietary, standardized aqueous extract of *Terminalia arjuna* (TA) bark, has previously shown promising cardiovascular health benefits in healthy young athletic adults and is now being tested to determine its ability to support left ventricular ejection fraction and associated parameters in a diverse population.

Participants and Methods: Healthy adults aged 30–70 years (n=72) were included in the study to investigate the effect of 400 mg/day of E-OJ-01 when administered for 8 weeks on myocardial pumping capacity, primarily left ventricular ejection fraction (LVEF). The secondary endpoints were improvement in diastolic filling (E/A) ratio, rate pressure product (RPP), and fatigue severity scale (FSS) score. The effect of the intervention on blood lipids and gamma-glutamyltransferase (GGT) levels was also explored. The safety of the intervention was evaluated by monitoring adverse events, vitals (heart rate (HR), blood pressure (BP), and body temperature (BT)), and liver (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT)) and kidney function (serum creatinine).

Results: E-OJ-01 increased the LVEF by 6.28% (percentage change) from the baseline compared with 0.24% (percentage change) in the placebo group ($p<0.05$). It reduced fatigue (22.52%), RPP (1.54%), and GGT levels (5.90%) from the baseline. No adverse events related to the intervention were observed during the study.

Conclusion: The study showed that E-OJ-01 could improve cardiac pumping capacity by significantly increasing LVEF and reducing fatigue in a diverse, healthy population.

Keywords: heart health, ejection fraction, endothelial health, pre-workout supplement, exercise capacity

Introduction

Maintenance of cardiovascular health is important for all ages, especially for the aging population. The prevalence of cardiovascular disease nearly doubled from 1990 to 2019.[1] The vast majority of aging individuals with or without heart failure demonstrate increased sympathetic influences leading to higher oxygen demand during intense physical activity.[2] Studies have shown that with every 10-year increase in biological age, LVEF decreases by 1%.[3] Reduction in LVEF may affect heart health and increase fatigue and feelings of exertion during physical activity. The recommended approach to support optimal cardiovascular health includes exercise, a healthy diet, and traditional botanicals with known heart health benefits, such as the bark of *Arjuna* (*Terminalia arjuna*).[3–6] In a previous study, supplementation with a proprietary extract of TA bark to young, exercising athletes increased LVEF, reduced fatigue, and decreased feelings of exertion during a treadmill test.[6]

Several marketed products in the heart health category contain ingredients that are thought to have a beneficial effect on heart health.[7,8] These include omega-3 polyunsaturated fatty acids,[9,10] coenzyme Q10,[11,12] L-arginine,[13] L-citrulline,[14]

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astaxanthin,[15] grape seed extract,[16] hawthorn extract,[17] dietary nitrates,[18] and minerals like zinc,[19] copper,[20] and magnesium.[21] It has been proposed that these ingredients act through different pathways to support cardiac function, including amplifying nitric oxide production, enhancing myocardial contractility, alleviating arterial stiffness, improving endothelial function, providing anti-oxidant support, and modulating other risk factors like serum lipid levels and blood pressure. However, only a few of these supplements have benefits supported by evidence generated through well-designed studies.[8] Moreover, to date, the effect of these supplements on LVEF has only been evaluated in heart failure patients to investigate their add-on benefit to standard medical therapy. Few studies have been conducted on clinically healthy individuals without signs and symptoms of cardiac dysfunction. There is a need to evaluate dietary supplement ingredients in a more diverse population to determine an ingredient's ability to support cardiac health. Enovate Biolife identified this window of opportunity and developed a proprietary product, E-OJ-01 (Oxyjun^{TM}), which consists of a standardized aqueous extract of TA bark.

Several clinical studies have been conducted to investigate the effect of TA bark in improving cardiac health, and the results were generally positive. However, participants in these studies were often ailing and were being treated for a clinical condition.[22–27] With this preliminary evidence supporting TA's cardiovascular health benefits, E-OJ-01 was developed to help support cardiac health in adults. In a previous clinical study, E-OJ-01 increased LVEF leading to higher cardiac output and decreased myocardial performance index in younger adults.[6] In another study, E-OJ-01 improved cardiovascular health-related markers in an obese population.[28]

Encouraged by these promising results, the present study was conducted to investigate the benefits of E-OJ-01 on left ventricle pumping capacity (LVEF) and associated parameters such as E/A ratio, RPP, lipid profile, GGT, and fatigue severity in overweight to obese individuals belonging to a wider age range. We used M-mode echocardiography in the study for the estimation of LVEF. M-mode echocardiography providing superior temporal resolution helps readily appreciate subtle changes in the absence of left ventricular regional wall motion abnormalities. M-mode recordings of the left ventricle are considered an accurate method for calculating left ventricular ejection fraction via the Teichholz method.[29] As the study targeted recruiting healthy individuals, M-mode served as an acceptable method for assessing LVEF. Safety was also assessed by monitoring the vitals, liver and kidney function, and occurrence of any adverse event throughout the study.

Materials and Methods

Study Design

The study was designed as a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of the investigational product (IP), E-OJ-01, on cardiovascular health, primarily LVEF, in a diverse population of adults. The secondary objectives of the study were change in left ventricular relaxation factor - E/A ratio, myocardial oxygen consumption by RPP, and fatigue by FSS. Additionally, the effect of the IP on other endpoints, namely, lipid profile using blood high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides (TG) levels, as well as vascular flexibility using serum GGT levels, were explored in the study. The safety and tolerability of E-OJ-01 were evaluated by monitoring adverse events throughout the study duration, measuring vitals (BP, HR, & BT), and change in laboratory parameters, including SGOT, SGPT & creatinine, from baseline to the end of the study.

