Original Communication

Trans-resveratrol supplement lowers lipid peroxidation responses of exercise in male Wistar rats

Masoud Nasiri[1], Saja Ahmadizad[2], Mehdi Hedayati[3], Tayebe Zarekar[2], Mehdi Seydyousefi[4], and Zeinab Faghfoori[5,6]

[1] Faculty of Sport Sciences, Razi University of Kermanshah, Iran
[2] Department of Biological Sciences in Sport, Faculty of Sport Sciences and Health, Shahid Beheshti University G.C., Tehran, Iran
[3] Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Department of Physical Education and Sport Sciences, Bojnourd Branch, Islamic Azad University, Bojnourd, Iran
[5] Food Safety Research Center (salt), Semnan University of Medical Sciences, Semnan, Iran
[6] Department of Nutrition, School of Nutrition and Food Sciences, Semnan University of Medical Sciences, Semnan, Iran

Abstract: Physical exercise increases free radicals production; antioxidant supplementation may improve the muscle fiber's ability to scavenge ROS and protect muscles against exercise-induced oxidative damage. This study was designed to examine the effects of all-trans resveratrol supplementation as an antioxidant to mediate anti-oxidation and lipid per-oxidation responses to exercise in male Wistar rats. Sixty-four male Wistar rats were randomly divided into four equal number (n = 16) including training + supplement (TS), training (T), supplement (S) and control (C) group. The rats in TS and S groups received a dose of 10 mg/kg resveratrol per day via gavage. The training groups ran on a rodent treadmill 5 times per week at the speed of 10 m/min for 10 min; the speed gradually increased to 30 m/min for 60 minutes at the end of 12th week. The acute phase of exercise protocol included a speed of 25 m/min set to an inclination of 10° to the exhaustion point. Superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) activity, non-enzymatic antioxidants bilirubin, uric acid, lipid peroxidation levels (MDA) and the total antioxidant capacity (TAC) were measured after the exercise termination. The data were analyzed by using one-way ANOVA. The result showed that endurance training caused a significant increase in MDA level [4.5 ± 0.75 (C group) vs. 5.9 ± 0.41 nmol/l (T group)] whereas it decreased the total antioxidant capacity [8.5 ± 1.35 (C group) vs. 7.1 ± 0.55 mmol/l (T group)] ($p = 0.001$). In addition, GPx and CAT decreased but not significantly ($p > 0.05$). The training and t-resveratrol supplementation had no significant effect on the acute response of all variables except MDA [4.3 ± 1.4 (C group) vs. 4.0 ± 0.90 nmol/l (TS group)] ($p = 0.001$) and TAC [8.5 ± 0.90 (C group) vs. 6.6 ± 0.80 mmol/l (TS group)] ($p = 0.004$). It was concluded that resveratrol supplementation may prevent exercise-induced oxidative stress by preventing lipid peroxidation.

Keywords: Resveratrol, endurance training, oxidative stress, acute exercise, lipid peroxidation

Introduction

Regular physical activity such as aerobic exercise is associated with lower health risk such as cardiovascular disease, cancer and diabetes [1]. However in 1978, it was reported for the first time that exercise induces oxidative stress [2]. Since then, a growing body of evidence has shown that strenuous physical exercise has the potential to increase free radicals production that leads to oxidative stress [3]. The oxidative stress disrupts the equilibrium between oxidants and antioxidant balance and may lead to oxidative damage in cellular macromolecules such as proteins, lipids and DNA. An imbalance of redox system is associated with the pathogenesis of a variety of diseases, such as cancer, diabetes, cardiovascular and neurodegenerative diseases [4]. The effect of exercise on redox balance is extremely complicated and depends on the individual characteristics including age, gender and exercise parameters with different intensities, durations and frequencies [2, 5, 6]. Several studies have indicated that single bout of aerobic and anaerobic exercise may induce an acute state of oxidative stress [7, 8]. Human body has a defense system to prevent oxidative damage by converting the harmful reactive oxygen species (ROS) into less reactive molecules or remove them altogether [9]. The rapid increase in the concentration of oxidants during exercise produces antioxidants enzymes and provides a mean to metabolize the dietary antioxidants [10]. The antioxidant defense system of the body includes

antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione reductase (GR), etc.), non-enzymatic antioxidants such as vitamin A, vitamin C, vitamin E and coenzyme Q10 with L-glutamine [11]. There is a moderating interaction between the endogenous and dietary antioxidants; as a result antioxidant supplementation may improve the muscle fiber's ability to scavenge ROS and protect the exercising muscle against exercise-induced oxidative damage and fatigue. However, antioxidant nutrients deficiency could induce an increased susceptibility to exercise-induced damage and thus leads to impaired exercise performance [12, 13]. Recently, the question of whether or not athletes should use antioxidant supplementation is an important and highly debated topic and there is an enormous type of vitamins, minerals and extracts marketed as antioxidant supplements [12, 14]. Resveratrol is a natural polyphenolic compound present in grains, grape seed extracts and red wine [15]. In vivo and in vitro studies have provided evidence that show the neuroprotective, antiatherogenic, antithrombotic, anti-hypercholesterolemic, anti-inflammatory, antioxidant, proangiogenic, vaso-relaxing and anticancer effects of resveratrol [16–18]. The mechanism of action of resveratrol is complex and its antioxidant nature provides substantial evidence for its health benefits [19, 20]. Although the effect of t-resveratrol on the antioxidant capacity is known, however, there is a lack of research finding in regard to the effect of this supplement during exercise on antioxidant capacity. Therefore, the current study was designed to examine the effect of 12 weeks of training in addition to a t-resveratrol supplementation on the resting levels plus the response of antioxidant capacity to one bout of exercise.

Materials and methods

Animals

Sixty-four male Wistar rats (6 weeks of age, weighing 122.4 ± 29.2 g) were purchased from the Pasteur Institute of Iran. The animals were housed under controlled environmental conditions at 21–28 °C under a 12:12-h light-dark cycle and 50% humidity. The rats had access to food (a standard rat diet) and water ad libitum. Their body weight of was measured weekly. The study protocol was approved by the Ethics Committee of the Shahid Beheshti University Experimental Medicine Research and Application Center (Tehran, Iran, No. 6ECRIES). After 1 week of adaptation to the laboratory conditions, the animals were randomly assigned into the equal numbers including training + supplement (TS), training (T), supplement (S), and control (C) groups (Figure 1).

Supplementation protocol

The trans-resveratrol supplement was purchased from Enzo life company (Switzerland, with production number – BML-FR 104-0500 SIRT1 activator). Rats in TS and S groups received trans-resveratrol suspended in ethanol 2% at a dose of 10 mg/kg body weight per day via gavage. The same amount of solution (2% ethanol) with distilled water was given to the control group during the exercise.

Training protocol

The animals ran on a rodent treadmill (Aria Model, Pishro Andishe Sanaat, Tehran, Iran) in an endurance exercise program. The entire exercise program was performed at 65% of VO2max 5 times a week at a speed of 10 m/min for 10 min at the same time of a day (17). The speed and duration of endurance training gradually increased up to 30 m/min for 60 minutes at the end of the 12^{th} week. Half of the rats were slaughtered 48 h after the last exercise session to determine the effects of the exercise programs. The remaining rats performed the acute exercise protocol at a speed of 25 m/min with 10° inclination to the exhaustion point. The rats in the control group only walked on the treadmill at a low speed for 10 to 15 minutes per day and 3 times per week.

Blood sampling

After the last exercise and acute exercise session, the animals were anesthetized by injection of intraperitoneally at a dose of 30–50 mg/kg ketamine (Tocris, Bristol, UK) and a dose of 3–5 mg/kg xylasine (Iman-Saba, Iran) of body weight. Then, using a 10-cc syringe impregnated with heparin, blood samples were collected directly from the heart.

Biochemical analysis

The blood samples were centrifuged at 1200 g for 15 minutes to separate blood plasma. The antioxidant level and the activity of enzymes in plasma samples including (SOD, CAT, and GPX) was measured by a commercial chemical colorimetrical assay kit according to manufacturer's protocol (ZellBio GmbH, Ulm, Germany). The malondialdehyde (MDA) and total antioxidant capacity (TAC) levels were measured by colorimetric method using the commercial kits (ZellBio GmbH, Ulm, Germany). The Bilirubin (Darman Faraz Kave Co, Iran) was assessed spectrophotometrically according to the method described in the kit purchased. The uric acid assay was done by kit purchased from Pars Azmoon Company, Tehran, Iran.

