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Effect of E-OJ-01 on Cardiac Conditioning in Young Exercising Adults: A Randomized Controlled Trial

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Background and Aim: Cardiac health is a determinant of athletic performance. A body of data suggests that in healthy young adults, an increase in maximal cardiac output leads to an increase in endurance. *Terminalia arjuna* (TA) has been studied for multiple benefits in cardiovascular health although its effects as a cardioprotective ergogenic aid require further exploration. The current trial was planned to study the effect of the proprietary TA extract (E-OJ-01) on the markers of cardiac conditioning in healthy young adults.

Study Question: No study has assessed the effect of TA extract on cardiac conditioning by improvement of left ventricular ejection fraction (LVEF) in young exercising individuals.

Study Design, Measures and Outcomes: A randomized, double-blind, placebo-controlled, parallel group study was conducted to determine the efficacy and safety of E-OJ-01 for use as an ergogenic supplements in young exercising adults. This trial was registered at ClinicalTrials.gov (NCT02207101) and reported according to Consolidated Standards of Reporting Trials (CONSORT) requirements. Thirty-two healthy males, aged 18–40 years performing regular endurance exercise, were randomly assigned to 400 mg of E-OJ-01 or placebo for 56 days. LVEF, right and left ventricular Myocardial Performance Index, and Borg Rated Perceived Exertion (RPE) were assessed at baseline, day 28, and day 56; creatine kinase-MB and troponin-T were assessed at baseline and at day 56.

Results: As compared with placebo, 56 days of E-OJ-01 supplementation significantly improved the LVEF ($P = 0.0001$) and decreased the right ventricular Myocardial Performance Index ($P = 0.001$). The fatigue level captured by Borg Scale after completion of exercise showed a greater decrease in the E-OJ-01 group as compared with placebo. Creatine kinase-MB and troponin-T did not change significantly.

Conclusions: TA (E-OJ-01) significantly increased cardiovascular efficiency and improved the cardiac conditioning in young healthy adults.

Keywords: young exercising adults, Borg rated perceived exertion, left ventricle ejection fraction, Myocardial Performance Index, dietary supplement, E-OJ-01

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INTRODUCTION

The global awareness of physical health is growing exponentially. The benefits of exercise, such as increased muscle mass, decreased fat stores, and increased body kinesthetic intelligence are indisputable.[1] The improvement in the physical performance of exercising individuals as compared with sedentary people is connected with both muscular

and cardiocirculatory adaptations consisting of an increase in the stroke volume, a retaining of vasodilatory response, and an enhanced inotropic state.[2] However, during intense endurance training, a high pressure is developed within contracting muscle groups leading to occluded muscle blood flow which increases after-load of the heart, in turn limiting the cardiac ejection fraction and stroke volume.[3] Left ventricular ejection fraction (LVEF) is proportional to cardiac output and one of the key determinants of the exercise endurance.[4] Reduction in LVEF has a detrimental effect on cardiac conditioning during athletic performance. At the same time, ventricle Myocardial Performance Index (MPI) has emerged as an important predictor of exercise capacity with a negative correlation to oxygenation capacity and overall cardiac function.[5]

Currently, there are several agents that claim to improve endurance in athletes, such as anabolic steroids, human growth hormones, clenbuterol, erythropoietin, etc., but may have serious concerns and some of them have been included in prohibited list of the World Anti-Doping Agency for professional sports.[6–8] There are few supplements like resveratrol, quercetin, and garlic extract which claim to be cardioprotective; however, evidence suggests their lack of efficacy in such activity.[9] In light of the above facts, there seems a need for a product which can enhance cardiac function, ultimately increasing the endurance capacity.