The study was conducted under the supervision of family physicians from January 27, 2021 to September 02, 2021. The recruitment for the study was done at the preventive health clinics in Mumbai, India. The participants were screened for the eligibility criteria and randomly assigned to either the E-OJ-01 or matched placebo groups in a ratio of 1:1. Block randomization with a random block size of 4 was performed using StatsDirect software (ver. 3.1.17). The research statistician not involved in the study generated the random allocation sequence and secured the randomization chart with limited access. The participant, investigators, and researchers remained blinded to the group assignment throughout the study duration and data analysis. The study was registered at NIH Clinicaltrials.gov (NCT No: NCT04715126, dated January 20, 2021). The study results have been reported as per the Consolidated Standards of Reporting Trials (CONSORT)[61] statement (Table S1).

Participants

The study was conducted among adults aged ≥ 30 to ≤ 70 years with systolic BP ≥ 120 and ≤ 139 mm Hg and/or diastolic BP ≥ 80 and ≤ 89 mm Hg.[30] The participants having LVEF ≥ 39 and ≤ 60%,[31] BMI ≥ 25 to ≤ 34.9 kg/m^2, and normal serum levels of SGPT, SGOT and creatinine were included in the study. Females of childbearing age who were willing to use the accepted methods of contraception during the study were allowed to participate in the study. All the participants volunteered for the study and provided a written informed consent form before enrollment.

Individuals who had hyperglycemia (≥ 126 mg/dl), any clinically significant medical disorder, and abnormal thyroid-stimulating hormone (TSH) levels (<0.4 and > 4.0 IU/mL); used dietary supplements such as omega fish oil supplements, coenzyme Q10, vitamin K2 or drugs such as anti-hypertensives, proton pump inhibitors, loop diuretics, anticoagulants, barbiturates, anti-epileptics or anti-inflammatory medications were excluded from the study.

Interventions

The IP and placebo were manufactured in compliance with applicable Good Manufacturing Practices regulations and supplied by Enovate Biolife. The intervention group was administered E-OJ-01 at a dose of one capsule (400 mg) orally once a day after breakfast for 8 weeks, while the control group was administered the placebo (microcrystalline cellulose) at the same dose and regimen for 8 weeks. E-OJ-01 is a proprietary extract of TA bark standardized to a minimum of 30% polyphenols and 15% glycosides and free from arjunolic acid. In compliance with the recommendation of traditional and complementary medicine, 400 mg dose of E-OJ-01 extract with a herb extract ratio of 7:1, equivalent to 2.8 g of crude TA herb, was used for the study. The current dose of 400 mg of E-OJ-01 has been found absolutely safe in a study of young, healthy participants when administered for 56 days. This dose helped promote cardiac function in young, exercising adults by improving LVEF and right ventricular myocardial performance index while reducing fatigue.[6] To preserve the blinding, E-OJ-01 and placebo capsules were matched for size, shape, color, and texture. They were packed identically in terms of size, color, and labeling.

Study Procedures

Participants fulfilling inclusion-exclusion criteria visited the clinical trial sites for assessments on days 0, 28, and 56. LVEF and E/A ratio were assessed by a single qualified cardiologist using M-mode Doppler echocardiography (Philips Affiniti 30, Model 795218; Philips cardiac probe series No. S4-2) at the central echocardiography lab.

The E/A ratio is one of the most commonly used indices for assessing ventricular relaxation.[32] It is the ratio of the early E-wave to late A-wave ventricular filling peak velocities caused by left ventricular relaxation in early diastole and atrial contraction in late diastole, respectively. Normally, in a healthy adult, the E velocity is greater than the A velocity. However, with advancing age, the left ventricular wall may develop reduced elasticity, which can affect the degree of ventricular relaxation.[33,34]

Subsequently, myocardial stress was measured by calculating RPP (heart rate × systolic BP), a non-invasive, reliable indicator of myocardial oxygen consumption.[35] RPP varies with the physical activity status of an individual. During rest, the RPP varies between 7000 and 9000 mmHg/min. Physically active individuals have lower RPP, while those with sedentary lifestyles usually have higher RPP values due to increased oxygen demand and, eventually, a faster onset of fatigue during moderate physical stress.[36] All participants completed a self-reported fatigue severity scale[37] to estimate their subjective perception of fatigue severity during routine activities. The recall period for FSS was past seven days, and the participants were instructed to mark their responses keeping in view the level of their day-to-day activities. Additionally, the participants are requested to maintain the same dietary and physical exercise regime with no abrupt changes during the study.

Vascular elasticity is a determinant of optimal vascular function. Physical fitness has been found to delay age-related arterial stiffness. GGT is found to be a novel marker for arterial stiffness and positively correlates with brachial artery pulse wave velocity.[38] Therefore, it may serve as a valid marker for arterial stiffness in the absence of pulse wave velocity measurement. The study explored the effect of the product on serum GGT using an enzymatic colorimetric assay on Roche/Hitachi Cobas cSystems. The LDL, HDL, and triglycerides are part of a typical lipid profile used in clinical

settings to predict cardiovascular risk. Therefore, it is imperative to monitor the lipid profile of the participants in studies related to cardiac health. The lipid profile was performed using an enzymatic colorimetric assay on Roche/Hitachi Cobas cSystems.