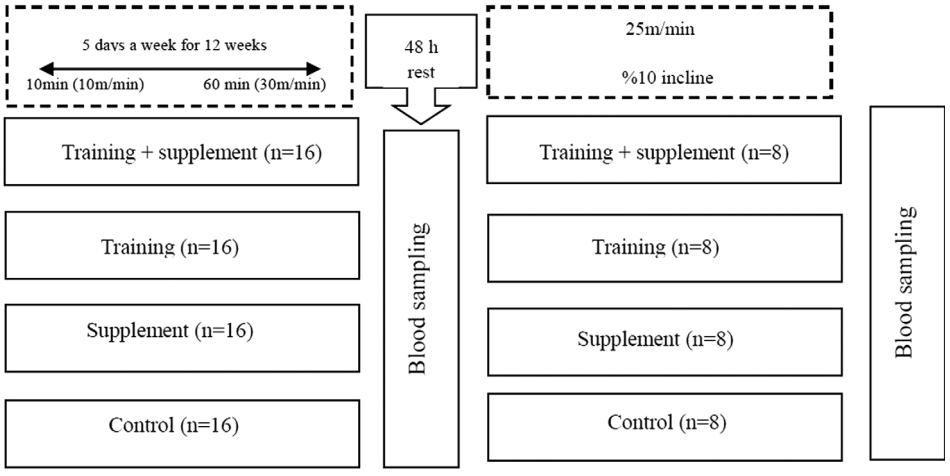

Figure 1. Schematic view of the protocol of study.

Statistical analysis

Statistical analyses were performed by the SSPS: PC software (version 21). Kolmogorov–Smirnov test was used to check normality of data and Levene's test was applied to examine the equality of variances. The hypothesis was tested by one-way analysis of variance (ANOVA) test and Bonferroni's post-hoc test was performed to locate the differences. All the hypothesis were tested at a significant level set to $\alpha = 0.05$

Results

The result of analysis of data showed a significant effect of 12 weeks of endurance training plus t-resveratrol administration on the levels of TAC ($p = 0.001$), SOD ($p < 0.001$) and MDA ($p = 0.001$) (Table 1). The level of TAC significantly increased in the S group compared to T and T&S groups. Resveratrol ($p < 0.001$), training ($p < 0.001$) and their combination ($p < 0.001$) significantly increased superoxide dismutase in compared to the control group. Also, training significantly increased MDA compared to the control group ($p = 0.04$). The result of one-way ANOVA test showed no significant effect for the 12 weeks endurance training plus t-resveratrol administration on resting levels of GPX, catalase, uric acid and bilirubin levels.

Table 2 indicates that training plus t-resveratrol administration had no significant effect on the acute response of all variables excerpt malondialdehyde ($p < 0.001$) and TAC ($p = 0.004$). pairwise intra-group comparison of data by using paired t-test in every group also showed no significant difference between the GPX, catalase, uric acid, and MDA from before to after acute activity, however, the change of bilirubin level ($p = 0.017$) was significant.

Discussion

This study was designed to investigate the effect of t-resveratrol supplementation on oxidative stress induced by exercise in rats. Exercise may lead to an imbalance between the reactive oxygen species and antioxidants in several ways including oxidative phosphorylation in mitochondria, catecholamines released during exercise, prostanoid metabolism, xanthineoxidase, NAD(P)H oxidase, and secondary sources such as the release of radicals by macrophages recruited to repair damaged tissue [21]. The results of the present study showed that endurance and acute training caused a significant increase in malondialdehyde level

Table 1. Changes in the level of variables of plasma after endurance exercise

	Control (n = 16)	Training (n = 16)	Supplement (n = 16)	Training + supplement (n = 16)
Variables	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Total antioxidant capacity (mmol/l)	8.5 ± 1.35[b]	7.1 ± 0.55[a]	9.3 ± 1.00[b]	7.3 ± 1.12[a]
Superoxide dismutase (U/l)	79 ± 19.00[a]	123 ± 13.00[b]	115 ± 11.00[b]	120 ± 7.00[b]
Glutathione peroxidase (U/l)	29.6 ± 3.48[a]	27.8 ± 4.71[a]	31.2 ± 6.32[a]	27.33 ± 5.16[a]
Catalase (U/l)	138.2 ± 15.5[a]	130.5 ± 19.77[a]	137.5 ± 15.4[a]	136.3 ± 13.74[a]
Malondialdehyde (nmol/l)	4.5 ± 0.75[a]	5.9 ± 0.41[b,d]	4.1 ± 0.71[a,c]	5.6 ± 0.46[a,d]
Bilirubin (mg/dl)	0.41 ± 0.12[a]	0.31 ± 0.19[a]	0.27 ± 0.08[a]	0.32 ± 0.12[a]
Uric acid (mg/dl)	2.35 ± 0.27[a]	2.26 ± 0.13[a]	2.40 ± 0.29[a]	2.41 ± 0.30[a]

[a,b]Significant differences between two groups was shown with different letters (p-value < 0.05).