In Indian traditional medicine, *Terminalia arjuna* (TA) has been frequently used for a plethora of cardiac morbidities. The TA bark extract has demonstrated dose-dependent reduction of blood pressure and heart rate in patients suffering from hypertension.[10] Various studies have been conducted to demonstrate the inotropic effects of TA extract on human heart in diseased populations.[11]

A review of studies on the cardiac effect of the herb outlines that TA helps to prevent fibrosis and oxidative damage to the heart and hence promoting activity of antioxidant enzymes when heart is under stress.[12] Moreover, antiinflammatory activity of TA prevents excessive injury. These actions have a cumulative cardiotonic effect, thus promoting healthy function of the heart muscle.[13]

An earlier attempt was made to demonstrate the ergogenic effect of TA in healthy young adults,[14] where the volunteers receiving treatment with TA demonstrated significant increase in maximum oxygen consumption capacity; however, mechanism for such effect remained unexplored. Also, another preclinical study demonstrated a decrease in the decay time of cell shortening in ventricular myocytes, thereby accelerating myocyte relaxation and a significant increase in the cardiac output.[15]

As yet, no study has assessed the effect of TA extract on cardiac conditioning in healthy individuals. Thus, Enovate Biolife attempted to develop a safe and effective ergogenic supplement with a primary objective of assessment of E-OJ-01 in increasing LVEF in young exercising individuals.

METHODS

Study settings, population, and recruitment

The study was conducted in the outpatient clinic of a cardiologist (principal investigator) holding a certification in ICH-GCP and trained in the study protocol. To avoid the observer's variability, all the echocardiography assessments were performed by the same cardiologist. A sample size of 32 participants was calculated using Stats Direct Version 3.0 to provide 80% power to the study targeting the improvement of LVEF in E-OJ-01 group as compared with placebo.

Thirty-two participants with age, body mass index, and body fat as 20.5 ± 2.0 years, 21.72 ± 3.54 kg/m^2, and 12.80% ± 2%, respectively for E-OJ-01 (n = 15) group and 20.5 ± 2.4 years, 21.69 ± 3.57 kg/m^2, and 12.17% ± 2%, respectively for placebo group (n = 17) were recruited for the study. Only males were included in the study to avoid variation of fatigue levels between sexes at the baseline.[16] Participants performing endurance exercise for not less than 3–4 hours per week for at least 12 weeks or more were included in the study. All the individuals included in the study had the left ventricle ejection fraction in the range of 55%–70%. Participants with anemia, cardiovascular disorders, metabolic syndrome, or any other underlying pathological conditions were excluded from the study. Smokers and tobacco users were excluded from the study. A written informed consent was provided by all. Ethical approval for the study was granted by the an Independent Ethics Committee (IEC-Aditya), registered with the Office for Human Research Protections in the US Department of Health and Human Services under registration number IRB00006475. Participant flow in the study is depicted in Figure 1.

On the screening visit, body fat was measured with a skin fold caliper (Lange; Beta Technology) using Faulkner method.[17] Systemic examination was performed, and vitals were recorded by the investigator. Venous blood was drawn for complete blood count, erythrocyte sedimentation rate, serum glutamic pyruvic transaminase, and serum creatinine. LVEF was measured by M-Mode echocardiography (Philips model HD15 2011, Yorba Linda, CA). Participants meeting the specified criteria were included in the study and

FIGURE 1. Participant flow diagram.

scheduled for further visit. The participants were familiarized to the protocol for graded exercise on the treadmill (Schiller-900 XL treadmill attached to Spandan Cardiac Workstation Version 4, Schiller AG, Altgasse, Baar, Switzerland) and were introduced to Borg 6–20 point Rated Perceived Exertion (RPE) Scale.

Participants were randomized into E-OJ-01 or placebo group using block randomization (StatsDirect version 3.0). Appropriate blinding was maintained for the participants, study team, and investigators. Study site was provided with sealed envelopes containing intervention codes that were to be opened only in case of a serious adverse event.