To monitor any untoward effect of the IP on the liver and kidney, serum levels of SGOT, SGPT (International Federation of Clinical Chemistry method without pyridoxal phosphate activation) and creatinine (enzymatic assay) were analyzed on Roche/Hitachi Cobas cSystems. Additionally, vitals were monitored throughout the study for safety evaluation of the study products. Participant diaries were used to monitor adverse or serious adverse events, intervention compliance, and concomitant medication intake.

Outcome Measures

The primary outcome of the study was a statistically significant improvement in the cardiac pumping capacity of study participants, as evaluated by an increase in LVEF at the end of the study (D56) from baseline (D0) compared with placebo.

The secondary outcomes were statistically significant improvement of ventricular relaxation as evaluated by a decrease in the E/A ratio; a decline in myocardial oxygen consumption as assessed by a decrease in RPP, and a reduction in fatigue of study participants as assessed by a decrease in FSS after 56 days of administration of the IP compared to the placebo.

The exploratory outcome was a significant decrease in serum GGT levels as a marker of vascular elasticity and an improvement in lipid profile after 8 weeks of IP compared with the placebo.

The safety outcomes were the number of adverse events and changes in vitals and serum levels of SGOT, SGPT and creatinine at the end of the study compared to placebo.

Statistical Analysis

The sample size for the study was based on available data for similar studies conducted on TA.[25,39] Considering an estimated screening failure rate of 30%, approximately 136 potential participants had to be screened to enroll 96 participants randomized into 2 groups in the ratio of 1:1, with 80 participants completing the study.

The demographic and baseline characteristics were compared for the intention-to-treat population. All the efficacy outcomes were analyzed for the per-protocol population, defined as the number of participants who completed the study without any major protocol violation. The data were visually assessed for normality and further checked and presented for the normal distribution using the Shapiro Wilk/Kolmogorov–Smirnov test wherever required. The data are mainly presented as mean, standard deviation (SD), and 95% confidence intervals (CI) unless stated otherwise. For continuous data, two-sided *t*-tests and for categorical variables, chi-square tests were used to compare the two groups. For inferential tests, p-value <0.05 and 95% CI were considered for statistical significance, and a two-tailed hypothesis was tested. The effect of the investigational products over time within groups was mainly calculated as the difference between the mean values at the end of the study (D56) and baseline (D0). The level of significance of the difference was calculated using a paired *t*-test. The between-group comparison for the change from baseline to the specific follow-up assessment visit in the study was made using analysis of covariance (ANCOVA) with intervention as a factor and respective baseline data as a covariate.

The safety population was defined as the randomized research participants who consumed at least one dose of the assigned investigational product. Any adverse events and changes in vitals were recorded during every follow-up visit. At the baseline and end of the study visit (D56), biochemical data were analyzed for comparison between the two groups. All the statistical analyses were performed using R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and XLSTAT Version 2021.3.1 (Data Analysis and Statistical Solution for Microsoft Excel) software.

Results

A total of 81 participants who were found eligible were randomly assigned to the two groups: E-OJ-01 (n=40) or placebo (n=41). Figure 1 represents the detailed participant disposition for the study.