Table 2. Changes in plasma level of variables after acute exercise

	Control (n = 8)	Training (n = 8)	Supplement (n = 8)	Training + supplement (n = 8)
Variables	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Total antioxidant capacity (mmol/l)	8.5 ± 0.90[a]	6.1 ± 0.90[b]	9.5 ± 0.30[a]	6.6 ± 0.80[b]
Superoxide dismutase (U/l*)	120 ± 16[a]	121 ± 14[a]	122 ± 19[a]	122 ± 11[a]
Glutathione peroxidase (U/l)	31 ± 5.30[a]	31.5 ± 4.50[a]	30.5 ± 4.10[a]	30 ± 5.20[a]
Catalase (U/l)	132 ± 17.00[a]	127 ± 17.00[a]	131 ± 13.00[a]	128 ± 16.00[a]
Malondialdehyde (nmol/l)	4.3 ± 1.40[a]	6.6 ± 1.50[b]	3.7 ± 0.60[a]	4.0 ± 0.90[a]
Bilirubin (mg/dl)	0.36 ± 0.11[a]	0.48 ± 0.16[a]	0.40 ± 0.18[a]	0.67 ± 0.16[a]
Uric acid (mg/dl)	2.38 ± 0.35[a]	2.21 ± 0.21[a]	2.49 ± 0.39[a]	2.33 ± 0.24[a]

*International unit for enzyme/Liter. [a,b]Significant differences between two groups was shown with different letters (p-value < 0.05).

and a decrease in total antioxidant capacity. The result of analysis showed that the enzymes of the antioxidant defense system including glutathione peroxidase and catalase decreased; however, these changes were not statistically significant. Aldehydes, mainly malondialdehyde, have been often applied as markers of oxidative stress in response to exercise [21]. In a research, it was demonstrated that in resting conditions, the malondialdehyde level was higher in sprint trained athletes and marathon runners compared to the control group but showed a progressive increase until 48 hr post-exercise session [22]. In trained swimmers, it was reported that the level of oxidative stress markers including lipoperoxidation products was increased [23]. Miyazaki et al. [24] evaluated the effect of high-intensity endurance training on exercise-induced oxidative stress. They reported a significant increase in lipid peroxidation in the erythrocyte membrane, but not in oxidative protein. Based on the findings of this study, the total antioxidant capacity is influenced by training. In a study, plasma total antioxidant capacity did not increase in response to a 30 min of exercise, despite an increase in MDA [25].

Excess ROS concentrations due to any prolonged exercise program especially in skeletal muscle may attenuate exercise performance by decreased muscular functionality, histological changes, and muscular soreness [26]. Athletes may use antioxidant supplements as a substance neutralizes the oxidative stress of exercise. There is a facilitative interaction between the endogenous and dietary antioxidants. Therefore, antioxidant supplementation may improve the ability of muscle fiber to scavenge ROS and protect the exercising muscle against exercise-induced oxidative damage and fatigue [27]. Resveratrol is a natural polyphenolic compound that facilitates the impact of exercise on endurance capacity; it became evident in mice with boosted aerobic endurance performance. Also, it has been shown that resveratrol may enhance performance, improve skeletal muscle function and heart tissue to a great extent [15, 28–30]. Several studies reported that resveratrol has a regulatory effect on muscle glycogen in rats with acute swimming exercise, but did not affect plasma leptin levels [31, 32].

Our findings support the potential of antioxidant activity of resveratrol to increase the total antioxidant capacity in plasma. This finding is agreement with the results of previous studies [33, 34].