Outcome measures

We considered LVEF as a primary outcome measure to study the effect of E-OJ-01 on the performance during endurance activities. Studies show that exercise gradually leads to cardiac conditioning with left ventricular remodeling.[18] LVEF is estimated as a percentage of outbound blood pumped from the heart with each heartbeat. A study by Abergel et al,[19] suggests that LVEF is considered as an important element for determining LV function. They postulated that the exercising young adults with LVEF >70% might be susceptible to hypertrophic cardiomyopathy and the ones with LVEF <52% may be characterized by higher LV dilation, leading to dilated cardiomyopathy.

Right Ventricle Myocardial Performance Index (RV-MPI), also known as Tei index, serves as the secondary objective of the study. It is a parameter of global function expressing systolic and diastolic ventricular performance.[20] The study explored the role of E-OJ-01 in protecting cardiac and skeletal muscles against exercise-induced insult. Cardiac biomarkers, creatine kinase isoenzyme (CK-MB) and cardiac troponin-T, analyzed using immunoassay (COBAS; Roche Diagnostics GmbH) are considered as gold standard for cardiomyocyte insult.[21]

A recent study suggests that "Time to exhaustion" performed on a treadmill is a reliable research tool to assess human endurance capacity in aerobically trained men.[22] Hence, we assessed the time taken to reach volitional fatigue with the help of Borg Rated Perceived Exertion Scale using a standardized graded treadmill protocol.[23]

Interventions

The product under investigation, E-OJ-01 (available under trademark Oxyjun, Enovate Biolife Pvt Ltd, India) is a proprietary extract of a single botanical species, TA bark. The extract was standardized for a total of 45% polyphenols (Arjunophenols) and glycosides (Terminalosides) in 2:1 ratio.

E-OJ-01 (400 mg of excipient-free TA extract) and the placebo (400 mg of microcrystalline cellulose), matched in weight and appearance, were provided to the participants in orange-colored "0" size hydroxypropylmethylcellulose capsules packed in high-density polyethylene bottles. E-OJ-01 and placebo were manufactured in a facility certified for good manufacturing practices by the local food and drug authority. Participants consumed one capsule daily after lunch for 56 consecutive days.

Study procedure

On the day of randomization, resting pulse rate and blood pressure were assessed and clinical examination was conducted by the cardiologist. The exercise protocol involved 1 minute warm up at the speed of 3 mph followed by an increase of 2% and 1 mph in gradient and speed respectively, every 3 minutes till volitional fatigue. Heart rate and blood pressure were recorded during the exercise using the cardiac workstation, whereas RPE was marked at the end of the exercise using Borg Scale.

Venous blood samples were collected within 5 minutes of exercise for CK-MB and troponin-T tests. LVEF and MPI were recorded.

The same routine was followed at the subsequent visits on day 28 and day 56. Treatment compliance of more than 80% was sought for the study.

Statistical analysis

SPSS software version 10.0 (IBM) was used for statistical analysis. Means, proportions, and their SD were used as summary statistics. Baseline characteristics of the groups were compared using 2 sample t tests. The significance of change from baseline to day 28 and day 56 within each group was analyzed for significance by paired t test. To compare the changes in LVEF between groups, analysis of variance was performed, using the baseline value as a covariate, and to adjust or correct the raw changes for comparison. Response categories of Borg RPE score between the groups were compared by χ^2 test. For all comparisons, a P value of 0.05 or less was considered significant.

RESULTS

The study achieved more than 90% compliance to the investigational product for participants in both the groups. Herein, the results obtained with respect to each outcome measure have been listed in detail.

The LVEF (mean, SD) for the E-OJ-01 and placebo group for day 0, 28, and 56 has been presented in Table 1. Supplementation with E-OJ-01 demonstrated a significant increase in LVEF at day 56 ($P < 0.05$). Analysis of covariance revealed that when the difference in mean baseline LVEF of the 2 groups was adjusted, the actual changes of LVEF at day 56 in the E-OJ-01 group was significantly greater than placebo group ($P < 0.05$). It is also evident that the upper 95% confidence limit for the placebo group did not overlap the lower 95% confidence limit for the active intervention group.