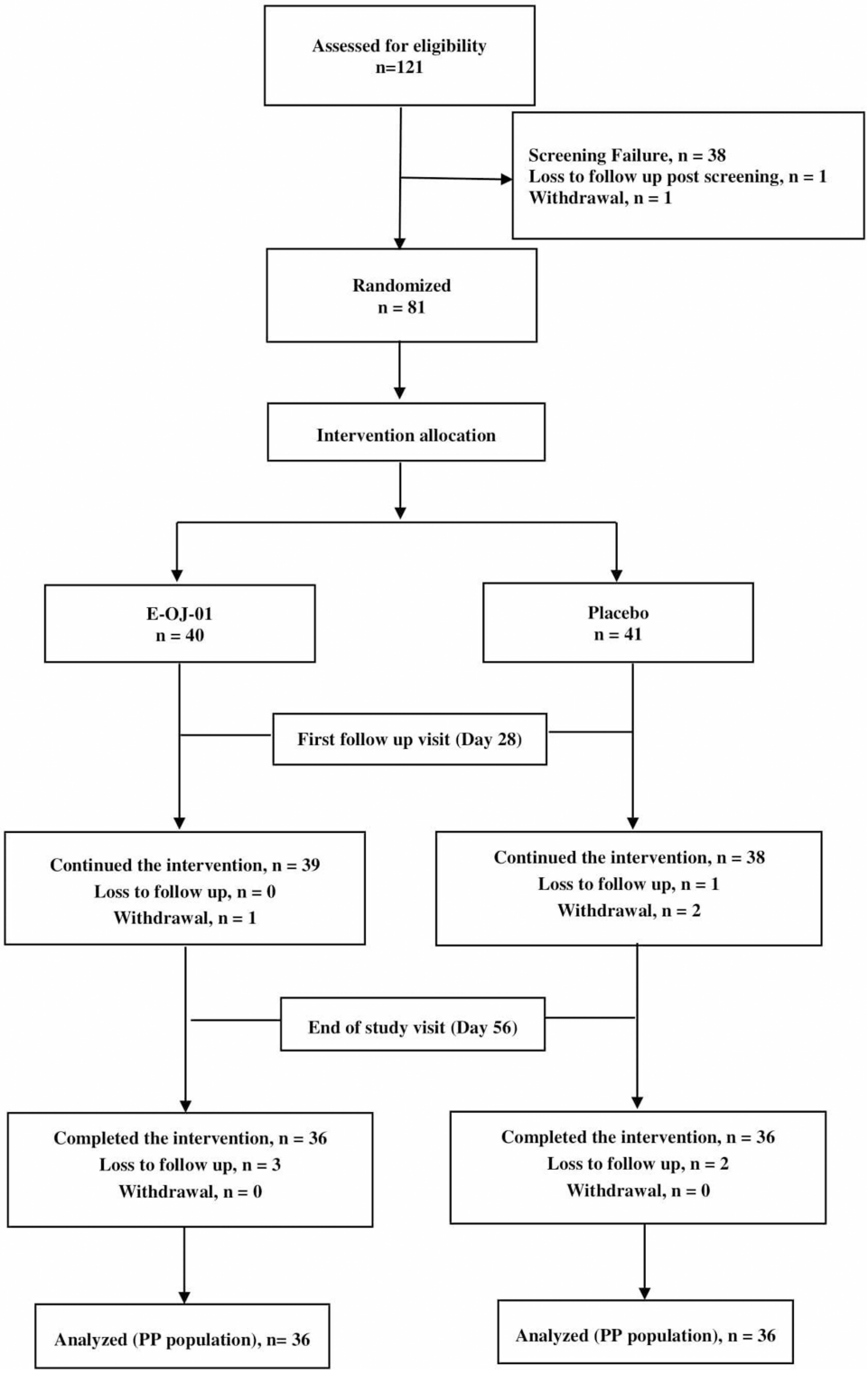

Figure 1 Participant disposition.

Demographic and Baseline Characteristics

The participants' demographic and baseline data are presented as mean (SD) and number (%) in Table 1. All the baseline characteristics were well-balanced ($p > 0.05$) across the two groups and conformed to the selection criteria defined for the study.

Table 1 Demographic and Baseline Characteristics of the Enrolled Participants

Parameters		E-OJ-01 (n=40)	Placebo (n=41)	Total (n=81)	p-value[a]
		Mean (SD)			
Age (years)		45.65 (8.13)	48.56 (8.28)	47.12 (8.28)	0.1144
Gender (n (%))	Male	25 (62.50%)	26 (63.41%)	51 (62.96%)	0.9321
	Female	15 (37.50%)	15 (36.59%)	30 (37.04%)	
BMI (kg/m2)		28.67 (2.83)	29.25 (2.98)	28.96 (2.90)	0.3720
SBP (mmHg)		128.99 (7.05)	128.28 (6.54)	128.63 (6.76)	0.6427
DBP (mmHg)		82.43 (2.46)	81.96 (2.53)	82.19 (2.49)	0.3997
Body temperature (°C)		36.35 (0.44)	36.33 (0.48)	36.34 (0.46)	0.8149
HR (beats/min.)		76.04 (8.98)	75.35 (7.91)	75.69 (8.41)	0.7153
LVEF (%)		57.98 (2.52)	58.02 (2.46)	58.00 (2.47)	0.9291
E/A ratio		1.19 (0.33)	1.15 (0.25)	1.17 (0.29)	0.5797
FBS (mg/dl)		104.93 (12.66)	104.97 (10.45)	104.95 (11.52)	0.9851
TSH (μIU/mL)		2.27 (0.84)	2.29 (0.85)	2.28 (0.84)	0.9509
SGPT (U/L)		19.96 (9.42)	22.26 (8.18)	21.12 (8.84)	0.2447
SGOT (U/L)		19.06 (5.61)	19.36 (6.35)	19.21 (5.96)	0.8277
Creatinine (mg/dl)		0.83 (0.17)	0.79 (0.17)	0.81 (0.17)	0.2704
HDL (mg/dl)		38.38 (9.81)	39.84 (7.25)	39.12 (8.59)	0.4495
LDL (mg/dl)		110.18 (32.43)	122.52 (36.68)	116.42 (34.98)	0.1131
TG (mg/dl)		139.94 (60.11)	146.40 (55.69)	143.21 (57.64)	0.6171
RPP		9813.43 (1321.34)	9669.74 (1169.58)	9740.69 (1241.10)	0.6055
FSS score		3.98 (1.58)	4.19 (1.55)	4.08 (1.56)	0.5489
GGT (IU/L)		28.98 (16.70)	43.50 (71.84)	36.33 (52.63)	0.2144

Notes: Percentages were calculated using the respective column header count as the denominator. [a]Two-sample *t*-test for continuous variables and Chi-Square test for categorical variables.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FSS, fatigue severity scale; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein LVEF; left ventricular ejection fraction; n, number of participants; RPP, rate pressure product; SBP, systolic blood pressure; SGPT, serum glutamic pyruvic transaminase, SGOT, serum glutamic oxaloacetic transaminase; TG, triglycerides; TSH, thyroid-stimulating hormone; SD, standard deviation.

Effect on the Primary Outcome

The primary outcome variable was a change in LVEF from baseline to the end of the study (D56). Group and visit-wise LVEF data are summarized in Table 2. The change in the LVEF was calculated and compared for the with-in group and between-group significance levels. Both E-OJ-01 and the placebo had comparable values of LVEF at baseline, ranging from 48% to 60% ($p>0.05$). After 56 days of intervention, the participants in the E-OJ-01 group showed a statistically significant increase from baseline LVEF values ($p<0.0001$). However, in the placebo group, no significant change was observed in LVEF on D56 ($p>0.05$).