However, the resveratrol consumption during 12 weeks of training had no significant effect on oxidative stress factor including MDA and antioxidant defense system. This finding is contradictory findings to previous investigations that showed the efficacy of resveratrol as an antioxidant and protective effect of resveratrol supplementation against exercise-induced oxidative damage. In a study conducted by Lafay et al. (2009) on elite male athletes in different professional sports, the use of grape seed extract for 1 month significantly increased the plasma antioxidant capacity irrespective of the measurement method [35]. The exercise-induced lipid peroxidation decreased when a combination of quercetin and resveratrol was used by fourteen athletes after they consumed these two compounds a week before the exercise program [36].

The result of one study showed that moderately trained cyclists when consumed antioxidant supplementation, it compensated oxidative stress induced by a 90 min exercise at 70% VO2max [37]. Resveratrol supplementation (25, 50, and 100 mg/kg body weight) protected against strenuous exercise-induced oxidative damage and lipid peroxidation by lowering the levels of lactate dehydrogenase, creatine kinase, malondialdehyde, 4-hydroxy-2-nonenal and 8-hydroxy-2'-deoxyguanosine in rats [38]. However, 1000 mg quercetin consumption for 6 weeks before and during 3 days of cycling does not guard against exercise-induced oxidative stress and inflammation [39]. In this regard, some factors such as dose, time of consumption, measurement and type of exercise may regulate the antioxidant effect of resveratrol during exercise.

Antioxidant enzyme superoxide dismutase is a major cellular defense against destructive superoxide radicals. The elevated SOD activity was associated with increased resistance to oxidative stress [40]. The result of present study showed that 12 weeks of endurance training resulted in significant changes in the enzymatic activity of superoxide dismutase in the training group, whereas, exercise and

supplements did not result in such a change after acute training. Superoxide dismutase provides a defense against the potential cytotoxicity of superoxide radicals. Although some conflicting results were found on acute exercise-induced changes in the activity of antioxidant enzymes, the activity of these enzymes typically increased in both training models. This result was found in the muscular tissue; a finding in line with the findings of some studies in erythrocytes [22, 41] as well as the heart tissue [42]. These findings was similar to the results of the present research that showed superoxide dismutase enzyme during the 12-week training period increased, but subsequently decreased in the acute response to exercise. Also, Alessio et al. (2003) showed a transient decline in the activity of the superoxide dismutase after a training period [43].

Bilirubin is one of the most useful clinical markers to diagnose severe liver necrosis and is the terminal product of heme metabolism in the bile; its elevated levels may be attributed to abnormalities of the liver [44]. The administration of the resveratrol-rich supplement may decrease its total levels in serum. Guinjoan Fan et al. (2009) reported a significant increase in uric acid concentrations and serum bilirubin after administration of toxins and concluded that structural and functional changes in the kidney and liver may be correlated and resveratrol may play a significant protective role [45]. Chevion et al. (2003) also observed increased levels of uric acid and plasma bilirubin following a training period by young men possibly due to the increased rate of pyrimidine nucleotide metabolism and damage to liver tissue [46]. Hyperbilirubinemia is associated with elevated oxidative stress and might lead to certain benefits for the body as an antioxidant [47]. Based on the results of present research, 12-week of training period plus resveratrol supplement administration caused no significant change in the amount of uric acid and plasma bilirubin. Such findings may be due to the mild-intensity endurance training. However, significant changes were found between the 12 weeks of training and acute response to training in plasma bilirubin levels; this result may be attributed to the high levels of exercise intensity and damage to the liver tissue due to increased oxidative stress. Assessing the effects of trans-resveratrol on oxidative stress responses both endurance and acute exercise are considered as the strength of the present study, however, more studies are needed to examine the effects of different doses of trans-resveratrol and changes of levels of the other oxidative stress markers such as 15(*S*)-8-*iso*-prostaglandin $F_{2\alpha}$. One limitation of our study was that the animal was forced to exercise; such intervention made the rats run on treadmill. This may cause unnecessary stress and have an impact on our findings.

In conclusion, this study suggests that exercise, whether endurance or strength, may increase oxidative stress. The use of antioxidant supplements may be a strategy to counter balance these adverse effects. However, further studies are needed to determine the effect of type and dose of supplements.

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Conflict of interest
The authors declare that there are no conflicts of interest.

ORCID
Zeinab Faghfoori
https://orcid.org/0000-0002-5312-6585

Zeinab Faghfoori, Ph.D.
Food Safety Research Center (SALT)
Semnan University of Medical Sciences
Oriental Side of Imam Hossein Hospital
Pazoki Street, Aradan
Semnan 3586133461
Iran
zfaghfoori@gmail.com