The RV-MPI reduction in E-OJ-01 group after 56 days of supplementation was significant as compared with the placebo group ($P = 0.002$). Effect of E-OJ-01 and placebo on RV-MPI has been demonstrated in Figure 2A. No significant change in LV-MPI was detected between the 2 groups after 28 or 56 days of supplementation.

The time to exhaustion did not differ significantly among the groups at day 28. However, on day 56, E-OJ-01 group showed a significant increase in time to exhaustion as compared with the placebo group ($P = 0.03$). Figure 2B demonstrates the mean time to exhaustion in both the groups. There was also a significant difference in the exertion level between the groups. At baseline, 12.5% participants in placebo group scored "Extremely hard," 75% scored "Very hard," and 12.5% scored the exercise as "Hard" on Borg Scale. The corresponding scores in the E-OJ-01 group were similar with 20%, 66.7%, and 13.3% of participants, respectively. After 28 days of supplementation, 62.5% participants in placebo group felt the exercise to be "Very hard" and the rest 37.5% perceived it to be "Hard." In contrast, in E-OJ-01 group, only 46.7% participants deemed the exercise to be "Very hard" and 33% had marked the exertion to be only "Hard." At this stage, 20% of participants in this group realized the ease and marked their exertion as "Somewhat hard" and none found the exercise "Very hard" any longer. Continuing further, at the end of

Table 1. Effect of E-OJ-01 on LVEF (%).

Duration	Placebo (n = 16)	E-OJ-01 (n = 15)	P
Day 0	64.08 ± 1.52	65.33 ± 1.70	0.31
Day 28	64.91 ± 1.96	66.90 ± 2.31	0.1353
Day 56	65.39 ± 2.30	69.02 ± 3.13	0.0001*

*Change of 3.69% ($P = 0.001$) indicates significant difference in LVEF at day 56 among the groups (by ANOVA).

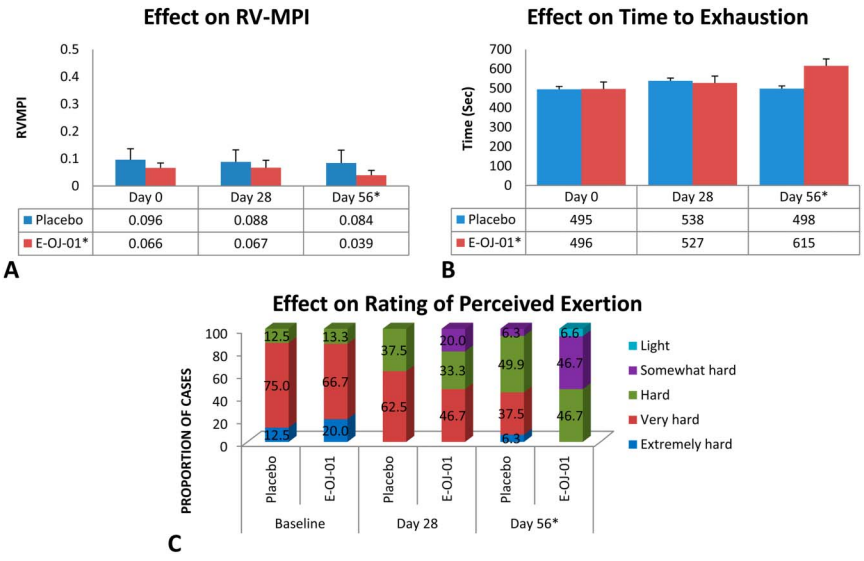

FIGURE 2. Effect of E-OJ-01 on (A) Right Ventricular Myocardial Performance Index (RV-MPI), (B) time to exhaustion, and (C) rating of perceived exertion on Borg Scale. (A) *Significant decrease of RV-MPI in E-OJ-01 group at day 56 ($P = 0.002$). (B) *At day 56, the time taken to reach exhaustion was significantly higher in E-OJ-01 group ($P = 0.026$). (C) *Significant number of individuals in E-OJ-01 group ($P = 0.018$) perceived reduced level of exertion at day 56.