Table 2 Effect of Investigational Product on LVEF (%)

Visit (Day)	E-OJ-01 (n=36)		Placebo (n=36)		p-value[a]
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Baseline (D0)	58.00 (2.61)	57.12–58.88	58.19 (2.36)	57.39–58.99	
End of study (D56)	61.64 (4.24)	60.21–63.07	58.33 (2.33)	57.54–59.12	
Change at D56	3.64 (3.45)	2.47–4.81	0.14 (1.36)	−0.32–0.60	<0.0001
p-value[b]	<0.0001		0.5427		

Notes: [a]Calculated using ANCOVA with intervention and visit as factor and baseline as covariate vs placebo. [b]Calculated using paired *t*-test.
Abbreviations: CI, confidence interval; D0, day 0; D56, day 56; LVEF, left ventricular ejection fraction; n, number of participants; SD, standard deviation.

The between-group analysis clearly shows that at the end of the study, a mean percentage increase of 6.28% in LVEF from baseline in the E-OJ-01 group was statistically significant compared to the 0.24% increase in the placebo (p<0.0001) (Figure 2).

Effect on Secondary Outcomes

The E/A ratio was assessed at baseline and at the end of the study as a secondary outcome. No significant change in the baseline E/A ratio was observed in the E-OJ-01 and placebo groups at the end of the study (Table 3).

The difference between the two groups for RPP was not statistically significant. However, a decreasing trend (1.54%) was observed in RPP at the end of 56 days in the E-OJ-01 group from the baseline values, while in the placebo group, it almost remained the same (Table 3).

After 56 days of intervention, the effect size of E-OJ-01 vs placebo on fatigue severity was −0.62 (95% CI: −1.29–0.06); however, it was not statistically significant (p=0.0739). A statistically significant reduction in the fatigue severity score from baseline (22.52%) was observed in the E-OJ-01 group. At the same time, there was less than a 10% reduction in fatigue in the placebo group (Table 3). Question-wise analysis of FSS revealed a statistically significant decrease in the score of question about fatigue's interference with physical functioning (Q4) (p = 0.033). A similar trend was observed for the score related to the fatigue effect on sustained physical functioning (Q6) (p=0.031) and restrictions related to performing certain duties and responsibilities due to fatigue (Q7) (p=0.017) in the E-OJ-01 group compared to the placebo at D56.

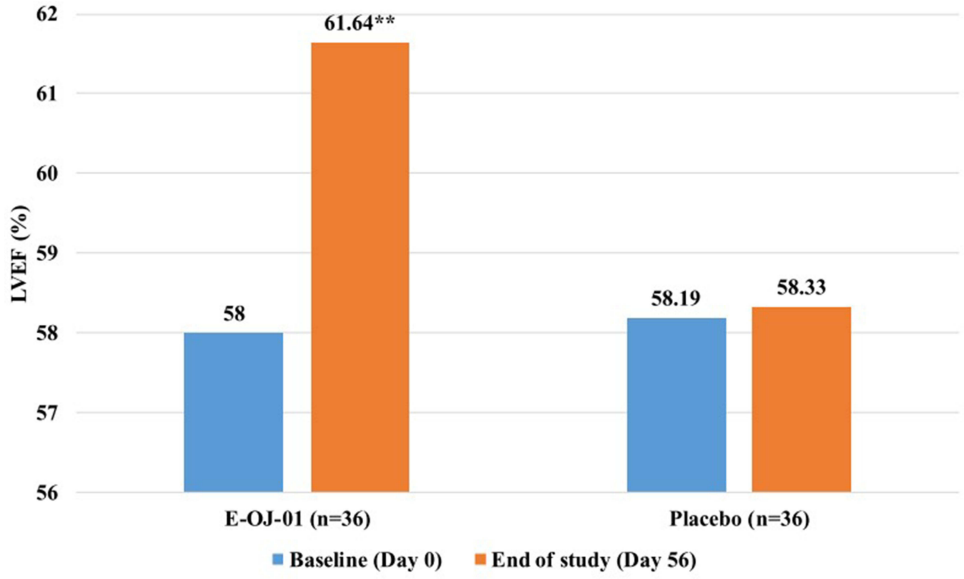

Figure 2 Effect of investigational product on LVEF. **p<0.0001.
Abbreviation: LVEF, left ventricular ejection fraction.

Table 3 Effect of Investigational Product on Secondary and Exploratory Outcomes

Outcome Measures	Visit (Day)	E-OJ-01 (n=36)		Placebo (n=36)		p-value[a]
		Mean (SD)	95% CI	Mean (SD)	95% CI	
E/A ratio	Baseline (D0)	1.19 (0.33)	1.08–1.31	1.16 (0.26)	1.07–1.24	
	End of study (D56)	1.16 (0.29)	1.07–1.26	1.12 (0.26)	1.04–1.21	
	Change at D56	−0.03 (0.20)	−0.10 - 0.04	−0.03 (0.22)	−0.11 - 0.04	0.7505
	p-value[b]	0.3675		0.3874		
SBP (mmHg)	Baseline (Day 0)	129.75 (6.78)	127.46–132.04	128.30 (6.81)	125.99–130.60	0.1912
	End of study (D56)	128.92 (6.08)	126.86–130.97	128.56 (5.74)	126.61–130.50	
	Change at D56	−0.83 (2.71)	−1.75–0.08	0.26 (3.03)	−0.77–1.29	
	p-value[b]	0.0735		0.6113		
DBP (mmHg)	Baseline (Day 0)	82.51 (2.52)	81.66–83.37	82.05 (2.69)	81.14–82.96	0.9281
	End of study (D56)	82.58 (2.62)	81.70–83.47	82.33 (2.47)	81.50–83.17	
	Change at D56	0.07 (3.18)	−1.01–1.14	0.29 (2.20)	−0.46–1.03	
	p-value[b]	0.8964		0.4387		
HR (beats/minute)	Baseline (Day 0)	76.10 (8.53)	73.21–78.98	75.36 (7.00)	72.99–77.72	0.8070
	End of study (D56)	75.36 (8.06)	72.63 -78.09	75.28 (7.89)	72.61 -77.95	
	Change at D56	−0.74 (7.66)	−3.33–-1.86	−0.08 (6.38)	−2.24–2.08	
	p-value[b]	0.5681		0.9414		
RPP	Baseline (D0)	9880.44 (1283.7)	9446.10–10,314.79	9671.17 (1074.12)	9307.74–10,034.60	
	End of study (D56)	9728.54 (1252.7)	9304.69–10,152.39	9684.29 (1164.1)	9290.42–10,078.17	
	Change at D56	−151.9 (1021.88)	−497.66–193.85	13.12 (837.75)	−270.34–296.57	0.6159
	p-value[b]	0.3785		0.9257		
FSS score	Baseline (D0)	4.04 (1.62)	3.49–4.59	4.13 (1.59)	3.59–4.67	
	Week 4 (D28)	3.65 (1.61)	3.11–4.20	4.14 (1.72)	3.56–4.72	
	Change at D28	−0.39 (1.35)	−0.85–0.07	0.01 (1.61)	−0.54–0.55	0.1809
	p-value[b]	0.093		0.9727		
	End of study (D56)	3.13 (1.57)	2.60–3.66	3.78 (1.55)	3.26–4.31	
	Change at D56	−0.91 (1.82)	−1.52–0.29	−0.35 (1.65)	−0.9–0.21	0.0739
	p-value[b]	0.0051		0.2159		

Notes: [a]Calculated using ANCOVA with intervention and visit as factor and baseline as covariate vs placebo. [b]Calculated using paired *t*-test.
Abbreviations: CI, confidence interval; D0, day 0; D56, day 56; DBP, diastolic blood pressure; HR, heart rate; FSS, fatigue severity scale; n, number of participants; RPP, rate pressure product; SBP, systolic blood pressure; SD, standard deviation.

Effect on Exploratory Outcomes

The lipid profiles of the participants are presented in Table 4. There was no significant change in the lipid parameters. Serum levels of GGT were assessed at baseline and at the end of the study. At the end of the study, the GGT level in the E-OJ-01 levels decreased by 5.90%, while in the placebo group, it increased significantly by 8.60% at the end of the

Table 4 Effect of Investigational Product on Exploratory Outcomes

Outcome Measures	Visit (Day)	E-OJ-01 (n=36)		Placebo (n=36)		p-value[a]
		Mean (SD)	95% CI	Mean (SD)	95% CI	
HDL (mg/dl)	Baseline (D0)	38.89 (10.21)	35.43–42.34	39.51 (7.5)	36.97–42.04	
	End of study (D56)	39.76 (10.61)	36.17–43.35	38.36 (7.37)	35.86–40.85	
	Change at D56	0.88 (4.59)	−0.67–2.43	−1.15 (6.8)	−3.45–1.15	0.1518
	p-value[b]	0.2585		0.3175		
LDL (mg/dl)	Baseline (D0)	112.09 (32.93)	100.94–123.23	119.36 (35.08)	107.49 −131.22	
	End of study (D56)	107.83 (31.78)	97.08–118.58	113.44 (34.71)	101.70–125.18	
	Change at D56	−4.26 (20.83)	−11.30–2.79	−5.92 (25.37)	−14.50–2.67	0.9708
	p-value[b]	0.2285		0.1706		
TG (mg/dl)	Baseline (D0)	140.36 (60.97)	119.73–160.99	145.26 (58.84)	125.35–165.16	
	End of study (D56)	140.64 (63.29)	119.23–162.05	150.99 (66.09)	128.63–173.35	
	Change at D56	0.28 (40.8)	−13.53–14.08	5.73 (51.47)	−11.68–23.15	0.5403
	p-value[b]	0.9680		0.5085		
GGT (IU/L)	Baseline (D0)	29.16 (16.44)	23.60–34.72	33.72 (21.18)	26.55–40.88	
	End of study (D56)	27.44 (18.09)	21.32–33.56	36.62 (24.51)	28.33–44.91	
	Change at D56	−1.72 (8.61)	−4.63–1.19	2.9 (7.96)	0.21–5.59	0.0289
	p-value[b]	0.2389		0.0354		

Notes: [a]Calculated using ANCOVA with intervention and visit as factor and baseline as covariate vs placebo. [b]Calculated using paired *t*-test.
Abbreviations: CI, confidence interval; D0, day 0; D56, day 56; GGT, gamma-glutamyltransferase; HDL, high-density lipoproteins; LDL, low-density lipoproteins; n, number of participants; SD, standard deviation; TG, triglycerides.

study, and the change between the groups was statistically significant (p=0.0289) Table 4. The change in GGT can be attributed to vascular health in the absence of significant liver abnormality and a history of alcohol consumption.