day 56, no participant in the E-OJ-01 group and 6.3% of participants in the placebo group perceived the exercise to be "Extremely hard." At the end of the study, a significant number of individuals in E-OJ-01 group ($P = 0.018$) perceived reduced level of exertion as compared with baseline. The overall effect of E-OJ-01 was significantly superior to placebo in reducing perceived exertion. Change in Borg Scale of perceived exertion from baseline to day 28 and day 56 is shown in Figure 2C.

Data pertaining to cardiac biomarkers are presented in Table 2. Mean serum CK-MB values were in clinically normal range (5–25 IU/L) in both the groups. Although, the baseline value in E-OJ-01 group was higher than placebo at baseline, both the groups showed insignificant decrease at day 56. Mean values for troponin-T at baseline were insignificantly different between the study groups and the decrease in troponin-T at day 56 was also insignificant among the groups ($P = 0.47$). The study participants did not report any serious adverse events in the course of the 56 days of study.

Table 2. Effect of TA extract on cardiac biomarkers.

Biomarker	Duration	Placebo (n = 16)	E-OJ-01 (n = 15)	*P*
CK-MB (IU/L)	Day 0	18.88 ± 4.23	23.47 ± 7.14	0.05
	Day 56	18.62 ± 3.58	21.71 ± 6.35	0.56
Troponin-T (ng/L)	Day 0	5.5 ± 2.3	6.6 ± 2.0	0.17
	Day 56	5.3 ± 2.0	5.9 ± 2.6	0.47

Intergroup statistical significance (*P*) was assessed by ANOVA.

DISCUSSION

Fifty-six days supplementation with TA bark extract (E-OJ-01) resulted in significant improvement in cardiac conditioning in exercising young adults. This cardiac conditioning was associated with improvement of the exercise performance.

Under this study conditions, E-OJ-01 showed a significant improvement in LVEF which directly correlates with cardiac output.[24] Previous studies have reported that in veteran athletes, an increase in cardiac output results in increased maximal oxygen carrying capacity (VO_2 max) after slow adaptation over years of exercise.[4,25] However, prolonged intense exercise is reported to result in a transient reduction in LVEF and is commonly designated as "cardiac fatigue."[26] Although, this study recruited only male participants, in normal circumstances, the sex difference does not significantly influence the left ventricular remodeling.[27]

MPI has also been used as a prognostic tool for cardiac hypertrophy and myocardial ischemia.[28] Hence, effect of supplementation on LVEF as well as MPI was indicative of cardiac muscle health. Right ventricular

Table 3. CONSORT checklist.

Section	Item	Standard CONSORT description	Extension for nonpharmacologic trials	Reported on page no.
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the experimental treatment, comparator, care providers, centers, and blinding status	1–3 of 18
Introduction				
Background	2	Scientific background and explanation of rationale		4–5 of 18
Methods				
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	When applicable, eligibility criteria for centers and those performing the interventions	5 of 18
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	Precise details of both the experimental treatment and comparator	6 of 18
	4A		Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants	6 of 18
	4B		Details of how the interventions were standardized	6 of 18
	4C		Details of how adherence of care providers with the protocol was assessed or enhanced	6 of 18
Objectives	5	Specific objectives and hypotheses		7 of 18
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors)		7–8 of 18
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	When applicable, details of whether and how the clustering by care providers or centers was addressed	6 of 18
Randomization–sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)	When applicable, how care providers were allocated to each trial group	7 of 18
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned		7 of 18

(*Continued on next page*)

Table 3. (*Continued*) CONSORT checklist.