Safety Outcomes

Vitals (BP, HR, and BT) and serum levels of SGOT, SGPT, and creatinine were assessed at baseline and at the end of the study to monitor any change in the liver or kidney function due to the administration of the investigational product. Within group analyses showed no significant changes in the vitals and serum levels of liver or kidney function biomarkers at the end of the study compared with their baseline values in both groups. Additionally, no significant difference was observed in the E-OJ-01 group compared with the placebo (Tables 3 and 5).

Adverse event monitoring was performed during the entire duration of the study. A total of four participants reported AEs during the study period, 3 in E-OJ-01 (fever and cough (n=1); chest pain and acidity (n=2)) and 1 (Cold, cough, and body ache) in the placebo group. On causality assessment, it was concluded that these AEs were not related to the investigational products.

One serious adverse event was reported during the study, with the participant complaining of breathlessness on D20. The event was resolved without sequelae. After the causality assessment of the event, the investigator concluded that it was not related to the investigational product; however, the participant was withdrawn from the study, considering his health condition.

Overall, the concomitant medication usage was only reported in 4 participants, 3 (anti-allergic (n=1), antacid (n=2)) in E-OJ-01 and one (anti-allergic (n=1)) in the placebo group.

Table 5 Effect of Investigational Product on Safety Parameters

Outcomes	Visit (Day)	E-OJ-01		Placebo		p-value[a]
		Mean (SD)	95% CI	Mean (SD)	95% CI	
BT (°C)	Baseline (Day 0)	n=40		n=41		
		36.35 (0.44)	36.21–36.49	36.33 (0.48)	36.18–36.48	
	End of study (D56)	n=36		n=36		
		36.44 (0.39)	36.31–36.58	36.36 (0.35)	36.25–36.48	
	Change at D56	n=36		n=36		
		0.07	−0.07–0.21	0.05	−0.10–0.20	0.8134
	p-value[b]	0.3014		0.5161		
SGPT (U/L)	Baseline (Day 0)	n=40		n=41		
		19.96 (9.42)	16.95–22.97	22.26 (8.18)	19.68–24.84	
	End of study (D56)	n=36		n=36		
		19.68 (9.45)	16.48–22.88	24.44 (18.19)	18.28–30.59	
	Change at D56	n=36		n=36		
		0.54 (6.04)	−1.50–2.59	2.20 (13.79)	−2.47–6.86	0.5133
	p-value[b]	0.5921		0.3457		
SGOT (U/L)	Baseline (Day 0)	n=40		n=41		
		19.06 (5.61)	17.27–20.86	19.36 (6.35)	17.35–21.36	
	End of study (D56)	n=36		n=36		
		19.76 (6.47)	17.57–21.95	20.20 (9.87)	16.86–23.54	
	Change at D56	n=36		n=36		
		0.75 (3.73)	−0.51–2.01	1.21 (6.32)	−0.93–3.35	0.7094
	p-value[b]	0.2361 (T)		0.2593 (T)		
Creatinine (mg/dl)	Baseline (Day 0)	n=40		n=41		
		0.83 (0.17)	0.78–0.89	0.79 (0.17)	0.74–0.85	
	End of study (D56)	n=36		n=36		
		0.84 (0.22)	0.77–0.92	0.82 (0.16)	0.76–0.87	
	Change at D56	n=36		n=36		
		0.01 (0.11)	−0.02–0.05	0.01 (0.08)	−0.02–0.04	0.9418
	p-value[b]	0.4658		0.3745		

Notes: [a]Calculated using ANCOVA with intervention and visit as factor and baseline as covariate vs placebo. [b]Calculated using paired *t*-test.
Abbreviations: BT, body temperature; CI, confidence interval; D0, day 0; D56, day 56; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SD, standard deviation.

Discussion

The current study was a randomized, double-blind, placebo-controlled investigation to evaluate the potential of E-OJ-01 In increasing ventricular pumping capacity, primarily LVEF. The study was conducted on 30–70-year-old participants

with normal to marginally reduced LVEF as per the criteria recommended by the American College of Cardiologists. The results showed that oral administration of 400 mg of E-OJ-01 for 56 days was effective in improving the LVEF in participants. The effect on LVEF in the E-OJ-01 group was statistically significant compared with the placebo group. Among secondary outcomes, E-OJ-01 had a positive effect on the participants' perceived level of fatigue after 56 days. The results of the FSS revealed that significant between-group differences were noticed for responses to physical functioning and restrictions in performing certain duties and responsibilities. This shows that E-OJ-01 has the potential to improve the physical functioning of the participants.

The data analysis of CHAMP-HF (Change the Management of Patients with Heart Failure), a prospective registry of outpatients with heart failure with reduced ejection fraction, showed LVEF an improvement of ≥5% in ≈50% of registered cases over a median follow-up of 16 months with suboptimal use of guideline-directed medical therapy.[40] In this study, the researchers preassigned an increase of ≥5% as a clinically meaningful improvement in LVEF based on the meta-analysis conducted by Kramer et al, 2010.[41] Considering that our study was conducted in apparently healthy participants who were overweight to obese with marginally reduced LVEF, an increase in LVEF (3.64%) indicates a preventive potential of the product in at-risk populations. The current increase in LVEF is in agreement with our previous study, where an increase of 3.69% in LVEF from the baseline was observed in the exercising young adults after 56 days of E-OJ-01 administration. In that study, participants were evaluated using a standardized, graded treadmill protocol. Time to exhaustion and exertion were reported using the Borg Rated Perceived Exertion Scale. The increase in the LVEF correlated well with the increase in time to exhaustion during exercise performance. Both parameters were improved significantly after 56 days of oral administration of E-OJ-01.[6] This improvement might be due to the positive inotropic effect of the phytoconstituents of E-OJ-01[42] and is likely to enhance the exercise capacity in aging individuals.

The myocardial stress measured as RPP was not significantly reduced, but a trend of reduction (approx. 1.54%) in participants in the E-OJ-01 group was observed. Meanwhile, there was an increase in the RPP value in the placebo group. Since RPP is an indicator of physical fitness, this indicates that E-OJ-01 may help enhance physical performance, as observed previously.[6] Also, E-OJ-01 has a more pronounced effect on ventricular contraction rather than relaxation, as evident from its effect on LVEF and E/A ratio.

The E-OJ-01 group showed a significant reduction in serum GGT levels at the end of the study compared with the placebo (p-value = 0.0289). GGT level is an established marker of the degree of endothelial function and other cardiovascular-related factors.[43,44] Preclinical studies have shown that TA aqueous extracts have cardiovascular benefits, possibly due to their polyphenol phytoconstituents.[45–47] Evidence generated from observational research indicates that diets rich in polyphenols, which are well-known anti-oxidants,[48,49] can also help in maintaining cardiovascular health.[50] The results demonstrated in this study indicate that the proposed mechanisms of action for E-OJ-01 may include the positive inotropic effect leading to reduced myocardial stress.[42]

Previous clinical studies on TA extract/bark powder were primarily conducted in patients with chronic cardiovascular conditions. The study conducted by Maulik SK et al, 2016[25] demonstrated that TA aqueous extract administered for 12 weeks could not improve LVEF values. The previous studies[23,24,27] have lacked adequate power for the generalization of the results. To date, only one study investigating healthy adult individuals has been reported.[51] In that study, the efficacy of TA extract was investigated on the participants' physical performance and cardiorespiratory endurance. However, the study's sample size (n=10) was too small to draw any significant conclusion. Other dietary supplement ingredients, which claim to have a beneficial effect on cardiac health, have also been tested. These studies have mostly evaluated efficacy based on cardiac structure or function measures,[52–54] except dietary nitrates and β-alanine have also been tested in healthy young adults for cardiorespiratory fitness[55] and enhancing exercise tolerance and performance.[56] The studies conducted on healthy individuals focused on the incidence of major cardiovascular events as primary outcome measures after long-term administration of dietary supplementation.[57] Others were observational studies[58] that mainly relied on self-reported intake data. Several systematic reviews[59,60] have been conducted on the role of nutritional supplements in cardiovascular health. However, these also focused on heart failure studies and concluded that evidence supporting these nutritional supplement ingredients is weak and controversial, and further well-designed randomized clinical trials are warranted to confirm their benefits.

Our study is a well-designed randomized study that evaluated the efficacy of E-OJ-01 in a diverse, healthy population and has shown promising results related to cardiovascular benefits. These benefits place E-OJ-01 as a potential cardio-protective option for aging and exercising adults who want to enhance their cardiac performance, per se, and during exercise. However, there are some limitations of this study. Firstly, a study with larger sample size is warranted. Secondly, the population studied was apparently healthy and had preserved LVEF; therefore, the observed mean increase in the LVEF holds limited clinical significance for an ailing population with reduced LVEF. Thirdly, we used M-mode echocardiography to measure LVEF as the participants were healthy and also because sophisticated methods such as single-photon emission computed tomography, contrast-enhanced left ventriculogram, cardiac computed tomography, and cardiac magnetic resonance imaging that are currently used to measure LVEF are either invasive or expose the individuals to hazardous radioactive contrast medium. The effect on vascular stiffness needs to be reassessed using a gold standard method such as pulse wave velocity.

Conclusion

This randomized, placebo-controlled clinical study showed that E-OJ-01 helps increase LVEF and therefore, improves cardiac pumping capacity in overweight to obese adults. The product, at a dose of 400 mg/ once a day, helps decrease fatigue without any adverse effects.

Abbreviations

AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; BP, blood pressure; BT, body temperature; CI, confidence interval; D0, day 0; D28, day 28; D56, day 56; E/A, E-wave/A-wave; FSS, fatigue severity score; GGT, gamma-glutamyltransferase; HDL, high-density lipoproteins; HR, heart rate; IP, investigational product; ITT, intention-to-treat; LDL, low-density lipoproteins; LVEF, left ventricular ejection fraction; n, number of participants; RPP, rate pressure product; SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TA, *Terminalia arjuna*; TG, triglycerides; TSH, thyroid-stimulating hormone.

Ethics Approval and Informed Consent

This study complies with the Declaration of Helsinki, ICH-GCP, and Ethical guidelines for biomedical research on human participants 2006, issued by the Indian Council of Medical Research (ICMR), India. The study was approved by ACEAS-Independent Ehics Committee, India (CDSCO Reg. No. ECR/281/Indt/GJ/2017/RR-21 dated 04/02/2021 and OHRP & DHHS IRB No. IRB00011046; IORG No.: IORG0009271 dated 26/05/2022) (Protocol code EB/200401/OXYJUN/AH, Ver. 1.0; date of approval: 24/08/2020). The investigators informed all the participants about the risks and benefits involved during participation in the study. Only those participants who were willing to give written consent voluntarily were recruited for the study.

Data Sharing Statement

The data presented in this study are available at a reasonable request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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SS is affiliated with Enovate Biolife, reports personal fees from Enovate Biolife during the conduct of the study, and reports no other potential conflicts of interest in relation to this work. The other authors declare no conflicts of interest in relation to this work.

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