Section	Item	Standard CONSORT description	Extension for nonpharmacologic trials	Reported on page no.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		7 of 18
Blinding (masking)	11A	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	Whether or not those administering cointerventions were blinded to group assignment	7 of 18
	11B		If blinded, method of blinding and description of the similarity of interventions	7 of 18
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	When applicable, details of whether and how the clustering by care providers or centers was addressed	9 of 18
Results				
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)—specifically, for each group, report the number of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe deviations from study as planned, together with reasons	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Figure 1
Implementation of intervention	New item		Details of the experimental treatment and comparator as they were implemented	8 of 18
Recruitment	14	Dates defining the periods of recruitment and follow-up		-
Baseline data	15	Baseline demographic and clinical characteristics of each group	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group	6 of 18
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat;" state the results in absolute numbers when feasible (eg, 10/20, not 50%)		6 of 18 & Figure 1
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval)		9–11 of 18

(*Continued on next page*)

Table 3. (*Continued*) CONSORT checklist.

Section	Item	Standard CONSORT description	Extension for nonpharmacologic trials	Reported on page no.
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory		10 of 18
Adverse events	19	All important adverse events or side effects in each intervention group		11 of 18
Discussion				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	11–13 of 18
Generalizability	21	Generalizability (external validity) of the trial findings	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	NA
Overall evidence	22	General interpretation of the results in the context of current evidence		13 of 18

NA, not applicable.

health is of primary concern in athletes, as there is a drastic change in the morphology due to extreme training. Reduction of the RV-MPI is projected to have a positive effect on future heart health[29] as well as on endurance capacity of athletes.[28]

In young athletes with optimal blood hemoglobin and oxygen transportation, VO_2 max is hypothesized to be directly proportional to cardiac output and inversely correlates with MPI.[30] Administration of E-OJ-01 demonstrated a significant increase in LVEF and a statistically relevant decrease in RV-MPI.

Rated perceived exertion on Borg Scale along with increased time to exhaustion are practical measures of global exercise intensity. Meta-analysis of multiple studies has shown that RPE can be correlated with predict VO_2 max in healthy trained athletes.[31] It has also been shown that higher VO_2 max levels correlate well with the individual's capacity to use oxygen with less dependence on the anaerobic pathway.

In this study, we observed a significant increase in time to exhaustion as well as a decreasing trend in exertion in the group receiving the TA extract. After 56 days administration, we observed that E-OJ-01 was able to improve various central factors for physical endurance such as left ventricular ejection fraction, time to exhaustion, and Borg RPE score.

We also analyzed the effect of TA extract on safety markers, CK-MB and troponin-T. We observed that with a controlled age group and same exercise protocol, there was a decreasing trend in CK values in a group receiving E-OJ-01, indicating cardioprotective potential of the product. Troponin-T, a specific marker of cardiac injury, was comparable in E-OJ-01 group to that of placebo.

Based on the findings of the study, we deduce that the E-OJ-01 was able to increase LVEF and decrease MPI without causing any cardiac injury. This study successfully demonstrates the extract's ability to enhance the performance and also protect the heart in young exercising adults. Currently, there is a void for a supplement which enhances the exercise performance effectively by improving the cardiac conditioning. E-OJ-01 has indeed shown some promising results to fulfill this unmet need of young athletes.

A further elaborative study on veteran athletes with prominent cardiac changes may be useful to confirm the utility of E-OJ-01 as a "cardioprotective ergogenic aid."

CONCLUSIONS

E-OJ-01 increases LVEF, thus leading to increased cardiac output. It also decreases MPI, which is an important determinant for cardiac musculature size. An increase in the cardiac output, as well as a reduction in MPI, is expected to increase VO_2 max. E-OJ-01 also demonstrated an antifatigue potential by reducing RPE score. E-OJ-01 seems to be safe for use as a sports supplement under the conditions studied as demonstrated by normal troponin-T and CK-MB levels. No adverse event was reported in the study.

CONSORT STATEMENT

The current manuscript adheres to the "Consolidated Standards of Reporting Trials" guidelines. The compliance to the guidelines has been demonstrated in Table 3.

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